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The perioperative use of Levosimendan as a means of optimizing the surgical outcome in patients with severe heart insufficiency undergoing cardiac surgery.

Die perioperative Anwendung von Levosimendan zur Optimierung des chirurgischen Ergebnisses bei Patienten mit schwerer Herzinsuffizienz, die sich einer Herzoperation unterziehen.

Inauguraldissertation

zur Erlangung des Doktorgrades der

Medizin

der Universitätsmedizin

der Johannes Gutenberg-Universität Mainz

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Mainz, 2019

Tag der Promotion: 30. Juni 2020

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ACC	American College of Cardiologists
ACEI	Angiotensin-converting enzyme inhibitors
ACS	Acute Coronary Syndrome
AF	Atrial Fibrillation
AHA	American Heart Association
AHF	Acute Heart Failure
AIVR	Accelerated Idioventricular Rhythm
AMI	Acute Myocardial Infarction
ANT	Adenine Nucleotide Translocase
APOB	Apolipoprotein B
ARB	Angiotensin Receptor Blockers
ATP	Adenosine Triphosphate
AV	Atrioventricular
BiVAD	Biventricular Assist Device
BMI	Body Mass Index
BNP	Brain Natriuretic Peptide
BSA	Body Surface Area
BTT	Bridge to Transplantation
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CAM	Cell Adhesion Molecules
CCS	Canadian Cardiovascular Society
cGMP	cyclic Guanosine Monophosphate
CI	Cardiac Index

CK	Creatine Kinase
CKMB	Myocardial Creatine Kinase
CMR	Cardiac Magnetic Resonance imaging
CO	Cardiac Output
CPB	Cardiopulmonary Bypass
CrCl	Creatinine Clearance
CRP	C - Reactive Protein
CRT	Cardiac Resynchronization Therapy
CyP-D	Cyclophilin-D
DNA	Deoxyribonucleic Acid
DT	Destination Therapy
ECC	Extracorporeal Circulation
ECLS	Extracorporeal Life Support
ECM	Extracellular Matrix
EDV	End Diastolic Volume
EF	Ejection Fraction
eNOS	endothelial Nitric Oxide Synthase
ESC	European Society of Cardiology
ESV	End Systolic Volume
EuroSCORE	European System for Cardiac Operative Risk Evaluation
FFP	Fresh Frozen Plasma
GFR	Glomerular Filtration Rate
HDL	High Density Lipoprotein
HF	Heart Failure
HFmrEF	Heart Failure with mid-range Ejection Fraction

HFpEF	Heart Failure with preserved Ejection Fraction
HFrEF	Heart Failure with reduced Ejection Fraction
HMG-CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A
HR	Heart Rate
IABP	Intraaortic Balloon Pump
ICD	Implantable cardioverter-defibrillator
IFN-g	Interferon-g
IHD	Ischemic Heart Disease
IL-1	Interleukin 1
IMM	Inner Mitochondrial Membrane
IPC	Ischemic Preconditioning
LA	Left Atrium
LBBB	Left Bundle Branch Block
LDL	Low Density Lipoprotein
LDLR	LDL Receptor
LV	Left Ventricle
LVAD	Left Ventricular Assist Device
LVEF	Left Ventricular Ejection Fraction
MAP	Mean Arterial Pressure
MCP-1	Monocyte Chemoattractant Protein-1
MCSF	Macrophage Colony-stimulating Factor
MI	Myocardial Infarction
MMP	Matrix Metalloproteinases
mPTP	mitochondrial Permeability Transition Pore
MRA	Mineralocorticoid/aldosterone Receptor Antagonists

NO	Nitric Oxide
NOS	Nitric Oxide Synthase
NP	Natriuretic Peptide
NSTEMI	Non-ST-elevation Myocardial Infarction
NYHA	New York Heart Association
OMT	Optimal Medical Therapy
PCSK9	Proprotein Convertase Subtilisin/Kexin type 9
PCWP	Pulmonary Capillary Wedge Pressure
PET	Positron Emission Tomography
PiC	Phosphate Carrier
PKC	Protein Kinase C
PLT	Platelets
PTCA	Percutaneous Coronary Angioplasty
PTP	Permeability Transition Pore
RA	Right Artium
RAAS	Renin-Angiotensin-Aldosetrone-System
RBBB	Right Bundle Branch Block
RBC	Red Blood Cells
RIC	Remote Ischemic Conditioning
RISK	Reperfusion Injury Salvage Kinase
ROS	Reactive Oxygen Species
RRT	Renal Replacement Therapy
RV	Right Ventricle
RVAD	Right Ventricular Assist Device
RVEF	Right Ventricular Ejection Fraction

SIRS	Systemic Inflammatory Response Syndrome
SOD	Superoxide Dismutase
STEMI	ST-elevation Myocardial Infarction
STS	Society of Thoracic Surgeons
SV	Stroke Volume
SVI	Stroke Volume Index
SVR	Systemic Vascular Resistance
TnC	Troponin C
TNF-α	Tumor Necrosis Factor alpha
TnI	Troponin I
TnT	Troponin T
UA	Unstable Angina
VA-ECLS	Venoarterial Ectracorporeal Life Support
VEGF	Vascular Endothelial Growth Factor
VSMC	Vascular Smooth Muscle Cell
WHO	World Health Organisation

1. PREFACE

In recent years the number of patients with severely impaired myocardial function has been steadily increasing. This increase is primarily attributable to the aging of the population and improved treatment of acute myocardial infarction. Over the last decade the frequency of surgical procedures carried out in patients with heart failure has been constantly increasing. This group of high risk patients was considered to be inoperable some decades ago, but they nowadays consist part of a cardiac surgeon's daily clinical practice. Patients with poor left ventricular function usually require inotropic drug support immediately after cardiopulmonary bypass. Indeed, preexisting impaired ventricular function is further compromised by variable degrees of myocardial injury as a result of ischemia during aortic cross clamping. Therefore physicians involved in the treatment of such patients including surgeons, anesthesiologists and intensivists are increasingly confronted with the challenging perioperative management of patients with heart failure.

Significant improvements have been made in treating patients with heart failure, mainly due to a better understanding of the undelying pathophysiological mechanisms. However, despite the steadily improved experience in the management of these patients and the evolution of pharmacological and mechanical means to support impaired heart function, the successful treatment and the survival of patients with severe heart failure still remains a great challenge in cardiac surgery. This constant increase of high risk patients as candidates for cardiac surgery has led to an increasing use of pharmacologic support in the form of vasodilator and inotropic therapy. Traditionally, perioperatively used inotropic agents, such as epinephrine, dobutamine and milrinone are limited by significant increases in myocardial oxygen consumption, proarrhythmia, or neurohormonal activation. They tend to enhance myocardial contractility by increasing cyclic adenosine monophosphate concentrations, which ultimately increases the myocardial concentrations of calcium. Over the last years a new pharmacological agent, Levosimendan, has started being used in the daily practice during an operation as well as postoperatively in the intensive care unit, promising to ameliorate the haemodynamic condition of these patients.

The aim of the current study is to evaluate the possible positive preoperative and postoperative effect of Levosimendan, a new inodilator in the treatment of

decompensated heart failure. This new inotropic agent has already shown promising effects in the treatment of cardiac surgical patients with high perioperative risk or compromised left ventricular function, as well as in rescue therapy of patients with difficult weaning from cardiopulmonary bypass. Levosimendan has a unique mechanism of action. Briefly, levosimendan binds to the regulatory protein troponin C (TnC) and stabilizes the Ca^{2+}-bound conformation of TnC, thereby allowing unopposed interaction between actin and myosin filaments and enhancing the rate and extent of myocyte contraction.

Over the last years many patients with low ejection fraction have been admitted to our ward and received a variety of cardiac surgical procedures. Levosimendan has been widely used in such patients over the last years with promising postoperative results. This study will retrospectively include such patients with preoperative low ejection fraction who underwent heart surgery in our department. The group of patients who were treated with levosimendan will be compared to a similar historical group of patients with heart failure who underwent similar procedures in the past and did not receive this medical treatment.

2. ISCHEMIC HEART DISEASE

Ischemic heart disease consists a major part of the nosological entity of cardiovascular disease, which also includes hypertension, stroke, valvular, muscular and congenital heart disease. About 15% of worldwide mortality is attributable to ischemic heart disease, making it the leading cause of death globally. It is the most important and most common contributor to the development of heart failure, accounting for up to 50% of cases (1).

The current treatment of ischemic heart disease consists of medical pharmacological therapy and revascularization procedures including thrombolysis, percutaneous coronary angioplasty (PTCA) and coronary artery bypass grafting (CABG) through open heart surgery. The main goals of these treatments are establishing reperfusion in coronary arteries, enhancement of coronary blood flow, reduction of myocardial oxygen consumption, avoidance of the incidence of arrhythmic disorders and in cases of patients with acute myocardial infarction limitation of the infarct size and loss of vital myocardium. Despite intensive pharmacological therapies and the

increasing use of evolving surgical and interventional procedures which are nowadays widely available in clinical practice, the prognosis of patients with heart failure due to ischemic heart disease remains unfortunately poor (2, 3).

2.1. Atherosclerosis

The term atherosclerosis is used to describe a chronic inflammatory condition of the vessel wall. Atherosclerosis is the pathological basis of peripheral vascular, coronary artery and cerebrovascular diseases, all major causes of mortality and morbidity throughout the world. Despite the development of effective cholesterol reducing agents and lifestyle modification initiatives, only modest decreases in rates of atherosclerosis and its clinical manifestations have been achieved over the last decades (4, 5).

It is considered to be a complex, chronic disease which is traditionally thought of as the accumulation of fibrofatty deposits in the intima of medium and large muscular arteries, a passive process and an inevitable aspect of aging. Current knowledge has however shown that it consists a complex interplay of lipid metabolism, active cellular interactions, inflammation, and matrix remodelling (4-6). The most appropriate approach to the definition of atherosclerotic lesions would therefore be a dynamic process which evolves from fatty streaks to stable or unstable plaques (4).

Scientific understanding of the pathogenesis of atherogenesis is constantly developing. From Virchow's observations 160 years ago we are nowadays familiar with the endothelial response to injury as inflammatory, involved in all stages of atherosclerosis (6). The following paragraphs are intended to give a general overview of the main factors and pathophysiological mechanisms involed in the several phases of atherosclerotic development. The main vascular modifications which take part in atherosclerotic disease are summarized in Table 1.

Vascular modification	Characteristics
Intimal thickening	Layers of smooth muscle cells (SMCs) and extracellular matrix. More frequent in coronary artery, carotid artery, abdominal aorta, descending aorta, and iliac artery.
Fatty streak	Abundant macrophage foam cells mixed with SMCs and

	proteoglycan-rich intima
Pathologic intimal thickening	Layers of SMCs in proteoglycan-collagen matrix aggregated near the lumen. Underlying lipid pool: acellular area rich in hyaluronan and proteoglycans with lipid infiltrates.
Fibroatheromas	Acellular necrotic core (cellular debris). Necrotic core is covered by a thick fibrous cap=SMCs in proteoglycan-collagen matrix.
Vulnerable plaque	Thin-cap fibroatheroma'. Type I collagen, very few/absent SMCs. Fibrous cap thickness is ≤65 μm.
Ruptured plaque	Ruptured fibrous cap. Presence of luminal thrombus. Larger necrotic core and increased macrophage infiltration of the thin fibrous cap.

Table 1. Vascular modifications in atherosclerotic disease. SMCs smooth muscle cells.

(Source: Bergheanu SC, Bodde MC, Juke JW. Pathophysiology and treatment of atherosclerosis. Current view and future perspective on lipoprotein modification treatment. Neth Heart J. 2017 Apr; 25(4): 231–242.)

2.1.1. Endothelial dysfunction

Normal endothelium helps maintain vascular homeostasis. This can be achieved by secreting vasodilatory nitric oxide (NO) as well as vasoconstrictors such as endothelin and angiotensin II (6). NO inhibits inflammation, proliferation and thrombosis. NO is produced in endothelial cells from its precursor L-arginine via the enzymatic action of endothelial NO synthase (eNOS) (7). In the vascular wall, NO activates soluble guanylate cyclase in vascular smooth muscle cells (VSMCs), leading to elevation of cyclic guanosine monophosphate (cGMP), activation of cGMP-dependent protein kinase (PKG), and vasorelaxation (8).

Alterations in NO secretion and vasoconstrictive or vasodilatory response respectively are among the earliest pathologies noted in vascular disease, often preceeding the formation of atherosclerotic lesions (9). Conventional cardiovascular risk factors favor a reduction in L-arginin induced nitric oxide synthesis, leading to an increase in reactive oxygen species (ROS) and subsequent oxidative stress (Figure 1) (6). The impairment of the nitric oxide mediated vasodilation is therefore considered to be the hallmark of endothelial dysfunction.

The oxidation of low-density lipoprotein (LDL) is a well-known major mechanism of atherosclerosis (10). Since NO prevents oxidative modification of LDL, impaired production or activity of NO leads to events that promote atherosclerosis, such as vasoconstriction, platelet aggregation, smooth muscle cell proliferation and migration, leukocyte adhesion and oxidative stress (11). Oxidized LDL cholesterol increases the synthesis of caveolin-1, which by inactivating eNOS, inhibits the normal NO production (12). In patients with dysfunctional endothelium, the loss of flow-mediated and catecholamine-stimulated NO release permits the vasoconstriction by catecholamines. Thus the reduced production of NO leads to impaired vasodilation and exaggerated coronary vasoconstriction and consequently to myocardial ischaemia (13, 14).

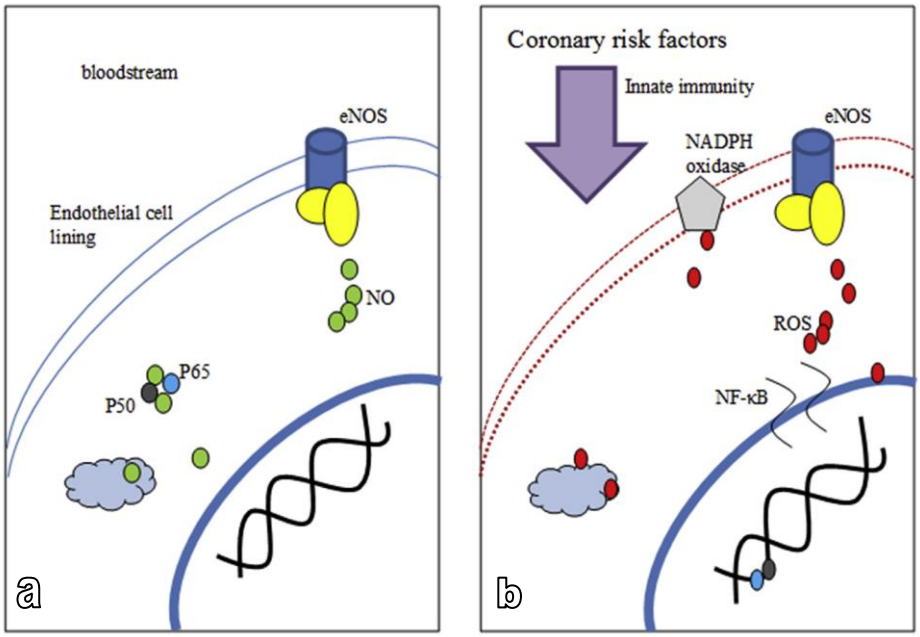


Figure 1. a. Normal endothelial physiology induced by NO. **b.** Endothelial activation is characterized by increased membrane permeability and production of ROS which alter the function of cellular constituents, leading to phosphorylisation of transcription factors and mitochondria, as well as protease activation (eNOS, p50/p65 nuclear factor-kB [NF-kB] transcription factor, nicotinamide adenine dinucleotide phosphate [NADPH]).

(Source: Brown RA, Shantsila E, Varma C, Lip GYH. Current understanding of atherogenesis. Am J Med 2017; 130(3): 268e82.)

Perturbations in hemodynamics also play a major role in endothelial dysfunction (4). Cardiovascular risk factors including smoking, hypertension, diabetes, obesity, hyperhomocysteinemia and hypercholesterolemia contribute to these hemodynamic

perturbations (6, 9, 15). The role of hemodynamics can be demonstrated by the non-random distribution of atherosclerotic lesions, which have a strong predilection for regions of turbulent, high pressure flow, such as the branch points of the aorta (4-6, 14). Endothelial cells are believed to alter their gene expression in response to shear stress.

Endothelial dysfunction appears already during the early phases of atherosclerosis, before the plaque formation can be identified through angiographic or echocardiographic. Damage to the endothelium causes a severe disturbance to the balance between vasoconstriction and vasodilation and initiates the processes that promote or exacerbate atherosclerosis. Such processes include endothelial permeability, platelet aggregation and generation of cytokines (11, 16).

2.1.2. Lipid metabolism disorders

Hyperlipidemia and abnormal lipid metabolism play a crucial role in the development of atherosclerosis. High plasma levels of LDL are considered to be atherogenic, while high density lipoproteins (HDL) on the contrary appear to be significant atheroprotective (17). This is due to the function of HDLs in reverse cholesterol transport, which brings cholesterol from the periphery to the liver for degradation. Statins act by lowering LDL via inhibiting 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase. HMG-CoA reductase is the rate-controlling enzyme of the mevalonate pathway, the metabolic pathway that produces cholesterol and other isoprenoids. Statins, diet and exercise can also lead to an increase in the plasma levels of HDL (4, 17).

The creation of fatty streaks in the vascular wall is a result of increased circulating lipid concentrations and lipid insudation of the intima, particularly from LDL cholesterol. Cholesterol and phospholipids within these early accumulations are susceptible to oxidation by enzymes such as myeloperoxidases, lipoxygenases, NADPH oxidases, and nitric oxide synthases (4, 17). Oxidized LDLs and ROS that result are toxic and induce endothelial dysfunction, inflammation and increased vascular permeability (17). There is subsequent upregulation of leukocyte adhesion molecules by the endothelium, further inciting migration of lymphocytes and macrophages. Macrophages take up LDLs via endocytosis and then transport them to lysosomes to be degraded, but oxidized LDLs are less susceptible to degradation.

Thus a macrophage transitions into a foam cell when it becomes inundated with cholesterol faster than it can be degraded (Figure 2) (4, 17).

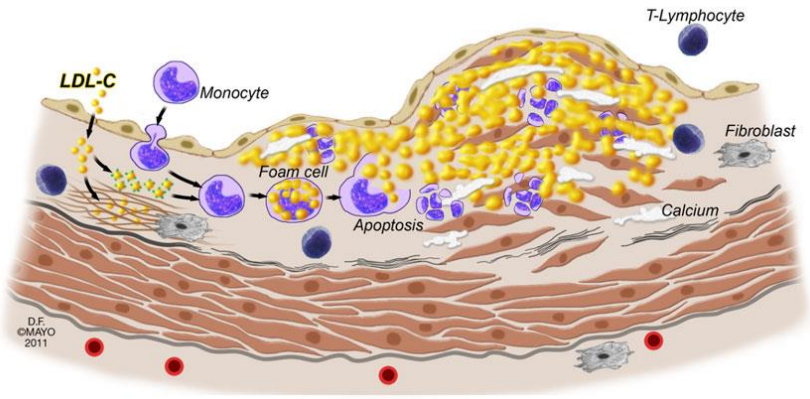


Figure 2. The role of oxidized LDL cholesterol in the formation of foam cells and the development of an atherosclerotic plaque.

(Source: www.mayo.edu/research/labs/atherosclerosis-lipid-genomics/research/genetics-of-atherosclerosis)

2.1.3. Inflammation and the role of cytokines and macrophages

The two mechanisms described above, endothelial dysfunction and abnormal lipid metabolism lead to the release of many pro-inflammatory molecules. A wide variety of inflammatory cells and cytokines are involved at all stages of atherosclerosis (4). The upregulation of several cell adhesion molecules (CAM), such as ICAM1, VCAM1 and P-selectin leads to increased binding of inflammatory cells. Circulating monocytes and leukocytes initially bind CAMs on the endothelial surface, but several chemokines are additionally required for recruitment of these cells into the subendothelial space. Among the most commonly expressed chemokines in these atherosclerotic lesions are monocyte chemoattractant protein-1 (MCP-1), macrophage colony-stimulating factor (MCSF) and interferon-g (IFN-g). MCP-1 activates leukocyte integrin, resulting in firm initial monocyte attachment (18). MCSF promotes scavenger receptor protein synthesis and differentiation of monocytes into macrophages and IFN-g promotes plaque development and foam cell formation (18). Once monocytes enter the subendothelial space, they may mature and evolve into macrophages. Mature macrophages are able to take up oxidized LDL and turn into foam cells (Figure 2). Macrophages are however not just merely passive storage “vessels” for LDL, but they also actively promote inflammation, T lymphocyte activation, and additional macrophage migration through the secretion of cytokines

like interleukin 1 (IL-1), IL-6, IL-12, and MCP-1 (4, 18, 19). The IL-1 family of cytokines upregulates CAM expression and regulates the activation of macrophages and lymphocytes (19). IL-6 has been implicated in angiogenesis, re-vascularization, and induction of C-reactive protein (CRP) and vascular endothelial growth factor (VEGF) expression (18). IL-12 has been implicated in the activation of T cells (19). Macrophages also produce matrix metalloproteinases, which can remodel the extracellular matrix and potentially weaken plaque stability (5). The localization of macrophages near sites of plaque rupture supports the notion that macrophages are involved in matrix degradation and plaque instability (18). T lymphocytes comprise a significant portion of inflammatory cells in atherosclerotic plaques. T cells are a significant producer of IFN-g and tumor necrosis factor alpha (TNF-α). These factors promote atherosclerosis by enhancing macrophage activation and uptake of oxidized LDL. They can also induce macrophage apoptosis, which contributes to the necrotic core and reduces plaque stability (19). TNF-α also upregulates CAM expression and stimulates vascular smooth muscle cell (VSMC) migration (18).

2.1.4. Vascular smooth muscle cells activation

Activation of VSMCs offers a significant contribution to the development of atherosclerosis. Quiescent VSMCs maintain a contractile phenotype, with expression of smooth muscle actin alpha (ACTA2) and smooth muscle myosin heavy chain (MYH11) (4, 5). Normally there are only few smooth muscle cells in the intima, but in atherosclerotic plaques they can be plentiful. Activated VSMCs downregulate these markers and enter a synthetic state, where they proliferate and produce extracellular matrix (ECM) proteins. This increases the size of the plaque lesion, but conversely also helps provide structural stability (5, 20). Apoptosis and necrosis of VSMCs can contribute both to the necrotic core and also detract from the structural stability of the plaque. Areas of rupture often show reduced VSMCs and increased macrophages. Dying VSMCs also upregulate inflammatory factors such as IL-1, which further promotes inflammation and endothelial dysfunction (20). Even viable VSMCs show signs of premature aging, expressing senescence associated β-galactosidase activity and upregulating their secretion of proinflammatory IL-6 and MCP-1 (20).

2.1.5. Extracellular matrix modification and calcification

The cellular components of atherosclerotic plaques interact with and actively modify their extracellular matrix (ECM). Matrix metalloproteinases (MMP) are a family of zinc-dependent endopeptidases that function to degrade the ECM (4, 21). Macrophages are as already mentioned a major producer of these enzymes. Several MMPs are purported to promote atherosclerosis, including MMP-2, MMP-8, and MMP-12 (21). The mechanisms are unclear, but they appear to promote the accumulation of macrophages, possibly through the liberation of matrix entrapped growth factors and cytokines (21). MMPs have been implicated in plaque destabilization, with MMP-1, MMP-9, MMP-12 showing localization in the fibrous cap and shoulder of plaques. Increased levels of these enzymes have been associated with thinning of fibrous caps (21).

Calcification and matrix remodeling in atherosclerotic plaques may have both protective and pathological qualities. For instance, while calcification decreases arterial elasticity and contributes to stenosis, it can also help strengthen the plaque and reduce the risk of rupture (21, 22). Large areas of plaque calcification, particularly in the cap area, can be associated with better stability (22). Depending on the stage of the plaque, the benefits may outweigh the risks or vice versa. However, extensive vascular calcification is still a marker of cardiovascular risk, possibly as a surrogate for overall atherosclerotic disease burden (4, 22).

2.1.6. Platelet activation

Increasingly platelets are being recognized as important contributors to inflammation and both innate and adaptive immune responses. Activated platelets interact with all types of leucocytes, particularly monocytes, leading to upregulation of a wide range of proinflammatory functions, such as release of proinflammatory cytokines, production of reactive oxygen species, and endothelial adhesion (6). This is mediated through intracellular compartments containing a-granules, lysosomes, and dense core granules, as well as a complex membranous system allowing storage and release of the various factors (23).

2.1.7. Genetic factors of atherosclerosis

The traditional clinical risk factors for atherosclerosis and cardiovascular disease, such as gender, age, dyslipidemia, diabetes, smoking, hyperhomocysteinemia, hypertension and family history remain relevant today. Most of these risk factors are predictive of atherosclerosis and are often co-existent. While not traditionally regarded as a genetic disease, an understanding of the genetic factors of atherosclerosis is nowadays considered to be essential. When it comes to atherosclerosis, high plasma LDL has long been identified as a clinical risk factor. There are several monogenic conditions associated with familial hypercholesterolemia. These include aberrations in LDL receptor (LDLR), apolipoprotein B (ApoB), and proprotein convertase subtilisin/kexin type 9 (PCSK9), which encodes a protein that degrades LDL receptor (24). Since LDLR interacts with ApoB, loss of function mutations in either can disrupt this interaction and prevent the uptake and breakdown of LDL by the liver. Conversely, gain of function mutations in PCSK9 can lead to the excess degradation of LDLR, also resulting in increased plasma LDL (24). Consequently, these patients have a markedly higher incidence of cardiovascular disease.

However, the majority of people who suffer from atherosclerosis do not present a clearly defined monogenetic abnormality. Population based genetics studies have relied extensively on genome-wide association studies (GWAS) to help identify single nucleotide polymorphisms (SNPs) that may serve as genetic markers for increased cardiovascular disease risk. Nonetheless, these methods have uncovered dozens to hundreds of potentially relevant genes, involved in processes ranging from lipid metabolism to regulation of endothelial or smooth muscle cell phenotype (25). Understanding the genetics of atherosclerosis progresses may let genetic factors may find a place on risk nomograms and thus influence clinical decision making in the future (26).

2.1.8. Rupture of the unstable plaque and arterial infarction

All the above mentioned factors and processes are often combined and gradually contribute to the formation of an atheromatous plaque. The rupture of plaques is considered to be the common pathophysiological substrate of acute coronary syndromes (ACS), involving unstable angina (UA), and ST-elevation or transmural

(STEMI) and non-ST-elevation or non-transmural (NSTEMI) myocardial infarction. When episodes of stable angina are associated with plaque rupture and formation of intraplaque thrombus, then UA is associated with thrombi that project, but do not occlude the lumen of the coronary artery, thus preserving some antegrade flow in the artery. Several potential mechanisms of UA attacks, such as constriction of coronary artery, intermittent change in size of thrombus and platelet disposition, have been proposed. Acute myocardial infarction (AMI), on the other hand, occurs when total coronary artery occlusion develops. In case of transmural (STEMI) infarction, occlusion develops over a relatively short time frame of a few hours and persists for at least 6-8 hours. The infarcted tissue is a structurally homogenous entity, i.e. all the involved myocardium dies at around the same time. Non-transmural (NSTEMI) infarcts have a different structure, built up by the coalescence of many small areas of necrosis of very different ages. A factor in limiting the spread of necrosis and preserving the subepicardial zone is the existence of collateral flow to the affected artery. The development of AMI results in apoptosis and necrosis of myocardiocytes (27).

2.2. Myocardial ischemia and infarction

Myocardial ischemia occurs because of a mismatch between coronary blood flow and myocardial metabolic requirements. This happens when the rate of oxygen and metabolic substrates delivery to the myocardium is insufficient to meet the myocardial energy requirements for a given myocardial workload. Coronary atherosclerosis and other diseases reduce the supply of oxygenated blood by obstructing the coronary artery system. Although the obstructions may not be enough to produce myocardial ischemia at rest, increases in myocardial oxygen demand during physical activities can precipitate myocardial ischemia. Some patients may develop transient increases in the degree of coronary artery obstruction as a result of platelet and thrombus formation or through increased coronary vasomotor tone. In addition, in the presence of other cardiac diseases, especially those that cause a pressure load on the left ventricle, myocardial oxygen demand may outstrip the ability of normal coronary arteries to provide oxygenated blood, resulting in myocardial ischemia or infarction. Acute obstruction of a coronary artery may result in necrosis, the extension of which is determined by the width of the area in danger, collateral circulation, regional metabolic oxygen demand in the beginning of ischemia and the duration of ischemia.

The manifestations of ischemic heart disease have their basis in a complex pathophysiology of multiple factors that affect myocardial oxygen supply and demand (3). Early revascularization can rescue more of the affected myocardium, yet may also lead to severe contractility disorders (myocardial stunning or hibernation).

2.3. Impact of ischemia to myocardial cellular metabolism

During ischemia, substantial changes occur in cardiac energy metabolism, as a consequence of the reduced oxygen availability. Some of these metabolic changes are beneficial and may help the heart adapt to the ischemic state. However, most of the changes are maladaptive and contribute to the severity of the ischemic injury leading to stunned or hibernating myocardium, cell death and ultimately to contractile dysfunction. Dramatic changes in cardiac metabolism and contractile function also occur during myocardial reperfusion as a consequence of the generation of oxygen free radicals, loss of cation homeostasis, depletion of energy stores, and changes in subcellular activities. This condition is known as ischemia/reperfusion injury.

During acute ischemia the relative substrate concentration is the prime factor defining preference and utilization rate. Allosteric enzyme regulation and protein phosphorylation cascades modulate the concentration effect. The expression of metabolic genes is also dynamically regulated in response to developmental and pathophysiological conditions, leading to long-term adjustments. Specific nuclear receptor transcription factors and co-activators regulate the expression of these genes (28). The prolongation of ischemia or restoration of the coronary flow, alterations in ions and overall Ca^{2+} homeostasis occur, together with an oxidative stress mediated by oxygen free radicals, which are not adequately counteracted by the cellular antioxidant defence mechanisms. All these biochemical alterations lead to membrane damage, mitochondrial swelling, and irreversible deterioration of contractile function (9).

Ischaemia does not only cause changes to the cell's glucose supply routes but also to glycolysis pathways because of the transition from aerobic to anaerobic glycolysis. The available cytosolic glucose is metabolized by anaerobic glycolysis and becomes the main source of ATP. The efficiency of this process is much lower than that of aerobic glycolysis coupled to oxidative phosphorylation. Consumption quickly exceeds production of ATP, and the intracellular concentration of ATP decreases

dramatically. The degree of glycolysis inhibition is in fact directly proportional to the severity of coronary flow restriction (30). Ischaemia also influences the metabolism of lipids. During ischaemia the cytosolic concentrations of fatty acids, acyl-CoA and acylcarnitine rise gradually (31, 32). The accumulation of these amphiphilic compounds in ischemic tissues has some significant functional implications. They dissolve readily in cell membranes and affect the functional properties of membrane proteins. Decreased activity of Na^+/K^+-ATPase and the sarcoplasmic and endoplasmic reticulum Ca^{2+}-ATPase pumps, as well as the activation of ATP-dependent potassium channels, reduces the inwardly rectifying potassium current and prolongs the opening of Na^+ channels, delaying their inactivation. The accumulation of amphiphilic compounds produces a time-dependent reversible reduction in gap-junction conductance (32, 33).

Intracellular acidosis is a severe consequence of cellular ischemia. The metabolic modifications mentioned above lead to an increased production of protons. As a result the buffering capacity of the cell is quickly saturated. Intracellular acidosis interferes directly and indirectly with the optimal functioning of the cell by increasing intracellular Na+ through the activation of Na^+/H^+ exchangers and by Ca^{2+} activation of Na^+/Ca^{2+} exchangers, increasing the production of free radicals; changing the affinity of different proteins, such as enzymes and troponin C, to Ca^{2+}; modifying tertiary protein structures; inhibiting enzymes; and disrupting the function of sarcoplasmic pumps and carriers. The main source of protons during ischemia comes from the production of lactate from pyruvate by lactate dehydrogenase. The accumulation of extracellular lactate greatly reduces the effectiveness of the lactate/proton cotransporter, preventing the removal of protons. Additionally, the residual metabolic activity also contributes to acidosis, as the hydrolysis of an ATP molecule releases a proton (32, 33).

2.4. Changes in the ionic cellular equilibrium

The ionic homeostasis of a cell is highly influenced when ischaemia occurs. The two major changes are the loss of ionic transmembrane gradients, which causes membrane depolarization, and increased intracellular sodium ($[Na^+]$), which is responsible for inducing a rise in the intracellular calcium ($[Ca^{2+}]$) levels, leading to cellular oedema (34, 35).

Cellular depolarization occurs very rapidly after the onset of ischemia. Both the inhibition of the Na^+/K^+-ATPase and the opening of ATP-dependent K^+ channels play a crucial role. Cellular depolarization is characterized by a negative outgoing current and a decrease in the extracellular concentrations of Na^+, Cl^- and Ca^{2+}, as well as an increase in the extracellular concentration of K^+. Progressive depolarization of the cell also promotes prolonged activation of voltage-dependent sodium channels. The accumulation of sodium in the cytosol is multifactorial. Acidosis stimulates Na^+/H^+ exchangers to purge cellular H^+, which results in increased intracellular Na^+ (34, 35). This net movement of Na^+ is accompanied by osmotic water movement. Moreover, inhibition of the Na^+/K^+-ATPase due to a lack of ATP prevents the removal of excess intracellular Na^+. The high intracellular concentration of Na^+ affects the function of other membrane transporters, such as the Na^+/Ca^{2+} antiporter, an accelerator. This allows the extrusion of sodium from the cell at the expense of an intracellular accumulation of Ca^{2+}. The massive entry of calcium into the cell disrupts the mechanisms that regulate its intracellular concentration and induces the release of calcium from the intracellular endoplasmic reticulum stores. The lack of ATP prevents calcium excretion into the interstitium and its sequestration in the endoplasmic reticulum. The accumulation of cytosolic calcium induces degradation of membrane phospholipids and cytoskeletal proteins, alters both calcium affinity and efficiency of proteins involved in contractility, activates nitric oxide synthase (NOS) and proteases such as calpains and caspases, promotes the production of free radicals and alters the tertiary structure of enzymes such as xanthine dehydrogenase, which is converted to xanthine oxidase (36, 37). Moreover, the local membrane depolarisation causes the creation of injury current. Injury currents flowing from the depolarized ischemic regions to normal healthy regions result in the appearance of ST segment elevation or depression, depending upon whether the ischemic region is non-transmural, subendocardial (ST depression) or transmural (ST elevation). The injury current may create reentry circuits in the margins of the ischaemic and non/ischaemic area resulting in the manifestation of ventricular arrythmias and ventricular fibrillation.

2.5. Production of free radicals

Free radical oxygen species (ROS) are highly reactive chemical compounds because they have unpaired electrons in their electron cloud. ROS are capable of oxidizing cellular constituents such as proteins, deoxyribonucleic acid (DNA), membrane

phospholipids and other adjacent biological structures. In addition to their role in ischemia, ROS are constitutively generated during metabolic processes and have an important role in cell signalling. Mitochondrial respiration constitutively produces a small amount of ROS, primarily the superoxide anion O_2^- at complexes I and III of the electron transport chain. The anion is rapidly converted to hydrogen peroxide (H_2O_2) by metalloenzymes and superoxide dismutase (SOD). Cellular stress, particularly oxidative stress, dramatically increases mitochondrial ROS production by disrupting and later inhibiting oxidative phosphorylation. Moreover, the rise in mitochondrial calcium increases ROS production and greatly decreases the antioxidant capacity of mitochondria by decreasing the glutathione peroxidase concentration and SOD activity (38, 39).

2.6. Cellular necrosis

Necrosis is characterised by the rapid loss of cellular homeostasis, rapid swelling as a result of the accumulation of water and electrolytes, early plasma membrane rupture and disruption of cellular organelles (40). Different patterns of necrosis have been described. Coagulation necrosis, resulting from severe, persistent ischaemia, is present usually in the central region of infarction. The coagulation necrosis results in the arrest of muscle cells in the relaxed state and is characterised by shrinkage and loss of nucleus. The other form, contraction band necrosis, results primarily from severe ischaemia followed by reflow (reperfusion). It is caused by calcium ion influx into dying cells, resulting in the arrest of cells in the contracted state and is characterised by contracted myofibrils in contraction bands and mitochondrial damage with calcification and vascular congestion (41).

2.7. Apoptosis

Although myocyte necrosis was thought to be the sole cause of death in myocardial infarction for a long time, several studies provide growing evidence that apoptosis plays an important role in the process of myocyte loss after AMI, as well as in the process of LV remodeling and development of heart failure (42, 43). Apoptosis, a form of programmed cell death, represents a highly regulated and energy-requiring process by which activation of specific signalling cascades leads to cell death (44).

Apoptosis plays an important role in various physiological processes including embryogenesis, normal tissue homeostasis and aging (43, 45). However, excessive or insufficient apoptosis results in many diseases, including cancer, some infectious, autoimmune and neurological diseases (43, 46). Several recent studies have also demonstrated an important role of apoptosis in ischemic heart disease. Apoptosis significantly contributes to myocyte cell death in AMI and occurs predominantly in the peri-infarcted region (43, 47). High grade of apoptosis is present also at the subacute phase of MI and correlates with parameters of progressive LV remodelling (48). Moreover, patients who developed symptomatic heart failure shortly after AMI were associated with significantly increased apoptotic rates (42). Thus apoptosis is shown to play an important role in determining infarct size, extent of LV remodeling and development of early symptomatic heart failure after AMI (43).

3. ISCHEMIA-REPERFUSION INJURY

The immediate restoration of coronary perfusion through the various revascularisation procedures (thrombolysis, percutaneous coronary intervention of coronary artery bypass surgery) is crucial regarding the amount of myocardium which can be saved and therefore the clinical outcome of the patient. The process of restoring blood flow to the ischemic myocardium, however, can induce further injury to the myocardium. This phenomenon, termed myocardial reperfusion injury, can paradoxically reduce the beneficial effects of myocardial reperfusion (49). The injury culminates in the death of cardiac myocytes that were viable immediately before myocardial reperfusion (50). Myocardial reperfusion injury was first postulated in 1960 by Jennings et al. in their description of the histologic features of reperfused ischemic canine myocardium. They reported cell swelling, contracture of myofibrils, disruption of the sarcolemma, and the appearance of intramitochondrial calcium phosphate particles (51).

This form of myocardial injury, which by itself can induce cardiomyocyte death and increase infarct size, may in part explain why, despite optimal myocardial reperfusion, the rate of death after an acute myocardial infarction approaches 10%, and the incidence of cardiac failure after an acute myocardial infarction is almost 25% (49, 52).

The injury to the heart during myocardial reperfusion causes **four types** of cardiac dysfunction (26):

I. The first type is **myocardial stunning**, a term denoting the “mechanical dysfunction that persists after reperfusion despite the absence of irreversible damage and despite restoration of normal or near-normal coronary flow.” The myocardium usually recovers from this reversible form of injury after several days or weeks (49, 53, 54).
II. The second type of cardiac dysfunction, the **no-reflow phenomenon**, was originally defined as the “inability to reperfuse a previously ischemic region.” It refers to the impedance of microvascular blood flow encountered during opening of the infarct-related coronary artery (49, 55).
III. The third type of cardiac dysfunction, **reperfusion arrhythmias**, is potentially harmful, but effective treatments are available (49, 56).
IV. The last type is **lethal reperfusion injury**. Some researchers have suggested that reperfusion only exacerbates the cellular injury that was sustained during the ischemic period (57). The cardiomyocyte death associated with the irreversible, lethal form of myocardial reperfusion injury diminishes the infarctreducing effects of myocardial reperfusion by independently inducing cardiomyocyte death. For this reason, lethal reperfusion injury would be expected to adversely affect clinical outcomes after an acute myocardial infarction, and it may contribute to the mortality despite early and successful reperfusion (49).

The main cellular disorders which take place during ischemia and reperfusion are briefly demonstrated in figure 3. During ischemia, oxygen levels become critically low, cells change from aerobic to anaerobic glycolysis, generating lactate, cellular acidosis, and increased proton concentrations. The regulatory mechanism of acidosis increases the intracellular Na^+ concentration. This stimulates Na^+/K^+-ATPase leading to an overload of Ca^{2+}, which cannot be stored in the sarcoplasmic reticulum due to lack of ATP to activate its transporter. During reperfusion, oxygen concentration rises and the recovery of ATP production in the presence of Ca^{2+} causes calcium oscillations, promoting mitochondrial permeability transition pore (PTP) opening, which leads the outer membrane to rupture, and the release of Cyt-C, which activates caspase-mediated apoptosis.

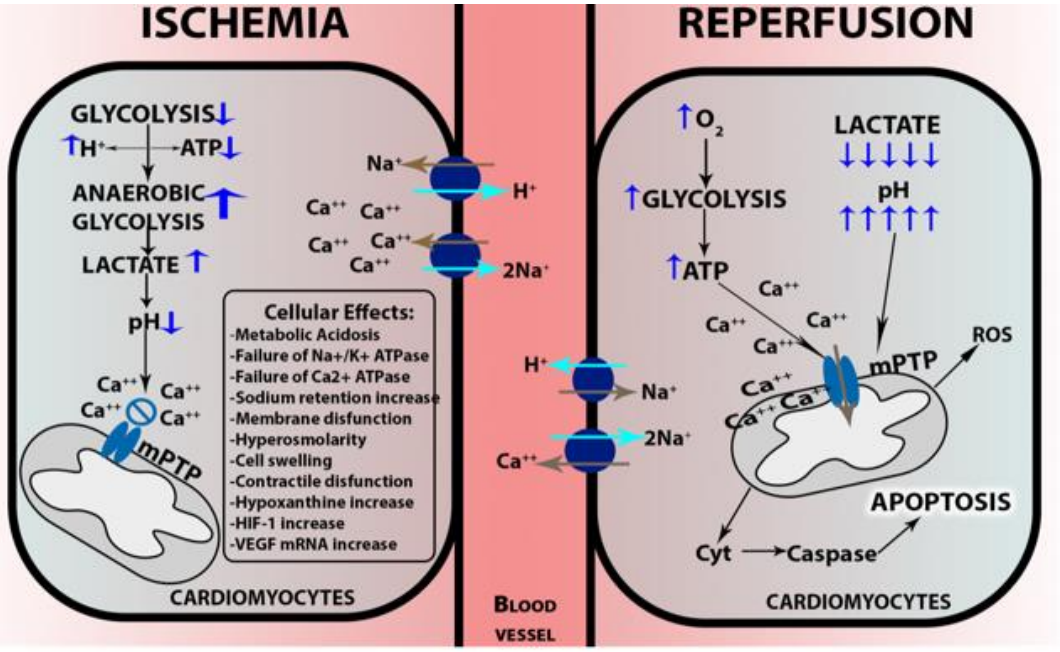


Figure 3. Cellular damage in ischemia-reperfusion.

(Source: Alpuche J, Quírino L, Sánchez-Vega JT, Yap J, Pérez-Campos E, Cabrera-Fuentes HA. The Role of Platelets in Ischemic Conditioning. Cond Med. 2018 Oct;1(6):313-318.)

3.1. Myocardial Stunning

The term myocardial stunning refers to the transient myocardial dysfunction that persists after reperfusion, despite the absence of irreversible myocardial damage (54, 58, 59). The duration of myocardial stunning far exceeds the duration of the previous ischemia. Transient occlusion of coronary perfusion for 15 minutes may for example cause contraction disorders beyond 24 hours. Myocardial stunning causes not only systolic but also diastolic myocardial dysfunction and is usually diagnosed by the persistent contractile disorder that progressively improves over time, as long as normal coronary flow is definitively restored (58, 59).

A number of hypotheses have been proposed to explain the pathogenesis of stunned myocardium. The main factors and mechanisms involved and potential therapeutic approaches are presented below in figure 4 and table 2. The most probable mechanisms responsible for myocardial stunning are the damage caused by the generation of oxygen-derived free radicals, disruption of calcium intracellular homeostasis and possibly the change in the structure of contractile myofilaments as well as decreased myofilament sensitivity to calcium. With reperfusion, production of

free oxygen radicals causes damage to the sarcolemma and cause a large influx of calcium. Calcium activates endogenous proteases (calpains) that reduce the response of myofilaments to calcium. This injury to the myofilaments most likely leads to a decrease in sensitivity to calcium and the decrease in postischemic contractile function, which is characteristic of stunned myocardium. In this regard, the severity of damage to the myofilaments and possible mechanisms involved in eliciting stunning may be determined by the intensity and/or duration of the ischemic insult. If this large calcium discharge is prevented, myocardial stroke does not occur. Diastolic dysfunction may be due to the disruption of calcium-induced relaxation (54, 58, 60, 61).

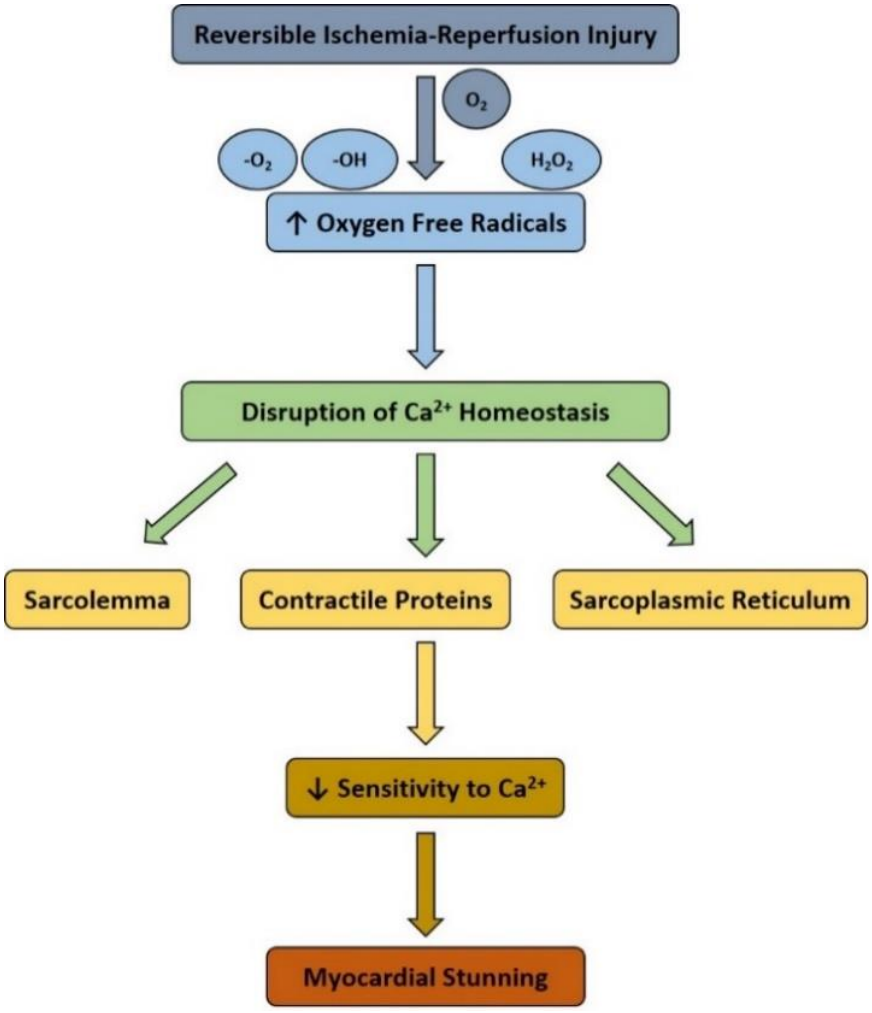


Figure 4. The main factors involved in the pathogenesis of myocardial stunning.

(Source: Gross GJ, Kersten JR, Warltier DC. Mechanisms of postischemic contractile dysfunction. Ann Thorac Surg. 1999 Nov;68(5):1898-904.)

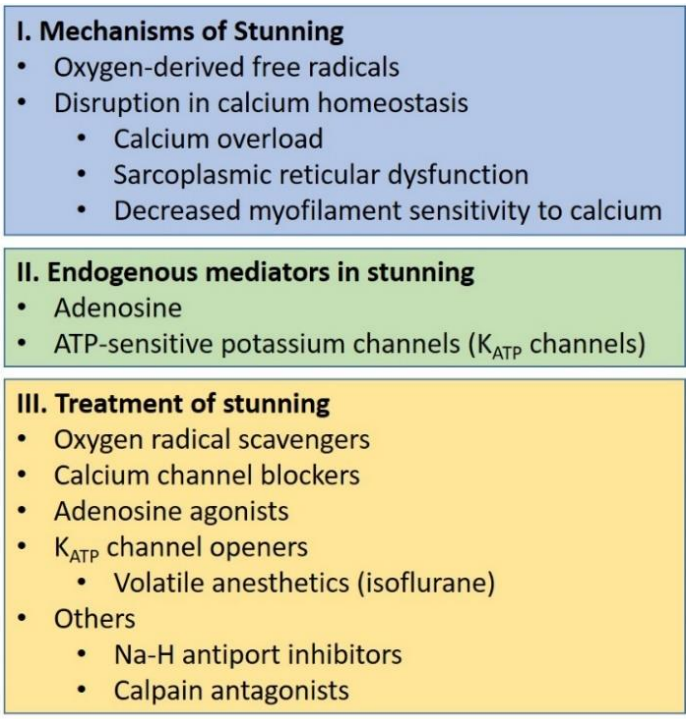


Table 2. Mechanisms responsible for myocardial stunning and potential therapeutic approaches.

(Source: Gross GJ, Kersten JR, Warltier DC. Mechanisms of postischemic contractile dysfunction. Ann Thorac Surg. 1999 Nov;68(5):1898-904.)

3.2. Myocardial Hibernation

The term myocardial hibernation was initially used to describe chronic wall contractility disorders in patients with chronic ischemic heart disease, without however having experienced a myocardial infarction. This entity represents a new state of equilibrium of the heart in response to chronic hypoperfusion, with reduced contractility and reduced peripheral oxygen demand and consumption, so that myocardial cells can remain viable (62, 63). After revascularization, regional contractile function and ventricular ejection fraction are restored to normal.

The experimental counterpart is characterized by: 1) sustained perfusion-contraction matching, 2) recovery of contractile function upon reperfusion, and 3) lack of necrosis; frequently, there is also 4) recovery of metabolism during ongoing ischemia, and 5) the potential for recruitment of inotropic reserve, and therefore recovery of function upon reperfusion (64).

Through hibernation, despite the persistent hypoperfusion, a new state of cellular energy equilibrium is achieved in which levels of concentration of lactic acid and high

energy phosphates remain normal. Morphologically, hibernating myocardium displays features of dedifferentiation, with loss of cardiomyocytes and myofibrils, and of degeneration, with increased interstitial fibrosis. Regardless of whether or not hibernating myocardium has reduced baseline blood flow, and regardless of whether its morphology appears more dedifferentiated or degenerative, it will benefit from reperfusion, as will the patient's prognosis (65). However if revascularisation takes place in the late phase of remodelling, then the recovery potential is questionable.

The hibernating myocardium undergoes morphological changes with loss of its sarcomeres and diminishing the size of mitochondria and the endoplasmic reticulum. Remaining sarcomeres ingest larger amounts of glucose, resulting in glycogen deposition in the myocardium. This kind of morphological change is called dedifferentiation and does not seem to be as stable as originally believed and probably reflects apoptotic death. By restoring coronary circulation, the rate of functional and morphological recovery depends on the extent of changes in myocytes and of interstitial fibrosis. This could explain why the reduction in coronary flow observed in cases of hibernation is not necessarily relevant. Restoring coronary flow with coronary artery bypass surgery (66) or percutaneous angioplasty (67) implies an impressive improvement in contractility and increase in ejection fraction. Improvement of myocardial function is so spectacular that coronary artery bypass surgery is considered to be the treatment of choice in cases of patients with severe heart failure of ischemic aetiology. Recruiting the hibernating parts of the myocardium through reperfusion is the best option when conservative treatment fails.

The time course and extent of recovery after revascularization of viable dysfunctional myocardium are variable. Although fibrosis is a major determinant, myocyte structural and molecular remodeling may also play important roles. Delayed recovery of hibernating myocardium in the absence of scar may reflect persistent reductions in the amounts of contractile and metabolic proteins. Even in the absence of infarction, the delayed improvement in left ventricular function after revascularization of hibernating myocardium is associated with an incomplete reversal of the molecular phenotype and the stimulation of new cardiomyocytes originally lost via regional apoptosis from reversible ischemia. Although revascularization appeared to stimulate myocyte proliferation, the persistence of small immature myocytes may have contributed to delayed functional recovery (68). Several adjunctive treatments, such as intracoronary stem cells (69) and growth factors (70), have been proposed as

methods to accelerate functional recovery following revascularization of high-risk patients with heart failure, as well as those in whom complete revascularization is not technically feasible. The benefits of such therapeutic strategies, particularly stem cell therapy for patients with chronic symptomatic systolic heart failure due to ischemic and nonischemic cardiomyopathy remain however unclear. Stem cells are a promising therapeutic modality, however more data are required from larger blinded trials to determine which combination of cell type and delivery mode will yield the most benefit with avoidance of harm (71).

Stress echocardiography using dobutamine can be used to assess the existence of viable myocardium in the ischemic area as well as the reversibility of systolic dysfunction in patients to undergo reperfusion procedures. Improvement of contractility is inversely proportional to the degree of myocardial fibrosis. Administration of dobutamine increases the myocardial oxygen requirements, which aggravates the functioning of the hibernating myocardium. Thus, the emergence of a new area with a contrctility disorder or the reduction of the ejection fraction suggest the presence of hibernation and predict the improvement of cardiac function after reperfusion. Conversely, improvement in myocardial function after the administration of dobutamine demonstrates the presence of an infract area, a positive response of healthy areas and the absence of hibernation (72).

Advances in other cardiac imaging techniques have further contributed to knowledge in the area, first with thallium-201 imaging, then later with Tc-99m-based tracers for SPECT imaging and metabolic tracers used in conjunction with positron emission tomography (PET), most commonly F-18 FDG in conjunction with blood flow imaging with N-13 ammonia or Rb-82 Cl. More recently, cardiac magnetic resonance imaging (CMR) has contributed further information in combination with either late gadolinium enhancement imaging or dobutamine stress (73, 74).

Similar to myocardial stunning, the hibernating myocardium has recruitable areas that improve their contractility after administration of positive inotropic agents. In contrast to myocardial stunning, however, the increase in this contractility is accompanied by an increased production of lactic acid and myocyte necrosis. Functionality improves with afterload reduction, but the definitive and long-term treatment is reperfusion (64-68).

3.3. No-reflow Phenomenon

Despite an open infarct-related artery, breakdown of or obstruction to coronary microvasculature can markedly reduce blood flow to the infarct zone. This effect is known as the no-reflow phenomenon. Advances in imaging modalities have improved visualization of no reflow, showing its frequency to be higher than was estimated by clinical judgment alone (55). No reflow or slow flow occurs in 3–4% of all percutaneous coronary interventions, and is most common after emergency revascularization for acute myocardial infarction. In this setting no reflow is reported to occur in 30% to 40% of interventions when defined by myocardial perfusion techniques such as myocardial contrast echocardiography (75).

This phenomenon is important because it correlates with infarct size and provides useful prognostic information. No reflow is associated with reduced left ventricular ejection fraction, left ventricular remodeling, and poor clinical outcomes, placing patients with this effect in a high-risk group among reperfused patients (55). It is independently associated with increased occurrence of malignant arrhythmias, cardiac failure, as well as in-hospital and long-term mortality (75).

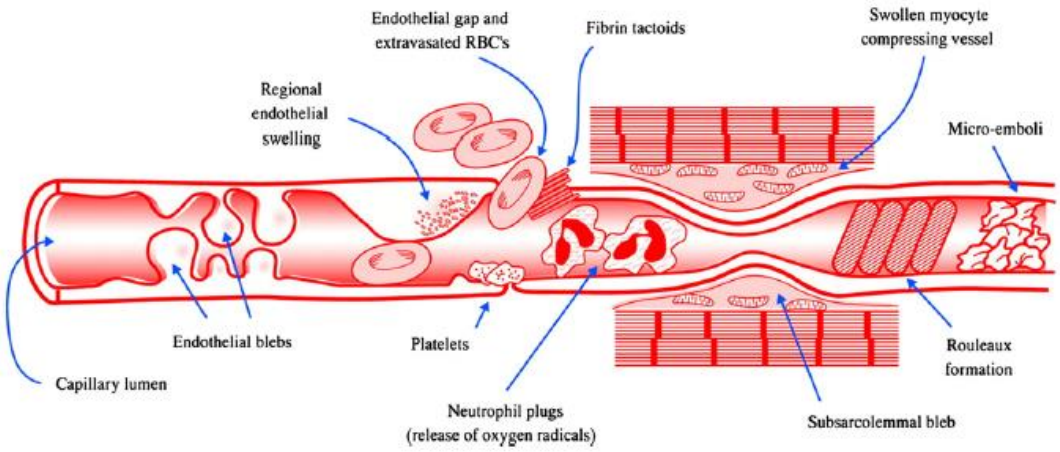


Figure 5. Schematic figure, summarizing different mechanisms, involved in the development of no-reflow, and accompanying ultrastructural alterations of the microvascular bed.

(Source: Reffelmann T, Kloner RA. The "no-reflow" phenomenon: basic science and clinical correlates. Heart. 2002 Feb;87(2):162-8.)

Both animal models of experimental myocardial infarction and clinical studies have provided evidence of impaired microvascular perfusion after reperfusion.

Characteristics of no-reflow found in basic science investigations, such as distinct perfusion defects, progressive decrease of resting myocardial flow with ongoing reperfusion and functional vascular alterations are paralleled by clinical observations demonstrating similar features. The main pathophysiologic mechanisms involved are summarized in figure 5 (76).

The focus of reperfusion therapy is shifting towards improved myocardial perfusion, which could promote functional recovery of viable muscle, reduce infarct expansion, and increase the delivery of blood-borne components, thereby accelerating the healing process (55).

Previously the no-reflow phenomenon has been difficult to treat effectively, but recent advances in the understanding of the pathophysiology of no reflow have led to several novel treatment strategies. These include prophylactic use of vasodilator therapies, mechanical devices, ischaemic postconditioning and potent platelet inhibitors. As no reflow is a multifactorial process, a combination of these treatments is more likely to be effective than any of these alone (75).

3.4. Reperfusion Arrhythmias

The time of reperfusion is often accompanied by ventricular arrhythmias, i.e. reperfusion arrhythmias (77). Reperfusion arrhythmias originate as a consequence of the complex of cellular and humoral reactions accompanying the opening of coronary artery. The primary cause of their generation are considered to be the chemically defined substances that are produced and accumulated in the myocardium during reperfusion. The key role is ascribed to free oxygen radicals but of importance are also other substances such as calcium, thrombin, platelet activating factor, inositol triphosphate, angiotensin II and others. These chemical mediators of reperfusion arrhythmias operate as modulators of cellular electrophysiology causing the complex changes at the level of ion channels.

It is supposed that in the genesis of reperfusion arrhythmias, unlike ischemic arrhythmias operate nonreentrant mechanisms such as abnormal or enhanced automacy and triggered activity due to afterdepolarizations. As a typical reperfusion arrhythmia is considered an early (within 6 hours after start of thrombolysis), frequent (>30 episodes/hour) and repetitive (occurring during >3 consecutive hours)

accelerated idioventricular rhythm (AIVR). AIVR with such characteristics has a high specificity and positive predictive accuracy but relative low sensitivity as a predictor of reperfusion. Thus, in occurrence of AIVR, recanalization of infarction-related coronary artery is very probable, but in absence of AIVR reperfusion is still not excluded (78).

The following arrhythmias are regarded also as markers of reperfusion:

- frequent premature ventricular complexes
- a significant increase of episodes in nonsustained ventricular tachycardia
- sinus bradycardia
- high-degree atrioventricular blocks

The genesis of lethal reperfusion injury and reperfusion arrhythmias concentrates around intracellular calcium overload for both events. This conformity in their pathological basis leads to the conclusion that reperfusion arrhythmias and fatal reperfusion injury should be considered to have the same underlying pathophysiology. Reperfusion arrhythmias can therefore be seen as a marker of fatal reperfusion injury instead of an independent entity (77). Reperfusion arrhythmias are an important noninvasive marker of successful recanalization of infarction-related coronary artery. However, they are also a sign of reperfusion injury and a finding which may limit the favourable effect of reperfusion (78).

3.5. Mediators of lethal reperfusion injury

During myocardial reperfusion, the acute ischemic myocardium is subjected to several abrupt biochemical and metabolic changes, which compound the changes generated during the period of myocardial ischemia. These are described below and are being summarized in figure 6.

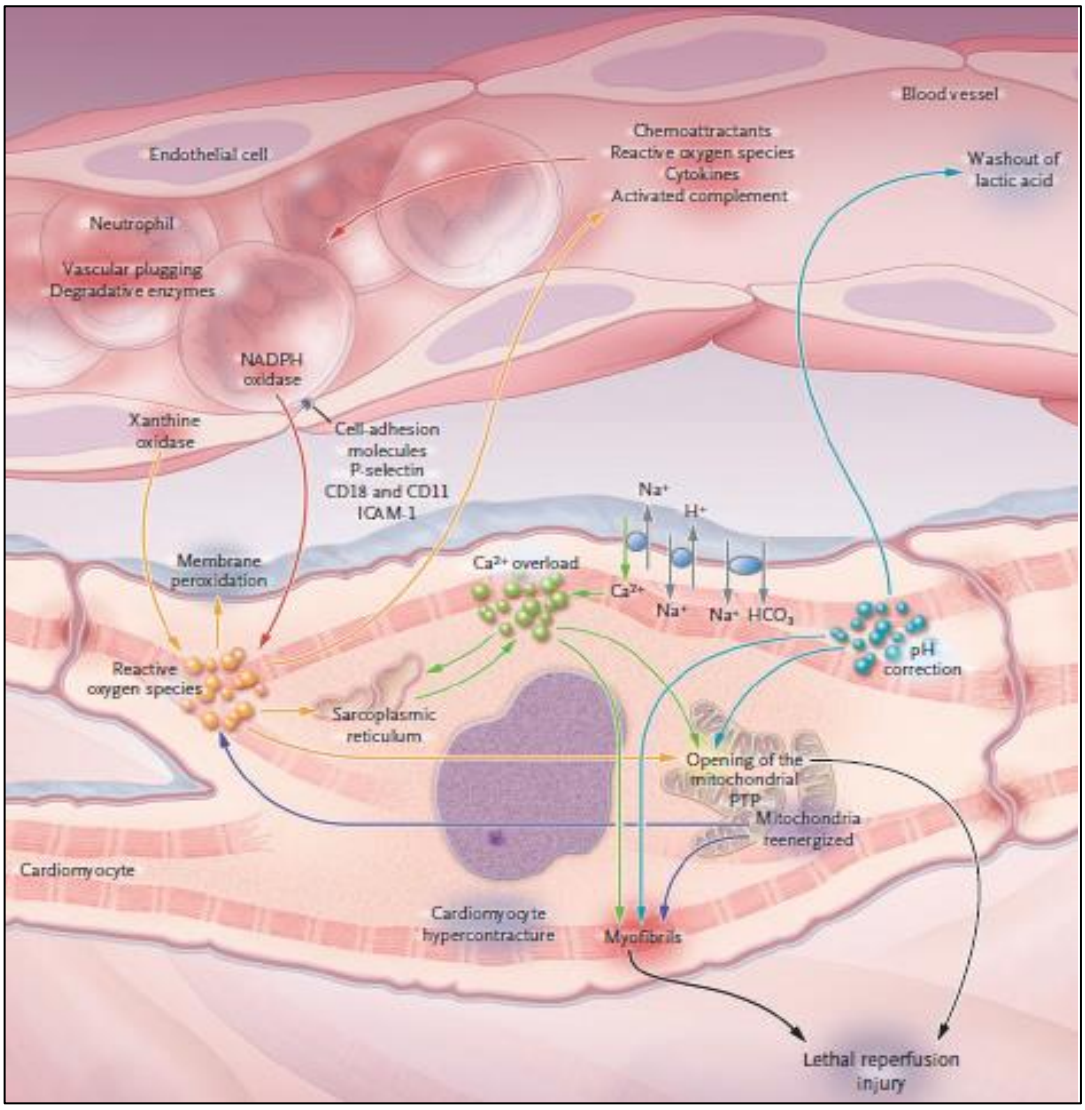


Figure 6. Major mediators of lethal reperfusion injury.

(Source: Yellon DM, Hausenloy DJ. Myocardial Reperfusion Injury. N Engl J Med 2007;357:1121-35.)

3.5.1. Oxygen paradox

Experimental studies have established that the reperfusion of ischemic myocardium generates oxidative stress, which itself can mediate myocardial injury (49, 79). Oxidative stress is part of the oxygen paradox, in which the reoxygenation of ischemic myocardium generates a degree of myocardial injury that greatly exceeds the injury induced by ischemia alone (49, 80). Oxidative stress during myocardial reperfusion also reduces the bioavailability of the intracellular signaling molecule, nitric oxide, thereby removing its cardioprotective effects. These effects include the inhibition of neutrophil accumulation, inactivation of superoxide radicals, and improvement of coronary blood flow (81).

3.5.2. Calcium paradox

At the time of myocardial reperfusion, there is an abrupt increase in intracellular Ca^{2+}, which is secondary to sarcolemmal-membrane damage and oxidative stress–induced dysfunction of the sarcoplasmic reticulum. These two forms of injury overwhelm the normal mechanisms that regulate Ca^{2+} in the cardiomyocyte; this phenomenon is termed the calcium paradox (49, 82). The result is intracellular and mitochondrial Ca^{2+} overload, and this excess of Ca^{2+} induces cardiomyocyte death by causing hypercontracture of the heart cells and mitochondrial PTP opening (82).

3.5.3. pH paradox

The rapid restoration of physiologic pH during myocardial reperfusion, which follows the washout of lactic acid and the activation of the sodium–hydrogen exchanger and the sodium–bicarbonate symporter, contributes to lethal reperfusion injury. This phenomenon is termed the pH paradox (49, 83).

3.5.4. Inflammation

After an acute myocardial infarction, the release of chemoattractants draws neutrophils into the infarct zone during the first 6 hours of myocardial reperfusion, and during the next 24 hours they migrate into the myocardial tissue. This process is facilitated by cell-adhesion molecules. These neutrophils cause vascular plugging and release degradative enzymes and reactive oxygen species (84).

3.5.5. Metabolic modulation

Several experimental and numerous clinical studies have examined the cardioprotective potential of therapy with glucose, insulin, and potassium administered as an adjunct to myocardial reperfusion (85). These studies have been conducted on the premise that ischemic myocardium benefits more from metabolizing glucose than from fatty acids (49). However recent clinical evidence reported no cardioprotective benefit from therapy with glucose, insulin, and potassium as an adjunct to myocardial reperfusion in patients with acute myocardial infarction (86).

3.5.6. Mitochondrial permeability transition pore

The major role of mitochondria in the heart is the provision of ATP by oxidative phosphorylation to drive the contractile cycle and maintain ionic homeostasis. Oxidative phosphorylation requires the permeability barrier of the inner mitochondrial membrane (IMM) to be maintained. However, mammalian mitochondria contain a latent non-specific pore within their inner membrane, known as the mitochondrial permeability transition pore (mPTP) (87). Under normal physiological conditions mitochondria synthesise ATP to meet the energy needs of the beating heart. Here calcium acts as a signal to balance the rate of ATP production with ATP demand. However, when the heart is overloaded with calcium, especially when this is accompanied by oxidative stress, mitochondria embrace their 'darker side', and induce necrotic cell death of the myocytes. This happens acutely in reperfusion injury and chronically in congestive heart failure. Here calcium overload, adenine nucleotide depletion and oxidative stress combine forces to induce the opening of mPTP. The molecular nature of the mPTP remains controversial but current evidence implicates a matrix protein, cyclophilin-D (CyP-D) and two inner membrane proteins, the adenine nucleotide translocase (ANT) and the phosphate carrier (PiC) (Figure 7) (88).

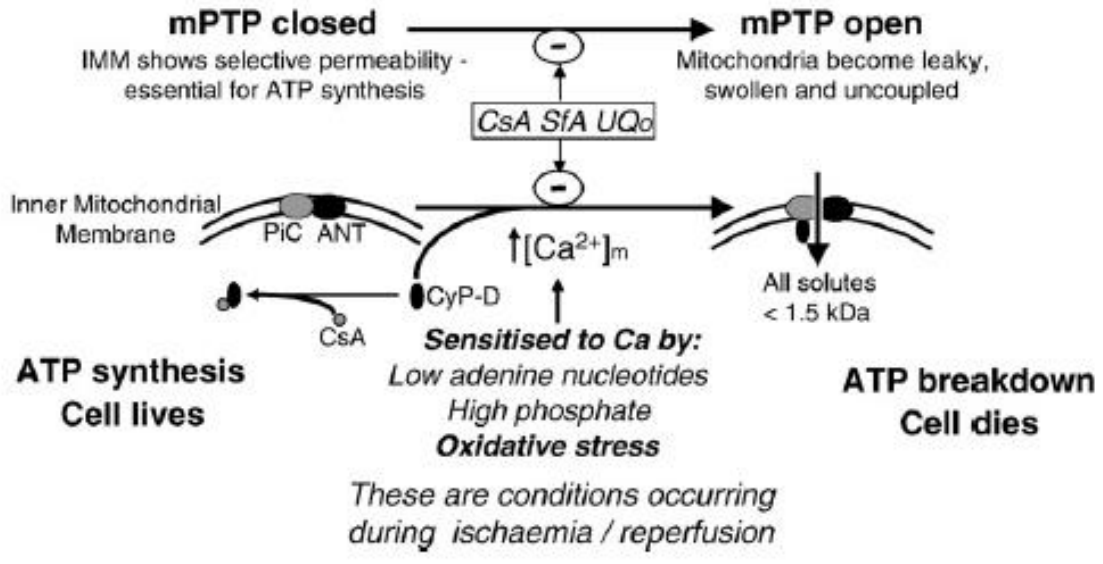


Figure 7. An overview of the proposed mechanism of the mitochondrial permeability transition pore and the consequences of its opening.

(Source: Halestrap AP, Pasdois P. The role of the mitochondrial permeability transition pore in heart disease. Biochimica et Biophysica Acta 1787 (2009) 1402–1415.)

The mitochondrial permeability transition pore (PTP) is a nonselective channel of the inner mitochondrial membrane. Opening the channel collapses the mitochondrial membrane potential and uncouples oxidative phosphorylation, resulting in ATP depletion and cell death (89). During myocardial ischemia, the mitochondrial PTP remains closed, only to open within the first few minutes after myocardial reperfusion in response to mitochondrial Ca^{2+} overload, oxidative stress, restoration of a physiologic pH, and ATP depletion (90). Therefore, the mitochondrial PTP is a critical determinant of lethal reperfusion injury, and as such it is an important new target for cardioprotection (49).

3.5.7. The Reperfusion Injury Salvage Kinase (RISK) pathway

The Reperfusion Injury Salvage Kinase (RISK) Pathway, refers to a group of pro-survival protein kinases (including Akt and Erk1/2), which confer powerful cardioprotection. When activated specifically at the time of myocardial reperfusion, the RISK pathway provides an amenable pharmacological target for cardioprotection (91). In a sense, the RISK pathway mediates a form of programmed cell survival (49). There is extensive preclinical evidence that activation of the RISK pathway by pharmacologic agents such as insulin, erythropoietin, adipocytokines, adenosine, volatile anesthetics, natriuretic peptides and statins, when administered specifically at the time of myocardial reperfusion or by mechanical interventions such as ischemic preconditioning or postconditioning reduce myocardial infarct size by up to 50% (91-93). These treatments recruit various survival pathways providing cardioprotection. The cardioprotection has been attributed to inhibition of mitochondrial PTP opening, improved uptake of Ca^{2+} in the sarcoplasmic reticulum, and the recruitment of antiapoptotic pathways (49, 91). The several agents which can activate the RISK pathway are summarized in figure 8.

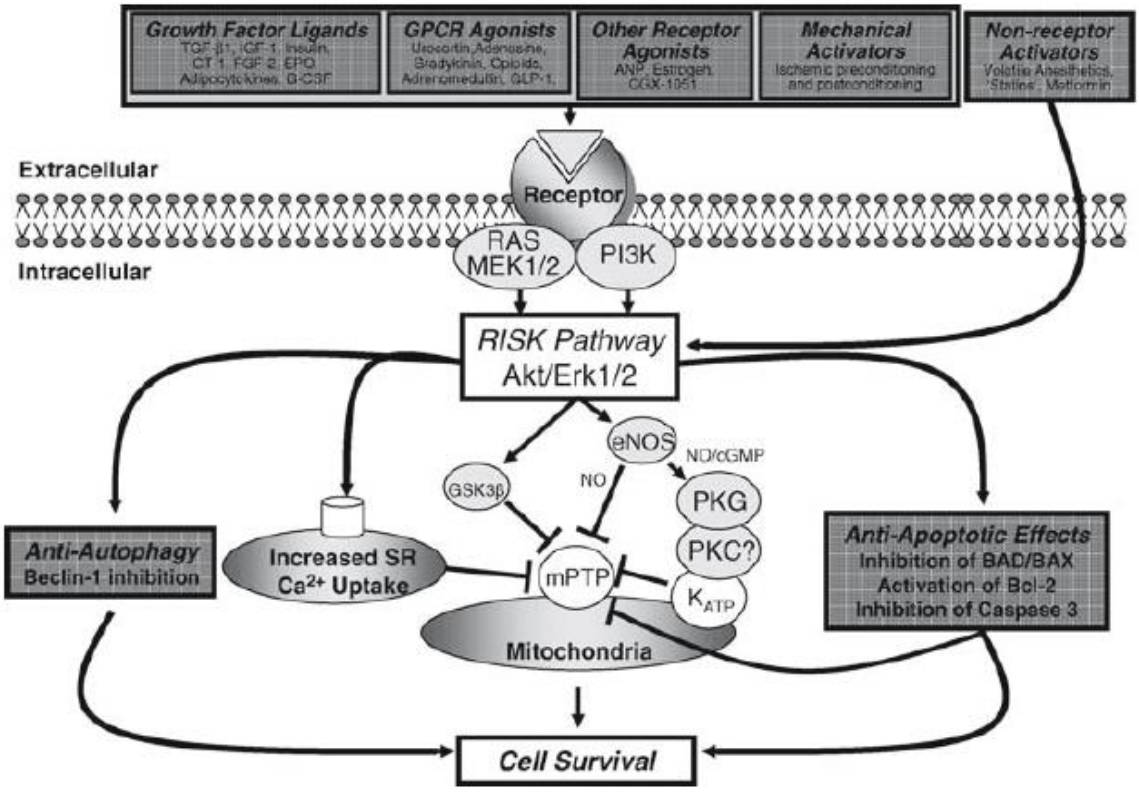


Figure 8. Scheme demonstrating the diverse variety of agents which activate the Reperfusion Injury Salvage Kinase (RISK) pathway in both a receptor and non-receptor mediated manner.

(Source: Hausenloy DJ, Yellon DM. Reperfusion injury salvage kinase signalling: taking a RISK for cardioprotection. Heart Fail Rev. 2007 Dec;12(3-4):217-34.)

4. APPLIED PHYSIOLOGY AND PATHOPHYSIOLOGY

The failure of cardiac output to meet the metabolic needs of the body mobilizes various reversal mechanisms that result in increased intravascular volume and vascular tone (94). These mechanisms tend to restore cardiac output to normal levels, but they also cause pressure increases in left cavities and pulmonary circulation. In this way, most patients with congestive heart failure have sufficient cardiac output to meet the metabolic needs at rest, yet with increased pulmonary pressures that cause pulmonary congestion. Lack of tolerance during exercise is probably due to increased pulmonary pressures and not to inadequate cardiac output (95). For this reason, the syndrome of circulatory distress due to impaired left ventricular function is called congestive heart failure. Additionally, congestive heart failure may also occur in patients with diastolic dysfunction whose systolic function remains intact (96).

4.1. Basic parameters of circulatory physiology

4.1.1. Frank–Starling law

The Frank–Starling law of the heart (Figure 9) represents the relationship between stroke volume and end diastolic volume. The law states that the stroke volume of the heart increases in response to an increase in the end diastolic volume, when all other factors remain constant. As a larger volume of blood flows into the ventricle, the blood stretches the cardiac muscle fibers, leading to an increase in the force of contraction. The Frank-Starling mechanism allows the cardiac output to be synchronized with the venous return, arterial blood supply and humoral length, without depending upon external regulation to make alterations. The Frank-Starling relationship is an intrinsic property of myocardium by which increased length (or ventricular volume) results in enhanced performance during the subsequent contraction. This relationship appears to be very important in cardiac function because increased venous return and the corresponding increase in end-diastolic volume result in greater stroke volume during the next beat. The ventricles can thus accommodate increased venous return by means of a more vigorous contraction that ejects the greater volume of blood from the heart (97-101).

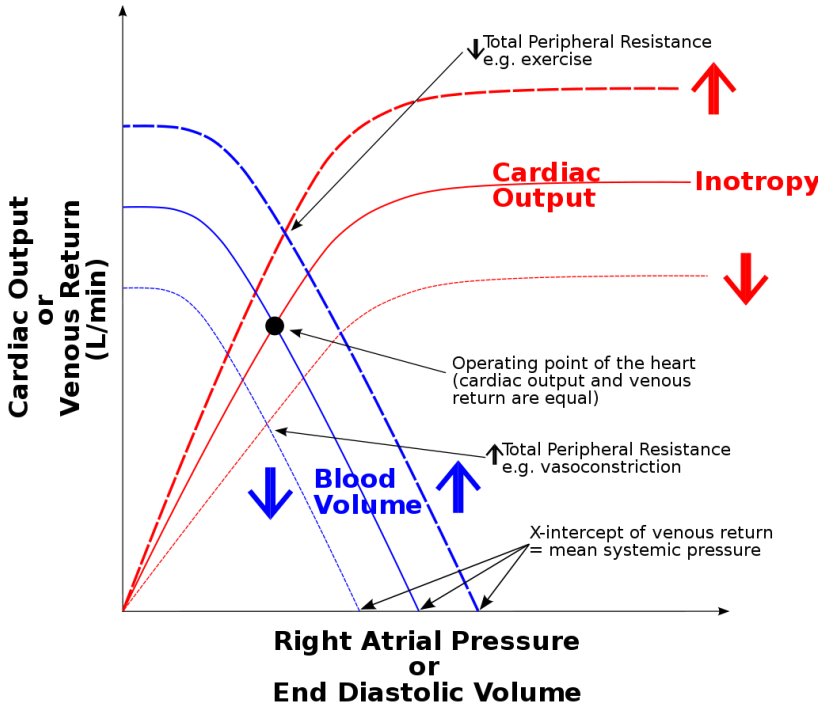


Figure 9. Cardiac function curve illustrating the Frank–Starling law of the heart, the y-axis often describes the stroke volume, stroke work, or cardiac output. The x-axis often describes end-diastolic volume, right atrial pressure, or pulmonary capillary wedge pressure.

Although the physiological significance of the Frank-Starling relationship is widely appreciated, its cellular basis is not well understood. One hypothesis is that more cross-bridges interact with actin at longer sarcomere lengths due to length-dependent reductions in lateral spacing between thick and thin filaments. Due to closer proximity to actin more crossbridges bind and thereby increase contractile force (Figure 10). Measurements in permeabilized myocardium held at constant length have shown that osmotic compression increases force at each [Ca^{2+}]. Thus, the greater Ca^{2+} sensitivity of force at long lengths can be achieved at short lengths by reducing fiber diameter. Moreover, osmotic compression actually eliminates the length dependence of Ca^{2+} sensitivity. This evidence suggests that lateral filament spacing is a primary determinant of the Frank-Starling relationship. Diameter and filament separation are likely to increase or decrease in concert, but these changes need not be proportionate because the shape of the muscle cross section can change with stretch or with osmotic compression (101, 102).

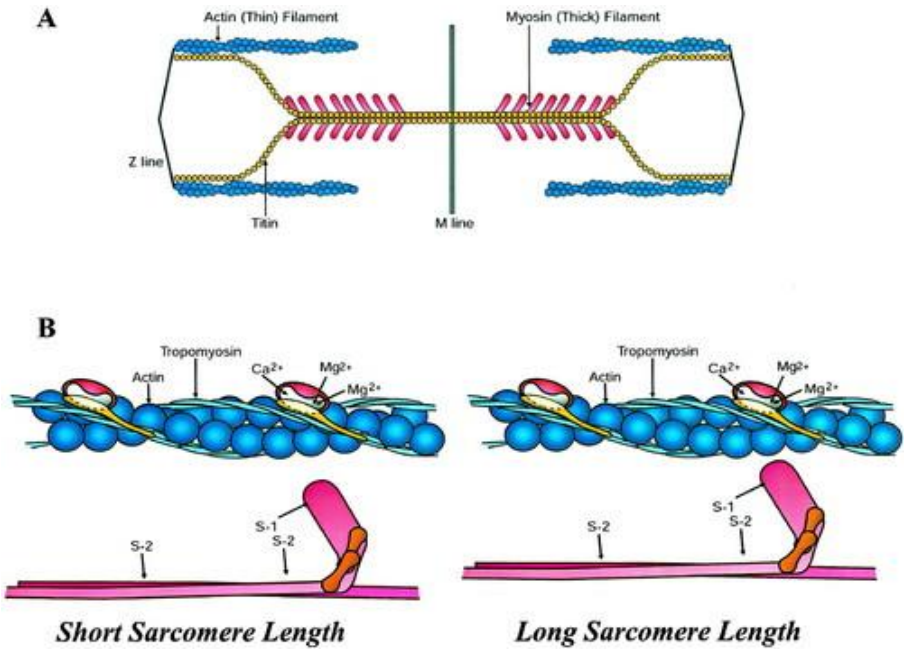


Figure 10. Myocardial sarcomere and myofilaments. **A.** Diagram of the sarcomere showing approximate spatial relationships of thick and thin filaments and putative interactions of titin with the filaments, which would give rise to radial and axial restorati restorative forces when the sarcomere is stretched. **B.** Diagram of the thick and thin filaments illustrating the decrease in lateral separation at long lengths. The probability of crossbridge interaction increases at long lengths due to closer proximity to actin.

(Source: Moss RL, Fitzsimons DP. Frank-Starling relationship=long on importance, short on mechanism. Circ Res. 2002 Jan 11;90(1):11-3.)

4.1.2. Preload

Preload is the end diastolic volume that stretches the right or left ventricle of the heart to its greatest dimensions under variable physiologic demand. In other words, it is the initial stretching of the cardiomyocytes prior to contraction; therefore, it is related to the sarcomere length at the end of diastole. Parameters such as ventricular end diastolic volume or pressure are used to measure preload since the ideal length of the cardiac sarcomere cannot be measured. Passive filling of the ventricle and subsequent atrial contraction thus allows an echocardiographically volumetric measurement. Preload is theoretically most accurately described as the initial stretching of a single cardiomyocyte prior to contraction. The term end-diastolic volume is better suited to the clinic, although not exactly equivalent to the strict definition of preload. Atrial pressure is a surrogate for preload (98, 103).

Quantitatively, preload can be calculated as:

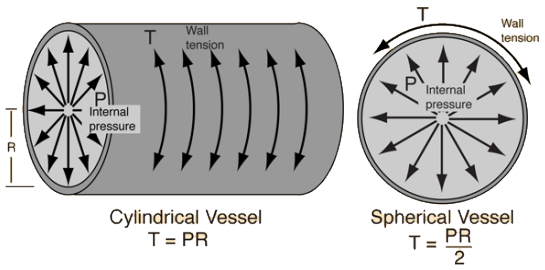
$$\frac{LVEDP \cdot LVEDR}{2h}$$

(LVEDP = Left ventricular end diastolic pressure, LVEDR = Left ventricular end diastolic radius (at the ventricle's midpoint), h = thickness of the ventricle)

Preload is measured in pressure units (mm Hg)

This calculation is based on the Law of Laplace which states that:

$$\text{wall stress} = \frac{(pressure) \times (radius)}{2 \times (wall\ thickness)}$$



Preload is affected by venous blood pressure and the rate of venous return. These are affected by venous tone and volume of circulating blood. Preload is related to the ventricular end-diastolic volume; a higher end-diastolic volume implies a higher preload. However, the relationship is not simple because of the restriction of the term preload to single myocytes. Preload can still be approximated by the inexpensive echocardiographic measurement end diastolic volume or EDV. Preload increases

with exercise (slightly), increasing blood volume (overtransfusion, polycythemia) and neuroendocrine excitement (sympathetic tone) (98).

4.1.3. Afterload

Afterload is the end load against which the heart contracts to eject blood. Afterload is readily broken into components: one factor is the aortic pressure the left ventricular muscle must overcome to eject blood. The greater the aortic/pulmonary pressure, the greater the afterload on the left/right ventricle, respectively. Following Laplace's law, the tension upon the muscle fibers in the heart wall is the pressure within the ventricle multiplied by the volume within the ventricle divided by the wall thickness (this ratio is the other factor in setting the afterload). Afterload can also be described as the pressure that the chambers of the heart must generate in order to eject blood out of the heart and thus is a consequence of the aortic pressure (for the left ventricle) and pulmonic pressure or pulmonary artery pressure (for the right ventricle). The pressure in the ventricles must be greater than the systemic and pulmonary pressure to open the aortic and pulmonic valves, respectively. As afterload increases, cardiac output decreases. Cardiac imaging is a somewhat limited modality in defining afterload because it depends on the interpretation of volumetric data (98, 104).

Afterload is largely dependent upon aortic pressure. Systemic hypertension increases the LV afterload because the LV must work harder to eject blood into the aorta. This is because the aortic valve will not open until the pressure generated in the left ventricle is higher than the elevated blood pressure in the aorta. Pulmonary hypertension indicates a regionally applied increase in afterload dedicated to the right side of the heart, divided and isolated from the left heart by the interventricular septum. Aortic stenosis often increases afterload because the left ventricle must overcome the pressure gradient caused by the calcified and stenotic aortic valve in addition to the blood pressure in order to eject blood into the aorta. In the long-term, the increased afterload will result in LV hypertrophy to account for the increased work required. Aortic Regurgitation increases afterload because a percentage of the blood that is ejected forward regurgitates back through the diseased aortic valve. Mitral regurgitation decreases afterload. The remaining blood loaded into the LV is optimally ejected out through the aortic valve. With an extra pathway for blood flow

through the mitral valve, the left ventricle does not have to work as hard to eject its blood (98, 104).

4.1.4. Stroke volume

Stroke volume (SV) is the volume of blood pumped from the left ventricle per beat. Stroke volume is calculated using measurements of ventricle volumes from an echocardiogram and subtracting the end-systolic volume (ESV) from the end-diastolic volume (EDV). The term stroke volume can apply to each of the two ventricles of the heart, although it usually refers to the left ventricle (98, 103, 104).

$$SV = EDV - ESV$$

Stroke volume index (SVI) is a method of relating the SV to the size of the person Body surface area (BSA).

$$SVI = \frac{SV}{BSA} = \frac{(CO/HR)}{BSA} = \frac{CO}{HR \times BSA}$$

The normal range is between 35 and 65 ml/beat/m².

Stroke volume is dependent upon the difference between end diastolic volume and end systolic volume. The three primary factors involved are preload, afterload and contractility.

4.1.5. Cardiac output and cardiac index

Cardiac output (CO) is a term used in cardiac physiology that describes the volume of blood being pumped by the heart, in particular by the left or right ventricle, per unit time. Cardiac output is the product of the heart rate (HR) and the SV.

$$CO_{[L/min]} = SV_{[L/beat]} \times HR_{[beats/min]}$$

There are a number of clinical methods to measure cardiac output, ranging from direct intracardiac catheterization to non-invasive measurement of the arterial pulse. Each method has advantages and drawbacks. Relative comparison is limited by the absence of a widely accepted "gold standard" measurement. Cardiac output can also

be affected significantly by the phase of respiration, as intra-thoracic pressure changes influence diastolic filling and therefore cardiac output. This is especially important during mechanical ventilation, in which cardiac output can vary by up to 50% across a single respiratory cycle (98, 104). Figure 11 shows the factors which can affect CO.

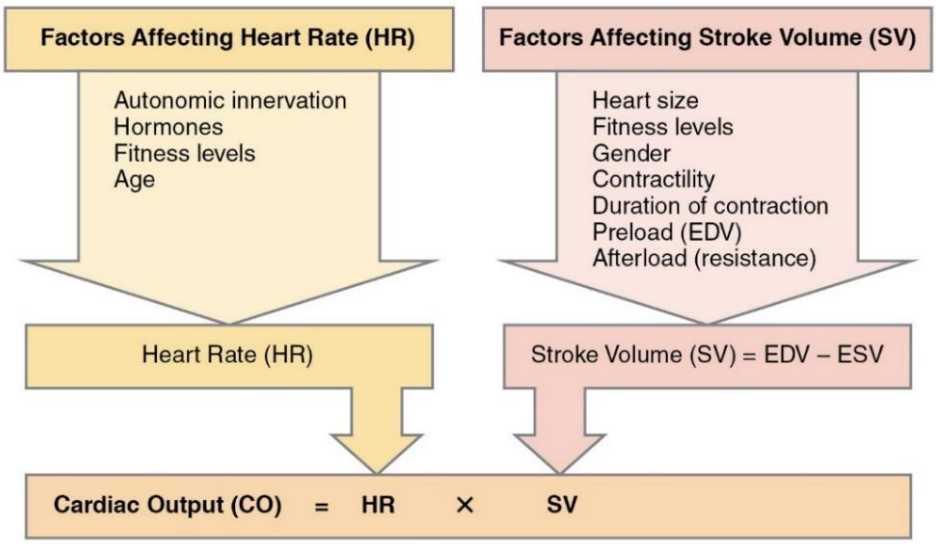


Figure 11. Major factors influencing heart rate and stroke volume and consequently cardiac output.

(Source: Illustration from Anatomy & Physiology, Connexions Web site. http=//cnx.org/content/col11496/1.6)

Cardiac index (CI) is a haemodynamic parameter that relates the (CO) from left ventricle in one minute to BSA, thus relating heart performance to the size of the individual. The unit of measurement is litres per minute per square metre (L/min/m^2) (98, 104).

$$CI_{[l/min/m^2]} = \frac{CO_{[l/min]}}{BSA_{[m^2]}}$$

$$CI_{[l/min/m^2]} = (SI_{[ml/beat/m^2]} \times HR_{[bpm]})/1000$$

The normal range of cardiac index at rest is 2.6–4.2 L/min/m^2. The cardiac index is frequently measured and used in both intensive care medicine and cardiac intensive care. The CI is a useful marker of how well the heart is functioning as a pump by

directly correlating the volume of blood pumped by the heart with an individual's body surface area. If the CI falls acutely below 2.2 L/min/m^2, the patient may be in cardiogenic shock (98, 104).

4.1.6. Ejection Fraction

The ejection fraction (EF) of the left heart, known as the left ventricular ejection fraction (LVEF), is calculated by dividing the stroke volume by the end-diastolic volume. LVEF is an indicator of the effectiveness of pumping into the systemic circulation. The EF of the right heart, or right ventricular ejection fraction (RVEF), is a measure of the efficiency of pumping into the pulmonary circulation (98, 104).

$$EF(\%) = \frac{SV}{EDV} \times 100$$

The 2016 European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic heart failure subdivided heart failure into 3 categories on the basis of LVEF (105):

- normal or preserved LVEF [≥50%]
- moderately reduced LVEF [in the range of 40–49%]
- reduced LVEF [<40%]

4.1.7. Pressure-Volume work

The intraventricular pressure-volume loop is a time-independent representation of the cardiac cycle, where the instantaneous intraventricular pressure and volume is plotted (Figure 12). In diastole from B to C, the ventricle receives blood from the left atrium. The small increase in ventricular pressure reflects passive expansion and elastance of the myocardial wall. Pressure and volume increase with a slope that is related to contractility. The green line represents minimal contractility. The line starts from the ventricular dead volume that is a virtual minimal volume of blood, which can never be ejected. A steep rise in pressure occurs from C to D, with no change in ventricular volume (the isovolumetric contraction). At D the aortic orifice opens, because the end-diastolic pressure in the aorta is passed. During the rapid ejection

phase, the fall in ventricular blood volume, is accompanied by a continuous increase in pressure. During ejection the volume falls by a size equal to stroke volume, pressure rises and falls until the residual ventricular volume is attained. The last ejection phase is slow, because the pressure decreases towards A, where the aortic orifice closes. The last event from A to B is the isovolumetric relaxation with a sharp drop in pressure at constant volume (98, 104).

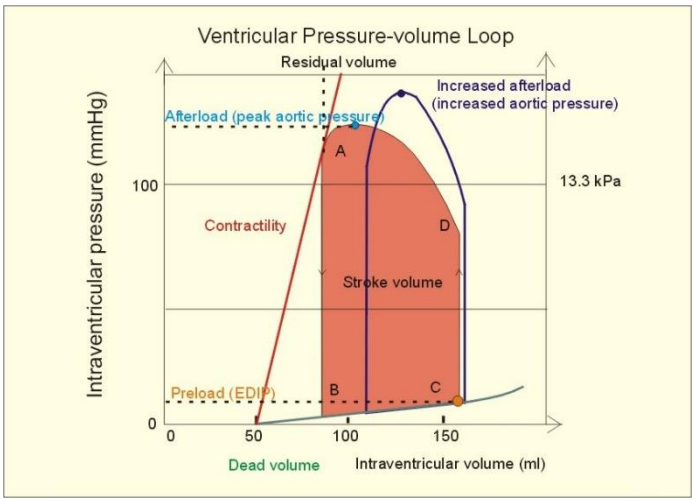


Figure 12. The left ventricular pressure-volume loop from a healthy person at rest. The pressure-volume loop is a widely applicable pathophysiological tool.

(Source: http=//www.zuniv.net/physiology/book/chapter10.html)

4.2. Mechanical disorders of the myocardium

In normal myocardium, during the systole, the length and thickness of the myocardial fiber changes by 15-20% compared to its condition during the diastole (shortening and thickening). Myocardial ischemia causes a decrease in systolic shortening and thickening and a paradoxical early systolic lengthening and thinning as well as postsystolic thickening and shortening of the myocardial fiber (106).

Wall motion disorders due to ischemic aetiology are echocardiographically known as hypokinesia (reduced mobility), akinesia (lack of mobility) and dyskinesia (paradoxical motility). Because of local interactions, distant well perfused areas of the myocardium show a notable increase in their mobility. However, this increased mobility is characterized as paradoxical and does not fully compensate for disturbed motility of the ischemic myocardium (107). Ischemia also causes diastolic dysfunction. The contraction disorder (postsystolic shortening and thickening) is

accompanied by an increase in the time of isovolumic relaxation and a reduction in the maximum ventricular filling flow. In addition, ischemia reduces the compliance of the ventricle. This decrease is proportional to the extent and duration of ischemia and is further reduced by coronary artery occlusion. The decrease in compliance is not limited to the ischemic area but extends to distant and well perfused areas. A reduction in contractility is also seen in areas not involved in the infarction due to obstruction of the coronary blood vessels that perfuse the particular areas that have occurred earlier and to the loss of collateral networks from the new occlusion of the responsible vessel known as ischemia at distance (108). This effect contributes to the abrupt increase in left ventricular end-diastolic pressure, which is often observed after regional myocardial ischemia (109).

When ischemia or necrosis influences a large area of the myocardium a heart failure occurs (110). Reduction of SV and fall in CO cause hypotension and tachycardia and reduce coronary flow. Increase of enddiastolic pressures also contributes to the reduction of coronary flow and increased wall stress causes increased O_2 consumption by the myocardium (111). All of these factors interact and deteriorate ischemia. The fall in CO causes some further impairment of peripheral tissue perfusion. Reactive mechanisms include sympathetic stimulation and water retention in an attempt to increase preload. These mechanisms however deteriorate the condition due to an increase in myocardial O_2 requirements and an increase in the afterload (112). Figure 13 demonstrates the changes of the left ventricular pressure-volume loop in patients with heart failure.

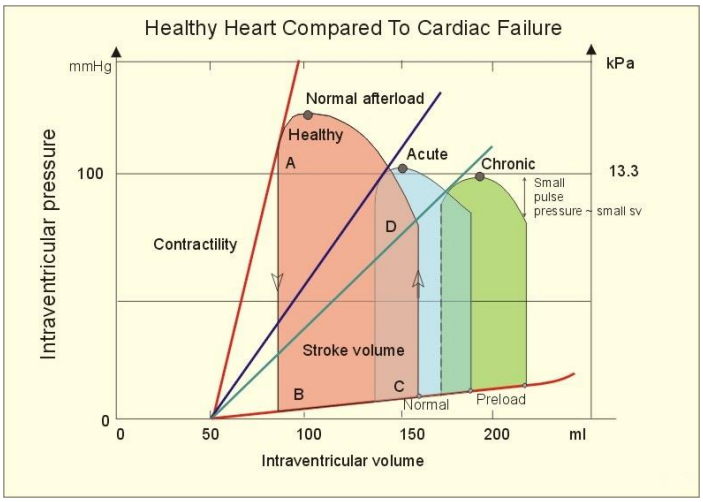


Figure 13. Left ventricular pressure-volume loops in a healthy person (red) and for persons with acute (blue area) or chronic, congestive (green area) cardiac failure.

(Source: http=//www.zuniv.net/physiology/book/chapter10.html)

4.2.1. Systolic myocardial dysfunction

The term systolic myocardial dysfunction defines the impairment of ejection capacity of the LV and it can be evaluated and quantified through the EF. The induction of myocardial ischemic damage implies the reduction of left ventricular ejection capacity, stroke volume, cardiac output, blood pressure and dP/dt ratio, while at the same time there is an increase in the endsystolic volume, whose rate of growth is the most prominent mortality prognostic factor after acute coronary syndromes ACS (113). The induction of dyskinesia entails a significant reduction in SV of the LV. Dilatation of the ventricular area is a result of slipping of the necrotic myocytes, resulting in thinning and extension of the infarct zone (114).

The dilation caused by the onset of the infarction, according to Laplace's law, increases wall tension and therefore causes more dilation. The degree of ventricular dilation depends on the extension of the infarct, the viability of the involved artery and the activation of the renin-angiotensin-aldosterone system (RAAS) and may be modified by inhibitors of the particular system, even in the absence of symptomatic left ventricular dysfunction. Gradually, an increase in stiffness as a result of tissue oedema, cellular infiltration and fibrosis of the ventricular zone is observed, resulting in reduced dyskinesia and improved left ventricular function (115, 116).

The occurrence of symptomatic heart failure is associated with specific parameters of the left ventricle. The reduction in compliance occurs early in small-scale infarctions. In cases where the affected part of the myocardium exceeds 15%, there is a reduction in the ejection fraction, while the left ventricular end-diastolic pressure and its volume may increase. The presence of signs and symptoms of heart failure increases with the number of areas of abnormal left ventricular mobility. An area with an abnormal contraction of more than 25% causes the onset of heart failure, while cardiogenic shock occurs in excess of 40% (113).

4.2.2. Diastolic myocardial dysfunction

The induction of ischemia and infarction affects the left ventricular diastolic function as the maximal rate of decrease in left ventricular pressure (peak -dP/dt) decreases, the time variable of the fall in ventricular pressure and the early increase in enddiastolic pressure of the left ventricle. Gradually increases in enddiastolic volume

are observed while diastolic blood pressure returns to normal levels. Infarct size determines the grade of diastolic dysfunction (117, 118).

Normal diastolic function is defined as the filling of the LV capable of achieving a satisfactory SV without increasing left ventricular filling pressure and the pressure of the pulmonary circulation. When EF is reduced, a larger enddiastolic volume is required to maintain an adequate SV. Therefore the filling that the heart needs to achieve sufficient SV depends on its systolic performance. Insufficient filling that leads to low cardiac output mobilizes compensation mechanisms that eventually increase pressure in pulmonary circulation. In this way diastolic dysfunction disorders are not accompanied by a fall in CO at rest but by pulmonary congestion. In patients with systolic dysfunction, if the increase in the enddiastolic volume is not accompanied by a pathological increase in pulmonary circulation pressures, a satisfactory compensation of the systolic dysfunction is achieved. If, on the other hand, the increased enddiastolic volume leads to a pathologic increase in pulmonary artery pressure, then the systolic dysfunction also results in diastolic dysfunction. In this sense, systolic dysfunction is the most common cause of diastolic dysfunction (117, 118).

Diastolic dysfunction however may also occur without the presence of systolic dysfunction. In this case, it may be due to disturbance of the ventricular filling, reduced ventricular compliance or external ventricular pressure. The most common cause of primary diastolic dysfunction is the decrease in compliance. When this occurs, significantly higher intraventricular pressures develop to fill the ventricle with the same enddiastolic volume. If the decrease in compliance is high, ventricular filling is achieved only with a disproportionate increase in pressure, but this also leads to congestion. In this way reduced ventricular compliance may cause pulmonary congestion and congestive heart failure without the coexistence of a systolic dysfunction (117, 118).

Decreased compliance may be due to hypertrophic cardiomyopathy, ischemia or relaxation disorders. The hypertrophy of LV is another cause of decreased compliance. It helps to restore myocardial tension to normal levels and helps maintain systolic function in patients with aortic valve stenosis or chronic hypertension, but it negatively impacts diastolic dilatation and ultimately leads to diastolic dysfunction (117, 118).

4.3. Cardiac remodeling

A common consequence of the MI is the appearance of changes in the size, shape and thickness of the LV involving the entire cavity including the affected areas, but also areas which were not directly involved in the MI. These changes are collectively referred to as remodeling of the ventricles. Remodeling is a process which affects the ventricular function and the prognosis of the disease. Both dilatation and hypertrophy contribute to remodeling. Cardiac remodelling is the central mechanism of heart failure progression in patients with IHD, occurring usually as a consequence of AMI. Postinfarction remodelling can be divided into an early phase (within 72 hours) and a late phase (beyond 72 hours) (119, 120).

4.3.1. Early remodeling

Early remodelling involves expansion of the infarct zone and collagen degradation, which may result in early ventricular rupture or aneurysm formation (121). Infarct expansion results from the degradation of the intermyocyte collagen struts by serine proteases and from the activation of matrix metalloproteinases (MMPs) released from neutrophils (122). Infarct expansion occurs within hours of myocyte injury, results in wall thinning and ventricular dilatation, and causes the elevation of diastolic and systolic wall stresses (123). Substantial changes in circulatory haemodynamics trigger the sympathetic adrenergic system, which stimulates catecholamines, activates the renin-angiotensin-aldosterone system (RAAS), and stimulates the production of endothelins, and atrial and b-type natriuretic peptides (ANP and BNP). Positive inotropic, chronotropic and also vasodilatory effects from this sympathetic stimulation result in hyperkinesis of the noninfarcted myocardium and temporary circulatory compensation by reduction of systemic vascular resistance and left ventricular filling pressure (119). However, although the neurohormonal activation initially serves an adaptive role, in later stages the responses become pathological and contribute adversely to remodelling and ultimately to the progress of heart failure. In addition, neurohormonal activation may precipitate further ischaemia by increasing oxygen demand and predisposing to arrhythmias (124).

4.3.2. Late remodelling and scar formation

Late remodelling involves the left ventricle globally and is associated with time-dependent dilatation, distortion of ventricular shape and hypertrophy. Hypertrophy is an adaptive response during postinfarction remodelling that offsets increased load, attenuates progressive dilatation, and stabilizes contractile function. It is initiated by neurohormonal activation, myocardial stretch, activation of the RAAS, and by paracrine/autocrine factors. Especially enhanced norepinephrine release contributes to the hypertrophy (125).

Myocardial repair and scar formation is triggered by cytokines released from injured myocytes. Before collagen synthesis tissue repair is initiated by the formation of a fibrin-fibronectin matrix to which myofibroblasts become adherent (126). Deposition of collagen occurs predominantly in the infarct zone, but also in noninfarcted myocardium. Collagen is detectable microscopically by day 7 and its deposition then increases dramatically, such that by 28 days, the necrotic myocytes are entirely replaced by fibrous tissue. After the formation of a scar that equilibrates distending and restraining forces, collagen formation is down-regulated and most fibroblasts undergo apoptosis (122).

4.4. Activation of Renin-Angiotensin-Aldosterone-System

The circulating renin-angiotensin-aldosterone system (RAAS) plays an important role in the maintenance of cardiovascular homeostasis. It has been demonstrated that endogenous RAS exists in target tissues that are important in cardiovascular regulation. Myocardial areas that have not been necrotic following myocardial infarction show an activation of the renin-angiotensin system and cause increased angiotensin II production. Angiotensin II leads to the production of various growth factors, such as platelet growth factor (PGF) and transforming growth factor beta (TGFb), which cause hypertrophy of non-infarcted myocardium and regulate the tone and structure of the coronary vessels. Further actions of angiotensin II are the secretion of endothelin, PAI-1 and aldosterone, which cause vasoconstriction, decreased fibrinolysis and increased sodium retention, respectively (127, 128).

5. CLINICAL PRESENTATIONS OF ISCHEMIC HEART DISEASE

Ischaemic heart disease (IHD), caused as mentioned before by an imbalance between the supply and demand of oxygen to the heart, may be symptomatic or asymptomatic and it may have a stable or a progressive course. IHD is classified on the basis of its symptomatology and severity (98).

5.1. Stable angina pectoris

Stable angina pectoris is the main symptom/form of IHD. The pathological substrate for angina is almost invariably atheromatous narrowing of the coronary arteries. It is usually considered that a coronary artery must be narrowed by at least 50-70% in luminal diameter before coronary blood flow is inadequate to meet the metabolic demands of the heart with exercise or stress. In this case the stenosis can be defined as significant (129). The importance of stenosis depends also on the length and number of stenoses. Angina pectoris results from myocardial ischaemia, which is caused by an imbalance between myocardial oxygen requirements and oxygen supply. Increased oxygen demand may occur due to increase in heart rate, left ventricular wall stress or contractility. Oxygen supply, on the other hand, is determined by coronary blood flow and coronary arterial oxygen content. The precipitating factors causing angina due to increased myocardial oxygen consumption include exercise, mental stress, fever, cold, tachycardia from any cause, thyrotoxicosis, and hypoglycaemia (130). Typical angina pectoris is substernal, across mid-thorax, anteriorly, can locate also in arms, shoulders, neck, and interscapular region. It is characterized by a burning, heavy or squeezing feeling, is precipitated by exertion or emotion and is promptly relieved by rest or by nitroglycerin. The typical episode of angina pectoris usually begins gradually and reaches its maximum intensity over a period of minutes before dissipating (129-131). If the symptoms remain the same for several weeks and constantly occur under the same physical or mental stress, the condition is described as “stable” angina pectoris (95-97). Stable angina pectoris is classified by severity into 4 classes according to the Canadian Cardiovascular Society (CCS) (Table 3) (132).

Class I	Angina occurs with strenuous or rapid or prolonged exertion at work or recreation. Ordinary physical activity, such as walking and climbing stairs, does not cause angina.
Class II	Slight limitation of ordinary activity. Angina occurs on walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold, in wind or when under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.
Class III	Marked limitation of ordinary physical activity. Walking one to two blocks on the level and climbing more than one flight in normal conditions.
Class IV	Inability to carry on any physical activity without discomfort – anginal syndrome may be presented at rest.

Table 3. Classification of stable angina pectoris according to the Canadian Cardiovascular Society (CCS).

5.2. Silent myocardial ischemia

Silent myocardial ischaemia is defined as objective documentation of myocardial ischaemia in the absence of angina or anginal equivalents. It has been explained by the ability of patients to produce endogenous opioids that raise the pain threshold, by autonomic neuropathy and also by a defect in the cerebral cortex. Silent ischaemia and infarction are more frequent in the elderly, women and diabetics (133). Patients with silent ischaemia can be divided into three types:

- **Type I patients** have no symptoms at any time in spite of obstructive IHD.
- **Type II patients** have silent ischaemia after experiencing AMI
- **Type III patients**, the most common group, have either concurrent chronic stable angina, unstable angina or Prinzmetal angina.

Patients experiencing episodes of silent myocardial ischaemia have been found to have a worse prognosis compared with those without silent ischaemia (133, 134).

5.3 Acute coronary syndromes

The term acute coronary syndromes (ACS) refers to several important nosological entities, ranging from unstable angina (UA), subendocadrial or non-ST-elevantion myocardial infarction (NSTEMI) and transmural or ST-elevation myocardial infarction (STEMI) to sudden cardiac death (SCD).

ACS are worldwide a severe cause of morbidity and mortality. NSTEMIs and UA account for approximately 2.5 million hospital admissions per year worldwide, while STEMIs are responsible for another one million hospitalizations, respectively (135).

The complexity of postmortem and clinical observations suggests that it is unlikely to identify a common cause for the phenotype of ACSs. To better understand the multiple causes of coronary instability, it would be desirable to construct a pathogenetic classification of ACS based on simple clinical descriptors (Figure 14). The multiple causes of coronary instability can therefore categorized in 3 homogeneous groups of patients with a similar clinical presentation (136):

1) Patients who have obstructive atherosclerosis and systemic inflammation.

2) Patients who have obstructive atherosclerosis without systemic inflammation.

3) Patients without obstructive atherosclerosis.

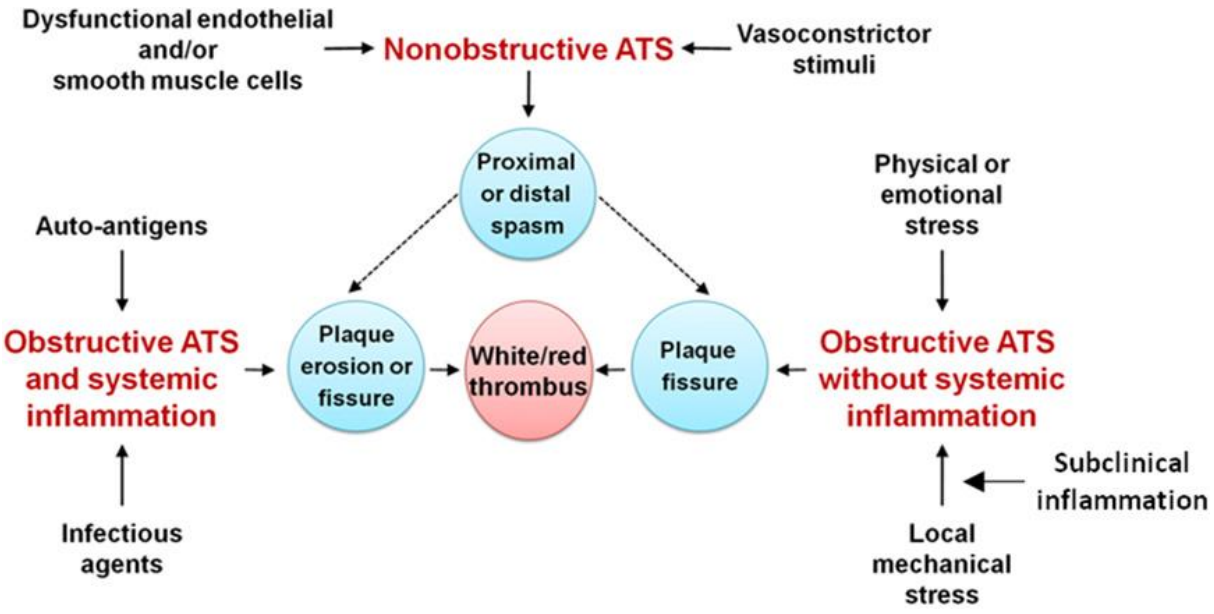


Figure 14. The pathogenetic classification of acute coronary syndrome (ACS) based on simple clinical descriptors.

(Source: Crea F, Liuzzo G. Pathogenesis of acute coronary syndromes. J Am Coll Cardiol. 2013 Jan 8;61(1):1-11.)

5.3.1. Unstable angina and Prinzmetal (variant) angina

The currently used definition of unstable angina pectoris depends on the presence of one or more of the following features (98):

1) Crescendo angina (more severe, prolonged or frequent) superimposed on an existing pattern of relatively stable, exertion-related angina pectoris.

2) Angina pectoris of new onset (usually within 1 month), which is brought on by minimal exertion.

3) Angina pectoris at rest as well as with minimal exertion.

A classification of UA is presented in Table 4 (135).

Class I	New-onset, severe or accelerated angina. Patients with angina of less than 2 months' duration, severe angina or angina occurring three or more times per day or angina that is distinctly more frequent and precipitated by distinctly less exertion. No rest pain in the last 2 months.
Class II	Angina at rest. Subacute. Patients with one or more episodes at rest during the preceding month, but not within the preceding 48 hours.
Class III	Angina at rest. Acute. Patients with one or more episodes at rest within the preceding 48 hours.

Table 4. Classification of unstable angina.

(Source: Hamm CW, Braunwald E. A classification of unstable angina revisited. Circulation 2000;102(1):118-22.)

Prinzmetal's (variant) angina is an unusual and uncommon form of angina secondary to myocardial ischaemia that occurs almost exclusively at rest, is usually not precipitated by physical exertion or emotional stress and is associated with ST-segment elevations in electrocardiogram (136). Variant angina is demonstrated to be due to coronary artery spasm, which narrows the coronary artery resulting in myocardial ischaemia (104). Endothelial dysfunction, an increased platelet aggregation together with changes in autonomic tone can trigger the vasospasms (137, 138). Also dysfunction of K^+-ATP channels may have role in variant angina (139).

5.3.2. Acute myocardial infarction (NSTEMI and STEMI)

Acute myocardial infarction (AMI) represents the most critical and serious form of IHD. Although the death rate from AMI has continuously declined over the past decades, its development together with all complications is fatal for about one third of the patients (140). Almost all AMIs result from coronary atherosclerosis, generally with superimposed coronary thrombosis. During the natural evolution of atherosclerotic plaques an abrupt transition may occur, characterized by plaque rupture. After plaque rupture there is an exposure of substances that promote platelet activation and aggregation, thrombin generation and ultimately thrombus formation. The thrombus interrupts the blood flow and leads to an imbalance between oxygen supply and demand and, if this imbalance is severe and persistent, to myocardial necrosis. After onset of infarction, the first ultrastructural changes are noted already within 20 minutes. The first irreversible changes are seen after about 1-2 hours from onset of AMI. After about 6 hours of continuous occlusion the entire jeopardized area becomes necrotic. The infarction process results in the formation of a fibrous scar with interspersed intact muscle fibers after about 6 weeks from onset of the process (141). The WHO criteria for diagnosis of AMI were established in 1994 and required that at least two of three elements be present for diagnosis; these criteria have been used for several decades for diagnosis of AMI (141). A revised definition of AMI has been proposed by European and American cardiology societies in 2000. This was necessary in order to achieve a better risk stratification and subsequent treatment (142). A universal definition of myocardial infarction was finally offered in 2007 (143). The new third universal definition of myocardial infarction was published in 2012 and is based on troponin elevation together with ischemic symptoms, ischemic ECG changes, and imaging evidence. MIs are classified into five types as to whether they are spontaneous, secondary to imbalance between coronary artery blood supply and demand, related to sudden death, or related to revascularization procedures. The definition is based on a rise and/or fall in troponin levels occurring in a clinical setting and is presented in table 5 (144).

The term acute myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions, any one of the following criteria meets the diagnosis for MI:
Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin) with at least one of the following: o Symptoms of ischemia o New or presumed new significant ST-segment-T wave (ST-T) changes or new left bundle branch block (LBBB) o Development of pathological Q waves in the ECG o Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality o Identification of an intracoronary thrombus by angiography or autopsy
Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before biomarker values would be increased.
Percutaneous coronary intervention (PCI) related MI is arbitrarily defined by elevation of troponin values >5 X the 99th percentile URL for troponin if the pre-procedure value is normal. If baseline values are elevated but are stable or falling, an increase of >20 % is required. In addition, patients should have either: (i) symptoms suggestive of myocardial ischemia or (ii) new ischemic ECG changes or (iii) angiographic findings consistent with procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.
Coronary artery bypass grafting (CABG) related MI is arbitrarily defined by elevation of cardiac biomarker values (>10 X 99th percentile URL) in patients with normal baseline troponin values. In addition either: (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Table 5. Definition of myocardial infarction and criteria for acute myocardial infarction.

(Source: White H1, Thygesen K, Alpert JS, Jaffe A. Universal MI definition update for cardiovascular disease. Curr Cardiol Rep. 2014;16(6):492.)

Five types of MI are defined based on pathological, clinical, and prognostic differences (Table 6). Each type has different implications for patients and may require a different management (144).

Type 1	Spontaneous myocardial infarction
Type 2	MI secondary to an ischemic imbalance
Type 3	MI resulting in death when biomarker values are unavailable
Type 4a	MI related to percutaneous coronary intervention (PCI)
Type 4b	MI related to stent thrombosis
Type 4c	MI related to restenosis
Type 5	MI related to coronary artery bypass grafting (CABG)

Table 6. Universal classification of MI.

(Source: White H1, Thygesen K, Alpert JS, Jaffe A. Universal MI definition update for cardiovascular disease. Curr Cardiol Rep. 2014;16(6):492.)

Hospital mortality is higher in patients with STEMI than in NSTEMI patients (7% vs 3-5%), although the six month mortality is similar in these two patient groups (12% and

13% respectively) (145, 146). Long-term mortality is however higher in NSTEMI patients than in STEMI (147). This differentiation in the median and long-term mortality is due to the different patient profiles, given that NSTEMI patients are older, with coexisting underlying conditions, especially diabetes mellitus and renal insufficiency (148).

As mentioned before most ACS cases are a consequence of coronary atherosclerosis, in combination with coronary artery thrombosis. There exists however a small percentage of cases of non-atherosclerotic coronary artery disease. Such non-atherosclerotic causes of ACS are arteritis, trauma, dissection, thromboembolism, congenital abnormalities, cocaine abuse and iatrogenic complications of cardiac catheterization (149).

6. HEART FAILURE

6.1. Definition of heart failure

According to the definition given in the 2016 European guidelines heart failure (HF) is a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress (105). Patients can however present with a symptomatic structural or functional cardiac abnormalities before clinical symptoms become apparent. These abnormalities are precursors of HF. Recognition of these precursors is important because they are related to poor outcomes, and starting treatment at the precursor stage may reduce mortality in patients with asymptomatic systolic LV dysfunction. Demonstration of an underlying cardiac cause is central to the diagnosis of HF. This is usually a myocardial abnormality causing systolic and/or diastolic ventricular dysfunction. However, abnormalities of the valves, pericardium, endocardium, heart rhythm and conduction, or often a combination of these abnormalities can also cause HF. Identification of the underlying cardiac problem is crucial for therapeutic reasons, as the precise pathology determines the specific treatment used (105).

According to this modern definition, the fact is taken into account that approximately half of the patients also suffer from heart failure despite having a normal systolic function. Heart failure with impaired left ventricular function, however, is the longer known and better characterized clinical entity.

6.2. Epidemiology of heart failure

According to the last European guidelines, the prevalence of HF is approximately 1–2% of the adult population in developed countries, rising to ≥10% among people >70 years of age (105, 150). Among people >65 years of age presenting to primary care with breathlessness on exertion, one in six will have unrecognized HF, mainly patients with preserved left ventricular ejection fraction (LVEF) (105, 151). The lifetime risk of HF at age 55 years is 33% for men and 28% for women (152). The proportion of HF patients with normal LVEF ranges from 22 to 73%, depending on the definition applied, the clinical setting, age and sex of the studied population, previous myocardial infarction and the year of publication (105). Data on temporal trends based on hospitalized patients suggest that the incidence of HF may be decreasing, more for HF with reduced LVEF than for HF with normal LVEF (153). These two categories of patients with HF seem to have different epidemiological and aetiological profiles. Patients with reduced LVEF are older, more often women and more commonly have a history of hypertension and atrial fibrillation (AF), while a history of myocardial infarction is less common (153, 154).

Over the last 30 years, improvements in treatments and their implementation have improved survival and reduced the hospitalization rate in patients with reduced LVEF, although the outcome often remains unsatisfactory. The most recent European data demonstrate that 12-month all-cause mortality rates for hospitalized and stable/ambulatory HF patients were 17% and 7%, respectively, and the 12-month hospitalization rates were 44% and 32%, respectively (105, 155). In patients with HF (both hospitalized and ambulatory), most deaths are due to cardiovascular causes, mainly sudden death and worsening HF. All-cause mortality is generally higher in patients with reduced LVEF than those with preserved LVEF (155, 156). Hospitalizations are often due to non-cardiovascular causes, particularly in patients with normal LVEF (105).

According to the German Society of Cardiology (Deutsche Geselschaft für Kardiologie - DGK), the prevalence in the normal population for heart failure is 2-3%. The prevalence increases with increasing age in the 70- to 80-year-olds to more than 10% (157, 158). In the process, half of all patients die within 4 years after diagnosed with HF, depending on etiology, age, comorbidities and individual progression of the disease. 40% of patients admitted to hospital for heart failure die within one year or are readmitted during this period (158). Data from the the nationwide German database suggest that more women than men were recorded as having congestive heart failure (66% vs. 34%). The various health insurance companies paid 2.3 times more for patients with than without congestive heart failure. Nearly three quarters of the cost for these patients (72%) resulted from in-patient care. Moreover, costs for drugs were three times higher (1073 € vs. 366 €). Rising healthcare costs are expected and will play an important economic role in the healthcare system (159). Significant increases in heart failure are observed worldwide, especially in the developed countries (160).

6.3. Defining heart failure patients regarding the ejection fraction

The main terminology used to describe HF is historically based on measurement of the LVEF. HF comprises a wide range of patients, from those with normal LVEF [typically considered as ≥50%; HF with preserved EF (HFpEF)] to those with reduced LVEF [typically considered as <40%; HF with reduced EF (HFrEF)] (Table 7). Patients with an LVEF in the mid-range of 40–49% represent a ‘grey area’, which we now define as HF with moderate reduced EF (HFmrEF). Differentiation of patients with HF based on LVEF is important due to different underlying aetiologies, demographics, co-morbidities and response to therapies. It is mostly in patients with HFrEF that therapies have been shown to reduce both morbidity and mortality (105, 161).

The diagnosis of HFpEF is more challenging than the diagnosis of HFrEF. Patients with HFpEF generally do not have a dilated LV, but instead often have an increase in LV wall thickness and/or increased left atrial (LA) size as a sign of increased filling pressures. Most have additional ‘evidence’ of impaired LV filling or suction capacity, also classified as diastolic dysfunction, which is generally accepted as the likely cause of HF in these patients. However, most patients with HFrEF also have diastolic

dysfunction, and subtle abnormalities of systolic function have been shown in patients with HFpEF. Patients with HFmrEF most probably have primarily mild systolic dysfunction, but with features of diastolic dysfunction (105).

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction

Table 7. Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF).

(Source: Ponikowski P, Voors AA, Anker SD et al. ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016 Jul 14;37(27):2129-2200.)

6.4. Aetiology of heart failure

Coronary artery disease is responsible for about 2/3 of all cases of heart failure, followed by hypertension. Other causative factors are non-ischemic heart disease. These include dilated cardiomyopathy (DCM), cardiomyopathies induced by alcohol, diabetes and medications (including chemotherapy), and peripartum cardiomyopathy. Viral, hypertensive, metabolic and valvular cardiomyopathy are also included. Genetic factors are also discussed as triggers of cardiomyopathy (105, 162). Table 8 offers an overview of the main factors responsible for heart failure.

Main causes of heart failure	
Coronary artery disease	various manifestations (eg myocardial infarction, ischemic cardiomyopathy)
Arterial hypertension	Often associated with left ventricular hypertrophy and preserved systolic function
Cardiomyopathies	Dilated, hypertrophic obstructive, restrictive, right ventricular, arrhythmogenic, unclassified
Medical	Overdose of beta blockers, calcium channel inhibitors, antiarrhytmic agents, chemotherapy
Toxins	Alcohol, cocain, trace elements (cobalt, arsenic)
Endocrinologic	Diabetes, hypo- or hyperthyroidism, Cushing syndrome, renal failure, acromegaly, pheochromocytoma
Alimentary / metabolic	Thiamine deficiency, selenium deficiency, carnitine deficiency, Obesity, cachexia
Infiltrative	Sarcoidosis, Amyloidosis, Hemochromatosis, connective tissue diseases
Other	HIV infection, peripartum cardiomyopathy, terminal renal insufficiency, Chagas disease

Table 8. Main causes of heart failure.

(Source: Pocket Leitlinien der DGK 2009, Hoppe 2009)

6.5. Classification of heart failure

Currently, various systems of clinical classification based on underlying clinical grade of heart failure are used.

6.5.1. Killip classification

The oldest classification for the severity classification of the acute heart failure is the Killip classification. This classification has prognostic significance (163, 164). It was developed by Killip and Kimball in 1967 in patients with acute myocardial infarction and should allow a simple clinical assessment of the hemodynamic consequences of acute myocardial infarction with prognosis. It includes the classification according to clinical and hemodynamic aspects into four degrees of severity, which correlate directly with the mortality of myocardial infarction. "Killip I" indicates uncomplicated myocardial infarction without signs of pulmonary congestion. "Killip II" is defined as pulmonary congestion in <50% of lung sections, third heart sound, and cervical venous stasis associated with elevated CVD. "Killip III" appears in the form of

pulmonary oedema with rattle noise in >50% of the lungs. Killip IV corresponds to cardiogenic shock (163). The classification is presented in table 9.

Killip Classification of heart failure	
Class I	Individuals with no clinical signs of heart failure.
Class II	Individuals with rales or crackles in the lungs, an S3, and elevated jugular venous pressure.
Class III	Individuals with frank acute pulmonary edema.
Class IV	individuals in cardiogenic shock or hypotension (systolic blood pressure <90 mmHg), and evidence of peripheral vasoconstriction (oliguria, cyanosis or sweating).

Table 9. The Killip classification of heart failure.

(Source: Killip T, Kimball JT. Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients. Am J Cardiol. 1967 Oct; 20(4): 457-464.)

6.5.2. Forrester classification

Another option for the classification of acute heart failure is provided by the so-called Forrester classification (Figure 15). This was established in 1977 and originally dealt only with patients who suffered an acute myocardial infarction. Based on clinical and hemodynamic criteria, Forrester identified the following four Patient groups, grouped into two pairs (165):

- The first pair describes the situation "normal peripheral perfusion versus hypoperfusion": such a distinction can be made on the one hand by typical clinical signs such as peripheral cyanosis, flat pulse, cold wet skin, hypotension, tachycardia and oliguria. On the other hand, measurable hemodynamic criteria (cardiac output index <2.2 L/min/m²) are used.
- The second couple discusses the issue of "pulmonary congestion versus hypovolemia": the clinical signs of the current fluid status are both wet rales and radiographic signs of pulmonary congestion. As a hemodynamic criterion, differentiation via pulmonary capillary occlusion pressure (PCWP) is possible (stasis sign at PCWP >18 mmHg).

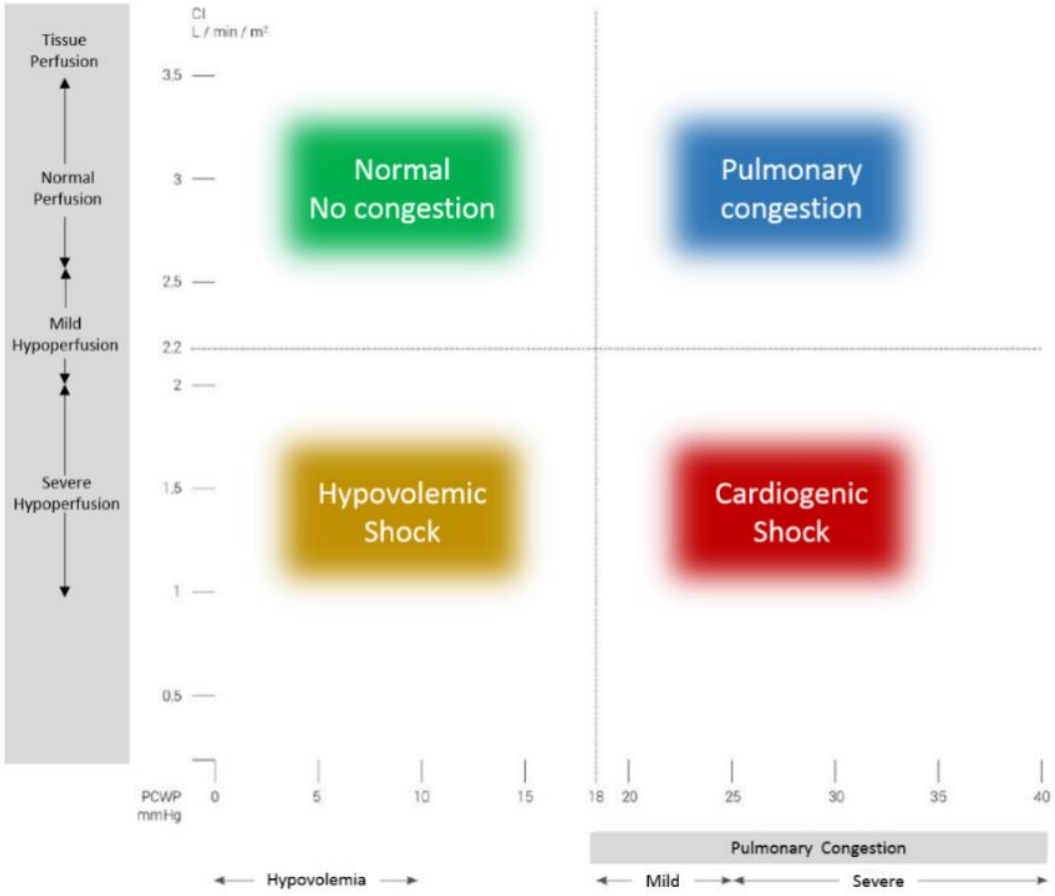


Figure 15. The Forrester classification of heart failure.

(Source: Modified from Dickstein K, et al. ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Eur Heart J. 2008 Oct; 29(19): 2388-2442.)

The four quadrants of the Forrester classification represent using clinical and hemodynamic criteria in field I the normal situation, in field II those of acute pulmonary edema, in field III those of hypovolemic shock and in field IV those of cardiogenic shock. Prognostically, these four aspects are completely different. Patients grouped in field III had a mortality of 22.4%, while in field IV mortality was 55.5% more than twice as high (166). Compared to the Killip classification, a pathogenetically oriented approach, which also permits a differentiated therapeutic approach, is pursued beyond the purely descriptive classification of severity. However, the fact that an invasive hemodynamic monitoring with a Swan-Ganz catheter is required makes this method more difficult to apply and not always suitable for broad clinical use in emergency and acute care. In the most favourable case, the

classification according to Killip and the Forrester classification are used in combination for the treatment decision (165, 166).

6.5.3. Nohria classification

The Nohria classification, also known as "Clinical Severity Classification", which is mainly used in patients with cardiomyopathies, is a classification according to the clinical severity in patients with acute heart failure and refers exclusively to the clinical criteria of the Forrester classification, without assuming invasive haemodynamic monitoring (167). Patients are also divided into four groups for peripheral perfusion and pulmonary congestion: group A - warm and dry, group B - warm and wet, group C - cold and dry, group D - cold and wet (Figure 16). On the one hand, the clinical diagnostic criteria include congestive criteria such as orthopnoea, jugular vein congestion, rales, hepatojungular reflux, ascites, peripheral oedema, and pulmonary flap tone audible to the left. On the other hand, signs of hypoperfusion, such as low pulse amplitude, pulsus alternans, symptomatic hypotension, cold extremities, and memory and cognitive disorders. The prognostic significance of this classification has been proven and established (167).

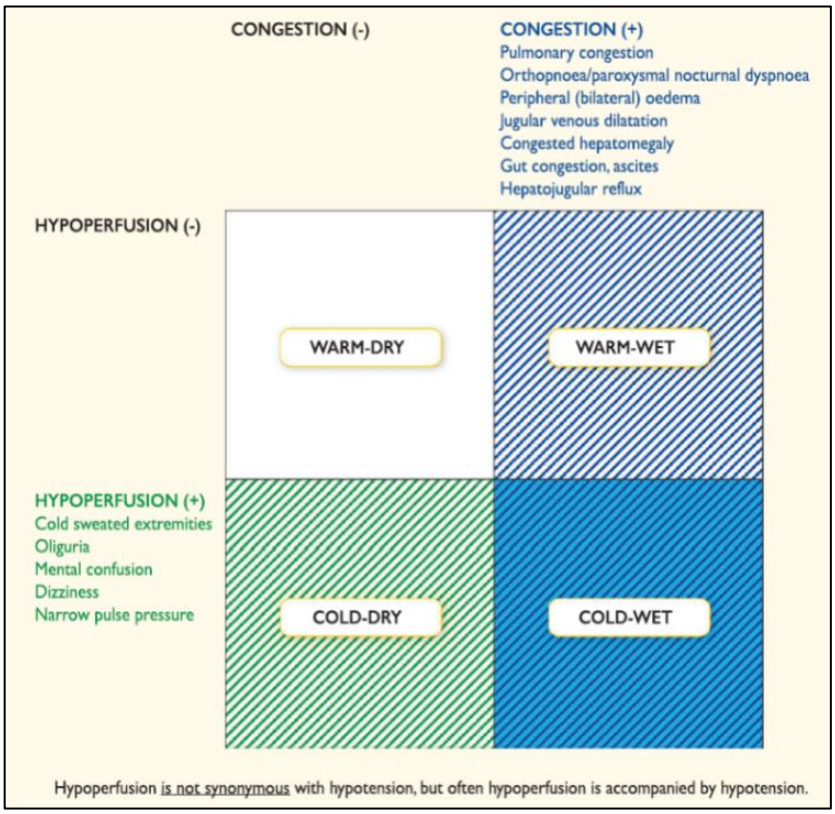


Figure 16. Clinical profiles of patients with acute heart failure based on the presence/absence of congestion and/or hypoperfusion.

(Source: Ponikowski P, Voors AA, Anker SD et al. ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016 Jul 14;37(27):2129-2200.)

6.5.4. NYHA classification

The most commonly used classification of heart failure is the staging of the New York Heart Association (NYHA), which was first published in 1928, has since been revised several times and last revised in 1994 (168, 169). This classification is functionally based on subjective complaints and performance in stages of I-IV (Table 10) (169). However, a NYHA stage is not a stable condition and can change in the same patient. In addition, there is a poor correlation between NYHA stage and ejection fraction (170). However, a correlation with mortality can be observed (171).

NYHA Class	Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea.
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea.
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity with discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Table 10. The NYHA classification of heart failure.

(Source: The Criteria Committee of the New York Heart Association. (1994). Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels (9th ed.). Boston: Little, Brown & Co. pp. 253–256.)

6.5.5. ACC/AHA classification

In 2001, the American Heart Association (AHA) in cooperation with the American college of cardiologists (ACC) presented one classification, which takes into account the development and progression of the disease. This classification includes four stages A-D (Table 11) (172). It should be emphasized that stadiums A and B are not strictly referring to a chronic heart failure, but only an asymptomatic cardiac

dysfunction or a pre-stage of the heart failure. Advanced disease stages are only subsumed in stage D and clearly underrepresented.

AHA/ACC Clasification	
Stage A	Patients at risk for heart failure who have not yet developed structural heart changes (i.e. those with diabetes, those with coronary disease without prior infarct).
Stage B	Patients with structural heart disease (i.e. reduced ejection fraction, left ventricular hypertrophy, chamber enlargement) who have not yet developed symptoms of heart failure.
Stage C	Patients who have developed clinical heart failure.
Stage D	Patients with refractory heart failure requiring advanced intervention (i.e. biventricular pacemakers, left ventricular assist device, transplantation).

Table 11. The AHA/ACC classification of heart failure.

(Source: Yancy CW et al. American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA Guideline for the Management of Heart Failure. Circulation. 2013 Oct; 128(16): e240-e327.)

At this point it should be stressed that the ACC/AHA classification is much different than the NYHA functional classification system, in that there is no moving backwards to prior stages. Once symptoms develop, stage C heart failure is present and stage B will never again be achieved. In the NYHA classification, in contrast, patients can move between class I and class IV relatively quickly, as these are all designated on symptoms alone.

6.6. Diagnosis of heart failure in the non-acute setting

For patients presenting with symptoms or signs for the first time, non-urgently in primary care or in a hospital outpatient clinic, the probability of HF should first be evaluated based on the patient's prior clinical history, presenting symptoms, physical examination (e.g. bilateral oedema, increased jugular venous pressure, displaced apical beat) and resting ECG. If all elements are normal, HF is highly unlikely and other diagnoses need to be considered. If at least one element is abnormal, plasma natriouretic peptides (NP) should be measured, if available, to identify those who need echocardiography (an echocardiogram is indicated if the NP level is above the exclusion threshold or if circulating NP levels cannot be assessed) (105).

6.7. Pharmacological treatment of chronic heart failure

No treatment has yet been shown, convincingly, to reduce morbidity or mortality in patients with HFpEF or HFmrEF. However, since these patients are often elderly and highly symptomatic, and often have a poor quality of life, an important aim of therapy may be to alleviate symptoms and improve well-being (177, 178). As far as the HFrEF patients are concerned, optimal medical therapy is crucial regarding the quality of life and the prognosis of these patients (105).

The goals of treatment in patients with HF are to improve their clinical status, functional capacity and quality of life, prevent hospital admission and reduce mortality. The fact that several drugs for HF have shown detrimental effects on long-term outcomes, despite showing beneficial effects on shorter-term surrogate markers, has led regulatory bodies and clinical practice guidelines to seek mortality/morbidity data for approving/recommending therapeutic interventions for HF. However, it is now recognized that preventing HF hospitalization and improving functional capacity are important benefits to be considered if a mortality excess is ruled out (105, 173, 174). Figure 17 presents pharmacological treatment recommended from the ESC.

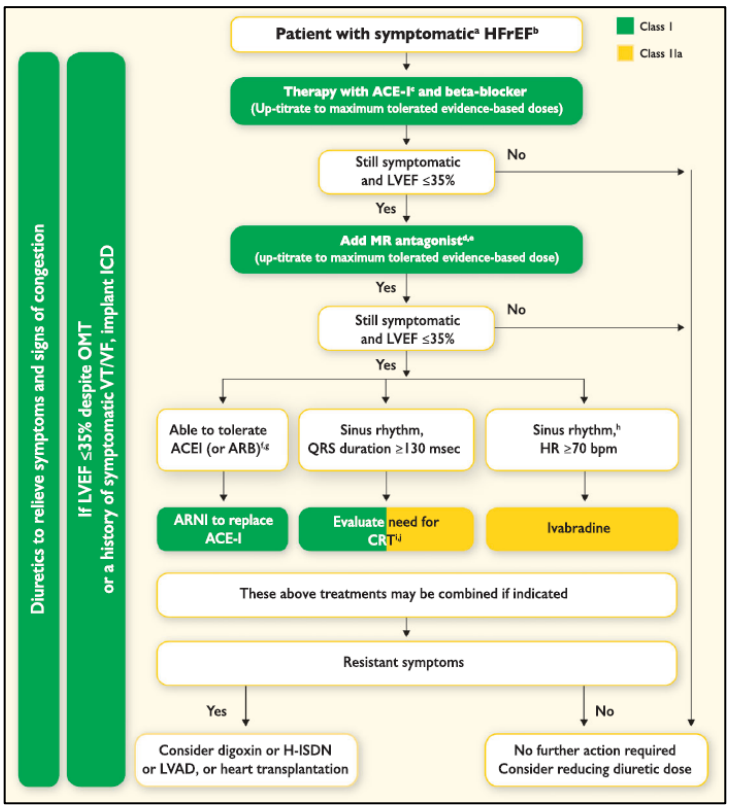


Figure 17. The recommended therapeutic algorithm for a patient with symptomatic heart failure with reduced ejection fraction.

(Source: Ponikowski P, Voors AA, Anker SD et al. ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016 Jul 14;37(27):2129-2200.)

6.7.1 Angiotensin-converting enzyme inhibitors (ACEI)

ACEIs have been shown to reduce mortality and morbidity in patients with HFrEF and are recommended unless contraindicated or not tolerated in all symptomatic patients. ACEIs should be up-titrated to the maximum tolerated dose in order to achieve adequate inhibition of the RAAS. ACEIs are also recommended in patients with asymptomatic LV systolic dysfunction to reduce the risk of HF development, HF hospitalization and death (105, 175, 176).

6.7.2. Beta-blockers

Beta-blockers reduce mortality and morbidity in symptomatic patients with HFrEF, despite treatment with an ACEI and, in most cases, a diuretic, but have not been tested in congested or decompensated patients (179, 180). There is consensus that beta-blockers and ACEIs are complementary, and can be started together as soon as the diagnosis of HFrEF is made. There is no evidence favouring the initiation of treatment with a beta-blocker before an ACEI has been started (181). Beta-blockers are recommended in patients with a history of myocardial infarction and asymptomatic LV systolic dysfunction to reduce the risk of death (105).

6.7.3. Mineralocorticoid/aldosterone receptor antagonists (MRA)

MRAs block receptors that bind aldosterone and, with different degrees of affinity, other steroid hormone (e.g. corticosteroids, androgens) receptors. Spironolactone or eplerenone are recommended in all symptomatic patients (despite treatment with an ACEI and a beta-blocker) with HFrEF and LVEF ≤35%, to reduce mortality and HF hospitalization (182, 183).

6.7.4. Diuretics

Diuretics are recommended to reduce the signs and symptoms of congestion in patients with HFrEF, but their effects on mortality and morbidity have not been studied in randomaized control trials. It has been shown that in patients with chronic HF, loop and thiazide diuretics appear to reduce the risk of death and worsening HF and to improve exercise capacity (184). The aim of diuretic therapy is to achieve and maintain euvolaemia with the lowest achievable dose (105).

6.7.5. Angiotensin receptor neprilysin inhibitor (ARNI)

ARNIs are a new therapeutic class of agents acting on the RAAS and the neutral endopeptidase system. The first in class is LCZ696, which is a molecule that combines the moieties of valsartan and sacubitril (neprilysin inhibitor) in a single substance. By inhibiting neprilysin, the degradation of NPs, bradykinin and other peptides is slowed. High circulating A-type natriuretic peptide (ANP) and BNP exert physiologic effects through binding to NP receptors and the augmented generation of cGMP, thereby enhancing diuresis, natriuresis and myocardial relaxation and anti-remodelling. ANP and BNP also inhibit renin and aldosterone secretion. Selective AT1-receptor blockade reduces vasoconstriction, sodium and water retention and myocardial hypertrophy. To minimize the risk of angioedema caused by overlapping ACE and neprilysin inhibition, the ACEI should be withheld for at least 36 h before initiating sacubitril/valsartan. Combined treatment with an ACEI (or ARB) and sacubitril/valsartan is contraindicated (185).

6.7.6. If-channel inhibitor

Ivabradine slows the heart rate through inhibition of the If channel in the sinus node and therefore should only be used for patients in sinus rhythm. Ivabradine reduced the combined endpoint of mortality or hospitalization for HF in patients with symptomatic HFrEF or LVEF ≤35%, in sinus rhythm and with a heart rate ≥70 bpm (186).

6.7.7. Angiotensin II type I receptor blockers (ARB)

ARBs are recommended only as an alternative in patients intolerant of an ACEI. Candesartan has been shown to reduce cardiovascular mortality (187). Valsartan showed an effect on hospitalization for HF in patients with HFrEF receiving background ACEIs. Therefore, ARBs are indicated for the treatment of HFrEF only in patients who cannot tolerate an ACEI because of serious side effects (188).

6.7.8. Combination of hydralazine and isosorbide dinitrate

There is no clear evidence to suggest the use of this fixed-dose combination therapy in all patients with HFrEF. A combination of hydralazine and isosorbide dinitrate may be considered in symptomatic patients with HFrEF who can tolerate neither ACEI nor ARB (or they are contraindicated) to reduce mortality (105).

6.7.9. Digoxin and other digitalis glycosides

Digoxin may be considered in patients in sinus rhythm with symptomatic HFrEF to reduce the risk of hospitalization, although its effect on top of beta-blockers has never been tested. The effects of digoxin in patients with HFrEF and AF have not been studied in RCTs, and recent studies have suggested potentially higher risk of events (mortality and HF hospitalization) in patients with AF receiving digoxin (189). In patients with symptomatic HF and AF, digoxin may be useful to slow a rapid ventricular rate, but it is only recommended for the treatment of patients with HFrEF and AF with rapid ventricular rate when other therapeutic options cannot be pursued. Digitalis should always be prescribed under specialist supervision. Given its distribution and clearance, caution should be exerted in females, in the elderly and in patients with reduced renal function. In the latter patients, digitoxin should be preferred (105, 190).

6.8. Cardioverter and defibrillator therapy

A high proportion of deaths among patients with HF, especially those with milder symptoms, occur suddenly and unexpectedly. Many of these are due to electrical

disturbances, including ventricular arrhythmias, bradycardia and asystole, although some are due to coronary, cerebral or aortic vascular events. Treatments that improve or delay the progression of cardiovascular disease will reduce the annual rate of sudden death, but they may have little effect on lifetime risk and will not treat arrhythmic events when they occur. Implantable cardioverter-defibrillators (ICDs) are effective in preventing bradycardia and correcting potentially lethal ventricular arrhythmias. Some antiarrhythmic drugs might reduce the rate of tachyarrhythmias and sudden death, but they do not reduce overall mortality and may increase it. ICDs are widely used as primary and secondary prevention of sudden cardiac death (105).

On average, patients with IHD are at greater risk of sudden death than patients with DCM and therefore, although the relative benefits are similar, the absolute benefit is greater in patients with IHD (191). Patients with longer QRS durations may also receive greater benefit from an ICD, but these patients should often receive a CRT device (192).

6.9. Cardiac resynchronization therapy (CRT)

CRT improves cardiac performance in appropriately selected patients and improves symptoms and well-being and reduces morbidity and mortality. Of the improvement in quality-adjusted life-years (QALYs) with CRT among patients with moderate to severe HF, 2/3 may be attributed to improved quality of life and 1/3 to increased longevity (193).

Not all patients respond favourably to CRT. Several characteristics predict improvement in morbidity and mortality, and the extent of reverse remodelling is one of the most important mechanisms of action of CRT. Patients with ischaemic aetiology will have less improvement in LV function due to myocardial scar tissue, which is less likely to undergo favourable remodelling (193, 194). Conversely, women may be more likely to respond than men, possibly due to smaller body and heart size (195). QRS width predicts CRT response. But QRS morphology has also been related to a beneficial response to CRT. Patients with left bundle branch block (LBBB) morphology are more likely to respond favorably to CRT, whereas there is less certainty about patients with non-LBBB morphology. However, patients with LBBB morphology often have wider QRS duration, and there is a current debate about whether QRS duration or QRS morphology is the main predictor of a beneficial

response to CRT. When LVEF is reduced, RV pacing may exacerbate cardiac dyssynchrony. This can be prevented by CRT, which might improve patient outcomes (196). Patients with HFrEF who have received a conventional pacemaker or an ICD and subsequently develop worsening HF with a high proportion of RV pacing, despite optimal medical therapy (OMT), may be considered for upgrading to CRT (105).

6.10. Left ventricular assist device therapy

Use of OMT, advanced pacemakers, and implantable defibrillators has changed prognosis in HF dramatically. However, 0.5–5% of patients respond poorly to standard therapy and develop chronic advanced HF. Prognosis in advanced HF remains poor, with a 1-year mortality of 25–50% (197). While heart transplantation provides excellent survival and quality of life for eligible patients, only a few can be offered this treatment due to shortage of donor organs. More than 60% of patients are transplanted in high-urgency status, leaving little chance for patients listed for less urgent transplantation. Three times more patients are listed for heart transplantation annually than are actually transplanted, and the mortality rate on the Eurotransplant waiting list in 2013 was 21.7% (198).

Implantable left ventricular assist device (LVAD) technology has improved considerably, and the currently used continuous flow devices may last >10 years in a patient. LVADs have been used for decades in very advanced HF or cardiogenic shock primarily as a bridge to transplantation (BTT). Improvements in technology, especially the advent of smaller, durable continuous flow (CF) pumps, coupled with a shortage of donor hearts for transplantation, have led to use of LVADs in a much broader population of patients in the last 10 years. LVADs are being used increasingly both as BTT and as destination therapy (DT) (Table 12).

Bridge to decision (BTD)/ Bridge to bridge (BTB)	Use of short-term MCS (e.g. ECLS or ECMO) in patients with cardiogenic shock until haemodynamics and end-organ perfusion are stabilized, contra-indications for long-term MCS are excluded (brain damage after resuscitation) and additional therapeutic options including long-term VAD therapy or heart transplant can be evaluated.
Bridge to candidacy (BTC)	Use of MCS (usually LVAD) to improve end-organ function in order to make an ineligible patient eligible for heart transplantation.
Bridge to transplantation (BTT)	Use of MCS (LVAD or BiVAD) to keep patient alive who is otherwise at high risk of death before transplantation until a donor organ becomes available.
Bridge to recovery (BTR)	Use of MCS (typically LVAD) to keep patient alive until cardiac function recovers sufficiently to remove MCS.
Destination therapy (DT)	Long-term use of MCS (LVAD) as an alternative to transplantation in patients with end-stage HF ineligible for transplantation or long-term waiting for heart transplantation.

Table 12. Terms describing various indications for mechanical circulatory support.

(Source: Ponikowski P, Voors AA, Anker SD et al. ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016 Jul 14;37(27):2129-2200.)

Current studies report 1- and 2-year survival after LVAD implantation of 80% and 70%, respectively (199). Current 2- to 3-year survival rates in carefully selected patients receiving the latest continuous flow devices are excellent, and comparable to early survival after heart transplantation (200).

Patients receiving LVAD devices as BTT have a post-transplant survival rate similar or better than those not requiring or receiving bridging (200). Despite technological improvements, bleeding, thromboembolism (both of which can cause stroke), pump thrombosis, driveline infections and device failure remain significant problems and affect the long-term outcome of patients (105).

Evaluation of RV function is crucial since postoperative RV failure greatly increases perioperative mortality and reduces survival to, and after, transplantation. If RV

failure is expected to be potentially reversible, temporary (days to weeks) extracorporeal right ventricular assist device (RVAD) support using a centrifugal pump in addition to LVAD implantation may be considered. For patients with chronic biventricular failure or a high risk for persisting RV failure after LVAD implantation, implantation of a biventricular assist device (BiVAD) may be necessary. Patients requiring long-term BiVAD support must be transplant-eligible, as BiVAD therapy is not suitable for destination therapy. The outcomes of BiVAD therapy are inferior to those for LVAD therapy and therefore the indication for VAD therapy should be discussed before RV function deteriorates. The implantation of a total artificial heart with removal of the native heart should be restricted to selected patients who cannot be treated with an LVAD (unrepairable ventricular septal defect, cardiac rupture) (105).

6.11. Heart Transplantation

Heart transplantation is an accepted treatment for end-stage HF. Although controlled trials have never been conducted, there is a consensus that transplantation significantly increases survival, exercise capacity, quality of life and return to work compared with conventional treatment. Apart from the shortage of donor hearts, the main challenges in transplantation are the consequences of the limited effectiveness and complications of immunosuppressive therapy in the long term. The indications and contraindications for heart transplantation have recently been updated and are summarized in Table 13. It needs to be considered that some contraindications are transient and treatable. While an active infection remains a relative contraindication to heart transplantation, patients with HIV, hepatitis, Chagas disease and tuberculosis can be considered as suitable candidates provided certain strict management principles are adhered to by the transplantation teams. In patients with cancer requiring heart transplantation, a close collaboration with oncology specialists should occur to stratify each patient according to risk of tumour recurrence (105, 201).

Patients to consider	End-stage HF with severe symptoms, a poor prognosis, and no remaining alternative treatment options. Motivated, well informed, and emotionally stable. Capable of complying with the intensive treatment required postoperatively.
Contra-indications	Active infection. Severe peripheral arterial or cerebrovascular disease. Pharmacologically irreversible pulmonary hypertension (LVAD should be considered with a subsequent re-evaluation to establish candidacy). Cancer (a collaboration with oncology specialists should occur to stratify each patient as to their risk of tumour recurrence). Irreversible renal dysfunction (e.g. creatinine clearance <30 mL/min). Systemic disease with multi-organ involvement. Other serious co-morbidity with poor prognosis. Pre-transplant BMI >35 kg/m^2 (weight loss is recommended to achieve a BMI <35 kg/m^2). Current alcohol or drug abuse. Any patient for whom social supports are deemed insufficient to achieve compliant care in the outpatient setting.

Table 13. Indications and contra-indications for heart transplantation.

(Source: Ponikowski P, Voors AA, Anker SD et al. ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016 Jul 14;37(27):2129-2200.)

6.12. Acute heart failure

6.12.1. Definition of acute heart failure

According to the 2016 ESC guidelines of heart failure acute heart failure (AHF) refers to rapid onset or worsening of symptoms and/or signs of HF. It is a life-threatening medical condition requiring urgent evaluation and treatment, typically leading to urgent hospital admission. AHF may present as a first occurrence (de novo) or, more frequently, as a consequence of acute decompensation of chronic HF, and may be caused by primary cardiac dysfunction or precipitated by extrinsic factors, often in patients with chronic HF. Acute myocardial dysfunction (ischaemic, inflammatory or

toxic), acute valve insufficiency or pericardial tamponade are among the most frequent acute primary cardiac causes of AHF. Decompensation of chronic HF can occur without known precipitant factors, but more often with one or more factors, such as infection, uncontrolled hypertension, rhythm disturbances or non-adherence with drugs/diet (Table 17).

Acute coronary syndrome.
Tachyarrhythmia (e.g. atrial fibrillation, ventricular tachycardia).
Excessive rise in blood pressure.
Infection (e.g. pneumonia, infective endocarditis, sepsis).
Non-adherence with salt/fluid intake or medications.
Bradyarrhythmia.
Toxic substances (alcohol, recreational drugs).
Drugs (e.g. NSAIDs, corticosteroids, negative inotropic substances, cardiotoxic chemotherapeutics).
Exacerbation of chronic obstructive pulmonary disease.
Pulmonary embolism.
Surgery and perioperative complications.
Increased sympathetic drive, stress-related cardiomyopathy.
Metabolic/hormonal derangements (e.g. thyroid dysfunction, diabetic ketosis, adrenal dysfunction, pregnancy and peripartum related abnormalities).
Cerebrovascular insult.
Acute mechanical cause: myocardial rupture complicating ACS (free wall rupture, ventricular septal defect, acute mitral regurgitation), chest trauma or cardiac intervention, acute native or prosthetic valve incompetence secondary to endocarditis, aortic dissection or thrombosis.

Table 14. Factors triggering acute heart failure.

(Source: Ponikowski P, Voors AA, Anker SD et al. ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016 Jul 14;37(27):2129-2200.)

6.12.2. Pathophysiology of acute heart failure

Often, the pathophysiological process is initiated as a result of ischemic or myocardial heart disease. Irrespective of its etiology, acute heart failure is usually associated with decreased cardiac output. The heart is no longer able to supply the tissue with enough blood and therefore with sufficient oxygen. Therefore, the tissue metabolism is not adequate both at rest and under stress, which subsequently leads

to pathophysiological changes, such as a downregulation of beta-receptors, sympathoadrenergic stimulation, altered intracellular Ca^{2+} homeostasis, negative force-frequency relationship, and changes in the kidney function (202, 203).

Hypoperfusion leads to a sympathoadrenergic counterregulation (with increased release of epinephrine, norepinephrine), activation of the vasopressor system (via ADH) and a vascular response to induce myocardial failure. Activation of these systems in the early phase of the disease represents a favorable compensation mechanism for providing adequate blood pressure and sufficient organ perfusion. Increasing and prolonged activation thereafter however causes a worsening of the hemodynamic situation and leads to a vicious circle. These must be interrupted to stabilize organ perfusion and circulation again. The failing heart has to fight against the increased resistance in the left ventricular ejection tract, which is caused by an arteriolar constriction and increase in afterload. Concomitant venous vasoconstriction leads to an increase in both right- and left-ventricular preload with a consecutive increase in myocardial wall sterss (204). The resulting hypoperfusion activates proinflammatory cytokines (IL-1β, TNF-α, etc.), which, inter alia, increase capillary permeability and increase the risk of increased fluid influx into the interstitium, leading to further deterioration of peripheral oxygenation. In the maximum version, this leads to interstitial pulmonary edema (205).

6.12.3. Cardiogenic shock

Cardiogenic shock is defined by end organ hypoperfusion as the result of acute heart failure. This includes all cardiac or extracardiac diseases that lead to an immediate dysfunction of the heart and subsequently to a shock condition (206). In most cases, the development of cardiogenic shock is based on acute myocardial infarction. Due to acute systolic, but also diastolic dysfunction results in a sudden reduction in cardiac output (207). Main symptoms are marked by persistent hypotension with systolic blood pressure values below 90 mmHg of more than 30 minutes duration and an increased heart rate above 80/min, clinical signs of organ hypoperfusion in the form of reduced urinary output (<0.5 ml/kg/h), conspicuously cold extremities and mental changes such as agitation or confusion. However, even normotensive blood pressure values and pronounced tachycardia can mask an already occurred inferior perfusion. The normal or elevated blood pressure values result here due to an

endogenous vasoconstriction, which leads to a further reduction of cardiac output by increased peripheral resistance. Invasively measured parameters (such as a CI of <1.8 L/min/m² body surface area with a pulmonary capillary occlusion pressure PCWP of >18 mmHg) are already clear diagnostic markers. The prognosis of cardiogenic shock is still serious. Despite the use of all interventional and therapeutic options, mortality rates are about 60% (208, 209). In patients with acute myocardial infarction, cardiogenic shock due to infarction remains the leading cause of death despite immense advances in interventional care (with a mortality rate of approximately 40%) (209, 210).

7. MYOCARDIAL DYSFUNCTION AND LOW CARDIAC OUTPUT SYNDROME AFTER CARDIAC SURGERY

Over the past decade, there has been a significant decline in cardiac surgery associated mortality, despite an increase in procedural complexity. Although the average perioperative mortality currently is 1-2%, the rate of major cardiovascular complications remains high (211). Low cardiac-output syndrome (LCOS) is the most common and the most serious complication and is associated with increased morbidity, short- and long-term mortality, and healthcare resource utilization. This syndrome is characterized by decreased heart pump function, leading to reduced oxygen delivery (DO_2) and subsequent tissue hypoxia. The most common definition of LCOS also includes reduction in the CI to <2.0 L/min/m^2 and a systolic blood pressure of <90 mmHg, in conjunction with signs of tissue hypoperfusion (cold periphery, clammy skin, confusion, oliguria, elevated lactate level) in the absence of hypovolemia. The use of inotropic agents or mechanical circulatory support always is required to improve patient hemodynamics (212, 213).

Acute renal failure, neurologic and pulmonary complications and atrial fibrillation are the most common consequences of LCOS. Furthermore, mortality among patients who develop LCOS after cardiac surgery can exceed 20% (213, 214). Numerous demographic and intraoperative and postoperative factors might be responsible for the development of LCOS (213, 215). High-risk cardiac patients, especially those with preoperative LV systolic dysfunction (LVEF<35%), develop LCOS more frequently than do patients with a normal LVEF and must receive special attention during the perioperative period (216).

Myocardial dysfunction following cardiac surgery using extracorporeal circulation (ECC) is often overlooked not only in patients with impaired preoperative myocardial function but also in patients with normal EF (217).

Together with the reduction of the cardiac index, both the left and right ventricular ejection fraction is reduced and even up to 35-75% compared to the preoperative values (218). The factors contributing to the onset of cardiac dysfunction are myocardial ischemia due to aortic cross-clamping, inadequate cardioprotection, hypothermia and cardioplegia, surgical trauma, incomplete surgical reperfusion, systemic inflammatory responses including complement cascade activation, ischemia-reperfusion injury, alter at ions in signal transduction systems, as well as the extended use of inotropic agents (219-223). The paradox is that while many of the above-mentioned techniques are used to limit myocardial damage, they can in themselves induce it (218).

Cardiac dysfunction after ECC can be described as a form of myocardial stunning (53, 224). The heart undergoing surgery is subjected to reperfusion ischemia injury at various phases of the operation resulting in Ca^{2+} accumulation and generation of free ROS in the cytoplasm of the myocardial cell and the edema of these cells (225). The generally described stunning refers to a restricted region of the myocardium (regional stunning). The myocardial dysfunction after ECC concerns however the whole heart (global dysfunction). The global systolic function of the heart is impaired and the dysfunction includes both ventricles (226).

Weaning from cardiopulmonary bypass (CPB) is a crucial phase in which myocardial dysfunction can be fully manifested and consequently inotropic support is needed. Typically myocardial dysfunction after CPB is biphasic. Recovery of the myocardium after the initial decline is followed by a period of further dysfunction reaching the lowest point 3-6 hours after the end of CPB. Usually the time required for complete recovery of the myocardium is 8-24 hours, although in patients with impaired systolic function preoperatively this time may be longer. This knowledge is particularly important because it determines the decision to initiate non-inotropic support as well as its dosis and duration (219).

Ventricular dysfunction is not just about systolic function, as diastolic function is also severely influenced. The wall compliance decreases and the volume-pressure curve of the diastole is shifted upward, resulting in either insufficient ventricular filling or

sufficient ventricular filling with increased pressures that cause the reduction in coronary driving pressure causing subendocardial ischemia (217).

After the removal of aortic clamp, the beginning of reperfusion and rewarming of the heart in cases of hypothermic cardioplegic arrest, myocardial function gradually improves (217). Myocardial conditions that were chronic ischemic and were hibernating are now adequately perfused through the new grafts and may show a spectacular improvement in their functionality, while some other areas that were adequately perfused preoperatively through the coronary arteries may exhibit a stunning pattern. Eventually, areas of active ischemia may coexist due to a mechanical problem or a lack of complete reperfusion for technical reasons (217).

The total systolic function continues to improve after exiting for some time, but at some point in the next few hours it can deteriorate again. The cause of this phenomenon is not clear and includes mechanisms such as closure of the sternum which can cause tamponade conditions. Other possible reasons may be an incomplete rewarming and further hypothermia during transfer to the intensive care unit, embolism of air or thrombus in the coronary circulation, myocardial edema due to mechanical manipulations or due to reduced osmotic pressure or even the continuation of reperfusion injury (217). CPB time also plays an important role. It has been demonstrated that when the CPB time exceeds 150min the rates of myocardian dysfunction and demand on inotropic support are higher, even in patients with normal systolic function (227).

As mentioned before, the following pathophysiologic mechanisms of LCOS should be highlighted:

i. Left ventricular LV systolic dysfunction
ii. Right ventricular (RV) systolic dysfunction
iii. Diastolic dysfunction, also called heart failure with preserved ejection fraction

The aforementioned mechanisms may occur isolated or in combination. Conditions such as valvular heart disease, pulmonary hypertension, mechanical valve dysfunction, and respiratory failure, also contribute to LCOS development (Figure 18) (216).

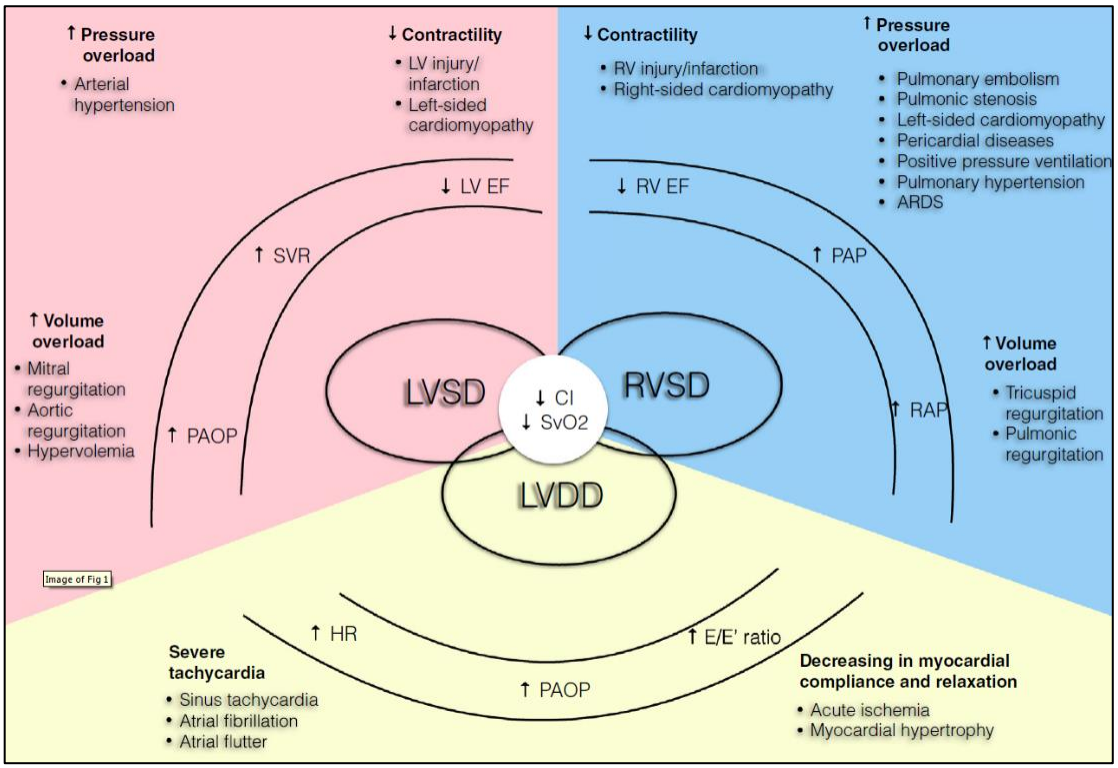


Figure 18. A schematic presentation of the pathophysiology of postoperative LCOS. The most common causes and typical signs are presented.

(Source: Lomivorotov VV, Efremov SM, Kirov MY, Fominskiy EV, Karaskov AM. Low-Cardiac-Output Syndrome After Cardiac Surgery. J Cardiothorac Vasc Anesth. 2017 Feb;31(1):291-308.)

7.1. Left ventricular systolic dysfunction

LV function is a derivative of preload, afterload, and contractility; LV systolic dysfunction occurs due to loss of functional myocytes or a decrease in their function. In most cases, the loss of functional myocytes develops as a result of necrosis due to impaired coronary circulation and ischemia/reperfusion injury or the less-understood phenomenon of apoptosis. A loss of function of vital myocytes commonly is transient during stunning or may be refractory to reversal with conditions such as infection; tachycardia; cardiac valvular disease; metabolic abnormality (acidosis, hypoglycemia, hypocalcemia); exposure to cardiac toxins; idiopathic dilated cardiomyopathy; and genetic disorders (familial dilated cardiomyopathy, hypertrophic cardiomyopathy, muscular dystrophies). The impairment of cardiac response to preload leads to dramatic decreases in CO and oxygen delivery to other organs, increased left atrial pressure and capillary wedge pressure, and cardiogenic pulmonary edema. Although

the LV usually works against relatively high systemic arterial pressure, the significant afterload increase also may induce LV systolic dysfunction (216).

7.2. Left ventricular diastolic dysfunction

LCOS sometimes is associated with preserved LVEF. In such cases, the contractile function of the myocardium is diminished, despite preserved global systolic performance. These conditions result from the inability of the ventricular chamber to accept an adequate volume of blood, despite normal preload, and present as diastolic dysfunction. However, diastolic dysfunction may be accompanied by either impaired or preserved ejection fraction. From a pathophysiologic perspective, diastolic dysfunction is characterized by abnormal relaxation and filling of the LV during the diastolic phase of the cardiac cycle that may be caused by the following mechanisms: 1) severe tachycardia (upon atrial fibrillation), 2) decreased myocardial compliance, and 3) impaired ventricular relaxation. The processes intimately involved in the development of diastolic dysfunction, at the cardiomyocyte level, relate to calcium removal from the cytosol and calcium homeostasis, the adequacy of cross-bridge detachment, and intrinsic functional cytoskeletal element disorders (228).

Diastolic dysfunction is a widespread phenomenon, occurring in up to 70% of cardiac patients postoperatively. Despite its high prevalence, diastolic dysfunction alone often is insufficient to induce the development of acute heart failure; however, in combination with other predisposing factors, such as atrial fibrillation, impaired coronary perfusion, and arterial hypertension, it may lead to decompensation. Diastolic dysfunction therefore is believed to be an early sign of myocardial ischemia (229, 230).

The close relationship between the systolic and diastolic functions of the LV should be acknowledged. Thus, inotropic catecholamine stimulation affects both systole and diastole and may enhance diastolic dysfunction, whereas reduced LVEF leads to increased end-systolic volume and prolongs the diastolic phase of the cardiac cycle (216, 230).

7.3. Right ventricular dysfunction

The principal pathophysiologic mechanisms of RV dysfunction include increased RV preload, increased RV afterload, impaired right coronary artery perfusion, and decreased contractility (231). The specific features of RV perfusion and their alterations during increased pulmonary artery pressure are important to understand. Physiologically, perfusion of the right coronary artery, in contrast to the left coronary artery, occurs during both diastole and systole. Under conditions of pulmonary hypertension, the RV pressure increases and leads to decreased right coronary artery perfusion, explaining why diastolic arterial pressure maintenance is highly important for providing optimal left and right coronary blood flow (232).

In postoperative settings, RV dysfunction often develops due to a combination of mechanisms. Thus, cardiac patients encounter many conditions associated with RV failure. Perioperative RV ischemia and infarction are major causes of contractility impairment. Tricuspid or pulmonic regurgitation leads to excessive volume preload, whereas left-sided valvular disease or cardiomyopathy, pulmonary hypertension or embolism, acute respiratory distress syndrome, and high positive-pressure ventilation are common causes of pressure overload. Taking into account that the RV normally provides low-pressure perfusion of the pulmonary vasculature, it is highly sensitive to even moderate pulmonary artery pressure increases. RV failure may develop due to pulmonary hypertension or contractile impairment associated with a rapid progression of RV dilation, resulting in a rise in end-diastolic RV pressure. These alterations lead to an interventricular septum shift toward the already underfilled LV chamber, reducing LV preload and decreasing CO (233, 234).

8. CARDIOPROTECTION IN CARDIAC SURGERY

8.1. Cardioplegia

Since the beginning of cardiac surgery in the 1950s, multiple techniques have been used to protect the heart during the surgical requirement for elective global ischemia (and the still, relaxed, bloodless field that this provides the surgeon for repair of the lesion). Most of these techniques have been discarded (235). The principles of successful myocardial protection consist of a rapid and complete induction of

cardioplegic cardiac arrest, minimization of metabolic alterations of the myocardium during ischemia by adding subtrates to cardioplegic solution, and adequate reperfusion with post-cardiac arrest recovery. The ideal cardioplegic substance leads to a rapid diastolic cardiac arrest, which is persistent and rapidly reversible when needed. It has no toxic side effects on the heart or other organs (236).

The resting membrane potential of the cardiomyocyte is approximately -85 mV. If external (adjacent cells, pacemaker stimulation, mechanical stimulation) or internal (pacemaker cell) stimulation increases the membrane potential >-75 mV, a rapid increase in sodium (I_{Na}) initially determines a rapid increase in membrane potential. From a potential of approximately -65 mV I_{Na} is deactivated again. At a threshold potential of approximately -40 to -35 mV open L-type calcium channels ($I_{Ca,L}$). The short-term rapid sodium influx leads to complete depolarization. Prolonged calcium influx maintains the typical plateau phase of depolarization (Figure 19). The intracellular calcium induces via sarcoplasmic ryanodine receptors (RyR2) the influx of sarcoplasmic calcium into the cytosol (calcium-triggered calcium release). The strongly increased cytosolic calcium level induces contraction of the heart muscle cell via bonds to troponin C. Restrictive electrical potential is restored at the end of the action potential by various, sometimes ATP-dependent calcium, sodium and potassium transport processes (236).

This results in various targets for cardioplegia (Figure 19): extracellular hyperkalaemia can depolarize the membrane potential, thus preventing further depolarizations. Potassium channel openers (e.g. adenosine) can shift the membrane potential towards hyperpolarization so that the threshold potential cannot be reached. The I_{Na} can be blocked by class I antiarrhythmic drugs. The calcium influx and thus the electromechanical coupling can be inhibited by the following measures:

- extracellular calcium depletion (e.g., Bretschneider cardioplegia) or
- Blocking I_{Ca}, L using calcium antagonists (verapamil, diltiazem)

The current gold standard, established over 30 years ago, is hyperkalemic (moderately increased extracellular potassium) cardioplegia; this technique revolutionized cardiac surgery, allowing significant surgical advancement with relative safety (235).

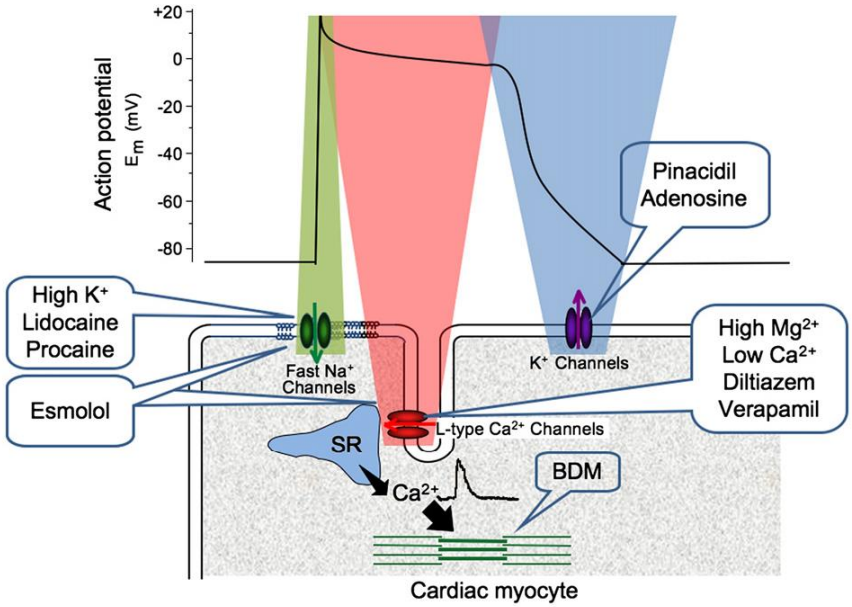


Figure 19. The potential cellular targets for cardioplegic arrest and their influence on the action potential of the cell membrane.

(Source: Chambers DJ, Fallouh HB. Cardioplegia and cardiac surgery: pharmacological arrest and cardioprotection during global ischemia and reperfusion. Pharmacol Ther. 2010 Jul;127(1):41-52.)

8.1.1. Intracellular vs. extracellular type

Cardioplegic solutions with an electrolyte composition similar to that of the cytoplasm are referred to as intracellular type solutions ("Bretschneider solution" in Europe, "Roe's cardioplegic solution" in the United States). They have a low sodium concentration and thus lead to a depletion of extracellular sodium to the loss of cell membrane potential, so that no triggering of action potentials is possible. Extracellular type cardioplegic solutions (including St. Thomas, Calafiore, Buckberg) contain high levels of potassium and low sodium and induce depolarized cardiac arrest. For this purpose, a target range between -65 and -35 mV is sought, since I_{Na} and $I_{Ca,L}$ are deactivated in this area. This prevents depolarization and calcium overload of the cardiomyocytes. This area is reached at an extracellular potassium concentration between 10 and 30 mmol/l (236).

8.1.2. Crystalloid solutions vs. blood cardioplegia

Blood cardioplegia uses the patient's own blood, mixed with cardioplegic solution. The following advantages of blood cardioplegic solutions are seen: Reduction of

myocardial ATP depletion, buffering properties and radical scavenging property. The osmotic properties of proteinaceous blood cardioplegia reduce myocardial edema formation. Potential disadvantages of blood cardioplegia result from the limited view in the surgical field during the intermittent administration of cardioplegia (237). Several randomized studies comparing blood to crystalloid cardioplegia demonstrated a reduced rate of postoperative LCOS, improved contractility, and lower release of myocardial necrosis parameters following the use of blood cardioplegia. Hard endpoints such as mortality, kidney failure and heart failure were not significantly affected (236, 238).

8.1.3. Warm vs. cold solutions

The myocardial oxygen demand, based on the heart weight (at rest at 37°C about 10 ml/100g/min), is already considerably reduced (to about 5 ml/100g/min) and due CPB. Cardioplegic solutions reduced to approximately 10% of baseline (1 ml/100g/min). By cooling the myocardium, this reduction can be extended (reduction by 50% for each 10°C cooling, Van't Hoff rule), so that at a temperature of the myocardium of 10°C still an oxygen requirement of 0.3 ml/100g/min exists. The myocardial ischemia tolerance extends reciprocally (239). From this it has long been deduced that the cooling of the myocardium must be an indispensable part of the myocardial protection. However, cooling causes endothelial dysfunction, myocardial edema formation by inactivation of Na^+/K^+-ATPase, reduction of membrane stability and left shift of the oxygen binding curve (240). Cold-blood cardioplegia and topical cooling may also cause postoperative conduction disturbances and arrhythmias (241). More recent data show no significant difference between warm and cold blood cardioplegia in terms of clinical and laboratory outcome measures. There was a tendency for improved results when using warm-blooded cardioplegia (236, 242, 243).

8.1.4. Polarized vs. depolarized arrest

As mentioned before almost universally cardioplegic concepts involve using a hyperkalemic cardioplegic solution and these solutions have become the gold standard for myocardial protection for more than 20 years. Despite the extensive and continued research aimed at improving these basic hyperkalemic cardioplegic

solutions, patients undergoing surgery almost invariably experience some degree of postoperative dysfunction. It is likely that this relates to the depolarizing nature of hyperkalemic solutions, which results in ionic imbalance caused by continuing transmembrane fluxes and the consequent maintenance of high energy phosphate metabolism, even during hypothermic ischemia (244). A potentially beneficial alternative to hyperkalemic cardioplegia is to arrest the heart in a "hyperpolarized" or "polarized" state, which maintains the membrane potential of the arrested myocardium at or near to the resting membrane potential. At these potentials, transmembrane fluxes will be minimized and there should be little metabolic demand, resulting in improved myocardial protection. Several studies have explored these alternative concepts for myocardial protection. The use of compounds such as adenosine or potassium channel openers, which are thought to induce hyperpolarized arrest, have demonstrated some improved protection after normothermic, or short periods of hypothermic, ischemia when compared to hyperkalemic (depolarized) arrest (244). “Magnesium cardioplegia” and “esmolol cardioplegia” has been shown to exert superior protection with comparable safety profiles to that of hyperkalemic cardioplegia (245). However, the significant clinical superiority of these techniques is highly debated and these alternative techniques require further examination and investigation to challenge the traditional view that hyperkalemic arrest is best.

8.2. Volatile Anesthetics

Volatile halogenated anesthetics are used widely worldwide for anesthetic management of cardiac procedures. According to the CABG guidelines from the American College of Cardiology Foundation and the American Heart Association, volatile anesthesia can be useful in reducing the risk of perioperative myocardial ischemia and infarction (class of recommendations IIa; Level of Evidence A) (246). A meta-analysis of 22 studies involving 1,922 patients showed that a halogenated anesthetic regimen was associated with improved outcomes after cardiac surgery. Specifically, volatile anesthetics were associated with significant reductions in the incidence of myocardial infarctions and mortality. Moreover, the need for inotropic support also was reduced significantly in the volatile anesthetic group (216, 247).

8.3. Endogenous therapeutic strategies for cardioprotection

Inadequate cardioprotection during cardiac surgery, particularly in high-risk patients, is associated with worse clinical outcomes. Therefore, novel therapeutic strategies are required to reduce and prevent post-surgical complications. In this regard, it is possible to 'condition' the heart to protect itself from the detrimental effects of acute IRI by subjecting it to brief non-lethal episodes of ischaemia and reperfusion (248, 249). Importantly, the 'conditioning' stimulus may be applied either prior to [ischaemic preconditioning (IPC)], (250) after the onset of (ischaemic perconditioning), (251) or at the end of the index ischaemic event and at the time of reperfusion (ischaemic postconditioning), (252) making it possible to intervene at several different time points during cardiac surgery.

8.3.1. Ischaemic preconditioning

In 1986, Murry et al. first discovered that the heart could be 'conditioned' to protect itself from MI, using brief non-lethal cycles of myocardial ischaemia and reperfusion (250). This phenomenon, which has been termed IPC, has been shown to offer ubiquitous cardioprotection in all animal species tested using a wide variety of experimental in vivo and in vitro IRI models (248). IPC was the first 'conditioning' strategy to be applied in the clinical setting of CABG surgery. Patients randomized to receive IPC at the time of surgery had preserved ATP levels in ventricular biopsies (253) and less peri-operative myocardial injury as evidenced by lower serum troponin concentrations (254). A number of clinical studies have investigated IPC in the setting of CABG surgery, showing that IPC was associated with fewer ventricular arrhythmias, less inotropic requirements, and a shorter intensive care unit stay (248, 255).

Early preconditioning occurs 5-15 minutes after the stimulus and lasts 1-2 hours (256). Delayed or second window preconditioning occurs 24 hours after the stimulus and lasts for 72 hours (257). Different mechanisms are involved in the manifestation of the two types of preconditioning. In the early preconditioning during the stimulation phase a number of mediators (norepinephrine, bradykinin, endothelin, opioids, and adenosine) are released, promoting protein kinase C (PKC) movement in the cellular membrane and mitochondria. During the ischemic phase the released adenosine activates the PKC which causes phosphorylation of the K^+-ATP channels. The result

of this phosphorylation is the cell membrane hyperpolarization, the shortening of phase 2 of the action potential and ultimately the decrease in calcium influx, which ultimately provides cardioprotection (258, 259). In delayed preconditioning, modified gene transcription and translation leads to the synthesis of endogenous proteins such as acute phase proteins, proto-oncogenes and various antioxidants. The activation of PKC plays an important role by migrating to the perinuclear area where it promotes gene expression and activates mitochondrial protein kinase (MAPK). The acute phase proteins promote the protein synthesis while at the same time contribute to the degradation of the due to ischemia damaged proteins. Another important mechanism that is involved is the NO synthesis and its effect on the K^+-channels (260).

8.3.2. Remote ischaemic preconditioning

The major disadvantage of IPC as a cardioprotective strategy in patients undergoing CABG surgery is that it requires the 'conditioning' stimulus to be applied directly to the heart, which may not be practical and could actually be harmful due to the risk of arterial thrombo-embolism from cross-clamping and declamping the aorta. The discovery that the 'conditioning' stimulus could be applied to an organ or tissue away from the heart (a phenomenon termed remote ischaemic conditioning, RIC), (261) and the demonstration that the 'conditioning' stimulus could be applied non-invasively using a standard blood pressure cuff placed on the upper or lower limb has facilitated the translation of RIC into the clinical setting (262). The actual mechanism underlying RIC is currently unclear but has been attributed to either a humoral or neurohormonal pathway which links the remote organ or tissue to the heart (262, 263). Several studies have shown some positive effects of this method, especially if combined with volatile anesthetics (264-266). Further clinical studies are however required to characterize the RIC stimulus and to investigate the patient population which is most likely to benefit from this therapeutic strategy.

8.3.3. Ischaemic postconditioning

In 2003, Zhao et al. first demonstrated that the ischaemic canine heart could be 'conditioned' at the onset of myocardial reperfusion, by interrupting coronary reflow with short-lived episodes of LAD occlusion and reflow (252). The mechanistic

pathways underlying ischaemic postconditioning (IPost) cardioprotection are complex and some of them are similar to those utilized by IPC (267). Ischaemic postconditioning has been applied in pediatric cardiac surgery showing some promising benefits (268, 269). Clearly, the risk of clamping the aorta in younger patients with relatively non-atherosclerotic aortas is not as great when compared with adult patients undergoing CABG or valve surgery. Whether this invasive cardioprotective strategy can impact on clinical outcomes in patients undergoing cardiac surgery remains to be determined (248).

9. RISK STRATIFICATION IN CARDIAC SURGERY

For each intervention on patients, the risk and benefit must be weighed. This is becoming increasingly important in the field of cardiac surgery in the context of demographic change. Over the last decades various scoring systems have been established which, based on known predictors of perioperative mortality, enable a risk stratification in cardiac surgery. In the USA, the Society of Thoracic Surgeons (STS) score has established itself. In Europe, the European System for Cardiac Operative Risk Evaluation (EuroSCORE) and its further development EuroSCORE II is generally used more frequently.

9.1. EuroSCORE I & II

To better estimate the perioperative mortality risk in cardiac surgery, the EuroSCORE model was developed (270). There are an additive and a logistic version in which 17 variables that significantly influence the intraoperative and postoperative course are included. In the case of the original additive EuroSCORE, each variable was assigned a score of 0-3 and the individual results were added together (271, 272). The assigned value varied depending on Significance for the operation, so that the gender "female", for example, the value of 1 and a LVEF <30% has been assigned a value of 3. This weighting of the individual factors allowed the perioperative mortality risk to be estimated fairly accurately. Further development of the original idea led to the production of the logistic EuroSCORE II, which included not only the mere presence but also the extent of risk factors (e.g., pulmonary hypertension, graduated to none, moderate and severe), thus making more efficient risk assessment possible,

especially for high-risk patients. The logistic EuroSCORE II concept was published in 2003, it is the continuation of the additive EuroSCORE of 1999 and the score was launched at the 2011 EACTS meeting in Lisbon (272). Based on the scores obtained, the EuroSCORE gives a percentage value that reflects the estimated perioperative mortality. In general, the EuroSCORE II values of 0-2% are considered to be low, those of 2-5% to medium, and those of >5% to high perioperative risks.

9.2. STS score

The STS score was published in 2007 and has been available since then as well as the EuroSCORE as an online calculator (273). Like the EuroSCORE, the STS score also uses preoperative risk factors to calculate, among other things, postoperative mortality risk. However, the risk factors used here are somewhat more detailed. The collection of these extended risk factors allows the STS score to make various other predictions in addition to postoperative mortality, such as the probability of a reoperation or a prolonged ventilation time. However, the prediction of these additional endpoints only applies to patients who undergo isolated CABG surgery (274). Despite the large number of additionally considered risk factors, both the EuroSCORE II and the STS score show a comparably good discrimination between high- and low-risk patients, but limited accuracy, especially in the prediction of high-risk patients (275). Furthermore, the accuracy and discrimination of any scores vary with respect to the different ways to intervene in different heart conditions. Above all, the predicted mortality often exceeds the observed mortality by a factor of 2. Further revisions of these scores in the future are probably indicated, especially since this is based on a study population, which had been operated about several years ago and that in the meantime, there has been a continuous improvement in both surgical techniques and perioperative patient care (274).

10. MECHANICAL CIRCULATORY SUPPORT

For patients with either chronic or acute HF who cannot be stabilized with medical therapy, MCS systems can be used to unload the failing ventricle and maintain sufficient end-organ perfusion. Patients in acute cardiogenic shock are initially

treated with short-term assistance using extracorporeal, non-durable life support systems so that more definitive therapy may be planned (105).

10.1. Intraaortic balloon pump

The first publication of intra-aortic balloon counter-pulsation appeared in 1962 by S. Moulopoulos (276, 277). The device and the balloons were then developed for commercial use between 1967 and 1969. The first clinical implant was performed at in 1967. The patient, a 48-year-old woman, was in cardiogenic shock and unresponsive to traditional therapy. An intraaortic balloon pump (IABP) was inserted by a cut down on the left femoral artery. Pumping was performed for approximately 6 hours. Shock reversed and the patient was discharged. Since then it consists the most widely used mechanical support system in cardiac infarction patients in cardiogenic shock, for more than five decades (278-281). The main mode of action of the IABP is the reduction of afterload, which relieves the work of the ventricle and additionally causes an increase in coronary perfusion (280).

A balloon of about 40 ml is introduced in the Seldinger technique and implanted percutaneously over the femoral artery. The balloon is advanced under X-ray control or transesophageal echocardiography until the transition of the aortic arch into the descending aorta, the tip of the balloon coming to lie about two centimeters below the ostium of the left subclavian artery and ideally ends in the abdominal aorta above the level of the renal arteries. The functionality of the IABP is based on the principle of counterpulsation. The balloon is filled with helium gas during diastole, triggered by ECG or blood pressure measurement (281, 282). On the other hand, the sudden deflation of the balloon immediately before systole leads to a reduction in the afterload for the left ventricle, resulting in a moderate increase in left ventricular ejection fraction and cardiac output. In addition, left ventricular end-diastolic volume and oxygen consumption are reduced (279, 282, 283). This procedure enjoyed a Class 1 recommendation by 2012 and 2013 in both the European and US guidelines (105, 284, 285). Despite these clear recommendations of the professional associations, it was observed in various surveys and registries that only around 20-30% of patients in cardiogenic shock were treated with IABP (286). For years, the effectiveness and role of the IABP has been controversially discussed.

The IABP -Shock II trial in 2009, showed no significant reduction in 30-day mortality in comparison to the optimal medical therapy (OMT) in patients with cardiogenic shock in the context of myocardial infarction. In addition, there were no differences in secondary endpoints, such as serum lactate, renal function, SAP (Simplyfied Acute Physiology Score) II, CRP, levels of catecholamine doses, and duration of catecholamine infusions. The evaluation of the safety endpoints, e.g. However, severe bleeding, peripheral ischemic complications, sepsis, and insult revealed that IABP support is considered "safe" in cardiogenic shock due to infarction (287-289). In the current recommendations, the indication for IABP insertion in cardiogenic shock has been downgraded to grade IIIB and the routine use of IABP in cardiogenic shock is no longer recommended (105, 279, 286). It should be emphasized that a sensible use of the IABP requires a measurable intrinsic performance of the left ventricle. In the case of a severely restricted pumping function or complete arrest of the left ventricle, other systems which ensure adequate organ perfusion and thus possibly prevent the formation of a multi-organ failure or stabilize the patient sufficiently to carry out diagnostic and therapeutic procedures in the sense of "bridge-to-diagnostic" concept is considered (290).

10.2. Impella® pump

The companies Abiomed and Impella Cardiosystems offer the axial rotary pump (Impella®) in versions with 2.5 L/min and 5 L/min pumping power. The first can be placed percutaneously in the left ventricle at a diameter of 12 French across the femoral artery through the aortic valve, the second must be open surgically implanted. The blood is then aspirated from the left ventricle and delivered into the ascending aorta. On the one hand, this improves the flow in the coronary arteries, on the other hand, the myocardial oxygen consumption seems to be lowered (291, 292).

Impella® offers a better left ventricular relief without increase in afterload compared to other mechanical support systems (293). In the ISAR-SHOCK 2008 study, the Impella® 2.5 and intra-aortic balloon counterpulsation in patients with cardiogenic shock after myocardial infarction were prospectively randomized for placement, hemodynamic effects and mortality. In the first 30 minutes, a significantly earlier increase in cardiac index was observed in the Impella® group. However, statistically significant differences in disease progression and mortality were not observerd (294,

295). Disadvantages are the higher costs compared to the IABP, the need for surgical implantation of the Impella® 5, the increased hemolysis rate due to the high rotational speeds of up to 30,000 rpm and the insufficient support of the cardiac output of the small Impella® in cardiogenic shock (296, 297).

10.3. TandemHeart®

The TandemHeart® system consists of a low-prime-volume (10 cm^3) extracorporeal centrifugal pump with flow rates of up to 5 L/min. The inflow cannula is inserted into the femoral vein and is advanced across the interatrial septum into the left atrium; the outflow cannula returns oxygenated blood to the femoral artery. By eliminating an external membrane oxygenator, the foreign surface of the extracorporeal circulation is significantly reduced. This system is therefore primarily suitable for patients with left ventricular failure without concomitant severe pulmonary dysfunction (298). Compared to IABP, TandemHeart® appears to provide better hemodynamic stabilization with improved cardiac index, mean arterial pressure and reduced cardiac work with consecutively lower cardiac oxygen consumption. However, higher rates of complications, especially bleeding, were observed at the same time (299, 300).

10.4 Extracorporeal life support systems (ECLS)

This critical evaluation and downgrading of the indications of the IABP has created a new impetus to reflect on the role of alternative short-term mechanical support devices, such as veno-arterial extracorporeal life support (VA-ECLS), which can provide partial or full circulatory support (301, 302). In addition, VA-ECLS can provide respiratory support in patients suffering from severe, combined cardiac and pulmonary failure. Studies have indicated beneficial effects in patients with cardiogenic shock in acute on chronic heart failure and cardiac arrest (303).

In a VA-ECLS circuit, central venous blood is drained, relayed through an extracorporeal pump and oxygenator and then re-infused into the arterial compartment. A modern ECLS circuit consists of several components including venous and arterial cannulas, tubing, a membrane oxygenator with gas blender, a continuous-flow centrifugal pump and a heat exchanger to compensate for extracorporeal heat loss. VA-ECLS was originally derived from (CPB) but differs in

several aspects (301). In cardiogenic shock, arterial and venous femoral percutaneous cannulation via the Seldinger technique allows for rapid initiation of VA-ECLS without need for a central approach via sternotomy. Furthermore, it can be performed virtually everywhere inside and outside the hospital environment (304). Consistent with Poiseuille's law, narrower, longer cannulas result in larger resistance, which may in turn reduce extracorporeal blood flow or necessitate pressures outside the clinically acceptable range for a given pump speed. Drainage of central venous blood can best be achieved through relatively large 21–25 French (Fr) multistage cannulas. Arterial cannulas are narrower (15–19 Fr) and shorter and allow injection of oxygenated blood retrogradely into the descending aorta. Centrifugal pumps, being used in modern VA-ECLS circuits, are designed to provide a flow of 60–120 ml/kg/min (range of 2–10 l/min). Maximum achievable extracorporeal blood flow depends on many other ECLS circuit and patient characteristics, such as caval vein diameters, volume status, thoraco-abdominal pressures, flow capacity of the oxygenator and maximally tolerable negative and positive pressures (±300 mm Hg). Membrane oxygenators are made up of selectively permeable membranes, facilitating blood and gas flow to allow gas exchange (301).

The main goal of VA-ECLS in refractory cardiogenic shock is to provide immediate circulatory and respiratory stabilisation, while accounting for sufficient cardiac unloading. Although no randomised controlled trials exist on the effectivity of VA-ECLS, observational studies have shown survival benefits in comparison to conventional therapy and Class IIb and Class IIa recommendations have been specified by European (305) and American (306) guidelines, respectively. To maximise the potential of cardiac recovery and prevent impending multi-organ failure, early initiation of VA-ECLS has been proposed (307). Observational evidence further suggests that in Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) level 1 patients (so called 'crash-and-burn' patients), temporary clinical optimisation with VA-ECLS prior to left ventricular assist device (LVAD) support improves outcome as compared to direct implantation of a permanent LVAD (308). The main indications and contraindication regarding the application of ECLS are summarized in table 15.

VA-ECLS is an increasingly used cardiac and circulatory support modality, which can provide immediate stabilisation in patients with otherwise refractory cardiogenic shock. In the absence of randomised trials, observational studies have suggested a

reduction in mortality as compared to conventional treatment. VA-ECLS should be taken into consideration in well-selected cases. Management of VA-ECLS is complex and requires constant support of trained personnel. For this reason, the application of this support technique should be confined to centres with sufficient experience, ongoing exposure and a close and well-organised multidisciplinary team (301).

Extracorporeal Life Support (ECLS)	
Indications	**Contraindications**
Refractory cardiogenic shock due to: • Acute coronary syndrome (with or without mechanical complications) • Acute valvular heart disease • Acute deterioration of non-ischaemic cardiomyopathy • Acute myocarditis • Tako Tsubo cardiomyopathy • Intractable arrhythmias • Pulmonary embolism	**Absolute:** • Recent intracranial haemorrhage or infarction • Uncontrolled coagulopathy • Multi-trauma with high risk of bleeding • Irreversible cardiac disease with no prospect for permanent ventricular assist device implantation or heart transplantation • Aortic dissection and severe aortic regurgitation • Unrecoverable heart and not a candidate for transplant or VAD • Chronic organ dysfunction (emphysema, cirrhosis, renal failure) • Compliance (financial, cognitive, psychiatric, or social limitations) • Prolonged CPR without adequate tissue perfusion.
Refractory cardiac arrest	**Relative:** • Contraindication for anticoagulation • Advanced age • Obesity
Post-cardiotomy cardiogenic shock	

Table 15. Indications and contraindications for ECLS.

(Source: Modified from C. L. Meuwese, et al. Extracorporeal life support in cardiogenic shock: indications and management in current practice. Neth Heart J. 2018 Feb; 26(2): 58–66.)

11. INOTROPIC AND VASOACTIVE AGENTS IN THE TREATMENT OF ACUTE AND POSTOPERATIVE HEART FAILURE

The ideal positive inotropic agent should be able to increase the contractility of both ventricles without causing a significant increase of the heart rate, preload, afterload and metabolic requirements of the myocardium. It should not affect diastolic function and not reduce coronary perfusion pressure and thus blood supply to the heart (309). It should also have a rapid onset of action, a short half-life and a short time of titration. Unfortunately, not only is there no ideal inotropic agent but also commonly used agents are always accompanied by restrictions on their use (309).

11.1. Catecholamines

Catecholamines are the most widely used agents in clinical practice and exert their positive inotropic activity through the stimulation of β-adrenergic receptors.

Catecholamine are monoamine neurotransmitters, an organic compound that has a catechol (benzene with two hydroxyl side groups next to each other) and a side-chain amine. Catechol can be either a free molecule or a substituent of a larger molecule, where it represents a 1,2-dihydroxybenzene group. Catecholamines are derived from the amino acid tyrosine, which is derived from dietary sources as well as synthesis from phenylalanine. Catecholamines are water-soluble and are 50%-bound to plasma proteins in circulation. Through a specific Protein C, the adenyl cyclase of cAMP, the end result of their action is an increase in intracellular concentration of Ca^{2+} (Figure 20).

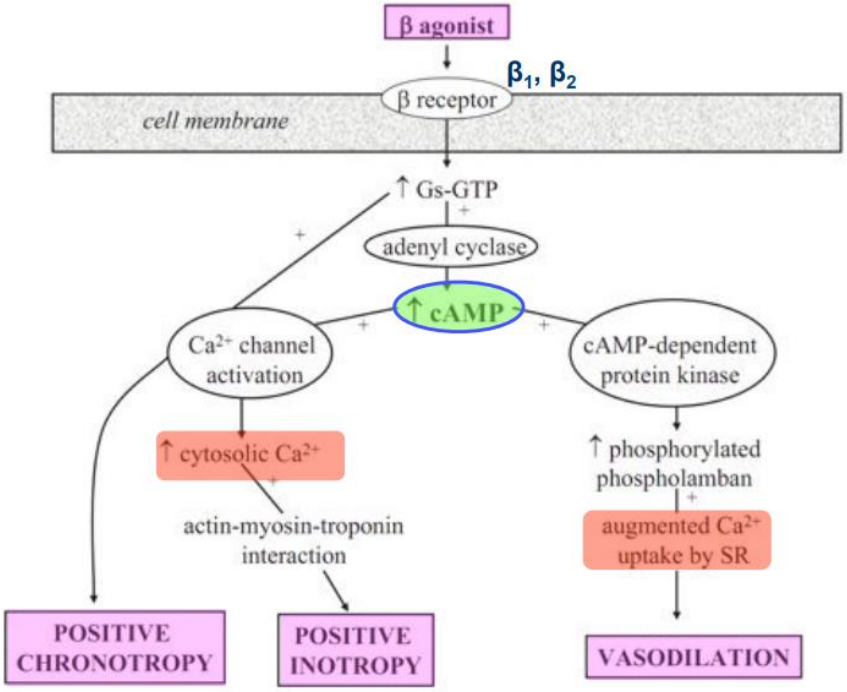


Figure 20. Intracellular actions of β-adrenergic agonists.

(Source: Overgaard CB, Dzavík V. Inotropes and vasopressors: review of physiology and clinical use in cardiovascular disease. Circulation. 2008 Sep 2;118(10):1047-56.)

They are divided into very powerful (epinephrine, norepinephrine, isoproterenol) and medium strength (dopamine, dopexamine, dobutamine). Dopamine and dopexamine belong to the indirectly acting β-agonists, as part of their action is achieved through the release of norepinephrine or through the inhibition of its reuptake (310, 311). Their cardiovascular effects are determined by their preferential action on different receptors (Table 16).

Agent	Dose (μg/kg/min)	α_1	α_2	β_1	β_2	D	Main Effects
Norepinephrine	0,01-3	+++++	+++++	++	0	0	Vasoconstriction: +++ Ino/Chronotropy: +
Epinephrine	0,01-3	+++++	+++	+++	++	0	Low doses: β-effects High doses: α-effects
Dopamine	>5	+++++	?				Vasoconstriction: +
	2-5			++++	++		Inotropy: ++ Chronotropy: ++
	0,5-2	0	0	0	0	+++++	Vasodilation: +++
Dobutamine	2-20	+	?	++++	++	0	Ino/Chronotropy: +++ Vasodilation: +
Isoproterenol	0,15	0	0	+++++	+++++	0	Inotropy: + Chronotropy: +++ Vasodilation: +++

Table 16. Receptor affinity and haemodynamic effects of the most common catecholamines.

Dopamine, an endogenous central neurotransmitter, is the immediate precursor to norepinephrine in the catecholamine synthetic pathway. The dose-dependent dopamine action (dopamine receptor D_1 & D_2 stimulation) is not specific and is influenced by regulation and density of the receptors as well as by its interactions with other agents (310, 311). At low doses (0.5 to 3 μg/kg/min), stimulation of dopaminergic D_1 postsynaptic receptors concentrated in the coronary, renal, mesenteric, and cerebral beds and D_2 presynaptic receptors present in the vasculature and renal tissues promotes vasodilation and increased blood flow to these tissues. Dopamine also has direct natriuretic effects through its action on renal tubules. The clinical significance of “renal-dose” dopamine is somewhat controversial, however, because it does not increase glomerular filtration rate, and a renal protective effect has not been demonstrated. At intermediate doses (3 to 10 μg/kg/min), dopamine weakly binds to β_1-adrenergic receptors, promoting norepinephrine release and inhibiting reuptake in presynaptic sympathetic nerve terminals, which results in increased cardiac contractility and chronotropy, with a mild increase in SVR. At higher infusion rates (10 to 20 μg/kg/min), α_1-adrenergic receptor mediated vasoconstriction dominates (312). In the past, it was considered the first choice inotropic drug for relatively mild conditions, but its use diminishes as it often causes tachycardia and has a weaker inotropic effect than epinephrine and causes much higher ventricular filling pressures compared to dobutamine in order to achieve the desired hemodynamic effects (310, 311).

Dopexamine (a synthetic dopamine analogue) other than its dopaminergic activity exhibits greater affinity for β_2 than β_1 adrenergic receptors, resulting in increased visceral and renal blood flow. But in the management of cardiac surgery patients it seems to cause frequent and serious tachycardias, which is of course not desirable (313).

Dobutamine is a synthetic catecholamine with a strong affinity for both β_1- and β_2-receptors, which it binds to at a 3:1 ratio. With its cardiac β_1-stimulatory effects, dobutamine is a potent inotrope, with weaker chronotropic activity. Vascular smooth muscle binding results in combined β_1-adrenergic agonism and antagonism, as well as β_2-stimulation, such that the net vascular effect is often mild vasodilation, particularly at lower doses (<5 µg/kg/min). Doses up to 15 µg/kg/min increase cardiac contractility without greatly affecting peripheral resistance, likely owing to the counterbalancing effects of α_1-mediated vasoconstriction and β_2-mediated vasodilation. Vasoconstriction progressively dominates at higher infusion rates. Despite its mild chronotropic effects at low to medium doses, dobutamine significantly increases myocardial oxygen consumption. Tolerance can develop after just a few days of therapy, due to downregulation of adrenergic receptors and malignant ventricular arrhythmias can be observed at any dose. In cardiac surgery patients, dobutamine increases coronary flow and oxygen supply to the myocardium compared to dopamine, which appears to adversely affect the metabolic balance. These beneficial effects are unfortunately eliminated by the induction of tachycardia, which is also one of the determinants of the increase in oxygen consumption by the myocardium (312, 314).

Norepinephrine, the major endogenous neurotransmitter liberated by postganglionic adrenergic nerves, is a potent α_1-adrenergic receptor agonist with modest β-agonist activity, which renders it a powerful vasoconstrictor with less potent direct inotropic properties (Figure 21). Norepinephrine primarily increases systolic, diastolic, and pulse pressure and has a minimal net impact on CO. Furthermore, this agent has minimal chronotropic effects, which makes it attractive for use in settings in which heart rate stimulation may be undesirable. Coronary flow is increased owing to elevated diastolic blood pressure and indirect stimulation of cardiomyocytes, which release local vasodilators. Prolonged norepinephrine infusion can have a direct toxic effect on cardiac myocytes by inducing apoptosis via protein kinase A activation and

increased cytosolic Ca^{2+} influx. The administration of norepinephrine is highly useful in conditions with low peripheral resistances (312, 315).

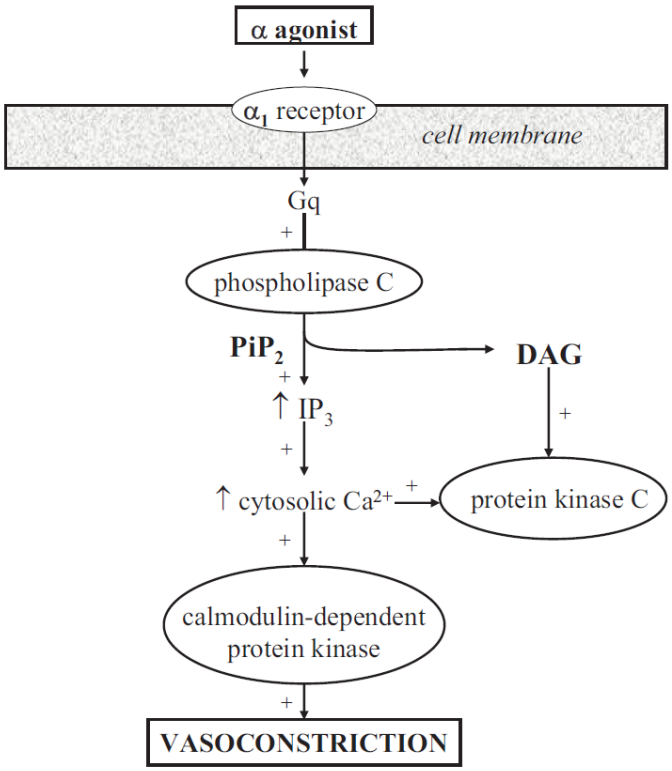


Figure 21. Postulated mechanisms of intracellular action of α_1-adrenergic agonists.

(Source: Overgaard CB, Dzavík V. Inotropes and vasopressors: review of physiology and clinical use in cardiovascular disease. Circulation. 2008 Sep 2;118(10):1047-56.)

Epinephrine is an endogenous catecholamine with high affinity for β_1-, β_2-, and α_1-receptors present in cardiac and vascular smooth muscle. β-adrenergic effects are more pronounced at low doses and α_1-adrenergic effects at higher doses. Coronary blood flow is enhanced through an increased relative duration of diastole at higher heart rates and through stimulation of myocytes to release local vasodilators, which largely counterbalance direct α_1-mediated coronary vasoconstriction. Arterial and venous pulmonary pressures are increased through direct pulmonary vasoconstriction and increased pulmonary blood flow. High and prolonged doses can cause direct cardiac toxicity through damage to arterial walls, which causes focal regions of myocardial contraction band necrosis, and through direct stimulation of myocyte apoptosis (312, 316).

The combination of norepinephrine and dobutamine is currently the most favored inotropic treatment and seems to be superior to traditional therapy with dopamine.

Epinephrine is not recommended as the first-line therapy. When considering global hemodynamic effects, epinephrine is as effective as norepinephrine-dobutamine. Nevertheless, epinephrine is associated with a transient lactic acidosis, higher heart rate and arrhythmia, and inadequate gastric mucosa perfusion. Thus, the combination norepinephrine-dobutamine appears to be a more reliable and safer strategy (317, 318).

Isoproterenol is a potent, nonselective, synthetic β-adrenergic agonist with very low affinity for α-adrenergic receptors. It has powerful chronotropic and inotropic properties, with potent systemic and mild pulmonary vasodilatory effects. Its stimulatory impact on stroke volume is counterbalanced by a β_2-mediated drop in systemic vascular resistance (SVR), which results in a net neutral impact on CO (312). Its use is limited in patients with CAD due to the often caused tachycardias, is however still used in the treatment of bradyarrhythmias and atrioventricular blocks.

Phenylephrine presents a potent synthetic α-adrenergic activity and virtually no affinity for β-adrenergic receptors. It can be primarily used as a rapid bolus for immediate correction of sudden severe hypotension. It can for example be used to raise mean arterial pressure (MAP) in patients with severe hypotension and concomitant aortic stenosis, to correct hypotension caused by the simultaneous ingestion of sildenafil and nitrates, to decrease the outflow tract gradient in patients with obstructive hypertrophic cardiomyopathy, and to correct vagally mediated hypotension during percutaneous diagnostic or therapeutic procedures. This agent has virtually no direct heart rate effects, although it has the potential to induce significant baroreceptor-mediated reflex rate responses after rapid alterations in MAP.

11.2. Phosphodiesterase inhibitors

Phosphodiesterase 3 is an intracellular enzyme associated with the sarcoplasmic reticulum in cardiac myocytes and vascular smooth muscle that breaks down cAMP into AMP. Phosphodiesterase inhibitors (PDIs) increase the level of cAMP by inhibiting its breakdown within the cell, which leads to increased myocardial contractility (Figure 22). These agents are potent inotropes and vasodilators and also improve diastolic relaxation (lusitropy), thus reducing preload, afterload, and SVR (312). Unlike sympathomimetic amines, PDE III inhibitors produce no tolerance and

possess the distinct advantage of directly decreasing pulmonary vascular resistance (319). **Milrinone** is the PDI most commonly used for cardiovascular indications. In its parenteral form, it has a longer half-life (2-4 hours) than many other inotropic medications. This drug is particularly useful if adrenergic receptors are downregulated or desensitized in the setting of chronic HF, or after chronic β-agonist administration. **Amrinone** is used less often because of important side effects, which include doserelated thrombocytopenia (312). Low-dose oral **enoximone** has recently been evaluated in several small clinical trials, especially its effects during co-administration with beta-blockers (320). Another drug, **vesnarinone**, a mixed PDE inhibitor and ion-channel modifier that has modest, dose-dependent, positive inotropic activity, but minimal negative chronotropic activity, has improved haemodynamics and quality of life in small trials (321). However, in the largest outcome study, the VEST trial with 3833 patients with severe heart failure, a dose-dependent increase in mortality was identified (322).

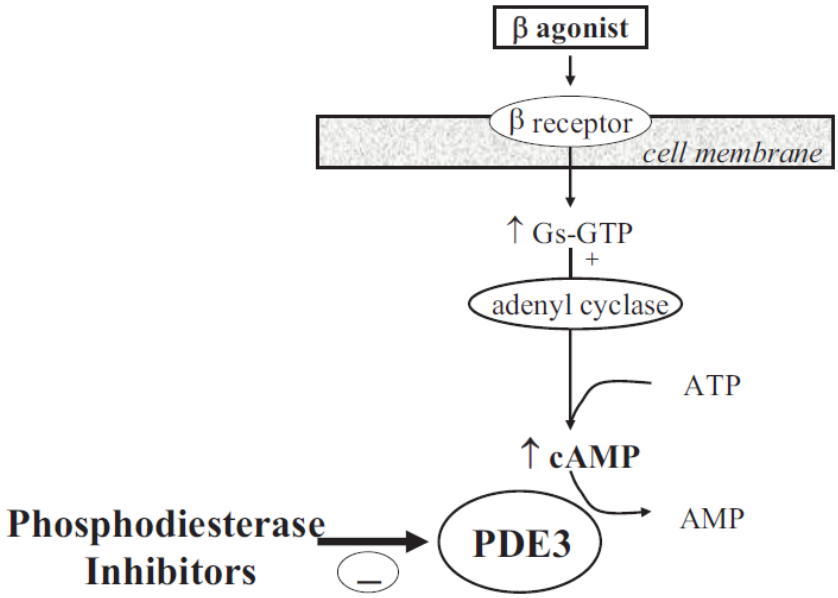


Figure 22. Basic mechanism of action of PDIs.

(Source: Overgaard CB, Dzavík V. Inotropes and vasopressors: review of physiology and clinical use in cardiovascular disease. Circulation. 2008 Sep 2;118(10):1047-56.)

11.3. Vassopressors

Isolated in 1951 (323), the nonapeptide **vasopressin** or “antidiuretic hormone” is stored primarily in granules in the posterior pituitary gland and is released after increased plasma osmolality or hypotension, as well as pain, nausea, and hypoxia.

Vasopressin is synthesized to a lesser degree by the heart in response to elevated cardiac wall stress and by the adrenal gland in response to increased catecholamine secretion (324). It exerts its circulatory effects through V_1 (V_{1a} in vascular smooth muscle, V_{1b} in the pituitary gland) and V_2 receptors (renal collecting duct system). V_{1a} stimulation mediates constriction of vascular smooth muscle, whereas V_2 receptors mediate water reabsorption by enhancing renal collecting duct permeability. Vasopressin causes less direct coronary and cerebral vasoconstriction than catecholamines and has a neutral or inhibitory impact on CO, depending on its dose-dependent increase in SVR and the reflexive increase in vagal tone. A vasopressin-modulated increase in vascular sensitivity to norepinephrine further augments its pressor effects. The agent may also directly influence mechanisms involved in the pathogenesis of vasodilation, through inhibition of ATP-activated potassium channels, attenuation of nitric oxide production, and reversal of adrenergic receptor downregulation. The pressor effects of vasopressin are relatively preserved during hypoxic and acidotic conditions, which commonly develop during shock of any origin (312).

Table 17 summarizes the main effects and the indications of the most commonly used pharmacologic agents including Levosimendan which will be thoroughly described on the following section.

Agent	Dose (μg/kg/min)	Main Effects	Indication
Norepinephrine	**0,01-3 (α >>> β)**	**⇧⇧Afterload ⇧Contractility**	Shock (septic + cardiogenic), RV failure, postcardiotomy shock
Epinephrine	**0,01-0,5 (α = β)**	**⇧⇧Afterload ⇧⇧Contractility Inopressor**	**ACLS,** shock (septic + cardiogenic), postop. LCOS, bradycardia
Dobutamine	**2-20 (β_1-adrenergic)**	**⇧Contractility ⇩Afterload**	Cardiogenic shock, acute heart failure, postop. LCOS, septic cardiomyopathy, bradycardia
Dopamine	**0,5-2 (D-receptors)**	**Renal vasodilation**	**⇧ Mortality in comparison with NE → obsolete**
	3-5 (β-adrenergic)	**⇧Contractility ⇩Afterload**	
	>5 (α-adrenergic)	**⇧Afterload**	
Milrinone	**0,125-0,75 (PDE_{III}-I)**	**⇧Contractility ⇩Afterload Inodilator**	Heart failure, postop. LCOS, **Effective in patients with β-blockade**
Levosimendan	**0,1-0,2 (Bolus: 6-12 μg/kg) (Ca-sensitization)**	**⇧Contractility ⇩Afterload Inodilator**	Heart failure, postop. LCOS, **Effective in patients with β-blockade**

Table 17. The main effects and indications of inotropic agents.

12. CALCIUM SENSITIZERS – LEVOSIMENDAN

β-adrenergic receptors, phosphodiesterase inhibitors and digoxin have been extensively used as inotropic agents to improve hemodynamic parameters in patients with heart failure. Due to their 'retrograde' mechanism of action interfering with stimulation-contraction conjugation they do not lack side effects which include the accumulation of calcium in the cytoplasm that could potentially cause cardiac arrhythmias and myocardial damage and eventually lead to cell death (325, 326). These agents also consume large amounts of energy for the required intracellular calcium metabolism. Both β-agonists and phosphodiesterase inhibitors cause a double and a threefold increase of heat and work to increase the intensity of the contraction through an expensive and uneconomic for the body procedure (327).

An alternative way of increasing contractile intensity is the 'antegrade' mechanism in which the binding of troponin C (TnC) to calcium or myofilament response for the existing number of calcium ion-TnC junctions is altered. This mechanism provides the desired hemodynamic effect without increasing energy consumption and avoiding the accumulation of calcium and its adverse effects. Calcium sensitizers are a recently developed class of inotropic agents, levosimendan being the most well-known (325, 328). The 'antegrade' mechanism of action of Levosimendan is compared to other inotropic agents in figure 23.

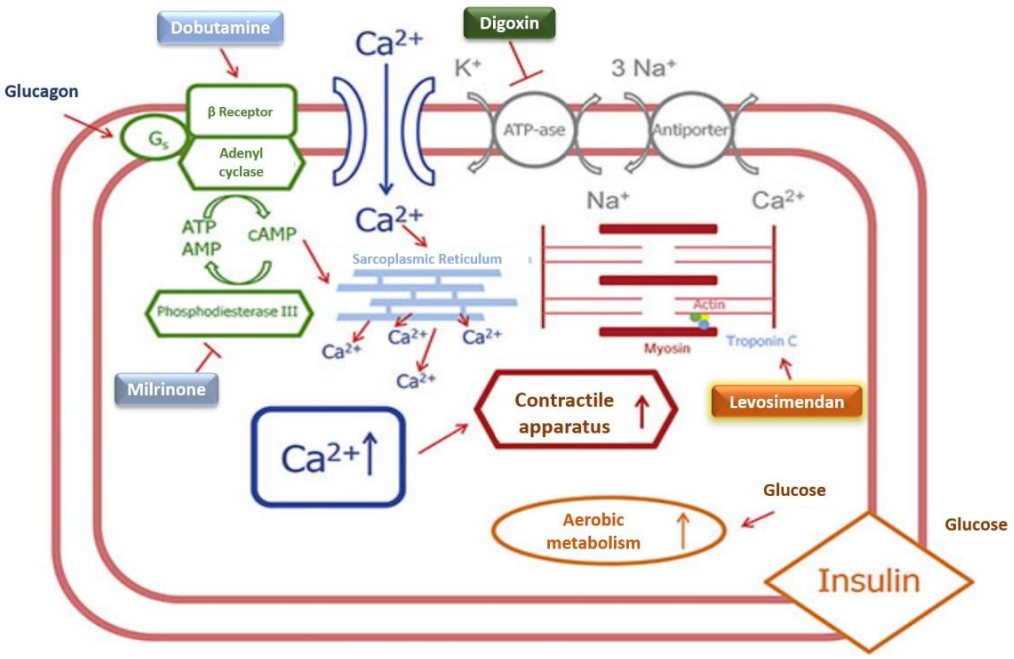


Figure 23. Mechanisms of action of inotropic agents in the cardiac muscle cell.

(Source: Modified from Furrer F, Giambara C. The choked heart. Praxis 2012;101:919-22.)

12.1. Chemistry

Levosimendan [(R)-[[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl] hydrazono] propanedinitrile] is the active enantiomer of simendan, a pyridazinone-dinitrile derivative and belongs to a new class of drugs, the calcuium sensitizers. The structural formula of levosimendan is presented in figure 24. Levosimendan is a moderately lipophilic drug with a molecular weight of 280.3 daltons. It is a weak acid with pKa 6.3. Solubility of levosimendan in distilled water and phosphate buffer (pH 8) is poor (0.04 mg/ml and 0.9 mg/ml, respectively). Solubility in ethanol is 7.8 mg/ml and therefore levosimendan in its pharmaceutical composition (levosimendan 2.5 mg/ml infusion concentrate) is diluted in ethanol (329).

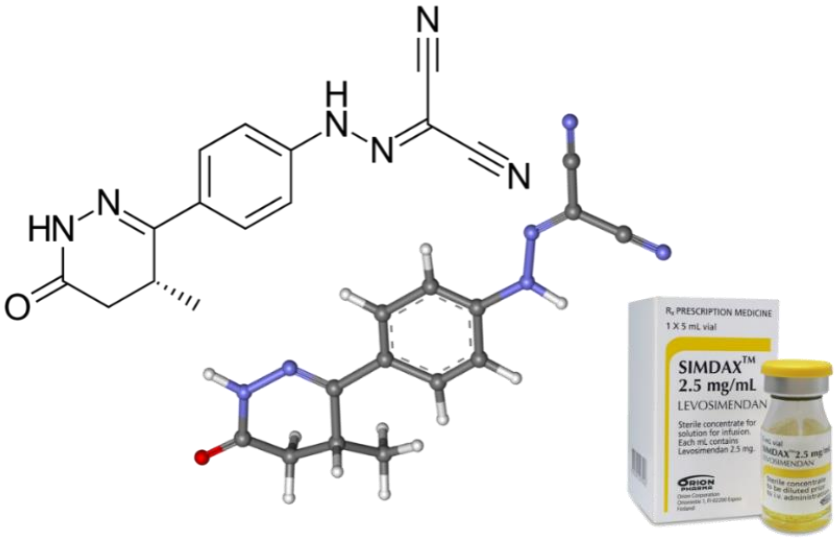


Figure 24. Structural formula of levosimendan.

12.2. Mechanism of action

Levosimendan has three key mechanisms of action which are responsible for its positive inotropic, vasodilatatory and cardioprotective effects (330):

1. **Calcium sensitisation** by selective binding to calcium-saturated cardiac troponin C increases the contractile force of the cardiac myocytes without affecting relaxation (331, 332).

2. **Opening of K_{ATP} channels in vascular smooth muscle cells** elicits both arterial and venous vasodilation as well as improvement in coronary artery circulation (333, 334).

3. **Opening of K_{ATP} channels in the mitochondria of cardiomyocytes** achieves a cardioprotective effect in situations when the heart is subjected to ischaemic events (335, 336).

Through calcium sensitisation, levosimendan improves cardiac contractility in the failing heart without affecting muscle electrophysiology (337). Through the opening of K_{ATP} channels in vascular smooth muscle cells, levosimendan improves oxygen supply to the myocardium (338). Because levosimendan augments myofibril contractions by increasing calcium sensitivity rather than by increasing intracellular calcium, it is not associated with increased myocardial oxygen demand, ischaemia, or tolerance, conditions sometimes incurred with agents traditionally used to treat decompensated heart failure. In brief, the mechanism of action for levosimendan involves three clinically relevant features that are specific to the cardiovascular system; levosimendan acts on the contractile apparatus of the myocardial cells, on the vascular smooth muscle cells and on the mitochondria of the cardiomyocytes via independent, but complementary, mechanisms (338, 339).

12.2.1. Positive inotropic effect

The heart muscle consists of cardiac myocytes that show a striated subcellular structure: each cell contains myofibrils with actin and myosin filaments, which form the contractile apparatus. The actin filaments are associated with the regulatory proteins tropomyosin and troponin, which is complex of three smaller proteins (TnC, TnI, and TnT) (Figure 25A). When intracellular Ca^{2+} concentration increases, TnC becomes Ca^{2+}-saturated, which triggers the contraction. When calcium is removed from the cytosol, TnC, now Ca^{2+}-free, allows the sarcomere relaxation. Levosimendan selectively binds to Ca^{2+}-saturated cardiac TnC (Figure 25B) (340). By binding to TnC and stabilising the TnC-Ca^{2+} complex, levosimendan enhances the sensitivity of the myofilament and facilitates the actin-myosin cross-bridge formation (340). The calcium sensitisation effect of levosimendan has been shown in many in vitro models from skinned fibres to isolated hearts (333, 337, 341, 342). Levosimendan has positive inotropic effects in normal and heart failure models (343,

344). The formation of the TnC-Ca^{2+}-levosimendan complex is calcium-dependent and calcium sensitivity is enhanced only when intracellular calcium concentration is elevated (337). As a result of this unique property, levosimendan increases contractile force during systole when intracellular calcium concentration is increased. Importantly, levosimendan does not impair relaxation during diastole when intracellular calcium concentration is decreased or even improves relaxation (345). Levosimendan has been shown to increase contractility considerably with only a modest increase in intracellular calcium, even in ventricular muscle strips from end-stage failing human hearts. This finding is significant in relation to clinical effect in that levosimendan does not increase energy consumption and the risk of proarrhythmic events is low (346, 347). Other agents shown to improve cardiac output, such as milrinone, have different mechanisms of action from levosimendan (340). In fact, milrinone increases cardiac contractility, but it does so by increasing intracellular calcium concentrations, thereby increasing energy consumption and the potential for arrhythmia (348).

Calcium sensitisation with levosimendan offers increased cardiac contractility:

- Without increasing intracellular calcium.
- Without increasing oxygen consumption.
- Without affecting cardiac rhythm and relaxation (342, 346, 347, 349).

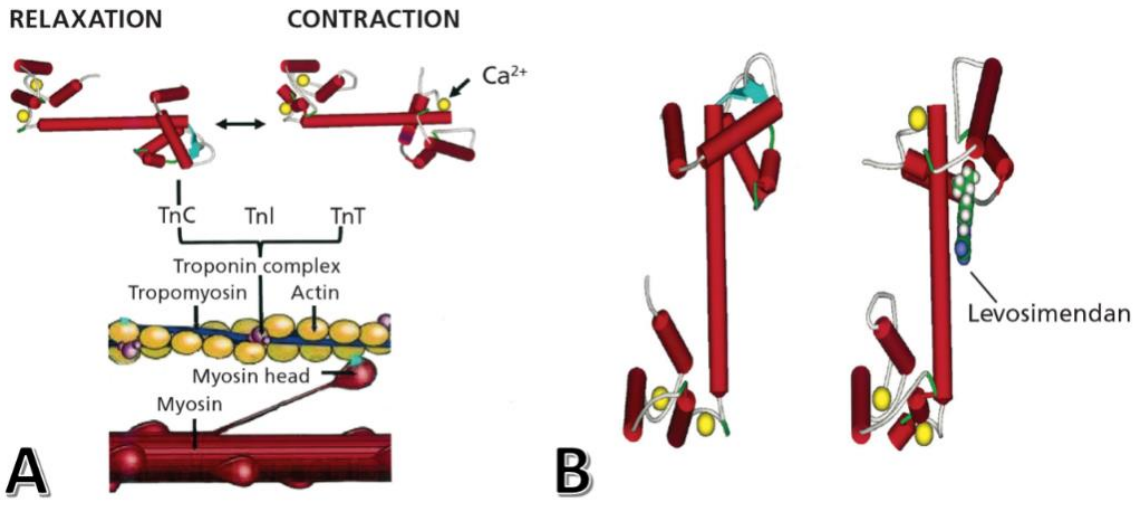


Figure 25. A. Role of troponin C in the mechanism of contraction. **B.** Levosimendan selectively binds to calcium saturated cardiac troponin C.

(Source: Product monograph Simdax®, 2018 Orion Corporation, Espoo, Finland.)

12.2.2. Vasodilatatory effect

Vasodilation with levosimendan results from the opening of K_{ATP} channels; it reduces preload and afterload, and improves oxygen supply to the myocardium. Vasodilation with levosimendan has been demonstrated in both arterial and venous vascular beds, and in the coronary arteries (333, 350, 351). Opening of K_{ATP} channels has also been observed in ventricular myocytes - an effect that may help to protect ischaemic myocardium. The opening of K_{ATP} channels by levosimendan has been both electrophysiologically and pharmacologically demonstrated in arterial and venous preparations and in coronary arteries (333, 350). It has also been shown that the venodilatory effect of levosimendan on the noradrenaline-constricted human portal vein or serotonin-constricted human saphenous vein is also mediated by the opening of K_{ATP} channels. In addition, some pharmacological findings indicate that levosimendan may open the calcium-dependent potassium channels in arteries and veins as well as voltage dependent potassium channels in coronary arteries (352). In light of the above-mentioned studies, it seems that levosimendan may preferentially stimulate K_{ATP} channels in small resistance vessels. In large conductance vessels the vasodilatation appears to be mediated mainly through opening of voltage- as well as calcium-dependent potassium channels (353).

12.2.3. Cardioprotective effect

By opening mitochondrial adenosine triphosphate-dependent potassium (mitoK_{ATP}) channels, levosimendan protects the heart against ischaemia-reperfusion injury (335, 336, 338). The fact that levosimendan can prevent or limit myocyte apoptosis via the activation of mitoK_{ATP} channels provides a potential mechanism whereby this agent might protect cardiac myocytes during episodes of acute heart failure as well as in chronic heart failure situation (335, 354, 355).

12.2.4. Phosphodiesterase III inhibitor effect

Levosimendan and OR-1896 have also shown the potential to cause a moderate increase in intracellular calcium concentration via phosphodiesterase inhibition. In particular, the phosphodiesterase III inhibition with an increase in intracellular cAMP concentration is in the foreground (356). However, this fact does not affect the

positive inotropic effects of levosimendan in the normal therapeutic concentrations, as this effect occurs only at high doses of the drug (357).

12.2.5. Antiinflammatory effect

In previous studies, heart failure was simultaneously associated with elevated plasma levels of pro-inflammatory cytokines such as TNF-α, IL-6 and IL-1β, and increased oxidative stress, which in turn increased the rate of apoptosis of the heart muscle and endothelial cells responsible (358). Several studies have also shown an association between the elevation of TNF-α and IL-6 plasma levels, with an acceleration of disease progression and increased mortality in heart failure patients (359). At the same time, subsequent studies indicate that levosimendan has anti-inflammatory and anti-apoptotic properties by reducing the circulation of proinflammatory cytokines and soluble inducers of apoptosis (360, 361).

12.2.6. Effects on the pulmonary circulation

Effects of levosimendan on pulmonary circulation have been studied in an animal model after pulmonary arterial vasculitis and were found to cause pulmonary vasodilation in reversible at least pulmonary hypertension (362). In another study, a significant reduction in pulmonary vascular resistance in healthy animals was observed after administration of levosimendan (363), whereas in rat model reduction of proinflammatory factors (IL-1β, inflammatory macrophage protein 2), nitric oxide and metalloproteinases 2 and 9 following administration of the agent to intubated animals (364). Research interest has been developed around the action of levosimendan in the lungs, in shock conditions. Differences in acid-base balance, electrolytes and muscle enzymes following congestion of the femoral artery have been studied in rabbits treated with levosimendan and iloprost. After stopping the ischemia, levosimendan not only had better results than prostaglandin but also in pulmonary tissue preparations showed less tissue damage from oxidative products such as free ROS (365).

12.2.7. Electrophysiologic effects

The limitation of inotropic support due to the susceptibility to lethal arrhythmias is known. Levosimendan promotes atrioventricular conduction and the recovery of myocardial excitability (366). The prolongation of the monophasic potential is mild, with the result that the risk of ventricular arrhythmias is minimal as long as the QT interval in the electrocardiogram is not prolonged. In another study, prolongation of energy potential during ischemia through K^+-ATP channel activation reduces ventricular arrhythmogenesis and late repolarization (367).

Adding levosimendan to the category of drugs that increase myocardial contractility is a milestone, as it does not affect calcium levels. For this purpose, 10 patients were electrophysiologically studied without suffering from cardiac disease and a large amount of the agent was administered. Concerning effects on rhythm generation, the drug increased the sinus incidence significantly (from 62 to 71 beats). The venous recovery time was reduced by 160 to 280 ms for a 600-400 ms pacing cycle). Also, AH interval did not show a change in sinus rhythm or atrial pacing. The same was observed for HV interval. The refractory period in the atrioventricular junction was reduced by 40-63 ms, at vaginal myocardium by 22 to 33 ms, while in the ventricle by 5 to 9 ms on average. The drug increased the duration of energy potential by 9 to 17 ms to 50% and by 5 to 15 ms to 90% of repolarization on average. The QT interval during endogenous rhythm and/or atrial pacing did not change, although it decreased mildly when corrected for sinus incidence (368). The results indicate that levosimendan in brief intravenous prospers the rate of formation and conduction in cardiac slow conduction tissue, enhances the excitability recovery and slow ventricular repolarisation. The actions in the ventricular myocardium are of minor importance and therefore the risk of causing ventricular arrhythmias is not expected to be great (368).

12.3. Pharmacokinetics - Pharmacodynamics

Levosimendan is extensively metabolised before excretion into urine and faeces. The main pathway is conjugation with glutathione to form inactive metabolites. The minor pathway (approximately 6% of the total levosimendan dose) is reduction in the intestine to an intermediate metabolite (OR-1855), which is further acetylated to the active metabolite, OR-1896 (369). Levosimendan is excreted as conjugates via the

urine and faeces and only traces of unchanged levosimendan are found in experimental animals and in man (370, 371). Levosimendan metabolism is illustrated in figure 26. The metabolite OR-1896 has been shown to have haemodynamic and pharmacologic properties similar to those of the parent drug in preclinical models. Preclinical findings suggest that cytochrome P450 (CYP) enzymes do not play any role in the metabolism of levosimendan or its metabolites OR-1855 and OR-1896 (341, 343, 353, 369, 372).

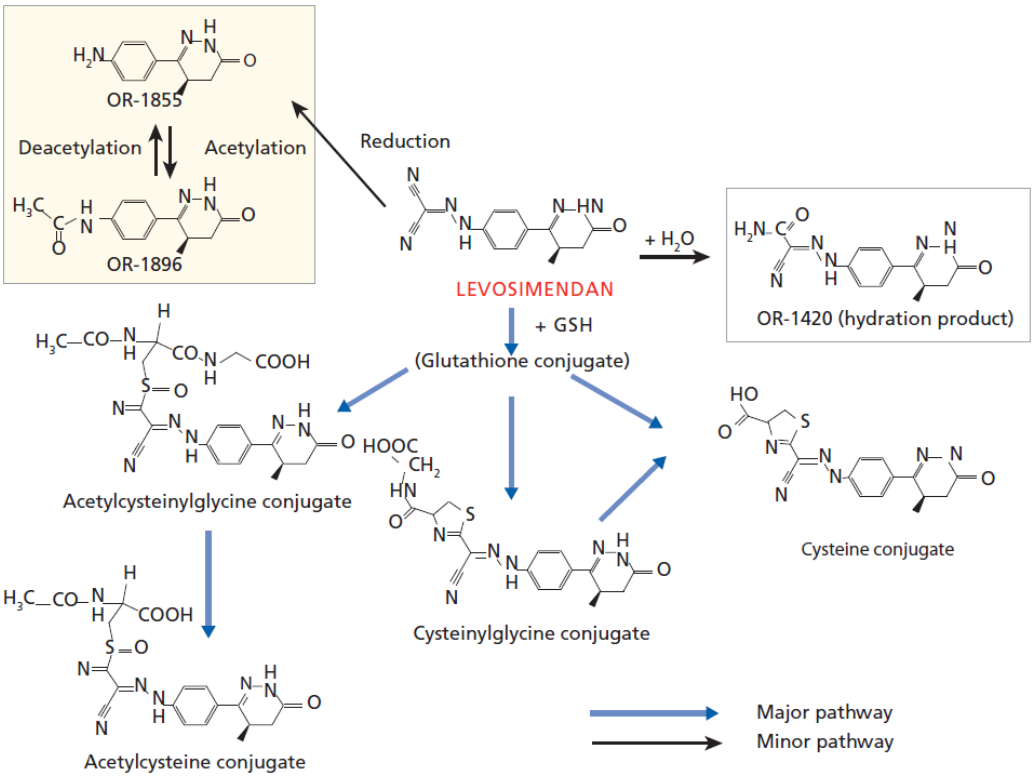


Figure 26. Metabolic pathways of Levosimendan.

(Source: Product monograph Simdax®, 2018 Orion Corporation, Espoo, Finland.)

The terminal elimination half-life ($t_{1/2el}$) of levosimendan is about 1 hour both in healthy volunteers and in patients with heart failure (Table 18) and it rapidly disappears from the circulation after the infusion is stopped. Levosimendan is highly bound to plasma proteins (97-98%) (371). Plasma concentrations of levosimendan increase dose-proportionally (373). The mean elimination half-life values for the levosimendan metabolites OR-1855 and OR-1896 are approximately 80 hours and their plasma protein binding is about 40% (Table 18) (373, 374). The time curves of the concentrations of levosimendan and the metabolite OR-1896 are shown in figure 27.

Variable	Levosimendan	Metabolite OR-1896
$t_{1/2el}$ (h)	1.1 - 1.4	77.4 - 81.3
CL_{tot} (l/h/kg)	0.18 - 0.22	na
V_c (l/kg)	0.33 - 0.39	na
Protein binding (%)	97	42

Table 18. Pharmacokinetic variables of levosimendan and its active metabolite OR-1896.

$t_{1/2el}$ = terminal elimination half-life, CL_{tot} = total clearance, V_C = volume of distribution based on area under the curve (AUC), na = not assessed.

(Source: Product monograph Simdax®, 2018 Orion Corporation, Espoo, Finland.)

The activity of the enzyme responsible for the acetylation, the N-acetyltransferase, is known to differ considerably in man. Most Caucasian populations in Europe and North America have 40% to 70% slow acetylators, whereas most Asian populations have only 10% to 30% slow acetylators (375). The acetylator status of a patient affects the pharmacokinetics of levosimendan metabolites, but not that of the parent drug. In rapid acetylators, the OR-1896 levels were significantly higher and OR-1855 significantly lower; in slow acetylators the opposite was seen. However, the effects on heart rate, blood pressure, pulmonary capillary wedge pressure and cardiac output were similar in the two acetylator types. These findings could be explained either by assuming that both metabolites are active in man or by the fact that the differences in OR-1896 levels seen in the study were too small to produce different haemodynamic responses (376).

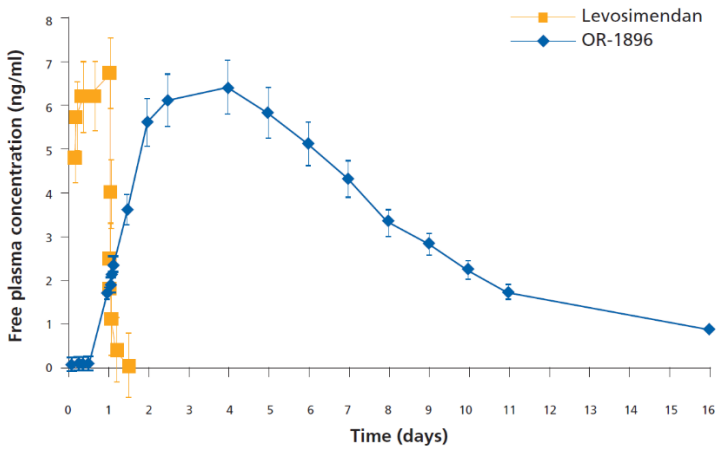


Figure 27. Free plasma concentrations of levosimendan and OR -1896 during and after a 24-h infusion.

(Source: Kivikko M, Antila S, Eha J, et al. Pharmacokinetics of levosimendan and its metabolites during and after a 24-hour continuous infusion in patients with severe heart failure. Int J Clin Pharmacol Ther. 2002;40(10):465-71.)

In patients undergoing cardiac surgery, the formation of the metabolites OR-1855 and OR-1896 was delayed compared to patients with chronic heart failure. In chronic heart failure, the peak concentrations of the metabolites were seen 2-4 days after starting the infusion, compared to 6 days in patients undergoing cardiac surgery (374, 377). The reason is not fully known, but may be related to initiation of therapy following a fasting state and the use of broad-spectrum antibiotics. These conditions reduce populations of intestinal bacteria involved in the acetylation of levosimendan, leading to reduced/delayed formation of metabolites OR-1855 and OR-1896. The steady state plasma concentrations of the parent drug were somewhat lower in cardiac surgery patients than in chronic heart failure with the AUC 14% lower with similar dosing (377).

12.4. Dosis

Levosimendan therapy can be recommended to begin with a 10-minute bolus of 6 to 24 µg/kg/min, followed by continuous infusion of 0.05 to 0.2 µg/kg/min over 24 hours (378). The initial rapid dosing is optional and in many studies have been omitted for better tolerability (379). If patients present hypotension (systolic blood pressure <90 mmHg), either the bolus dose can be dispensed with or it is possible to additionally administer low-dose norepinephrine (380). In addition, if signs of volume depletion appear, it makes sense to consider cautious fluid administration under adequate monitoring. In most cases, patients show an improvement in hemodynamic function over the next 24 hours, as evidenced by an increase in urinary output and a significant reduction in PCWP (Pulmonary Capillary Wedge Pressure) (381).

12.5. Tolerance, side effects and toxicity

Levosimendan is commonly well tolerated by patients with moderate to severe heart failure, with an overall prevalence of adverse effects up to 17-29%, comparable to placebo (17-20%). Most adverse effects are based on its property as a vasodilator and are dose-related. They include headache (5% of patients), hypotension (5% of

patients), dizziness (1-10% of patients) and nausea (1-10% of patients). Prior to the application of levosimendan, any pre-existing arrhythmia should be controlled and evaluated because the agent may increase ventricular frequency. Arrhythmias that have been observed are varied, with ventricular rhythm disorders seen at 1.3%, sinus tachycardia at 2.4%, atrial fibrillation at 1.4%, and ventricular tachycardia at 1%. The adverse clinical effects may be even more extreme in cases where it is not possible to increase the SV or in cases that have not effective high filling pressures or present significantly reduced filling pressures. Thus, it is not recommended to administer the agent in cases with blood pressure below 85 mmHg (382-384).

Levosimendan may reduce hematocrit levels and hemoglobin concentration due to a rise in circulating blood volume due to redistribution of fluid in the vessels and secondary to venous and arterial vasodilation. It can also lower potassium levels in the blood due to stimulation of the sympathetic system, which causes the intracellular transport of the ion. Paradoxically, myocardial ischaemia has been reported up to 2% of the patients due to excessive peripheral vasodilation (326).

Given the particular pharmacokinetics with the long half-life of the drug, it is clear from the evidence of adverse events that 83% of these occurred during treatment and a further 17% afterwards. Most of these are observed within the first 3 days after the agent's administration is started.

There is no particular risk of human toxicity with regard to the short-term administration of levosimendan and the proposed dosages. In experimental animals, it is not teratogenic but causes a decrease in the degree of osteoporosis in rat embryos. At early stages of pregnancy, the factor reduced the number of Corpus luteum, zygote implantation and neonates per pregnancy. In experimental animals, it is excreted in breast milk (385).

12.6. Combination with other agents

Various studies have shown that the combination of levosimendan and dobutamine is safe and effective in patients with severe heart failure. An increase in the hemodynamic effect of dobutamine was even observed (386). Although concomitant beta-blocker therapy reduced the inotropic and vasodilatory properties of dobutamine, no loss of efficacy was reported with levosimendan in such a situation

(387). Levosimendan may also be used in combination with norepinephrine in patients with low initial systolic blood pressure to maintain adequate organ and tissue perfusion (387, 388).

12.7. Importance of the application time

Currently levosimendan is used at different timepoints namely preoperatively, intraoperatively and postoperatively. It is higly important to choose the right time to administer the drug, especially in terms of cost and benefit compared to conventional inotropic drugs. Thus, the question arises as to the optimal timing of levosimendan administration, taking into account the clinical condition of the patient. Tasouli et al. examined patients with a LVEF <35% and a NYHA Stage III-IV undergoing cardiac surgery and Levosimendan was administered at a dosis of 0.1 µg/kg/min for 24 to 48 hours as part of a randomized study, either intraoperatively or postoperatively in the intensive care unit. During intraoperative levosimendan therapy, a significantly shorter ICU stay as well as total hospital stay was observed. The levels of the inflammatory parameter C-reactive protein (CRP) of intraoperative levosimendan-treated patients also showed significantly lower values than in the postoperatively treated patients. No significant results were obtained in terms of ventilation duration, maximum CRP, maximum creatinine and hemofiltration. In particular, the shortening of hospital stay and the trend towards a better clinical outcome are convincing arguments for the intraoperative or preoperative use of levosimendan in the clinical practice (379). Tritapepe et al. conducted a prospective, randomized, double-blind study comparing the outcome of patients undergoing elective CABG surgery and receiving levosimendan immediately prior to surgery with a placebo-administered control group. The results showed in the study group in contrast to the control group a significantly shorter ventilation time and a better CI with lower TnI values with significantly lower inotropic support (389). Another study dealt even more precisely with the administration time point. They retrospectively divided a small study population into 3 groups, one group receiving levosimendan for anesthesia induction, one during weaning from the heart-lung machine and one group receiving the drug postoperatively. The results clearly showed a better postoperative course of groups 1 and 2. All inotropic drugs could be discontinued in these groups within 24 h and only one IABP implantation was necessary. In the third group, however, there was a prolonged catecholamine requirement as well as an increased indication for the IABP

system. It was also shown that Group 1 even achieved a slightly better overall outcome compared to Group 2 (390). Another study carried out in 2014 was able to confirm that prophylactic preoperative administration 12 hours before the start of the operation showed significantly better effects, even compared to administration at anesthesia induction, and that preoperative and intraoperative administration of levosimendan is superior to administration on exit from the heart-lung machine. Therefore, the authors suggest a correlation with the efficacy of the effective metabolites of levosimendan, as the effect of the metabolites is by far superior when administered 12 hours preoperatively (391). Overall, levosimendan appears to be suitable for pharmacological preconditioning due to its cardioprotective and anti-ischemic properties to reduce postoperative myocardial stupefaction. It seems that early preoperative administration has a slightly better effect than administration on anesthesia induction or only on leaving the heart-lung machine.

12.8. Most important randomized multicenter clinical trials on levosimendan

12.8.1. Clinical trials in heart failure

LIDO (The Levosimendan versus Dobutamine Study)

The 2002 LIDO study compared dobutamine with levosimendan in 203 patients with severe heart failure and symptoms of low-output syndrome in a double-blind, randomized study in 26 centers in 11 European countries. 103 patients were randomized into the levosimendan group. The dobutamine group included 100 patients. The levosimendan group under continuous hemodynamic monitoring received a loading dose of levosimendan of 24 µg/kg for 10 min as an intravenous infusion followed by a continuous intravenous infusion of 0.1-0.2 µg/kg/min over 24 hours. Dobutamine was administered without an initial dose at a continuous dose of 5 µg/kg/min for 24 hours. The primary endpoint defined was the occurrence or evidence of haemodynamic improvement. This was achieved in 28% (29 patients) of levosimendan and in 15% (15 patients) of the dobutamine group. In another endpoint, mortality was assessed within the first 31 days or 180 days after administration of levosimendan. In both cases, a significantly lower mortality rate was

demonstrated in the levosimendan group (7.81% vs. 17% and 26% vs. 38%, respectively). With regard to the hospitalization rate, this was comparatively lower in the levosimendan group (133 days vs. 157 days). In a sub-analysis of the LIDO study, it was observed that the use of beta-blockers did not adversely affect the haemodynamically beneficial effects of levosimendan (387).

RUSSLAN (The Randomized Study on Safety and Effectiveness of Levosimendan in Patients with Left Ventricular Failure Due to an Acute Myocardial Infarct)

In 2002, Moiseyev et al. in the double-blind, placebo-controlled, randomized and parallel-group design RUSSLAN study, examined the safety and efficacy of levosimendan in various doses in 504 patients with left heart failure after acute myocardial infarction. The levosimendan group received a bolus of 6-24 µg/kg for 10 min, followed by a levosimendan infusion of 4 hours in 4 increasing doses (0.1-0.4 µg/kg/min). Invasive hemodynamic parameters were not collected. The primary endpoint was defined as the occurrence of complications such as significant hypotension or myocardial ischemia. In the five treatment groups, no significant differences in the primary endpoint were observed. At the selected maximum dose with a bolus of 24 µg/kg body weight and subsequent continuous infusion of 0.4 µg/kg/min, there was a more frequent occurrence of hypotension and myocardial ischemia compared to the highest dose placebo group. The secondary endpoints included mortality risk, worsening heart failure, symptom control of heart failure, and long-term mortality. The levosimendan group had a lower mortality risk (11.7% vs. 19.6%), a reduction that persisted after 6 months. A dose-dependency was not found in the mortality. The number of patients whose heart failure continued to deteriorate was also lower than in the placebo group (384).

REVIVE (Randomized EValuation of Intravenous LeVosimendan Efficacy I und II)

REVIVE I was designed as a pilot study, the results of which were mainly intended for the conception of REVIVE II. It included 100 patients with acutely decompensated chronic heart failure (mean ejection fraction 20%). Levosimendan was compared to

placebo. The primary endpoint was defined here as a mixed endpoint that classified the clinical condition of the included patients by 3 categories (improved condition, unaltered condition and worsened condition) after 24 hours and after 5 days. No statistically significant superiority of levosimendan versus placebo was observed (392).

The subsequent prospective, pivotal, pivotal study, pivotal study **REVIVE II** examined the administration of levosimendan versus placebo to 600 patients with acute decompensated chronic heart failure (mean EF around 23%) who were hospitalized and despite receiving intravenous diuretics continued to present dyspnea at rest. All patients were treated with intravenous diuretics prior to admission, and about a quarter received intravenous vasodilators or positive inotropics. The treated group received a 10 minute initial dose of 6-12 µg/kg levosimendan followed by a continuous infusion of 0.05-0.2 µg/kg/min for up to 24 hours in addition to standard therapy. The outcome was largely consistent with REVIVE I and was also a mixed clinical endpoint, evaluating the clinical benefit that included both the judgment of the treating physician and that of the patient. An additional measurement time 6 hours after start of infusion was also assessed. The result for the primary endpoint was statistically significant ($p=0.015$) in favor of the calcium sensitizer. With levosimendan, more patients improved in their clinical symptomatology than with standard therapy alone (19.4% vs. 14.6%, respectively). In addition, less worsening of symptoms was reported in patients on levosimendan (19.4% vs 27.2%, $p<0.015$). As long as the secondary endpoints are concerned, a statistically significant reduction in the plasma BNP concentration was observed after 24 hours under levosimendan therapy. In addition, a shorter length of stay in the clinic of 7 vs. 8.9 days was observed. Finally, fewer patients on levosimendan needed additional intervention therapy. Overall mortality was numerically higher in the levosimendan group over the first 90 days than in the placebo group (15% versus 12%). In a post-hoc analysis it was shown that a systolic blood pressure <100 mmHg or a diastolic blood pressure <60 mmHg before starting therapy increased the mortality risk (380).

CASINO study (The Calcium Sensitizer or Inotrope or None in Low-Output Heart Failure Study)

In the double-blind, randomized CASINO study, Zairis et al. in 2004 examined the treatment of congestive heart failure with low cardiac output (NYHA stage IV, EF <35%) with levosimendan vs. Dobutamine or placebo. Originally, this study was designed for 600 subjects. The primary endpoint was established as a combination of death or rehospitalization due to worsening of heart failure. Mortality was evaluated at one, six and twelve months, respectively. Due to a survival benefit in the levosimendan group, which resulted in an interim analysis of the data, the study was discontinued early after 6 months after 299 patients. At one month, differences in mortality were found, being 6.1% for levosimendan, 8.2% for placebo and 12.8% for dobutamine (p=0.04 for dobutamine vs. placebo). At six months mortality was 15.3% for levosimendan, 24.7% for placebo and 39.6% for dobutamine (p=0.0001 for levosimendan vs. dobutamine, p=0.04 for levosimendan vs. placebo, p=0.04 for placebo vs. dobutamine). Here it could be demonstrated that levosimendan improves the prognosis in patients with low cardiac output syndrome (393).

SURVIVE (Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support)

In the double-blind, randomized SURVIVE trial, Mebazaa et al. in 2007 compared levosimendan to the standard inotropic drug dobutamine in a group of 1327 patients hospitalized with acutely decompensated severe heart failure and in need of intravenous inotropic support due to insufficient response to intravenous diuretics and / or vasodilators. Levosimendan was administered as an initial dose of 12 µg/kg for 10 minutes followed by a continuous infusion of 0.05-0.2 µg/kg/min for a maximum of 24 hours; Dobutamine was given at a dosage of at least 5 µg/kg/min for 24 hours; however, the infusion could be continued as long as it was clinically indicated. Overall mortality was defined as the primary endpoint after 180 days. There was no statistically significant difference between levosimendan and dobutamine (26.1% and 27.9%, hazard ratio 0.91, 95% CI: 0.74 to 1.13, p=0.401). The survival advantage with levosimendan-treated patients could not be confirmed. At the secondary endpoints, as in REVIVE, a statistically significant reduction in the plasma BNP concentration was observed after 24 hours under calcium sensitizers.

The other secondary endpoints (including 24-hour symptom scores, 180-day hospitalization shortening) did not show statistically significant differences compared to dobutamine (394). In a follow-up work published in 2009, Mebazaa et al. reported a significantly lower mortality rate on day 5 of the levosimendan group, in which the patients were on therapy with beta-blockers (395). Similar relationships have already been observed in the LIDO study.

BELIEF

In the BELIEF study published in Brazil in 2008, 115 patients with severe chronic heart failure of various origins (ischemic, idiopathic, Chagas disease, etc.) who needed intravenous therapy despite optimal standard oral therapy were examined and followed-up for one year. Levosimendan was given over a period of 24 hours with or without bolus administration. The therapeutic goal was defined as clinical stabilization with subsequent discharge from inpatient hospital care, without the need for additional inotropic or vasoactive support. This was achieved in 79% of patients and not achieved in 21%. The bolus dosis did not seem to play an important role as a significant drop in blood pressure occurred less frequently in only 20% of patients who received only continuous infusion. In the multivariable analysis performed, low blood pressure, which occurred before or during levosimendan therapy, was an independent factor in the need for longer hospitalization with additional required measures. It was discussed here whether the administration of a bolus necessarily makes sense, since the therapeutic effective level of levosimendan is built up after 3-4 hours without a bolus and thus a lower blood pressure drop can be circumvented at lower blood pressure values (396).

12.8.2. Clinical trials in cardiac surgery

CHEETAH study

In 2017 a multicenter, randomized, double-blind, placebo-controlled trial was published in New England Journal of Medicine, involving patients in whom perioperative hemodynamic support was indicated after cardiac surgery, according to prespecified criteria. The study was performed in 14 centers in Italy, Russia and

Brazil. Patients were randomly assigned to receive levosimendan (in a continuous infusion at a dose of 0.025 to 0.2 μg/kg/min) or placebo, for up to 48 hours or until discharge from the ICU, in addition to standard care. The primary outcome was 30-day mortality. The trial was stopped for futility after 506 patients were enrolled. A total of 248 patients were assigned to receive levosimendan and 258 to receive placebo. There was no significant difference in 30-day mortality between the levosimendan group and the placebo group (32 patients [12.9%] and 33 patients [12.8%], respectively; absolute risk difference, 0.1 percentage points; 95% confidence interval [CI], −5.7 to 5.9; p=0.97). There were no significant differences between the levosimendan group and the placebo group in the durations of mechanical ventilation (median, 19 hours and 21 hours, respectively; median difference, −2 hours; 95% CI, −5 to 1; p=0.48), ICU stay (median, 72 hours and 84 hours, respectively; median difference, −12 hours; 95% CI, −21 to 2; p=0.09), and hospital stay (median, 14 days and 14 days, respectively; median difference, 0 days; 95% CI, −1 to 2; p=0.39). There was no significant difference between the levosimendan group and the placebo group in rates of hypotension or cardiac arrhythmias. Some positive trends in renal function were noted. Concluding, in patients who required perioperative hemodynamic support after cardiac surgery, low-dose levosimendan in addition to standard care did not result in lower 30-day mortality than placebo (397).

LEVO-CTS study

This multicenter, randomized, placebo-controlled, phase 3 trial was published in 2017. The efficacy and safety of levosimendan in patients with a left ventricular ejection fraction of 35% or less who were undergoing cardiac surgery with the use of cardiopulmonary bypass were here evaluated. Patients were randomly assigned to receive either intravenous levosimendan (at a dose of 0.2 μg/kg/min for 1 hour, followed by a dose of 0.1 μg/kg/min for 23 hours) or placebo, with the infusion started before surgery. The two primary end points were a four-component composite of death through day 30, renal-replacement therapy through day 30, perioperative myocardial infarction through day 5, or use of a mechanical cardiac assist device through day 5; and a two-component composite of death through day 30 or use of a mechanical cardiac assist device through day 5. A total of 882 patients underwent randomization, 849 of whom received levosimendan or placebo and were included in the modified intention-to-treat population. The four-component primary end point

occurred in 105 of 428 patients (24.5%) assigned to receive levosimendan and in 103 of 421 (24.5%) assigned to receive placebo (adjusted odds ratio, 1.00; 99% confidence interval [CI], 0.66 to 1.54; p=0.98). The two-component primary end point occurred in 56 patients (13.1%) assigned to receive levosimendan and in 48 (11.4%) assigned to receive placebo (adjusted odds ratio, 1.18; 96% CI, 0.76 to 1.82; p=0.45). The rate of adverse events did not differ significantly between the two groups. Prophylactic levosimendan did not result in a rate of the short-term composite end point of death, renal-replacement therapy, perioperative myocardial infarction, or use of a mechanical cardiac assist device that was lower than the rate with placebo among patients with a reduced left ventricular ejection fraction who were undergoing cardiac surgery with the use of cardiopulmonary bypass. However, levosimendan group had statistically significantly less LCOS events (18% vs. 26%, p=0.007) and needed less inotropic support (55% vs. 63%, p=0.02), and cardiac index improved more (2.86±0.61 vs. 2.68±0.65 L/min/m^2; p<0.001) in levosimendan treated patients (398).

LICORN study

The aim of this study was to assess the ability of preoperative levosimendan to prevent postoperative low cardiac output syndrome. Is consists of a randomized, double-blind, placebo-controlled trial conducted in 13 French cardiac surgical centers. Patients with a left ventricular ejection fraction less than or equal to 40% and scheduled for isolated or combined coronary artery bypass grafting with cardiopulmonary bypass were enrolled from June 2013 until May 2015 and followed during 6 months (last follow-up, November 30, 2015). Patients were assigned to a 24-hour infusion of levosimendan 0.1 µg/kg/min (n=167) or placebo (n=168) initiated after anesthetic induction. Composite end point reflecting low cardiac output syndrome with need for a catecholamine infusion 48 hours after study drug initiation, need for a left ventricular mechanical assist device or failure to wean from it at 96 hours after study drug initiation when the device was inserted preoperatively, or need for renal replacement therapy at any time postoperatively. It was hypothesized that levosimendan would reduce the incidence of this composite end point by 15%in comparison with placebo. Among 336 randomized patients (mean age 68 years; 16% women), 333 completed the trial. The primary end point occurred in 87 patients (52%) in the levosimendan group and 101 patients (61%) in the placebo group

(absolute risk difference taking into account center effect, −7% [95% CI, −17% to 3%]; p=0.15). Predefined subgroup analyses found no interaction with ejection fraction less than 30%, type of surgery, and preoperative use of β-blockers, intra-aortic balloon pump, or catecholamines. The prevalence of hypotension (57% vs 48%), atrial fibrillation (50% vs. 40%), and other adverse events did not significantly differ between levosimendan and placebo. To sum up, among patients with low ejection fraction who were undergoing coronary artery bypass grafting with cardiopulmonary bypass, levosimendan compared with placebo did not result in a significant difference in the composite end point of prolonged catecholamine infusion, use of left ventricular mechanical assist device, or renal replacement therapy. These findings do not support the use of levosimendan for this indication (399).

13. AIM OF THIS STUDY

In recent years, a new concept has started to emerge in the pharmacological treatment of acute heart failure, cardiogenic shock and postoperative low cardiac output. The focus shifted from the sole stimulation and increase in contractility, such as that achieved by catecholamines, to greater relief of the ventricle, which seems to be achievable through the administration of a relatively new group of substances, the calcium sensitizers. In single case reports, case series and several studies, the efficacy of the most prominent representative of the group of calcium sensitizers, levosimendan, has already been demonstrated in heart failure patients and cardiac surgery patients. In the present work, the use of levosimendan is retrospectively analyzed in cardiac surgery patients of Westpfalz-Klinikum in Kaiserslautern to investigate different parameters of an unselected patient material and to gain experience for the use of levosimendan in cardiac surgery. The aim of the study was the evaluation of a standardized perioperative treatment concept using the calcium sensitizer levosimendan in patients with highly impaired left ventricular function. The following postoperative parameters were be compared between the two groups in order to evaluate the effect of levosimendan application:

- Short term survival in hospital (10 days and 30 days).
- Long term survival and follow up in 6 months, 1 year, 2 years and 3 years.
- Rehospitalization and number of postoperative readmissions to the hospital related to heart failure.

- Postoperative physical ability, and symptomatology (Classification according to NYHA and CCS).
- Preoperatitive and postoperative systolic heart function - ejection fraction.
- Kidney function, postoperative renal failure, need for renal replacement therapy.
- Cardiopulmonary Bypass parameters (total bypass time, aortic cross-clamp time).
- Invasive ventilation time, weaning from ventilator.
- Perioperative need for inotropic support.
- Need for mechanical support with IABP.
- Frequency of postoperative arrhythmias.
- Postoperative need for transfusion of blood products (RBCs, FFPs and PLTs).

The following laboratory values including the preoperative value and the values of the first five postoperative days were also be compared between the two groups:

- Hemoglobin
- C-reactive protein (CRP)
- Troponin I (Unltrasensitive)
- Creatine Kinase (CK)
- Myocardial creatine kinase (CK-MB)
- Creatinin
- Creatinin clearance
- Glomerular filtration rate (GFR)
- pH
- Lactic acid

The influence of the modified therapeutic concept on extracorporeal circulation parameters, clinical and laboratory parameters and mortality was thoroughly evaluated. The necessary data were collected as mentioned before retrospectively.

14. MATERIALS AND METHODS

14.1. Study design and patient data collection

The present study concerns a retrospective data analysis. Data were collected from 314 consecutive patients treated in the period from 24.12.2008 to 22.03.2017 in the department of cardiothoracic and vascular surgery of the Westpfalz-Klinikum Hospital in Kaiserslautern, regarding cases of patients with pre-existing preoperative heart failure undergoing cardiac surgery. 184 patients were given a preoperative and perioperative additive therapy with the calcium sensitizer levosimendan and they have been compared to a historical control group of 130 patients with similar characteristics who received conventional treatment.

The definitions of chronic heart failure, acute heart failure or cardiogenic shock mentioned above were used. All patients were postoperatively treated in the intensive care unit and were later transferred to the intermediate care unit and finally to the normal ward. Patients who were treated with levosimendan were comprehensively informed about the application of the substance and informed about the effects, side effects and overall concept. The data collection took place via the central digital archive of the Westpfalz-Klinikum hospital in Kaiserslautern (Orbis®, HYDMedia®).

The documentation of the primary data spanned the period of the clinical stay and ended with discharge, transfer to another hospital, or death of the patient. The laboratory parameters were extracted from the standard software programme used in our hospital (Ixserv®). The follow-up data were collected either through our archive or through direct contact with the patients, their relatives or their general practitioner / family doctor. The last update of the patients' actual condition was carried out on 31.01.2019. To record the patients, these were numbered in chronological order. A selection of the patient collective was not done. All patients were treated according to the treatment regimen of the current guidelines of the European Society of Cardiology (ESC) and European Association of Cardiothoracic Surgery (EACTS); Exceptional case decisions were made individually.

14.2. Inclusion and exclusion criteria

Inclusion criteria:

The study exclusively recruited patients with a diagnosis of heart failure who met the following criteria:

- Patients undergoing cardiac surgery with the assist of the extracorporeal circulation.
- Terminal heart failure (NYHA class III-IV, stage D ACC / AHA 2005).
- Clinical signs of decompensation with indication for therapy with the positive inotropic substance levosimendan.
- Preoperative left ventricular ejection fraction (LVEF) of ≤30% in TTE, TEE or MRI.
- Minimum age: 18 years.

Exclusion criteria:

Following the known precautions for the use of levosimendan and the exclusion of interference factors for the validity of the recorded measurements, patients with the following criteria were excluded from the study:

- Preoperative left ventricular ejection fraction (LVEF) of >30% in TTE, TEE or MRI.
- Patients who were conventionally (medical therapy) or interventionaly (PCI, TAVI etc.) treated.
- Patients with acute infective endocarditis.
- Severe acute or chronic liver disease.
- Systemic inflammatory syndrome (SIRS) or sepsis within the last 2 weeks prior to surgery.
- Patients who did not tolerate the administration of levosimendan due to excessive vasodilatatory effects.
- Patients who have not reached the age of 18, who are not consenting or consenting or who are participating in another study.

14.3. Application and dosis of Levosimendan

The product Simdax® of Orion Pharma was used with the active ingredient levosimendan. Each milliliter of the concentrate contains 2.5 mg of the substance. The basis for solution for infusion is one vial containing 5 ml of the active substance. 12.5 mg of the active ingredient were mixed with 50 ml of 0.9% NaCl solution to give an infusion solution containing 0.25 mg/ml and weight applied over a period of 24 hours. A bolus dose was dispensed with in this patient collective. All patients received levosimendan at a dose of 0.1 µg/kg/min as far as the hemodynamic situation allowed the administration in this dosis. The substance was infused via both central venous and peripheral venous accesses. In patients with mildly to moderately impaired renal or hepatic function, appropriate monitoring was performed. The administration was performed in the intensive care unit under monitoring of the vital parameters. The blood pressure was invasively monitored in all patients through catheterization of the radial artery. Special care was taken regarding the intravascular volume status of the patients providing them the appropriate infusion therapy. When vasodilatatory effects were seen, patients were treated with low-dose norepinephrine. The administration was interrupted in patients with persistent hypotension due to excessive vasodilatatory effects despite the additional support with intravenous fluids and norepinephrine. These patients were excluded from the study.

14.4. Ethics

Due to the project of the retrospective identification and use of patient data, the review of the study by the Ethics Commission at the state medical association (Landesärztekammer) of Rheinland-Paltinate was required. Following a successful presentation of the study protocol, a positive ethics vote was achieved on 16.06.2015 taking into account state hospital act (Landeskrankenhausgesetz §36 and §37) and the good clinical practice for trials on medicine products in the european community (ICH-GCP). In compliance with the listed requirements, the ethics committee confirmed that there are no ethics concerns and professional concerns.

14.5. Statistical analysis

In this retrospective cohort study, demographics, survival, pre and postoperative clinical data alongside laboratory parameters obtained at different timepoints were collected for 314 patients who underwent heart surgery. Results have been reported by Control and Levosimendan group to facilitate comparisons. Categorical variables have been summarized using frequencies and percentages whereas continuous variables via median, interquartile range (IQR) and mean in case of an underlying normal distribution. Histograms and bar charts have been used to display the distribution of continuous and categorical variables respectively.

Depending on the nature of the variables involved, the appropriate statistical test was applied to examine if there was a statistically significant difference in the two groups. The chi-squared test was used to assess the association of categorical variables. The Kruskal-Wallis test was used to evaluate the association of an ordinal and a categorical variable. The distribution of a continuous variables was inspected using either a histogram or a Shapiro-Wilk test to assess deviations from normality. Depending on the distribution of a continuous variable in each cohort, either the t-test or the Mann-Whitney test was used to assess for differences. Significance level was set to $p<0.05$ for all statistical tests.

The Kaplan-Meier method was used to estimate the probability of survival after heart surgery for the two patient groups. Survival estimates at different timepoints were presented alongside 95% confidence intervals. The log-rank test was used to assess whether there was a significant difference in the survival functions of the two groups.

Statistical analysis was conducted using STATA13.

15. RESULTS

15.1. Demographics

Despite the retrospective character of the study, the groups of patients are homogeneous with regard to the general demographic data. The demographic, biological and clinical characteristics at baseline are presented in Tables 19 and 20.

	Control (N: 130)	Levosimendan (N: 184)	P value
Gender (N, %)			0.551
Males	106 (81.54)	145 (78.80)	
Females	24 (18.46)	39 (21.20)	
Age (years)			
Median (IQR)	71 (63,76)	69 (63, 76.50)	0.703
Weight (kg)			
Median (IQR)	82.15 (75,88)	83.99, 85 (76,90)	0.087
Height (cm)			
Median (IQR)	174.5 (168, 178)	175 (168,178)	0.874
Body Mass Index (BMI)			
Median (IQR)	26.8 (25.40,28.70)	27.6 (25.5, 30.38)	0.072
Body surface area (BSA)			
Median (IQR)	1.99 (1.85, 2.06)	2.01 (1.91, 2.10)	0.096

Table 19. Patients' characteristics at baseline.

Distribution of gender was similar in the control and levosimendan group with males forming the majority, 81.54% and 78.80% respectively (p=0.551 from chi-squared test) (Figure 28).

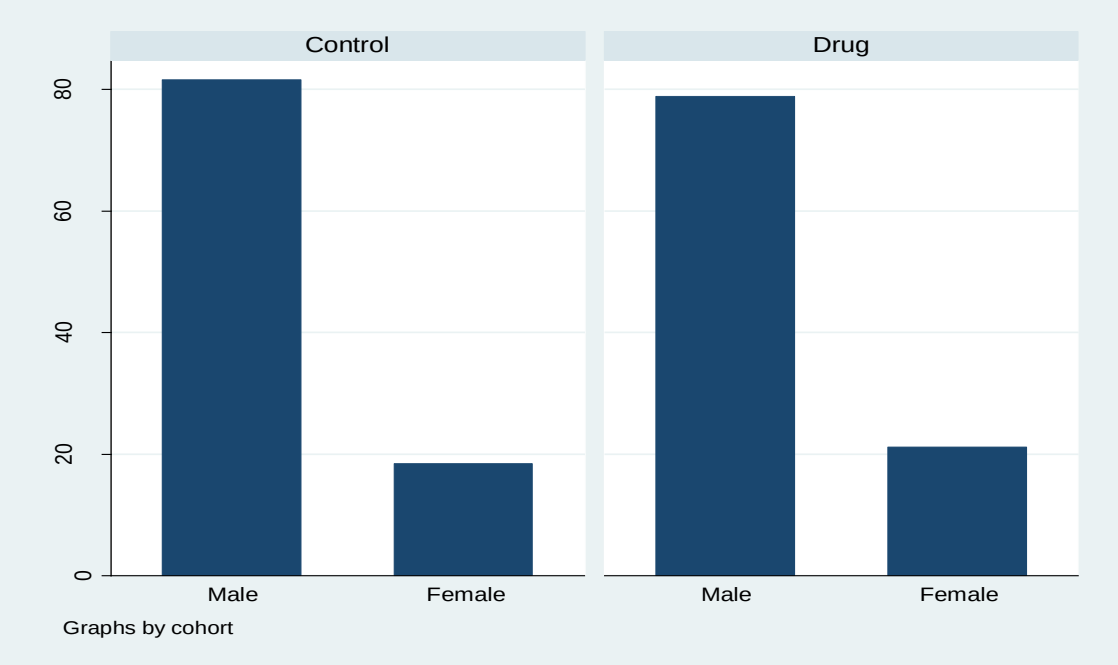


Figure 28. Frequency of participants' gender in the control and drug group.

Median age at operation was 71 and 69 years for the control and Levosimendan group respectively. No significant difference was observed (p=0.703). The age distribution is shown in figure 29.

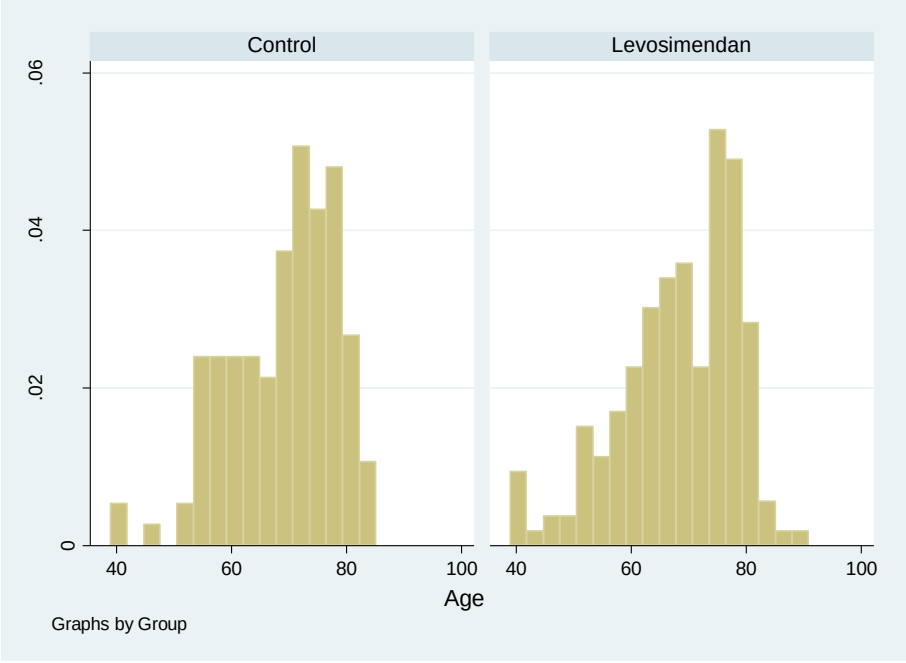


Figure 29. Histograms of age by group.

The Mann-Witney test showed no difference in the distribution of weight (p=0.087), height (p=0.874), body mass index (BMI) (p=0.072) and body surface area (BSA) (p=0.096) in the two groups. The distribution of the above parameters is shown in the following grafics (Figures 30-33).

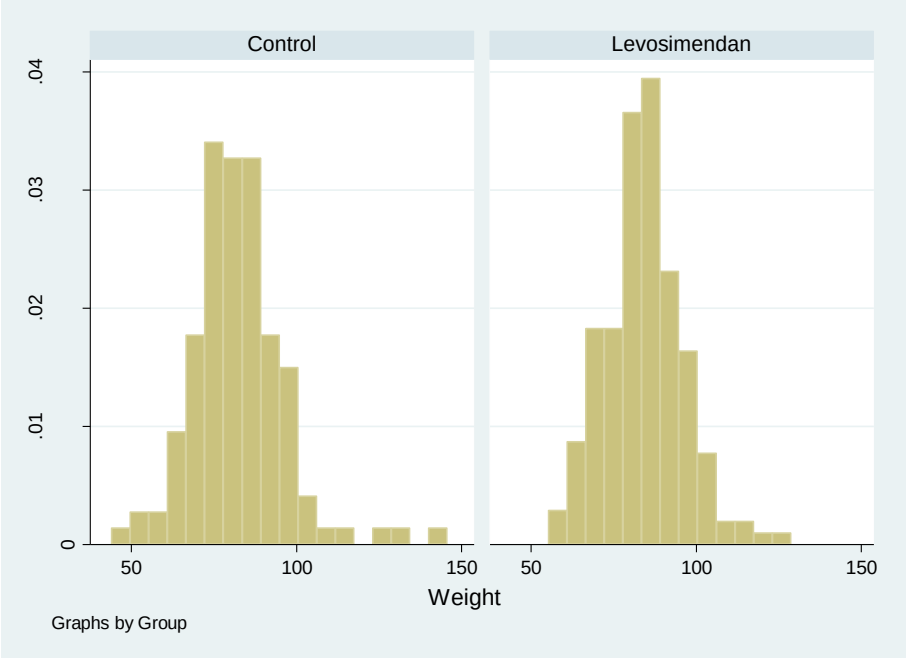


Figure 30. Histograms of weight by group.

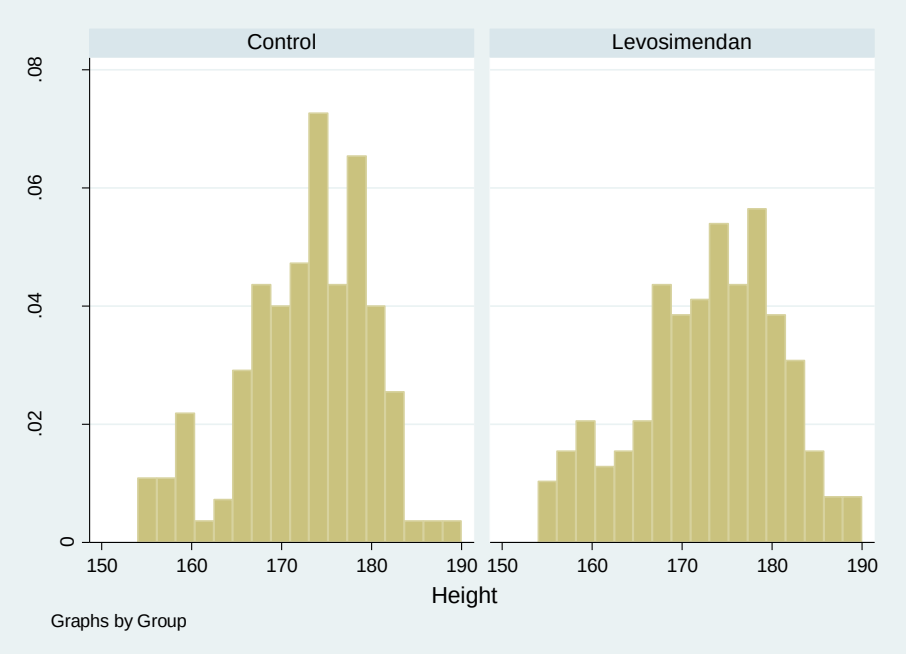


Figure 31. Histograms of height by group.

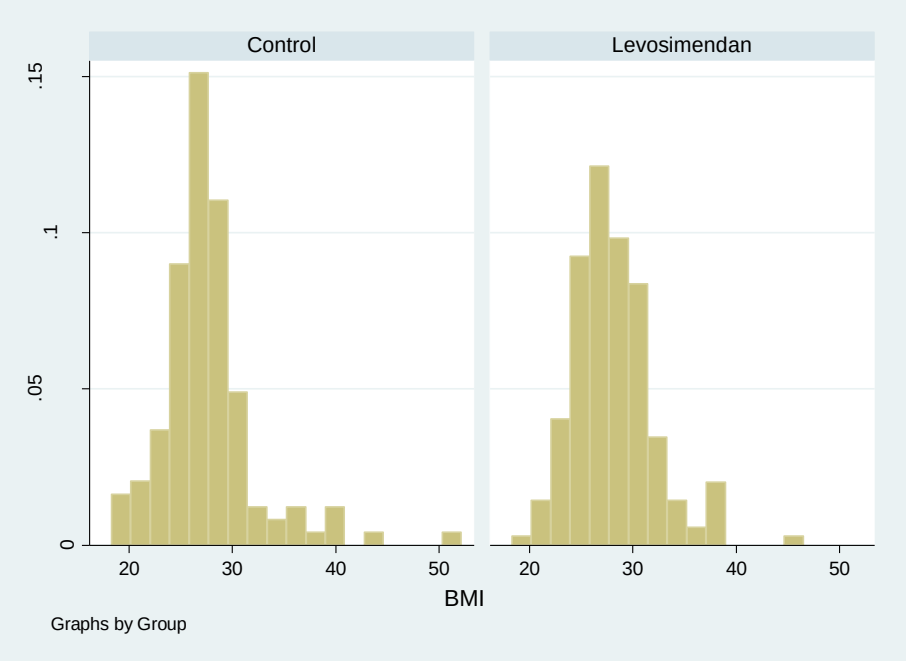


Figure 32. Histograms of BMI by group.

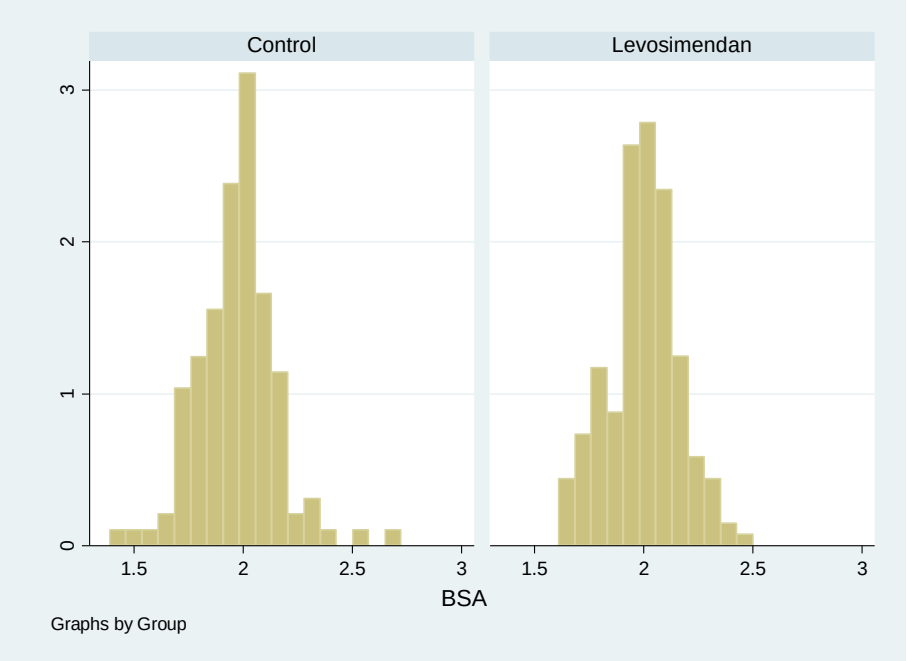


Figure 33. Histograms of BSA by group.

15.2. Clinical characteristics at baseline

The collected data regarding the preoperative clinical characteristics of the patients who took part in the study are presented in table 20.

	Control (N: 130)	Levosimendan (N: 184)	P value
Euroscore 1			
Median (IQR)	15.72 (8.07, 27.90)	22.80 (11.59, 42.52)	**<0.001**
Euroscore 2			
Median (IQR)	5.43 (3.41, 10.46)	8.82 (5.09, 17.10)	**<0.001**
ASA score (N, %)			
2	1 (0.77)	0 (0.00)	**0.048**
3	26 (20.00)	31 (16.85)	
4	89 (68.46)	116 (63.04)	
5	14 (10.77)	37 (20.11)	
Type of surgery (N, %)			
Elective/regular surgery	96 (73.85)	133 (72.28)	**0.759**
Emergency surgery	34 (26.15)	51 (27.72)	
Number of bypass grafts (N, %)			
0	15 (11.54)	21 (11.41)	**0.324**
1	5 (3.85)	9 (4.89)	
2	12 (9.23)	28 (15.22)	
3	42 (32.31)	57 (30.98)	
4	43 (33.08)	49 (26.63)	
5	12 (9.23)	20 (10.87)	
6	1 (0.77)	0 (0.00)	
Simple/Combination surgery (N, %)			
Simple surgery	95 (73.08)	118 (64.13)	**0.095**
Combination surgery	35 (26.92)	66 (35.87)	
Acute myocardial infarction (AMI) (N, %)			
No	94 (72.31)	137 (74.46)	**0.671**
Yes	36 (27.69)	47 (25.54)	
Arterial hypertension (N, %)			

No	9 (6.92)	8 (4.35)	**0.321**
Yes	121 (93.08)	176 (95.65)	
Pulmonary hypertension (N, %)			
No	119 (91.54)	128 (69.57)	**<0.001**
Yes	11 (8.46)	56 (30.43)	
Hyperlipidemia (N, %)			
No	35 (26.92)	37 (20.11)	**0.157**
Yes	95 (73.08)	147 (79.89)	
Diabetes mellitus (N, %)			
No	96 (73.85)	127 (69.02)	**0.353**
Yes	34 (26.15)	57 (30.98)	
Arrhythmias (N, %)			
No	105 (80.77)	128 (69.57)	**0.025**
Yes	25 (19.23)	56 (30.43)	
Renal failure (N, %)			
No	112 (86.15)	137 (74.46)	**0.012**
Yes	18 (13.85)	47 (25.54)	
Chronic obstructive pulmonary disease (COPD) (N, %)			
No	109 (83.85)	141 (76.63)	**0.118**
Yes	21 (16.15)	43 (23.37)	
Extracardiac arteriopathy (N, %)			
No	108 (83.08)	126 (68.48)	**0.003**
Yes	22 (16.92)	58 (31.52)	
Cerebrovascular accidents (N, %)			
No	124 (95.38)	159 (86.41)	**0.009**
Yes	6 (4.62)	25 (13.59)	
Dyspnoea classification (NYHA) (N, %)			
1	0 (0.00)	0 (0.00)	**0.032**
2	7 (5.38)	8 (4.35)	
3	66 (50.76)	72 (31.13)	
4	57 (43.85)	104 (56.52)	
Classification of angina (CCS) (N, %)			
0	3 (2.31)	3 (1.63)	**0.124**
1	6 (4.62)	10 (5.43)	

2	18 (13.85)	24 (13.04)	
3	60 (46.15)	65 (33.00)	
4	43 (33.08)	82 (44.57)	
Ejection fraction (EF)			
Median (IQR)	30 (25, 30)	20 (18.5, 30)	**<0.001**

Table 20. Patients' baseline clinical characteristics prior to surgery.

As shown in table 20, the distribution of Euroscore 1 and Euroscore 2 at baseline is significantly different in the two groups ($p<0.001$ from Mann-Whitney test in both cases). The mean Euroscore 1 was 15.72% for the control group and 22.80% for the Levosimendan group. This demonstrates that the patients included in the Levosimendan group were of higher perioperative risk than the control patients. This feature should be taken into account when comparing the survival rates between the two groups. The following boxplots (Figures 34-35) demonstrate the distribution of the measured scores.

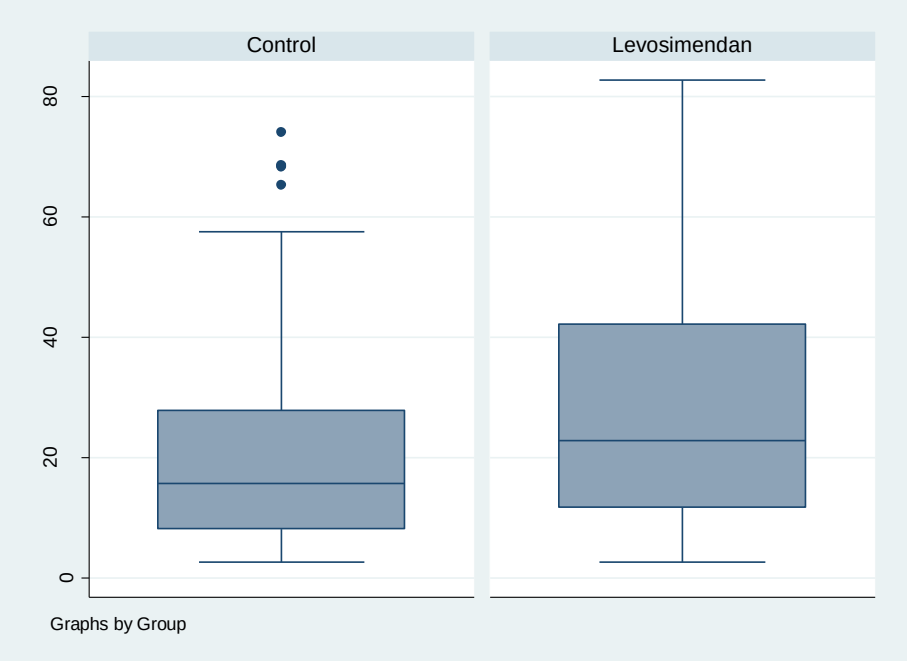


Figure 34. Boxplot of Euroscore 1 by group.

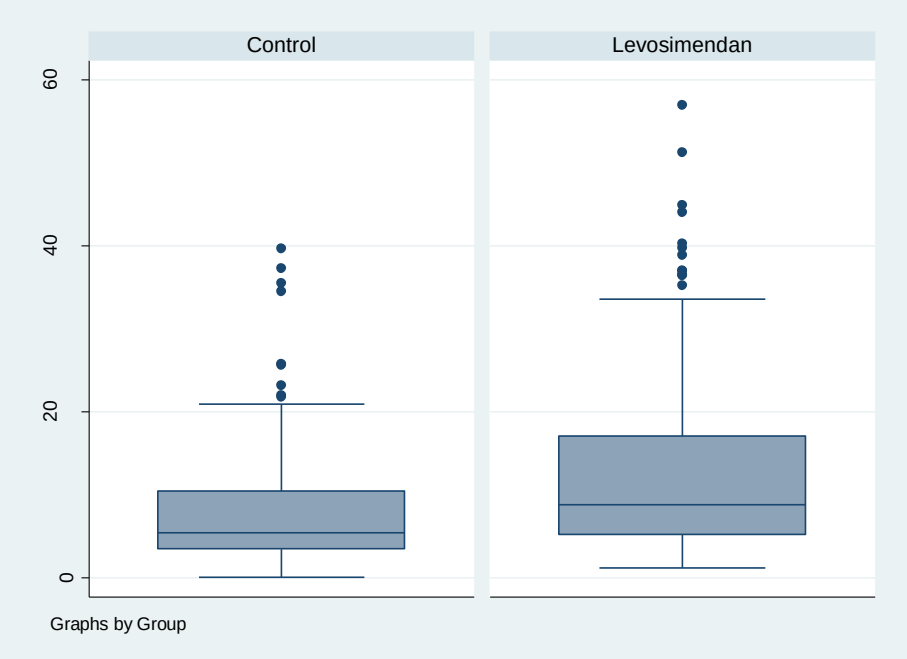


Figure 35. Boxplot of Euroscore 2 by group.

The American Society of Anesthesiologists (ASA) physical status classification system was developed to offer clinicians a simple categorization of a patient's physiological status that can be helpful in predicting operative risk. The Kruskal-Wallis test showed that the distribution of ASA class is also significantly different between the two groups (p=0.048). Most patients of both groups were of class 4 in the ASA classification. However, relatively more patients of the Levosimendan group were classified as ASA 4 and 5 than in the control group as shown in the graphic below. This parameter also demonstrates the higher preoperative risk of the patients in the Levosimendan group (Figure 36).

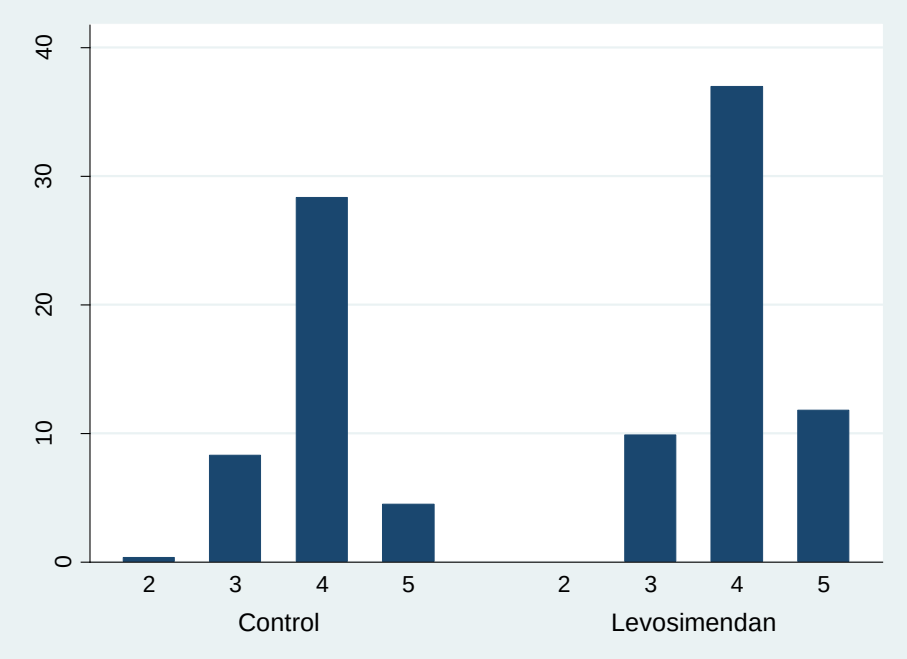


Figure 36. Frequency of ASA score in the two cohorts.

Ejection fraction was a crucial factor and a major inclusion criterium of this study. In order to study the improvement of EF after treatment the thorough evaluation of the preoperative baseline values is highly important. A significantly higher distribution of ejection fraction was observed in the controls ($p<0.001$ from Mann-Whitney test). The median EF was 30% for the control group and 20% for the levosimendan group. This result demonstrates that the grade of heart failure was higher in the levosimendan group (Figure 37).

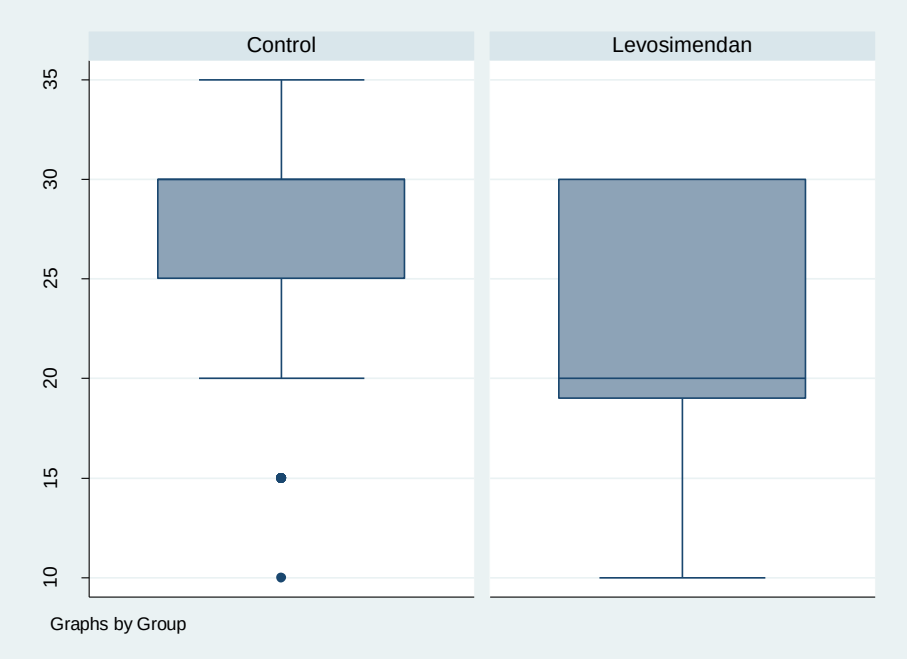


Figure 37. Boxplot of preoperative ejection fraction by group.

As for dyspnoea staging according to NYHA classification, it was noticed that 50.76% of patients in the control group experienced Stage 3 pre-operatively, whereas only 31.13% in the drug group (p=0.032). Dyspnoea at rest (NYHA 4) was however observed in 43.85% of the control group and in 56.52% of the Levosimendan group. The difference of NYHA class in the two groups is significant (Figure 38).

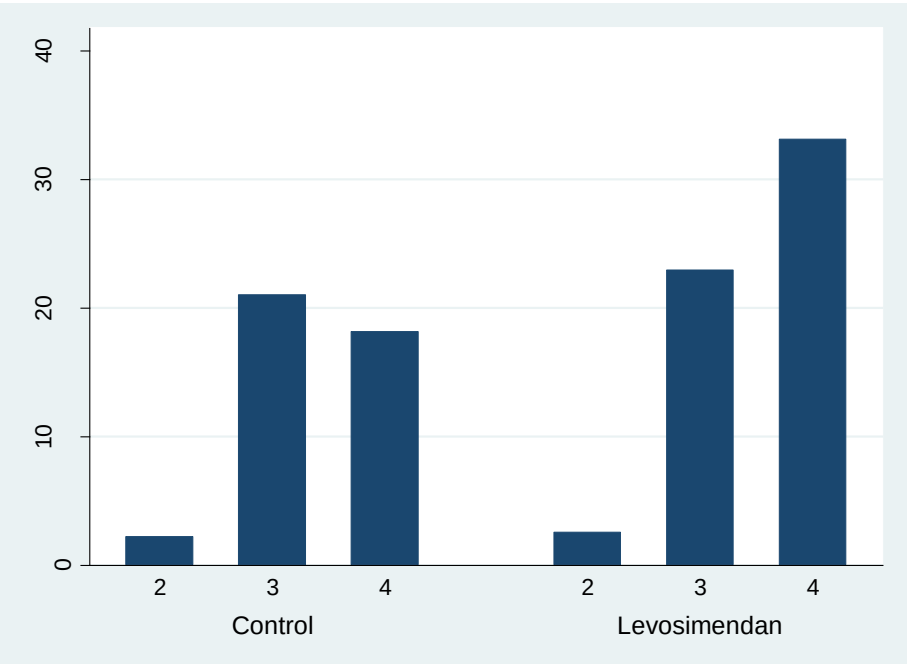


Figure 38. Staging of preoperative dyspnoea according to NYHA classification.

Regarding the staging of angina pectoris, table 20 shows that 46.15% of the control group and 33% of the Levosimendan group experienced angina symptoms during ordinary physical activity (Class 3), whereas 33.07% of the control group and 44.57% of the levosimendan group reported angina pectoris at rest (Class 4). The differences in the two groups were not statistically significant (Figure 39).

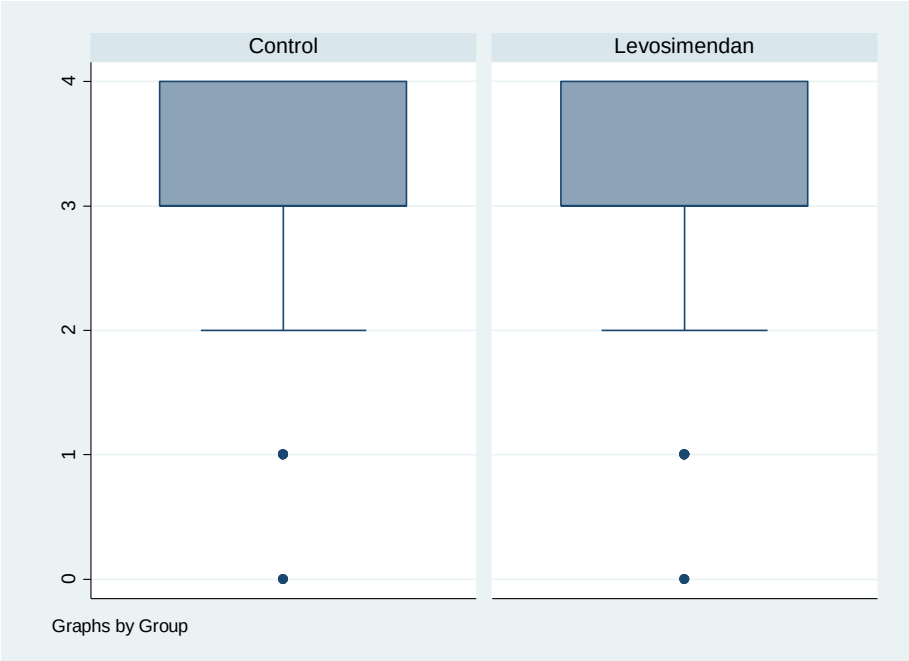


Figure 39. Frequency of staging of angina according to CCS in the two cohorts.

Not all patients included in this study were operated on an elective regular basis. A significant amount of patients needed to be operated on an emergency condition. The majority of cases in both groups underwent elective/regular surgery (73.85% and 72.28%). As far as this parameter is concerned the two groups showed no significant differences (Figure 40).

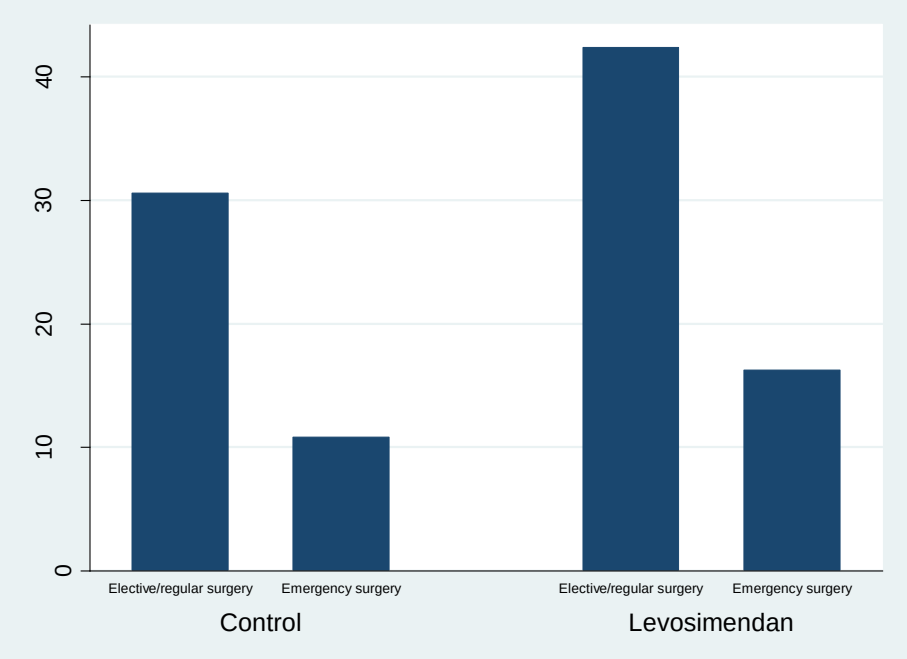


Figure 40. Frequency of type of surgery (regular of urgent) in the two cohorts.

The next figure presents the percentage of the patients who needed to be operated under acute myocardial infarction. 27.69% of the control group patients and 25.54% of the levosimendan group patients were presented with an acute myocardial infarction. There was no significant difference between the groups as far as this parameter is concerned (p=0.759) (Figure 41).

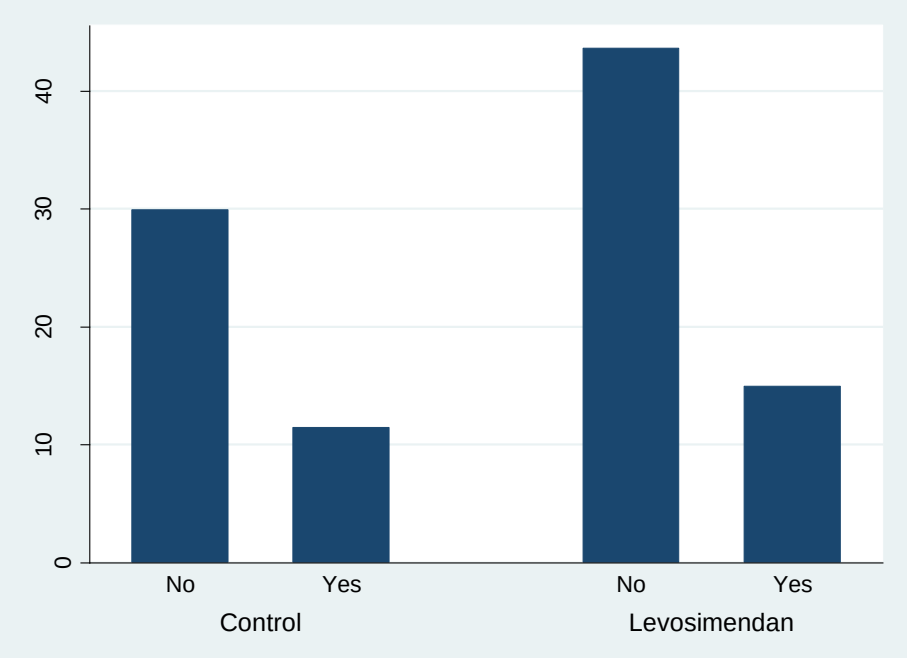


Figure 41. Frequency of preoperartive acute myocardial infarction in the two cohorts.

In a significant amount of patients more than one surgical procedures needed to be carried out (Bypassgrafting, aortic or mitral valve replacement or repair, surgery on the aorta or aoric root etc.) However no significant difference was observed between the two groups (p=0.095). 26.92% of the control group patients and 35.85% of the levosimendan group patients underwent a combined surgery (Figure 42).

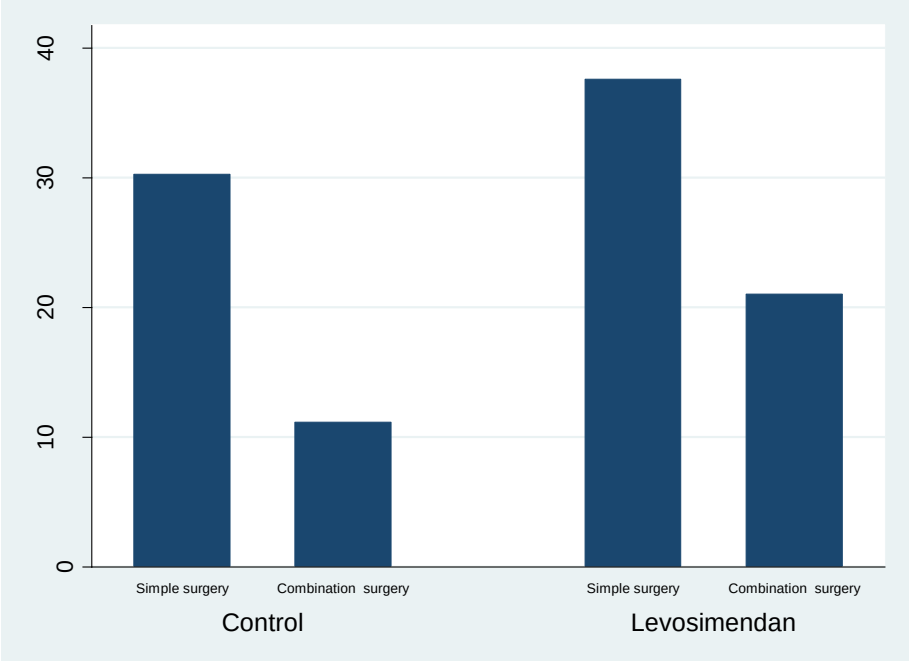


Figure 42. Frequency of simple or combined surgery in the two cohorts.

As far as the number of bypass grafts received by the patients is concerned, there was no significant difference between control and levosimendan group (p=0.324). The number of grafts are demonstrated in table 20 and figure 43.

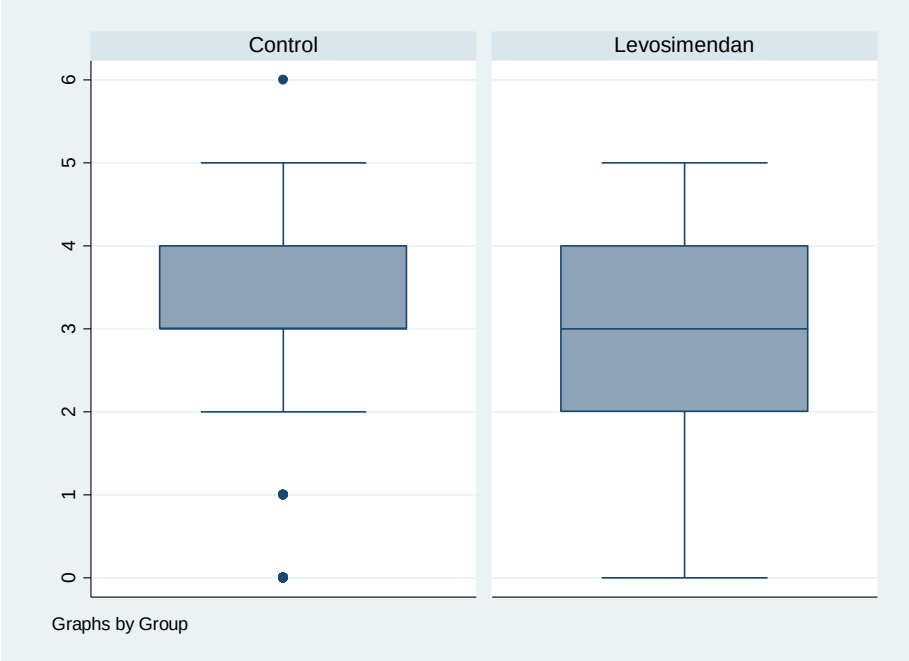


Figure 43. Boxplot of number of bypass-grafts by group.

The following data demonstrate the rest clinical features which characterize the comorbidity of the patients included in the study.

Occurrence of arrhythmias (Figure 44) before surgery was significantly different in the two groups, 19.23% in the controls and 30.43% in the drug group (p=0.030 from chi-squared test).

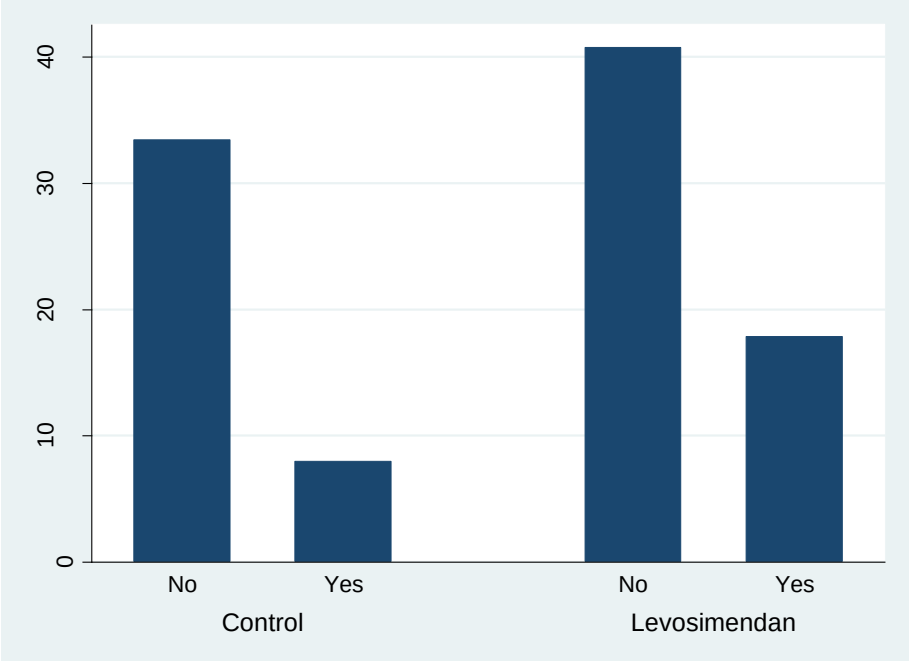


Figure 44. Frequency of arrhythmias prior to surgery in the two cohorts.

Similarly, the appearance of pulmonary hypertension before surgery (Figure 45) was significantly different in the two groups, 8.46% in the controls and 30.43% in the drug group ($p<0.001$ from chi-squared test).

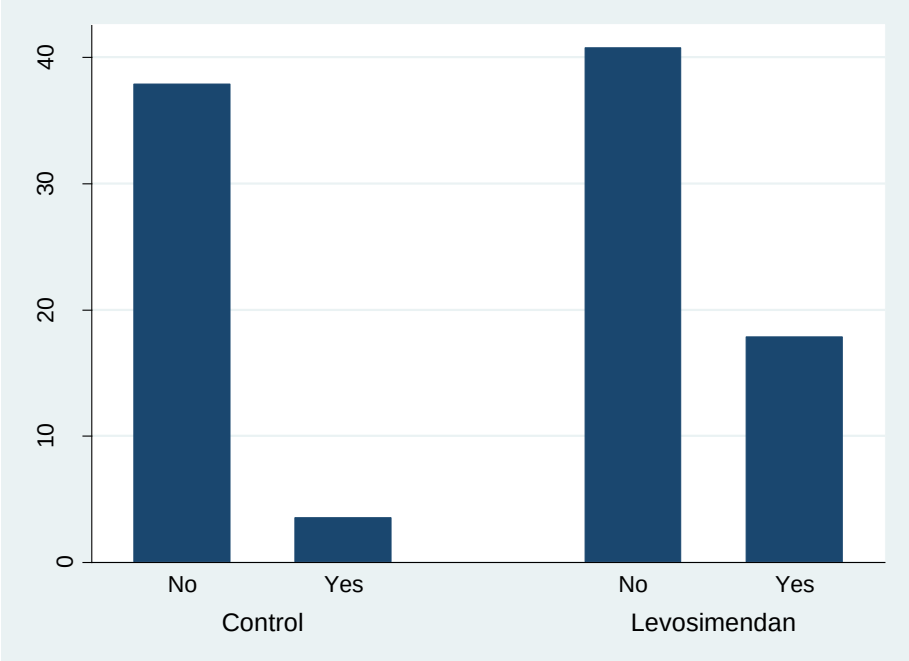


Figure 45. Frequency of pulmonary hypertension prior to surgery in the two cohorts.

The following risk factors were not significantly different between the two groups indicating a similar comorbidity profile for both groups. Arterial hypertension (Figure 46) was present in most patients of both groups, 93.08% and 95.65% for the control and levosimendan group respectively (p=0.321). 73.85% of the control group patients and 69.02% of the levosimendan group patients suffered from diabetes mellitus (p=0.353) (Figure 47). Hyperlipidaemia (Figure 48) was present in 26.92% of the controls and 20.11% in the drug group (p=0.175). COPD (Figure 49) was recorded in 16.15% of the control patients and 23.37% of the levosimendan patients (p=0.118).

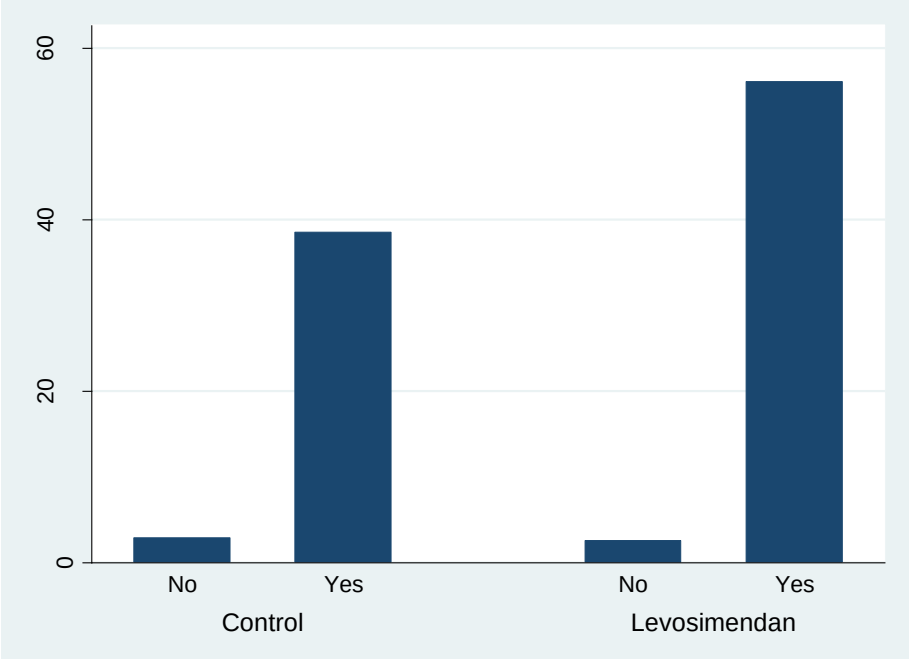


Figure 46. Frequency of arterial hypertension prior to surgery in the two cohorts.

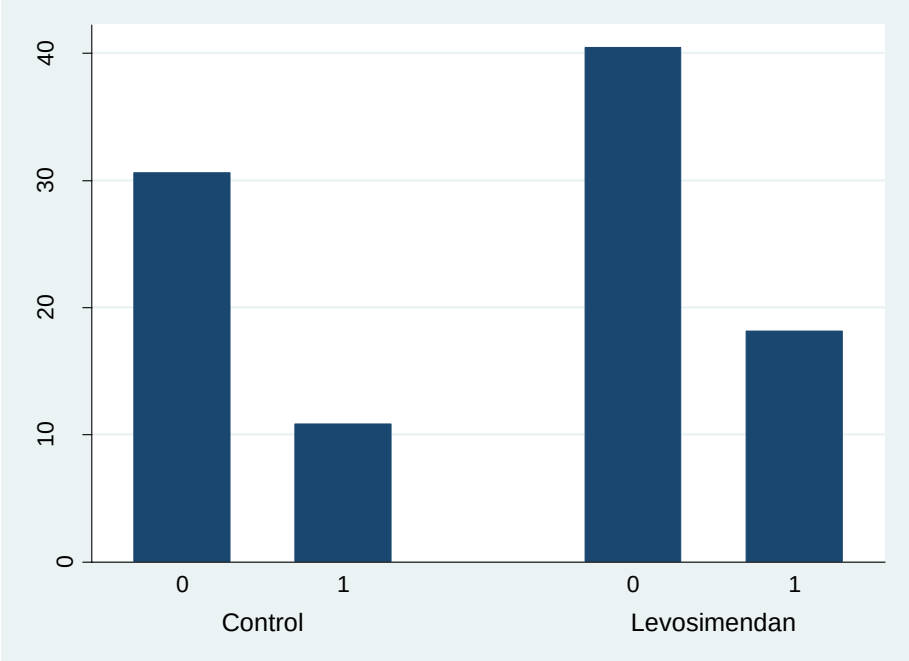


Figure 47. Frequency of Diabetes mellitus prior to surgery in the two cohorts.

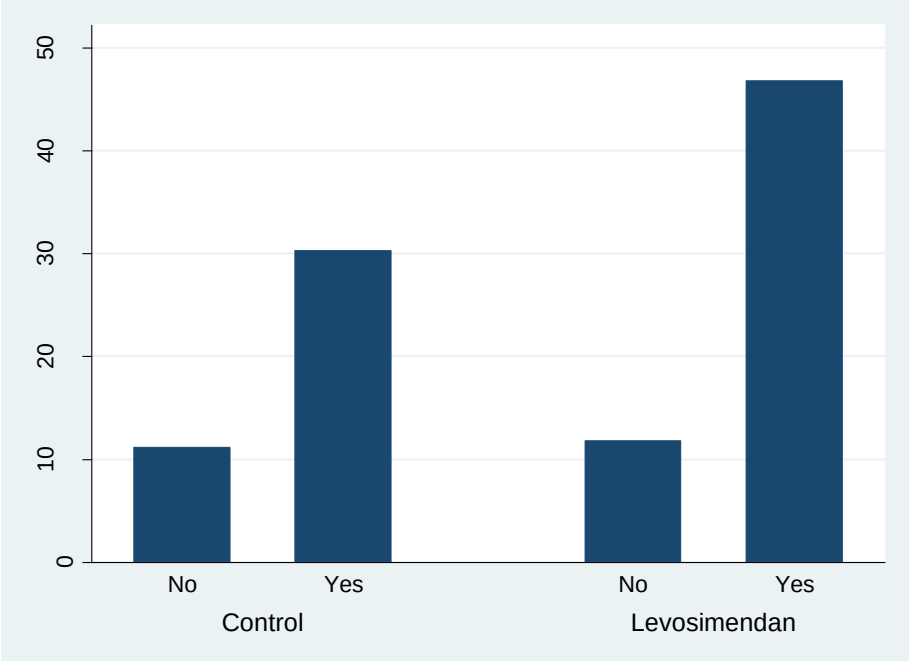


Figure 48. Frequency of Hyperlipidemia prior to surgery in the two cohorts.

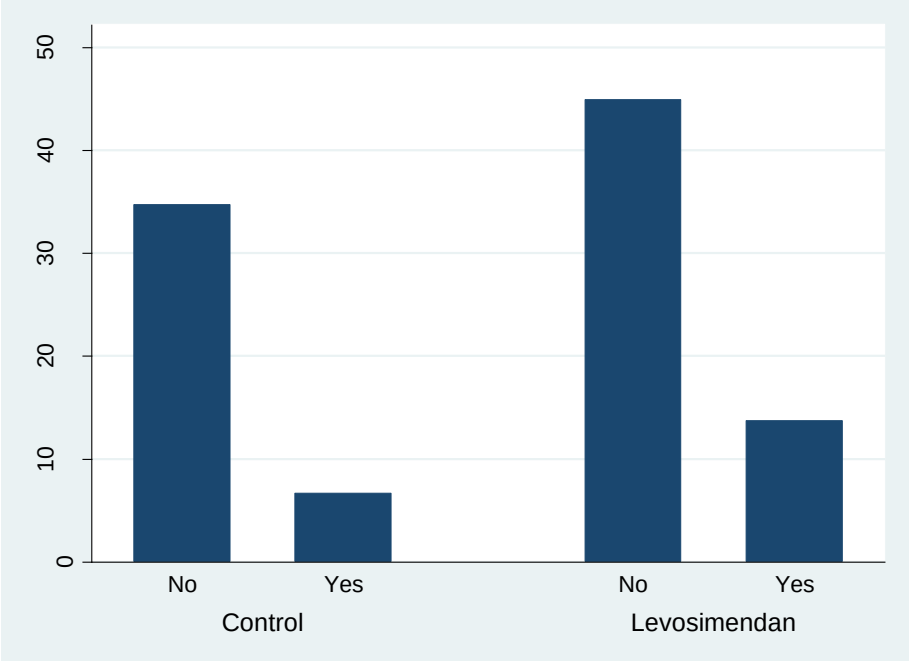


Figure 49. Frequency of chronic obstructive pulmonary disease prior to surgery in the two cohorts.

Finally, some significant differences were observed in the last 3 clinical parameters. 13.85% of control cases had renal failure versus 25.54% in the drug group (p=0.012) (Figure 50), 16.28% had extracardiac arteriopathy versus 31.52% in the levosimendan group (p=0.003) (Figure 51) and 4.62% had a cerebrovascular accident versus 13.59% in the drug group (p=0.009) (Figure 52).

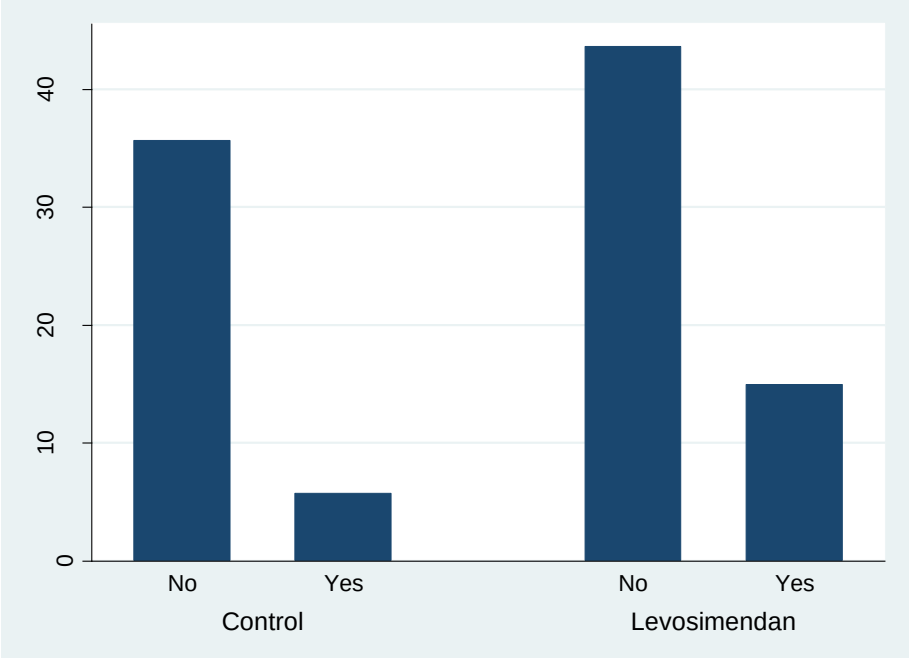


Figure 50. Frequency of renal failure prior to surgery in the two cohorts.

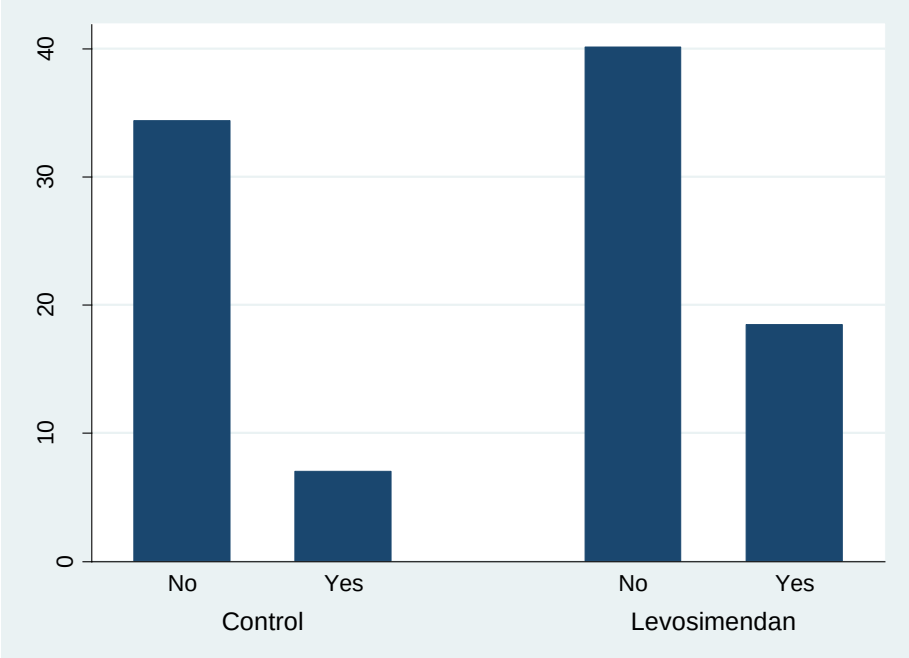


Figure 51. Frequency of extracardiac arteriopathy prior to surgery in the two cohorts.

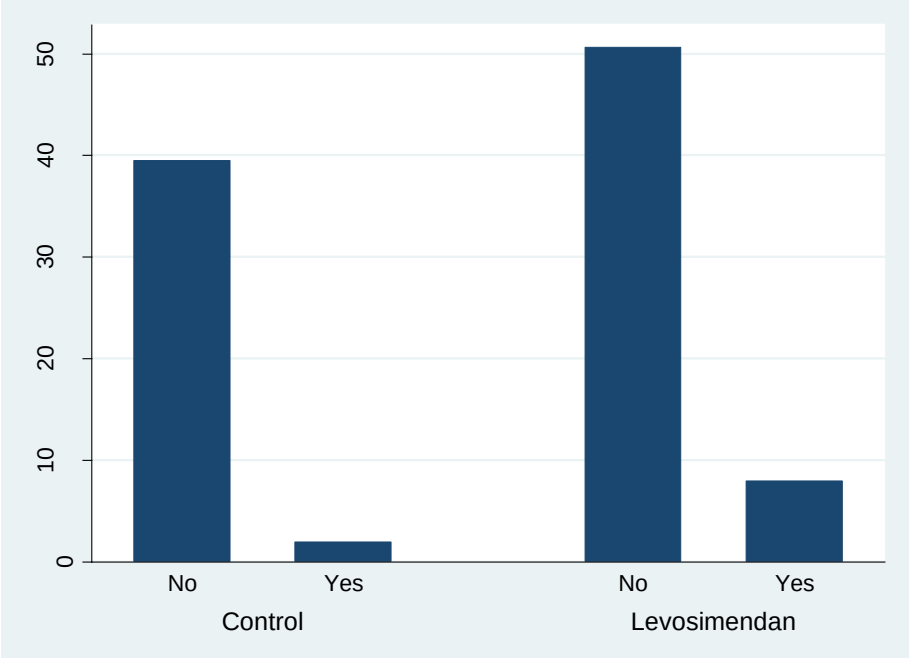


Figure 52. Frequency of cerebrovascular accidents prior to surgery in the two cohorts.

15.3. Intraoperative surgical times

The intraoperative data concerning the surgical times are shown below in table 21.

	Control (N:130)	Levosimendan (N: 184)	p value
Duration of surgery (min)			
Median (IQR)	218.00 (177.50, 262.75)	227.50 (184.00, 283.75)	**0.220**
Bypass-Time (min)			
Median (IQR)	113.00 (91.00, 154.00)	111.00 (82.00, 153.25)	**0.313**
Cross-Clamp-Time (min)			
Median (IQR)	78.00 (56.75, 103.25)	71.00 (54.00, 92.00)	**0.041**

Table 21. Intraoperative surgical times in the two cohorts.

Distribution of cross-clamp time (Figure 53) was significantly different in the two groups where median was 78 minutes in the control group and 71 minutes in the drug group, suggesting a trend towards longer cross-clamp time in the controls (p=0.041).

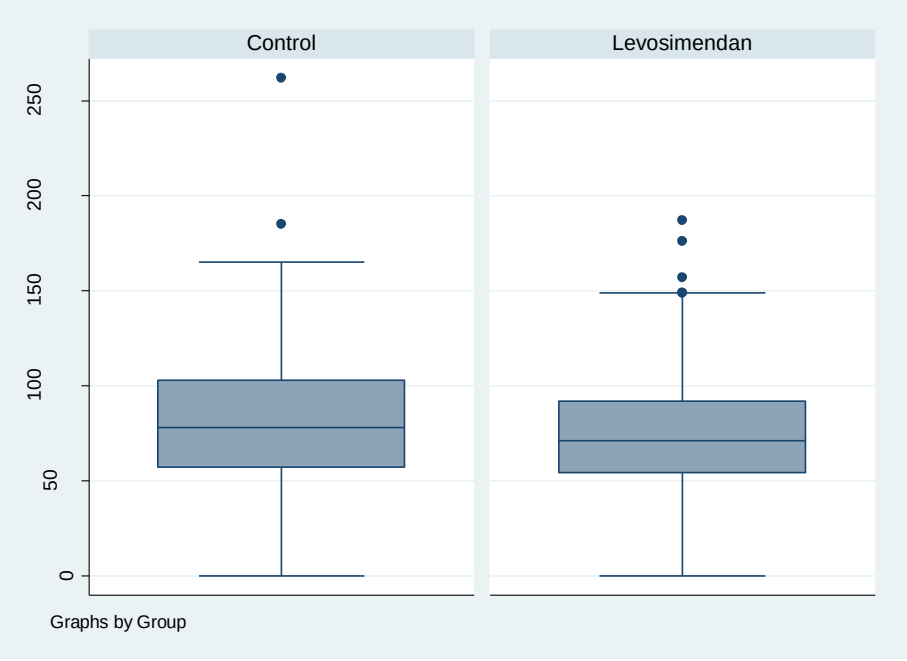


Figure 53. Boxplot of Cross-Clamp-Time (min) by group.

Duration of cardiopulmonary bypass (p=0.313) and the total duration of surgery (p=0.220 from Mann-Whitney test) were not significantly different in the two groups, as shown in figures 54 and 55.

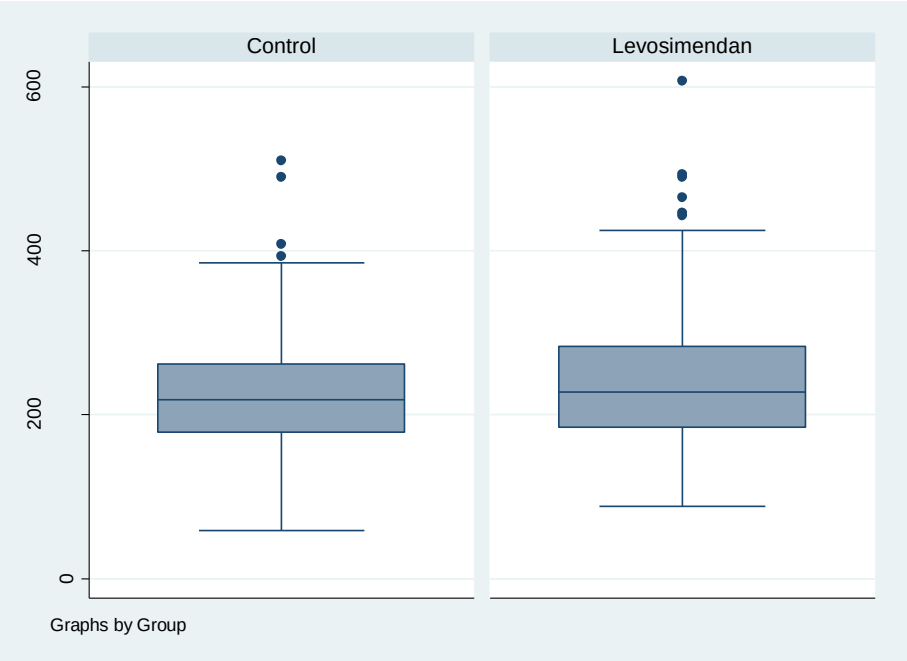


Figure 54. Boxplot of duration of surgery (min) by group.

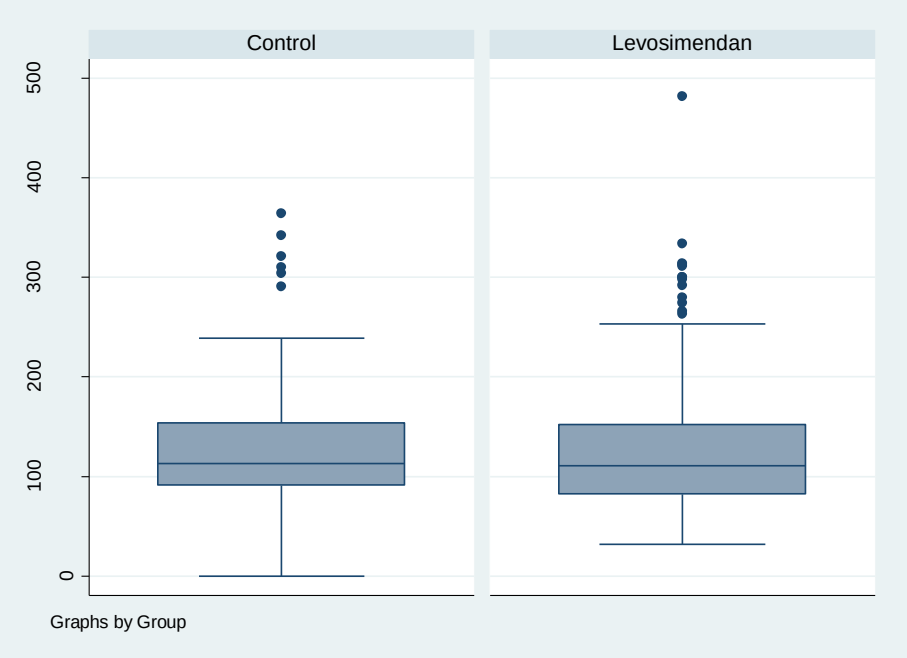


Figure 55. Boxplot of Bypass-time (min) by group.

15.4. Overall Survival

Survival was an important endpoint of this study. Survival rates in both groups were compared on the 10th, 30th day, on 6 months and 1, 2 and 3 years as shown in Table 22. Last follow-up update was on the 31st of January 2019.

Group	10 days	30 days	6 months	1 year	2 years	3 years
Control Median (IQR)	0.82 (0.75-0.88)	0.64 (0.55-0.71)	0.55 (0.46-0.63)	0.54 (0.45-0.62)	0.52 (0.43-0.60)	0.51 (0.42-0.59)
Levosimendan Median (IQR)	0.85 (0.79-0.90)	0.76 (0.69-0.82)	0.70 (0.62-0.76)	0.68 (0.61-0.75)	0.65 (0.58-0.72)	0.65 (0.57-0.71)

Table 22. Survival probability alongside 95% C.I. at different timepoints from operation date by cohort.

Figures 56-58 show the overall survival probability from date of surgery, estimated via the Kaplan-Meier (KM) method, by patient subgroup. The KM figure shows the superior overall survival of the levosimendan group compared to the control group (p=0.005 from log-rank test). Survival estimates at different timepoints for the two patient subgroups additionally show the consistently higher overall survival probability of the levosimendan subgroup throughout follow-up. Figures 56 and 57 show the survival probability of patient subgroups 30 days and 1 year after the date of surgery respectively (p=0.05 and p=0.02 from log-rank test). 3 years after surgery, 51% of cases were alive in the control group compared to 65% in the drug group (p=0.005), as shown in figure 58.

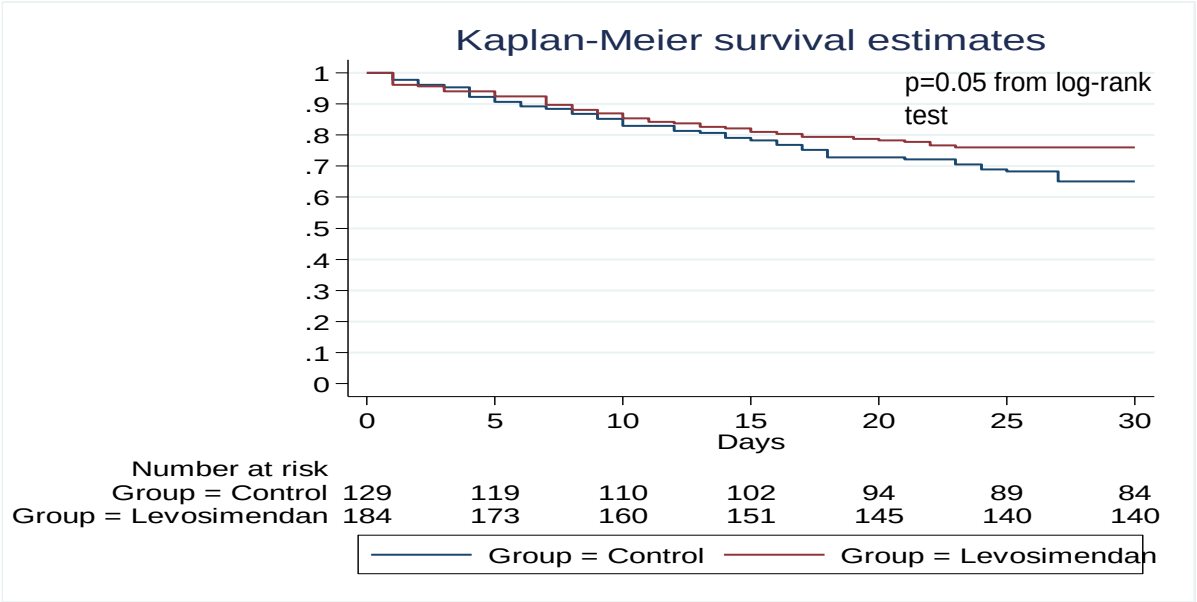


Figure 56. Overall survival from date of operation (30 days).

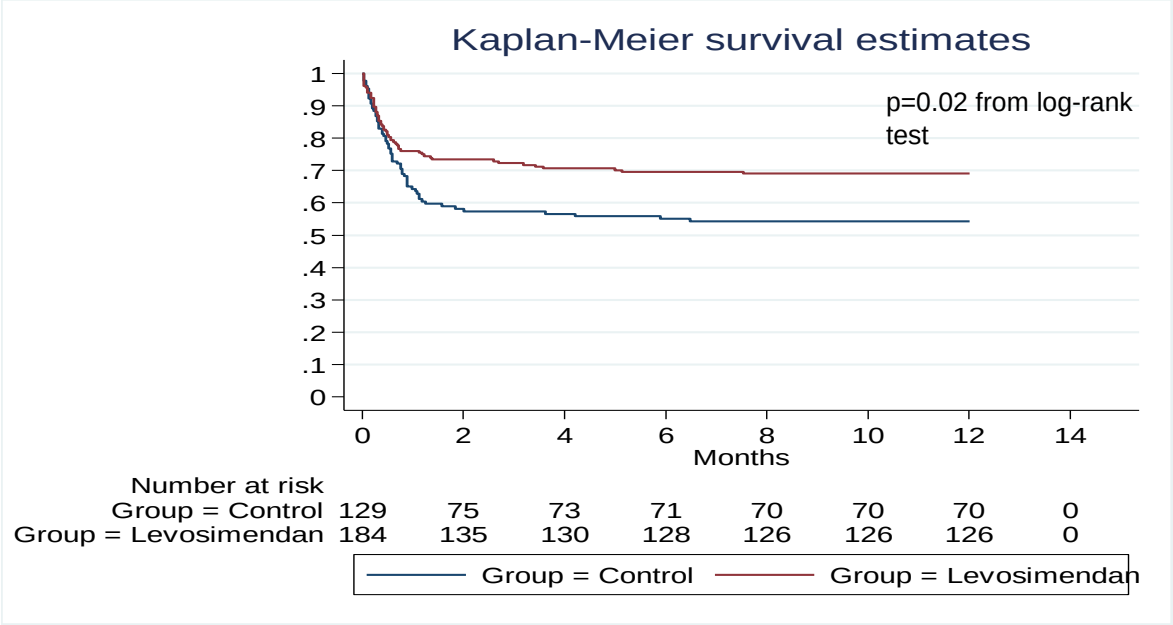


Figure 57. Overall survival from date of operation (1year).

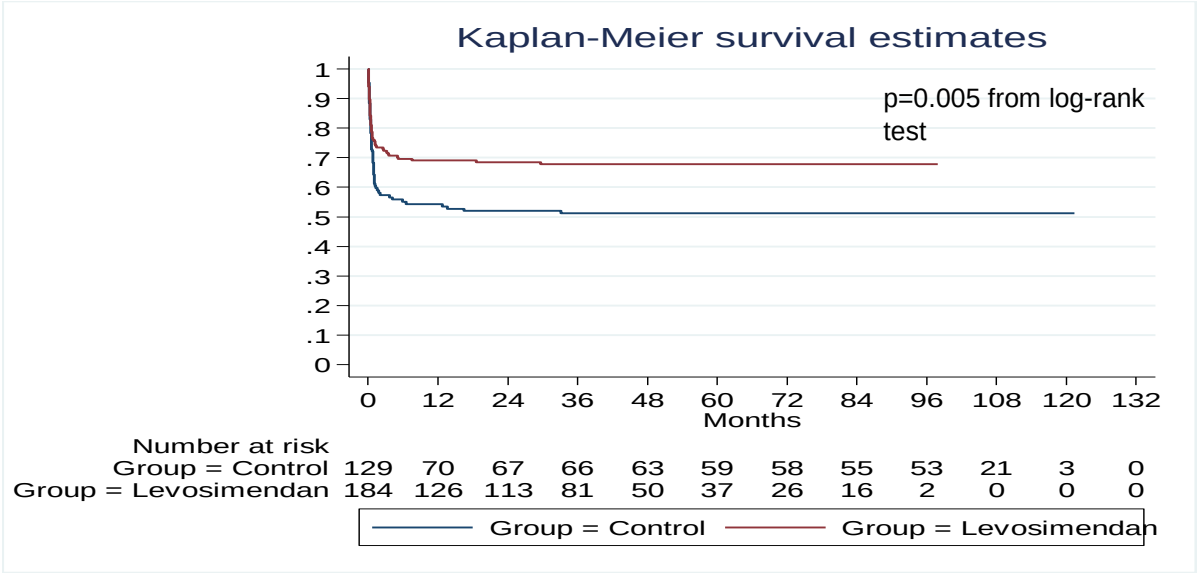


Figure 58. Overall survival from date of operation (3 years).

15.5. Postoperative parameters

Table 23 presents the frequency and percentage of the post-operative parameters in the two groups. A statistically significant difference between the two cohorts was observed for all variables except for the total platelet units transfused, support with IABP, duration of patient support with inotropic drugs in the ICU and hospitalization days. This is highly indicative of the positive effect of levosimendan versus the no treatment option before surgery.

	Control (N: 130)	Levosimendan (N: 184)	P value
Number of readmissions to hospital (N, %)			
0	2 (2.74)	74 (54.41)	**<0.001**
1	25 (34.25)	36 (26.47)	
2	30 (41.10)	16 (11.76)	
3	8 (10.96)	5 (3.68)	
4	5 (6.85)	2 (1.47)	
5	3 (4.11)	1 (0.74)	
6	0 (0.00)	2 (1.47)	
Number of readmissions to hospital			
Median (IQR)	2 (1, 2)	0 (0, 1)	**<0.001**
Dyspnoea staging (NYHA) (N, %)			
0	0 (0)	19 (10.33)	**<0.001**
1	14 (10.77)	76 (41.30)	
2	48 (36.92)	34 (18.48)	
3	22 (16.92)	11 (5.98)	

4	46 (35.38)	44 (23.91)	
Staging of angina (CCS) (N, %)			
0	6 (4.62)	66 (35.87)	**<0.001**
1	45 (34.62)	67 (36.41)	
2	30 (23.08)	9 (4.89)	
3	19 (14.62)	7 (3.80)	
4	30 (23.08)	35 (19.02)	
Postoperative Ejection fraction (EF)			
Median (IQR)	30.00(25.00, 30.00)	30.00(25.00, 39.50)	**0.025**
Need for hemodialysis (N, %)			
No	92 (70.77)	163 (88.59)	**<0.001**
Yes	38 (29.23)	21 (11.41)	
Artificial ventilation (days)			
Median (IQR)	2 (2, 4)	2 (1, 4)	**0.007**
Support with IABP (days)			
Median (IQR)	1 (0, 5.5)	2 (0, 4)	**0.810**
Units of red blood cells (RBC) transfused			
Median (IQR)	8.00 (4.00, 12.00)	4.00 (2.00, 11.50)	**<0.001**
Fresh frozen plasma (FFP) units transfused			
Median (IQR)	8.00 (4.00, 12.00)	4.00 (0.00, 8.00)	**<0.001**
Total platelet (PLT) units transfused			
Median (IQR)	0.00 (0.00, 2.00)	0.00 (0.00, 2.00)	**0.179**
Duration of support with inotropic drugs (days)			
Median (IQR)	4 (3, 6)	4 (2, 6)	**0.076**
Hospitalization days			
Median (IQR)	15 (13, 21)	16 (12.50, 26.50)	**0.405**
Postoperative arrhythmias (N, %)			
No	61 (46.92)	109 (59.24)	**0.031**
Yes	69 (53.08)	75 (40.76)	
Ejection fraction difference (ΔEF)			
Median (IQR)	0 (0, 5)	9 (2.50, 9.50)	**<0.001**
Intensive care unit (ICU) stay (days)			
Median (IQR)	7 (4, 9)	6 (4, 10)	**0.664**

Table 23. Postoperative parameters in the two groups.

A significantly higher distribution of **ejection fraction** (Figures 59 & 60) was observed in the drug group (p=0.025 from Mann-Whitney test). Taking into consideration the fact that the preoperative ejection fractions of the levosimendan group patients was significantly lower than in the control group patients, this makes the improvement of the postoperative EF even more significant.

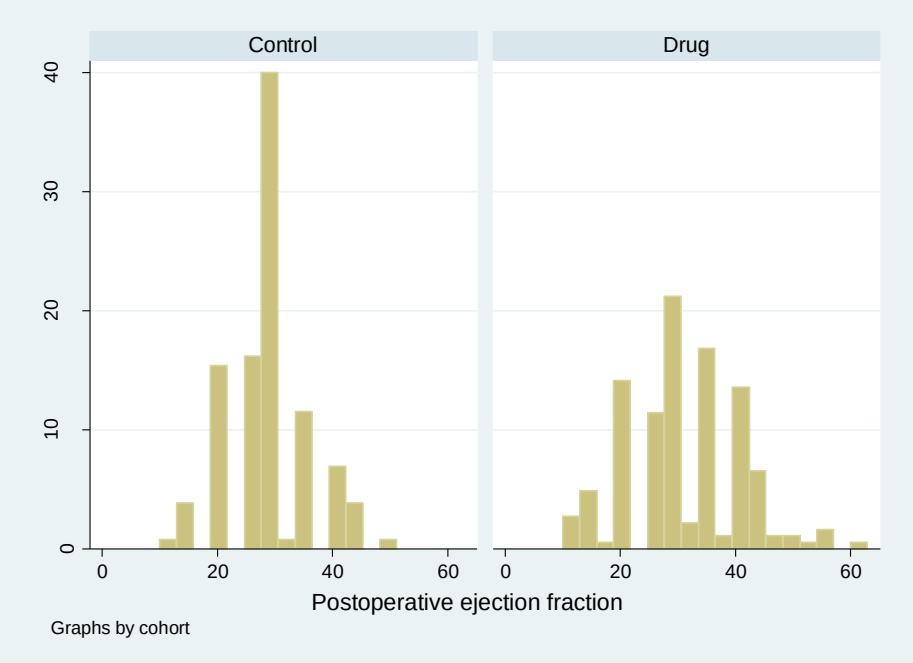


Figure 59. Histograms of post-operative ejection fraction by cohort.

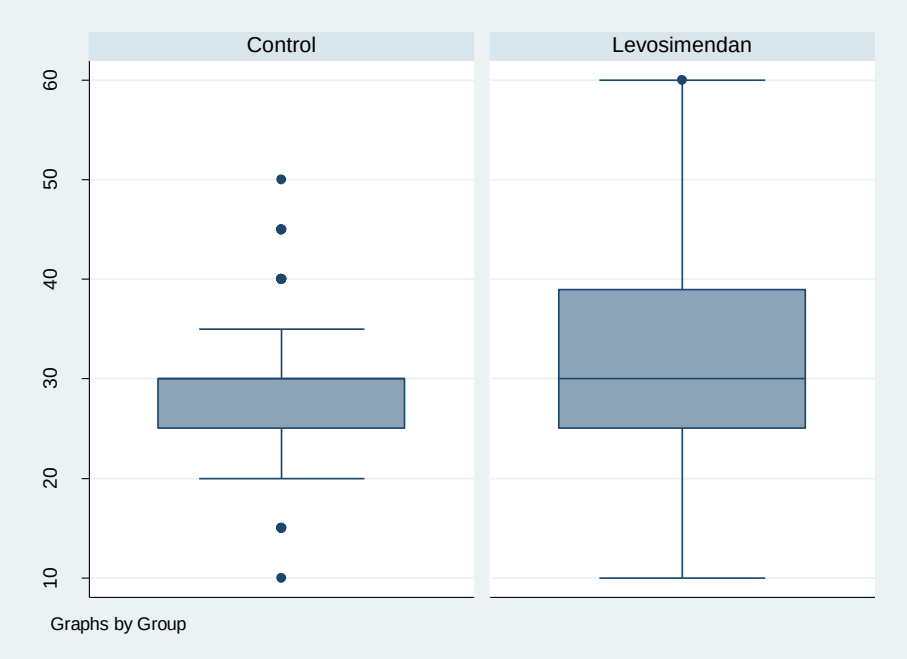


Figure 60. Boxplot of postoperative ejection fraction by cohort.

The difference (delta-EF / ΔEF) between preoperative and postoperative EF was estimated in all patients.

$$\Delta EF = EF_{postop} - EF_{preop}$$

Comparing the preoperative to the postoperative EF and in both groups, a significantly higher ejection fraction difference (ΔEF) was noticed in the levosimendan group (p<0.001), as shown in figure 61.

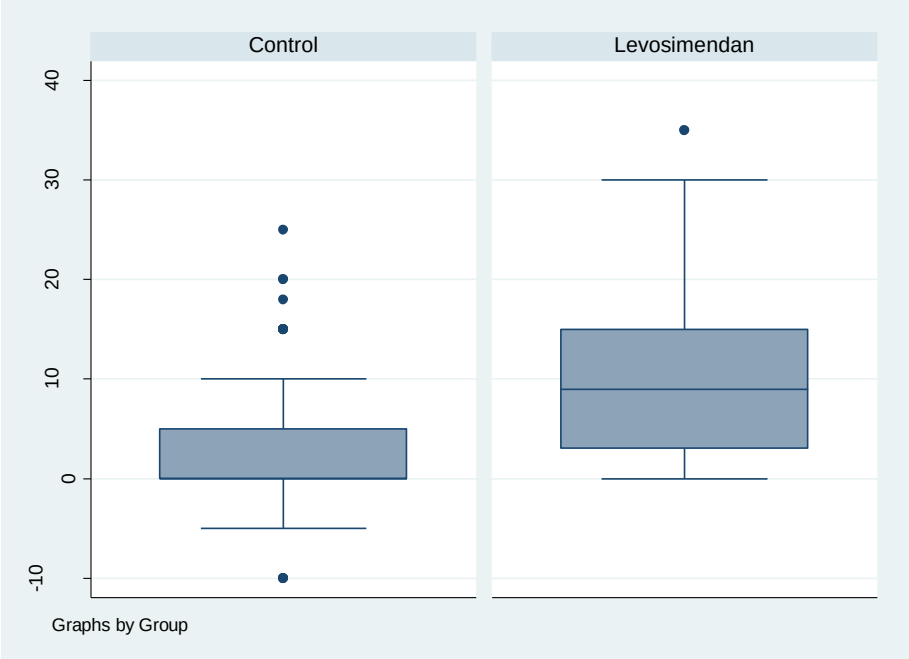


Figure 61. Boxplot of ejection fraction difference (ΔEF) by cohort.

Rehospitalization is another crucial parameter and consisted a further important endpoint in our study. As can be seen below (Figure 62), a significantly higher proportion of patients in the control group had two or more readmissions to the hospital after surgery compared to the levosimendan group (p<0.001 from Kruskal-Wallis test). The recorded readmission were of course related to cardiovascular aetiology and mostly to heart failure. Readmission irrelevant to heart failure were excluded.

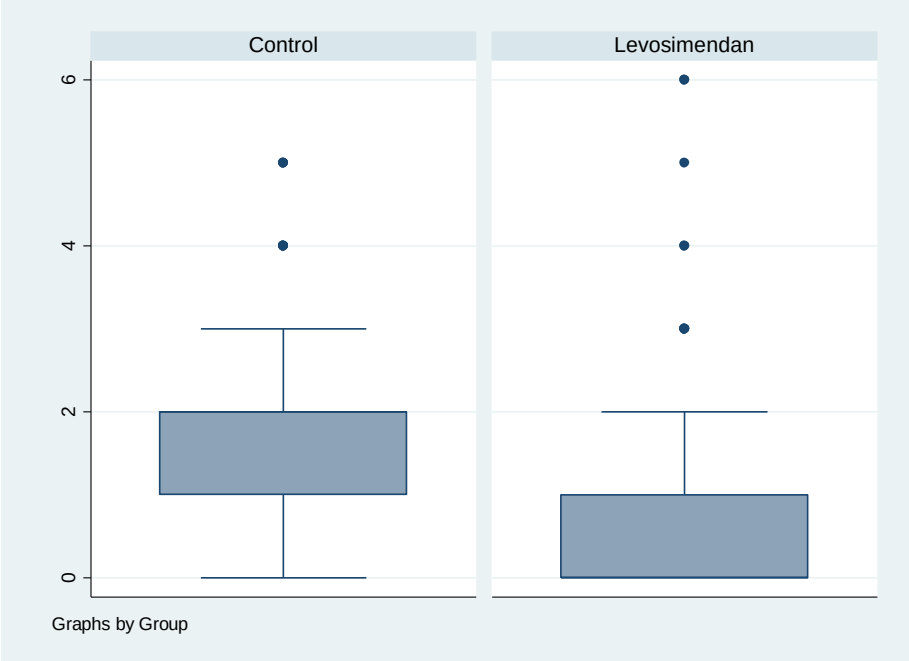


Figure 62. Boxplot of number of readmissions to hospital by cohort.

A similar trend was observed for **dyspnoea and angina** staging (Figures 63 & 64). It is worth noting that only 4.62% of patients in the control group experienced Stage 0 angina post-operatively, which is substantially lower than the 35.87% in the drug group. The recorded frequency of every NYHA and CCS stage preoperatively and postoperatively are shown and compared in the following graphics.

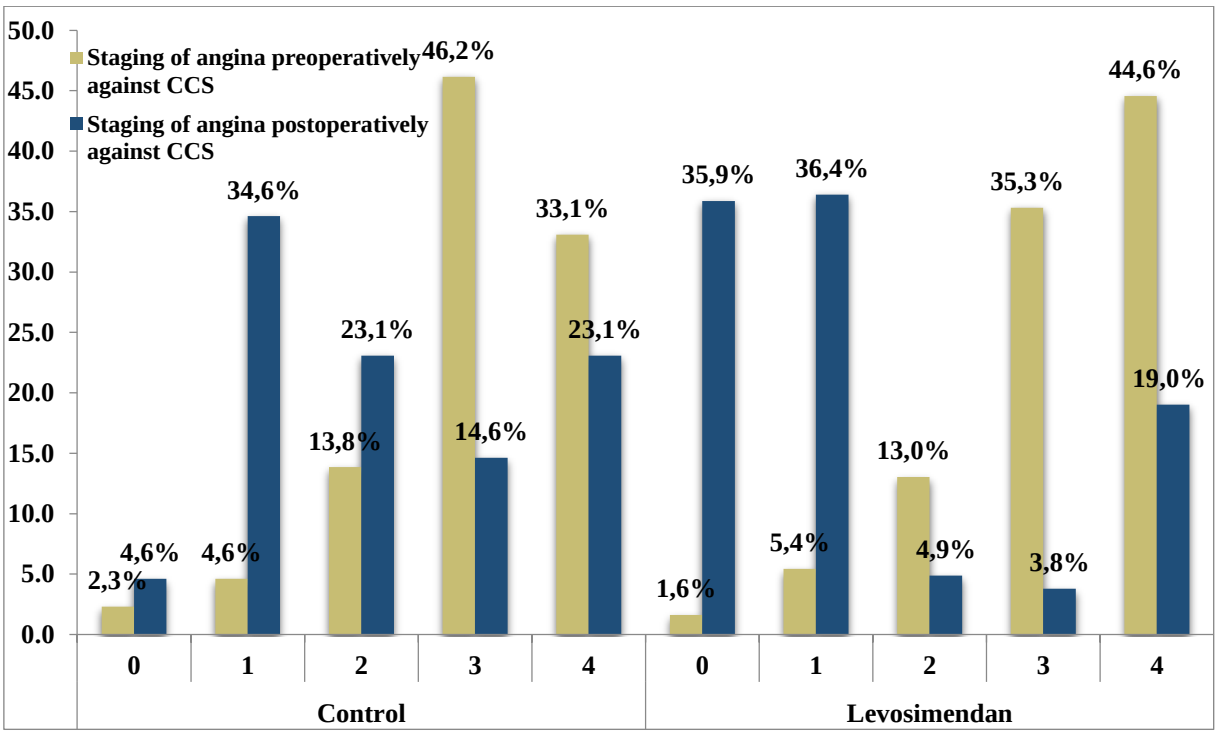


Figure 63. Frequency of every angina CCS class before and after surgery in the two cohorts.

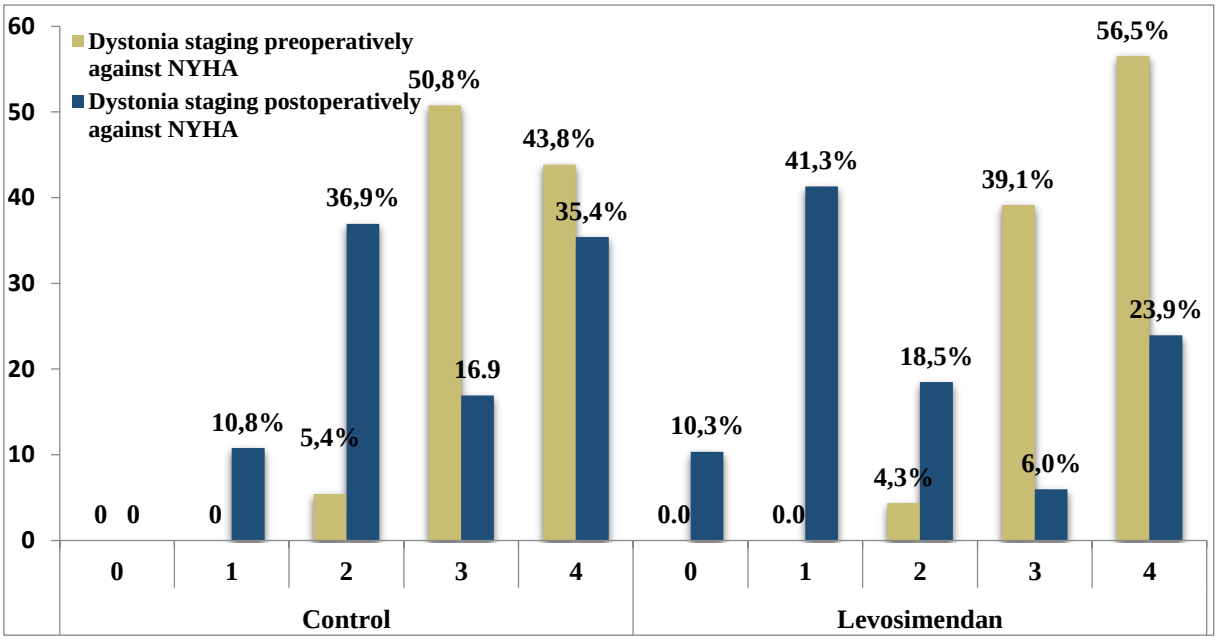


Figure 64. Frequency of dyspnoea NYHA class before and after surgery in the two cohorts.

Regarding the postoperative **hospitalization** of the patients (Figure 65) a tendency for longer length of stay was observed in the control group, the difference was however not statistically significant (p=0.405).

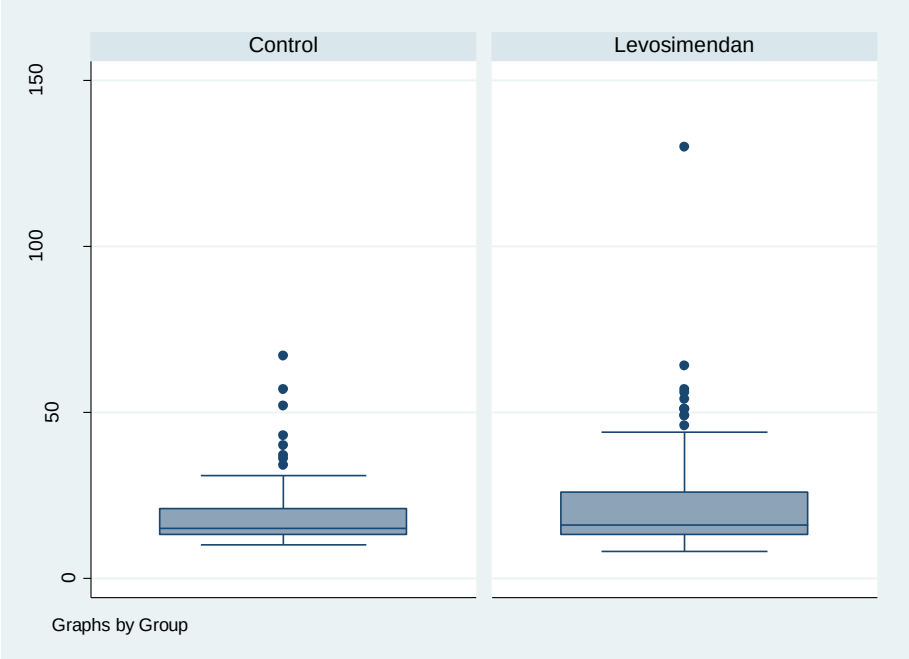


Figure 65. Boxplot of hospitalization (days) by cohort.

A similar tendency was observed regarding the **ICU stay** of the patients (Figure 66). A slightly longer length of stay was recorded in the control group patients (median: 7 days) compared to the levosimendan group patients (median: 6 days). The statistical analysis showed here again no significant difference (p=0.664).

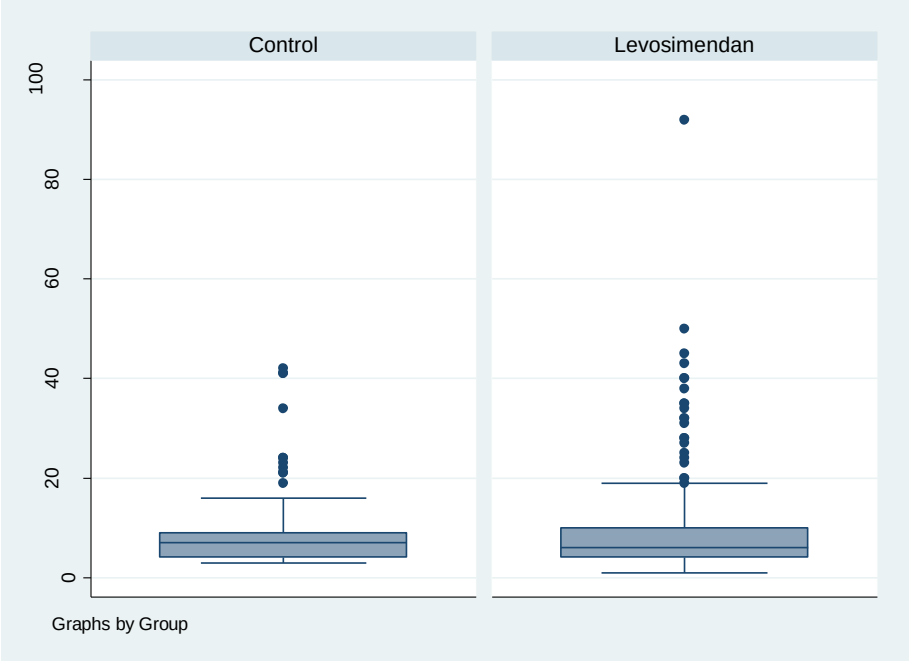


Figure 66. Boxplot of intensive care unit (stay in days) by cohort.

The patients of the levosimendan group appeared easier to wean from the ventilator and were sooner extubated compared to the control group patients (p=0.07). This finding may imply a possible lung protective effect of the drug (Figure 67).

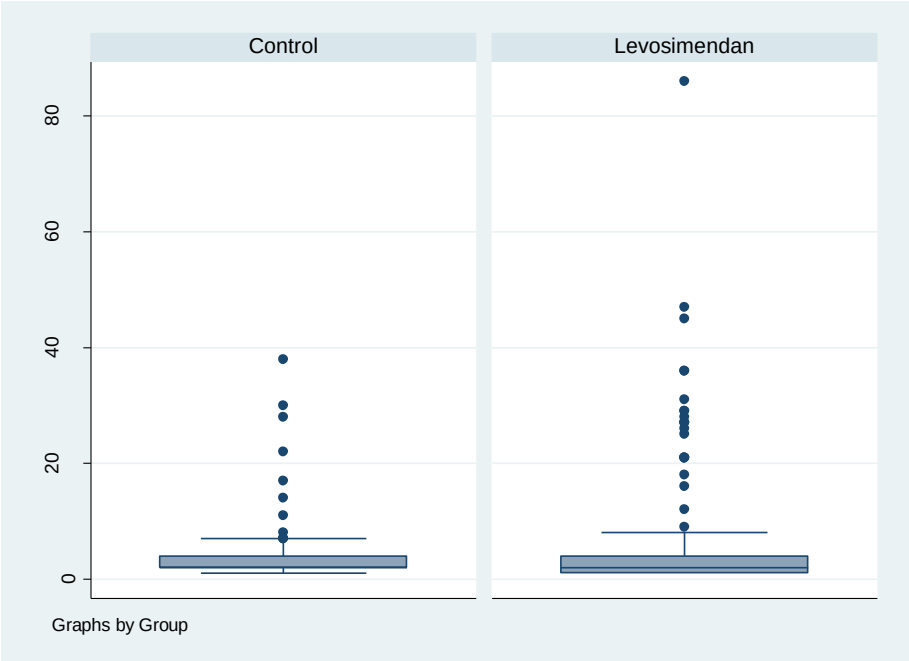


Figure 67. Boxplot of artificial ventilation (days) by cohort.

The need of inotropic support and administration of catecholamines was less in the levosimendan group (Figure 68), the difference appeared however to be not statisticall significant (p=0.076).

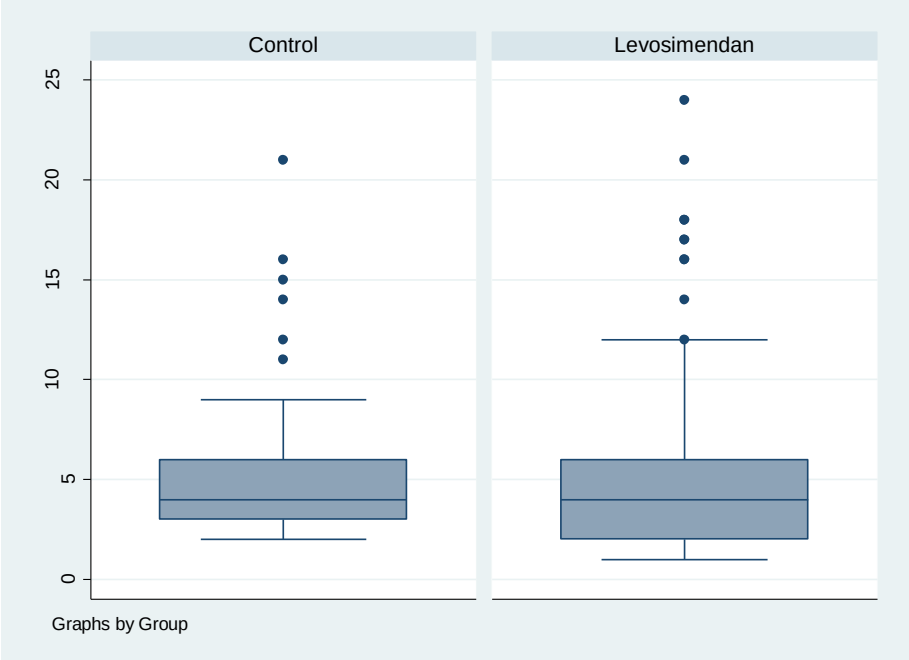


Figure 68. Boxplot of duration of patient support with inotropic drugs in the ICU (in days) by cohort.

A similar trend was observed regarding the need of mechanical circulatory support and the use of the IABP (Figure 69), where also no significant difference was observed between the two groups (p=0.810).

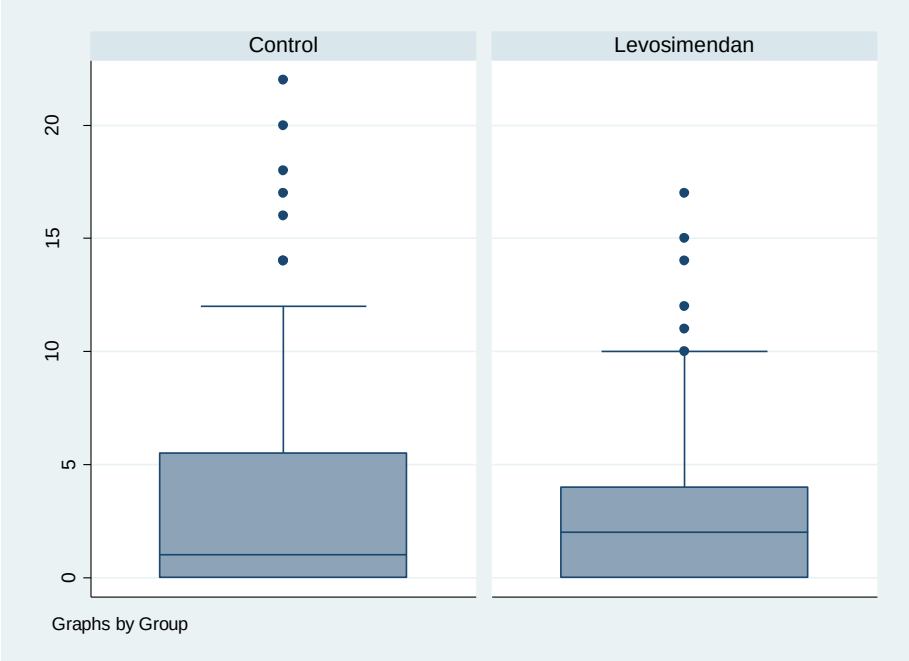


Figure 69. Boxplot of duration of support with IABP (days) by cohort.

Interestingly table 23 depicts that 29.23% of the control group needed **haemodialysis** after surgery, compared to only 11.41% in the drug group (p<0.001). A renal protective impact was clearly observed after administration of Levosimendan (Figure 70).

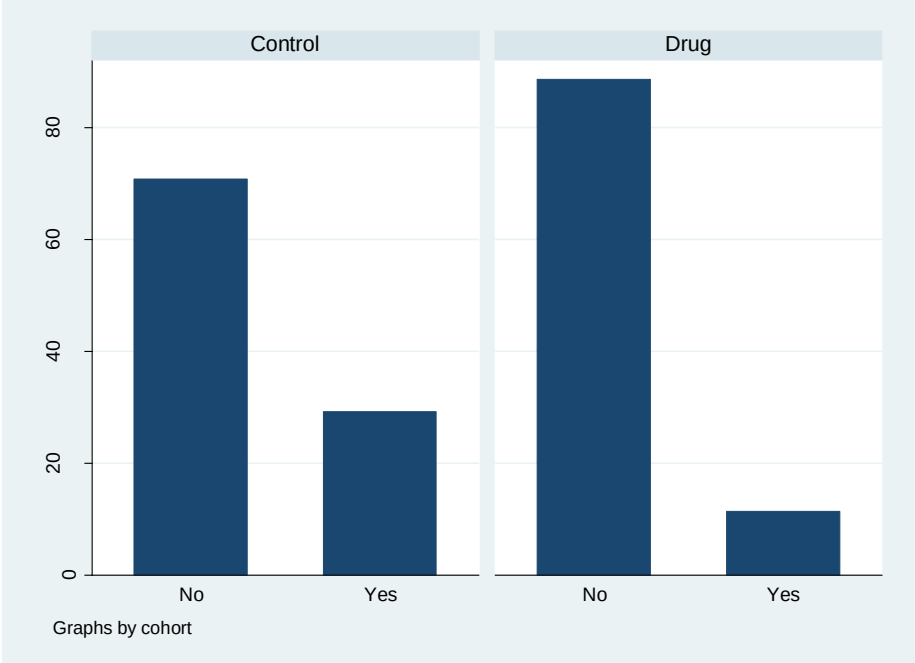


Figure 70. Need for haemodialysis by cohort.

Postoperative arrhythmias are very frequent after cardiac surgery and were recorded in patients from both groups (Figure 71). The frequency of such incidents was however significantly higher in the control group (53%) compared to the group treated with levosimendan (40.76%) (p=0,031).

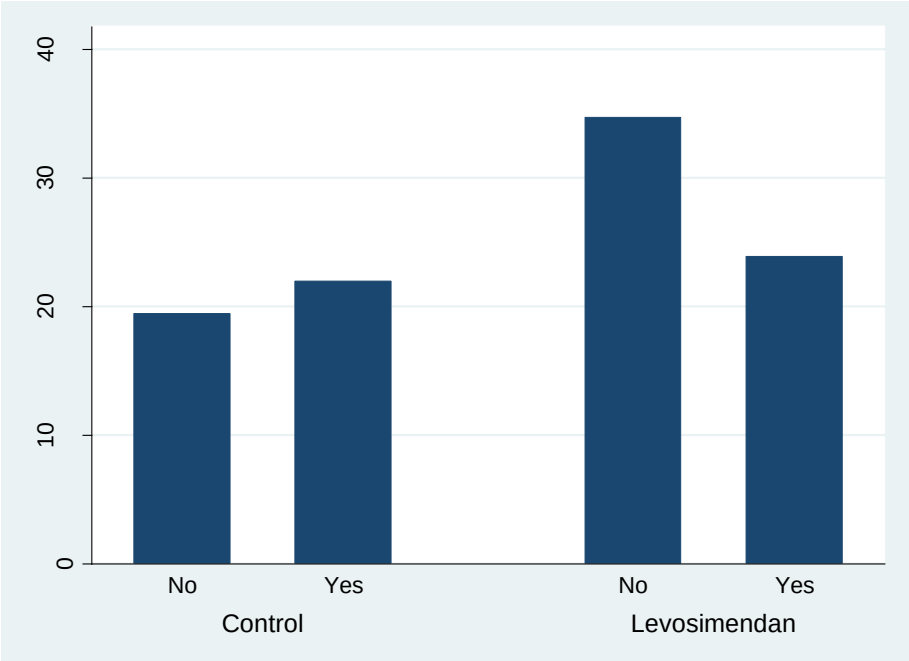


Figure 71. Frequency of postoperative arrhythmias by cohort.

A significantly higher quantity of erythrocytes (Figure 72) and fresh frozen plasma (Figure 73) units was required after surgery by the control group compared to the levosimendan group (p<0.001 for both parameters). No difference was observed regarding the need for platelet transfusion (p=0.179) (Figure 74).

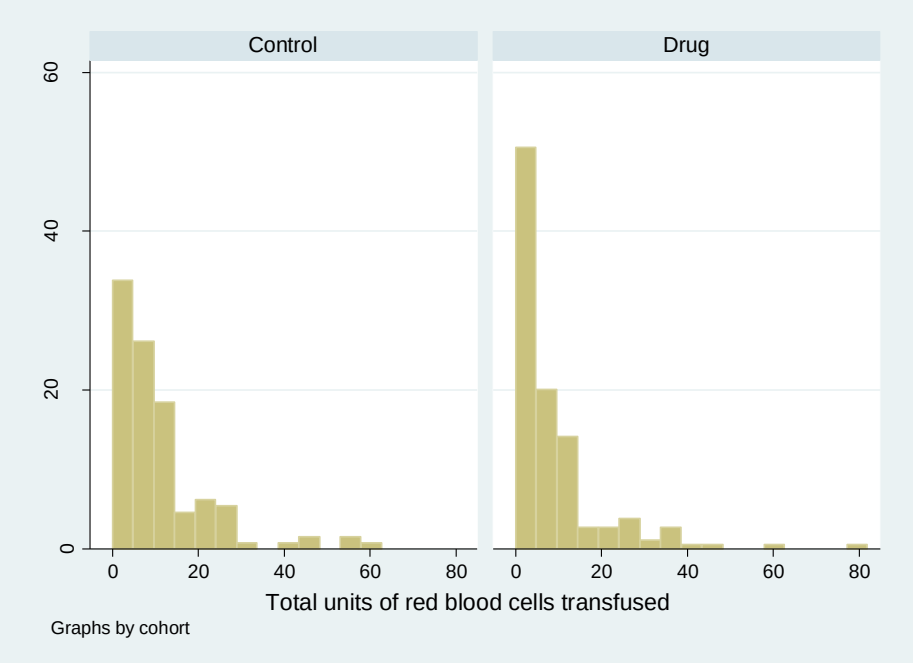


Figure 72. Histograms of total units of erythrocytes (RBC) transfused by cohort.

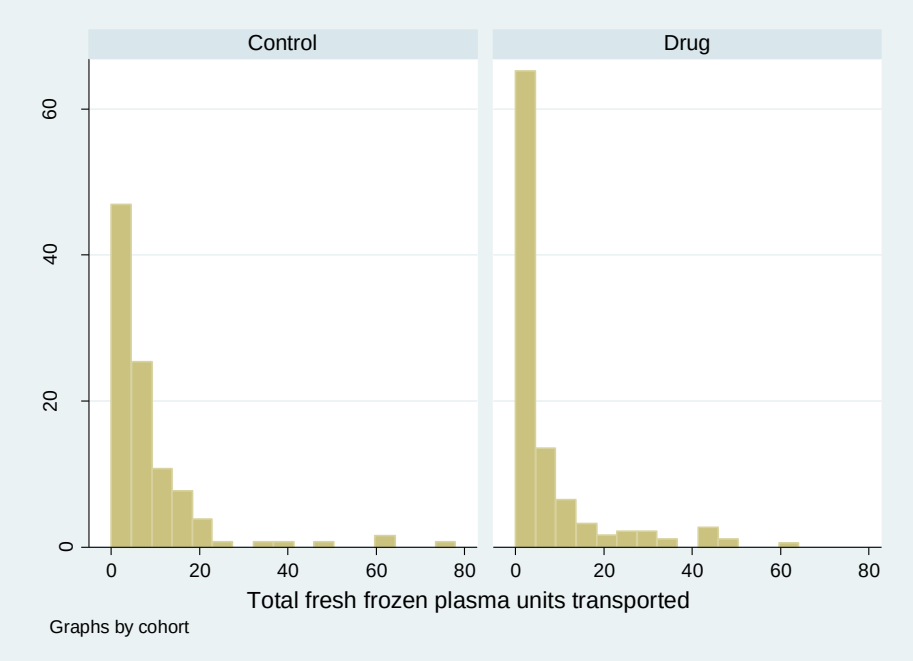


Figure 73. Histograms of fresh frozen plasma (FFP) units transported by cohort.

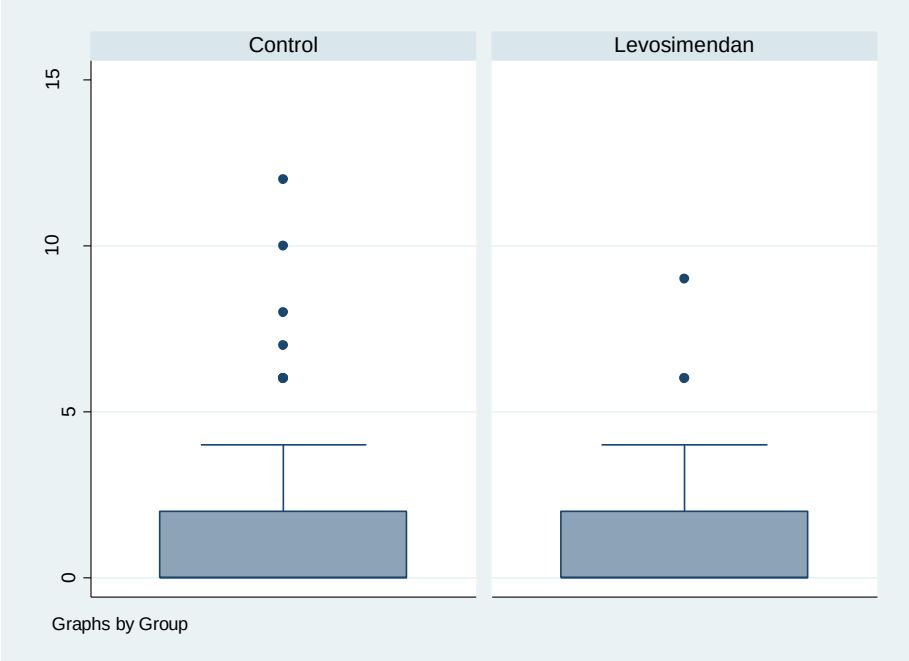


Figure 74. Boxplot of total platelet (PLT) units transfused by cohort.

15.6. Laboratory haematological and biochemical parameters

Blood chemistry laboratory parameters are used to estimate the function or degree of damage to an organ associated with the value. Monitoring the values through the course of time interesting conclusions on the extent of the original damage or new disturbances can be reached. Table 24 shows the median and IQR of blood parameters collected at different time points for the two patient cohorts.

These values were intended to provide evidence of a potential treatment benefit with levosimendan and were collected preoperatively, after arrival of the patient in the ICU and on the first 5 days after surgery. The blood samples were taken in the ICU in the standard care before the morning visit. The values are displayed in tabular form, followed by graphics that visually display the time course of the respective laboratory value. Indicated are again the arithmetic median and interquartile range (IQR) values.

	Control (N: 130)	Levosimendan (N: 184)	P value
Hemoglobin (g/dl) ; median (IQR)			
0 day prior to surgery	14.30 (12.50, 15.40)	13.40 (11.65, 14.95)	0.003
1 day of surgery	9.30 (8.55, 10.00)	9.80 (9.90, 10.70)	<0.001
2 1st postop. day	9.50 (8.6, 10.50)	9.8 (8.90, 10.80)	0.047
3 2nd postop. day	9.60 (8.90, 10.40)	9.6 (8.90, 10.40)	0.956
4 3rd postop. day	9.70 (9, 10.40)	9.5 (8.80, 10.30)	0.315
5 4th postop. day	10 (9.20, 10.80)	9.70 (8.90,10.70)	0.082
6 5th postop. day	10.40 (9.40, 11.30)	9.90 (9.10, 10.90)	0.028
C Reactive Protein (CRP) (mg/l) ; median (IQR)			
0 day prior to surgery	6.80 (3.60, 17.32)	9.34 (3.98, 22.33)	0.158
1 day of surgery	68.70 (34.70, 88.10)	40.30 (22.73, 72.73)	<0.001
2 1st postop. day	114.20 (78.40, 156.30)	106.13 (56.10, 186.30)	0.555
3 2nd postop. day	199.30 (159.10, 243.79)	194.29 (151.78, 239.86)	0.422
4 3rd postop. day	189.95 (147.20, 273.90)	171.67 (133.90, 227.84)	0.047
5 4th postop. day	148.80 (109.90, 236)	130.40 (90.30, 172.99)	<0.001
6 5th postop. day	120.40 (76, 192.70)	89.65 (55.50, 131.20)	<0.001
Troponin I (Tnl) (ng/ml); median (IQR)			
0 day prior to surgery	0.07 (0.03, 0.28)	0.08 (0.04, 0.52)	0.028
1 day of surgery	18.74 (8.31, 50)	9.90 (4.05, 24.75)	<0.001
2 1st postop. day	18.47 (7.17, 50)	9.74 (4.88, 28.83)	0.001
3 2nd postop. day	11.82 (5.43, 38.14)	5.62 (2.26, 17.64)	<0.001
4 3rd postop. day	8.94 (3.56, 26.94)	3.09 (1.13, 10.68)	<0.001
5 4th postop. day	5.13 (2.12, 17.61)	1.88 (0.73, 6.01)	<0.001
6 5th postop. day	3.96 (1.32, 10.35)	0.94 (0.36, 3.51)	<0.001
Creatine Kinase (CK) (U/l); median (IQR)			
0 day prior to surgery	93.50 (57, 147)	75.50 (48.50, 156)	0.114
1 day of surgery	796 (453, 1530.50)	503.50 (288.25, 1010.25)	<0.001
2 1st postop. day	1131 (597, 2026)	728.50 (374.50, 1741.50)	0.005

3 2nd postop. day	1109.5 (565, 2725)	738.50 (309, 2116.50)	0.014
4 3rd postop. day	852.50 (387, 1990)	464.5 (166.5, 1314)	<0.001
5 4th postop. day	561 (193, 1293)	266 (99, 792.50)	<0.001
6 5th postop. day	307.50 (102, 884)	135.50 (61, 389.50)	<0.001
Myocardial CK (CKMB) (U/l); median (IQR)			
0 day prior to surgery	17 (13,22)	21 (17,28)	<0.001
1 day of surgery	78 (40.50, 202.50)	41 (27.25, 77.50)	<0.001
2 1st postop. day	65 (40,148)	40.5 (24.5, 74.5)	<0.001
3 2nd postop. day	44 (29, 90)	30.5 (19,58)	<0.001
4 3rd postop. day	34 (21,71)	22 (14,39)	<0.001
5 4th postop. day	27 (18,46)	18 (12,28)	<0.001
6 5th postop. day	22 (16,36)	13 (9,21)	<0.001
Creatinine (mg/dl); median (IQR)			
0 day prior to surgery	1.05 (0.84, 1.30)	1.10 (0.92,1.47)	0.050
1 day of surgery	1.32 (0.99, 1.74)	1.11 (0.86, 1.52)	0.002
2 1st postop. day	1.45 (1.06, 1.94)	1.24 (0.89, 1.75)	0.005
3 2nd postop. day	1.65 (1.06, 2.78)	1.15 (0.81, 2)	<0.001
4 3rd postop. day	1.91 (1.13, 3.38)	1.22 (0.80, 2.07)	<0.001
5 4th postop. day	1.83 (1.14, 3.47)	1.20 (0.78, 2.19)	<0.001
6 5th postop. day	1.89 (1.16, 3.25)	1.14 (0.80, 1.87)	<0.001
Creatinine clearance(ml/min); median (IQR)			
0 day prior to surgery	72.59 (54.59, 91.31)	71.59 (47.96, 100.54)	0.506
1 day of surgery	56.23 (43.30, 76.45)	70.23 (47.42, 102.23)	0.001
2 1st postop. day	49.83 (40.33, 69.79)	63.80 (44.38, 97.12)	0.002
3 2nd postop. day	43.33 (26.47, 73.29)	64.64 (35.60, 106.67)	<0.001
4 3rd postop. day	38.92 (20.74, 65.81)	65.13 (36.50, 102.78)	<0.001
5 4th postop. day	42.30 (19.41, 69.19)	63.98 (32.23, 107.84)	<0.001
6 5th postop. day	39.79 (20.92, 66.35)	69.13 (36.99, 104.59)	<0.001
Glomerular filtration rate (GFR) (ml/min); median (IQR)			
0 day prior to surgery	68.40 (55, 82.30)	63.29 (46, 82.98)	0.061
1 day of surgery	52.20 (38.90, 72)	64.95 (43.73, 86.32)	0.002
2 1st postop. day	47.6 (33.20, 66.70)	57.45 (38.30, 83.58)	0.004
3 2nd postop. day	42 (20.80, 66.40)	59.29 (32.52, 90.57)	<0.001
4 3rd postop. day	33.30 (15.50, 63.20)	58.90 (29.80, 88)	<0.001

5 4th postop. day	34.40 (15.20, 63)	61.87 (28.61, 91.70)	<0.001
6 5th postop. day	33.10 (18.10, 65.70)	65.56 (35.70, 89.90)	<0.001
Blood pH; median (IQR)			
0 day prior to surgery	7.42 (7.41, 7.43)	7.41 (7.39, 7.43)	<0.001
1 day of surgery	7.33 (7.27, 7.37)	7.33 (7.29, 7.36)	0.942
2 1st postop. day	7.36 (7.32, 7.40)	7.39 (7.36, 7.42)	<0.001
3 2nd postop. day	7.40 (7.36, 7.43)	7.42 (7.39, 7.44)	0.001
4 3rd postop. day	7.40 (7.36, 7.43)	7.42 (7.39, 7.44)	0.003
5 4th postop. day	7.40 (7.37, 7.42)	7.42 (7.39, 7.44)	0.002
6 5th postop. day	7.40 (7.38, 7.42)	7.41 (7.40, 7.43)	0.001
Lactic acid (mmol/l); median (IQR)			
0 day prior to surgery	0.90 (0.70, 1.20)	1.10 (0.90, 1.30)	<0.001
1 day of surgery	3.10 (2.03, 6.20)	2.15 (1.43, 3.88)	<0.001
2 1st postop. day	3.20 (2.10, 5.10)	2.30 (1.60, 4.25)	0.001
3 2nd postop. day	2.30 (1.60, 3.20)	1.60 (1.20, 2.40)	<0.001
4 3rd postop. day	2.10 (1.40, 3.20)	1.40 (1,2)	<0.001
5 4th postop. day	1.80 (1.20, 2.40)	1.20 (1, 1.70)	<0.001
6 5th postop. day	1.60 (1.20, 2.20)	1.10 (0.90, 1.50)	<0.001

Table 24. Blood parameters at different timepoints in the two cohorts.

Haemoglobin

The protein haemoglobin is the iron-containing metalloprotein contained in the erythrocytes and is primarily responsible for the transport of oxygen in the blood, but also fulfills a buffer function. Its concentration determines the amount of oxygen that can be absorbed and transported by the blood (400).

The preoperative haemoglobin value was significantly higher in the Control group (p=0.003) showing a higher trend to anemia in the levosimendan group. The measured hemoglobin values seem to be higher in the levosimendan group patients on the day of surgery and on the 1st postoperative day (p<0.001 and p=0.047 respectively). The comparison of the values on the operation day, and on the 2nd, 3rd and 4th postoperative day showed no significant differences between the two groups. The only significant difference in the postoperative values was observed on the 5th postoperative day, again in favour of the control group.

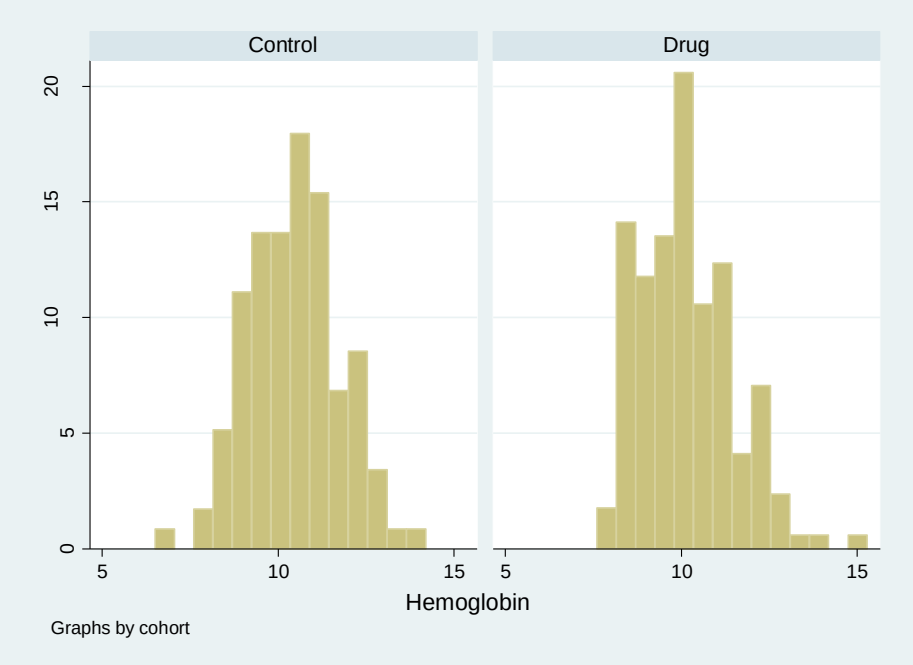
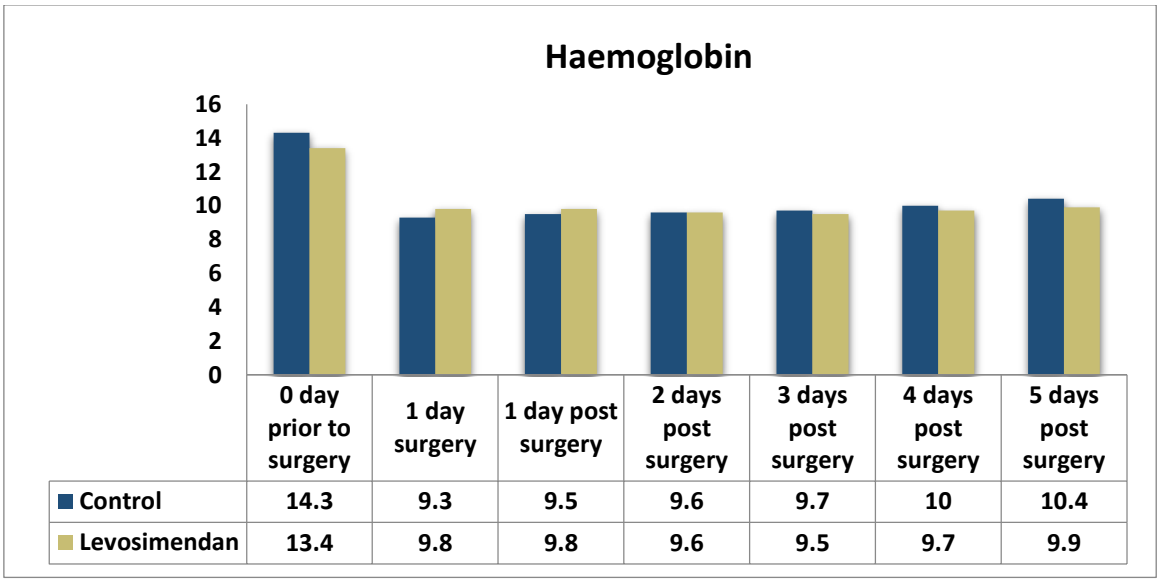


Figure 75. Histograms of haemoglobin on the 5th postoperative day in the two groups.



	0 day prior to surgery	1 day surgery	1 day post surgery	2 days post surgery	3 days post surgery	4 days post surgery	5 days post surgery
Control	14.3	9.3	9.5	9.6	9.7	10	10.4
Levosimendan	13.4	9.8	9.8	9.6	9.5	9.7	9.9

Figure 76. Distribution of hemoglobin values in the two cohorts.

C Reactive Protein (CRP)

C-reactive protein (CRP) is an annular (ring-shaped), pentameric protein found in blood plasma, who's circulating concentrations rise in response to inflammation and is therefore mainly used as an inflammation marker. It is an acute-phase protein of

hepatic origin that increases following interleukin-6 secretion by macrophages and T cells. Its physiological role is to bind to lysophosphatidylcholine expressed on the surface of dead or dying cells (and some types of bacteria) in order to activate the complement system via C1q. Myocardial infarction in humans provokes an acute phase response, and C-reactive protein (CRP), the classical acute phase plasma protein, is deposited together with complement within the infarct. CRP and complement activation are major mediators of ischemic myocardial injury (402, 403).

CRP differed significantly from three days onwards post-surgery. This implies a lower grade of inflammatory response of the patients who were treated with levosimendan.

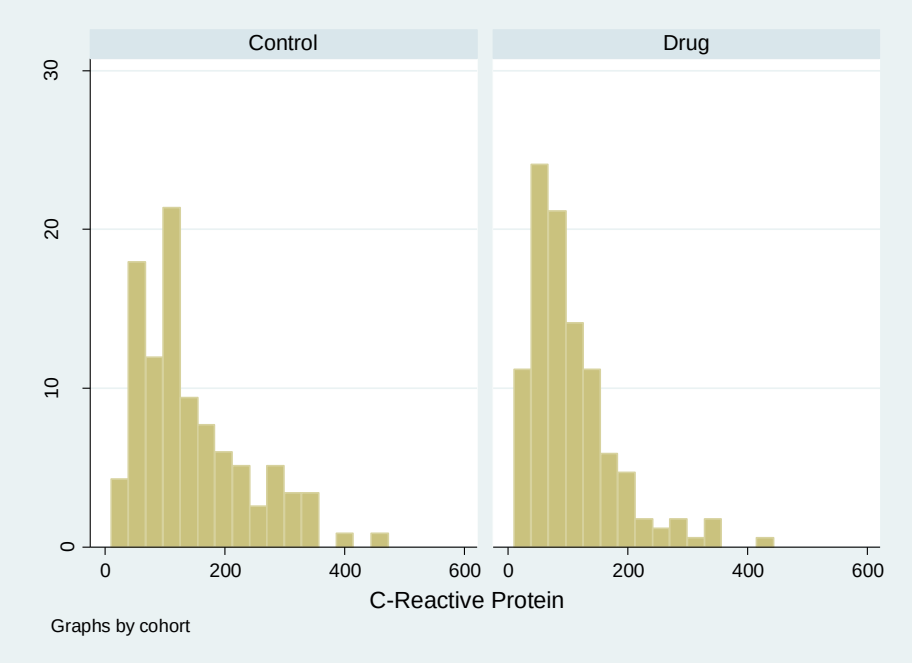


Figure 77. Histograms of CRP at 5 days after surgery in the two cohorts.

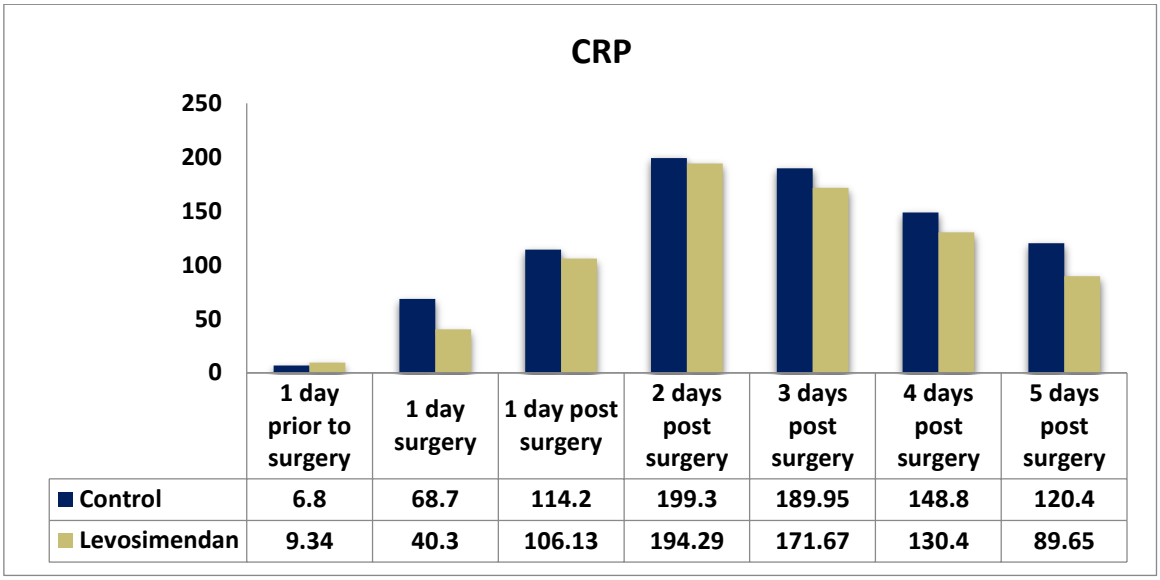


Figure 78. Distribution of CRP values in the two cohorts.

Troponin I

Troponin I is considered to be a specific marker of cardiac damage and, for the diagnosis of acute myocardial infarction. For more than 15 years cardiac troponin I (cTnI) has been known as a reliable marker of cardiac muscle tissue injury. It is considered to be more sensitive and significantly more specific in diagnosis of the myocardial infarction than the "golden marker" of last decades – CK-MB, as well as total creatine kinase, myoglobin and lactate dehydrogenase isoenzymes. Troponin I is not entirely specific for myocardial damage secondary to infarction. Other causes of raised Troponin I include chronic renal failure, heart failure, subarachnoid haemorrhage and pulmonary embolus (401).

Troponin I levels differed significantly between the two groups across all time points. Indicatively, median of troponin I was 18.47 and 9.90 on the 1st postoperative day in the control and levosimendan groups respectively. This finding supports the hypothetical cardioprotective effect of levosimendan showing less myocardial damage to the patients treated with the drug.

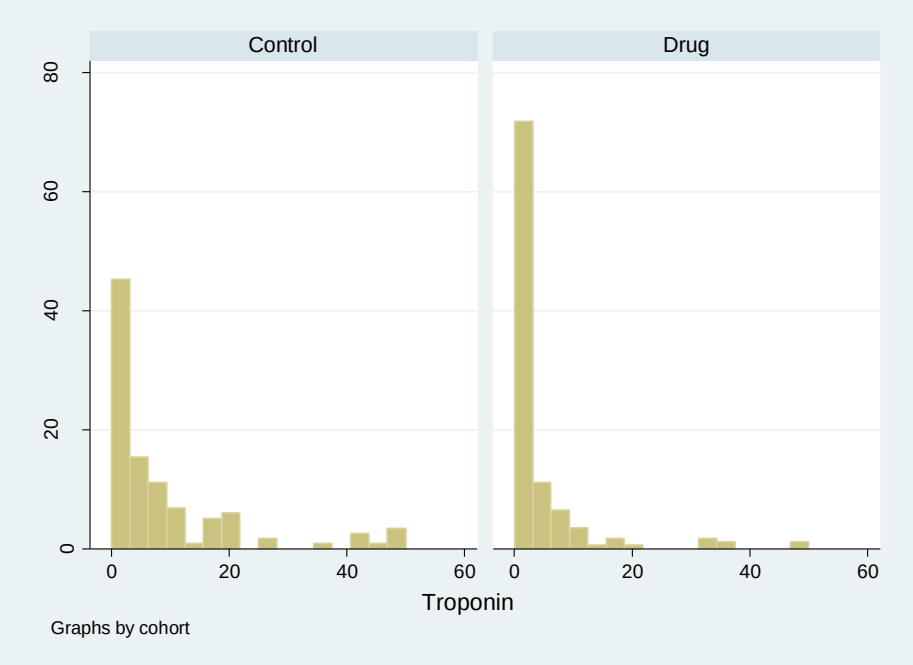
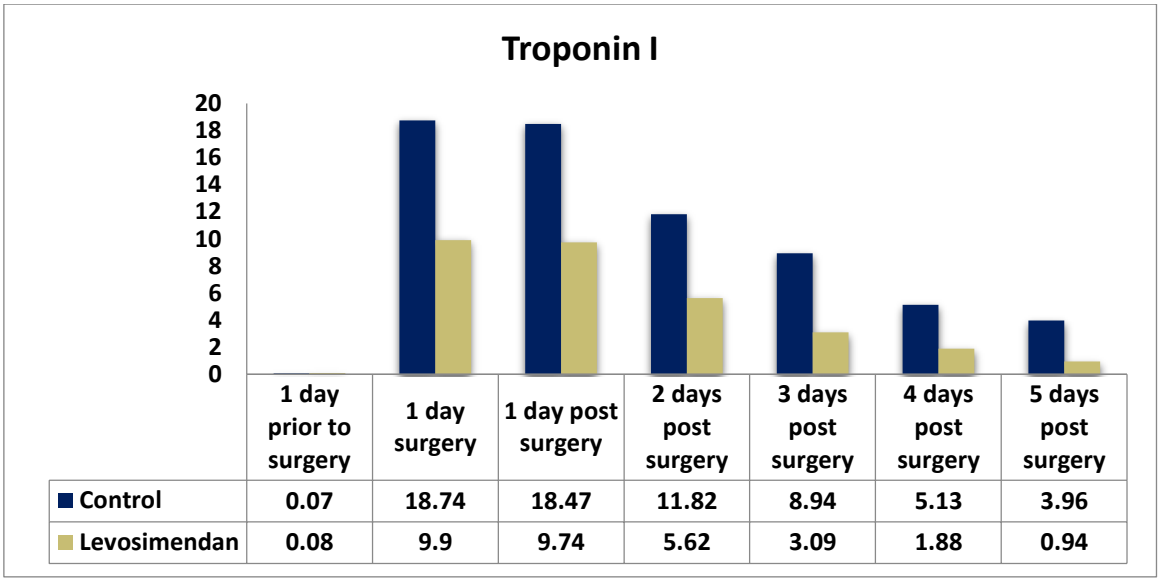


Figure 79. Histograms of troponin on the 5th postoperative day in the two cohorts.



	1 day prior to surgery	1 day surgery	1 day post surgery	2 days post surgery	3 days post surgery	4 days post surgery	5 days post surgery
Control	0.07	18.74	18.47	11.82	8.94	5.13	3.96
Levosimendan	0.08	9.9	9.74	5.62	3.09	1.88	0.94

Figure 80. Distribution of troponin I in the two cohorts.

Creatine Kinase (CK) and Myocardial Creatinine Kinase (CK-MB)

The enzyme creatine kinase (CK) is used to diagnose heart and skeletal muscle damage. By changing the concentration in the blood can be concluded on the extent of the damage done. A subtype of creatine kinase (CKMB) allows more specific conclusions about damage to the heart. An increasing proportion of CKMB indicates

a myocardial infarction or other damage. These values are less sensitive than troponin, they offer however an additive evaluation of the extense and course of myocardial infarction.

A significant difference between the two cohorts with regards to the distribution of CKMB was observed across all time points. A similar finding was seen for CK except for the first day prior to surgery. Along with the troponin results, these results also suggest a positive cardioprotective effect of levosimendan.

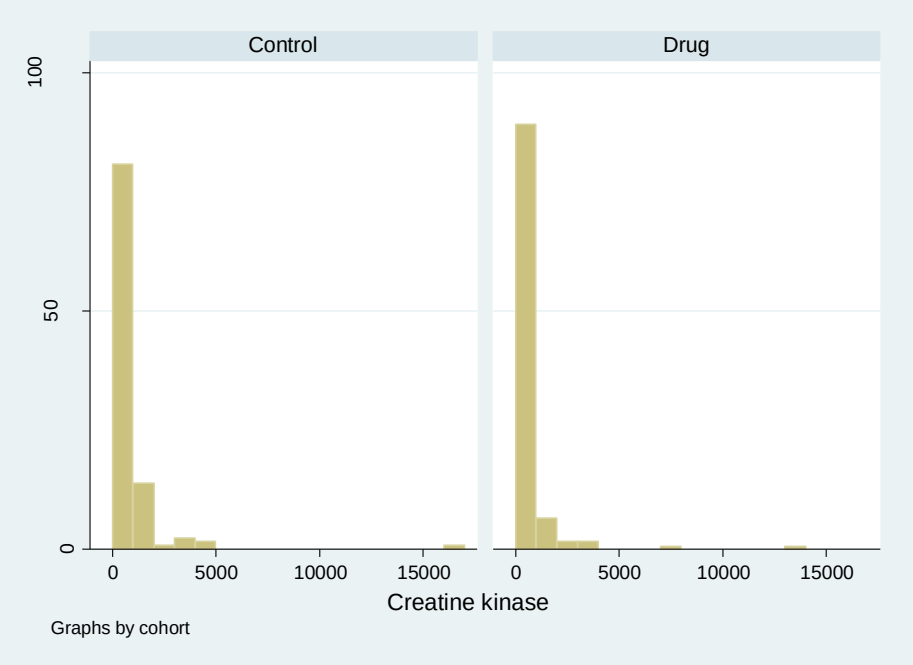
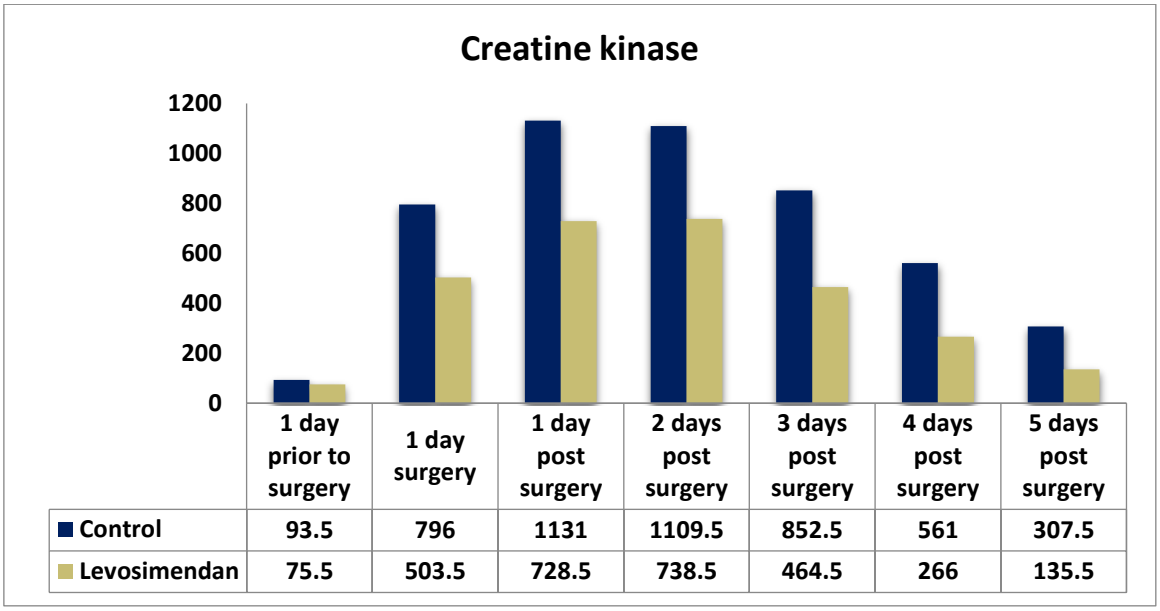


Figure 81. Histograms of CK on the 5th postoperative day in the two cohorts.



	1 day prior to surgery	1 day surgery	1 day post surgery	2 days post surgery	3 days post surgery	4 days post surgery	5 days post surgery
Control	93.5	796	1131	1109.5	852.5	561	307.5
Levosimendan	75.5	503.5	728.5	738.5	464.5	266	135.5

Figure 82. Distribution of CK in the two cohorts.

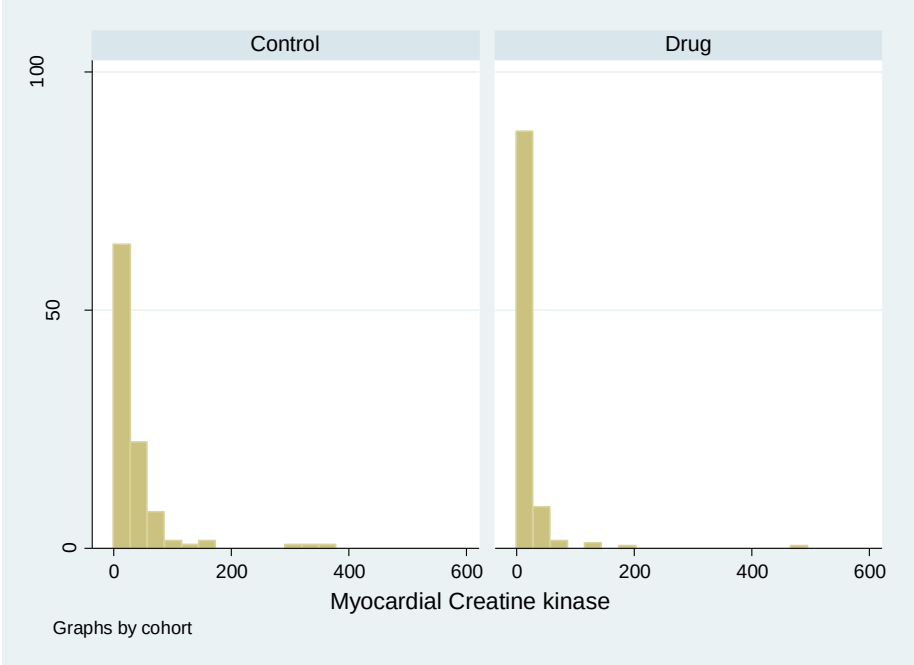


Figure 83. Histograms of CKMB on the 5th postoperative day in the two cohorts.

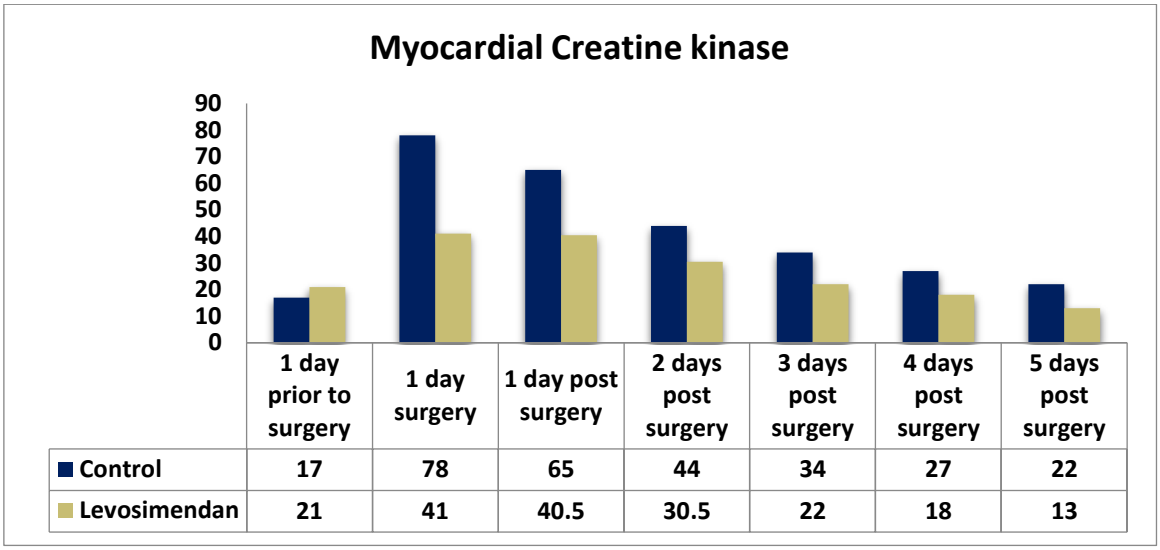


Figure 84. Distribution of CKMB in the two cohorts.

Renal Function (Creatinine, Creatinine Clearance, Glomerular Filtration Rate - GFR)

Creatinine is a metabolic end product that is excreted via the kidneys. It is used as a marker of the degree of kidney function. Since, in the case of impaired renal function, the creatinine in the blood accumulates relatively slowly, an early diagnosis is not possible. Therefore, the determination of creatinine concentration often leads to retrospective evidence of impaired renal function. The glomerular filtration rate (GFR) is used as a specific and sensitive marker of renal function. It describes the flow rate of filtered fluid through the kidney, representing the volume of fluid filtered from the renal glomerular capillaries into the Bowman's capsule per unit time. It can be calculated using the following equation:

$$GFR = \frac{\text{Urine Concentration} \times \text{Urine Flow}}{\text{Plasma Concentration}}$$

Creatinine clearance rate (C_{Cr} or CrCl) is the volume of blood plasma that is cleared of creatinine per unit time. GFR is equal to the Clearance Rate when any solute is freely filtered and is neither reabsorbed nor secreted by the kidneys.

Renal impairment after cardiac surgery is present in the majority of patients. Factors involved, besides impaired cardiac function and existing kidney damage, are the presence of diabetes mellitus and advanced age, as well as the adverse effects of

CPB, regional hypoperfusion on extracorporeal circulation, and hemodilution through the extracorporeal circulation (404).

Postoperatively, in both groups there was an initial slight increase in the glomerular filtration rate. In the course of the documented values appeared to be regressive until they are again close to the baseline or slightly below. A significant difference between the two cohorts with regards to the distribution of the postoperative creatinine and creatinine clearance parameters in the two groups was however observed across all time points. For example, median creatinine clearance on the 2nd postoperative day was 64.64 in the drug group versus 43.33 in the controls ($p<0.001$). Median values of GFR were higher in the Levosimendan group over all time points, except for the day prior surgery. For instance, on the 5th postoperative day, median GFR was 65.56 versus 33.10 in the controls ($p<0.001$). These findings demonstrate a possible positive nephroprotective effect o levosimendan, the administration of which seems to provide a better postoperative renal function.

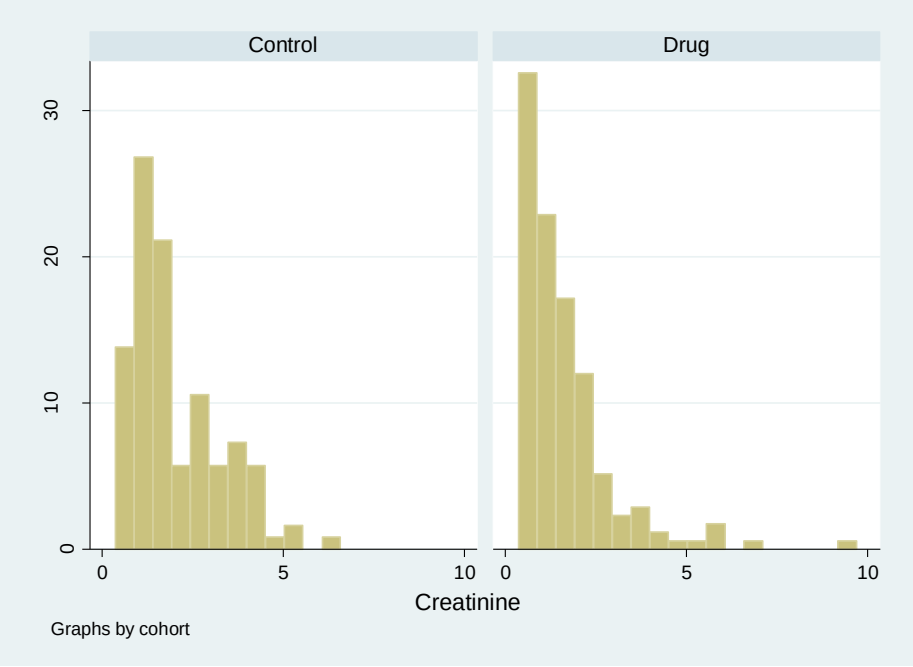
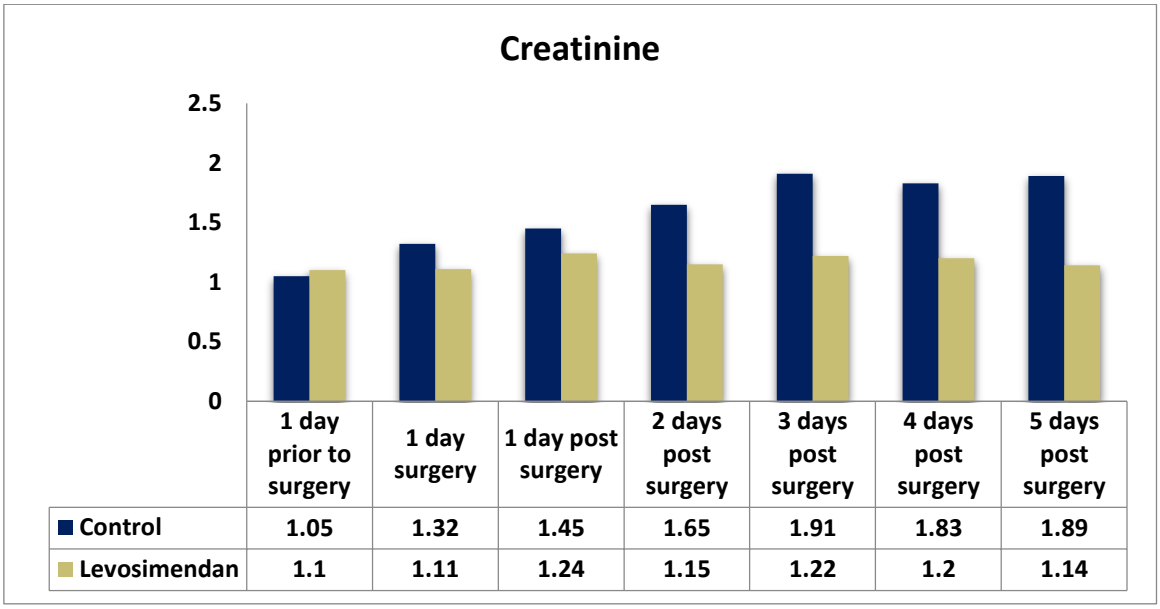


Figure 85. Histograms of creatinine on the 2nd postoperative day in the two cohorts.



	1 day prior to surgery	1 day surgery	1 day post surgery	2 days post surgery	3 days post surgery	4 days post surgery	5 days post surgery
Control	1.05	1.32	1.45	1.65	1.91	1.83	1.89
Levosimendan	1.1	1.11	1.24	1.15	1.22	1.2	1.14

Figure 86. Distribution of creatine values in the two cohorts.

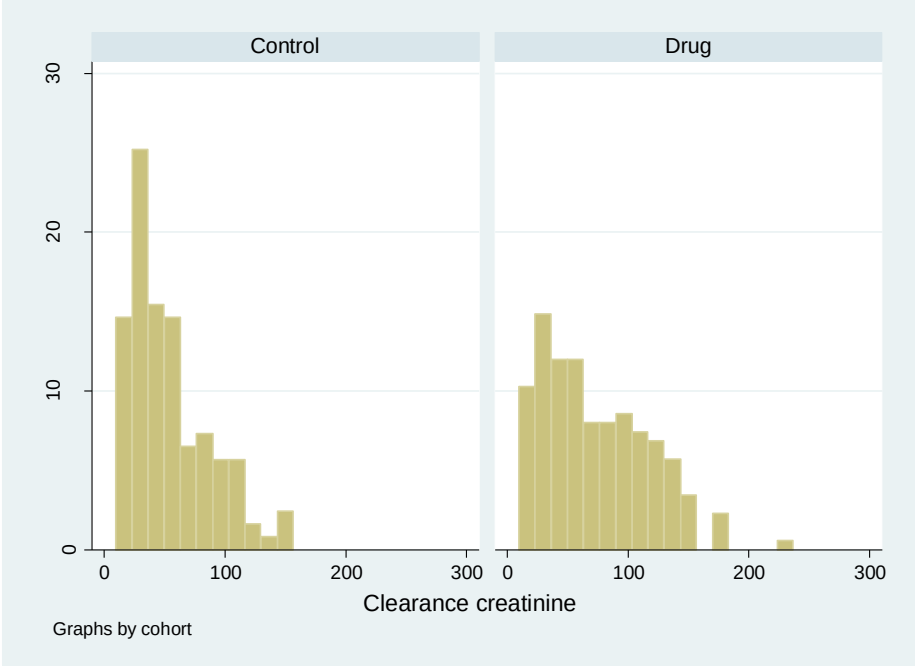
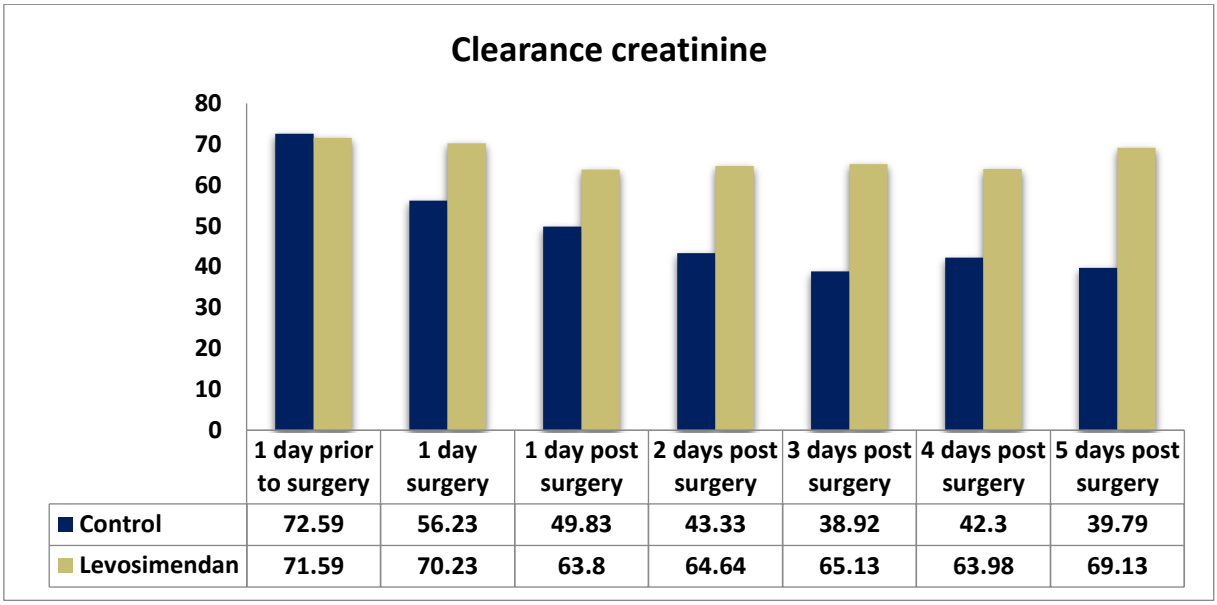


Figure 87. Histograms of creatinine clearance on the 2nd postoperative day in the two cohorts.



	1 day prior to surgery	1 day surgery	1 day post surgery	2 days post surgery	3 days post surgery	4 days post surgery	5 days post surgery
Control	72.59	56.23	49.83	43.33	38.92	42.3	39.79
Levosimendan	71.59	70.23	63.8	64.64	65.13	63.98	69.13

Figure 88. Distribution of Clearance creatinine in the two cohorts.

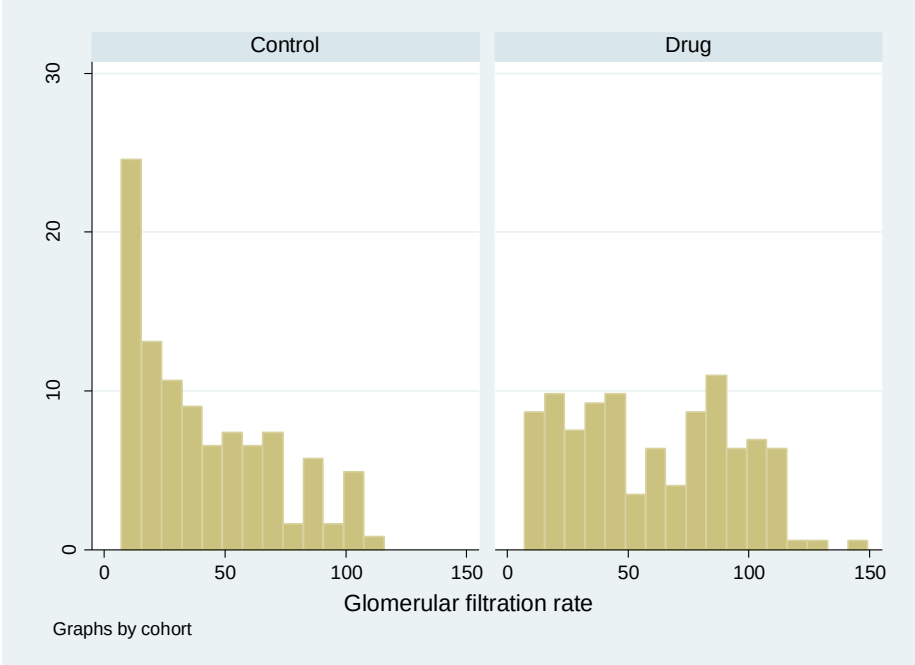
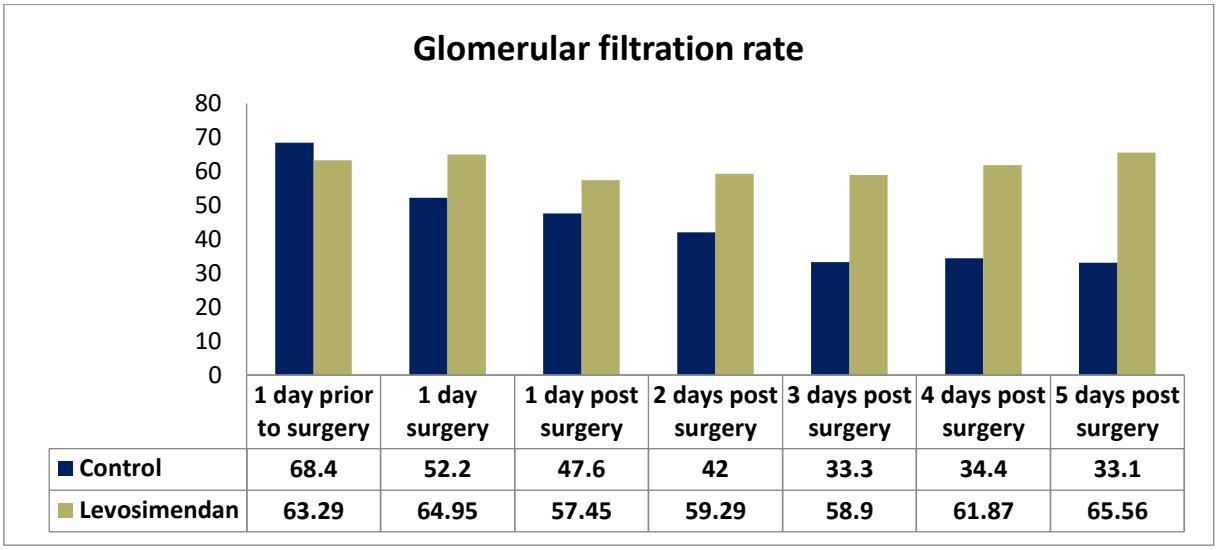


Figure 89. Histograms of GFR on the 3rd postoperative day in the two cohorts.



	1 day prior to surgery	1 day surgery	1 day post surgery	2 days post surgery	3 days post surgery	4 days post surgery	5 days post surgery
Control	68.4	52.2	47.6	42	33.3	34.4	33.1
Levosimendan	63.29	64.95	57.45	59.29	58.9	61.87	65.56

Figure 90. Distribution of GFR in the two cohorts.

Blood pH

Acid–base balance is the homeostatic regulation of the pH of the body's extracellular fluid (ECF). The proper balance between the acids and bases (i.e. the pH) in the ECF is crucial for the normal physiology of the body, and cellular metabolism. The pH of the intracellular fluid and the extracellular fluid need to be maintained at a constant level (405).

The distribution of pH was different between the two groups over all time points, showing a higher tendency to acidosis in the control group. This may suggest a possible metabolic effect of levosimendan.

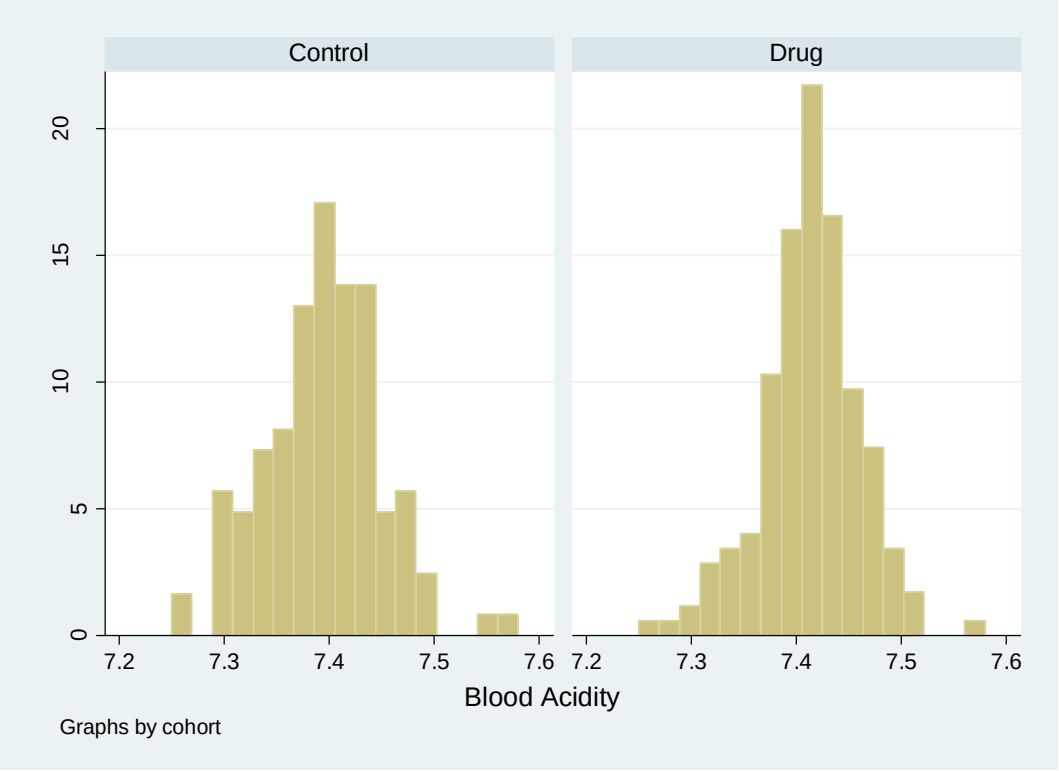
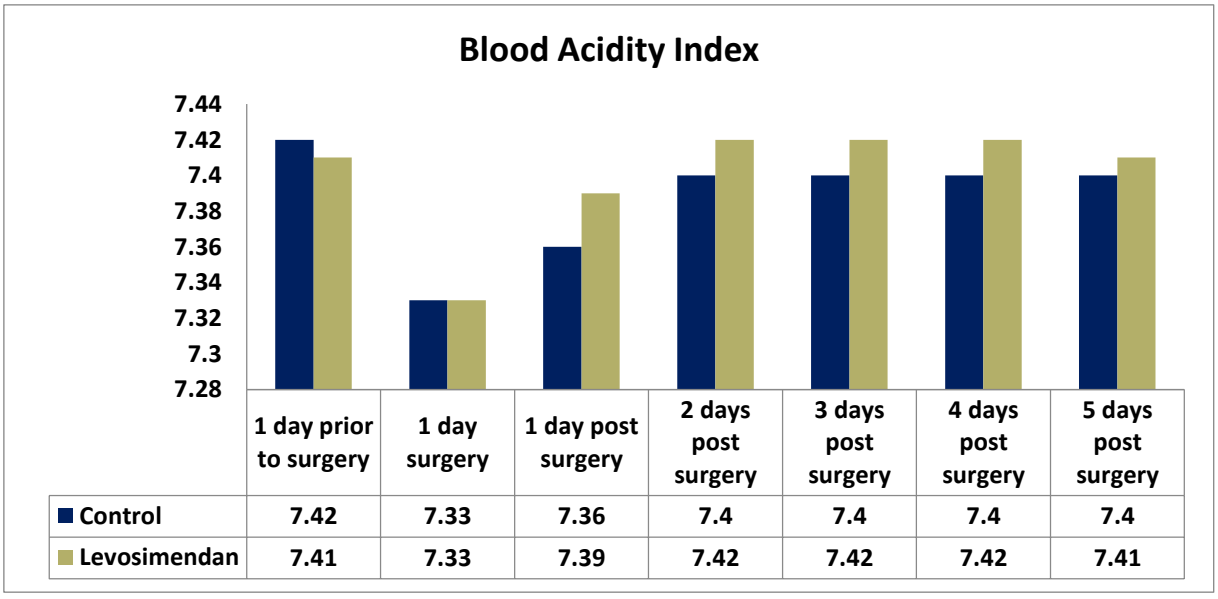


Figure 91. Histograms of pH on the 2nd postoperative day in the two groups.



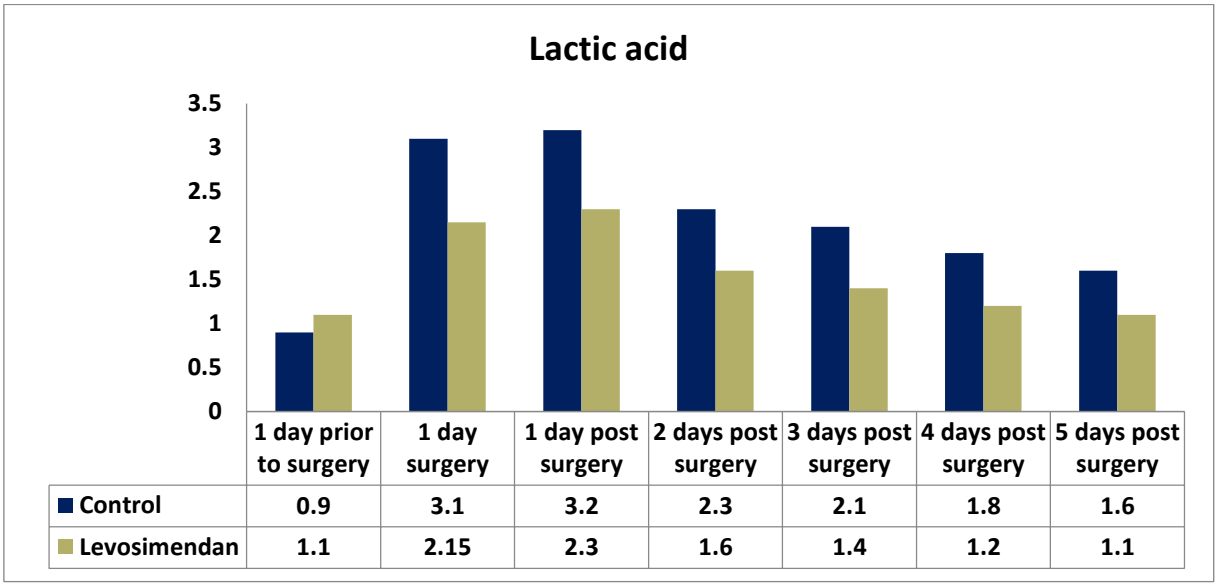
	1 day prior to surgery	1 day surgery	1 day post surgery	2 days post surgery	3 days post surgery	4 days post surgery	5 days post surgery
Control	7.42	7.33	7.36	7.4	7.4	7.4	7.4
Levosimendan	7.41	7.33	7.39	7.42	7.42	7.42	7.41

Figure 92. Distribution of pH values in the two cohorts.

Lactic acid

Lactic acid value allows an assessment of the adequacy of blood circulation and thus also the supply of oxygen to the tissues. The lactic acid values and their course were therefore used as markers for the circulatory function and the quality of the tissue perfusion.

The distribution of lactic acid was significantly different between the two groups over all time points. Median lactic acid was 2.30 on the 2nd postoperative day versus 1.60 in the Levosimendan group (p<0.001). This finding demonstrates again the possible positive inotropic effect of levosimendan and its metabolites and their protection against postoperative low cardiac output syndrome.



	1 day prior to surgery	1 day surgery	1 day post surgery	2 days post surgery	3 days post surgery	4 days post surgery	5 days post surgery
Control	0.9	3.1	3.2	2.3	2.1	1.8	1.6
Levosimendan	1.1	2.15	2.3	1.6	1.4	1.2	1.1

Figure 93. Distribution of Lactic acid in the two cohorts.

16. DISCUSSION

16.1. Baseline characteristics

The comparison of the two study groups with regard to their baseline characteristics and the preoperative status shows that although the groups were similar and overall homogenous, they differed on a few points. The distribution of Euroscore 1 and Euroscore 2 at baseline was significantly different in the two groups (p<0.001), showing a higher perioperative risk in the levosimendan group. Furthermore, the

distribution of ASA score is significantly different in the two groups (p=0.048) supporting the higher risk profile of the patients of the levosimendan group. Occurrence of arrhythmia before surgery was significantly different in the two groups, 19.23% in the controls and 30.43% in the drug group (p=0.030). Similarly, the appearance of pulmonary hypertension before surgery was significantly different in the two groups, 8.46% in the controls and 30.43% in the drug group (p<0.001). The same applies to preoperative renal function. In the controls, 13.85% of cases had renal failure versus 25.54% in the drug group (p=0.012), 16.28% had arteriopathy versus 31.52% in the levosimendan group (p=0.003), 4.62% had a cerebrovascular accident versus 13.59% in the drug group (p=0.009). A significantly higher distribution of ejection fraction was observed in the controls (Median of 30% for control group vs. 20% for levosimendan group, p<0.001).

These are all essential factors that can significantly influence the outcome and thus, despite the overall homogeneity of the two groups, such different values may lead to a worse prognosis for patients of the study group.

16.2. Postoperative survival

The data collected on postoperative survival show significant differences between the two groups. The Kaplan–Meier estimator shows the superior overall survival of the levosimendan group compared to the control group (p=0.005). Survival estimates at different time points for the two patient subgroups additionally show the consistently higher overall survival probability of the levosimendan subgroup throughout follow-up. The 10-days survival was similar in the two groups (82% for the control group vs. 85% for the levosimendan group). On the 30th day after surgery 64% of the control patients and 76% of the levosimendan patients were alive (p=0.05). At 6 months after surgery survival was estimated at 55% for the control group and 70% for the levosimendan group, showing a significant difference at this time point (p=0.02). 1-year follow-up showed a survival rate of 54% for the control group patients and 68% for the levosimendan group patients (p=0.02). At 2 years the follow-up showed that 52% of the control and 65% of the levosimendan patients had survived (p=0.005). 3 years after surgery, 51% of cases were alive in the control group compared to 65% in the drug group (p=0.005). It is worthy of consideration that the median survival

timepoint was not reached for the levosimendan group during follow-up, which adds to the previous findings suggesting a positive effect of the drug on survival outcomes.

Several small trials suggest that levosimendan is associated with a favorable outcome in patients undergoing cardiac surgery. However, as mentioned in chapter 12.8.2. recently published larger-scale trials did not provide evidence for a similar benefit from levosimendan.

One of the first meta-analyses on levosimendan use in cardiac surgery patients published by Zangrillo et al. in 2008 included a total of 139 patients from 5 randomized controlled studies and despite showing a significant reduction in postoperative cardiac troponin peak release, it did not show any improvement of survival in the patients treated with levosimendan (406). A meta-analysis of 10 randomized controlled trials by Landoni et al. in 2010 showed that the preoperative administration of levosimendan has a highly significant effect. Immediate postoperative mortality was significantly reduced in the levosimendan group ($p=0.003$) (407). In a larger scale analysis from 2012, the Landoni group again achieved similar results in 5480 patients from 45 studies. Here, the overall mortality rate in the levosimendan group was 17.4%, in the control group 23.3% (408). Also Maharaj et al. came to a similar conclusion in a meta-analysis of 17 studies involving a total of 729 patients. The mortality rate in the study group was 4.9%, while in the control group it was higher at 11.4% (409). A study by Levin et al. in 2012, in which 252 patients with preoperatively poor EF received CABG operations and were randomized to either levosimendan or placebo administration 24 hours before surgery, showed a marked improvement in 30-day survival in the preconditioned group versus placebo group. The mortality rate here in the levosimendan group was 3.8%, whereas in the control group 12.4% (410). Hernandez et al. included 654 patients from 13 studies in their analysis. Levosimendan was associated with a significant reduction in postoperative mortality, as 5.2% (18/344) versus 12.6% (39/310) in the control arm ($p=0.001$) (411). Harrison et al. meta-analysed 1155 patients who participated in 14 randomized controlled trials of perioperative Levosimendan administration. Pooled results demonstrated a reduction in mortality with levosimendan ($p=0.008$). Subgroup analysis showed that this benefit was confined to the low-EF studies ($p<0.001$). No benefit was observed in the preserved-EF subgroup ($p=0.66$) (412). Another meta-analysis in 2015 by Lim et al. included fourteen studies and demonstrated that levosimendan reduced early

mortality in patients with reduced ejection fraction (5.5% vs. 9.1%) (413). A large meta-analysis was carried out in Italy in 2015 by Belletti et al. analysing all randomized trials published in the last 20 years to investigate the effect of inotropes and vassopressors on mortality. A total of 28.280 patients from 177 trials were included. Overall, pooled estimates showed no difference in mortality between the group receiving inotropes/vasopressors and the control group [4255/14 036 (31.7%) vs. 4277/14 244 (31.8%), risk ratio=0.98 (0.96-1.01), p for effect=0.23, p for heterogeneity=0.30, I^2=6%]. Levosimendan was the only drug associated with improvement in survival (414). A similar analysis was carried out by Greco et al. in 2015. The objective of this study was to conduct a meta-analysis on the effects of inodilators on survival in adult cardiac surgery patients, and to compare and rank these drugs, as they had not been adequately compared in head-to-head trials. The following drugs were evaluated: dobutamine, enoximone, levosimendan, and milrinone. The data were based on 2647 patients in 46 trials. Only the use of levosimendan was associated with decrease in mortality when compared with placebo (posterior mean of OR, 0.48; 95% CI, 0.28–0.80). The posterior distribution of the probability for each inodilator to be the best and the worst drug showed that levosimendan was the best agent for the improvement of patient survival after cardiac surgery (90.8%, as posterior distribution derived by Bayesian hierarchical model with Markov Chain Monte Carlo algorithm) (415). Chen et al. in 2017 analysed seventeen studies involving a total of 2756 patients. Levosimendan therapy was associated with a significant reduction in 30-day mortality (RR 0.67; 95% CI, 0.49 to 0.93; p=0.02) and reduced the risk of death in single-center trials (RR 0.49; 95% CI, 0.30 to 0.79; p=0.004) and in subgroup trials of inferior quality (RR 0.39; 95% CI, 0.17 to 0.92; p=0.02). However, in multicenter and in high-quality subgroup-analysis trials, no significant difference in mortality was observed between patients who received levosimendan therapy and controls (p>0.05). In high-quality subgroup trials, levosimendan therapy was associated with reduced mortality in patients in a preoperative low-EF subgroup (RR 0.58; 95% CI, 0.38 to 0.88; p=0.01) (416). Sanfilippo et al. in 2017 published a meta-analysis of six RCTs, five of which investigated only patients with LVEF ≤ 35% and one of which included predominantly patients with LCOS. Mortality was similar overall (OR 0.64 [0.37, 1.11], p=0.11) but lower in the subgroup with LVEF < 35% (OR 0.51 [0.32, 0.82], p=0.005), showing that Levosimendan reduces mortality in patients with preoperative severely reduced LVEF but does not affect overall mortality (417). Zhou et al. included a total of 30

randomized controlled trials in their analysis in 2018. The pooled results indicated that perioperative administration of levosimendan was associated with a reduction in postoperative mortality [5.8% vs 8.5%; odds ratio 0.66, 95% confidence interval 0.50-0.86, p=0.002; I^2=17.1%; 25 trials; 3239 patients]. A subanalysis was conducted for trials published after 2015, and it suggested that levosimendan could not reduce the postoperative mortality (OR=0.91, 95% CI 0.63-1.31, p=0.626; I^2=0.9%) (418). A recent work by Chen et al. in 2018 showed that Levosimendan did not result in a reduction in mortality in adult cardiac surgery patients. A total of 25 RCTs enrolling 2960 patients met the inclusion criteria; data from 15 placebo-controlled randomized trials were included for meta-analysis. Pooled analysis showed that the all-cause mortality rate was 6.4% (71 of 1106) in the levosimendan group and 8.4% (93 of 1108) in the placebo group (OR, 0.76; 95% CI, 0.55-1.04; p=0.09) (419). In one more recent meta-analysis Wang et al. conclude that Levosimendan reduces the rate of death and other adverse outcomes in patients with low EF undergoing cardiac surgery, but results remain inconclusive. Data from 2152 patients in 15 randomized clinical trials demonstrated a reduction in postoperative mortality in the levosimendan group [RR = 0.53, 95% CI (0.38-0.73), I^2=0]. However, the result showed that the conclusion may be a false positive (420). Twenty-five studies (3247 patients) were included in another meta-analysis by Qiang et al. in 2018. Pooled data indicated that levosimendan reduced mortality after cardiac surgery (OR: 0.63, 95% CI: 0.47-0.84, p=0.001). However, this reduction was restricted to patients with low (<50%) LVEF (OR 0.49, 95% CI: 0.35-0.70, p=0.0001) (421). Finally in one of the latest meta-analyses published in 2019 Ng et al. demonstrated that in comparison to the placebo cohort, the levosimendan cohort showed a significant reduction in mortality (TSA = inconclusive; p=0.002; I^2=0%; FEM: OR 0.56; 95% CI 0.39, 0.80), especially in the subgroups of preoperative severe low LVEF ≤ 30% (p=0.003; OR 0.33; 95% CI 0.16, 0.69), preoperative administering of levosimendan (p=0.001; OR 0.46; 95% CI 0.29, 0.74) and patients who had bolus followed by infusion of levosimendan (p=0.005; OR 0.50; 95% CI 0.30, 0.81). However, the effect on mortality was not significant in the subgroup analysis of high quality trials (p=0.14; OR 0.73; 95% CI 0.47, 1.12). Given the low level of evidence, the results of this meta-analysis neither support nor oppose the use of levosimendan in cardiac patients with preoperative low LVEF (422).

In conclusion it must be mentioned that the evidence from studies published in the last 3 years questioned whether perioperative administration of levosimendan was associated with better clinical outcomes in adult patients undergoing cardiac surgery. For the future elucidation of this hypothesis, however, further prospective, if possible randomized studies with a specific question about long-term implications are necessary.

16.3. Effect on operative times and weaning from CPB

Total operation time, cardiopulmonary bypass time and cross-clamp time were recorded in all patients. Distribution of cross-clamp time was significantly different in the two groups where median was 78 minutes in the control group and 71 minutes in the drug group, suggesting a trend towards longer cross-clamp time in the controls (p=0.041). Duration of cardiopulmonary bypass (p=0.313) and the total duration of surgery (p=0.220) were not significantly different in the two groups. The average total operating times of the two patient groups hardly differ. Bias factors such as changes in the team composition in the both areas of anaesthesia and surgical staff, the variability of individual patients or any other individual factors were not able to be taken into consideration, but these may also have contributed to the staggering times. Overall, the proximity of the averages shows that the surgical treatment of the two groups hardly differs.

These data are contradictory to the most literature reports in which levosimendan seems to facilitate weaning from CPB (423, 424). Administration of levosimendan significantly enhanced primary weaning from CPB compared with placebo in patients undergoing 3-vessel on-pump CABG. The need for additional inotropic or mechanical therapy during weaning was also decreased (424). A decisive criterion here is the aggravating complexity of the interventions, which the patients had to undergo, in conjunction with the preoperatively significantly impaired cardiac performance. Taking this under consideration one can understand how difficult it is to standardize such parameters. For this reason further studies designed and powered to detect relevant clinical outcomes are needed before justifiable practice advisories can be made.

16.4. Postoperative clinical parameters

16.4.1. Postoperative ejection fraction

The most crucial and interesting parameter needed to be evaluated in this study was the evolution of the patients' EF postoperatively. As mentioned in the beginning the patients included in this study presented preoperatively a severely decreased EF under 30%. Almost all patients showed some degree of improvement of their EF postoperatively. As mentioned before, a significantly higher distribution of EF was observed in the levosimendan group postoperatively ($p=0.025$). The median for both groups was 30%, but the distribution of the values showed a better left ventricular function in the patients who were treated with levosimendan. This finding supports the hypothesis of the positive inotropic and cardioprotective effects of levosimendan. This conclusion becomes even stronger if the fact that a significantly higher distribution of EF was observed in the controls ($p<0.001$) preoperatively. The median preoperative EF was 30% for the control group and 20% for the levosimendan group. This makes the amelioration of the postoperative EF even more significant in the levosimendan group considering the fact that the grade of heart failure was even higher in these patients before the operation. For this reason apart from the EF absolute values, the difference between preoperative and postoperative EF was also statistically tested. Comparing the preoperative to the postoperative EF in both groups, a significantly higher ejection fraction difference (ΔEF) was noticed in the levosimendan group (0 for the control group vs. 9 for levosimendan group, $p<0.001$). This parameter makes our conclusion on the positive effect of levosimendan even stronger.

16.4.2. Rehospitalization

Equally important to the survival rates is also the quality of life of patients who survived. An important factor that we decided to control and has to our knowledge not yet been mentioned in the existing literature is the frequency of readmissions of the patients to the hospital due to problems associated with heart failure. The number of new hospital readmissions three years after surgery were recorded for all patients. This was achieved by recording the new admissions in our hospital archive and by directly asking the patients or their general practitioners during the follow up. The recorded readmissions were of course limited to admissions due to cardiac aetiology.

Figure 61 demonstrates a significantly higher proportion of patients in the control group had two or more readmissions to hospital after having been discharged compared to the levosimendan group ($p<0.001$). The median for the control group was 2 readmissions and 0 for the levosimendan group ($p<0.001$). This evidence supports the positive long-term effect of levosimendan in heart failure patients.

16.4.3. Postoperative angina pectoris and dyspnoea

During the follow-up all living patients who were included in the study were also asked to describe whether they still experience angina and dyspnoea symptoms and at what grade. Then they were classified according to the CCS and NYHA classification. The amount of patients in every class of angina and dyspnoea symptomatology are detailed demonstrated in figures 63 and 64. We compared the preoperative to postoperative classifications in both groups and found a clear tendency for more asymptomatic patients postoperatively in the Levosimendan group. 4.62% of patients in the control group experienced stage 0 angina postoperatively, which is substantially lower from the 35.87% in the drug group ($p<0.001$). Angina class 1 was reported by 34.62% of the control patients and 36.62% by the levosimendan treated patients, a difference which was slightly significant. However when comparing the higher classes of angina there is an obvious difference in favour of the levosimendan group. For instance 23.08% of the control group patients experienced class 2 angina compared to 4.09% of the levosimendan group patients. As far as dyspnoea is concerned, a similar trend was observed. NYHA class 0 for example was not reported by any patient of the control group (0%), whereas 10.33 of the levosimendan group patients described no limitation of physical activity due to dyspnoea ($p<0.001$) after the operation. Class 1 NYHA was reported by 10.77% of the control patients and by 41.3% of the levosimendan treated patients. Higher classes were as seen in table 23 more frequently reported in the control group.

These results lead to the conclusion that the patients who belong to the study group did not only experience significantly better survival rates, but also have a better quality of life with less symptoms after surgery.

16.4.4. Duration of mechanical ventilation, ICU and total hospital stay

In the present work, the duration of artificial ventilation presented a significant difference between the two groups (p=0.007), whereas the ICU and total hospital stay did not differ significantly.

The patients treated with levosimendan presented an easier and less complicated weaning from the ventilator and were sooner extubated compared to the control group patients (p=0.07). This suggests a possible lung protective effect of the drug. There are experimental data in the literature which support the protective effect of levosimendan against lung injury (425, 426).

On average, levosimendan treated patients spent 16 days in the hospital and 6 days in the intensive care unit. Patients in the control group, on the other hand, remained hospitalized for 15 days and spent 7 days in the ICU. Both Landoni et al. as well as Lim et al. showed in their meta-analyses that there was a significant reduction in hospital stay in patients treated with levosimendan (408, 413). Treskatsch has shown in his study that early administration of levosimendan can also produce better results in terms of ventilation time (427). Kodalli et al. however, in their double-blind, randomized study with a total of 30 patients, showed no significant differences in ventilation duration and duration of intensive care stay (428). Finally Qiang et al. showed in their meta-analysis that levosimendan significantly shortened the duration of the intensive care unit stay (weighted mean differences -0.49 day, 95% CI: -0.75 to -0.24, p=0.0002) and mechanical ventilation use (weighted mean differences -2.30 hours, 95% CI: -3.76 to -0.84, p=0.002) (421). The data received from the literature are to be discussed with regard to the current study. Administration of levosimendan seemed in our study to have a positive effect as far the artificial ventilation and the weaning from ventilator are concerned, but no significant influence on the reduction of a patients stay in the ICU and overall in the hospital. On the one hand, we were not able to identify any significant differences in terms of the parameters mentioned. On the other hand, the treated group would expect much longer periods of ICU and hospital stay regarding the higher risk profile of these patients as discussed above. This suggested that prophylactic administration of levosimendan may have a positive effect on postoperative ventilation and duration of ICU and hospital stay. However, a more reliable statement can only be made by further studies with a special focus on these parameters.

16.4.5. Support with inotropic agents and IABP

The need for inotropic support and administration of catecholamines was slightly, yet not significantly less in the levosimendan group patients (p=0.076). If the higher cardiovascular risk of the study group patients is taken into consideration, this fact may support the hypothesis of the cardioprotective effect of levosimendan and shows a faster recovery of myocardium after treatment.

These conclusions are generally supported by most literature reports in which a reduced catecholamine requirement after preconditioning with levosimendan was generally found. Several studies have shown that the early use of levosimendan leads to a significantly reduced need for inotropic support. (429, 430) However, due to the retrospective nature of this study, catecholamine control is not standardized. It is difficult to find out how closely the i.v. fluid volume and catecholamine dose was controlled in our patients. A more restrictive fluid infusion volume would be conceivable in patients with more complex interventions and an initially worse EF, which subsequently results in an increased vasopressor requirement. All these points could be clarified within the framework of a prospective investigation with a broad standardization of therapy control in order to investigate the actual effect of levosimendan on the need for further circulatory support.

As far as the use of the IABP is concerned, no significant difference was observed between the two groups (p=0.810). The duration of the mechanical circulatory support and the efficacy of the weaning of IABP was similar in both groups.

16.4.6. Postoperative arrhythmias

Postoperative arrhythmias, mostly concerning postoperative atrial fibrillation (POAF) are one of the most frequent complications after cardiac surgery. In patients undergoing cardiothoracic surgery an incidence of 16–46% has been reported, whereas in noncardiothoracic surgery, reported incidence of POAF varies between 0.4% and 12%. POAF can be observed during all the postoperative course, with a peak between the 2nd and 5th postoperative day. POAF is a major complication after cardiac surgery which can lead to high rates of morbidity and mortality, an enhanced length of hospital stay, and an increased cost of care. Several studies have attempted to identify predictors of POAF, with advanced age persisting as the most potent and consistent risk factor, followed by a history of AF, chronic obstructive

pulmonary disease, and several operative characteristics (431). POAF is postulated to be a multifactorial phenomenon; however, some major pathogeneses have been proposed, including inflammatory pathways, oxidative stress, and autonomic dysfunction (432).

Postoperative arrhythmias were recorded in many patients of both groups. The frequency of such incidents was however significantly higher in the control group (53%) compared to the group treated with levosimendan (40.76%) (p=0.031). In order to adequately evaluate this finding the preoperative prevalence of arrhythmias should also be taken under consideration. Occurrence of arrhythmias before surgery was significantly different in the two groups, 19.23% in the controls and 30.43% in the drug group (p=0.030). This comparison demonstrates that although the occurrence of arrhythmias was higher in the patients of levosimendan group, they presented significantly less arrhythmias postoperatively compared to the control group.

According to Abacilar et al., the prophylactic administration of levosimendan leads to a significant reduction in the incidence of POAF, especially after isolated CABG intervention (433). This statement is also supported by many other studies and meta-analyses. Thus, De Hert et al. reported similar results in 2008 in a randomized study of 3 study groups. The group receiving levosimendan prior to surgery presented significantly lower rates of atrial fibrillation postoperatively than the groups receiving levosimendan intraoperatively during surgery, or never received levosimendan, but were treated with milrinone instead (434). All these results lead to the suggestion of a prophylactic antiarrhythmic effect of levosimendan.

16.4.7. Postoperative renal function and need for haemodialysis

Cardiac surgery is associated with a high risk for peri- and postoperative complications. In consequence, protecting organ function in the operative setting plays an important role for improving patient outcome. Postoperative renal dysfunction is associated with increased mortality of 60-90% and prolonged stays on the ICU and in the hospital (404, 435). Its incidence has been reported as up to 55%; acute kidney injury is also associated with development of chronic kidney disease (436, 437). The aetiology of acute kidney injury after cardiac surgery is known to be

multifactorial and includes inflammatory response, oxidative stress, transient haemodynamic derangement and ischaemia-reperfusion injury (438, 439).

In our study significant differences have been recorded between the levosimendan and the control group in terms of postoperative renal function. Both the GFR, creatinine clearance and the rest values for acute renal failure show significant differences. 18 patients (13.85%) of the control group and 47 patients (25.54%) of the levosimendan group presented an impaired renal function before surgery presenting a significant difference ($p=0.012$) in favour of the control group. In both groups an initial slight GFR decrease was observed directly after surgery. On the following postoperative days all values of renal function appeared to be regressive until they almost reached the baseline. A significant difference between the two cohorts with regards to the distribution of the postoperative creatinine and creatinine clearance parameters was recorded across all time points ($p<0.001$). Median values of GFR were higher in the levosimendan group over all time points, except for the day prior to surgery ($p<0.001$). A significantly higher need for postoperative renal replacement therapy (RRT) was also observed in the control group ($p<0.001$). 38 patients of the control group (29.23%) and 21 patients of the levosimendan group (11.41%) needed RRT after surgery. All above findings suggest a protective impact of Levosimendan as far as renal function is concerned. It is also here important to stress that preoperative impaired renal function is a key factor in acute postoperative renal failure. With this knowledge, the results obtained are even more significantly positive for the study group.

The nephroprotective effect of levosimendan is thought to be due to its immunomodulatory, antiinflammatory, and antioxidant properties. Although levosimendan's effect on blood flow to the kidneys during cardiopulmonary bypass is not known, levosimendan significantly improved the ischaemia-reperfusion injury in renal tubules in previous animal studies and therefore has the potential to improve renal function (440). The influence of levosimendan in the preglomerular vascular resistance is shown in figure 94.

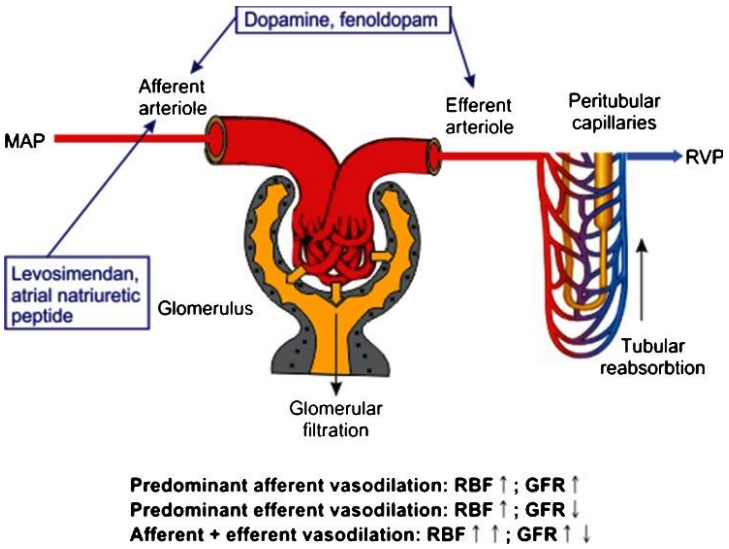


Figure 94. Differential effects of renal vasodilators on preglomerular (afferent arteriole) and postglomerular (efferent arteriole) vascular resistance sections.

(Source: Yilmaz MB, Grossini E, Silva Cardoso JC, et al. Renal effects of levosimendan: a consensus report. Cardiovasc Drugs Ther. 2013 Dec;27(6):581-90. doi: 10.1007/s10557-013-6485-6.)

A study by Bragadottir et al. in 2013, showed an effective vasodilation, especially of the preglomerular vessels, leading to an improved renal blood flow and glomerular filtration rate, without increasing the renal oxygen demand. This resulted in a reduced incidence of acute renal failure and the need to RRT (441). Also the results of Baysal et al. in 2014 support this hypothesis. In a prospective, double-blind, randomized study with a total of 128 participants, significantly better creatinine and GFR values were recorded in the levosimendan-treated group. The use of dialysis therapy was also significantly less frequent in the study group (442). Lim et al. in their meta-analysis of 14 controlled, randomized trials showed that postoperative acute renal failure was lower with levosimendan therapy (7.4% vs. 11.5%) (413). In the meta-analysis by Landoni et al. in 2010 on the contrary, no improvements in acute renal failure could be found (407). Ristikankare et al. in 2012 came to a similar conclusion that levosimendan did not have a significant influence on the kidney function measuring specific kidney markers such as Urine N-acetyl-β-glucosaminidase (U-NAG), Serum cystatin C and plasma creatinine (443). In 2013 a panel of 25 scientists and clinicians from 15 European countries convened and reached a consensus on the current interpretation of the renal effects of levosimendan described both in non-clinical research and in clinical study reports. Most reports on the effect of levosimendan indicated an improvement of renal function in heart failure, sepsis and

cardiac surgery settings. However, study designs differed from randomized, controlled studies to uncontrolled ones. Importantly, in the largest HF study (REVIVE I and II) no significant changes in the renal function were detected (444). Another meta-analysis by Zhou et al. in 2015 included 13 trials with a total of 1345 study patients. They concluded that levosimendan reduced the incidence of postoperative AKI (40/460 vs 78/499; OR, 0.51; 95% CI, 0.34-0.76; p=0.001; I^2=0.0%) and renal replacement therapy (22/492 vs 49/491; OR, 0.43; 95% CI, 0.25-0.76; p=0.002; I^2=0.0%) (445). In 2018 Kim et al. performed an arm-based hierarchical Bayesian network meta-analysis including 95 randomised controlled trials with 28,833 participants. Among other agents, levosimendan significantly decreased the rate of postoperative renal dysfunction compared with placebo (446). Finally, a recent meta-analysis by Qiang et al. in 2018 including 25 studies (3247 patients) demonstrated that the administration of levosimendan significantly reduced the incidence of postoperative acute kidney injury (OR 0.55, 95% CI: 0.41-0.74, p<0.0001) and renal replacement therapy use (OR 0.56, 95% CI: 0.39-0.80, p=0.002) (421).

However it is important to mention that all existing meta-analyses came across with the problem of significant heterogeneity regarding the criteria for diagnosing postoperative renal dysfunction (AKIN criteria, RIFLE criteria, KDIGO criteria, etc.). Given the lack of a standard definition of renal dysfunction, the results of these meta-analyses should be applied only cautiously to clinical practice. A standardisation of renal outcome definitions in further studies is required in order to establish more reliable evidence (446).

16.4.8. Haemoglobin and need for transfusion of blood products

CABG is a surgical procedure that causes sufficient hemoglobin loss to require blood-product transfusion in around 50% of patients (447). Once recovery from surgery has taken place, there is rarely any requirement for further blood transfusion. CPB is associated with coagulopathy and platelet count reduction. In particular, prolonged CPB and circulatory arrest with hypothermia result in more pronounced alterations of the coagulation systems. Bleeding induced by coagulopathy requires transfusion of allogeneic blood or blood products. Fresh frozen plasma (FFP) and platelets include coagulation factors and thus ameliorate coagulopathy. However, allogeneic blood transfusions, may have many adverse effects, including

anaphylactic shock and transfusion-related acute lung injury (TRALI). In addition, transfusion-transmitted viral infections or graft-versus-host disease may occur in case of allogenic blood transfusion. Horvath et al. described that each RBC unit transfused was associated with a 29% increase in crude risk of major infection ($p<0.001$). Among RBC recipients, the most common infections were pneumonia (3.6%) and bloodstream infections (2%) (448). Moreover several studies have shown that perioperative transfusions are associated with increased morbidity and mortality and reduced long-term survival, mainly through immune modulation and tumor promotion (447, 449). However Dardashti et al. showed that when pre-operative Hb levels and renal function are taken into account, moderate transfusions of RBC after CABG surgery do not seem to be associated with reduced long-term survival (450). Therefore, increasing attention is being paid toward the use of blood-sparing techniques and transfusion behaviors. Guidelines on transfusion practices in cardiothoracic surgery have been published, but there still is a considerable variation in transfusion practices nationally and internationally (451, 452). Efforts to change transfusion behaviors and decrease transfusion rates in cardiac surgery have persistent effects for several years, but more still needs to be done because the transfusion rate is still high and inappropriate allogeneic transfusions may still be common in different clinical scenarios (453).

In our study a significantly higher amount of erythrocytes and fresh frozen plasma units transfusion was required after surgery in the Control group compared to the Levosimendan group ($p<0.001$ for both parameters). Both groups presented a low need for platelet unit transfusions and the difference was not significant between the two groups ($p=0.179$).

Haemoglobin values were also recorded in all patients for the first 5 postoperative days. As far as the preoperative values are concerned a significant difference was observed in favour of the control group which presented a median value of 14.3 g/dl whereas the levosimendan patients 13.4 g/dl ($p=0.003$). Significant differences were observed on the operation day, directly after the transfer of the patient in the ICU (9.3 g/dl in the control group vs. 9.8 g/dl in the levosimendan group, $p<0.001$) and on the first postoperative day (9.5 g/dl in the control group vs. 9.8 g/dl in the levosimendan group, $p=0.047$) with the levosimendan group presenting better haemoglobin levels. On the second, third and fourth postoperative day the differences were not significant ($p=0.956$, 0.315 and 0.082 respectively). On the fifth postoperative day the difference

was significant again, however this time the control group presented higher levels (10.4 g/dl in the control group vs. 9.9 g/dl in the levosimendan group, p=0.028). This difference may be explained by the fact that the control patients had a higher preoperative median value, and after recovery on the fifth postoperative day, both groups reached values that reflect the baseline levels. The higher RBC transfusion rates should also be taken into consideration while interpreting these results. There is no obvious explanation of the reduced need for transfusions in the levosimendan group, but this may be correlated with the possible limitation of the adverse effects of CPB in this group, reducing the coagulopathy and therefore the perioperative bleeding and transfusion need. The fact that the Control group consists of a historical group of patients should also be considered, as other, probably more liberal transfusion concepts may have been used at the time those patients were operated.

16.5. Postoperative laboratory parameters

16.5.1. Postoperative inflammatory response

CPB initiates a systemic inflammatory response syndrome (SIRS) after open-heart surgery that is mediated by compartment activation, cytokine production and neutrophil sequestration in the lungs and may lead to several complications. The exact mechanism of this complex reaction has not been fully determined (454). The mechanism of SIRS during CPB includes the interaction of blood and artificial surface and endotoxemia. The interaction of blood and artificial surface is initiated by protein adsorption. As a result of series of chain reactions, the numerous powerful inflammatory mediators, including hormones and autacoids, are formed and released. Subsequently, the contact system, coagulation system, complement system, fibrinolysis system, and leukocytes, platelets, and endothelial cells, are all activated to participate in the interaction of blood and artificial materials. These activations of different systems and blood cells can interact and magnify each other. CPB-associated endotoxemia has been demonstrated to intensify and deteriorate SIRS during CPB (455).

The CRP values were in our study regularly determined for the detection or assessment of inflammation. The preoperative values did not differ significantly between the two groups (p=0.158). A significant difference was observed directly

after surgery (p<0.001), which may imply a better tolerance of the CBP in the levosimendan group. A strong increase in CRP levels was recorded in both groups on the second postoperative day and the differences on the first two postoperative day were not significant (p=0.555 and p=0.422 respectively). Thereafter, the CRP values were regressive in both groups. A slight difference was recorded on the third postoperative day in favour of the levosimendan group (p=0.047). Significant differences of the CRP values were recorded on the fourth and fifth day (p<0.001 for both days), implying a faster recovery from the inflammatory response in the patients treated with levosimendan.

Our conclusion is supported be the few existing studies on this issue. Adamopoulos et al. and Trikas et al. in 2006, demonstrated a significant anti-inflammatory and anti-apoptotic effect of levosimendan. Adamopoulos et al. studied 96 patients, one-third of whom received levosimendan, dobutamine, or placebo, for proinflammatory and apoptotic factors. Interleukin-6, TNF-α and soluble FAS ligand values were measured. Here, only in the levosimendan group did a significant reduction of these three parameters occur (456). Trikas et al. included in their study 27 patients and were able to find a significant and long-lasting effect of levosimendan in terms of a reduction of interleukin-6 as well as soluble FAS ligand and TNF-α and the corresponding receptors TNF-R1 and -R2 (457).

16.5.2. Postoperative myocardial injury

A certain amount of myocardial injury is present in every patient undergoing cardiac surgery. Cardiac damage after cardiac surgery could lead to prolonged hospital stay as well as an increased perioperative mortality rate (458). Postoperative cardiac troponin (cTn) is increased in all patients undergoing cardiac surgery. Numerous factors can explain such an increase in cTn, even in the absence of postoperative MI (459). The type of surgery, the choice of cardioplegic solution and its mode of delivery, and the use of intraoperative aprotinin all influence postoperative cTn release in patients scheduled for cardiac surgery (458). Several studies have reported the prognostic significance of postoperative troponin measurements in relation to both short- and long-term outcomes (460, 461). Data from patients undergoing OPCAB surgery and aortic clamping suggest that coronary artery anastomosis per se does not lead to an important release of cTn in contrast with

more complex procedures (e.g., mitral valve replacement with human mitral valve homograft, Ross procedures, or some types of pediatric cardiac surgery) (462, 463). Another issue concerning the interpretation of postoperative cTn concentrations in terms of ischemic myocardial damage could be the frequent use of internal defibrillation before the end of CPB. However, it has been shown previously that internal defibrillation produces only early and minor elevations of cTn serum levels (464). A meta-analysis by Zangrillo et al. showed that the cTn release peak was lower in levosimendan-treated patients, a finding consistent with a beneficial cardioprotective effect. Moreover, this reduction of myocardial damage (postoperative cTn concentrations) appears to translate into outcome benefit (reduced hospital length of stay) (458).

In order to assess the potential myocardial injury and to monitor the recovery after it creatine kinase (CK) and its myocardial component (CKMB), as well as troponin I (cTnI) were measured on a daily basis. The trend of all parameters was similar in both study groups with a peak on the 1st postoperative day. cTnI levels differed significantly between the two groups across all time points ($p<0.001$). Indicatively, median of troponin I was 18.47 ng/ml and 9.90 ng/ml on the 1st postoperative day in the control and levosimendan groups respectively ($p<0.001$). A significant difference between the two cohorts with regards to the distribution of CKMB was observed across all time points ($p<0.001$). A similar finding was seen for CK ($p<0.001$). In summary, there is a perioperatively higher cardiac enzyme release in the control group, especially in the first 48 h, which could be taken as a sign of significantly higher heart damage in the control group. It can be hypothesized that the better preservation of early cardiac function with levosimendan may result in an improved global tissue perfusion with a better recovery from surgery.

16.5.3. Organ perfusion and metabolic balance

An arterial blood gas analysis was regularly performed during every day in the ICU, providing an adequate monitoring of the respiratory and metabolic condition of every patient. In order to assess the metabolic changes and the organ perfusion after surgery the lowest pH and the highest lactic acid values of every day were recorded and analyzed in all patients of the study. The distribution of pH appeared to be different between the two groups over all time points measured, showing a higher

tendency to acidosis in the control group. This finding suggests a possible positive metabolic effect of levosimendan reducing the degree of postoperative metabolic acidosis.

The distribution of lactic acid values was also significantly different between the two groups over all time points during the first five postoperative days. Median lactic acid was 2.30 mmol/l in the control group on the 2nd postoperative versus 1.60 mmol/l in the levosimendan group ($p<0.001$). In a study by Fang et al. in accordance to our study, 36 patients who needed intensive care due to severe sepsis showed, in addition to the improvement in the hemodynamic situation, lower measured lactate values in the group treated with levosimendan (465). A similar recent work of Xu et al. demonstrated that compared with dobutamine group, blood lactic acid at 24 h decreased significantly in levosimendan group [(1.97±1.10)mmol/L vs. (2.73±2.06) mmol/L, $p=0.002$]. Levosimendan seemed to improve cardiac systolic function and tissue perfusion in elderly patients with septic myocardial contractility impairment (466). To sum up our results implied once more the possible positive inotropic effect of levosimendan and its metabolites and their protection against postoperative low cardiac output syndrome.

17. LIMITATIONS OF THIS STUDY

As already discussed, the present work presents certain limitations, mostly because of its retrospective character and the possible inequality of the studied groups. As mentioned above there were significant differences in some of the parameters measured or recorded preoperatively, showing some heterogeneity between the two groups. These were attempted to minimize by making a consistent exclusion of patients who had insufficient data documentation. However this heterogenity did not seem to severely influence the conclusions that can be made when analysing the results. Despite the limitations of the outcome of this work, it also brings certain benefits. The data collected adequately reflect the use of levosimendan in everyday clinical practice. The number of patients involved and the amount of parameters recorded in every patient offer one more representative study to the existing literature of this issue. Furthermore, long-term data on levosimendan use offered by this study, sometimes even up to 5 years postoperatively so far haven’t been available in the literature.

18. SUMMARY

18.1. Summary in English

The prevalence of postoperative myocardial dysfunction following cardiac surgery is a relatively common phenomenon even in patients with a normal preoperative ventricular function and its grade depends on factors such as patient age, the kind of procedure performed and the existing co-morbidities. The phenomenon becomes much more intense and more difficult to treat in patients with pre-existing heart failure. This condition results in delayed recovery, organ failure, prolonged stay in the ICU and in the hospital, increased morbidity and mortality and significantly increased costs. When myocardial dysfunction is clinically significant it may jeopardize tissue perfusion. In this case the use of inotropic agents is necessary in order to support circulation until endogenous myocardial function is restored. The classic treatment strategies have traditionally focused on the use of catecholamines and, in particular, β-adrenergic agents, which are also characterized as first choice drugs due to their beneficial effects on myocardial contractility and cardiac output. However, the use of these sympathomimetic drugs can be accompanied by many side effects such as tachycardia, arrhythmias, adverse effects on ventricular load conditions and ultimately myocardial oxygen supply-consumption disorders. In addition, down-regulation of β-adrenergic receptors in patients with chronic heart failure may alleviate the response to exogenously administered catecholamines.

Levosimendan is a new inotropic drug, belonging to the class of calcium sensitizers. It increases myofilament calcium sensitivity during cardiac systole by binding to troponin C in a calcium-dependent manner. This interaction stabilizes the calcium-induced conformational change of tropomyocin, thereby augmenting actin-myocin cross-bridging without raising intracellular calcium concentrations. It also binds to and opens ATP-dependent potassium (K_{ATP}) channels, having a direct effect on vascular smooth muscle cells, causing vasodilation. The beneficial effects of levosimendan despite the existing controversy have already been described in many studies of the literature concerning internal medicine and surgical patients. The aim of this study is to evaluate whether benefits of levosimendan could be extended to improve the outcome of patients with low preoperative EF and myocardial dysfunction following cardiac surgery.

The results of this work show substantial positive effects of levosimendan on the short- and long-term outcome in patients with severely reduced ejection fraction undergoing cardiac surgery. The prophylactic administration of levosimendan significantly improved the short- and long-term outcomes of the treated patients. The results of this study can be summarized in the following conclusions:

- Levosimendan improves short- and long term survival after cardiac surgery.
- It significantly facilitates postoperative improvement of the EF.
- It provides a better hemodynamic stability and reduces the need for inotropic support of the patients.
- It does not affect the need for mechanical hemodynamic support with the IABP.
- It reduces mechanical ventilation time and facilitates a faster weaning from ventilator.
- It does not reduce the stay in the ICU and the total hospital stay.
- It reduces rehospitalization and readmissions to the hospital due to cardiac aetiology.
- These patients reported a better clinical symptomatology with less angina and dyspnea.
- It reduces the need for transfusion of blood products.
- It reduces the occurrence of postoperative arrhythmias.
- It provides a renal protective effect and reduces the need for renal replacement therapy.
- It reduces the systemic inflammatory response and provides a faster recovery from it.
- It limits the amount and extense of the inevitable myocardial injury after cardiac surgery.
- It ameliorates organ and tissue perfusion and metabolic balance postoperatively.

It is also important to mention that the purpose of this study was to demonstrate a possible positive effect of levosimendan as an additive treatment and not as a monotherapy, as the conventional medical, surgical and mechanical therapeutical means remain the cornerstone of the treatment of a cardiac surgery patient.

The mentioned limitations of a retrospective analysis with unequal basic characteristics were attempted to compensate with the help of a multivariate regression analysis. In order to allow a more precise quantification of the positive or potential negative effects of levosimendan, more prospective randomized studies would be necessary, in which the documentation and control of the other perioperative therapy are standardized and comprehensibly documented.

18.2. Summary in German / Zusammenfassung

Das Auftreten einer postoperativen myokardialen Dysfunktion nach einer Herzoperation ist ein relativ häufiges Phänomen, auch bei Patienten mit einer präoperativ normalen ventrikulären Funktion. Der Grad hängt von Faktoren wie dem Alter des Patienten, der Art des durchgeführten Eingriffs und den bestehenden Komorbiditäten ab. Das Phänomen ist bei Patienten mit vorbestehender Herzinsuffizienz viel intensiver und schwieriger zu behandeln. Dieser Zustand führt zu verzögerter Erholung, Organversagen, längerem Aufenthalt auf der Intensivstation und im Krankenhaus, erhöhter Morbidität und Mortalität und signifikant erhöhten Kosten. Wenn eine Myokardfunktionsstörung klinisch signifikant ist, kann sie die Gewebeperfusion gefährden. In diesem Fall ist die Verwendung von Inotropika erforderlich, um die Kreislaufverhältnisse zu verbessern, bis die endogene Myokardfunktion wiederhergestellt ist. Die klassischen Behandlungsstrategien konzentrierten sich traditionell auf die Verwendung von Katecholaminen und insbesondere von β-adrenergen Wirkstoffen, die aufgrund ihrer vorteilhaften Auswirkungen auf die Kontraktilität des Herzmuskels und das Herzzeitvolumen auch als Arzneimittel erster Wahl gelten. Die Anwendung dieser Sympathomimetika kann jedoch mit vielen Nebenwirkungen einhergehen, wie Tachykardien, Arrhythmien, nachteiligen Auswirkungen auf die ventrikulären Belastungszustände und letztendlich Störungen der Sauerstoffversorgung und des Sauerstoffverbrauchs des Herzmuskels. Darüber hinaus kann eine Herunterregulierung der β-adrenergen Rezeptoren bei Patienten mit chronischer Herzinsuffizienz die Reaktion auf exogen verabreichte Katecholamine reduzieren.

Levosimendan ist ein neues inotropes Medikament, das zur Klasse der Kalziumsensibilisatoren gehört. Es erhöht die Kalziumempfindlichkeit des Myofilaments während der Herzsystole, indem es in kalziumabhängiger Weise an

Troponin C bindet. Diese Wechselwirkung stabilisiert die Kalzium-induzierte Konformationsänderung von Tropomyocin, wodurch die Actin-Myocin-Überbrückung verstärkt wird, ohne die intrazellulären Kalziumkonzentrationen zu erhöhen. Es bindet und öffnet auch ATP-abhängige Kaliumkanäle (K_{ATP}), die eine direkte Wirkung auf die glatten Gefäßmuskelzellen haben und eine Vasodilatation verursachen. Die positive Wirkung von Levosimendan wurde trotz der bestehenden Kontroverse bereits in vielen Literaturstudien zur Inneren Medizin und zu chirurgischen Patienten beschrieben.

Ziel dieser Studie war es zu evaluieren, ob die Anwendung von Levosimendan erweitert werden kann, um das Ergebnis von Patienten mit niedriger präoperativer EF und Myokardfunktionsstörung nach einer Herzoperation zu verbessern.

Die Ergebnisse dieser Arbeit weisen deutliche positive Effekte von Levosimendan auf das kurz- und langfristige Ergebnis bei Patienten mit stark reduzierter Ejektionsfraktion, die sich einer Herzoperation unterziehen, nach. Die prophylaktische Verabreichung von Levosimendan verbesserte die kurz- und langfristigen Ergebnisse der behandelten Patienten signifikant. Die Ergebnisse dieser Studie können in den folgenden Schlussfolgerungen zusammengefasst werden:

- Levosimendan verbessert das kurz- und langfristige Überleben nach einer Herzoperation bei Patienten mit schwer eingeschränkter Pumpfunktion.
- Es unterstützt die postoperative Verbesserung der EF erheblich.
- Es bietet eine bessere perioperative hämodynamische Stabilität und verringert den Bedarf an inotroper Unterstützung für die Patienten.
- Der Bedarf an mechanischer hämodynamischer Unterstützung mit dem IABP wird dadurch nicht beeinträchtigt.
- Es reduziert die Beatmungszeit und ermöglicht ein schnelleres Entwöhnen vom Beatmungsgerät.
- Der Aufenthalt auf der Intensivstation und der gesamte Krankenhausaufenthalt werden nicht reduziert.
- Es reduziert die Rehospitalisierung und die Reaufnahmen in das Krankenhaus aufgrund von Herzinsuffizienz.
- Die Patienten erleben eine bessere klinische Symptomatik postoperativ mit weniger Angina und Dyspnoe.
- Es reduziert die Notwendigkeit der Transfusion von Blutprodukten.

- Es reduziert das Auftreten von postoperativen Arrhythmien.
- Es bietet eine renale Schutzwirkung und reduziert den Bedarf an Nierenersatztherapie.
- Es reduziert die systemische Entzündungsreaktion und sorgt für eine schnellere Erhohlung davon.
- Es begrenzt das Ausmaß und die Intensität der unvermeidbaren Myokardverletzung nach einer Herzoperation.
- Es verbessert die Perfusion von Organen und Gewebe und den Stoffwechsel nach der Operation.

Es ist wichtig zu erwähnen, dass der Zweck dieser Studie darin besteht, eine mögliche positive Wirkung von Levosimendan als additive Behandlung und nicht als Monotherapie aufzuzeigen, da die konventionellen medizinischen, chirurgischen und mechanisch-therapeutischen Mittel die Eckpfeiler der Behandlung dieser Patientengruppe bleiben.

Die genannten Einschränkungen einer retrospektiven Analyse mit ungleichen Basismerkmalen wurden versucht, mit Hilfe einer multivariaten Regressionsanalyse zu kompensieren. Um die positiven oder potenziellen negativen Wirkungen von Levosimendan genauer quantifizieren zu können, wären prospektivere randomisierte Studien erforderlich, in denen die Dokumentation und Kontrolle der anderen perioperativen Therapie standardisiert und nachvollziehbar dokumentiert werden.

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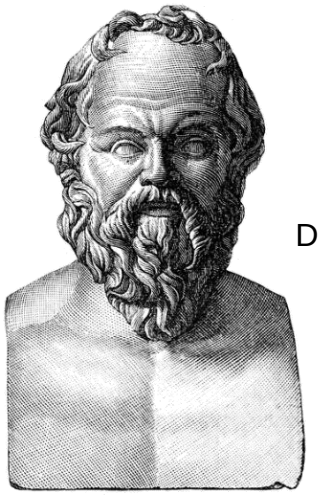
20. NOTE OF THANKS / DANKSAGUNG

Dem Chefarzt der Klinik für Thorax-, Herz- und Gefßchirurgie des Westpfalz-Klinikums in Kaiserslautern danke ich ganz herzlich für die Vergabe des interessanten und aktuellen Promotionsthemas und für die Möglichkeit meine wissenschaftliche Arbeit neben meiner klinischen Aufgaben in durchführen zu dürfen. Weiterhin danke ich ihm für die umgehende konstruktive und wertvolle Kritik an dieser Arbeit, ohne die eine Vollendung nicht möglich gewesen wäre.

Mein besonderer Dank gilt meinen Kollegen der Klinik für Thorax-, Herz- und Gefßchirurgie des Westpfalz-Klinikums in Kaiserslautern die mir mit Rat und Tat zur Seite standen und mir immer durch ihr fachspezifisches Wissen und ihre freundliche aufgeschlossene Art die nötige Motivation gaben, um diese Arbeit zu vollenden. Ihre gute Erreichbarkeit sowie unsere interessanten und angeregten Diskussionen werden mir immer in guter Erinnerung bleiben.

Weiterhin danke ich meiner Ehefrau, die immer ein offenes Ohr für meine Probleme und Bedenken hatte und durch aufmunternde Worte einen großen Anteil am Gelingen dieser Dissertation hat. Ohne ihre Unterstützung und ihre Geduld wäre die Durchführung dieser Arbeit nicht möglich gewesen.



«Ἓν οἶδα ὅτι οὐδὲν οἶδα -

Η μόνη αληθινή σοφία είναι η γνώση ότι δεν ξέρεις τίποτα. »

‚Ich weiß dass ich nichts weiß -

Die einzig wahre Weisheit ist das Wissen, dass du nichts weißt. ‘

Σωκράτης (470 - 399 π.Χ.), Έλλην Φιλόσοφος

Sokrates (470 - 399 v. Chr.), griechischer Philosoph

21. CURRICULUM VITAE / LEBENSLAUF

21.1. Angaben zur Person

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21.2. Arbeitserfahrung

Vom 01.03.2019 bis heute	Oberarzt der Klinik für Thorax-, Herz und Gefäßchirurgie des Westpfalz-Klinikums in Kaiserslautern, Rheinland-Pfalz.
Vom 01.08.2018 bis 28.02.2019	Funktionsoberarzt der Klinik für Thorax-, Herz und Gefäßchirurgie des Westpfalz-Klinikums in Kaiserslautern, Rheinland-Pfalz.
Vom 27.06.2018 bis 31.07.2018	Facharzt in der Klinik für Thorax-, Herz und Gefäßchirurgie des Westpfalz-Klinikums in Kaiserslautern, Rheinland-Pfalz.
Vom 07.02.2013 bis 26.06.2018	Assistenzarzt in der Klinik für Thorax-, Herz und Gefäßchirurgie des Westpfalz-Klinikums in Kaiserslautern, Rheinland-Pfalz.

Vom 06.08.2012 bis 06.02.2013	Assistenzarzt in der Abteilung für Allgemeinchirurgie des Caritas Krankenhauses (CTT) in Lebach, Saarland.
Vom 07.06.2012 bis 05.08.2012	Gastarzt in der Abteilung für Allgemeinchirurgie des Caritas Krankenhauses (CTT) in Lebach, Saarland.
Vom 06.06.2011 bis 06.06.2012	Assistenzarzt in der Klinik für Allgemein- und Viszeralchirurgie des “Agios Andreas” Maximalversorgungs-Krankenhauses in Patras, Griechenland. Parallel dazu Arzt in der Abteilung für Herz- und Thoraxchirurgie des Universitätsklinikums in Patras; Teilnahme an Diensten.
Vom 10.05.2010 bis 10.02.2011	Wehrdienst als Militärarzt in Arta und Patras, Griechenland und in Mathiatis, Zypern.
Vom 14.04.2009 bis 10.05.2010	Allgemeinmedizin (Landsarzt) im “Chatzikosta” Krankenhaus in Mesolonghi und im Gesundheitszentrum in Aetoliko, Griechenland. Parallel dazu Arzt in der Abteilung für Herz- und Thoraxchirurgie des Universitätsklinikums in Patras; Teilnahme an Diensten.
Vom 01.08.2008 bis 13.04.2009	Sportmedizin, Arzt in den Fußballspielen der Liga des Westlichen Griechenlands (IV) und der Achaia-Liga (V).

21.3. Ausbildung - Weiterbildung

27.06.2018	Facharzt für Herzchirurgie
01.12.2017	Fachkunde im Strahlenschutz – Röntgendiagnostik des Thorax
Von 17.11.2014 bis 21.11.2014	Praktikum (Clinical attachment) in Manchester Heart Centre, Manchester Royal Infirmary, Manchester, Großbritanien.
02.08.2012	Approbation als Arzt in Deutschland.

Vom 01.08.2007 bis 31.08.2007	Praktikum in der Abteilung für Herz- und Thoraxchirurgie - Herzzentrum des TAYS Universitätsklinikums in Tampere, Finnland.
Von 2002 bis 2008	Medizinstudium an der Universität Patras, in Patras, Griechenland.
Von 2003 bis 2012	Arzt und Sanitäter des Griechischen Roten Kreuzes.
Von 1999 bis 2002	Lyzeum in Patras, Griechenland.
Von 1996 bis 1999	Gymnasium in Patras, Griechenland.
Von 1990 bis 1996	Grundschule in Patras, Griechenland.

21.4. Kurse - Seminare

08.01.2019	Strahlenschutzkurs - Spezialkurs Interventionsradiologie
28.09.-06.10.2018	Seminarkongress Notfallmedizin, Arbeitsgemeinschaft Intensivmedizin e.V. (AIM), Arnsberg.
09-10.11.2017	Repetitorium zum Erwerb der Facharztanerkennung Herzchirurgie – Praxis, DGTHG, Aeskulap Akademie, Tuttlingen.
06-07.11.2017	Grundlagen der Medizinischen Begutachtung, Akademie für ärztliche Fortbildung in Rheinland-Pfalz, Mainz.
28-30.09.2017	Repetitorium zum Erwerb der Facharztanerkennung Herzchirurgie – Theorie, DGTHG, Aeskulap Akademie, Berlin.
21-24.03.2017	37th International Symposium on Intensive Care and Emergency Medicine, Brussel, Belgium.
20-21.01.2017	Gerinnung in Anästhesie und Intensivmedizin, Krankenhaus Nordwest GmbH, Köningstein.
07-08.11.2016	Enterale und parenterale Ernährungstherapie in der Intensivmedizin, Zertifizierung als Ernährungsbeauftragten ‚Ernährungsmanagement im Intensivbereich‘, Fresenius Konzernzentrale, Bad Homburg.
03-06.11.2016	Echo-, und Dopperechokardiographie Aufabaukurs, Deutsches Herzzentrum, Berlin.
08-11.09.2016	Echo-, und Dopperechokardiographie Grundkurs, Deutsches Herzzentrum, Berlin.
04.06.2016	Bronchoskopiekurs, Unniversitätsklinikum Mannheim.

Von 04.03.2016 bis 11.03.2016	Einführungskurs Intensivmedizin, Arbeitsgemeinschaft Intensivmedizin e.V. (AIM), Arnsberg.
24-25.04.2015	Spezialkurs Röntgendiagnostik, Westpfalz-Klinikum, Kaiserslautern.
20-22.03.2015	Kombi-Kurs Strahlenschutz, Westpfalz-Klinikum, Kaiserslautern.
Von 16.03.2015 bis 29.03.2015	Forschung chirurgischer Aktivitäten, einschließlich physiologischen Studien über die ex-vivo Schweineherz und Praktikum bezüglich der Aortenklappenimplantationen und aortocoronaren Bypassoperationen am Schweineherzen, in Surgical Skills Centre, Manchester Science Park, Manchester, Großbritanien.
Von 24.11.2914 bis 28.11.2014	Fortbildung in aortocoronaren Anastomosen, Aortenklappenimplantation, End-zu.End Anastomosen der Aorta an Schweineherzen in Surgical Skills Centre, Manchester Science Park, Manchester, Großbritanien.
13-15.06.2013	Kurs der mechanischer Kreislaufunterstützung (IABP und ECMO/ECLS), Maquett Akademie, Rastatt.
05.2013	ALS (Advanced Life Support) Kurs (Reanimationskurs) in Kaiserslautern.
05.2009	ATLS (Advanced Trauma Life Support) Kurs in Patras, Griechenland.
2003	BLS (Basic Life Support) und PHTLS (Prehospital Trauma Life Support) Kurs. Griechisches Rotes Kreuz, Patras, Griechenland.

21.5. Publikationen – Veröffentlichungen

1. Massive pulmonary embolism due to hydatid cysts: A rare postoperative complication of liver echinococcosis. Kotoulas S, Grapatsas K, **Leivaditis V**, Panagiotou I, Spiridakis E, Le UT, Osei-Agyemang T, Kotoulas C. Respir Med Case Rep. 2020 Apr 20;30:101054.

2. Common swelling of the dorsal thoracic wall brings an unexpected finding: elastofibroma dorsi. Kotoulas S, Grapatsas K, Georgiou C, Tsilogianni Z, **Leivaditis V**, Rufino MBL, Kotoulas C. Monaldi Arch Chest Dis. 2020 Jan 21;90(1).

3. The π-Circuit Technique in Coronary Surgery: Analysis of 1359 Consecutive Cases. Prapas SN, Pangiotopoulos IA, **Leivaditis VN**, Katsavrias KP, Prapa VS, Linardakis IN, Koletsis EN, Grapatsas K. Open J Cardiovasc Surg. 2019 Aug 27;11:1179065219871948.

4. Sclerosing Mediastinitis Causing Unilateral Pulmonary Edema Due to Left Atrial and Pulmonary Venous Compression. A Case Report and Literature Review. Panagopoulos N, **Leivaditis V**, Kraniotis P, Ravazoula P, Koletsis E, Dougenis D. Braz J Cardiovasc Surg. 2019 Jan-Feb;34(1):85-92.

5. Deep accidental hypothermia accompanied with cardiac arrest after alcohol and drug poisoning treated with extracorporeal life support. Grapatsas K, **Leivaditis V**, Panagiotopoulos I, Spiliotopoulos K, Koletsis E, Dahm M, Kosmidis C, Laskou S, Zarogoulidis P, Katsaounis A, Pavlidis E, Giannakidis D, Koulouris C, Mantalovas S, Konstantinou F, Amaniti A, Munteanu A, Surlin V, Sapalidis K, Kesisoglou I. Respir Med Case Rep. 2018 Jun 19;25:66-67.

6. A rare case of giant cell lung carcinoma with intracardiac extension via the pulmonary vein and thrombus formation. **Leivaditis V**, Koletsis E, Spiliotopoulos K, Grapatsas K, Tzelepi V, Dougenis D. J Surg Case Rep. 2018 Jun 25;2018(6):rjy144.

7. Hamman's syndrome (spontaneous pneumomediastinum presenting as subcutaneous emphysema): A rare case of the emergency department and review of the literature. Grapatsas K, Tsilogianni Z, **Leivaditis V**, Kotoulas S, Kotoulas C, Koletsis E, Iliadis IS, Dahm M, Trakada G, Veletza L, Kallianos A, Huang H, Kosmidis C, Karanikas M, Thomaidis V, Porpodis K, Zarogoulidis P. Respir Med Case Rep. 2017 Dec 11;23:63-65.

8. Successful treatment of postoperative massive pulmonary embolism with paradoxal arterial embolism through extracorporeal life support and thrombolysis. Grapatsas K, **Leivaditis V**, Zarogoulidis P, Tsilogianni Z, Kotoulas S, Kotoulas C, Koletsis E, Iliadis IS, Spiliotopoulos K, Trakada G, Veletza L, Kallianos A, Tsiouda T, Kosmidis C, Hohenforst-Schmidt W, Huang H, Haussmann R, Haussmann E, Dahm M. Respir Med Case Rep. 2017 Oct 31;23:1-3.

9. Malignant Pleura Mesothelioma: Clinical Perspectives. Grapatsas K, **Leivaditis V**, Zarogoulidis P, Dahm M, Iliadis IS, Tsilogianni Z, Koletsis E, Dimopoulos E, Vasilikos I, Rizos G, Gazos E, Baikoussis NG, Tsiouda T, Mparpmetakis N, Man YG, Kotoulas C. Oncomedicine 2017; 2: 121-125.

10. Community-acquired pneumonia: current data. Tsilogianni Z, Grapatsas K, **Leivaditis V**, Zarogoulidis P, Katsikogiannis N, Sarika E, Barbetakis N, Sarafis P, Paliouras D, Karapantzos I, Karapantzou C, Trakada G, Bakakos P. Ann Res Hosp 2017;1:25.

11. Smoking habit of children and adolescents: an overview. Grapatsas K, Tsilogianni Z, **Leivaditis V**, Dimopoulos E, Zarogoulidis P, Karapantzos I, Tsiouda T, Barbetakis N, Paliouras D, Chatzinikolaou F, Trakada G, Skouras V. Ann Res Hosp 2017;1:26.

12. Solitary fibrous tumor: A center's experience and an overview of the symptomatology, the diagnostic and therapeutic procedures of this rare tumor. Hohenforst-Schmidt W, Grapatsas K, Dahm M, Zarogoulidis P, **Leivaditis V**, Kotoulas C, Tomos P, Koletsis E, Tsilogianni Z, Benhassen N, Huang H, Kosmidis C, Kosan B. Respiratory Medicine Case Reports, Volume 21, 2017, Pages 99-104.

13. A rare case of unruptured aneurysm of left coronary sinus of Valsalva accompanied with patent foramen ovale and atrial fibrillation detected after cardiac etiology stroke. Hohenforst-Schmidt W, Grapatsas K, Zarogoulidis P, **Leivaditis V**, Kotoulas C, Tomos P, Benhassen N, Tsilogianni Z, Koletsis E, Haussmann E, Haussmann R, Huang H, Kosmidis C, Kosan B, Dahm M, Sinha A. Respiratory Medicine Case Reports, Volume 21, 2017, Pages 105-107.

14. Prevalence of Pectus Excavatum, Pectus Carinatum and the Most Common Occurring Simultaneous Diseases in About 9,000 Greek Male Soldiers". Grapatsas K, Zarogoulidis P, Tomos P, Kaselouris K, Sakellaridis T, Neofotistos K, **Leivaditis V**,

Grapatsa E, Skouras V, Papanikolaou Z, Tsilogianni Z, Karnesis L, Tsantilas A, Huang H, Chong B, Haussmann E, Kosan B, Dahm M, Piyis A. EC Pulmonology and Respiratory Medicine 3.3 (2017): 71-80.

15. Characteristics of smoking among young Greek males at the time of their recruitment in the army. Grapatsas K, **Leivaditis V**, Dimopoulos E, Tsilogianni Z, Grapatsa E, Dahm M, Zisis P, Hohenforst-Schmidt W, Kioumis I, Pataka A, Trakada G, Zarogoulidis P. J Res Hosp 2016.

16. Epidemiology, risk factors, symptomatology, TNM classification of Non Small Cell Lung Cancer. An overview while waiting the 8th TNM classification. Grapatsas K, **Leivaditis V**, Tsilogianni Z, HaussmannE, Kaplunov V, Dahm M, Zarogoulidis P, Hohenforst-Schmidt W, Tsakiridis K, Foroulis C, Paliouras D, Barbetakis N, Kosan B. Oncomedicine 2017; 2: 14-23.

17. Solitäres Pleurafibrom: Eine seltene Differentialdiagnose eines intrathorakalen Tumors. Was der Thoraxchirurg beachten sollte. Grapatsas K, **Leivaditis V**, Dula D, Dahm M, Kosan B. Zentralbl Chir 2016; 141.

18. Therapeutic modalities for Pancoast tumors. Panagopoulos N, **Leivaditis V**, Koletsis E, Alexopoulos P, Prokakis C, Baltayiannis N, Hatzimichalis A, Tsakiridis K, Zarogoulidis P, Zarogoulidis K, Katsikogiannis N, Kougioumtzi I, Machairiotis N, Tsiouda T, Machairiotis N, Madesis A, Vretzakis G, Kolettas A, Dougenis D. J Thorac Dis. 2014 Mar;6 Suppl 1:S180-93. doi: 10.3978/j.issn.2072-1439.2013.12.31.

19. Pancoast tumors: characteristics and preoperative assessment. Panagopoulos N, **Leivaditis V**, Koletsis E, Prokakis C, Alexopoulos P, Baltayiannis N, Hatzimichalis A, Tsakiridis K, Zarogoulidis P, Zarogoulidis K, Katsikogiannis N, Kougioumtzi I, Machairiotis N, Tsiouda T, Kesisis G, Siminelakis S, Madesis A, Dougenis D. J Thorac Dis. 2014 Mar;6 Suppl 1:S108-15. doi: 10.3978/j.issn.2072-1439.2013.12.29. Review.

20. Beta2-Adrenergic activation via administration of Atenolol/Formoterol combination increases contractility and coronary blood flow in isolated rat hearts. Watson DC, Sargianou M, **Leivaditis V**, Anagnostopoulos C. Hellenic J Cardiol. 2013 Sep-Oct;54(5):341-347.

21. Right-sided infective endocarditis: surgical management. Akinosoglou K, Apostolakis E, Koutsogiannis N, **Leivaditis V**, Gogos CA. Eur J Cardiothorac Surg. 2012 Mar 16.

22. Sutureless technique to support anastomosis during thoracic aorta replacement. Apostolakis EE, **Leivaditis VN**, Anagnostopoulos C. J Cardiothorac Surg. 2009 Nov 13;4:66.

23. Repair of injured right inferior pulmonary vein during mitral valve replacement. Apostolakis E, **Leivaditis VN**, Kallikourdis A, Dedeilias P. J Cardiothorac Surg. 2009 Nov 7;4:64.

24. Deep hypothermia and circulatory arrest in the surgical management of renal tumors with cavoatrial extension. Dedeilias P, Koletsis E, Rousakis AG, Kouerinis I, Zaragkas S, Grigorakis A, **Leivaditis V**, Malovrouvas D, Apostolakis E. J Card Surg. 2009 Nov-Dec;24(6):617-23. Epub 2009 Sep 2.

25. A safe technique of exposing of a "hidden" left anterior descending artery. Apostolakis E, Koletsis E, **Leivaditis V**, Lozos V, Dougenis D. J Card Surg. 2007 Nov-Dec;22(6):505-6; discussion 507.

21.6. Präsentationen in Kongresse

21.6.1. Vorträge

1. Molecular Approach to the Pathogenesis of Pulmonary Embolism. 10th Postgraduate Seminar on Cardiothoracic Surgery, 12 May 2006, Patras, Greece.

2. Molecular biology of the pathogenesis and progression of Barrett's esophagus . 3rd Scientific Symposium on Aortic and Esophageal Surgery, 4-5 May 2007, Patras, Greece.

3. The method of isolated heart perfusion according to the principle of Langendorff, as a means of studying cardiac function in modern research. 4th Panhellenic Scientific Symposium "Developments in Cardiothoracic Surgery with emphasis on modern research in Greece", 12-13 December 2009, Patras, Greece.

4. Dysphagia and shoulder pain bring an unexpected diagnosis: Pancreatitis of ectopic pancreatic tissue in mediastinum, Athens Crossroad, 12th Congress of the

Hellenic Society of Thoracic and Cardiovascular Surgerons, 8-10 November 2018. Athens, Greece.

5. Surgical repair of or a spontaneous lung herniation due to sternoclavicular joint dislocation, Athens Crossroad, 12th Congress of the Hellenic Society of Thoracic and Cardiovascular Surgerons, 8-10 November 2018. Athens, Greece.

21.6.2. Posterpräsentationen

1. Complications of the lower extremities after aortic bypass: Risk factors and prevention. Apostolakis E, Koletsis E, **Leivaditis V**, Prokakis C, Panagopoulos N, Charoulis N, Dougenis D. 7th Congress of the Hellenic Society of Thoracic & Cardiovascular Surgeons. 28-30 November 2008, Thessaliniki, Greece.

2. Ex vivo physiological study of isolated heart function with high-resolution CCD camera. Anagnostopoulos K, Grivas K, **Leivaditis V**, Moschovas A, Dougenis D. 4th Panhellenic Scientific Symposium "Developments in Cardiothoracic Surgery with Emphasis on Modern Research in Greece", 12-13 December 2009, Patras, Greece.

3. Indication and safety of fiberoptic bronchoscopy in the cardiothoracic intensive care unit. Grapatsas K, **Leivaditis V**, Tsilogianni Z. 22nd Congress of the balkan military medical committee, 25-28 September 2017, Belgrade, Serbia.

4. Synchronous lung and esophageal cancer: Current clinical experience over the treatment of this rare oncological entity. Grapatsas K, Dimopoulos E, Tsilogianni Z, **Leivaditis V**. 22nd Congress of the balkan military medical committee, 25-28 September 2017, Belgrade, Serbia.

5. Can sternoclavicular septic arthritis be treateted successfully with negative pressure wound therapy? Grapatsas K, **Leivaditis V**, Dimopoulos E, Tsilogianni Z. 22nd Congress of the balkan military medical committee, 25-28 September 2017, Belgrade, Serbia.

6. Successful treatment withi ECMO of a fulminant pulmonary embolism with acute respiratory insufficiency and at the same time total thromboembolism of the right popliteal artery by paradoxal embolism after thromboembolectomy of the left femoral artery. Grapatsas K, **Leivaditis V**, Tsilogianni Z. 22nd Congress of the balkan military medical committee, 25-28 September 2017, Belgrade, Serbia.

7. R0 successful surgical treatment of a monofocal hepatocellular carcinoma with cava intrusion and infiltration of the right atrium. Grapatsas K, **Leivaditis V**, Dimoloulos E, Tsilogianni Z. 22nd Congress of the balkan military medical committee, 25-28 September 2017, Belgrade, Serbia.

8. Transaortic transcatheter aortic valve replacement as alternative access. Grapatsas K, **Leivaditis V**, Dimopoulos E, Tsilogianni Z. 22nd Congress of the balkan military medical committee, 25-28 September 2017, Belgrade, Serbia.

9. Screening for pectus excavatum in a homogenous Greek male population. Grapatsas K, Dimopoulos E, Tsilogianni Z, Trelopoulos A, **Leivaditis V**. 22nd Congress of the balkan military medical committee, 25-28 September 2017, Belgrade, Serbia.

10. Second hand smoking in a homogenous Greek male population. Grapatsa E, Kotoulas S, Tsilogianni Z, **Leivaditis V**, Grapatsas K. 22nd Congress of the balkan military medical committee, 25-28 September 2017, Belgrade, Serbia.

11. Pneumonectomy with the use of extracorporeal circulation due to intracardiac extention of lung carcinoma. **Leivaditis V**, Koletsis E, Grapatsas K, Panagiotopoulos I, Stefatou KM, Spiliotopoulos K, Eforakopoulos F, Prokakis C, Stroumpos C, Margaritis E, Dougenis D. Athens Crossroad, 12th Congress of the Hellenic Society of Thoracic and Cardiovascular Surgerons, 8-10 November 2018, Athens, Greece.

12. Inflammation and stenosis of the trachea due to a Corynobacterium stratum infection. **Leivaditis V**, Koletsis E, Xaplanteri P, Spiliopoulou I, Grapatsas K, Eforakopoulos F, Prokakis C, Stroumpos C, Margaritis E, Stefatou KM, Dougenis D, Kolonitsiou F. Athens Crossroad, 12th Congress of the Hellenic Society of Thoracic and Cardiovascular Surgerons, 8-10 November 2018, Athens, Greece.

13. Hemostasis of a recurrent endobronchial bleeding through bronchial artery embolism. **Leivaditis V**, Koletsis E, Grapatsas K, Panagiotopoulos I, Stefatou KM, Spiliotopoulos K, Eforakopoulos F, Prokakis C, Stroumpos C, Margaritis E, Dougenis D. Athens Crossroad, 12th Congress of the Hellenic Society of Thoracic and Cardiovascular Surgerons, 8-10 November 2018, Athens, Greece.

14. The use of aortic vascular stent for the treatment of an endobronchial in-stent stenosis. **Leivaditis V**, Koletsis E, Grapatsas K, Panagiotopoulos I, Stefatou KM, Spiliotopoulos K, Eforakopoulos F, Prokakis C, Stroumpos C, Margaritis E, Dougenis

D. Athens Crossroad, 12th Congress of the Hellenic Society of Thoracic and Cardiovascular Surgerons, 8-10 November 2018, Athens, Greece.

15. Emergency treatment of an accidental deep hypothermia using an ECLS (Extracorporeal Life Support) system. **Leivaditis V**, Grapatsas K, Koletsis E, Panagiotopoulos I, Stefatou KM, Spiliotopoulos K, Dougenis D, Dahm M. Athens Crossroad, 12th Congress of the Hellenic Society of Thoracic and Cardiovascular Surgerons, 8-10 November 2018, Athens, Greece.

17. Simultaneous thrombus formation in left and right atrium in a patient with an embolic cerebrovascular accident. **Leivaditis V**, Grapatsas K, Koletsis E, Haussmann E, Haussmann R, Panagiotopoulos I, Spiliotopoulos K, Stefatou KM, Dougenis D, Dahm M. Athens Crossroad, 12th Congress of the Hellenic Society of Thoracic and Cardiovascular Surgerons, 8-10 November 2018, Athens, Greece.

18. Endovascular repair of a traumatic aortic isthmus rupture in a polytrauma patient. **Leivaditis V**, Karagkouni E, Kraniotis P, Koletsis E, Grapatsas K, Stroumpos C, Prokakis C, Eforakopoulos F, Margaritis E, Charoulis N, Panagiotopoulos I, Stefatou KM, Dougenis D. Athens Crossroad, 12th Congress of the Hellenic Society of Thoracic and Cardiovascular Surgerons, 8-10 November 2018, Athens, Greece.

19. Massive pulmonary embolism (MPE) is a diasastrous and fatal postoperative complication. Thrombolysis is the treatment if choice, although the interventional of surgical thrombectomy is the alternative one. Kotoulas S, Grapatasas K, **Leivaditis V**, Koletsis E, Dahm M. Athens Crossroad, 12th Congress of the Hellenic Society of Thoracic and Cardiovascular Surgerons, 8-10 November 2018, Athens, Greece.

21.7. Übrige wissentschaftliche Arbeit

Komplette Illustration der Monographie "The Lung Transplantation" von Efstratios Apostolakis, Dimitrios Dougenis, Efstratios Koletsis, Patras, 2008. ISBN: 978-960-930661-4.