Aus der Klinik und Poliklinik für Herzchirurgie
der Universitätsmedizin Rostock

Arrhythmias Analysis in post Myocardial Infarction CABG and CD133^{+} Bone Marrow Stem Cell Therapy PERFECT RCT Phase III

D i s s e r t a t i o n

zur Erlangung des Doktorgrades
der Medizin
der Universitätsmedizin Rostock

vorgelegt von
Mohamed Abdelhalim
aus Ägypten, Kairo

Rostock, 2021

https://doi.org/10.18453/rosdok_id00003774

Gutachter:

1. **Prof. Dr. med. Gustav Steinhoff**, Universität Rostock, Klinik für Herzchirurgie

2. **Univ. -Prof. Dr. med. Jasmin. Ortak**, Universität Rostock, Rhythmologie und klinische Elektrophysiologie

3. **PD Dr. med. et rer. nat. habil. Olaf Bergmann, PhD**, Technische Universität Dresden, Center for Regenerative Therapies Dresden

Jahr der Einreichung: 2021

Jahr der Verteidigung: 2022

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List of abbreviations

acLDL	Acetylated-low density lipoprotein
ACS	Acute Coronary Syndrome
ADH	Antidiuretic hormone
AF	Atrial fibrillation
AFib	Atrial fibrillation
AFlu	Atrial flutter
AGM	Aortic gonadal mesonephros
AKI	Acute kidney Injury
ANOVA	Analysis of variance - metric target variable
APB	Atrial premature beats
APC	Atrial premature complexes
ARDS	Adult respiratory distress syndrome
ASCs	Adult stem cells
AV	Atrioventricular
AV block	Atrioventricular lead block
AV node	Atrioventricular node
AV-Block	Atrioventricular lead block
AVNRT	Atrioventricular nodal reentry tachycardia
AVRT	Atrioventricular reentry tachycardia
BMSC	Bone marrow stem cell
BVAD	Biventricular assist devices
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CFUs	Endothelial colony-forming units
Circ	Circumflex artery
CK	Creatine kinase
CK-MB	Creatine kinase muscle-brain isoenzyme
CM	Cardiomyocytes
c-Myc	c-Myc gene
COPD	Chronic obstructive pulmonary disease
CPR	Cardiopulmonary resuscitation
CSC	Cardiac stem cells
Cx	Circumflex artery
CXCR4	C-X-C chemokine receptor 4
DAD	Delayed afterdepolarization
EAD	Early afterdepolarization
ECG	Electrocardiogram
Echo	Echocardiography
ECLS	Extracorporeal life support systems
EF	Ejection fraction
EPCs	Endothelial progenitor cells
ESCs	Embryonic stem cells
FAT	Focal (ectopic) atrial tachycardia
Flk1	Fetal Liver Kinase 1
hESC-CMs	Human Embryonic Stem Cell-Derived Cardiomyocytes
hESCs	human Embryonic stem cells
hPSCs	human Pluripotent stem cells
HSCs	Hematopoietic stem cells
IABP	Intra-aortic balloon pump
IART	Intra-atrial reentry tachycardia
ICAM-1	ICAM1 - Intercellular adhesion molecule 1
ICU	Intensive care unit
IHD	ischemic heart disease
IHS	In-hospital-Stay
IL - 1	Interleukin-1
iPSCs	Induced pluripotent stem cells
Isl-1+	Insulin gene enhancer protein ISL-1
KDR	Vascular endothelial growth factor receptor 2
Klf4	Kruppel Like Factor 4
LA	Left atrium
LAD	Left anterior descending artery
LCA	Left main coronary artery
LDH	Lactate dehydrogenase
LFA-1	Lymphocyte function-associated antigen 1
LV	Left ventricle
LVAD	Left ventricular assist devices
LVEF	Left ventricular ejection fraction
MACCE	Major adverse cardiac and cerebrovascular events
MANOVA	Multivariate analysis of variance
MI	Myocardial Infarction
MSCs	Mesenchymal stem cells
N.sig	Non-significant
NRG	Non -responder group
NRGOG	Non-responder subgroup of placebo group
NRG-SCG	Non-responder subgroup of stem cell group
NSTEMI	Non- ST elevation myocardial infarction
Oct3/4	Octamer-binding transcription factor 3/4
OM	Obtuse angle marginal branches
PACs	Premature atrial contractions
PCI	Percutaneous Coronary Intervention
PDA	Posterior descending artery
PET	Positron emission tomography
PG	Placebo group
PH	Potential of hydrogen
POAs	Postoperative arrhythmias
proBNP	Pro brain natriuretic peptide
PTCA	Percutaneous Transluminal Coronary Angioplasty
PVC	Premature ventricular contraction / Complexes
RA	Right atrium
RAAS	Renin - Angiotensin - aldosterone system
RCA	Right coronary artery
RCT	Randomized Clinical Trial
RCV	Retrograde coronary sinus
RG	Responder group
RG-PG	Responder subgroup of placebo group
RG-SCG	Responder subgroup of stem cell group
RV	Right ventricle
RVAD	Right ventricular assist devices
SA node	Sinoatrial node
SCG	Stem cell group
SCs	Stem cells
SDF-1	Stromal cell-derived factor 1
SDF-1α	Stromal cell-derived factor 1 alpha
Sig	Significant
Sox2	SRY (sex determining region Y)-box 2
SPECT	Single photon emission computed tomography
SR	Sinus rhythm
SSEA-1+	Stage-Specific Embryonic Antigen-1
STEMI	ST elevation myocardial infarction
SVES	Supra ventricular extrasystole
SVT	Supraventricular Tachycardia
TAH	Total artificial heart
TMLR	Trans myocardial Laser Revascularization
TNF	Tumor necrosis factor
VAD	Ventricular assist devices
VCAM-1	Vascular cell adhesion molecule 1
VE-cadherin	Vascular endothelial cadherin
VEGF	Vascular endothelial growth factor
VEGFR2	Vascular endothelial growth factor receptor 2
VES	Ventricular extrasystole
VF	Ventricular fibrillation
V-fib	Ventricular fibrillation
VLA-4	Very late antigen-4
VT	Ventricular Tachycardia

Introduction & Background

The present work examines the relationship between intramyocardial application of stem cell therapy (intramyocardial injection) combined with bypass surgery and expressed by response to recovery of heart function measured by left ventricular ejection fraction (LVEF), and the incidence of occurrence of postoperative arrhythmias. This work is based on the PERFECT phase III randomized clinical trial (RCT) [1] of intramyocardial $CD133^{+}$ application after Myocardial Infarction at the University of Rostock. The original clinical study protocol of the PERFECT RCT can be found in the "EU Clinical Trials Register" under the following EudraCT No.: **2006-006404-11**. It can also be found on https://clinicaltrials.gov/ under **NCT00950274.**

Anatomy of the coronary arteries

The arterial supply to the heart muscle takes place via two main coronary arteries. These arise from the left and right sinuses of Valsalva of the root of the aorta. The left main coronary artery (LCA) divides into the left anterior descending artery (LAD), it is also known as anterior interventricular artery, and the circumflex artery (Circ/Cx). The left anterior descending artery (LAD), which is the most important coronary artery, runs on the top of the heart in the interventricular groove anteriorly till it reach the apex giving off diagonal and septal branches. The circumflex artery (Cx) runs in the atrioventricular sulcus and gives off obtuse angle marginal branches (OM) which is also known as ramus marginalis sinister. Sometimes a third branch (Ramus intermedius) arises from the LCA instead of the first diagonal branch of LAD and runs between LAD und Cx.

The right coronary artery (RCA) continues in most cases as the right posterior descending artery (PDA) which is also known as posterior interventricular artery to the apex of the heart and gives off the Ramus coni arteriosi, the Ramus atrialis dexter and the Ramus marginalis dexter.

The left coronary artery supply areas include: left atrium, wall of the left ventricle including a large part of the interventricular septum and a small part of the front wall of the right ventricle, while right coronary artery supply areas include: the right atrium, the rest of the right ventricle, the posterior section of the interventricular septum, the SA and AV node. Depending on the origin of the postierior interventriular artery the blood

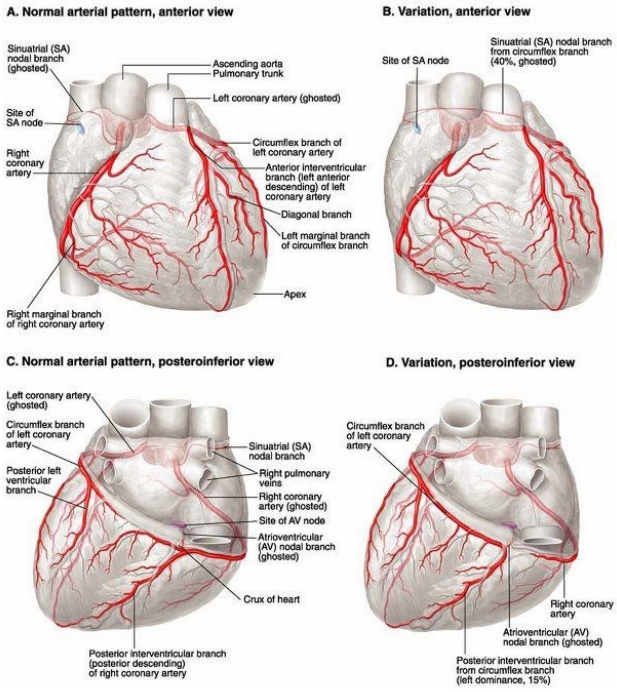

Fig. 0-0-1 CORONARY CIRCULATION *Lippincott Williams & Wilkins Atlas of Anatomy, 1st Edition.*2008 And **Explanation from** Julian, DG, *Cardiology 8th Edition*, Elsevier Saunders. 2005

supply of the heart can be categorized as right or left dominant supply type. There are also many variations of the perfused myocardial sections [3].

Ischemic heart disease (IHD)

Cardiovascular diseases are among the leading causes of death in Germany at 40.2% annually. Despite modern diagnostics and a wide range of therapy and intervention options, 342,000 patients die of cardiovascular disease each year. Of these alone, 55,300 succumb to the consequences of a heart attack. One of the cardiovascular diseases that cause a myocardial infarction is ischemic heart disease (IHD) which also known as coronary artery disease (CAD).

The IHD is a progressive narrowing of the lumen of the vascular tree of the heart that increases over years. The most common cause of this is chronic vascular inflammation, which is based on a cascade of biochemical and cellular reactions, the starting point of which is damage to the intima. That favors the deposition of calcified lipids, the so-called arteriosclerotic plaques. Clinically, it is expressed by the symptom of what so called angina pectoris [4]. Angina pectoris is defined as a sudden, seizure-like pain due to myocardial ischemia, accompanied by a feeling of tightness and shortness of breath that can last for minutes to hours.

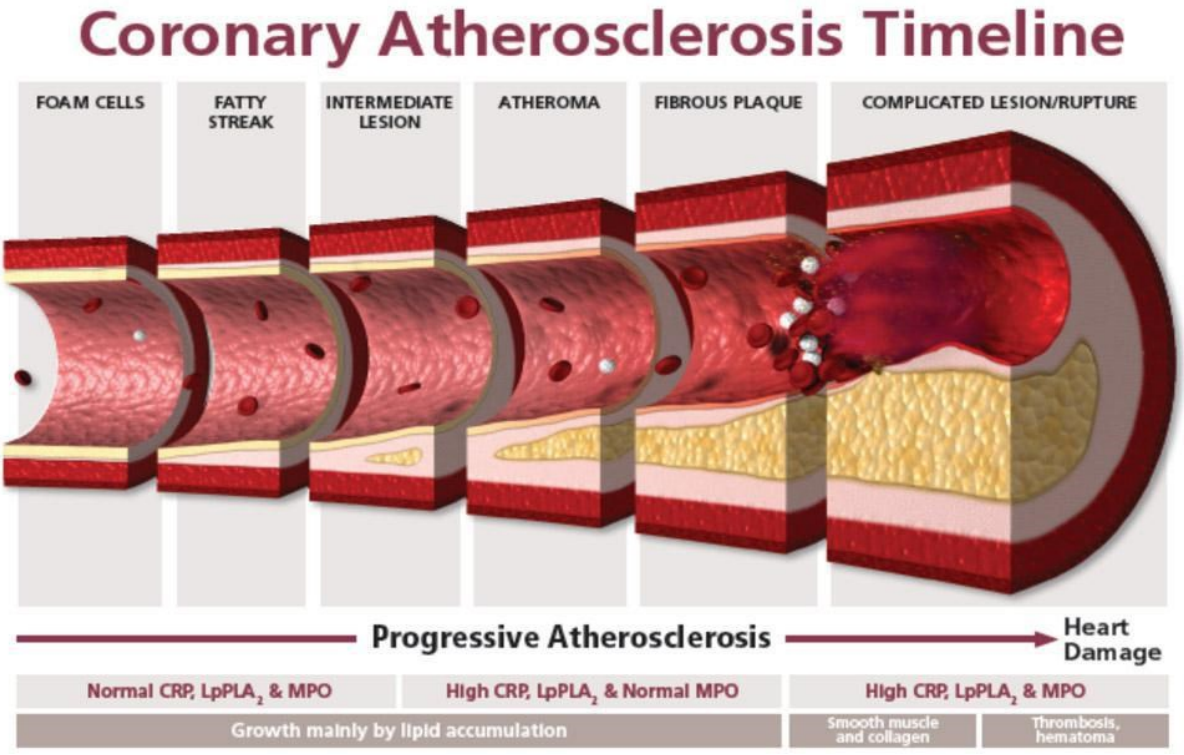

Fig 0-0-2 Coronary Atherosclerosis Timeline: https://www.kahnlongevitycenter.com/blog/measuring-artery-age-to-reverse-atherosclerosis

Atherosclerosis is a variable combination of changes in the intima, consisting of foci of fatty substances, complex carbohydrates, blood and blood components, connective tissue and calcium deposits associated with changes in the media of the vessels. Intimal damage can be caused by physical (arterial hypertension, Turbulence at vascular branches) and chemical stimuli (nicotine, hyperlipoproteinemia) or genetic predisposition. The pre-damage to the intima causes that water and plasma components are stored and become a gelatinous-edematous swelling of the intima. The stored lipoproteins will be engulfed by

macrophages. This creates the so-called foam cells, because the macrophages cannot completely lyse and break down the lipoproteins. The immigrated phagocytic macrophages and myocytes disrupt the cellular balance and thereby trigger a growth stimulus on the surrounding connective tissue. The newly formed connective tissue masses and proteoglycans lead to irreversible fibrous vascular wall changes which is known as plaques. By changing the PH due to the mediators released by the macrophages, precipitation occurs of cholesterol which is difficult to break down. The vascular connective tissue then changes into a central fatty necrosis mass. This condition corresponds to an atheroma. This atheroma can develop into an atherosclerotic ulcer. If there is a plaque or atheroma rupture and a subsequent coronary thrombosis within the coronary vessel, i.e. a complete occlusion of the vessel, this leads to a cut-off of perfusion with a consecutive cut-off of oxygen to the heart muscle [5] [6] [7].

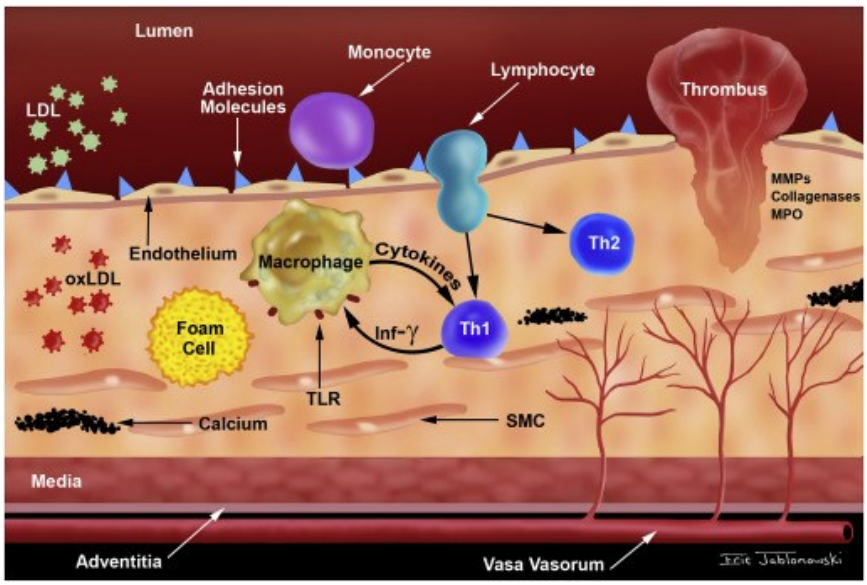

Fig. 0-0-3 Pathology of atherosclerosis: July 15, 2018 DOI :https://doi.org/10.1016/j.atherosclerosis.2018.07.014

An acute coronary artery occlusion causes the first metabolic disorders and thus within a few seconds a functional change in the affected cells because of the high energy requirement of the tissue. The low oxygen reserves of the myocardium are used up quickly. The provision of energy in the mitochondria of the cells is then switched from aerobic to anaerobic glycolysis. The lactate produced by it leads to increasing tissue acidosis [8]. As a result, the optimal PH level of the enzymes involved is no longer available, so that this metabolic pathway inhibits itself. With drop of the performance of anaerobic adenosine triphosphate and hence an energy deficiency, the basic needs of the myocardium can no longer be met. Eventually irreversible cell damage occurs which leads to heart attack. As a result of cell damage intracytoplasmic enzymes (especially creatinine phosphokinase and lactate dehydrogenase) escape, which can be detected serologically in most of the cases after a few hours. The cardiac muscle is disturbed in its integrity and performance due to the infarction, which ultimately results in heart failure.

The most involved sites for coronary sclerosis are located at the beginning of the third segment Large coronary arteries, with the left anterior descending artery (LAD) of the left main coronary artery (LCA) and the right coronary artery (RCA) are affected more often than the circumflex artery (RCX). Other preferred locations are shown by bifurcations and at branches of side branches. Rarely only one vessel is affected by arteriosclerosis which is known as a single-vessel disease. Especially in older age there are usually several main branches affected at the same time (multi-vessel disease). An acute coronary occlusion, as with a myocardial infarction, does not arise in the majority of cases on because of high-grade single-vessel coronary stenosis [9] [10].

Heart failure describes a mismatch between the amount of blood delivered by the heart and the need for blood in the periphery of the body. This leads to an undersupply of oxygenated blood, which has devastating consequences for the cardiovascular system. Due to the reduced peripheral blood volume, vascular receptors are activated, which initiate hormonal counter-regulation. Activation of the renin - Angiotensin - aldosterone system (RAAS) in the kidney to counteract volume deficiency, the activation of the sympathetic nerve by chemo- and baroreceptors to increase blood pressure and the increased antidiuretic Hormone (ADH) secretion of the pituitary gland to increase the intravascular blood volume play a decisive role. There is a volume load on the heart, which induces an increasing structural change in the heart and further increases heart failure. The result is dilated cardiomyopathy with relative heart valves insufficiency and a further progressive decrease in the pumping function of the heart.

In context of prevention studies, numerous risk factors and their influence on the coronary artery disease were identified. The term "risk factor" was first used in Relation to the Framingham study known [11]. These factors can be divided into non-modifiable and modifiable risk factors. The non-modifiable Risk factors include age, male sex, increased lipoprotein A and a positive family history [35] [29] [14]. Modifiable risk factors include nicotine abuse [15], increased low density lipoprotein (LDL), cholesterol [16], diabetes mellitus [17], arterial hypertension [18], high-fat food [19], physical inactivity, stress and psychosocial factors. By correcting the modifiable ones, there may be improvement in the prognosis.

In summary, acute and chronic ischemia are epidemiologically the most common cause of heart failure, which can be prevented therapeutically, both medicinal and interventional [20].

Pathophysiological changes in the ischemic damaged myocardium

The progressive morphological and functional changes in the coronary vessels lead to a relatively or absolutely reduction in blood flow to the heart muscle, which is known as primary coronary insufficiency. As a result - first under stress, then also in Rest - a mismatch between the heart muscle's need for energy providing substrates and oxygen and the actual offer (ischemia) occurs. This will be reflected in the form of angina pectoris. The chronic course of coronary insufficiency leads to a reduced coronary reserve.

As a result of acute myocardial ischemia, there is an intracellular energy deficit and thus an accumulation of end products of the anaerobic metabolism. Physiological electrolyte gradients

cannot be maintained by the cardiomyocytes, which leads to an uncontrolled inflow of ions into the heart muscle cell. Due to the subsequent influx of water caused by the pathologic changes in osmotic pressure, the cell swells and there is irreversible cell damage which ultimately leads to cell necrosis. Damage to the heart muscle activates inflammatory mediators and thus initiates the repair of the damaged myocardium.

Inflammatory mediators, such as interleukin 1 and TNF - α, induce the expression of selectins in endothelial cells. Selectins are membrane proteins of the endothelium that bind specifically to glycolic components of the leukocytes and thus enhance diapedesis of leukocytes into the defective tissue [21]. This occurs about twelve hours after cell death and thus represents the first step in the restructuring of the damaged myocardium [22].

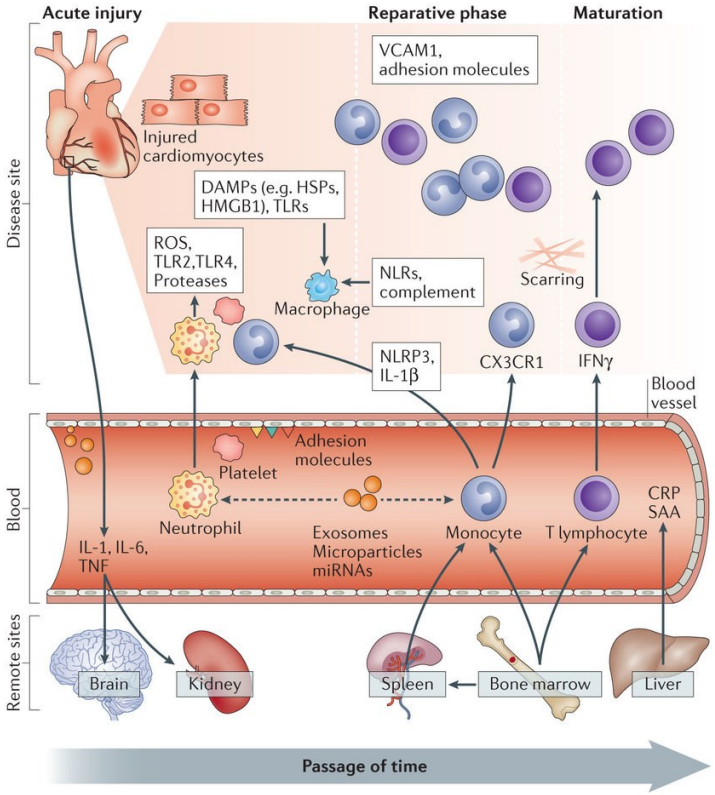

Fig 0-0-4 Inflammatory processes in cardiovascular disease DOI: 10.1038/nrcardio.2016.185

Granulation tissue begins to develop only on the third day after a myocardial infarction. It is a tissue that arises as part of the healing process. It consists of capillaries, macrophages and fibroblasts. The predominant cell type in this inflammatory phase are the macrophages which are responsible for the breakdown of the necrotic tissue [23]. Fibroblasts begin to synthesize collagen just two weeks after the infarction, and after six weeks the necrotic area is usually completely replaced by collagenous connective tissue [24]. This process, which is known as remodeling, leads consecutively to a restricted functionality of the myocardium due to the structural changes [25].

In addition, there is a close connection between the location of the infarct, the number of stenosed vessels and the patient's symptoms. The more vessels are closed by a stenosis, or the larger the original supply area of the stenosed vessel, the greater the proportions of the ischemic damaged myocardium and thus the extent of remodeling.

This essentially influences the clinical symptoms, which range from a silent infarction with little or no Symptoms to dyskinesias of the myocardium, cardiac arrhythmias, heart valve insufficiency up to sudden cardiac death [26].

Acute Coronary Syndrome (ACS)

Acute coronary syndrome (ACS) covers the spectrum of clinical pictures from unstable angina pectoris to transmural infarct. An unstable angina pectoris is characterized by an increase in intensity and duration of a known stable angina pectoris or its first manifestation [27]. If the complaint independent of stress, then it is called resting angina pectoris. If the angina pectoris symptoms progress further, this is also referred to as a pre-infarct syndrome, a precursor to myocardial infarction. This can take days or Hours before myocardial infarction happens. Patients with post-infarct angina pectoris are also considered to be clinically unstable. Especially patients within the first few days and weeks of an acute Inner layer infarct tend to develop again an angina and have high early mortality and high risk for a reinfarction [28]. By definition, the unstable angina pectoris and the pre-infarct syndrome are reversible myocardial ischemia and is not accompanied with underlying necrosis [29].

The pathophysiological basis of acute coronary syndrome is rupture or fissure an unstable atheromatous plaque. This happens after platelet activation to form an intracoronary thrombus that occlude the coronary vessel completely or partially [30]. Depending on the degree of stenosis or the thrombus size and the extent of collateral blood flow a persistent or intermittent myocardial ischemia with the risk of myocardial infection may develop.

Myocardial Infarction (MI)

The key symptom of myocardial infarction is the acute onset of, often in the left arm, neck, lower jaw, back or upper abdomen radiating retrosternal pain (angina pectoris). Half of all fatal heart attacks occur without any of the typical warning symptoms, which makes early diagnostic und thus therapeutic intervention difficult [31].

The heart attack in men occurs preferably in the 6th decade of life, in women in contrast, in the 7th decade of life. Between the ages of 35 and 55, men have a six-fold higher risk of myocardial infarction than women. The increased risk for men having myocardial infarction gradually resembles itself after the woman's menopause. Estrogen and / or testosterone is thought to be having a roll in this difference [32].

The transmural myocardial infarction is usually based on a complete thrombotic occlusion of a pre-existing stenosis of a coronary artery or its larger secondary branches [33]. The transition from ischemia to necrosis is a dynamic process, also known as infarction growth.

In the early phase, the affected infarction area is damaged and shows varying degrees of damaged ischemic and necrotic muscle areas. As a result of a coronary obstruction, however also the surrounding muscle areas that are not directly affected by the acute occlusion may be at risk of ischemia [34]. The cause of this is the collateral vessels, that have arisen in response

to previous ischemia cannot adequately supply blood to other muscle areas with adequate perfusion pressure.

If the coronary reserve is exhausted, the myocardial ischemia tolerance would be exceeded and necrosis would occur. It starts in the subendocardial layers due to the high end-diastolic ventricular pressure that exceeds perfusion pressure of the coronary arteries. The necrosis then proceeds from the subendocardium towards the subepicardium. Depending on the location of the coronary occlusion anterior, posterior, lateral and/or inferior wall as well as septal infarction or a combination may occur.

In most cases myocardial infarction occurs in the left ventricle and usually includes all layers of the myocardial wall (transmural infarction). In some only the subendocardial zone of the myocardium is affected (non-transmural infarction) [35]. The reason for the non-transmural infarction lies mostly due to a high degree of stenosis which does not completely occlude coronary vessel. But even a high-grade stenosis may cause a coronary insufficiency, which depending on the ischemia tolerance may lead eventually to a necrosis [36].

The ischemia tolerance of the heart muscle is individually variable and depends on the size of the less perfused areas, the hemodynamic situation and the blood flow in the collateral system. The formation of collateral vessels which is controlled by the chronic regional ischemia favors and can, in addition to the above situation, provide significant protection against infarction [37]. Ischemia tolerance of the normothermic myocardial tissue can already be exceeded after 30 minutes of a complete coronary artery occlusion. After about 6 hours the definite infarction size is reached which is almost that of supply area of the closed vessel [38]. The process of expansion of an infarction can be seen, however under certain circumstances, after 6 hours and up to weeks after the infarction [39] [40]. This condition is also called smoldering infarction or infarction extension. A persistent chest pain with electrocardiographically persistent ST segment changes and positive lab determinants are characteristic of this condition.

Complications of the early phase of myocardial infarction may be cardiac arrhythmia, cardiogenic shock, cardiac tamponade (after transmural infarction - in rare cases with formation of a hemorrhagic pericardial effusion or even tamponade), cardiac wall dilatation and eventually rupture [35], mitral valve insufficiency and the increased risk of a reinfarction. After a myocardial infarction, structural and functional changes occur to the necrotic area. This process is also known as "remodeling" [41].

Myocardial cell necrosis causes an irreversible loss of active cell wall tension in this area. The functional asynergy of the ventricle leads to a decreased ejection fraction. Depending on the size of the developing infarction scar, heart failure may occur. Other infarction complications include the development of an endocardial thrombosis or cardiac wall aneurysm.

The short-term prognosis of myocardial infarction patients depends on the location and size of the damaged muscle area and on the early initiation of the suitable revascularization procedure. The adjacent area of myocardium that shows reversible dysfunction can be

improved after successful reperfusion. In about 60% of the patients there is no significant hemodynamic disorders after a myocardial infarction. In the absence of rhythm disorders, one speaks of uncomplicated heart attack [42].

The long-term prognosis of myocardial infarction patients is affected by cardiac and non-cardiac factors. Cardiac factors include the extent of left ventricular impairment, extent of coronary stenosis and the occurrence of ventricular arrhythmia. Non-cardiac factors include the presence of atherosclerosis-promoting risk factors.

In addition to thrombotic occlusion there are less common reasons for myocardial infarction like coronary emboli, congenital vascular anomalies, coronary artery spasms (Prinzmetall angina, Tako-Tsubo cardiomyocardiopathy) or inflammatory systemic diseases.

A complete collapse of the coronary blood flow may lead to a global myocardial ischemia, in contrast to the regional myocardial ischemia in myocardial infarction. The reason for this is, among other things, higher-grade ventricular arrhythmias and terminal phase of a shock.

Myocardial motility disorders due to ischemia

The term ischemia means etymologically "retention of blood". This means a complete perfusion stop, for example due to a thrombus or embolus. In a broader sense, this includes the pathological reduction or abolition of blood supply to a tissue (organ, body part) in the case of circulatory disorders [43].

Within a few cardiac cycles after acute coronary occlusion, a reduction in the systolic wall thickening in the affected myocardial area takes place. Few cardiac cycles later a wall thinning occurs and replaces totally the systolic wall thickening [44]. The motility disorder of the ischemic area also affects the adjacent normally perfused tissue, so that a less than 1 cm wide myocardial zone shows a disturbance in the contractility [45]. This narrow zone directly surrounds the ischemic region and may be involved in contractile dysfunction through mechanical compression. This zone is directly surrounded by another zone of myocardium in which the contractility is increased.

In addition to permanent acute coronary occlusion, which leads to irreversible cardiac muscle damage, relative or chronic ischemia lead to changes in the functional features of the heart muscle. It is currently not clear whether it is an adaptation to ischemia, or a damage to the myocytes of any kind. The disturbed ischemic but still vital myocardium can be classified into "stunned" or "hibernating" myocardium [46].

"Stunned" myocardium

The "stunned" myocardium is characterized by a long-lasting reversible post-ischemic dysfunction after successful reperfusion [47]. The term "stunned" comes originally from boxing and describes a boxer who was dazed by a blow. The causal mechanisms of this reversible myocardial dysfunction are still not clear. No evidence of damage to the contractile apparatus could be proven. In this context, an energy deficiency also appears unlikely since the reperfused myocardium that shows reduced contractility under resting conditions can react with inotropic substances and then shows improvement in contractility [48]. There are various indications of the harmful effects of free radicals [49]. It was found, that the pharmacological reduction or the accelerated elimination of free radicals helps the recovery of the "stunned" myocardium significantly [50] [51]. An increased intracellular Calcium levels as the cause of persistent dysfunction is controversial [52].

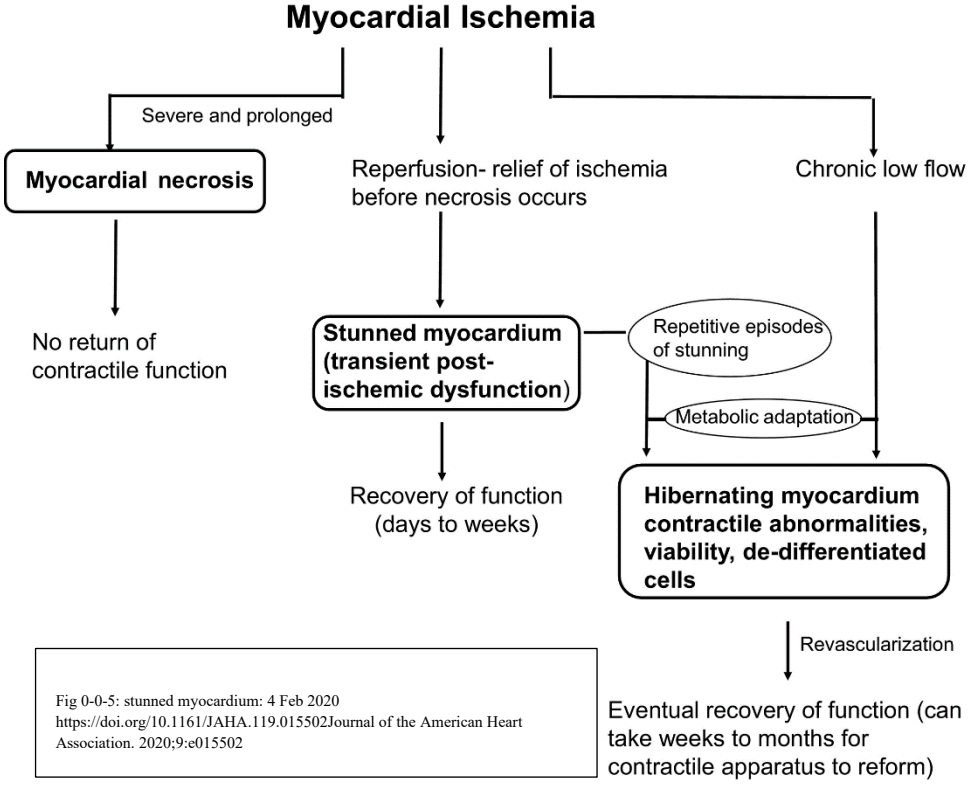

Fig 0-0-5: stunned myocardium: 4 Feb 2020 https://doi.org/10.1161/JAHA.119.015502Journal of the American Heart Association. 2020;9:e015502

Hibernating myocardium

The term "hibernation" describes an adaptive reduction in energy turnover during a special situation by reducing activity and thus energy requirements. In connection with myocardial ischemia “hibernation” would be described as a clinical condition of the myocardium that is characterized by a chronic, painless myocardial dysfunction, which shows improvement after reperfusion [53].

Ischemic preconditioning

Another phenomenon that occurs in the context of ischemic stress on the myocardium is called "ischemic preconditioning" [54]. Here brief episodes of reversible myocardial ischemia stress cause an improvement of the ischemia tolerance for subsequent occlusions [55]. The clinical

importance of preconditioning could include reducing the size of the infarct after successful thrombolysis if the infarct occurs because of angina pectoris [56].

The exact mechanisms of the phenomena mentioned have not been clarified in detail. Both the "ischemic preconditioning" and the myocardial "hibernation" contribute clinically to a better-preserved vitality of the myocardium and an improved metabolic situation during ischemia and thus represent certain adaptation mechanisms of the myocardium. "Stunning", on the other hand, is a poorly understood reversible phenomenon that is initially affects the global pumping function of the heart negatively.

Cardiogenic shock

Cardiogenic shock is considered as the most common cause of death in myocardial infarction [57] [58]. Research has shown that a shock symptom can appear not only if there is a loss of at least 40% of the left ventricular muscle mass [59] but also an incremental infarction or a new infarction in an already damaged left ventricle. The sudden failure of large areas of contractile muscle mass causes a decrease in ejection fraction and a subsequent reduction in cardiac output with a decrease in systolic pressure along with increased end-diastolic pressure. This leads to activation of the sympathetic nervous system as a compensatory mechanism to provide an additional work by the normal vital functional myocardium. This will lead to a deterioration in the energetic situation of the myocardial cells as a whole. A vicious circle arises that increase the myocardial damage and produce accelerated infarction.

Depending on the location and extent of the infarction area many complications may occur such as ventricular septal perforation, tear in papillary muscles or chordae tendinea and/or cardiac arrhythmias which can all lead to a shock [60]. A cardiogenic shock that is not responding to therapy may lead quickly to metabolic disorders, kidney failure, respiratory disorders (ARDS), sepsis and multi-organ failure.

Diagnostics of myocardial infarction (MI)

In the prehospital phase is based on the clinical symptoms and an electrocardiogram (ECG). Just 20 seconds after the start of ischemia ECG changes become visible. They are primarily based on regional disturbances in the spread of arousal due to ischemia and occur primarily as ST depression, however also as ST elevation.

In the hospital, the diagnosis is based on the detection of specific enzymes (CK, CK-MB, LDH) and protein markers (troponin). If there is an acute myocardial infarction, further examinations and therapeutic approaches are necessary.

Diagnostic imaging is required to detect ventricular wall motion as an expression of an ischemic change or to recognize the area with a perfusion deficiency. The non-invasive procedures include Echocardiography and myocardial scintigraphy.

The dysfunction of the myocardium as an expression of chronic or acute ischemia can be divided into three degrees of regional movement disorder:

- Hypokinesia are present when there is decreased systolic inward movement.
- Akinesia is characterized by the lack of wall movement.
- Dyskinesias are present when there is segmental during systole outward movement is coming.

Differentiation between vital and avital myocardium is possible with the dobutamine Stress echocardiography or via the representation of the metabolic function using positron emission tomography (PET) possible.

Coronary angiography is an invasive procedure with which, in addition to determination of size and function of the left ventricle, it can also identify the vessel that caused the infarction and describe the status of the rest of the coronary arteries. The knowledge gained thereby determines the further therapeutic action.

Therapeutic measures for the treatment of CAD and acute myocardial infarction

Depending on the symptoms and the time that has passed since the onset of symptoms, there are different therapeutic options.

Revascularization methods - overview

The basic therapeutic goal of myocardial infarction therapy, if possible, is to reduce the extent of necrosis to the minimum early as possible by restoring the blood supply.

In the prehospital phase, between the onset of symptoms and the arrival in the clinic, it is primarily a matter of reducing the heart's energy requirements and improve the oxygen supply. This includes nitro vasodilators, beta receptor blockers and oxygen when peripheral saturation is reduced. The progression of coronary thrombosis can be prevented by the use of anticoagulants such as heparin or by platelet aggregation inhibitors such as acetylsalicylic acid. Complications of myocardial ischemia like the occurrence of malignant arrhythmias and the development of a cardiogenic shock can be treated medicinally or additionally through the use of mechanical circulatory support systems.

Revascularization therapy is essentially based on three different treatment methods.

- Thrombolysis
- Percutaneous Coronary Intervention (PCI)
- The coronary artery bypass grafting operation (CABG)

If the Reperfusion attempts using lysis therapy and / or PCI fail and the patient continues with signs of ischemia, emergency CABG surgery remains the therapeutic method of choice [61] [62].

Medicinal lysis therapy

Medicinal lysis therapy was important for a long time, but is currently no longer often used. The patient is administered pharmacological substances (e.g. Streptokinase, Alteplase, Reteplase) that induces fibrinolysis, which makes it possible to reopen the vessel [63]. The limiting factor for the success of lysis therapy is the time that elapsed after the symptoms began [64]. The best result can be achieved in the "first golden hour" [65]. Ultimately, early and long-term mortality could only be significantly reduced if the pharmacological lysis therapy was administered to the patient within the 90 minutes after the onset of the infarction. However, it can be carried out up to twelve hours after the onset of symptoms [66]. The high reocclusion rate of up to 40% is due to the fact that the thrombolytic therapy, although initially successful, has no positive effect on the atherosclerotically altered endothelium of the previous closed vessel as well as the coronary artery may still have other coronary stenoses [67].

Percutaneous Coronary Intervention (PCI)

The most important therapeutic procedure in the meantime is the PCI, a minimally invasive therapeutic method, which is of great clinical importance in the acute and subacute phase of the heart attack. It is characterized in that, the atheromatous material in the vascular intima wall is compressed via an expandable balloon with a pressure of 5-12 atmospheres. The adjacent media and adventitia are locally overstretched and the coronary artery thus expanded. It is then followed by stent implantation if the closed vascular lumen is not sufficiently expanded. The beginnings of this mechanical dilatation process of arteriosclerotic stenoses date back to 1964 [68], which was called then Percutaneous Transluminal Coronary Angioplasty (PTCA). According to the current guidelines, the emergency PCI is indicated for persistent thoracic feeling of oppression, which persists for less than 48 hours, persistent ST segment elevation or newly developed left bundle branch block [4].

In contrast to lysis therapy, PCI enables mechanical opening of the stenosed coronary artery in acute transmural myocardial infarction. It succeeds in 87-97% of the cases and the Mortality rate is between 4% and 12% depending on the proportion of shock patients [69] [70] [71].

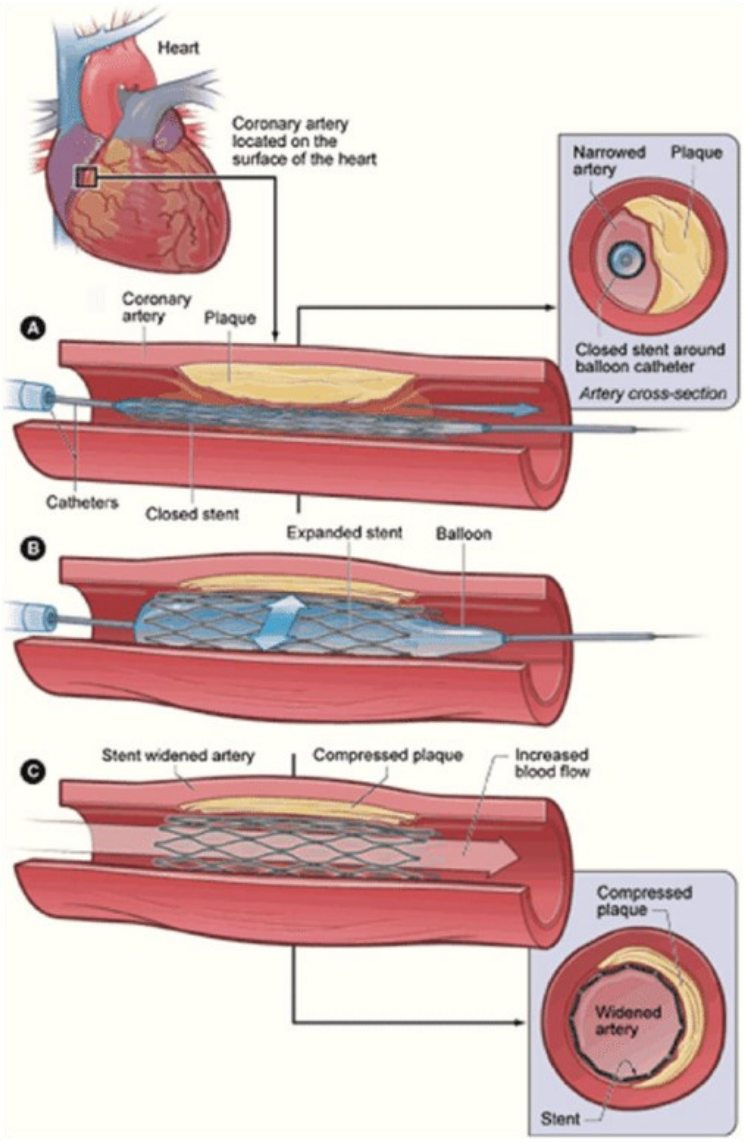

Fig 0-0-6 PCI: July 2017Mechanics of Advanced Materials and Modern Processes 3(1) DOI: 10.1186/s40759-017-0028-y

Rapid reperfusion of the heart muscle reduces the extent of myocardial necrosis and consecutively improves cardiac pumping [72]. Especially for multimorbid patients, this minimally invasive procedure carries a low risk with regard to possible peri- and post-interventional complications. An early start of therapy is decisive for the success of the treatment and lowering the mortality.

Contraindications and possible indications for surgical revascularization include the location or morphology of the stenoses, diffuse three-vessel disease, a chronic occlusion and the presence of an unprotected left main coronary artery stenosis.

The reduction of complications is based on the short anesthetic time, the lower blood loss and the small access route necessary for the procedure, which has a positive effect on the risk of developing post-interventional infections and cardiovascular diseases.

The Coronary artery bypass grafting operation (CABG)

Another way of therapy for diagnosed CAD or a condition after transmural myocardial infarction is bypass surgery, which in most cases, however, is indicated at the earliest two weeks after the acute event in the case of existing myocardial infarction. The first successful CABG operation was by Garrett and co-workers in 1964 created [73]. As early as 1971, Favaloro and Effler presented the CABG operation in the impending and acute myocardial infarction [74]. Basically, there is an indication for bypass surgery according to the national care guidelines if there is a significant left coronary main stenosis (≥ 50%) or a coronary multi - vessel disease with high grade proximal stenoses (> 70%) [75]. The bypass operation (surgical therapy) has long been established as preferable to PCI under the conditions mentioned above.

In the clinical study by Patrick W. Serruys et al. It could be shown that arterial bypass surgery in the presence of a 3 - vessel disease and up to 12 months postoperative is associated with fewer complications in terms of renewed myocardial infarction or cerebrovascular disease than the PCI [76]. Similar results were shown in the clinical study by Mohr W. et al. Within a five-year follow-up, the superiority of bypass surgery with regard to the endpoints of renewed myocardial infarction, reintervention and major adverse cardiac and cerebrovascular events (MACCE) was demonstrated in severe CAD [77].

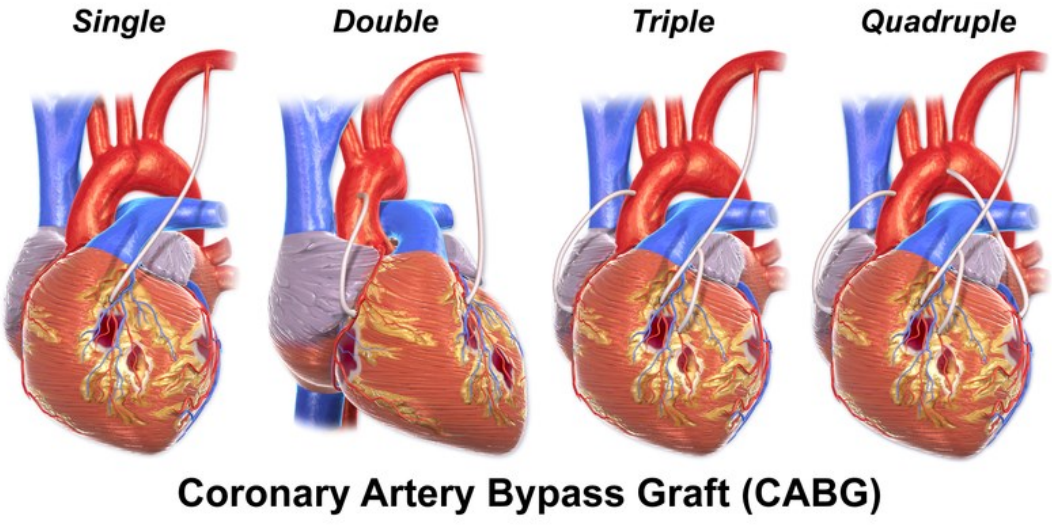

Fig. 0-0-7 CABG: Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014". WikiJournal of Medicine 1 (2). DOI:10.15347/wjm/2014.010. ISSN 2002-4436.

The surgical procedure consists of bypassing the stenosed coronary artery by means of a vein or artery, which is anastomosed to a coronary artery distal to the stenosis. The left and right internal thoracic arteries and the radial arteries preferably serve as arterial bypass material. Venous grafts (especially great saphenous vein) are also commonly used in several stenosed coronary arteries.

The reperfusion of the myocardial supply area subsequently results in a decrease in pectanginous complaints and an improvement in cardiac output [78]. A significant improvement in cardiac output can be expected above all if the bypass operation with high-grade stenosis is elective and the myocardium has not yet been irreversibly damaged by the reduced perfusion. If an infarction has already occurred, the bypass operation only improves

the entire myocardial perfusion. The already irreversibly damaged muscles do not benefit from the improved blood circulation [79].

Other surgical therapy procedures

Coronary endarterectomy

Endarterectomy is a procedure in which the atheromatous plaques including intima are surgically removed from the coronary artery using the so-called peeling plastic technique [138].

Transmyocardial Laser Revascularization (TMLR)

For patients with high-grade coronary sclerosis or very small coronary vessels (small vessel disease) the treatment options are severely limited. The TMLR stands next to the Bypass care as another therapy procedural option. Doing so with a carbon dioxide laser on the closed heart about 1 mm thick channels in almost all heart sections were made, which then lead to improved blood flow to the myocardium. This method is still used only in the USA. In the short term, compared to drug therapy less pectangional complaints [81]. However, the Benefits of this form of therapy in the long-term course (> 1 year) questioned [82] [83].

Supportive therapy procedures

Mechanical circulatory support systems

Mechanical circulatory support systems are used when heart failure or cardiogenic shock despite maximum drug therapy is imminent or has already occurred as part of a myocardial infarction. The damaged myocardium is given the opportunity to recover from a myocardial infarction or from “Low-output” syndrome after heart surgery [84] [85].

The simplest method of assisted circulation is the intra-aortic balloon pump (IABP) which was introduced in the late 1960s. A rapidly inflatable cylindrical balloon is either by means of percutaneous puncture using the Seldinger technique or surgically introduced into the femoral artery and into the descending aorta, distal to the left subclavian artery. According to the principle of counter-pulsation, the balloon is inflated during diastole and thus improves coronary blood flow. An emptying of the balloon just before opening the aortic valve causes a slight suction on the left ventricle and thus reduces the afterload. IABP can be used to stabilize the patient hemodynamically before a planned bypass operation and at the same time it serves prophylactically to support the cardiac pump function after successful revascularization [86] [87].

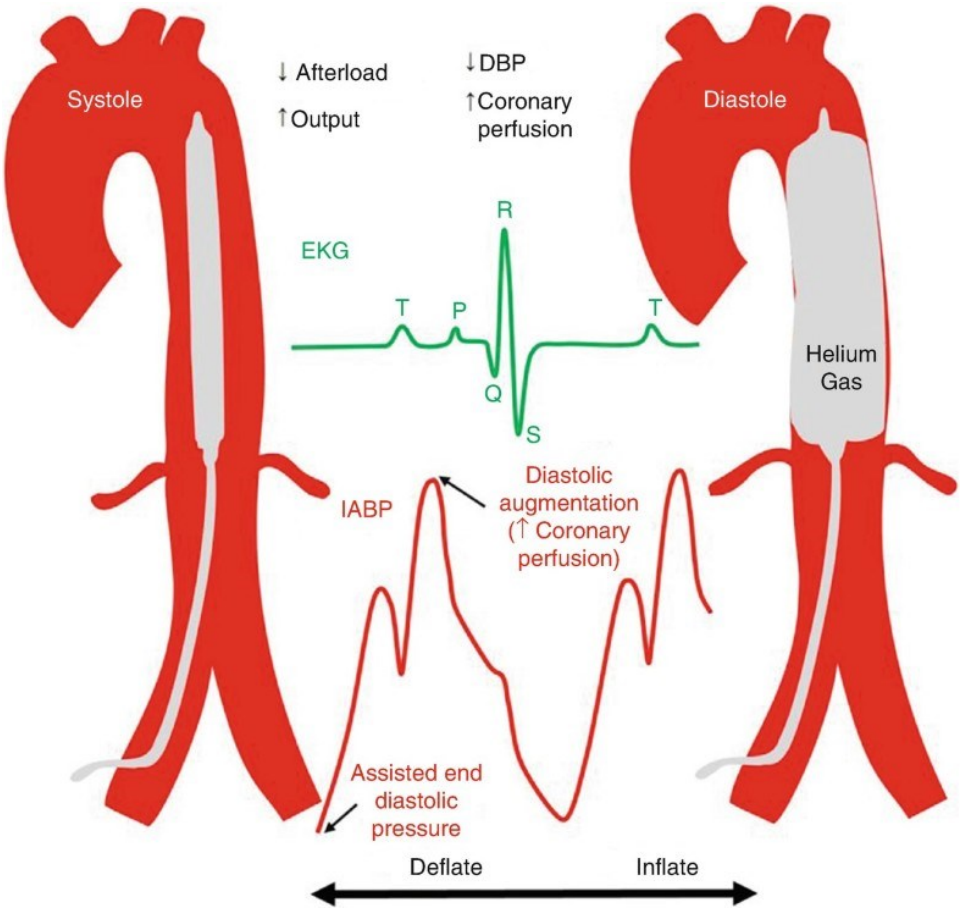

Fig 0-0-8 IABP: Bajan K. (2020) Intra-aortic Balloon Pump. In: Chawla R., Todi S. (eds) ICU Protocols. Springer, Singapore. https://doi.org/10.1007/978-981-15-0902-5_50

The use of other extracorporeal life support systems (ECLS) can be considered in patients in which The IABP does not succeed to stabilize the circulation or after Surgery in the weaning phase until there is adequate stabilization of the heart's pump function.

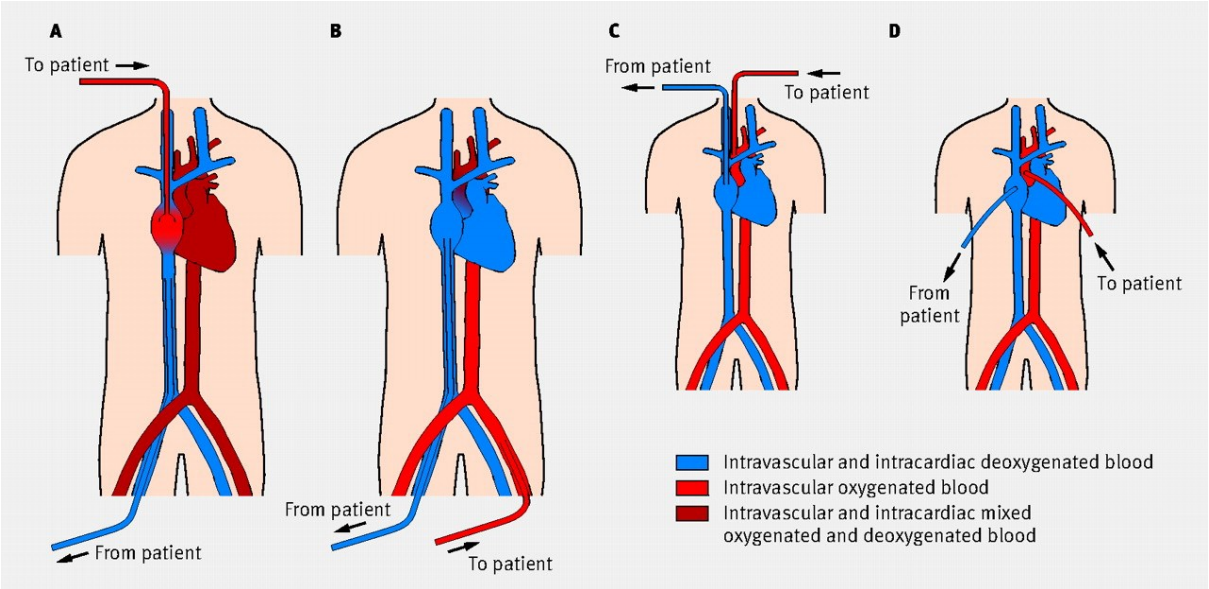

Fig 0-0-9 ECLS: BMJ 2010; 341 doi: https://doi.org/10.1136/bmj.c5317 (Published 02 November 2010)

In addition to non-pulsatile centrifugal pumps and turbines (Incor, DeBakey), pulsatile artificial pumping chambers (VAD - ventricular assist devices) are available [88]. Depending on the malfunctioning ventricle, these artificial ventricles can be called left (LVAD), right (RVAD) or biventricular (BVAD) support systems. It helps to maintain the peripheral circulation and at the same time give the affected ventricle a chance to be completely relieved until a definitive therapy plan is made bridge to therapy. These supporting systems can also be used as a bridge to recovery with the hope that after restoration of the coronary blood flow and the reversal of the reversible ischemic damage and after improving the pump function, the support system can be removed [89] [90] [91]. In some cases, the implantation is used as a bridge to a heart transplant [92], [93] or even until artificial heart transplantation (TAH - total artificial heart) could take place [94] [95].

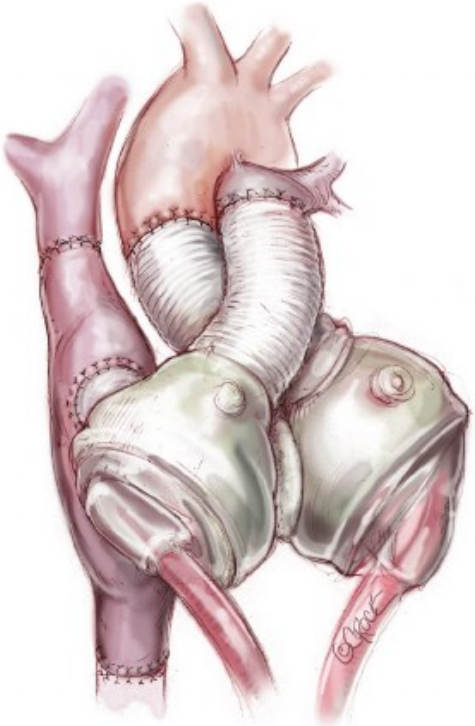

Fig. 0-0-10 TAH: November 2014Annals of Cardiothoracic Surgery 3(6):612 DOI: 10.3978/j.issn.2225-319X.2014.11.07.

Complications arising from the use of mechanical circulatory support systems include infections, thromboembolism, bleeding as a result of necessary anticoagulation and compartment syndrome of the lower extremity after using femoral artery as the access point for implantation [96] [97].

The relationship between the success of therapy and the development of acute heart failure after a myocardial infarction

A common complication after an acute heart attack is heart failure due to ventricular tachyarrhythmia (e.g. ventricular fibrillation), which, along with bradyarrhythmia (e.g. sinus node arrest) or intraventricular conduction blockage, are among the most common causes of death after a myocardial infarction.

Not only cardiac arrhythmia, but also the size of the infarct area has an impact on the development of acute heart failure. If the infarct area affects 15-20% of the left ventricle, consecutive left ventricular congestion and pulmonary edema can occur.

Basically, the extent of heart failure correlates closely with the lethality of acute myocardial infarction [98]. However, the hospital mortality could be reduced to up to five percent in this regard by the revascularizing therapy methods. Despite successful revascularization, five to ten percent of all patients die within two years of being discharged from the hospital as a result of chronic left heart failure [99].

The connection between the extent of the irreversible lesion of the myocardium, in the case of a condition after transmural myocardial infarction, and the limited success of therapy after revascularization therapy within the defective tissue prompted the examination of regenerative therapy methods in the field of cardiac surgery.

Further therapeutic measures for patients with ischemic damaged myocardium

Regenerative therapy methods, a modern medical science, pursue the restoration and repair of damaged or destroyed cells and tissues. They are indicated when the therapy methods described above are exhausted and do not achieve a therapeutic effect in the sense of an improvement in cardiac output.

In addition to stem cell therapy, there are other therapeutic approaches which have a positive effect on the regeneration and inflammation process of the damaged myocytes.

Therapy methods to reduce the inflammatory response within damaged myocytes

Various research groups are currently investigating the effects and functions of cytokines in the damaged myocardium.

Animal experiments have shown that genetically modified rats have an increased expression of VEGF - B, which leads to an improved vascularization within the myocardium and to a significant reduction of the infarct zone [100]. A similar result can be seen in the clinical study by Tio RA. et al, which showed a significant reduction of the ischemic segments after VEGF gene therapy [101]. Not only the improved perfusion but also the higher physical endurance after treatment with VEGF-encoded plasmids has been described in the literature [102].

In addition, the targeted blockage of interleukins could represent a new therapeutic approach. Experiments in mice clarified the connection between an increased concentration of interleukin 1 (IL - 1) and the reduction of the left ventricular ejection fraction of the heart [103]. At the same time, animal experiments were able to demonstrate a limitation of the inflammatory reaction and thus the improvement of the outcome after experimental myocardial infarction by means of a targeted blockage with IL - 1 antibodies [104]. The importance of cytokine-dependent tissue changes in the acute phase is also evident in the placebo-controlled clinical study by Dinarello CA. This shows that treatment with an IL - 1 receptor antagonist (anakinra) in 40 patients with a condition after a transmural myocardial infarction caused the heart 's ejection fraction to be significantly higher than in those who did not receive the appropriate therapy [105].

To date, however, clinical data regarding these therapeutic approaches are only available to a limited extent.

Cardiac stem cell therapy

Body cells which can differentiate into different cell types or tissues are generally referred to as stem cells. Depending on the type of stem cell and its influence, they have the potential to develop into any tissue (embryonic stem cells) or into certain specified tissue types (adult stem cells). Stem cells are able to generate a higher differentiated daughter cells, which in turn have stem cell properties. The ability of self-renewal and differentiation are the two criteria that all stem cells have in common. [106]

Totipotency is the ability of a cell to develop into all cells of an entire organism. Human embryos have totipotent cells up to the eight-cell stage, each of which could develop as an independent individual, as all embryonic and extraembryonic cell types can do. Extraembryonic structures, such as the placenta, are formed by the trophectoderm. The trophectoderm and the inner cell mass from which the actual embryo develops are the two cell groups that arise from the first division of the zygote (up to the eight-cell stage). They have the same ability as a fertilized egg.

Pluripotency: is the capability of some cells of producing all cell types of the actual embryo (cells of all three cotyledons) by division and differentiation, but not extraembryonic structures. These cells are called pluripotent cells [107][108]. The literature mentions other terms such as multipotency which may not differentiate into all cell types of the adult organism, but into many different cell types.

Depending on their origin, a distinction is made between embryonic and adult stem cells where adult stem cells can be found from birth to death in the bone marrow, umbilical cord blood, fatty tissue and peripheral blood. The adult body also needs stem cells to renew its tissue. The bone marrow is particularly rich with stem cells [109] which after artificial stimulation of the bone marrow can also be obtained from normal blood. The developmental potential of adult stem cells was previously seen as reduced compared to embryonic stem cells but growth factors can also be used to stimulate them to develop into specialized cell types. They retain their pluripotency even after 60 cell divisions [106]. Therefore, stem cells can theoretically renew or replace any destroyed tissue in the body.

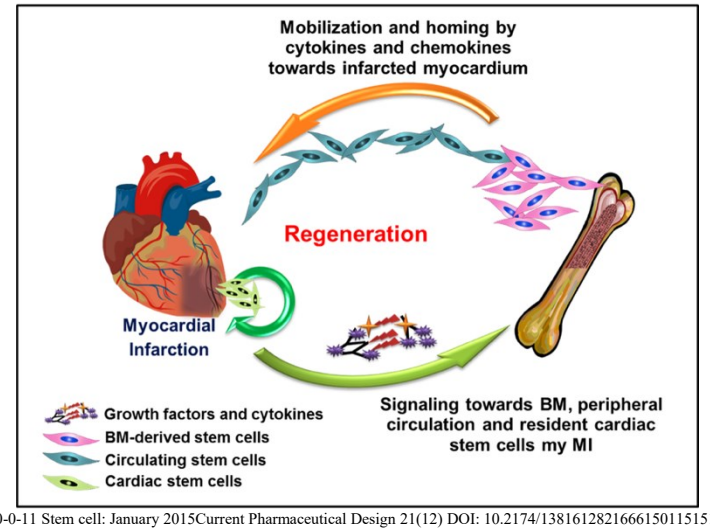

Fig. 0-0-11 Stem cell: January 2015Current Pharmaceutical Design 21(12) DOI: 10.2174/1381612821666150115151938

The bone marrow stem cells include Hematopoietic Stem Cells (HSCs), autologous Mononuclear (hematopoietic) Stem Cells (BMMSC), Endothelial Progenitor Cells (EPCs),

Mesenchymal Stem Cells (MSCs), Embryonic Stem Cells (ESCs), Cardiac Stem Cells (CSC) and Induced Pluripotent Stem Cells (iPSCs) [110][111].

Research groups began to investigate the regenerative effects of autologous stem cells in mice for the first time in the 1990s.

This therapy method can be described as the application of autologous, hematopoietic stem cells, which are administered intracoronary, intravenously or intramyocardially [112][113][114]. With intramyocardial application, a distinction can also be made between endocardial and epicardial application [115].

Hematopoeitic stem cells (HSCs)

are characterized by membrane markers like CD133+ and they are differentiated into blood and immune linage [116].

CD 133^{+} stem cells

Twenty years ago, a novel cholesterol interaction, a pentaspan membrane glycoprotein called prominin-1 (CD133), was identified as a surface marker of both neuronal (Weigman et al. 1997) and hematopoietic stem and progenitor cells (Yin et al. 1997) [117].

The CD133 antigen (prominin-1) is a 5 transmembrane glycoprotein with a molecular weight of approx. 120 kD. There are an N-terminal domain and two large glycosylated loops extracellularly, as well as two small cytoplasmic loops and the C-terminal protein intracellularly [117]. CD133 was described at first by Yin et al. in 1997 as a marker on hematopoietic CD34+ progenitor cells found in adult human blood and bone marrow as well as on foetal epithelial cells of liver and kidney. In the same year, Weigman and colleagues discovered Prominin, the homologous sequence analog in the mouse. In addition to the hematopoietic system and epithelial cells, prominin-1 (CD133) can be found in a large group of somatic stem and progenitor cells [118]. CD133 shows a remarkable cellular localization. On the plasma membrane CD133 is limited to certain areas. In the epithelial cells, prominin-1 is concentrated on the microvilli and similar protrusions of the apical plasma membrane. In non-epithelial cells, such as hematopoietic stem cells, prominin-1 is also enriched on the plasma membrane protrusions.

Little has been reported on the function of the CD133 receptor [119][120]. The CD133 molecule has been assigned a role as the organizer of the plasma membrane protrusions [121][122]. Recently, CD 133+ stem cells have been viewed as cells with great regenerative potential. In 2007 it was shown that human CD 133+ stem cells have the potential to differentiate towards both endothelial and myocardial cell lines [123].

Endothelial progenitor cells (EPCs)

is an important component of tissue regeneration of cardiovascular system [124][125][126] that was described in 1997 by Ashara et al. Cardiovascular lineage EPCs are characterized with their capability to express endothelial phenotypical markers like CD133, CD34, CD117, CD184, vascular endothelial growth factor receptor 2 (VEGFR2, KDR, Flk1), and vascular

endothelial cadherin (VE-cadherin). They also show some functional characteristics of endothelial cell in vitro and in vivo, such as acetylated-low density lipoprotein (acLDL) uptake and the formation of endothelial colony-forming units (CFUs). It was proved that circulating EPCs increase in number during the early phase of acute MI, which implies that these cells may contribute to healing processes [127][128][129][130].

Mesenchymal stem cells (MSCs)

are found in the BMSC pool [131] as well as perivascular tissue of all tissues and organs [132]. MSCs possess fibroblast clonal potency and shows multicellular differentiation into osteocytes, adipocytes and chondrocytes. They may play a role in induction and down regulation of T-lymphocyte response in graft-versus-host rejection [133].

Cardiac stem cells (CSC)

In 2003 Beltrami et al. was the first to describe Cardiac stem cells to have self-renewing c-kit+ cells in the adult heart which can be differentiated into cardiomyocytes, smooth muscle cells and endothelial cells and it can be used to regenerate myocardium and regain its functionality [134][135][136].

Embryonic stem cells (ESCs)

can differentiate into derivatives of all three germ layers [137]. Many studies demonstrated a strong cardiogenic potential of ESCs in vitro [138]. Clinical application could not be demonstrated as there are many problems faced the clinical application of the use of these cells such as ethical concerns, the risk of immune rejection, genetic instability and carcinogenic potential [139]. In 2013 Menasché could begin with the first phase I of his clinical trial (ESCORT) using human ESC-derived cardiac progenitors (Isl-1+ and SSEA-1+) embedded in a fibrin scaffold in six patients with severely impaired cardiac function which are scheduled for CABG. The first patient showed good results but it is still too early to evaluate the safety as well as the therapeutic benefit of these cells in humans [140].

Induced pluripotent stem cells (iPSCs)

are pluripotent SCs generated directly from somatic cells through a reprogramming process. A publication made by Takahashi and Yamanaka in 2006 stated the success of development of iPSCs from fibroblasts of a mouse by retroviral transduction of four different transcription factors (Oct3/4, Sox2, c-Myc, and Klf4) [141]. After one Year the same team succeeded to apply the same technology in human [142]. These iPSCs showed not only the ESC markers, morphology, proliferation as well as carcinogenic properties similar to ESCs but also possess cardiogenic potential [141][142][143]. Importantly, the iPSC-generation technology enables the creation of patient-specific pluripotent stem cells that can be used for genetic repair [144]. New protocols have been developed improving the efficiency and safety for the generating of iPSCs by using virus-free and non-integrative approaches [145][146][147][148][149][150][151][152]. iPSC-derived cardiomyocytes have not reach clinical grade yet.

Delivery techniques

Delivery techniques could be conventionally categorized into three groups: intracoronary delivery, intramyocardial application (including endoventricular, transepicardial and transvascular injections) and intravenous delivery (including retrograde coronary sinus (RCV) and peripheral intravenous infusions).

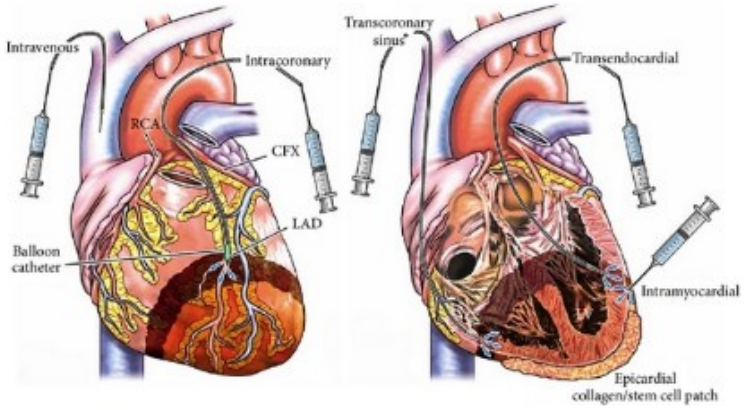

Fig. 0-0-12 Delivery techniques: January 2016Stem Cells International 2016(5):1-16 DOI: 10.1155/2016/9240652

Intracoronary application

It is introduced to reduce shedding of SCs to non-targeted organs to minimum. At first an angioplasty balloon is inflated in the proximal segment of the coronary arteries before SCs is injected (stop-flow technique). The angioplasty balloon will help transendothelial passage and migration into the infarcted zone. The local myocardial ischemia is a strong stimulus for chemokinesis of SCs due to stromal cell-derived factor 1 (SDF-1) and C-X-C chemokine receptor 4 (CXCR4) signaling [153][154][155]. This will facilitate the transmigration process (cell adhesion and extravasation) into the injured and ischemic but still viable tissue [156][157][158], which is sufficient to stimulate myocardial repair [159][160]. The intracoronary application of cultured cell types, like MSCs or skeletal myoblasts was associated with micro embolization and microvascular obstruction, therefore this approach should be only used in the smaller mononuclear BMSCs [161].

Intramyocardial application

Endoventricular intramyocardial injection

It is the direct intramyocardial injection of SCs into the myocardial target area. Percutaneous endoventricular injection of cell preparations is done by using one of the percutaneous transendocardial delivery catheters and is guided by fluoroscopic ventriculography [162][163][164] or by electromechanical mapping. The surgeon can distinguish in real time viable myocardium from non-viable, hibernating or scar tissue. Clinical studies proved safety and feasibility of the transendocardial intramyocardial injection in case of chronic heart failure [165], refractory angina [166] and in subacute MI [167]. Percutaneous injection is accompanied with high rate of cell loss and shedding to nontargeted organs.

Transepicardial application

SC implantation is done during CABG operation basically around the infarction area in left ventricle [167][168]. It cannot be used in septal myocardial segments. It is not easy to determine whether it has a therapeutic effect or not if it is done along with revascularizing operation. Epicardial delivery of bioengineered composite sheets containing SCs within, is a

new method of SC delivery. SC sheets adhere to the epicardial surface spontaneously, or as collagen-based patches [169][170].

Transvascular delivery

This way of SCs delivery can be done through transvenous or transarterial delivery under intravascular ultrasound (IVUS) guidance [171][172]. A perpendicular-positioned microneedle is then used to penetrate the coronary artery wall and allows the user to inject SCs directly into the perivascular space (tunica adventitia of the coronary artery) [173][174][175].

Intravenous delivery

Retrograde coronary sinus (RCV) infusion

RCV infusion is performed through femoral venous access. A conventional angioplasty balloon is then inflated in the mid portion of the coronary sinus followed by SC infusion. Clinical and preclinical studies showed safety, efficacy and high cell concentration of delivering through the coronary sinus [176][177][178]. Coronary sinus delivery method could be recommended in cases of severe aortic stenosis, severe peripheral artery disease or the formation of intraventricular thrombus which precludes percutaneous endoventricular injection. This Technique can also be done in patients with implanted defibrillator. Potential complications include coronary sinus rupture and embolization [179][180].

Peripheral intravenous infusion

Intravenous infusion is the safest and cheapest method of SC delivery. Its safety and feasibility have been shown in swine model of MI [181] and later in a phase I clinical study after delivery of allogeneic MSCs [182]. The study demonstrated a significant enhancement of the ejection fraction in the treated versus placebo groups after 12-month follow-up period, although the myocardial concentration of the SCs following intravenous injections is mere 0.5% [183].

Due to the better localization of surgical cell injection, intramyocardial and epicardial stem cell application is considered a promising form of application within cardiac stem cell therapy. In the case of catheter-applied intracoronary or endocardial stem cell application many disadvantages could be seen including stem cell loss, the unreachable location and the risk of microembolization especially with the intracoronary method [184].

Clinical studies have now shown that cardiac stem cell therapy is an effective, safe and easy to carry out regenerative therapy, which is increasingly establishing itself as a therapeutic measure in cardiac surgery and cardiology in patients with conventionally resistant ischemic cardiomyopathies.

Stem cells homing

The migration of hematopoietic stem cells via the blood, through the vascular system to the target organs or the bone marrow is known as the “homing” process [185]. During ontogenesis, the early precursors of the hematopoietic system are first formed in intraembryonic aortic gonadal mesonephros (AGM), and it appears very likely that such AGM-derived hematopoietic stem cells will migrate to and colonize the foetal liver which is the main place of embryonic blood formation. During the newborn stages, the hematopoietic stem cells migrate again. They leave the foetal liver and enter the bone marrow through the bloodstream. [186]

In the past 30 years it has been shown that post-neonatal hematopoietic stem cells still can migrate. [187] [188] “Homing” is not only a natural ongoing process, it also occurs in the context of pathological conditions in the sense of acute organ damage, such as the heart attack. Most of the stem cells in the bone marrow are normally at rest and show no proliferative activity. However, if there is an increased demand anywhere in the organism, these stem cells are activated and begin to proliferate and differentiate into progenitor cells. Eventually, stem and progenitor cells are mobilized into the peripheral blood. Some physiological as well as pathophysiological processes such as tissue ischemia lead to increased mobilization of stem and progenitor cells via stress signals before they enter the circulation from the bone marrow microcirculation via the sinusoids of the bone marrow. [189]

These signaling pathways and mechanisms are complex processes that result from the interaction of numerous factors (cytokines, chemokines, proteolytic enzymes, growth factors and adhesion molecules). [190]

Rolling and adhesions

During the homing process, hematopoietic stem cells are required to pass through the vessel wall in a process known as extravasation. The extravasation of hematopoietic stem cells is a multi-stage process similar to the extravasation of leukocytes in foci of inflammation and is mediated by adhesion molecules on the stem cell and endothelial side. First, the hematopoietic stem cells roll along the endothelium. Chemokines then activate adhesion molecules on the endothelial cell side, which ensure firm adhesion between hematopoietic stem cells and endothelial cells. Finally, the hematopoietic stem cells migrate through the endothelium into the bone marrow [191].

The homing process involves a cascade of events, the first critical step is known as “rolling”, in which the migrating cells interact initially with less affinity with the endothelial cells [192]. Various endothelial selectin molecules induced by inflammation mediators and by SDF-1α mediate the “rolling” of stem cells, [193][194][195][196][197].

The “rolling” phase is followed by the firm endothelial adhesion, which is a firm connection between the stem cell and the endothelial cell immediately before the extravasation. It is known that SDF-1α modulates the adhesion of cells to fibrinogen, fibronectin, stroma and endothelial cells. This effect of SDF-1α is demonstrated by the activation of various adhesion molecules on the surface of the target cells, e.g. Integrine. In addition, SDF-1α induces the LFA-1 / ICAM-1 and VLA-4 / VCAM-1 mediated solid adhesion and transendothelial migration of human CD34 + stem cells [195]. Various molecules, both on the stem cell and endothelial side, which contribute to the “homing” or adhesion of the stem cells have been described.

Stem cell therapy at cardiac surgery at the University of Rostock

Cardiac surgery at the University of Rostock has been dealing with the cardiac effects of hematopoietic stem cells since 2001 and has developed a new therapeutic approach for patients with chronic ischemic heart diseases.

The concept consists in the combination of an aortocoronary bypass operation and simultaneous intramyocardial stem cell application in patients with ischemic cardiomyopathies.

The autologous stem cells from the bone marrow are removed from the patient's iliac crest and then isolated using special antibodies [198]. The prerequisite for the implementation of this therapy method is the detection of hibernating tissue in the marginal area of the damaged myocardium [199]. Hibernating tissue is the tissue that is adequately supplied with blood for its own cell metabolism, but also does not have enough nutrients to actively participate in the contraction of the heart.

Due to the molecular adaptation, the cellular metabolism adapts to the hypoxic environment, the cell's own energy requirement is reduced, so that tissue necrosis within the myocardium does not occur.

Nevertheless, hibernating tissue retains the ability to influence itself through appropriate influencing factors, e.g. To structurally change stem cells or VEGFs and the resulting formation of new vessels [200].

The intramyocardial stem cell application takes place in the hibernating tissue and is therefore of therapeutic importance as a possible curative therapy method both in the treatment of acute myocardial infarction and in chronic ischemic and dilated cardiomyopathies [201][202].

Since 2001, the first clinical studies by the University of Rostock have shown that this therapy improves the vitality and pump function and thus the ejection fraction of the heart, which among other things is related to the potential of stem cells to differentiate into vascular cells [198][203][204][205].

The number of stem cells applied, the time chosen after the heart attack which should take place within a period of seven to twelve weeks after the myocardial infarction, and the preoperative LVEF which should not exceed 40 percent also influence the efficiency of stem cell therapy [206].

In order to test the efficacy, safety and medical benefit of the intramyocardial stem cells for patients, clinical studies for the phases I and II were developed and carried out at the University of Rostock.

Phases I, II and III of cardiac stem cell therapy

In the phase I clinical study, the safety and feasibility of intramyocardial stem cell application following bypass surgery on six patients were examined. All patients had a previous transmural myocardial infarction with a detectable, infarct-associated non-kinetic area. Other inclusion criteria were: detectable hibernating tissue, an ejection fraction of the heart between 25% - 50% and a minimum age of 18 years.

In order to record the success of the therapy, the patients were called in for follow-up examinations (Follow-Ups). These included the echocardiographic measurement of the ejection fraction of the heart as well as a detailed survey regarding well-being, new illnesses, physical performance and quality of life. During the follow - up examinations a clear increase in perfusion in the area of the infarct margin and an improved left ventricular ejection fraction (LVEF) by means of echocardiography and SPECT (single photon emission computed tomography) could be demonstrated within the first three months after the operation.

In none of the patients could neoplasia, ventricular arrhythmias or left ventricular tachycardias be detected up to three months after the therapy. Because of that, the combined therapy method of stem cell therapy and bypass surgery is considered to be a safe and practicable therapy method [207].

The phase II clinical study then dealt with the efficiency and again with the aspect of the safety of the therapy. A total of 43 patients were included in the study. 22 patients of which were treated with the combined procedure of stem cells and bypass surgery, whereas 21 patients only received conventional bypass surgery and thus formed the control group for the first group. The safety of the therapy was examined on the basis of many parameters including death, renewed myocardial infarction, renewed reintervention and ventricular arrhythmia and covered the period up to 12 months after the intervention. Statistically, there was a significant difference in LVEF and perfusion of the infarct margin in favor of patients treated with stem cells. In neither group there were undesirable side effects (death, renewed myocardial infarction, renewed restenosis and ventricular arrhythmias). The phase II clinical study therefore shows that the combined therapy of stem cells and bypass surgery is a safe and efficient therapy method [205].

Based on these results, there was a justification for continuing the combined therapy of stem cell application and bypass surgery for the indication mentioned above.

The phase III randomized clinical trial (PERFECT) was designed to assess clinical safety and again efficacy of intramyocardial $CD133^+$ bone marrow stem cell treatment combined with CABG after myocardial infarction for induction of cardiac repair and myocardial regeneration and the enhancement of LVEF at 180 days [1]. The study was conducted across six centers in Germany in October 2009 through March 2016 and stopped due slow recruitment in March 2015. A total of 82 post-infarction patients with chronic ischemia and reduced LVEF (25% - 50%) were included in the study. These were further divided into two subgroups with one of them receiving intramyocardial placebo and the other receiving a suspension of $CD133^+$. The original clinical study protocol of the PERFECT RCT [1] can be found in the “EU Clinical Trials Register” under the following EudraCT No.: **2006-006404-11.** or https://clinicaltrials.gov/ under **NCT00950274.**

The stem cell registry of the clinic for cardiac surgery at the University of Rostock

Since 2006, patients who meet the relevant criteria (verifiable hibernating tissue, had had a myocardial infarction at least two weeks before the stem cell application, ejection fraction of the heart between 25% - 50%, age of the patient over 18 years) have been treated with autologous stem cells at the University of Rostock. Since then, both these patients and the patients from the Phase I and Phase II studies have been examined at regular intervals with regard to the pumping function of the heart, the state of health and the quality of life.

Since the success of the therapy only manifests itself after a few weeks, the patients are interviewed at regular intervals as part of the follow-up examinations. Findings are requested from general practitioners and resident cardiologists, and some of the patients are examined directly in the cardiac clinic and polyclinic.

The follow-up examinations can be used to determine whether there has been a positive or negative development with regard to the cardiac output of each patient, or whether new diseases or cardiac complications (reinfarction, restenosis, hospital stay, cardiac rhythm disturbances) have occurred within the follow-up period.

In order to assess the efficiency and thus the effect of $CD133^+$ hematopoietic stem cells on cardiac output, the control group of phase II, consisting of patients who were treated electively with a bypass operation at the University of Rostock only after a transmural myocardial infarction, has been compared with the patients who received combined therapy.

All patients from phases I, II, III and all other patients treated with stem cells were included in a registry for the purpose of long-term follow-up with regard to safety and efficiency.

This registry forms the base of the present work on the therapeutic long-term efficacy of autologous myocardial stem cell application in combination with an aortocoronary bypass operation versus an aortocoronary bypass operation alone.

Cardiac arrhythmias

Arrhythmia, is a condition in which the heartbeat is irregular, too fast, or too slow. If heart rate is above 100 beats per minute in adults, it is called tachycardia, and if it is below 60 beats per minute, it is called bradycardia. Some types of arrhythmias have no symptoms. Symptoms if present may include palpitations or feeling a pause between heartbeats. In more serious cases, there may be lightheadedness, syncopal attack, shortness of breath or chest pain. While most types of arrhythmias are not dangerous, some predispose a person to complications such as stroke or heart failure. Others may result in sudden death.

Cardiac arrhythmias are a common complication after CABG operation, especially with increasing age. The most common rhythm disorder is atrial fibrillation (AF), but other forms of supraventricular arrhythmias such as atrial flutter, atrial tachycardia, ventricular tachyarrhythmias such as ventricular tachycardia, ventricular fibrillation or conduction disorders such as high-grade atrioventricular block can also occur. Some patients already have a history of arrhythmia, others experience it for the first time.

Postoperative causes of arrhythmia may be due to electrolyte imbalance, postoperative increase in adrenal function, atrial dilatation as a result of perioperative fluid overload, pulmonary hypertension, myocytes hyperexcitability after application of heart-lung-machine or as an inflammatory response that is mediated by inflammatory mediators released due to preoperative ischemia, postoperative reperfusion or as a part of stem cell stimulation [208][209][210][211][212].

Only supraventricular Tachycardia (SVT), supraventricular extrasystole (SVES), ventricular extrasystole (VES) and ventricular Tachycardia (VT) collectively are relevant to and included in our study.

Tachycardia arrhythmia

This group of cardiac arrhythmias is commonly referred to as supraventricular (SVT) and ventricular (VT) tachycardia. The following pages, however, only explain those rhythm disorders that are relevant to our study SVT, SVES, VES and VT collectively.

Supraventricular Tachycardia (SVT)

An SVT is to be considered when there are four or more pulses from a point above the bundle of His and the frequency is higher than that of the age norm. If this tachycardia lasts longer than thirty seconds, one speaks of "Sustained" - SVT, if the length is less than thirty seconds, it is a "non-sustained" SVT. In most cases there is a narrow QRS complex on the ECG.

The therapy of this arrhythmia depends on the hemodynamic state of the patient. In our study all types are included as SVT without differentiation.

Supraventricular Extrasystole (SVES)

Premature atrial contractions (PACs), also known as atrial premature complexes (APC) or atrial premature beats (APB), are a common cardiac dysrhythmia characterized by premature heartbeats originating in the atria. While the sinoatrial node typically regulates the heartbeat

during normal sinus rhythm, PACs occur if another area of the atria depolarizes before the sinoatrial node and triggers a premature heartbeat.

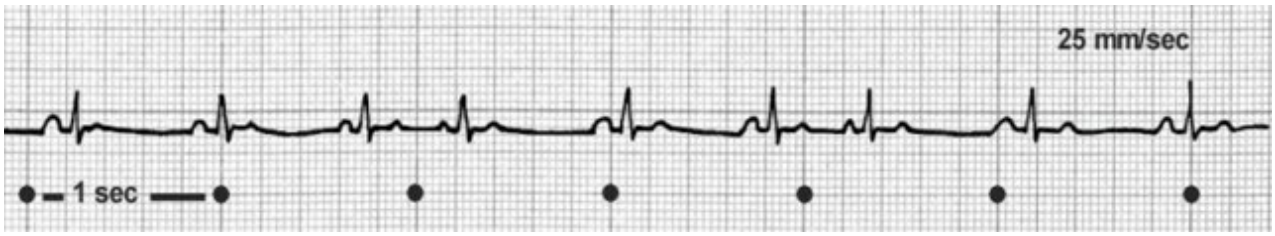

Fig. 0-1-1 Supraventricular Extrasystole: http://grundkurs-ekg.de

Intra-atrial reentry tachycardia / IART

In atypical atrial flutter reentry-circles appear in the atrium, which just after extensive atrial operations circulate around scar tissue. The tricuspid ring and the isthmus, however, are not involved in this form of circulation.

The typical atrial flutter, however, is a special case of an IART. It is characterized by circular excitation in the right atrium, which is more common counterclockwise or clockwise. The tricuspid valve or the Cavo-tricuspid Isthmus included as a zone of slow conduction.

Focal (ectopic) atrial tachycardia / FAT

In this form there is an extra "arousal center / focus" in the atrium in addition to the sinus node. Vagal-stimulation maneuver and adenosine administration lead to a brief termination of the AV transition, but has no direct influence on the focus. Beta blockers, sotalol or amiodarone are more suitable for this.

Atrial fibrillation

It is a rapid, irregular atrial actions which impair the atrial transport function and has an increased risk of thrombus formation. Atrial fibrillation is usually better than an IART depending on the heartrate. Cardioversion is the treatment of choice. With relapses and faster conversion can beta-blockers, digitalis or amiodarone be used for treatment. With drug-resistance AV node ablation can be considered.

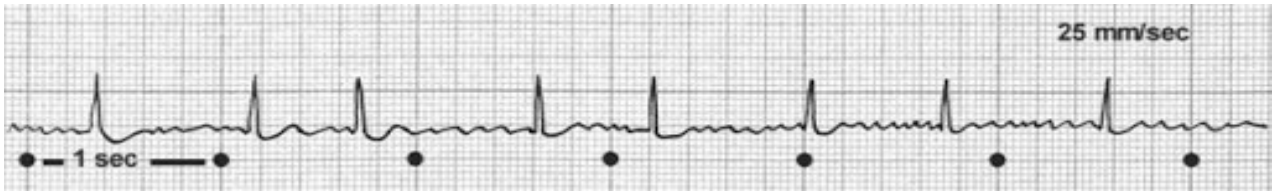

Fig. 0-1-2 Atrial fibrillation: http://grundkurs-ekg.de

On average, postoperative AF occurs on the 2nd – 3rd postoperative day [208][213][214], and symptoms such as hemodynamic instability [215], progressive heart failure or stroke [213] may occur [218][216][213][214][215][217]. This can extend the stay in an intensive care unit by a factor of 3 [219] and the entire hospital stay by 2–9 days with the associated increase in costs [220][208][209][218][219]. In addition, postoperative AF can increase the risk of mortality [218][216][217][219][221].

Reentry Tachycardia

Atrioventricular reentry tachycardia (AVRT)

AVRT creates a circular motion between the atrium and the ventricle due to an accessory conduction pathway. This is in the area of AV valve level, which is normally not the case in healthy people.

Therapy in the acute phase mainly consists of vagal-stimulation-maneuvers or in the administration of adenosine. In long-term therapy beta blockers or amiodarone have sufficient effect.

Atrioventricular nodal reentry tachycardia (AVNRT)

There are two functionally different conduction pathway in the area of the AV node, the "slow" and "fast pathway". Normally, the AV node relay over the "fast pathway". However, it does sometimes come to a block of this path - e.g. in the case of premature extrasystoles - where the SA node relays then via the "slow pathway". The resulting circular excitations are in most cases antegrade on the slow pathway and retrograde on the fast pathway. AVNRT is treated analogously to AVRT.

Ventricular Tachycardia (VT)

Ventricular tachycardia (VT) is a fast, abnormal heart rate that originate from the ventricles. VT is defined as 3 or more heartbeats in a row, at a rate of more than 100 beats a minute. If a VT episode lasts for more than a few seconds, it can become life-threatening. Sustained VT is when the arrhythmia lasts for more than 30 seconds, otherwise the VT is called nonsustained. The rapid heartrate decreases the filling time of the ventricles and a consequence doesn't give the heart enough time to fill with blood before it contracts again.

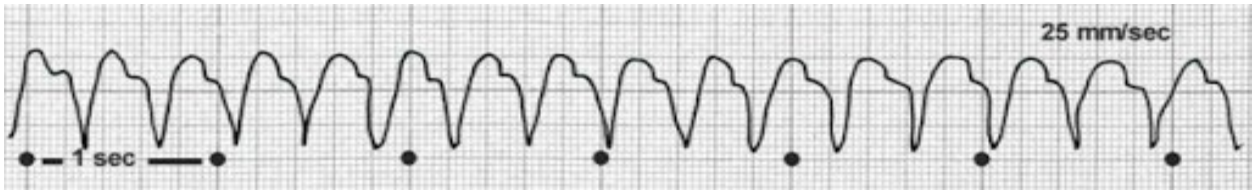

Fig. 0-1-3 Ventricle Tachycardia: http://grundkurs-ekg.de

Persistent ventricular tachyarrhythmias are rare and occur in 0.5–1.6% of all cases after cardio surgery [222][223][224], often associated with postoperative complications. Patients with postoperative ventricular tachycardia or ventricular fibrillation have higher 30-day mortality [225][226]. In the event of persistent ventricular tachycardia, a reversible cause such as hemodynamic instability, myocardial ischemia, electrolyte imbalance or septic shock should first be excluded. If ventricular tachycardia persists, usually drug therapy is indicated, preferably intravenous administration of amiodarone. Cardioversion may be indicated in the event of hemodynamic deterioration. In the event of hemodynamic instability in ventricular tachycardia or ventricular fibrillation, immediate defibrillation with cardiopulmonary resuscitation may be necessary [226].

Ventricular extrasystole (VES)

It is also known as a premature ventricular contraction (PVC). It is a common case where the heartbeat is initiated by Purkinje fibers in the ventricles instead of the sinoatrial node. It is characterized by the premature QRS complex on ECG that is of abnormal shape and great duration (generally >129 msec). PVCs may cause no symptoms or may be described as a "skipped beat" or felt as palpitations in the chest. The postoperative occurrence of isolated ventricular extrasystoles does not pose an increased risk of malignant ventricular arrhythmias and therefore requires no therapy.

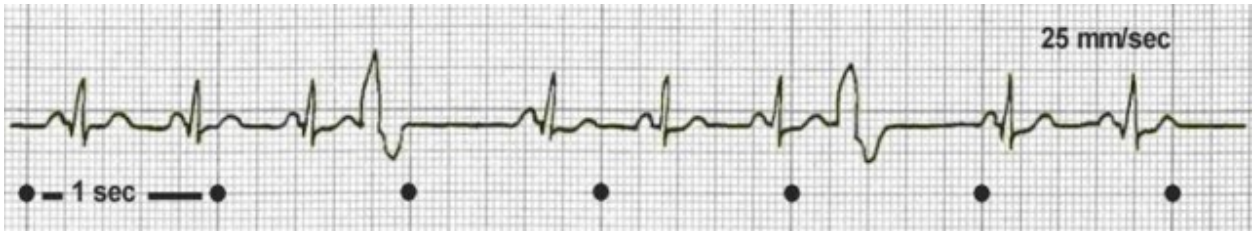

Fig. 0-1-4 Ventricle Extrasystole: http://grundkurs-ekg.de

Ventricular flutter

Ventricular flutter is an arrhythmia, more specifically a tachycardia affecting the ventricles with a rate over 250-350 beats/min. It is characterized on the ECG by a sinusoidal waveform without clear definition of the QRS and T waves. It has been considered as a possible transition stage between ventricular tachycardia and fibrillation, and is a critically unstable arrhythmia that can result in sudden cardiac death.

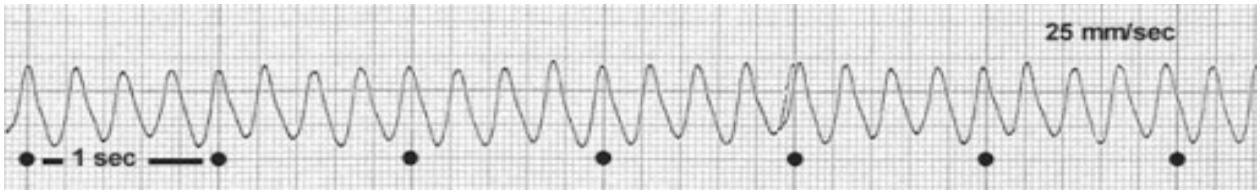

Fig. 0-1-5 Ventricle Flatter: http://grundkurs-ekg.de

Ventricular fibrillation (VF)

Ventricular fibrillation (V-fib or VF) is when the heart quivers instead of pumping due to disorganized electrical activity in the ventricles. It is a type of cardiac arrhythmia. Ventricular fibrillation results in cardiac arrest with loss of consciousness and no pulse. This is usually followed by death in case of absence of treatment. It should be treated with cardiopulmonary resuscitation (CPR) and defibrillation. Biphasic defibrillation may be better than monophasic. Epinephrine or amiodarone may be given if initial treatments are not effective.

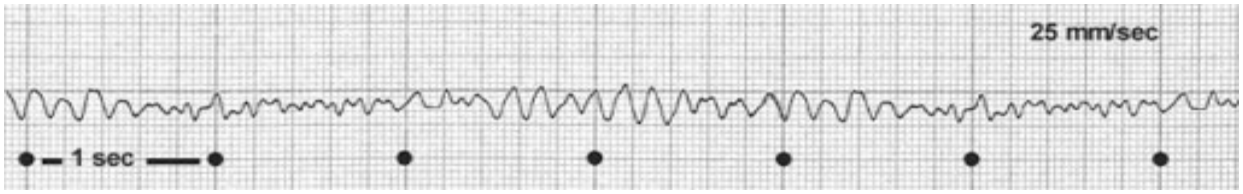

Fig. 0-1-6 Ventricle fibrillation: http://grundkurs-ekg.de

Bradycardia arrhythmia

Bradycardia is a slow heart rate below 60 beats per minute. According to the underlying pathology it is divided into AV Block if there is a decrease in the conduction speed of the conduction system and Sinus dysfunction if there are fewer pulses originate from the SA node.

Atrioventricular lead block (AV block)

Depending on the type of the AV block, it is defined as a delay or complete blocking of pulse transmission from the atrium to the ventricles.

There are three different forms:

AV block grade 1: There is a delay in the spread of excitation from the atrium to the chamber, which can be seen on the EKG with a P-Q Interval prolongation.

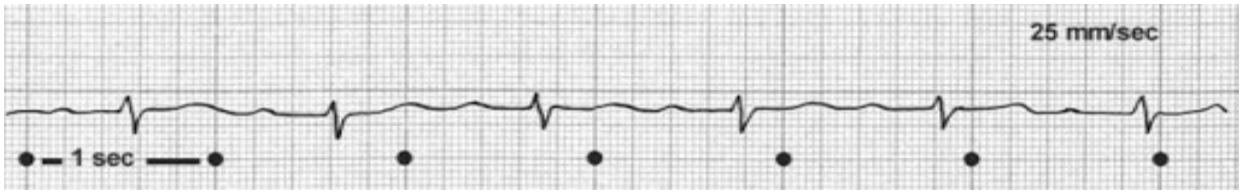

Fig. 0-1-7 AV-Block I°: http://grundkurs-ekg.de

AV block grade 2: A continuous prolongation of the P-Q interval until a blockage occurs. This is known as AV block type Wenckebach. However, if there is blockage without P-Q interval prolongation it would be called AV block type Mobitz. The latest can convert into a complete AV block.

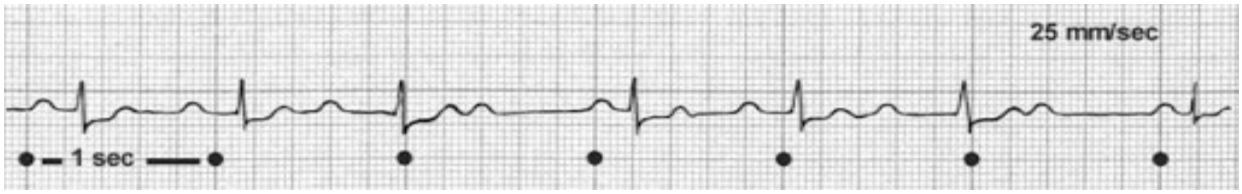

Fig. 0-1-8 AV-Block II° Mobitz 1: http://grundkurs-ekg.de

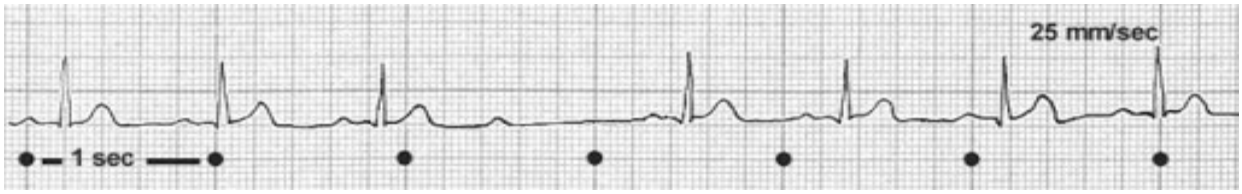

Fig. 0-1-4 AV-Block II° Mobitz 2: http://grundkurs-ekg.de

AV block grade 3: The complete AV block. It can be seen in ECG as AV dissociation. The atrial rhythm has no relation to the ventricular rhythm.

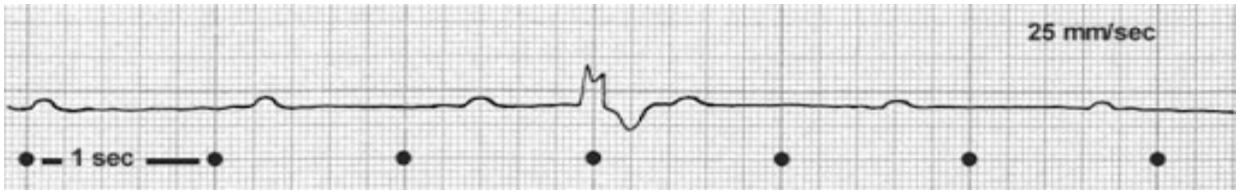

Fig. 0-1-9 AV-Block III°: http://grundkurs-ekg.de

AV blocks of the first and second degree can be used in both heart-healthy people as well occur after drug administration or postoperatively. Therapy for this bradycardia especially long-term and higher-grade AV blocks is pacemaker.

Sinus dysfunction

This bradycardia, also called "sick sinus syndrome", is particularly common in patients after surgical correction of a congenital heart defect. Thereby, a sinus bradycardia, sinus arrest and sinoatrial block occur individually or in combination. Intraatrial reentrant tachycardia (IART) can also occur and appears as tachycardia - Bradycardia syndrome. Bradycardia, if in need of therapy, then requires pacemaker implantation. Tachycardia on the other hand needs to be treated with catheter ablation as soon as possible.

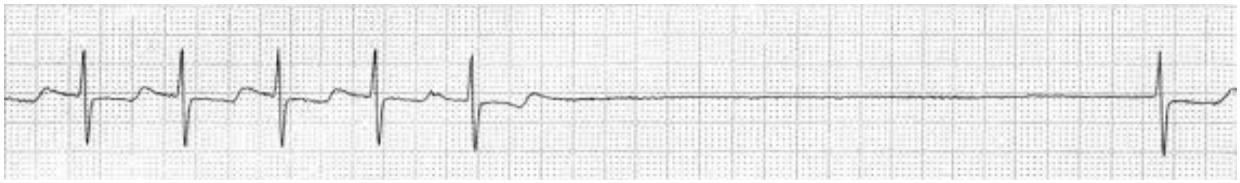

Fig. 0-1-10 Sick Sinus Syndrom: http://grundkurs-ekg.de

Arrhythmia after CABG

Arrhythmias are very common postoperative complications after cardiac surgery and play a very important role in morbidity and mortality. Atrial tachyarrhythmias are the most seen postoperative arrhythmia. Ventricular arrhythmias and bradyarrhythmias are less frequent [227].

The effect of each arrhythmia on the clinical status depends on its duration, ventricular rate, cardiac function, and patient comorbidities. In fact, arrhythmias that may be insignificant in young patients can affect greatly the postoperative morbidity and mortality in congenital heart disease [227, 228].

Arrhythmia management depends on its significance on the hemodynamic state and includes correction of the underlying correctable risk factors, as well as specific treatment for the arrhythmia itself.

Risk Factors

Many perioperative risk factors have been identified in atrial and ventricular vulnerability to postoperative arrhythmias (POAs), but their role is still unclear. Risk factors can be divided into patient as well as surgery related.

Patient related risk factors include age [228][229][230][231], structural heart disease [232][233][234][235][236] and extracardiac comorbidities such as obesity [237], preoperative stroke and COPD [238].

Surgery related risk factors such as trauma and inflammation [239], hemodynamic stress [240][241], ischemic injury [242], perioperative drugs as beta blockers [243][244] and digoxin [245], electrolytes disorders as in hypokalemia [246] and magnesium [247][248], preservation of anterior fat pad that contain parasympathetic ganglia [249] and other special conditions.

Supraventricular Tachyarrhythmias

Atrial fibrillation (AF) is the most common type of supraventricular arrhythmia after cardiac surgery and it has been reported in 15 to 40% of patients in the first few postoperative days after CABG [250][251][252]. It is often associated with other atrial tachycardia such as atrial flutter (AFlu) as a late postoperative complication of cardiac surgery [253], premature atrial complexes, and multifocal atrial tachycardia. Many electrophysiologic parameters may also enhance the development of AF [254][255]. AF can be transient and without hemodynamic consequences, but also it may lead to serious complications such as increased risk of acute kidney injury (AKI), hemodynamic instability, cardiac failure, stroke, and death [256][257][258].

The mean duration of atrial fibrillation (AF) in one report was shown to be between 11 n 12 hours where more than 90% of patients were in sinus rhythm after six to eight weeks postoperative [259][260]. In another report only 3 out of 116 patients who developed AF after CABG stayed in AF at six weeks postoperative [261].

Ventricular Tachyarrhythmias

Isolated Premature Ventricular Complexes (PVC) are common after surgery and insignificant. They do not show increased risk for development of malignant ventricular arrhythmias [262][263]. But frequent PVCs (>30 per hour) may influence negatively the ventricular function.

Ventricular Tachyarrhythmias

Sustained ventricular arrhythmias are not common postoperative and include ventricular tachycardia (VT) as well as ventricular fibrillation (VF). Reported rates after cardiac surgery is from 0.41% to 1.4% [264][265].

Possible causes include left ventricular dysfunction [266], electrolyte imbalances, hypoxia, hypovolemia, hemodynamic instability, myocardial ischemia and infarction, acute graft closure, reperfusion after stopping cardiopulmonary bypass, inotropes and use of antiarrhythmic drugs.

Patients with sustained ventricular arrhythmias have worse short term as well as long term prognosis. A mortality rate of up to 50% has been reported in such patients postoperative. Among those who survive up to 40% have a recurrence. 20% of which die from cardiac causes within two years [263][267].

Arrhythmia after stem cell implantation

Many studies and clinical trials were performed to investigate the improvement in cardiac functions using intramyocardial implantation of different types of stem cells specially CD133+. However, the focus on arrhythmia as a side effect was very limited and trivial. Some studies suggested that stem cells are in fact arrhythmogenic and promoted for further investigation [268].

It was suggested that if transplanted cells failed to structurally as well as functionally integrate into the myocardium of the host, it might increase the arrhythmogenic risk to patients. This depends on the transplanted cell type. Other potential causes to the arrhythmogenicity of stem cell transplantation may be re-entrant pathways, graft automaticity as well as certain methods of cell delivery.

Functional integration means that the electrical potential generated in one cell is strong enough to be transmitted and to propagate through gap junctions and depolarize neighboring cells [269]. Arrhythmia in injured heart occur due to the disruption of this structure through loss of desmosomes and gap junctions in ischemic disease [270]. One gap junction of particular importance is connexin-43 (Cx43) [271][272][269][170][273]. However, expression of Cx43 alone is not enough to suppress the arrhythmic risk of stem cell transplantation. Many other mechanisms exist.

Adult stem cells (ASCs) have been used in clinical trials [274][275] and human pluripotent stem cells (hPSCs) have been used in regenerating damaged mammalian hearts [276]. These stem cell-based therapies has been facing many challenges including the arrhythmogenic nature of stem cell derived cardiac grafts. This arrhythmic risk may be due to differences in electrophysiological maturity [277][278][279], cell orientation, gap junction isotypes as well as wave propagation between graft and the myocardium of the host. In vivo, the normal myocardial structure has an unmatched 3D-extracellular matrix, offering repeating mechanical stress (from rhythmic heart contractions), electrical stimulation, cell-cell signal production and topographical relationship among the cardiomyocytes (CM). When injured, the normal architecture is disturbed and CMs are replaced by scaring tissue and proliferative fibroblasts, which in turn causes damage in the heart's structural integrity and adverse remodeling. These architectural changes cause anisotrophy, which considered as substrates for reentrant arrhythmias. In addition, the prolongation in action potential may potentially cause early after-depolarizations, or delayed after-depolarizations.

Also, the hostile environment, the lack of normal myocardial architecture and the possibility for the introduction of cells in a microenvironment where normal cardiomyocyte fibers are replaced by scar tissue should be considered if introduction of exogenous cells for regenerative purposes is to be done.

Different mechanisms of arrhythmogenicity have been discussed for the arrhythmogenicity of stem cell transplantation.

Re-Entrant Pathways and Automaticity

In a study by Liao et al., the proarrhythmic risk of hESCs vs. hESC-CMs was investigated in a myocardial infarction (MI) mouse model [273]. The authors revealed high arrhythmogenesis in the hESC-CM population as well as prolonged action potential duration, which caused a higher rate of inducible VTs than the hESC group. The explanation for that may be due to the relative difference in action potential duration between transplanted hESC-CMs and intrinsic ventricular CMs which facilitates reentrant excitation or due to the ability of hESC-CMs to cause abnormal impulse initiations, serving as ectopic arrhythmic foci, early after-depolarization (EAD), or delayed after-depolarization (DAD). The in vivo experiments showed that although cardiomyocytes integrate with host myocardium, they show immature

electrophysiological properties that may cause less organized gap junctions [281]. These properties predispose the substrate to higher rates of arrhythmia.

Impurities in stem cell differentiation.

The process of differentiating hESC to cardiomyocytes is an imperfect one. The product of these protocols is never 100%, with isolated material often containing non-cardiac derivatives or residual of undifferentiated pluripotent stem cells that may form teratomas in vivo. This may explain that the arrhythmogenicity in stem cell transplantation may be due to the impurities of the transplanted graft. This hypothesis was checked and it suggested that immunological response may be responsible of that higher rates of arrhythmia [284] because transplantation of non-cardiac derivatives could stimulate a stronger immune response to the graft, leading to rejection and thereby increased arrhythmogenicity.

Confounding Factors

Additionally, there may be confounding factors that play role in arrhythmogenicity of stem cell which is in fact cell-independent [283]. These may include local injury or edema due to myocardial injection [281] as well as different methods of transplantation. Intramyocardial injection of stem cells is much more arrhythmogenic and may be responsible for the higher rates of ventricular tachycardia, than retrograde intracoronary delivery [284]. Injection of cell clusters via the intramyocardial route may serve to impede electrical conduction in the myocardium as well as stimulate inflammatory cells to release cytokine, which may result in higher rates of arrhythmias. Transplantation of mesenchymal stem cells also induces nerve growth and high sympathetic nerve density [285]. Increased sympathetic innervations may lead to improved contractility and LVEF. It may also cause arrhythmia in that already damaged myocardium [286].

Paracrine Effects

Many studies investigated how paracrine effects influence the electrical activity of the graft. Some demonstrated that secretion of factors such as chemokines, cytokines and growth factors from transplanted cells may have beneficial effects which is known as the ‘paracrine hypothesis’ [287]. These beneficial effects may include the release of cryoprotective molecules that increase survival rate of native cardiomyocyte, promote neovascularization, alter extracellular matrix resulting in remodeling that helps scar to gain strength and reduces ventricular dilation as well as improves contractility and finally help in activation and recruitment of resident cardiac stem cells [288]. Hwang and colleagues investigated the effects of paracrine media under hypoxic or normoxic conditions [289] in rats. This found that the hypoxic, but not normoxic, paracrine prevent sudden death in rats and lead to increased electrical stability by enhancing conduction in the border zone through recovery of gap junctions, minimizing the degree of fibrosis, and better modulating calcium regulatory ion channels.

Many studies could show no increase in ventricular arrhythmogenicity in patients treated with MSC and bone marrow progenitor [290][291][292][293]. Some studies have even showed an anti-arrhythmogenic effect after MSC implantation [294]. Nevertheless, it has also been discussed that paracrine effects of the MSCs may possess a beneficial effect in antagonizing the arrhythmogenic substrate.

Objectives

The primary aim of this work is to investigate the correlation between the intramyocardial stem cell implantation combined with bypass surgery expressed by the response to the therapy with enhancement in LVEF as well as perfusion and the incidence of the postinterventional cardiac arrhythmia expressed by ventricular and supraventricular arrhythmias.

The following hypotheses should be examined in the context of this work:

1. The intramyocardial application of autologous CD 133^+ stem cells in combination with an aortocoronary bypass operation is a safe therapy method and does not lead to the development of cardiac arrhythmias more often than mono therapy with aortocoronary bypass operation.
2. In patients who received CD 133^+ stem cells therapy, postinterventional cardiac arrhythmias occurred less frequently in comparison to patients who received placebo therapy only.
3. There is no correlation between the change in LVEF and the development of cardiac arrhythmias.

Materials & Methodology

Participants

This retrospective study is considered as an extension to the original randomized multicenter placebo controlled and double blinded phase III PERFECT trial [1] and is done using the already collected data from its whole patients' population where 119 patients were screened and only 82 from which were randomized to active or placebo therapy. The original clinical study protocol of the PERFECT RCT [1] can be found in the "EU Clinical Trials Register" under the following EudraCT No.: **2006-006404-11.** Also, can be found on https://clinicaltrials.gov/ under **NCT00950274.**

Our study examines the differences in rates of incidence of the postoperative cardiac arrhythmias in those remaining 82 Patients.

Inclusion and exclusion criteria:

All patients included in the randomized PERFECT trial phase III [1] were to be investigated. From those 82 Patients, 5 could not to be categorized whether they received active or placebo treatment and they were excluded from the whole study. The remaining 77 Patients (67 males, and 10 females) were subdivided depending on the type of treatment into two groups placebo (40 patients) and active treatment (37 patients) groups. They were also to be subdivided depending on the efficacy of the treatment into responder (39 patients) and non-responder (25 patients) groups. Such effect was determined depending on the postoperative increase of the left ventricular ejection fraction by more than 5%. In this subdivision 13 more patients were dropped out as they do not possess sufficient data on the postoperative development of the ejection fraction.

Stem cell Control

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Placebo	40	48,8	51,9	51,9
	Stemcell	37	45,1	48,1	100,0
	Total	77	93,9	100,0	
Missing	System	5	6,1		
Total		82	100,0		

Table 0-0- 1

Response / Non-Responder

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	25	30,5	39,1	39,1
	1	39	47,6	60,9	100,0
	Total	64	78,0	100,0	
Missing	System	18	22,0		
Total		82	100,0		

Table 0-0- 2

Stem cell Control * Response Crosstabulation

			Response		Total
			Non-responder (NRG)	Responder (RG)	
StemcellControl	Placebo (PG)	Count	14	20	34
		% within Response	56.0%	51.3%	53.1%
	Stemcell (SCG)	Count	11	19	30
		% within Response	44.0%	48.7%	46.9%
Total		Count	25	39	64
		% within Response	100.0%	100.0%	100.0%

Table 0-0- 3

Collected data:

The data representing the cardiac arrhythmias were collected in several settings. In this study the Holter ECG data collected in the preoperative visit (V1), the 10th postoperative day visit (V3) and 6 months postoperative visit (V5) will be investigated. Also, any cardiac arrhythmia documented during the In-hospital-Stay (IHS) up to 6 months postoperative will be included in our analysis.

Data Statistics										
		V1_VES_prcnt	V1_SVES_prcnt	V1_VT	V3_VES_prcnt	V3_SVES_prcnt	V3_VT	V5_VES_prcnt	V5_SVES_prcnt	DeltaEF
N	Valid	82	82	82	62	62	82	68	68	64
	Missing	0	0	0	20	20	0	14	14	18
Mean		1.8506	0.3026	0.04	1.3373	0.7165	0.05	1.4579	0.8034	9.56
Median		0.5000	0.1000	0.00	0.3000	0.1000	0.00	0.3550	0.1000	8.00
Mode		0.00	0.00	0	0.00	0.00	0	,00[a]	0.00	11
Std. Deviation		4.05190	0.66055	0.189	2.57059	1.53882	0.217	2.58363	1.70567	11.262
Minimum		0.00	0.00	0	0.00	0.00	0	0.00	0.00	-13
Maximum		23.40	4.99	1	11.60	7.62	1	12.60	8.50	42
Percentiles	25	0.1000	0.0100	0.00	0.1000	0.0000	0.00	0.1000	0.0048	2.00
	50	0.5000	0.1000	0.00	0.3000	0.1000	0.00	0.3550	0.1000	8.00
	75	1.4250	0.3000	0.00	1.3350	0.7075	0.00	1.5000	0.7100	16.75

Table 0-0- 4

Investigation devices:

ECG:

The electrocardiogram (ECG) is the recording of the electrical activities of all heart muscle fibers using an electrocardiograph (also called ECG device). The recording process is called electrocardiography. The electrocardiogram is also known as the heart voltage curve.

Every contraction of the heart muscle is preceded by an electrical excitation, which normally comes from the sinus node. It runs to the other heart muscle cells via the heart's own electrical conduction system made up of specialized heart muscle cells. These electrical voltage changes in the heart can be measured on the body surface and recorded over time. The result is a recurring picture of the heart electrical action. The ECG can be used to make a variety of statements about the properties and health of the heart. It should be noted that the surface ECG only shows the electrical activity of the heart muscle, but does not reflect the actual ejection performance.

Holter ECG:

The recording of the electrocardiogram over a longer period of time usually 24 hours is referred to as a long-term ECG. After its inventor, Norman J. Holter, this method is also known as the Holter ECG.

The long-term ECG is used to assess the extent of cardiac arrhythmias and also to detect rare arrhythmias. The most common is the continuous ECG recording over 24 hours with the help of portable recording devices, which can also reveal circulatory disorders of the heart.

Statistical methods:

The statistical analysis and interpretation of data were performed using the "**IBM SPSS Statistics for Microsoft windows version 27**" and "**Microsoft Excel**" software.

Methods of calculations

All target values are tested with suitable tests (2-tailed) at the 95% safety level.

1. **For categorical or nominal target variables using the chi-squared test (2-tailed) at the 95% level.**
   The chi squared test belongs to the group of likelihood ratio tests. This test compares the frequencies observed in the observed distribution with the expected frequencies within the framework of the uniform distribution assumed in the null hypothesis. The deviations from observed and expected frequencies are squared, added up as a weighted quotient and compared with the quantiles in the Chi-Square distribution table. These quantiles are also referred to as the critical value and correspond to the selected significance level. If the value of the chi squared test statistic is greater than the critical value from the distribution table, the null hypothesis is rejected in favor of the alternative hypothesis and the data cannot be said to be uniformly distributed.

2. **For metric values with the T-Test (2-tailed) at the 95% level.**
   For one or more cardinally scaled features, the T test compares the deviation of the mean values from one another, optionally two features from one another or one feature to a given value. If this exceeds the determined confidence range, the difference can be assumed to be significant. The T-test applies to homogeneity of variance (this is checked by the Levene's test). At the same time, the Welch test is also tested. Additionally, the non-parametric Wilcoxon's test is used to see whether solid results are achieved.

As further variables (Age, Gender, Time) are checked, the following models are used:

1. **ANOVA analysis of variance - metric target variable (MANOVA = with repeated measurements).**
   An analysis of variance can be used to examine the influence of independent variables on a dependent variable. The aim is to filter out differences between the respective mean values of the independent variables. The analysis of variance, also known as ANOVA, checks whether there are statistically significant differences between more than two groups.

2. **MANOVA multivariate analysis of variance**
   It is a procedure for comparing multivariate sample means. It is used when there are two or more dependent variables and is often followed by significance tests involving individual dependent variables separately.

3. **Logistic regression (binary target: yes, no).**
   Logistic regression models are used to examine the dependence of nominal dependent variables (e.g. response yes / no) on other independent variables that can have any measurement level. In addition to the significance level the parameters, the exp (B) should be considered. This is the odds ratio.

Results

Each type of cardiac arrhythmia (SVES, VES and VT) was documented using Holter ECG in every examination visit and cross checked, analyzed and compared in all subgroups.

Each type of documented cardiac arrhythmia (SVES, VES, SVT and VT) during the in-hospital stay for up to 6 Months was also cross checked, analyzed and compared in all subgroups.

The following abbreviations will be used to facilitate the discussion:

Abbreviations of Visits:

- V1: preoperative visit.
- V3: 10^{th} day or discharge day (the sooner of both)
- V5: 180 days postoperative.

Abbreviations of groups' names:

- Placebo group (n=40): PG
- Stem cell group (n=37): SCG
- Responder group (n=39): RG
- Non-responder group (n=25): NRG.
    - Responder subgroup of Placebo group (n=20): RG-PG
    - Non-Responder subgroup of Placebo group (n=14): NRG-PG
    - Responder subgroup of stem cell group (n=19): RG-SCG
    - Non-Responder subgroup of stem cell group (n=11): NRG-SCG

Abbreviations of significance values of tests:

- T-Test (2-tailed) (equal variance assumed): P1
- Welch's T-Test (2-tailed) (equal variance not assumed): P2
- Wilcoxon's Test (2-tailed): P3
- Pearson Chi-Square test (2-tailed): P4

Abbreviations of statistical values:

- Mean: μ
- Standard Deviation: SD
- Standard Error: SE

The significant P values will be written in bold and noted with:

- {sig.} for significant
- {n.sig.} for non-significant

Preoperative visit (V1)

VES

Preoperative (V1) VES percentage in Holter ECG was plotted in all 4 groups. The following demonstrates a comparison in the VES percentages. It shows a higher mean percentage in the stem cell group than in placebo group (SCG-μ=2.5535, SCG-SD=5.26948, SCG-SE=0.86630, PG-μ=1.0385, PG-SD=2.29054, PG-SE=0.36217, P1=0.102, P2=0.113, P3=0.064) {n.sig.}. The comparison between the responder and non-responder groups shows a higher mean percentage in the responder group than in the non-responder group (RG-μ=2.0705, RG-SD=4.2261, RG-SE=0.6767, NRG-μ=1.9920, NRG-SD=4.7232, NRG-SE=0.9446, P1=0.9450, P2=0.9464, P3=0.962) {n.sig.}. As we examined the placebo and stem cell groups separately the mean percentage was higher in the responder subgroup of placebo group (RG-PG-μ=1.43100, RG-PG-SD=3.04382, RG-PG-SE=0.68062, NRG-PG-μ=0.75429, NRG-PG-SD=1.19135, NRG-PG-SE=0.31840, P1=0.437, P2=0.376, P3=0.430) {n.sig.} and stem cell group (RG-SCG-μ=2.7437, RG-SCG-SD=5.19531, RG-SCG-SE=1.19189, NRSCG-μ=3.5673, RG-SCG-SD=6.84257, RG-SCG-SE=2.06311, P1=0.712, P2=0.734, P3=0.490) {n.sig.}.

The following graphs shows a comparison of median values of VES in V1 within all groups and subgroups.

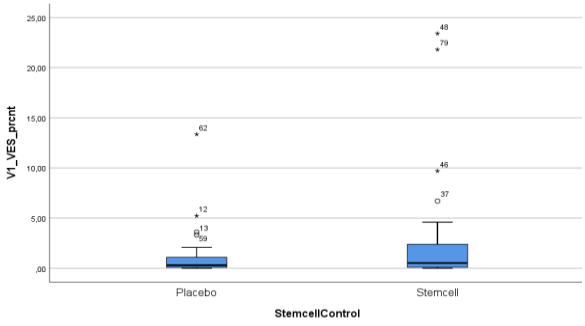

Fig. 1-1-1 Median VES arrhythmias in V1 in the whole population subdivided into placebo group und stem cell groups.

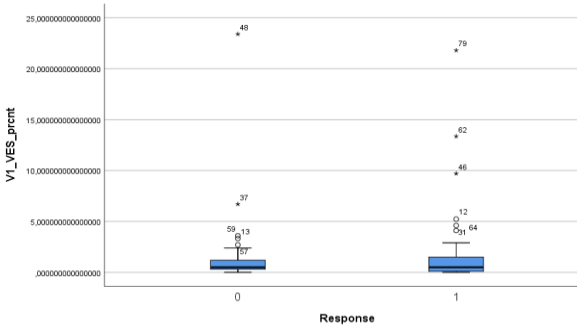

Fig. 1-1-2 Median VES arrhythmias in V1 in the whole population subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

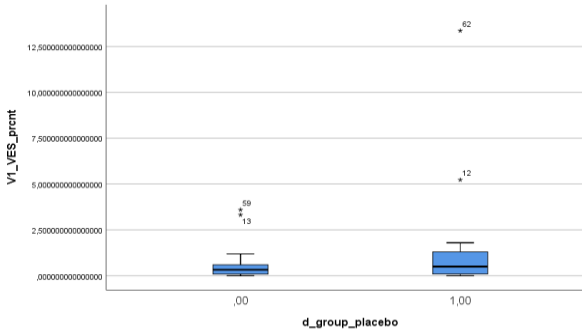

Fig. 1-1-3 Median VES arrhythmias in V1 in the placebo group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

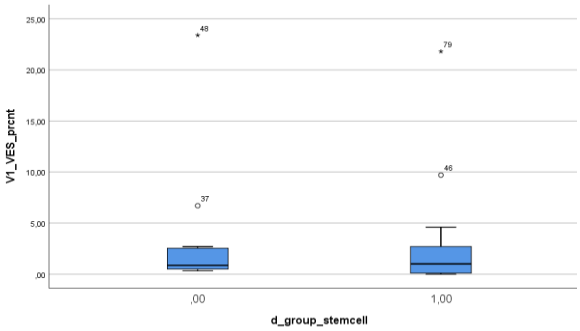

Fig. 1-1-4 Median VES arrhythmias in V1 in the stem cell group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

SVES

The preoperative (V1) SVES percentage in Holter ECG was also plotted in all 4 groups. The following demonstrates a comparison in the SVES percentages. It shows a higher mean percentage in the stem cell group (SCG-μ=0.4106, SCG-SD=0.92607, SCG-SE=0.15224, PG-μ=0.2344, PG-SD=0.30056, PG-SE=0.04752, P1=0.258, P2=0.275, P3=0.794) {n.sig.}. The comparison between the responder and non-responder groups shows a lower mean percentage in the responder group (RG-μ=0.2252, RG-SD=0.32163, RG-SE=0.05150, NRG-μ=0.5638, NRG-SD=1.08635, NRG-SE=0.21727, P1=0.072, P2=0.141, P3=0.064) {n.sig.}. As we examined the placebo and stem cell groups separately a higher mean percentage was shown in the responder subgroup of the placebo group (RG-PG-μ=0.3235, RG-PG-SD=0.37290, RG-PG-SE=0.08338, NRG-PG-μ=0.1504, NRG-PG-SD=0.16496, NRG-PG-SE=0.04409, P1=0.114, P2=0.077, P3=0.420) {n.sig.} but a significant lower mean percentage was demonstrated in the responder subgroup of the stem cell group (RG-SCG-μ=0.1217, RG-SCG-SD=0.22261, RG-SCG-SE=0.05107, NRG-SCG-μ=1.0900, NRG-SCG-SD=1.50105, NRG-SCG-SE=0.45258, **P1=0.009**, P2=0.059, **P3=0.001**) {sig.}.

The following graphs shows a comparison of median values of SVES in V1 within all groups and subgroups.

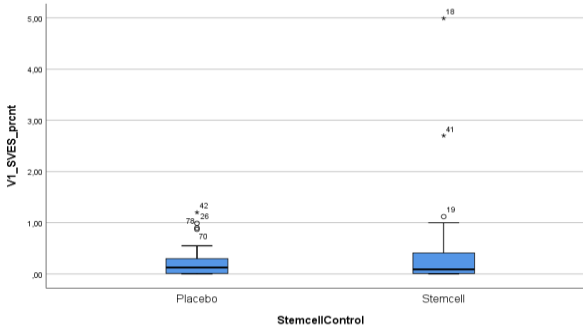

Fig. 1-2-1 Median SVES arrhythmias in V1 in the whole population subdivided into placebo group und stem cell groups.

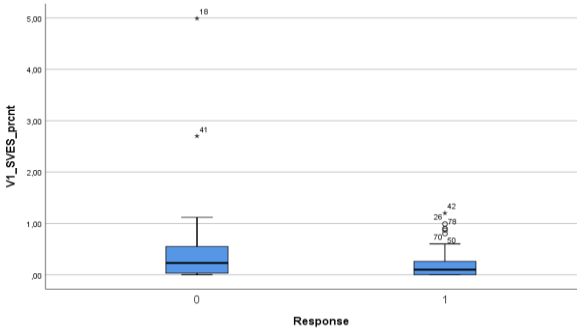

Fig. 1-2-2 Median SVES arrhythmias in V1 in the whole population subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

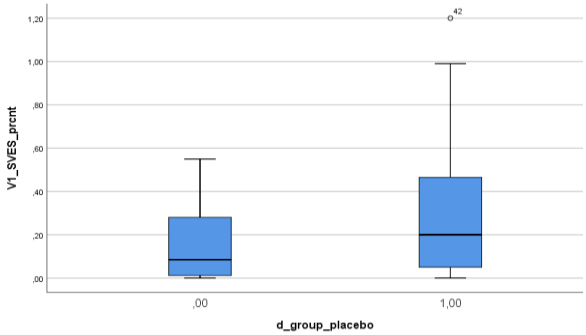

Fig. 1-2-3 Median SVES arrhythmias in V1 in the placebo group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

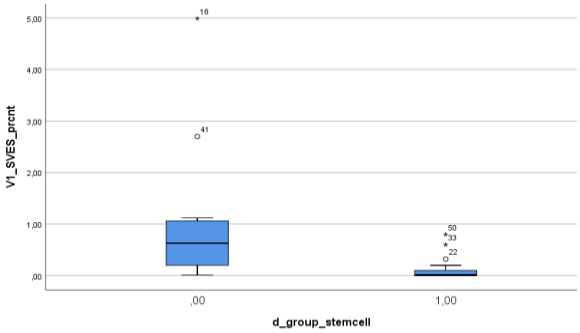

Fig. 1-2-4 Median SVES arrhythmias in V1 in the stem cell group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

VT

The preoperative (V1) VT data in Holter ECG was collected as a yes/no parameter. Therefore, it was plotted as count of patients who had developed VT in all 4 groups. The following [Fig.1-3-1] demonstrates a comparison in the patients count who had developed VT between the Placebo and stem cell groups in the whole cohort. It shows a higher count in the stem cell group (SCG=2, PG=1, P4=0.510) {n.sig.}. The comparison between the responder and non-responder groups shows a lower count in the responder group as showed in [Fig. 1-3-2] (RG=1, NRG=2, P4=0.315) {n.sig.}. As we examined the placebo [Fig.1-3-3] and stem cell [Fig.1-3-4] groups separately a higher count was shown in the responder subgroup of the placebo group as in the later subgroup no patient developed VT (RG-PG=1, NRG-PG=0, P4=0.396) {n.sig.} whereas a lower percentage was demonstrated in the responder subgroup of the stem cell group as no patient in the later subgroup developed VT (RG-SCG=0, NRG-SCG=2, P4=0.054) {n.sig.}.

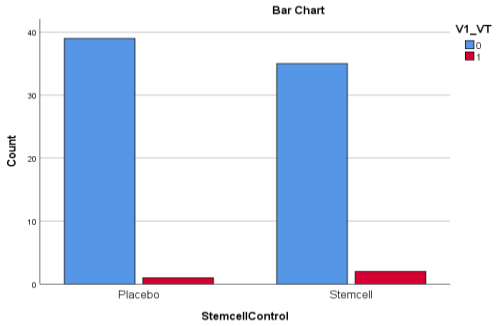

Fig. 1-3-1 VT arrhythmias in V1 in the whole population subdivided into placebo group und stem cell groups.

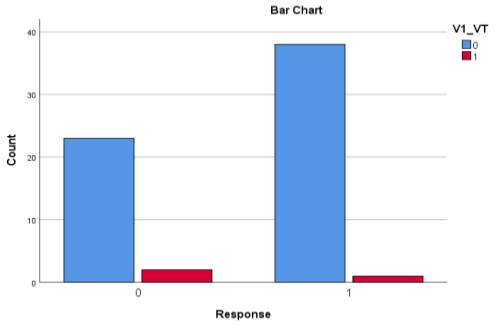

Fig. 1-3-2 VT arrhythmias in V1 in the whole population subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

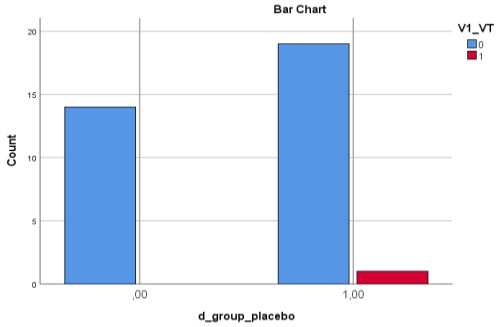

Fig. 1-3-3 VT arrhythmias in V1 in the placebo group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

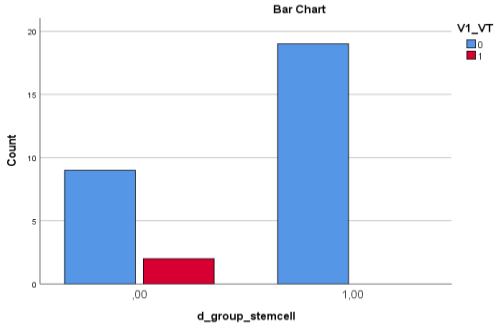

Fig. 1-3-4 VT arrhythmias in V1 in the stem cell group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

10th postoperative day Visit (V3)

VES

10th postoperative day Visit (V3) VES percentage in Holter ECG was analyzed again in all 4 groups. The following demonstrates a comparison in the VES percentages. It shows a lower mean percentage in the stem cell group (SCG-μ=1.5644, SCG-SD=3.06229, SCG-SE=0.54134, PG-μ=1.0950, PG-SD=1.93842, PG-SE=0.35390, P1=0.477, P2=0.471, P3=0.558) {n.sig.}. The comparison between the responder and non-responder groups shows also a significantly lower mean percentage in the responder group (RG-μ=1.0885, RG-SD=2.33414, RG-SE=0.40030, NRG-μ=2.0052, NRG-SD=3.16553, NRG-SE=0.69077, P1=0.223, P2=0.259, **P3=0.039**) {sig.}. As we examined the placebo and stem cell groups separately a lower mean percentage was shown in the responder subgroups in both groups. In Placebo group (RG-PG-μ=0.6460, RG-PG-SD=0.65934, RG-PG-SE=0.17024, NRG-PG-μ=2.0482, NRG-PG-SD=2.9364, NRG-PG-SE=0.88534, P1=0.084, P2=0.149, P3=0.221) {n.sig.} and stem cell group (RG-SCG-μ=1.4379, RG-SCG-SD=3.05912, RG-SCG-SE=0.70181, NRG-SCG-μ=1.9580, NRG-SCG-SD=3.56133, NRG-SCG-SE=1.12619, P1=0.684, P2=0.700, P3=0.089) {n.sig.}.

The following graphs shows a comparison of median values of VES in V3 within all groups and subgroups.

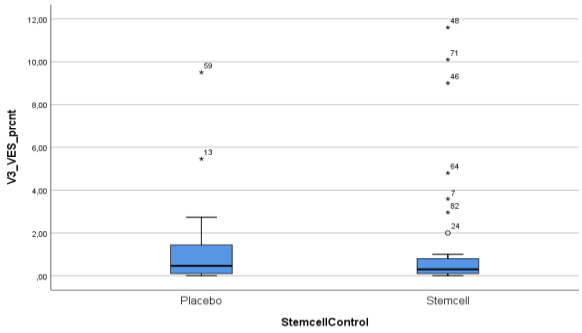

Fig. 2-1-1 Median VES arrhythmias in V3 in the whole population subdivided into placebo group und stem cell groups.

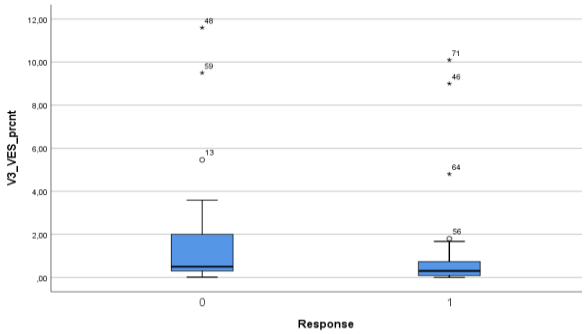

Fig. 2-1-2 Median VES arrhythmias in V3 in the whole population subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

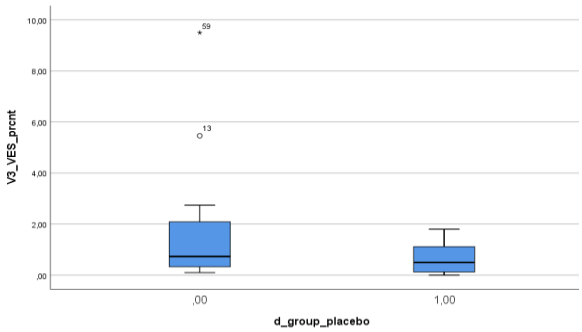

Fig. 2-1-3 Median VES arrhythmias in V3 in the placebo group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

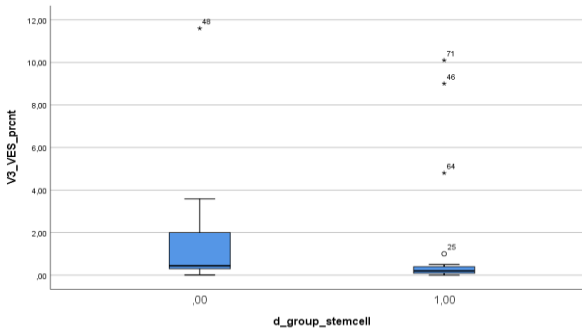

Fig. 2-1-4 Median VES arrhythmias in V3 in the stem cell group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

SVES

10th postoperative day Visit (V3) SVES percentage in Holter ECG was also analyzed in all 4 groups. The following demonstrates a comparison in the SVES percentages. It shows a higher mean percentage in the stem cell group (SCG-μ=0.7561, SCG-SD=1.39878, SCG-SE=0.24727, PG-μ=0.6743, PG-SD=1.69875, PG-SE=0.31015, P1=0.836, P2=0.837, P3=0.280) {n.sig.}. The comparison between the responder and non-responder groups shows a lower mean percentage in the responder group with a significant result (RG-μ=0.3281, RG-SD=0.50957, RG-SE=0.08739, NRG-μ=1.5671, NRG-SD=2.37087, NRG-SE=0.51737, **P1=0.005**, **P2=0.028**, **P3=0.030**) {sig.}. As we examined the placebo and stem cell groups separately a lower mean percentage was shown in the responder subgroup of the placebo group (RG-PG-μ=0.2973, RG-PG-SD=0.50307, RG-PG-SE=0.12989, NRG-PG-μ=1.4117, NRG-PG-SD=2.65501, NRG-PG-SE=0.80052, P1=0.123, P2=0.198, P3=0.429) {n.sig.} and a significantly lower mean percentage was demonstrated in the responder subgroup of the stem cell group (RG-SCG-μ=0.3524, RG-SCG-SD=0.52706, RG-SCG-SE=0.12092, NRG-SCG-μ=1.7380, NRG-SCG-SD=2.14403, NRG-SCG-SE=0.67800, **P1=0.012**, P2=0.073, **P3=0.021**) {sig.}.

The following graphs shows a comparison of median values of SVES in V3 within all groups and subgroups.

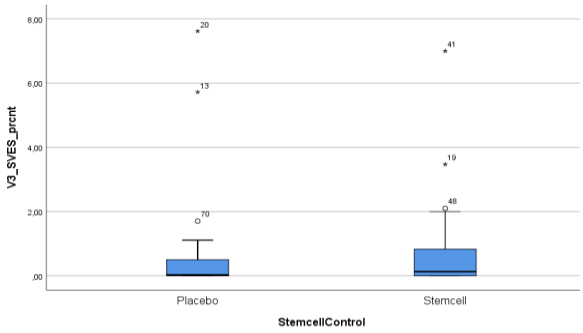

Fig. 2-2-1 Median SVES arrhythmias in V3 in the whole population subdivided into placebo group und stem cell groups.

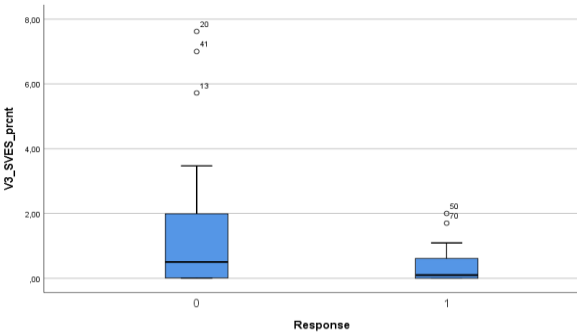

Fig. 2-2-2 Median SVES arrhythmias in V3 in the whole population subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

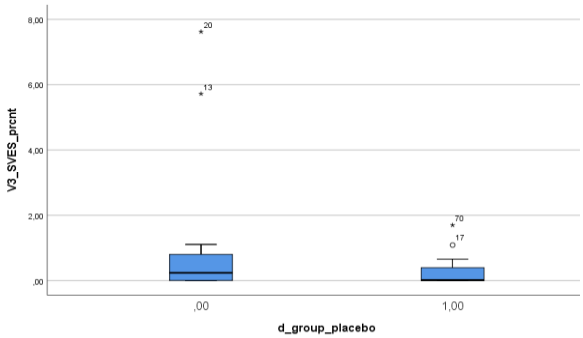

Fig. 2-2-3 Median SVES arrhythmias in V3 in the placebo group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

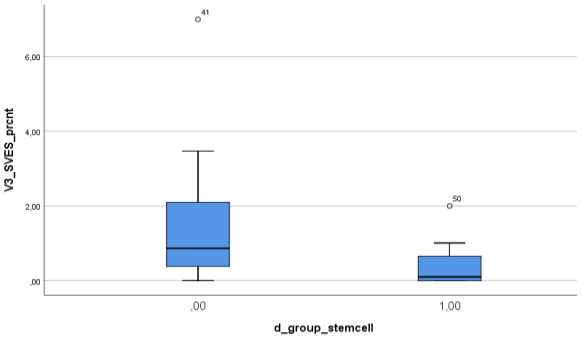

Fig. 2-2-4 Median SVES arrhythmias in V3 in the stem cell group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

VT

10th postoperative day Visit (V3) VT data in Holter ECG was collected also as a yes/no parameter. Therefore, it was plotted as count of patients who had developed VT in all 4 groups. The following [Fig.2-3-1] demonstrates a comparison in the patients count who had developed VT between the Placebo and stem cell groups in the whole cohort (PG=2, SCG=2, P4=0.936) {n.sig.}. It shows a higher count in the stem cell group. The comparison between the responder and non-responder groups shows a lower count in the responder group [Fig. 2-3-2] (RG=1, NRG=2, P4=0.315) {n.sig.}. As we examined the placebo [Fig.2-3-3] and stem cell [Fig.2-3-4] groups separately a similar count was shown in the responder and non-responder subgroups of the placebo group (RG-PG=1, =1, P4=0.794) {n.sig.} but a higher count was demonstrated in the responder subgroup of the stem cell group as no patient in this subgroup developed VT (RG-SCG=0, NRG-SCG=1, P4=0.181) {n.sig.}.

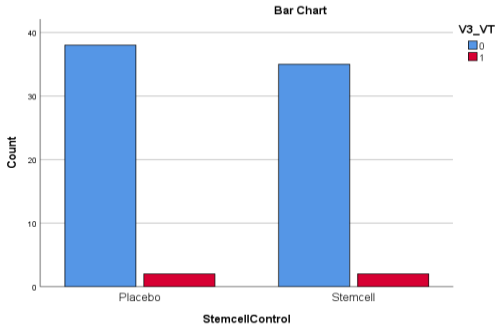

Fig. 2-3-1 VT arrhythmias in V3 in the whole population subdivided into placebo group und stem cell groups.

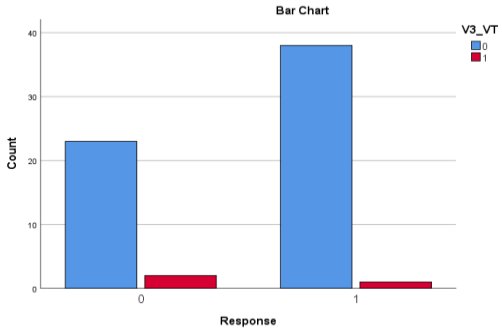

Fig. 2-3-2 VT arrhythmias in V3 in the whole population subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

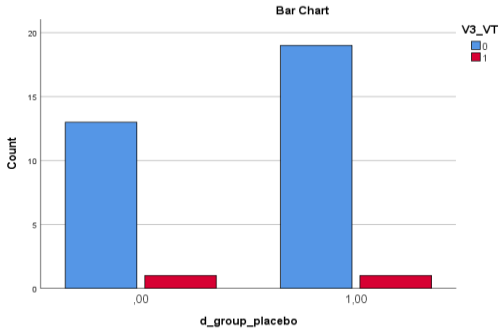

Fig. 2-3-3 VT arrhythmias in V3 in the placebo group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

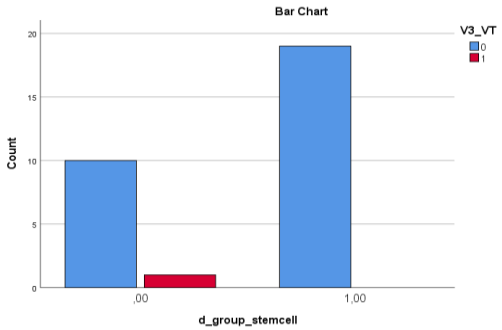

Fig. 2-3-4 VT arrhythmias in V3 in the stem cell group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

6 Month Visit (V5)

VES

6 Month Visit (V5) VES percentage in Holter ECG was plotted again in all 4 groups. The following demonstrates a comparison in the VES percentages. It shows a significantly higher mean percentage in the stem cell group (SCG-μ=2.3366, SCG-SD=3.34677, SCG-SE=0.62148, PG-μ=0.8046, PG-SD=1.57761, PG-SE=0.25262, **P1=0.014**, **P2=0.028**, **P3=0.020**) {sig.}. The comparison between the responder and non-responder groups shows a lower mean percentage in the responder group] (RG-μ=1.0466, RG-SD=1.91071, RG-SE=0.30996, NRG-μ=1.9329, NRG-SD=3.27687, NRG-SE=0.66889, P1=0.183, P2=0.238, P3=0.354) {n.sig.}. As we examined the placebo and stem cell groups separately a higher mean percentage was shown in the responder subgroup in the placebo group (RG-PG-μ=0.6530, RG-PG-SD=1.02404, RG-PG-SE=0.22898, NRG-PG-μ=0.7386, NRG-PG-SD=1.52676, NRG-PG-SE=0.40804, P1=0.846, P2=0.857, P3=0.471) {n.sig.} while in the stem cell group a significantly lower percentage was demonstrated in the same subgroup (RG-SCG-μ=1.4839, RG-SCG-SD=2.52767, RG-SCG-SE=0.59578, NRG-SCG-μ=3.6050, NRG-SCG-SD=4.33000, NRG-SCG-SE=1.36927, P1=0.112, P2=0.180, **P3=0.039**) {sig.}.

The following graphs shows a comparison of median values of VES in V6 within all groups and subgroups.

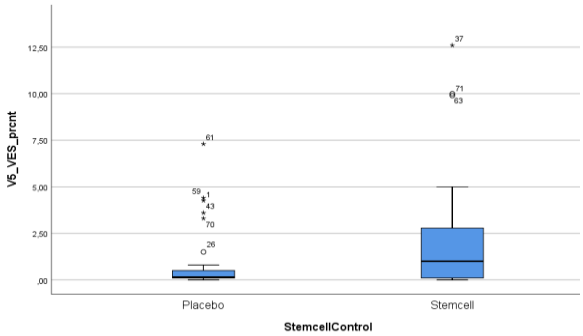

Fig. 3-1-1 Median VES arrhythmias in V5 in the whole population subdivided into placebo group und stem cell groups.

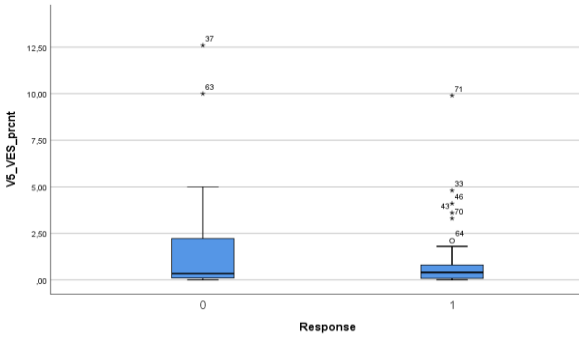

Fig. 3-1-2 Median VES arrhythmias in V5 in the whole population subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

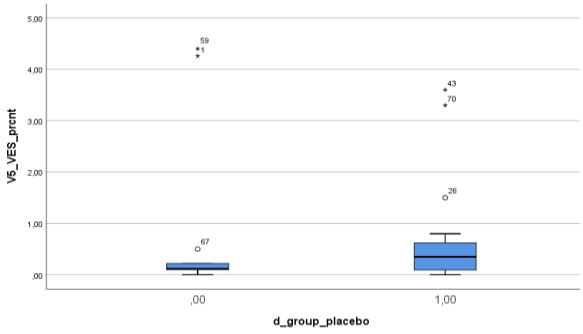

Fig. 3-1-3 Median VES arrhythmias in V5 in the placebo group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

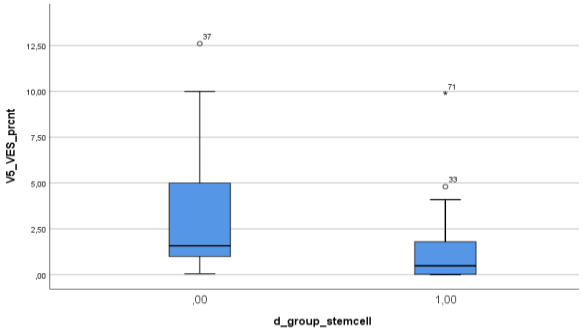

Fig. 3-1-4 Median VES arrhythmias in V5 in the stem cell group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

SVES

6 Month Visit (V5) SVES percentage in Holter ECG was also plotted in all 4 groups. The following demonstrates a comparison in the SVES percentages. It shows a significantly higher mean percentage in the stem cell group (SCG-μ=1.4306, SCG-SD=2.28251, SCG-SE=0.42385, PG-μ=0.3370, PG-SD=0.87595, PG-SE=0.14026, **P1=0.008**, **P2=0.020**, P3=0.168) {sig.}. The comparison between the responder and non-responder groups shows a lower mean percentage in the responder group (RG-μ=0.6496, RG-SD=1.56589, RG-SE=0.25402, NRG-μ=1.0222, NRG-SD=1.88459, NRG-SE=0.38469, P1=0.403, P2=0.424, P3=0.247) {n.sig.}. As we examined the placebo and stem cell groups separately a higher mean percentage was shown in the responder subgroup of the placebo group (RG-PG-μ=0.3290, RG-PG-SD=0.55944, RG-PG-SE=0.12510, NRG-PG-μ=0.0823, NRG-PG-SD=0.08591, NRG-PG-SE=0.02296, P1=0.113, P2=0.066, P3=0.153) {n.sig.} but a significantly lower mean percentage was demonstrated in the responder subgroup of the stem cell group (RG-SCG-μ=1.0059, RG-SCG-SD=2.17523, RG-SCG-SE=0.51271, NRG-SCG-μ=2.3380, NRG-SCG-SD=2.40165, NRG-SCG-SE=0.75947, P1=0.146, P2=0.164, **P3=0.018**) {sig.}.

The following graphs shows a comparison of median values of SVES in V6 within all groups and subgroups.

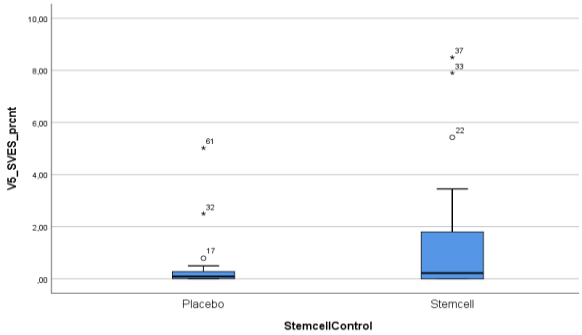

Fig. 3-2-1 Median SVES arrhythmias in V5 in the whole population subdivided into placebo group und stem cell groups.

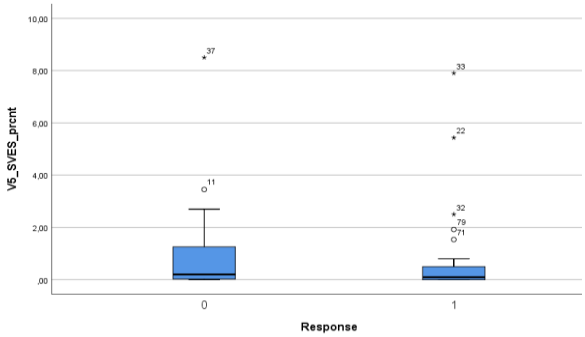

Fig. 3-2-2 Median SVES arrhythmias in V5 in the whole population subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

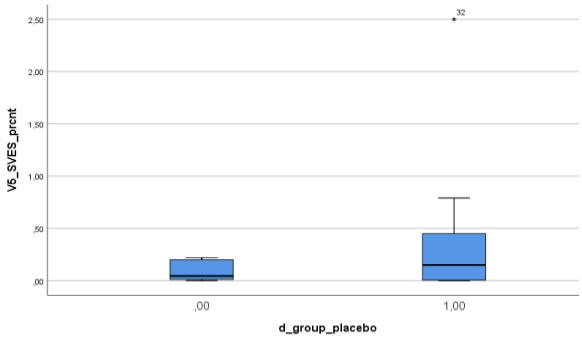

Fig. 3-2-3 Median SVES arrhythmias in V5 in the placebo group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

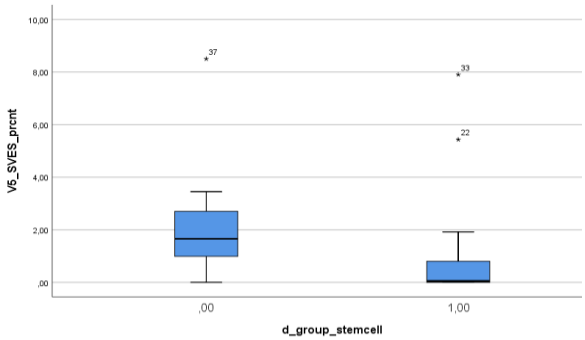

Fig. 3-2-4 Median SVES arrhythmias in V5 in the stem cell group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

VT

6 Month Visit (V5) VT data in Holter ECG was collected also as a yes/no parameter. Therefore, it was plotted as count of patients who had developed VT in all 4 groups. The following [Fig.3-3-1] demonstrates a comparison in the patients count who had developed VT between the Placebo and stem cell groups in the whole cohort. It shows a higher count in the placebo group (PG=3, SCG=2, P4=0.709) {n.sig.}. The comparison between the responder and non-responder groups shows the same count in the responder as well as non-responder group as showed in [Fig. 3-3-2] (RG=2, NRG=2, P4=0.643) {n.sig.}. As we examined the placebo [Fig.3-3-3] and stem cell [Fig.3-3-4] groups separately a higher count was shown in the responder subgroup of the placebo group as no patients in the non-responder subgroup developed VT (RG-PG=2, NRG-PG=0, P4=0.223) {n.sig.}. The opposite was shown in the stem cell group where a higher percentage was demonstrated in the non-responder subgroup and no patient in the responder subgroup developed VT (RG-SCG=0, NRG-SCG=2, P4=0.054) {n.sig.}.

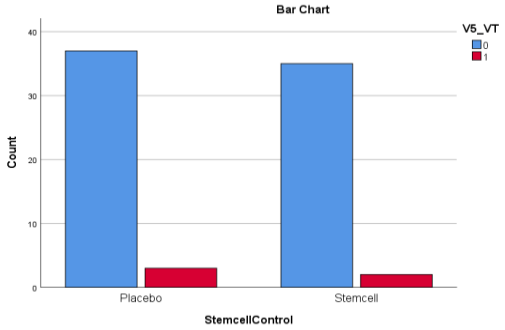

Fig. 3-3-1 VT arrhythmias in V5 in the whole population subdivided into placebo group und stem cell groups.

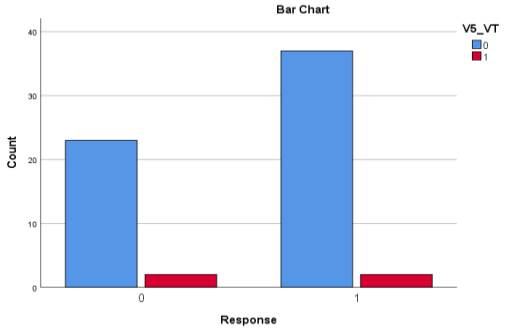

Fig. 3-3-2 VT arrhythmias in V5 in the whole population subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

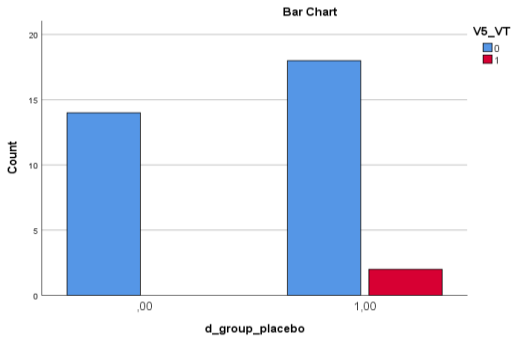

Fig. 3-3-3 VT arrhythmias in V5 in the placebo group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

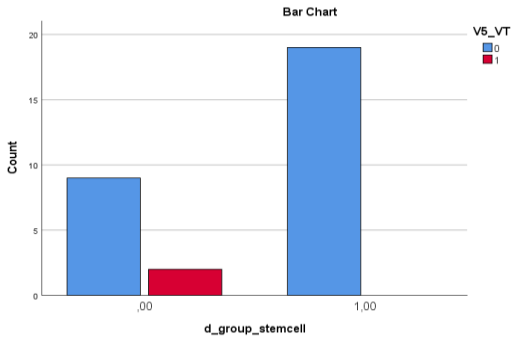

Fig. 3-3-4 VT arrhythmias in V5 in the stem cell group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

Progression of arrhythmia with time

MANOVA was used here to represent the progression through time of VES and SVES documented by Holter monitor in the three visits. This was also applied for all 4 groups. VT was documented as yes/no values and the model actually expects a metric target size.

VES

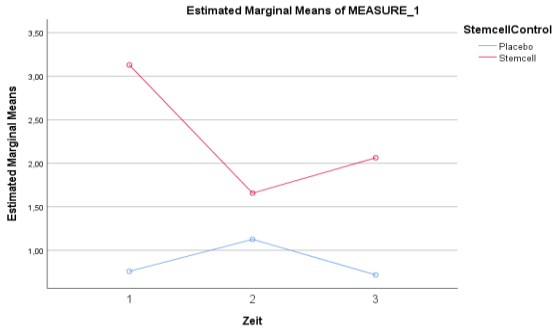

Fig. 4-1-1 progression of VES arrhythmias in relation to time starting from V1 until V5 in the whole population subdivided into placebo group und stem cell groups. (Table 1-1-1)

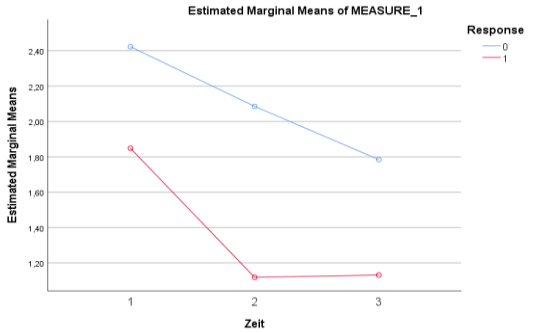

Fig. 4-1-2 progression of VES arrhythmias in relation to time starting from V1 until V5 in the whole population subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder (Table 1-1-2)

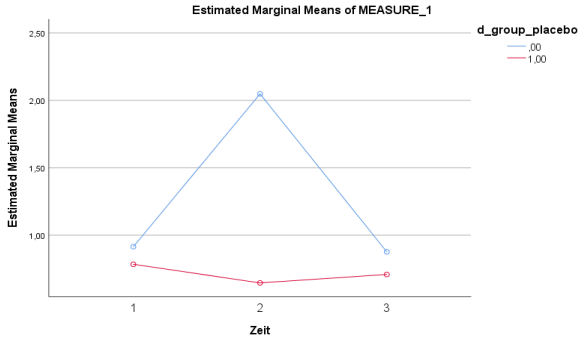

Fig. 4-1-3 progression of VES arrhythmias in relation to time starting from V1 until V5 in the placebo group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder (Table 1-1-3)

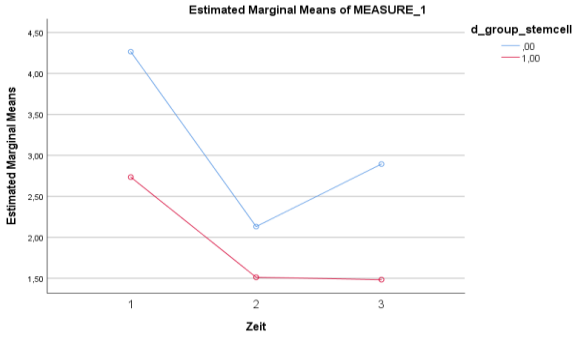

Fig. 4-1-4 progression of VES arrhythmias in relation to time starting from V1 until V5 in the stem cell group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder (Table 1-1-4)

Parameter Estimates VES (Stem cell vs. Placebo)								
Dependent Variable		B	Std. Error	t	Sig.	95% Confidence Interval		Partial Eta Squared
						Lower Bound	Upper Bound	
V1_VES_prcnt	Intercept	3.129	0.805	3.886	0.000	1.516	4.743	0.215
	[StemcellControl=0]	-2.371	1.129	-2.100	0.040	-4.633	-0.108	0.074
	[StemcellControl=1]	0[a]						
V3_VES_prcnt	Intercept	1.657	0.504	3.288	0.002	0.647	2.667	0.164
	[StemcellControl=0]	-0.531	0.707	-0.752	0.455	-1.948	0.885	0.010
	[StemcellControl=1]	0[a]						
V5_VES_prcnt	Intercept	2.063	0.442	4.662	0.000	1.176	2.950	0.283
	[StemcellControl=0]	-1.345	0.620	-2.169	0.034	-2.588	-0.102	0.079
	[StemcellControl=1]	0[a]						

Table 1-1-1

Parameter Estimates VES (Responder vs. Non-Responder)								
Dependent Variable		B	Std. Error	t	Sig.	95% Confidence Interval		Partial Eta Squared
						Lower Bound	Upper Bound	
V1_VES_prcnt	Intercept	1.848	0.793	2.330	0.024	0.256	3.441	0.096
	[Response=0]	0.574	1.291	0.445	0.658	-2.018	3.167	0.004
	[Response=1]	0[a]						
V3_VES_prcnt	Intercept	1.118	0.473	2.365	0.022	0.169	2.068	0.099
	[Response=0]	0.967	0.770	1.256	0.215	-0.579	2.513	0.030
	[Response=1]	0[a]						
V5_VES_prcnt	Intercept	1.132	0.425	2.660	0.010	0.278	1.985	0.122
	[Response=0]	0.653	0.692	0.943	0.350	-0.737	2.043	0.017
	[Response=1]	0[a]						

Table 1-1-2

Parameter Estimates VES (Responder vs. Non-Responder in placebo group)								
Dependent Variable		B	Std. Error	t	Sig.	95% Confidence Interval		Partial Eta Squared
						Lower Bound	Upper Bound	
V1_VES_prcnt	Intercept	0.784	0.344	2.278	0.032	0.074	1.494	0.178
	[d_group_placebo=,00]	0.131	0.529	0.247	0.807	-0.961	1.222	0.003
	[d_group_placebo=1,00]	0[a]						
V3_VES_prcnt	Intercept	0.646	0.506	1.276	0.214	-0.399	1.691	0.064
	[d_group_placebo=,00]	1.402	0.778	1.801	0.084	-0.205	3.009	0.119
	[d_group_placebo=1,00]	0[a]						
V5_VES_prcnt	Intercept	0.709	0.363	1.950	0.063	-0.041	1.459	0.137
	[d_group_placebo=,00]	0.168	0.559	0.300	0.767	-0.985	1.321	0.004
	[d_group_placebo=1,00]	0[a]						

Table 1-1-3

Parameter Estimates VES (Responder vs. Non-Responder in stem cell group)								
Dependent Variable		B	Std. Error	t	Sig.	95% Confidence Interval		Partial Eta Squared
						Lower Bound	Upper Bound	
V1_VES_prcnt	Intercept	2.735	1.437	1.903	0.069	-0.226	5.696	0.126
	[d_group_stemcell=,00]	1.531	2.490	0.615	0.544	-3.597	6.658	0.015
	[d_group_stemcell=1,00]	0[a]						
V3_VES_prcnt	Intercept	1.512	0.786	1.924	0.066	-0.107	3.131	0.129
	[d_group_stemcell=,00]	0.619	1.361	0.455	0.653	-2.185	3.423	0.008
	[d_group_stemcell=1,00]	0[a]						
V5_VES_prcnt	Intercept	1.484	0.718	2.067	0.049	0.005	2.962	0.146
	[d_group_stemcell=,00]	1.411	1.243	1.134	0.267	-1.150	3.971	0.049
	[d_group_stemcell=1,00]	0[a]						

Table 1-1-4

SVES

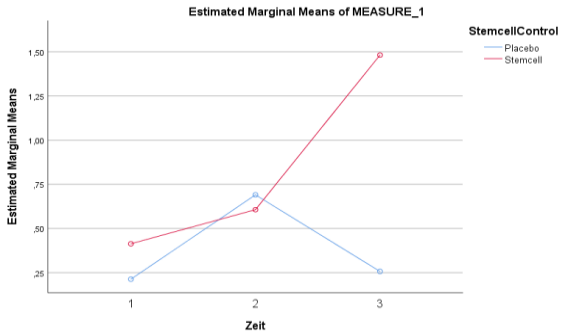

Fig. 4-2-1 progression of SVES arrhythmias in relation to time starting from V1 until V5 in the whole population subdivided into placebo group und stem cell groups. (Table 1-2-1)

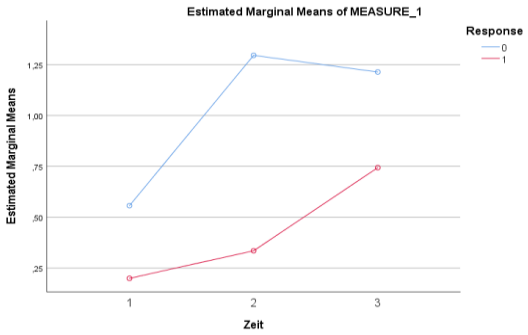

Fig. 4-2-2 progression of SVES arrhythmias in relation to time starting from V1 until V5 in the whole population subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder (Table 1-2-2)

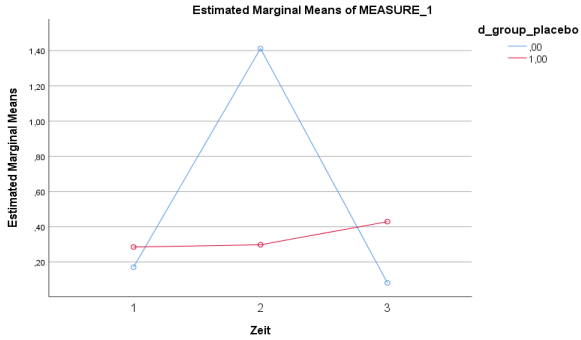

Fig. 4-2-3 progression of SVES arrhythmias in relation to time starting from V1 until V5 in the placebo group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder (Table 1-2-3)

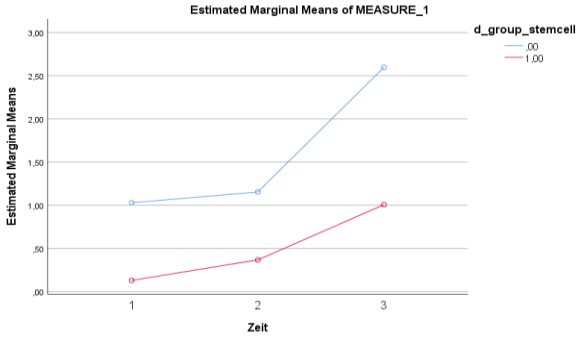

Fig. 4-2-4 progression of SVES arrhythmias in relation to time starting from V1 until V5 in the stem cell group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder (Table 1-2-4)

Parameter Estimates SVES (Placebo vs. Stem cell)								
Dependent Variable		B	Std. Error	t	Sig.	95% Confidence Interval		Partial Eta Squared
						Lower Bound	Upper Bound	
V1_SVES_prcnt	Intercept	0.413	0.132	3.129	0.003	0.149	0.678	0.151
	[StemcellControl=0]	-0.200	0.185	-1.082	0.284	-0.572	0.171	0.021
	[StemcellControl=1]	0[a]						
V3_SVES_prcnt	Intercept	0.606	0.259	2.343	0.023	0.088	1.125	0.091
	[StemcellControl=0]	0.084	0.363	0.232	0.818	-0.643	0.811	0.001
	[StemcellControl=1]	0[a]						
V5_SVES_prcnt	Intercept	1.482	0.312	4.746	0.000	0.856	2.107	0.291
	[StemcellControl=0]	-1.225	0.438	-2.799	0.007	-2.102	-0.348	0.125
	[StemcellControl=1]	0[a]						

Table 1-2-1

Parameter Estimates SVES (Responder vs. Non-Responder)								
Dependent Variable		B	Std. Error	t	Sig.	95% Confidence Interval		Partial Eta Squared
						Lower Bound	Upper Bound	
V1_SVES_prcnt	Intercept	0.199	0.123	1.622	0.111	-0.047	0.446	0.049
	[Response=0]	0.357	0.200	1.784	0.080	-0.045	0.759	0.059
	[Response=1]	0[a]						
V3_SVES_prcnt	Intercept	0.335	0.231	1.449	0.153	-0.129	0.799	0.040
	[Response=0]	0.960	0.376	2.552	0.014	0.205	1.716	0.113
	[Response=1]	0[a]						
V5_SVES_prcnt	Intercept	0.744	0.314	2.369	0.022	0.113	1.374	0.099
	[Response=0]	0.470	0.511	0.920	0.362	-0.556	1.496	0.016
	[Response=1]	0[a]						

Table 1-2-2

Parameter Estimates SVES (Responder vs. Non-Responder in Placebo group)								
Dependent Variable		B	Std. Error	t	Sig.	95% Confidence Interval		Partial Eta Squared
						Lower Bound	Upper Bound	
V1_SVES_prcnt	Intercept	0.285	0.074	3.868	0.001	0.133	0.437	0.384
	[d_group_placebo=,00]	-0.114	0.113	-1.010	0.322	-0.348	0.119	0.041
	[d_group_placebo=1,00]	0[a]						
V3_SVES_prcnt	Intercept	0.297	0.453	0.656	0.518	-0.639	1.233	0.018
	[d_group_placebo=,00]	1.114	0.697	1.598	0.123	-0.325	2.553	0.096
	[d_group_placebo=1,00]	0[a]						
V5_SVES_prcnt	Intercept	0.429	0.123	3.494	0.002	0.175	0.682	0.337
	[d_group_placebo=,00]	-0.348	0.189	-1.843	0.078	-0.737	0.042	0.124
	[d_group_placebo=1,00]	0[a]						

Table 1-2-3

Parameter Estimates SVES (Responder vs. Non-Responder in stem cell group)								
Dependent Variable		B	Std. Error	t	Sig.	95% Confidence Interval		Partial Eta Squared
						Lower Bound	Upper Bound	
V1_SVES_prcnt	Intercept	0.128	0.209	0.615	0.544	-0.302	0.559	0.015
	[d_group_stemcell=,00]	0.900	0.362	2.487	0.020	0.155	1.646	0.198
	[d_group_stemcell=1,00]	0[a]						
V3_SVES_prcnt	Intercept	0.366	0.186	1.972	0.060	-0.016	0.749	0.135
	[d_group_stemcell=,00]	0.787	0.322	2.445	0.022	0.124	1.450	0.193
	[d_group_stemcell=1,00]	0[a]						
V5_SVES_prcnt	Intercept	1.006	0.530	1.899	0.069	-0.085	2.097	0.126
	[d_group_stemcell=,00]	1.592	0.918	1.735	0.095	-0.298	3.482	0.107
	[d_group_stemcell=1,00]	0[a]						

Table 1-2-4

Correlation delta-EF with delta-V5-V1

The next section analyses a parametric as well as non-parametric correlation between the progression of cardiac arrhythmia and the change of left ventricular function (LVEF) was examined using delta-EF and the difference in percentages of the cardiac arrhythmia between V5 and V1. It showed no correlation though.

The whole cohort

Parametric Correlation (Pearson):				
		DeltaEF	Diff_V1_V5_VES_prcnt	Diff_V1_V5_SVES_prcnt
DeltaEF	Pearson Correlation	1	0.107	-0.070
	Sig. (2-tailed)		0.410	0.588
	N	64	62	62
Diff_V1_V5_VES_prcnt	Pearson Correlation	0.107	1	0.060
	Sig. (2-tailed)	0.410		0.642
	N	62	62	62
Diff_V1_V5_SVES_prcnt	Pearson Correlation	-0.070	0.060	1
	Sig. (2-tailed)	0.588	0.642	
	N	62	62	62

Table 2-1- 1

Nonparametric Correlation (Spearman and Kendall Tau)					
			DeltaEF	Diff_V1_V5_VES_prcnt	Diff_V1_V5_SVES_prcnt
Kendall's tau_b	DeltaEF	Correlation Coefficient	1.000	-0.016	-0.068
		Sig. (2-tailed)		0.855	0.445
		N	64	62	62
	Diff_V1_V5_VES_prcnt	Correlation Coefficient	-0.016	1.000	0.109
		Sig. (2-tailed)	0.855		0.220
		N	62	62	62
	Diff_V1_V5_SVES_prcnt	Correlation Coefficient	-0.068	0.109	1.000
		Sig. (2-tailed)	0.445	0.220	
		N	62	62	62
Spearman's rho	DeltaEF	Correlation Coefficient	1.000	-0.017	-0.091
		Sig. (2-tailed)		0.898	0.483
		N	64	62	62
	Diff_V1_V5_VES_prcnt	Correlation Coefficient	-0.017	1.000	0.149
		Sig. (2-tailed)	0.898		0.248
		N	62	62	62
	Diff_V1_V5_SVES_prcnt	Correlation Coefficient	-0.091	0.149	1.000
		Sig. (2-tailed)	0.483	0.248	
		N	62	62	62

Table 2-1- 2

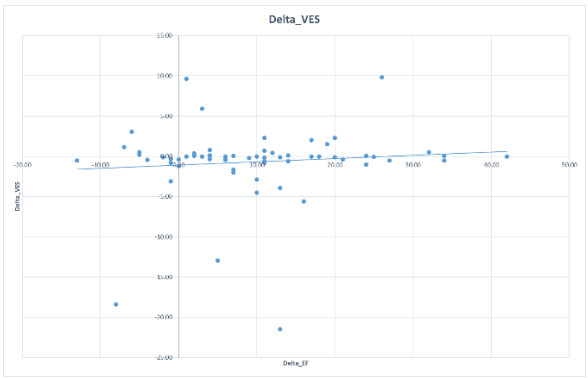

Fig. 5-1-1 a correlation between Delta EF and Delta VES in Holter monitor in the whole cohort

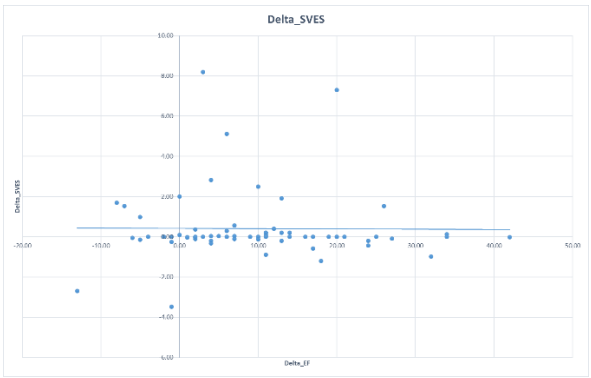

Fig. 5-1-2 a correlation between Delta EF and Delta SVES in Holter monitor in the whole cohort

The stem cell group

Parametric Correlation (Pearson):				
		DeltaEF	Diff_V1_V5_VES_prcnt	Diff_V1_V5_SVES_prcnt
DeltaEF	Pearson Correlation	1	0.141	-0.137
	Sig. (2-tailed)		0.476	0.486
	N	30	28	28
Diff_V1_V5_VES_prcnt	Pearson Correlation	0.141	1	0.090
	Sig. (2-tailed)	0.476		0.649
	N	28	28	28
Diff_V1_V5_SVES_prcnt	Pearson Correlation	-0.137	0.090	1
	Sig. (2-tailed)	0.486	0.649	
	N	28	28	28

Table 2-2- 1

Nonparametric Correlation (Spearman and Kendall Tau)					
			DeltaEF	Diff_V1_V5_VES_prcnt	Diff_V1_V5_SVES_prcnt
Kendall's tau_b	DeltaEF	Correlation Coefficient	1.000	0.003	-0.141
		Sig. (2-tailed)		0.984	0.301
		N	30	28	28
	Diff_V1_V5_VES_prcnt	Correlation Coefficient	0.003	1.000	0.160
		Sig. (2-tailed)	0.984		0.241
		N	28	28	28
	Diff_V1_V5_SVES_prcnt	Correlation Coefficient	-0.141	0.160	1.000
		Sig. (2-tailed)	0.301	0.241	
		N	28	28	28
Spearman's rho	DeltaEF	Correlation Coefficient	1.000	0.026	-0.223
		Sig. (2-tailed)		0.897	0.255
		N	30	28	28
	Diff_V1_V5_VES_prcnt	Correlation Coefficient	0.026	1.000	0.196
		Sig. (2-tailed)	0.897		0.318
		N	28	28	28
	Diff_V1_V5_SVES_prcnt	Correlation Coefficient	-0.223	0.196	1.000
		Sig. (2-tailed)	0.255	0.318	
		N	28	28	28

Table 2-2- 2

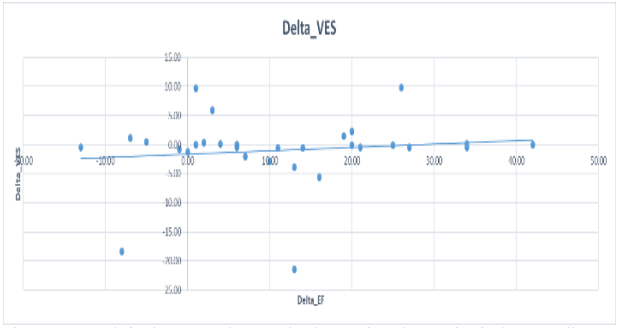

Fig. 5-4-1 a correlation between Delta EF and Delta VES in Holter monitor in the stem cell group

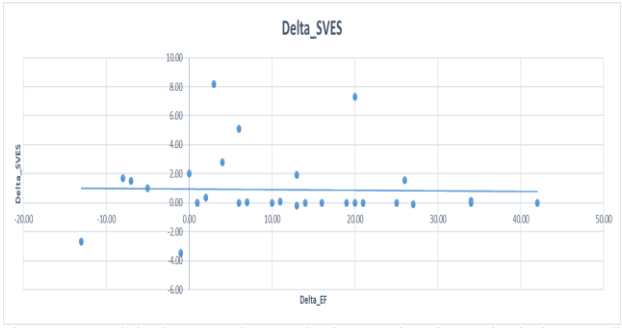

Fig. 5-4-2 a correlation between Delta EF and Delta SVES in Holter monitor in the stem cell group

The placebo group

Parametric Correlation (Pearson):				
		DeltaEF	Diff_V1_V5_VES_prcnt	Diff_V1_V5_SVES_prcnt
DeltaEF	Pearson Correlation	1	0.061	-0.231
	Sig. (2-tailed)		0.732	0.189
	N	34	34	34
Diff_V1_V5_VES_prcnt	Pearson Correlation	0.061	1	0.005
	Sig. (2-tailed)	0.732		0.979
	N	34	34	34
Diff_V1_V5_SVES_prcnt	Pearson Correlation	-0.231	0.005	1
	Sig. (2-tailed)	0.189	0.979	
	N	34	34	34

Table 2-3- 1

Nonparametric Correlation (Spearman and Kendall Tau)					
			DeltaEF	Diff_V1_V5_VES_prcnt	Diff_V1_V5_SVES_prcnt
Kendall's tau_b	DeltaEF	Correlation Coefficient	1.000	0.071	-0.022
		Sig. (2-tailed)		0.562	0.858
		N	34	34	34
	Diff_V1_V5_VES_prcnt	Correlation Coefficient	0.071	1.000	0.040
		Sig. (2-tailed)	0.562		0.743
		N	34	34	34
	Diff_V1_V5_SVES_prcnt	Correlation Coefficient	-0.022	0.040	1.000
		Sig. (2-tailed)	0.858	0.743	
		N	34	34	34
Spearman's rho	DeltaEF	Correlation Coefficient	1.000	0.104	-0.076
		Sig. (2-tailed)		0.558	0.668
		N	34	34	34
	Diff_V1_V5_VES_prcnt	Correlation Coefficient	0.104	1.000	0.060
		Sig. (2-tailed)	0.558		0.735
		N	34	34	34
	Diff_V1_V5_SVES_prcnt	Correlation Coefficient	-0.076	0.060	1.000
		Sig. (2-tailed)	0.668	0.735	
		N	34	34	34

Table 2-3- 2

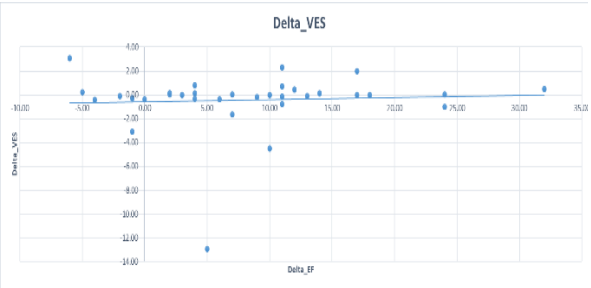

Fig. 5-5-1 a correlation between Delta EF and Delta VES in Holter monitor in the placebo group

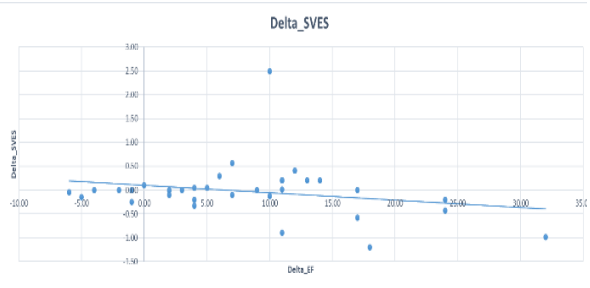

Fig. 5-5-2 a correlation between Delta EF and Delta SVES in Holter monitor in the placebo group

The responder group

Parametric Correlation (Pearson):				
		DeltaEF	Diff_V1_V5_VES_prcnt	Diff_V1_V5_SVES_prcnt
DeltaEF	Pearson Correlation	1	0.255	-0.123
	Sig. (2-tailed)		0.122	0.463
	N	39	38	38
Diff_V1_V5_VES_prcnt	Pearson Correlation	0.255	1	0.020
	Sig. (2-tailed)	0.122		0.905
	N	38	38	38
Diff_V1_V5_SVES_prcnt	Pearson Correlation	-0.123	0.020	1
	Sig. (2-tailed)	0.463	0.905	
	N	38	38	38

Table 2-4- 1

Nonparametric Correlation (Spearman and Kendall Tau)					
			DeltaEF	Diff_V1_V5_VES_prcnt	Diff_V1_V5_SVES_prcnt
Kendall's tau_b	DeltaEF	Correlation Coefficient	1.000	0.218	-0.213
		Sig. (2-tailed)		0.060	0.068
		N	39	38	38
	Diff_V1_V5_VES_prcnt	Correlation Coefficient	0.218	1.000	0.153
		Sig. (2-tailed)	0.060		0.188
		N	38	38	38
	Diff_V1_V5_SVES_prcnt	Correlation Coefficient	-0.213	0.153	1.000
		Sig. (2-tailed)	0.068	0.188	
		N	38	38	38
Spearman's rho	DeltaEF	Correlation Coefficient	1.000	0.319	-0.300
		Sig. (2-tailed)		0.051	0.067
		N	39	38	38
	Diff_V1_V5_VES_prcnt	Correlation Coefficient	0.319	1.000	0.213
		Sig. (2-tailed)	0.051		0.200
		N	38	38	38
	Diff_V1_V5_SVES_prcnt	Correlation Coefficient	-0.300	0.213	1.000
		Sig. (2-tailed)	0.067	0.200	
		N	38	38	38

Table 2-4- 2

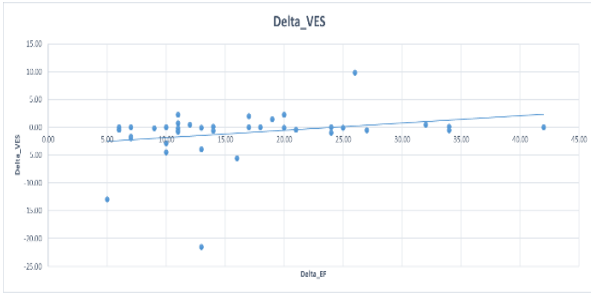

Fig. 5-3-1 a correlation between Delta EF and Delta VES in Holter monitor in the responder group

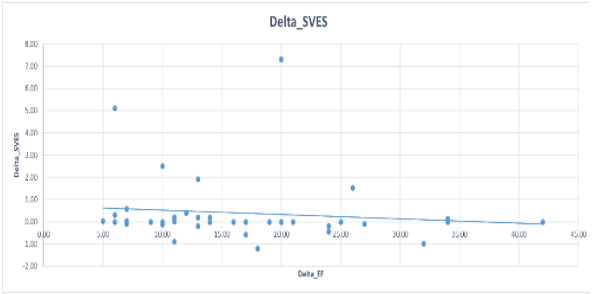

Fig. 5-3-2 a correlation between Delta EF and Delta SVES in Holter monitor in the responder group

The non-responder group

Parametric Correlation (Pearson):				
		DeltaEF	Diff_V1_V5_VES_prcnt	Diff_V1_V5_SVES_prcnt
DeltaEF	Pearson Correlation	1	0.389	0.084
	Sig. (2-tailed)		0.061	0.696
	N	25	24	24
Diff_V1_V5_VES_prcnt	Pearson Correlation	0.389	1	0.104
	Sig. (2-tailed)	0.061		0.627
	N	24	24	24
Diff_V1_V5_SVES_prcnt	Pearson Correlation	0.084	0.104	1
	Sig. (2-tailed)	0.696	0.627	
	N	24	24	24

Table 2-5- 1

Nonparametric Correlation (Spearman and Kendall Tau)					
			DeltaEF	Diff_V1_V5_VES_prcnt	Diff_V1_V5_SVES_prcnt
Kendall's tau_b	DeltaEF	Correlation Coefficient	1.000	0.136	-0.034
		Sig. (2-tailed)		0.368	0.822
		N	25	24	24
	Diff_V1_V5_VES_prcnt	Correlation Coefficient	0.136	1.000	0.081
		Sig. (2-tailed)	0.368		0.584
		N	24	24	24
	Diff_V1_V5_SVES_prcnt	Correlation Coefficient	-0.034	0.081	1.000
		Sig. (2-tailed)	0.822	0.584	
		N	24	24	24
Spearman's rho	DeltaEF	Correlation Coefficient	1.000	0.172	-0.035
		Sig. (2-tailed)		0.423	0.872
		N	25	24	24
	Diff_V1_V5_VES_prcnt	Correlation Coefficient	0.172	1.000	0.103
		Sig. (2-tailed)	0.423		0.633
		N	24	24	24
	Diff_V1_V5_SVES_prcnt	Correlation Coefficient	-0.035	0.103	1.000
		Sig. (2-tailed)	0.872	0.633	
		N	24	24	24

Table 2-5- 2

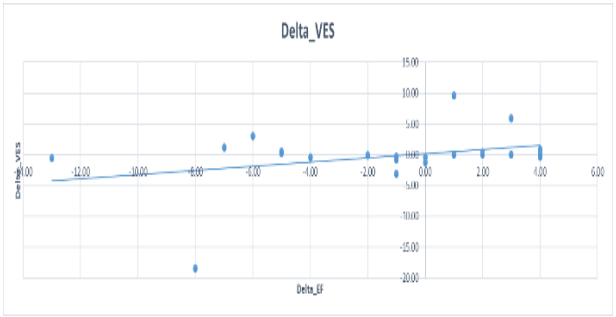

Fig. 5-2-1 a correlation between Delta EF and Delta VES in Holter monitor in the non-responder group

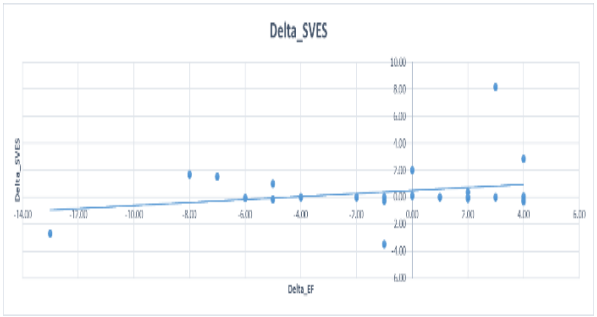

Fig. 5-2-2 a correlation between Delta EF and Delta SVES in Holter monitor in the non-responder group

In-Hospital-Stay arrythmias

The next section examined the collected data concerning the documented arrhythmia during the in-hospital stay. In this scenario we calculated the total number of days starting from the first day of the first episode of that particular type of arrhythmia and ending with the last day of the last episode of the same type of arrhythmia for up to 180 days postoperative.

SVT

The postoperative documented SVT duration was plotted in all 4 groups. The following demonstrates a comparison in the SVT total duration. It shows a longer mean duration in the stem cell group (SCG-μ=30.2703, SCG-SD=65.15650, SCG-SE=10.71166, PG-μ=15.2250, PG-SD=45.73866, PG-SE=7.23192, P1=0.242, P2=0.249, P3=0.430) {n.sig.}. The comparison between the responder and non-responder groups shows a shorter mean duration in the responder group (RG-μ=15.6154, RG-SD=47.43562, RG-SE=7.59578, NRG-μ=30.2400, NRG-SD=62.76629, NRG-SE=12.55326, P1=0.294, P2=0.325, P3=0.315) {n.sig.}. As we examined the placebo and stem cell groups separately, the responder subgroup of the placebo group showed a longer mean duration in the placebo group (RG-PG-μ=11.3500, RG-PG-SD=39.62890, RG-PG-SE=8.86129, NRG-PG-μ=27.0714, NRG-PG-SD=60.87625, NRG-PG-SE=16.26986, P1=0.368, P2=0.406, P3=0.870) {n.sig.} but a shorter one in the stem cell group (RG-SCG-μ=20.1053, RG-SCG-SD=55.23676, RG-SCG-SE=12.67218, NRG-SCG-μ=34.2727, NRG-SCG-SD=67.86323, NRG-SCG-SE=20.46153, P1=0.539, P2=0.564, P3=0.224) {n.sig.}.

The following graphs shows a comparison of median values of SVT duration up to 180 days postoperative within all groups and subgroups.

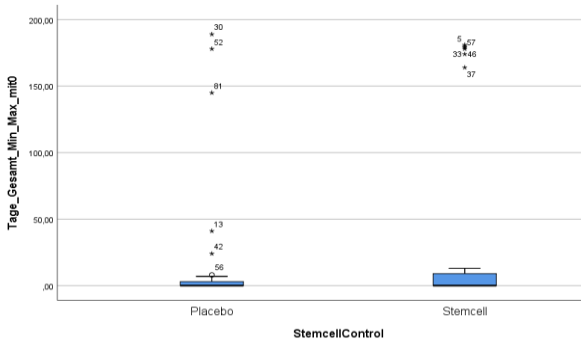

Fig. 6-1-1 Median duration of SVT arrhythmias during hospitalization in the whole population subdivided into placebo group und stem cell groups.

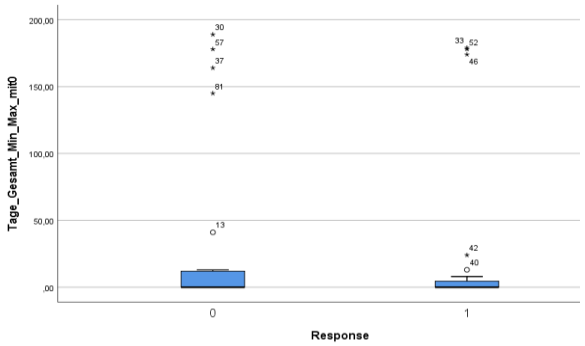

Fig. 6-1-2 Median duration of SVT arrhythmias during hospitalization in the whole population subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

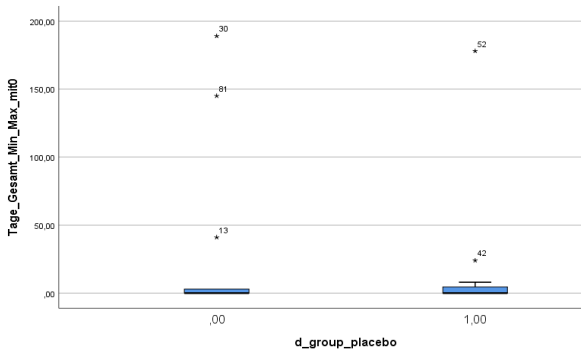

Fig. 6-1-3 Median duration of SVT arrhythmias during hospitalization in the placebo group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

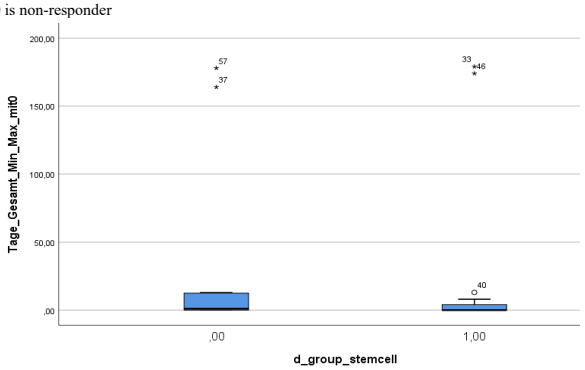

Fig. 6-1-4 Median duration of SVT arrhythmias during hospitalization in the stem cell group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

A parallel investigation to determine the number of patients that developed an ongoing SVT that extend beyond the 180 days period postoperative was also conducted in all 4 groups. The following [Fig.6-1-5] demonstrates a comparison in the number of patients with an ongoing arrhythmia between the Placebo and stem cell groups in the whole cohort. It shows a significantly higher number of patients in the stem cell group than the Placebo group (SCG=6, PG=1, **P4=0.036**) {sig.}. The comparison between the responder and non-responder groups shows a lower number in the responder group as showed in [Fig. 6-1-6] (RG=3, NRG=2, P4=0.964) {n.sig.}. As we examined the placebo [Fig.6-1-7] and stem cell [Fig.6-1-8] groups separately a higher count was shown in the responder subgroup of the placebo group (RG-PG=1, NRG-PG=0, P4=0.396) {n.sig.} but an equal number was demonstrated in the responder and non-responder subgroups of the stem cell group (RG-SCG=2, NRG-SCG=2, P4=0.552) {n.sig.}.

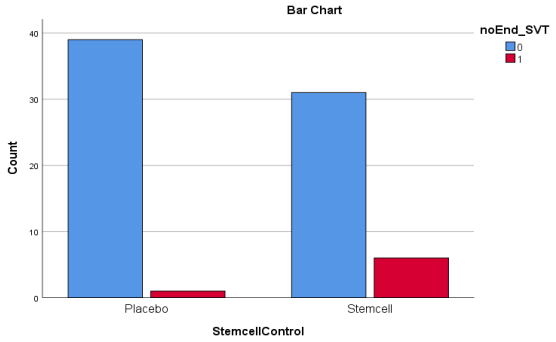

Fig. 6-1-5 number of patients with ongoing SVT in the whole population subdivided into placebo group und stem cell groups.

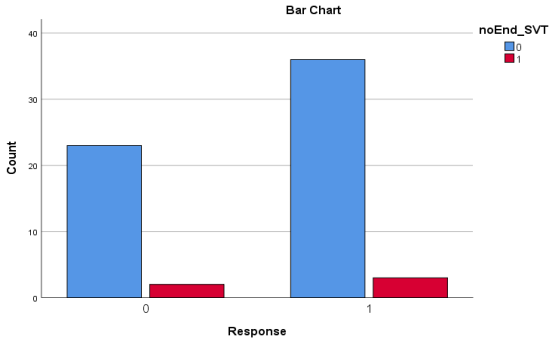

Fig. 6-1-6 number of patients with ongoing SVT in the whole population subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

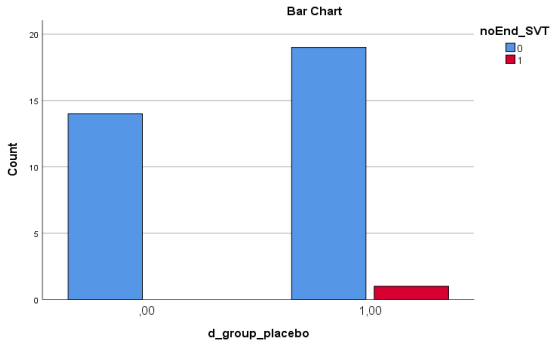

Fig. 6-1-7 number of patients with ongoing SVT in the placebo group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

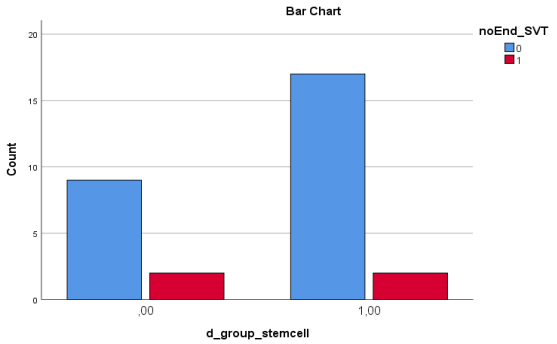

Fig. 6-1-8 number of patients with ongoing SVT in the stem cell group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

VT

The postoperative documented VT duration was plotted in all 4 groups. The following demonstrates a comparison in the VT mean duration. It shows a shorter mean duration in the stem cell group (SCG-µ=4.3514, SCG-SD=27.00845, SCG-SE=4.44016, PG-µ=6.6500, PG-SD=28.84312, PG-SE=4.56050, P1=0.720, P2=0.719, P3=0.175) {n.sig.}. The comparison between the responder and non-responder groups shows a shorter mean duration in the responder group as showed in (RG-µ=2.0769, RG-SD=10.30683, RG-SE=1.65041, NRG-µ=13.5200, NRG-SD=46.71199, NRG-SE=9.34240, P1=0.144, P2=0.239, P3=0.663) {n.sig.}. As we examined the placebo and stem cell groups separately a shorter mean duration was shown in the responder subgroups of both the placebo group (RG-PG-µ=4.0500, RG-PG-SD=14.28461, RG-PG-SE=3.19414, NRG-PG-µ=12.9286, NRG-PG-SD=46.12102, NRG-PG-SE=12.32636, P1=0.423, P2=0.496, P3=0.708) {n.sig.} as well as the stem cell group (RG-SCG-µ=0.0000, RG-SCG-SD=0.00000, RG-SCG-SE=0.00000, NRG-SCG-µ=14.2727, NRG-SCG-SD=49.70330, NRG-SCG-SE=14.98611, P1=0.215, P2=0.363, P3=1.000) {n.sig.}.

The following graphs shows a comparison of median values of VT duration up to 180 days postoperative within all groups and subgroups.

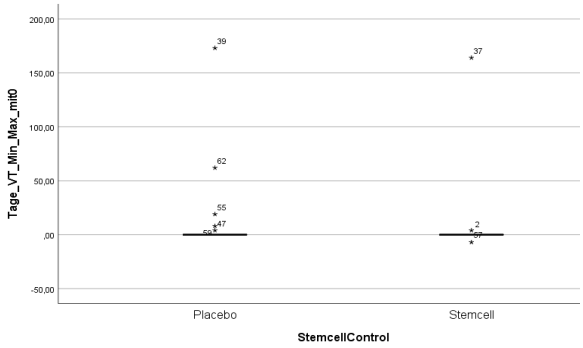

Fig. 6-2-1 Median duration of VT arrhythmias during hospitalization in the whole population subdivided into placebo group und stem cell groups.

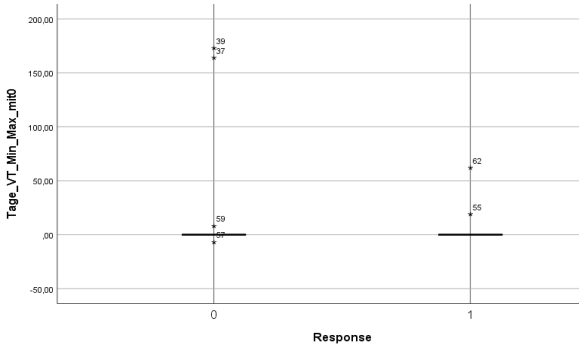

Fig. 6-2-2 Median duration of VT arrhythmias during hospitalization in the whole population subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

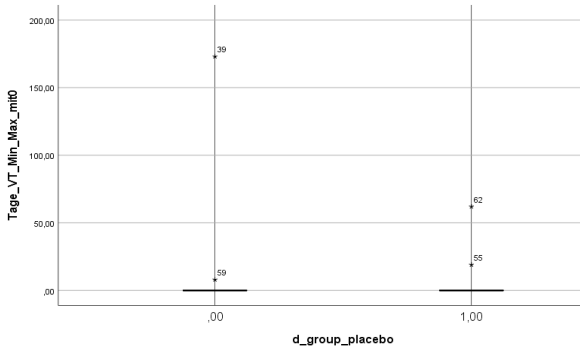

Fig. 6-2-3 Median duration of VT arrhythmias during hospitalization in the placebo group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

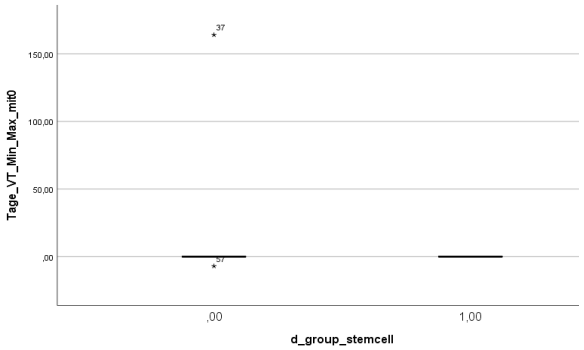

Fig. 6-2-4 Median duration of VT arrhythmias during hospitalization in the stem cell group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

The investigation to determine the number of patients that developed an ongoing (recurrent) VT that extend beyond the 180 days period postoperative was also conducted in all 4 groups. The following [Fig.6-2-5] demonstrates a comparison in the number of patients with an ongoing arrhythmia between the Placebo and stem cell groups in the whole cohort, where only one patient int non-responder subgroup of stem cell group met these criteria. It shows a higher number of patients in the stem cell group than the Placebo group (SCG=1, PG=0, P4=0.295) {n.sig.}. The comparison between the responder and non-responder groups shows a lower number in the responder group as showed in [Fig. 6-2-6] (RG=0, NRG=1, P4=0.208) {n.sig.}. As we examined the placebo [Fig.6-2-7] and stem cell [Fig.6-2-8] groups separately the responder as well as the non-responder subgroup of the placebo group showed no difference (RG-PG=0, NRG-PG=0) {n.sig.}. A lower number was demonstrated in the responder subgroup of the stem cell group (RG-SCG=0, NRG-SCG=1, P4=0.181) {n.sig.}.

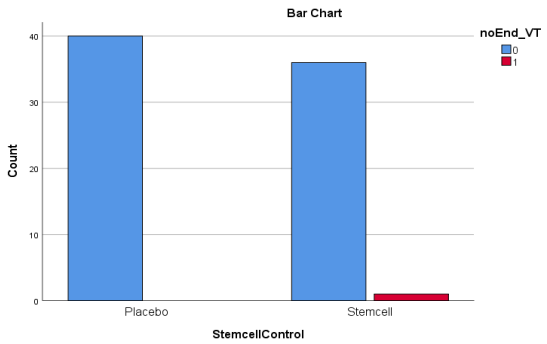

Fig. 6-2-5 number of patients with ongoing VT in the whole population subdivided into placebo group und stem cell groups.

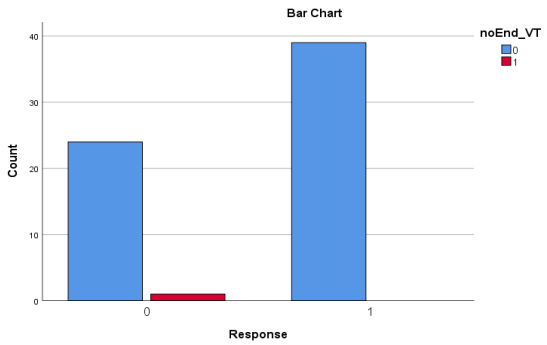

Fig. 6-2-6 number of patients with ongoing VT in the whole population subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

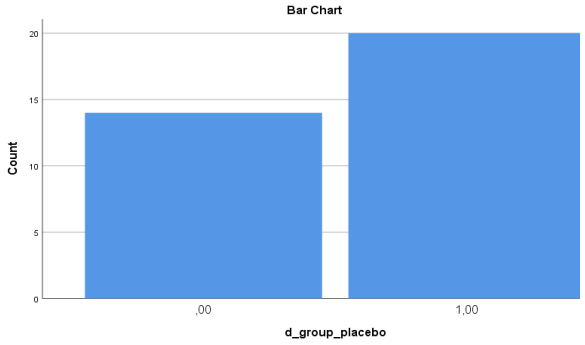

Fig. 6-2-7 number of patients with ongoing VT in the placebo group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

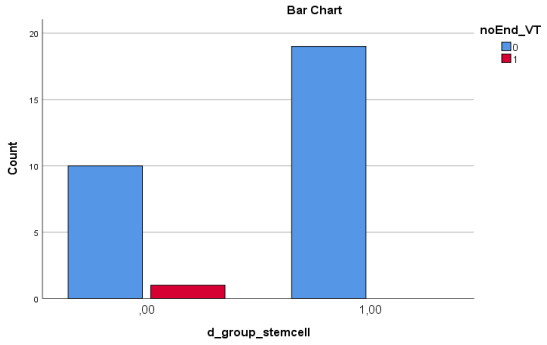

Fig. 6-2-8 number of patients with ongoing VT in the stem cell group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

SVES

The postoperative documented SVES duration was plotted in all 4 groups. The following demonstrates a comparison in the SVES mean duration. It shows a shorter mean duration in the stem cell group (SCG-μ=0.0270, SCG-SD=0.16440, SCG-SE=0.02703, PG-μ=4.6000, PG-SD=27.82436, PG-SE=4.39942, P1=0.321, P2=0.305, P3=0.584) {n.sig.}. The comparison between the responder and non-responder groups shows a longer mean duration in the responder group (RG-μ=0.2051, RG-SD=1.28103, RG-SE=0.20513, NRG-μ=0.0400, NRG-SD=0.20000, NRG-SE=0.04000, P1=0.526, P2=0.434, P3=0.767) {n.sig.}. As we examined the placebo and stem cell groups separately a longer mean duration was shown in the responder subgroup of the placebo group (RG-PG-μ=0.4000, RG-PG-SD=1.78885, RG-PG-SE=0.40000, NRG-PG-μ=0.0000, NRG-PG-SD=0.00000, NRG-PG-SE=0.00000, P1=0.411, P2=0.330, P3=0.403) {n.sig.} but a longer mean duration was demonstrated in the same subgroup of the stem cell group (RG-SCG-μ=0,0000, RG-SCG-SD=0.00000, RG-SCG-SE=0.00000, NRG-SCG-μ=0.0909, NRG-SCG-SD=0.30151, NRG-SCG-SE=0.09091, P1=0.194, P2=0.341, P3=0.189) {n.sig.}.

The following graphs shows a comparison of median values of SVES duration up to 180 days postoperative within all groups and subgroups.

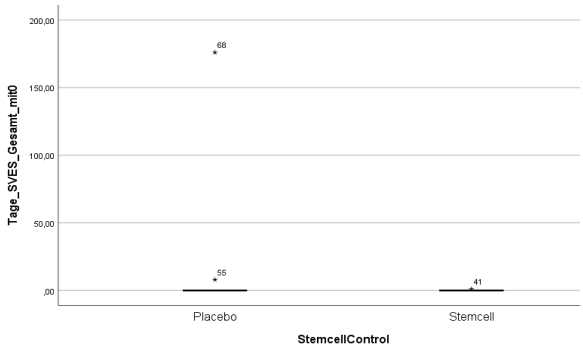

Fig. 6-3-1 Median duration of SVES arrhythmias during hospitalization in the whole population subdivided into placebo group und stem cell groups.

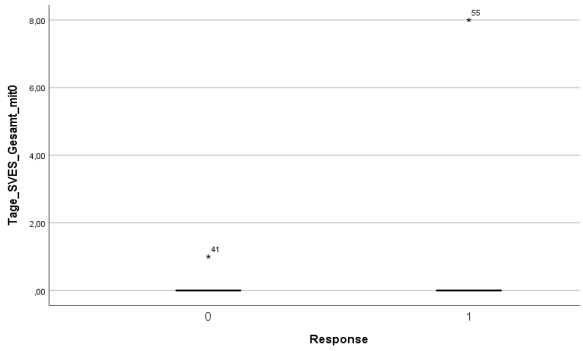

Fig. 6-3-2 Median duration of SVES arrhythmias during hospitalization in the whole population subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

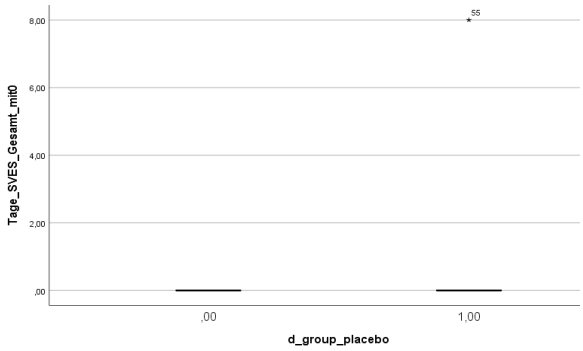

Fig. 6-3-3 Median duration of SVES arrhythmias during hospitalization in the placebo group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

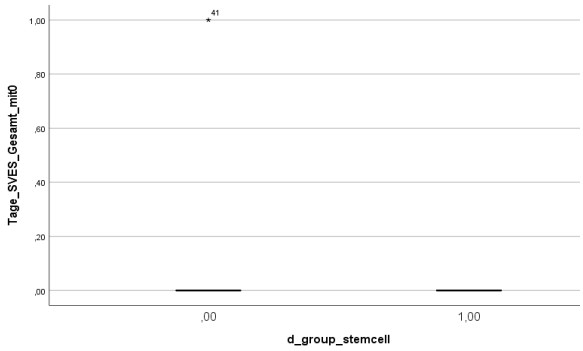

Fig. 6-3-4 Median duration of SVES arrhythmias during hospitalization in the stem cell group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

The investigation to determine the number of patients that developed an ongoing (recurrent) SVES that extend beyond the 180 days period postoperative was also conducted in all 4 groups. The following [Fig.6-3-5] demonstrates a comparison in the number of patients with an ongoing SVES between the Placebo and stem cell groups in the whole cohort, where only one patient in the Placebo group that could not be subcategorized to responder or non-responder met these criteria. It shows a lower number of patients in the stem cell group than the Placebo group (SCG=0, PG=1, P4=0.333) {n.sig.}. The comparison between the responder and non-responder groups could not show any patient that developed SVES as showed in [Fig. 6-3-6] (RG=0, NRG=0) {n.sig.}. As we examined the placebo [Fig.6-3-7] and stem cell [Fig.6-3-8] groups separately the responder as well as the non-responder subgroup of the placebo group (RG-PG=0, NRG-PG=0) {n.sig.} and stem cell group (RG-SCG=0, NRG-SCG=0) {n.sig.} could not show any patients with ongoing VT.

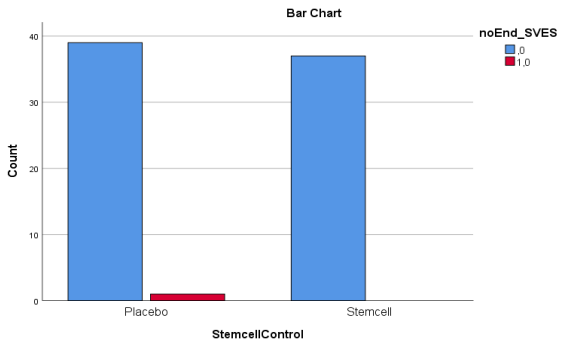

Fig. 6-3-5 number of patients with ongoing SVES in the whole population subdivided into placebo group und stem cell groups.

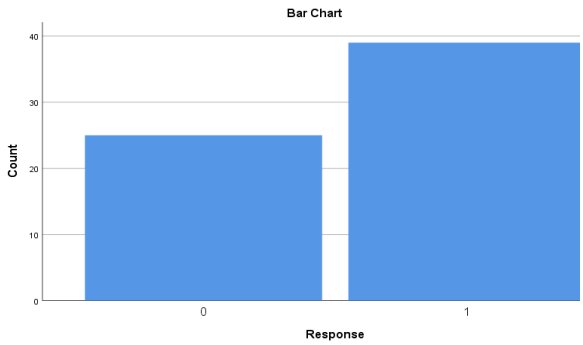

Fig. 6-3-6 number of patients with ongoing SVES in the whole population subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

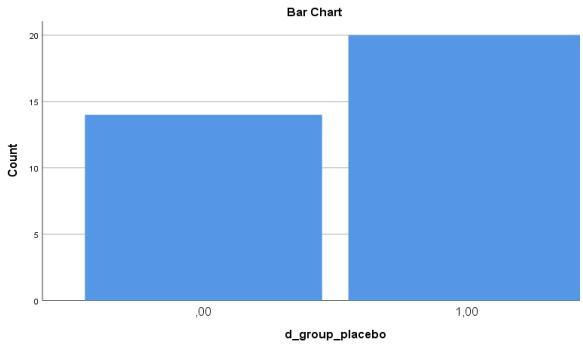

Fig. 6-3-7 number of patients with ongoing SVES in the placebo group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

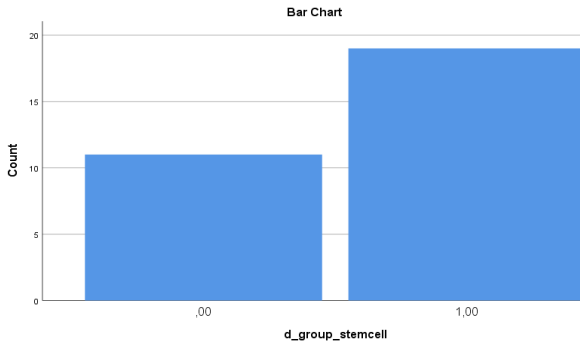

Fig. 6-3-8 number of patients with ongoing SVES in the stem cell group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

VES

The postoperative documented VES duration was plotted in all 4 groups. The following demonstrates a comparison in the VES duration. It shows a shorter mean duration in the placebo group (SCG-μ=32.4324, SCG-SD=107.21669, SCG-SE=17.62632, PG-μ=8.1250, PG-SD=35.94596, PG-SE=5.68356, P1=0.180, P2=0.196, P3=0.324) {n.sig.}. The comparison between the responder and non-responder groups shows a shorter mean duration in the responder group (RG-μ=12.4872, RG-SD=43.88854, RG-SE=7.02779, NRG-μ=28.3200, NRG-SD=111.34770, NRG-SE=22.26954, P1=0.427, P2=0.503, P3=0.918) {n.sig.}. As we examined the placebo and stem cell groups separately a longer mean duration was shown in the responder subgroup of the placebo group (RG-PG-μ=16.2500, RG-PG-SD=50.13232, RG-PG-SE=11.20993, NRG-PG-μ=0.0000, NRG-PG-SD=0.00000, NRG-PG-SE=0.00000, P1=0.236, P2=0.163, P3=0.230) {n.sig.} but a shorter mean duration was demonstrated in the same subgroup of the stem cell group (RG-SCG-μ=8.5263, RG-SCG-SD=37.16535, RG-SCG-SE=8.52632, NRG-SCG-μ=64.3636, NRG-SCG-SD=164.93652, NRG-SCG-SE=49.73023, P1=0.163, P2=0.293, P3=0.231) {n.sig.}.

The following graphs shows a comparison of median values of VES duration up to 180 days postoperative within all groups and subgroups.

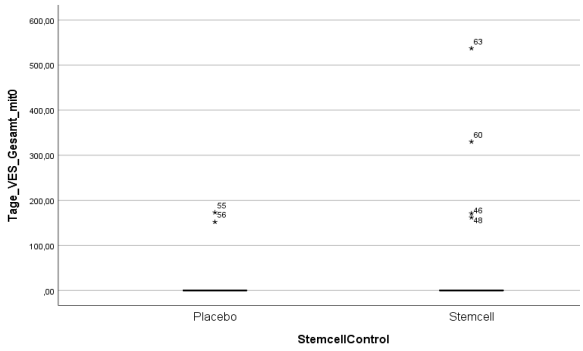

Fig. 6-4-1 Median duration of VES arrhythmias during hospitalization in the whole population subdivided into placebo group und stem cell groups.

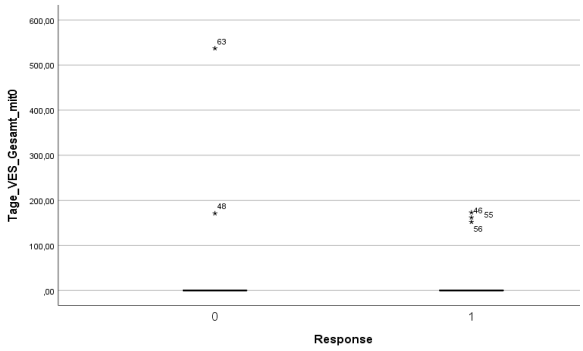

Fig. 6-4-2 Median duration of VES arrhythmias during hospitalization in the whole population subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

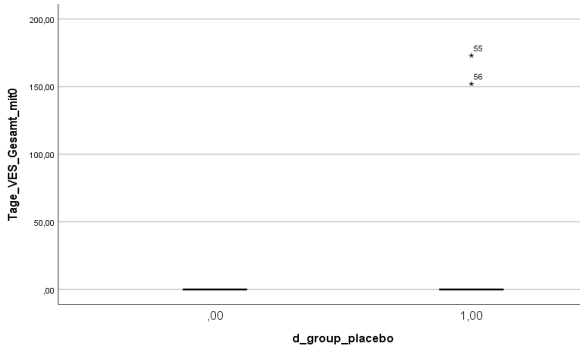

Fig. 6-4-3 Median duration of VES arrhythmias during hospitalization in the placebo group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

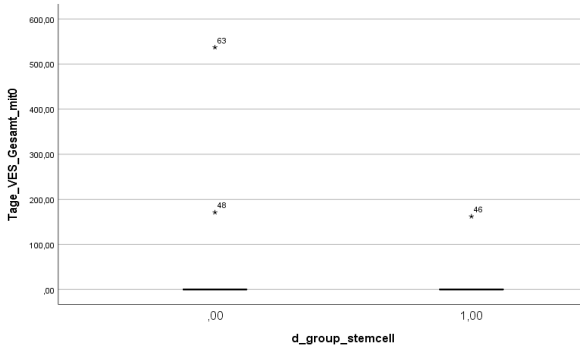

Fig. 6-4-4 Median duration of VES arrhythmias during hospitalization in the stem cell group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

The investigation to determine the number of patients that developed an ongoing VES that extend beyond the 180 days period postoperative was also conducted in all 4 groups. The following [Fig.6-4-5] demonstrates a comparison in the number of patients with an ongoing arrhythmia between the Placebo and stem cell groups in the whole cohort. It shows a higher number of patients in the stem cell group than the Placebo group (SCG=3, PG=2, P4=0.580) {n.sig.}. The comparison between the responder and non-responder groups shows a higher number in the responder group as showed in [Fig. 6-4-6] (RG=3 NRG=1, P4=0.552) {n.sig.}. As we examined the placebo [Fig.6-4-7] and stem cell [Fig.6-4-8] groups separately a higher count was shown in the responder subgroup of the placebo group (RG-PG=2, NRG-PG=0, P4=0.223) {n.sig.} but an equal number was demonstrated in the responder and non-responder subgroups of the stem cell group (RG-SCG=1, NRG-SCG=1, P4=0.685) {n.sig.}.

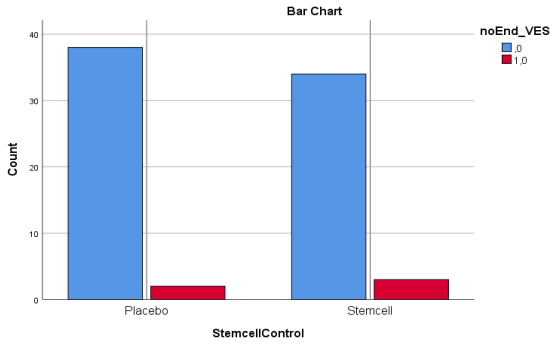

Fig. 6-4-5 number of patients with ongoing VES in the whole population subdivided into placebo group und stem cell groups.

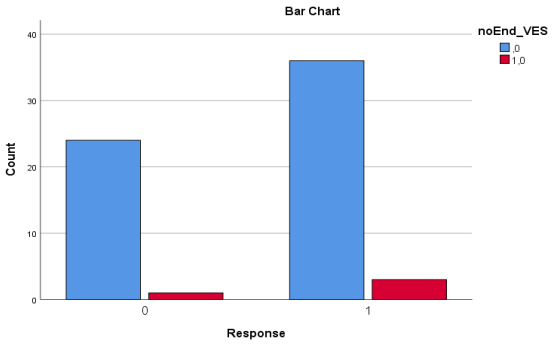

Fig. 6-4-6 number of patients with ongoing VES in the whole population subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

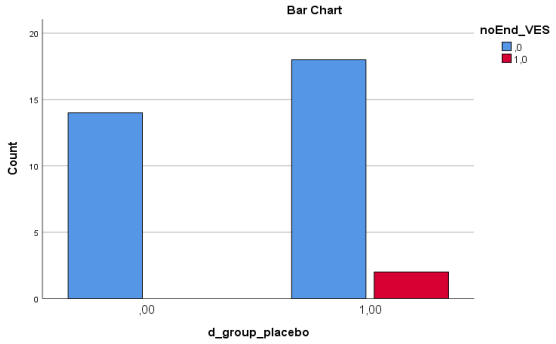

Fig. 6-4-7 number of patients with ongoing VES in the placebo group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

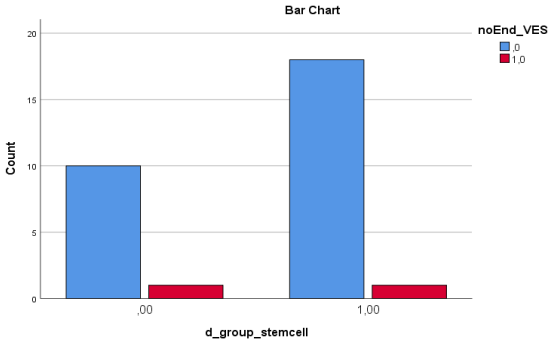

Fig. 6-4-8 number of patients with ongoing VES in the stem cell group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

Others

The postoperative documented duration of uncategorized arrhythmia was plotted in all 4 groups. The following demonstrates a comparison in the duration of unidentified arrhythmia. It shows a longer mean duration in the stem cell group (SCG-µ=96.1351, SCG-SD=215.39501, SCG-SE=35.41072, PG-µ=34.4500, PG-SD=66.21486, PG-SE=10.46949, P1=0.088, P2=0.102, P3=0,559) {n.sig.}. The comparison between the responder and non-responder groups shows a shorter mean duration in the responder group as showed in (RG-µ=30.3333, RG-SD=74.05167, RG-SE=11.85776, NRG-µ=93.6000, NRG-SD=222.89983, NRG-SE=44.57997, P1=0.105, P2=0.181, P3=0.267) {n.sig.}. As we examined the placebo and stem cell groups separately a shorter mean duration was shown in the responder subgroup of the placebo group (RG-PG-µ=31.7500, RG-PG-SD=64.42938, RG-PG-SE=14.40685, NRG-PG-µ=40.0000, NRG-PG-SD=71.26872, NRG-PG-SE=19.04737, P1=0.727, P2=0.733, P3=0.970) {n.sig.} as well as a in the responder subgroup of the stem cell group (RG-SCG-µ=28.8421, RG-SCG-SD=84.79535, RG-SCG-SE=19.45339, NRG-SCG-µ=161.8182 NRG-SCG-SD=321.71130, NRG-SCG-SE=96.99961, P1=0.096, P2=0.206, P3=0.107) {n.sig.}.

The following graphs shows a comparison of median values of the unidentified arrhythmias duration up to 180 days postoperative within all groups and subgroups.

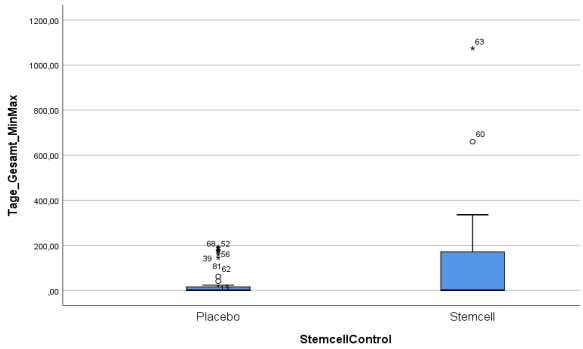

Fig. 6-5-1 Median duration of unidentified arrhythmias during hospitalization in the whole population subdivided into placebo group und stem cell groups.

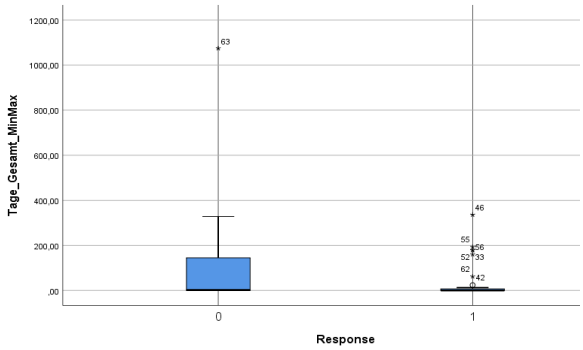

Fig. 6-5-2 Median duration of unidentified arrhythmias during hospitalization in the whole population subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

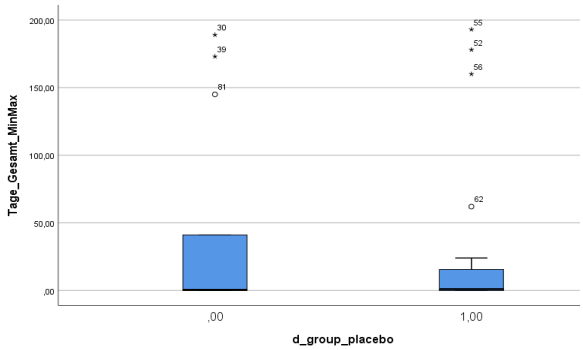

Fig. 6-5-3 Median duration of unidentified arrhythmias during hospitalization in the placebo group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

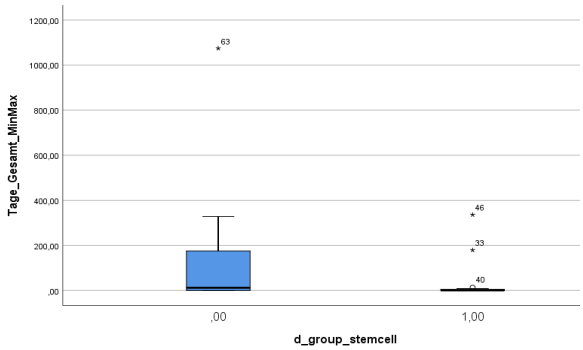

Fig. 6-5-4 Median duration of unidentified arrhythmias during hospitalization in the stem cell group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

The investigation to determine the percentage of patients that developed an ongoing unidentified arrhythmia that extend beyond the 180 days period postoperative was also conducted in all 4 groups. It showed only one patient that have an ongoing unidentified arrhythmia (recurrent) beyond the 180 days in the stem cell group which could not be assigned to any subgroup (P4=0.295). Again, the collected data was trivial to get a proper formulation as shown in [6-5-5], [6-5-6], [6-5-7] und [6-5-8].

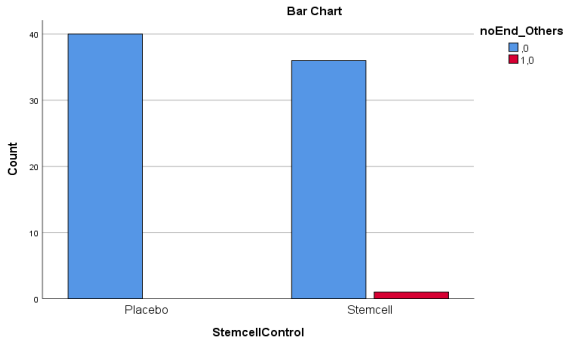

Fig. 6-5-5 number of patients with ongoing unidentified in the whole population subdivided into placebo group und stem cell groups.

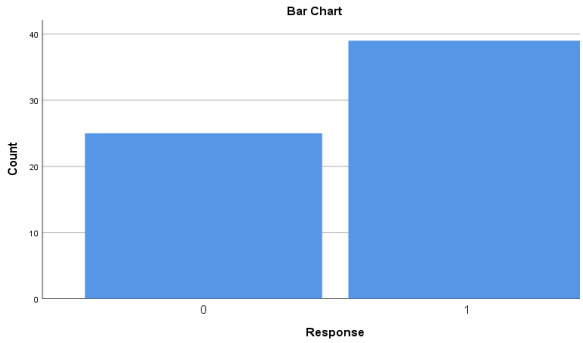

Fig. 6-5-6 number of patients with ongoing unidentified in the whole population subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

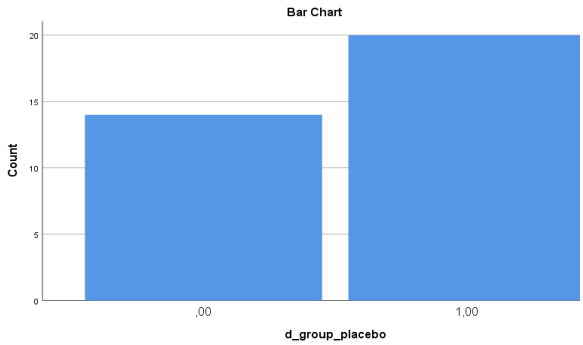

Fig. 6-5-7 number of patients with ongoing unidentified in the placebo group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

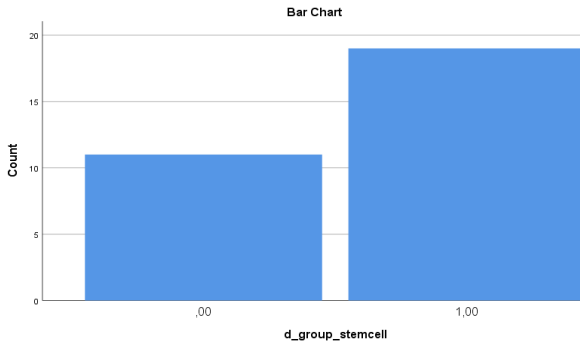

Fig. 6-5-8 number of patients with ongoing unidentified in the stem cell group subdivided into responder and non-responder groups where 1 is responder and 0 is non-responder

Discussion

The statistical analysis above showed that the patients in the study population were not evenly randomized from cardiac arrhythmia point of view. That resulted in starting the clinical trial with more patients with VES, SVES as well as VT in stem cell group than in placebo group. Other causes of arrhythmia were also neither included nor investigated in scope of this work.

It showed that VES occurred less often in the stem cell group in V3 than in V1 with a reduction in mean percentage from 2.5535% to 1.5644% and then showed a significant increase in V5 up to 2.3366%. On the other hand, the placebo group showed an increase at first in V3 than in V1 from 1.0385% to 1.0950% and later on in V5 a reduction to a mean percentage of 0.8046%. Also, it could be proved that VES occurred less frequently in responder than in non-responder subgroups in both the placebo and the stem cell groups. As we go forward in time from V1 to V5 the analysis showed an increase in the incidence of VES mean percentage in the responder subgroup of placebo group from 1.43100% in V1 to 0.6460% in V3 and then an increase to 0.6530% in V5. While in case of the stem cell group, the mean VES percentage in the responder subgroup did fall from 2.7437% in V1 to 1.4379% in V3 and then up to 1.4839% in V5. The non-responder subgroup of the stem cell group showed an initial decrease in VES mean percentage from 3.5673% in V1 down to 1.9580% in V3 and then showed a significant increase up to 3.6050% in V5. This may indicate that although the stem cell group started with more patients that exhibit VES more often than Placebo group, over time from V1 to V5, the responder subgroup of this stem cell group showed a significant decrease in the VES mean percentage while the non-responder showed a significant increase after initial decrease in the VES mean percentage. That means that the responder subgroup of the stem cell group that exhibited more VES benefited the most from the treatment with stem cell implantation from a cardiac arrhythmia point of view.

Concerning the SVES the analysis above showed once more that more patients that exhibited more often preoperative SVES were randomized in the stem cell group. It could show an increase of the SVES mean percentage of stem cell group form 0.4106% in V1 to 0.7561% in V3 and later on to 1.4306% with significance in V5 in comparison with the placebo group that showed an initial increase in SVES mean percentage from 0.2344% in V1 to 0.6743% in V3 and then a significant decrease to 0.3370% in V5. It also showed a low rate of incidence of SVES in the general responder group as well as the responder subgroup of the stem cell group in V1 with SVES mean percentage of 0.1217% that also stayed significantly low in V3 with SVES mean percentage of 0.3524% and later on showed an elevation in V5 with SVES mean percentage of 1.0059% but stays significantly low in comparison with the non-responder subgroup that showed a significant elevation from V1 with SVES mean percentage of 1.0900% to V3 with SVES mean percentage of 1.7380% to V5 with SVES mean percentage of 2.3380%. However, it also showed a low rate of incidence of SVES in the responder subgroup of placebo group with SVES mean percentage of 0.3235% in V1 as well as 0.2973% in V3 and 0.3290% in V5. On the other hand, the non-responder subgroup of the placebo group showed a decrease in the rate of incidence of SVES in comparison to the responder subgroup in spite of its initial elevation. This analysis could also prove that the stem cell group showed a significant increase in the rate of incidence of SVES if compared to the placebo group which showed a regression. That was accompanied by a decrease in the rate of occurrence of SVES in the responder subgroup of the same group in comparison with the non-responder subgroup. That means that

although stem cell implantation may have caused an increase in the rate of incidence of SVES, it could help the responder subgroup of the stem cell group to reduce the incidence rate of SVES.

Concerning the VT, the analysis could not show a correlation within the collected data. The cohort is too small and some groups ended up with one or even no patients. Further prospective clinical trials should be conducted to examine whether there is a correlation or not keeping in mind to overcome the limitations of this study such as cohort small size as well as the uneven randomization of the Patients.

The analysis could also confirm the absence of a correlation between the progression of SVES as well as VES determined by Delta-V1-V5 in both types of arrhythmias and the change in the LVEF determined by Delta-EF.

The analysis of the collected data from the documentation during the in-hospital stay could show a longer duration of SVT, VES as well as unidentified arrhythmia in the stem cell group with the general responder group and the responder subgroup of the stem cell group having shorter duration of arrhythmia while the responder subgroup of the placebo group having longer duration of SVT and VES. On the other hand, it could also show that placebo group has longer duration of VT and SVES where the responder subgroups of both placebo and stem cell groups showed a shorter duration in case of VT but longer in case of SVES. That is also consistent with the results of the three examination visits, where the responder subgroup of the stem cell group profited from this intramyocardial stem cell implantation.

The work of Almeida et al. in 2015 [268] suggested that stem cell implantation is arrhythmogenic depending of the type of the used stem cells and discussed the different mechanisms of its arrhythmogenicity and promoted for further studies to investigate in this matter. On the other hand, the work of Sadraddin et al. 2019 [294] showed that bone marrow derived stem cell implantation is in fact safe and may possess anti-arrhythmogenic characteristics most probably due to improving conduction in the border zone through recovery of gap junctions, minimizing the degree of fibrosis, and better modulating calcium regulatory ion channels, thereby leading to increased electrical stability.

This may be seen in this work as the study showed that intramyocardial stem cell implantation cause higher rate of incidence of SVES as well as VES and cause a prolongation of arrhythmia episodes for those who developed arrhythmia especially VES and SVES, however within a period of 180 days it could demonstrate that the responder subgroup of the stem cell group show in fact a reduction in the rate of incidence of SVES as well as VES and could shorten the arrhythmia episodes for those particular types of arrythmia. This may be in fact true according to both Almeida [268] and Sadraddin [294] if we took the time factor into consideration. In early phase it showed an increase of incidence of arrhythmia in the group of patients that were treated with stem cell implantation and later on showed a reduction in the rate of arrhythmia and a shortening of the duration of the arrhythmia episodes in the responder subgroup of this stem cell group where these stem cells enhanced the perfusion and thus myocardium contractility. This anti arrhythmic effect may be due to improving conduction in the border zone through recovery of gap junctions, minimizing the degree of fibrosis, and better modulating calcium regulatory ion channels, thereby leading to increased electrical stability. This may explain why only the responder subgroup of the stem cell group that exhibited improvement in left ventricular ejection fraction showed such antiarrhythmic effect.

Concerning the objectives of this work, the outcome of this analytical study could answer all of them. It could confirm that the intramyocardial application of autologous CD 133+ stem cells in combination with an aortocoronary bypass operation can be considered as a safe therapy method although it does lead to the development of more often but mostly non-serious cardiac arrhythmias than mono therapy with aortocoronary bypass operation as well as prolongation of the duration of postoperative SVT, VES and other unidentified types of arrhythmias.

It also could confirm that in patients who received CD 133+ stem cells therapy, postinterventional cardiac arrhythmias occurred more frequently in comparison to patients who received placebo therapy only, where in the responder subgroup of the stem cell group benefited the most from that intervention as it helped promoting to the regression of arrhythmias occur in this specific subgroup if compared with the non-responder subgroup.

Unfortunately, this study could confirm the absence of any correlation between the change in left ventricular function which is determined by the change in ejection fraction and the change in the rate of incidence of the different types of arrhythmias.

The key point of this treatment option is to identify the potential responder from the potential non-responder patient before starting this treatment method so that the patient gets maximal benefits of the treatment with least adverse effects.

Further trials shall be conducted focusing on the topic of this work taking into consideration and correcting the limitation points of this work as well as in depth studies and analyses to investigate the actual causes and mechanisms of arrhythmia after CABG combined with stem cell implantation other than what mentioned above and how to anticipate, avoid and eventually treat it.

Conclusion

The intramyocardial application of autologous CD 133+ stem cells in combination with an aortocoronary bypass operation can be considered as a safe therapy method although it does lead to the development of more often but mostly non-serious cardiac arrhythmias as well as prolongation of the duration of postoperative SVT, VES and other unidentified types of arrhythmias than mono therapy with aortocoronary bypass operation. The patients who responded to the treatment showed also a regression in the rate of incidence of arrhythmia over a period of time up to 6 months. This confirms that stem cell implantation is safe and even more effective than mono therapy with CABG. The key point here is to identify the potential responder from the potential non-responder patient before starting this treatment method so that the patient gets the maximal benefits of the treatment with least adverse effects. Further trials and studies shall be conducted focusing on the mechanism of development of arrhythmia after stem cell implantation and how to anticipate, avoid and eventually treat it. Also, further prospective trials shall be conducted focusing on the topic of this work taking into consideration and correcting the limitation points of this work.

Limitations of this study

1. Too small size cohort that resulted in some groups ending up with only one patient or even none. With small sample sizes, results can fail to reach statistical significance yet the effect is large and potentially clinical important.

2. Uneven randomization of the patients' population from cardiac arrhythmia point of view that resulted in stacking more patients with preoperative arrhythmias in one group and few in the other.

3. Poor data documentation about cardiac arrhythmia during the in-hospital stay concerning the identification of the arrhythmia as well as other causes of arrhythmia such as different measurement units for electrolytes, arrhythmic/antiarrhythmic medication and intravascular fluid status.

Summary

Myocardial infarction (MI) is the irreversible death (necrosis) of cardiac muscle as a result of prolonged lack of oxygen supply (ischemia). There are many treatment options for MI including but not limited to CABG and stem cell implantation. Stem cell regenerative therapies is a promising option for treating many diseases. Recent clinical trials have shown its safety and efficacy in improvement of the cardiac function after acute myocardial infarction but with variable results. The inability of the implanted stem cells to integrate into the host myocardium architecture may increase an arrhythmogenic risk to patients. This was investigated in this work and it was proven not to be entirely true. The PERFECT RCT phase III analysis investigated the bone marrow-derived stem cell expressing CD133+ in this particular aspect [1]. These patient groups included in the PERFECT RCT were further analyzed in the scope of this work to show whether this stem cell therapy method is a safe option or not from arrhythmogenicity point of view. The patients were divided into placebo control and stem cell group. Both groups were further classified into Responder and Non-Responder subgroups depending on the improvement in the cardiac function with more than 5%. These groups were cross-matched and checked in order to confirm our hypotheses. The outcome of this analysis showed indeed an increase in the incidence rate of non-serious Arrhythmias (SVES and VES) in stem cell group but also showed a significant reduction in this incidence rate over a period of time of up to 180 days only in the responder subgroup to the therapy. That confirmed the results of previous studies that were done in this field.

Zusammenfassung

Myokardinfarkt (MI) ist der irreversible Tod (Nekrose) des Herzmuskels infolge eines anhaltenden Sauerstoffmangels (Ischämie). Es gibt viele Behandlungsmöglichkeiten für MI, einschließlich, aber nicht beschränkt auf CABG- und Stammzellimplantation. Stammzellregenerative Therapien sind eine vielversprechende Option zur Behandlung vieler Krankheiten. Neue klinische Studien haben die Sicherheit und Wirksamkeit dieser Therapieoption zur Verbesserung der Herzfunktion nach akutem Myokardinfarkt gezeigt, jedoch mit variablen Ergebnissen. Die Unfähigkeit der transplantierten Stammzellen, sich in die Myokardarchitektur zu integrieren, kann das arrhythmogene Risiko für Patienten erhöhen. Dies wurde in dieser Arbeit untersucht und es wurde nachgewiesen, dass es nur zum Teil wahr ist. Die PERFECT RCT Phase III klinische Studie untersuchte die aus dem Knochenmark stammende Stammzelle, die CD133 + exprimiert, in diesem speziellen Aspekt [1]. Die Patientengruppen, die in PERFECT RCT Studie eingenommen wurden, wurden im Rahmen dieser Arbeit weiter analysiert, um zu zeigen, ob diese Stammzelltherapiemethode aus der Ansicht der Arrhythmogenität eine sichere Option ist. Die Patienten wurden in Placebo-Kontrolle und Stammzellgruppe unterteilt. Beide Gruppen wurden je nach Verbesserung der Herzfunktion mit mehr als 5% weiter in Responder- und Non-Responder-Untergruppen eingeteilt. Alle diese Gruppen wurden abgeglichen und überprüft, um unsere Hypothesen zu bestätigen. Das Ergebnis dieser Analyse zeigte zwar einen Anstieg der Inzidenzrate nicht schwerwiegender Arrhythmien (SVES und VES) in Stammzellenguppe, zeigte jedoch auch eine signifikante Verringerung dieser Inzidenzrate über einen Zeitraum von bis zu 180 Tagen nur in der Responder-Subgruppe. Dies bestätigte die Ergebnisse früherer Studien, die auf diesem Gebiet durchgeführt wurden.

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Selbstständigkeitserklärung

Ich erkläre hiermit, dass ich die vorliegende Arbeit ohne unzulässige Hilfe Dritter und ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe; die aus fremden Quellen direkt oder indirekt übernommenen Werken sind als solche kenntlich gemacht.

Die Arbeit wurde bisher weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer Prüfungsbehörde zur Erlangung eines akademischen Grades vorgelegt.

Rostock, den 01.04.2021

(Unterschrift)

[Abdelhalim, Mohamed]
[Lebenslauf]

[Pädagogischer Hintergrund, Bildung und Fähigkeiten]

02.06.2022

Lebenslauf

Persönliche Info:

Voller Name: **“ Mohamed Osama Mohamed Mohsen Abdelhalim”**

Nachname:	**Abdelhalim**
Vorname:	**Mohamed**
Geschlecht:	*Männlich*
Familienstand:	*Ledig*
Staatsangehörigkeit:	*Ägypter*
Geburtsdatum:	*17.08.1985*
Geburtsort:	*Ägypten, Kairo*

kontakt Informationen:

Straße: Wismarsche Str. 50
PLZ/Ort: 18057 Rostock
Land: Deutschland
Mobil: 01797101518
E-Mail: Dr.M.Abdelhalim@gmail.com

Sprachkenntnisse:

1. Deutsch
2. Arabisch
3. Englisch

Schulausbildung:

09.1990 - 06.2003	*Schulbildung in "Hafez Ibrahim experimental school" / Kairo / Ägypten.*
09.2003 - 06.2012	*Medizinische Fakultät der Universität Ain Shams, Ägypten.*
01.09.2012 - 31.08.2013	*Praktisches Jahr.*

Deutsche Anerkennung:

01.08.2013 - 14.06.2014	*Hospitation im Herzzentrum Duisburg in der Klinik für Herzchirurgie.*
20.05.2014	*Deutsche Approbation.*

Tätigkeiten und Weiterbildung:

15.06.2014 - 28.02.2019	*Assistenzarzt der Herzchirurgie im Evangelisches Klinikum Niederrhein (Herzzentrum Duisburg).*
01.04.2019 – 30.09.2019	*Assistenzarzt der Klinik und Poliklinik für Herz-, Thorax-, Gefäßchirurgie der Universitätsmedizin der Johannes-Gutenberg-Universität Mainz*
Seit dem 01.10.2019	*Assistenzarzt der Klinik und Poliklinik für Herzchirurgie der Universitätsmedizin Rostock*

Promotion:

Seit dem 01.10.2019	*Student an der Universität Rostock zur Promotion*
……..	*Promotion*

Fortbildungen:

22.10.2014 - 10.12.2014	*Echo Grundkurz.*
26.01.2015	*Rotem Workshop.*
03.06.2015	*Bronchoskopie Kurz.*

13.10.2015	*Fachkunde im Strahlenschutz in der Röntgen Diagnostik für den Bereich: "Notfalldiagnostik".*
11.06.2016 - 18.06.2016	*"Arzt im Rettungsdienst" Kurs.*
02.01.2017	*Fachkunde im Rettungsdienst.*
22.01.2019	*Fachkunde im Strahlenschutz in der Röntgen Diagnostik für den Bereich: "Gefäßsystem des Herzens" und "Thorax".*
24.01.2019	*Zusatzbezeichnung Notfallmedizin.*
31.08.2020 - 02.09.2020	*Modul I: Basis-Herzschrittmachertherapie*
14.09.2020 – 16.09.2020	*Modul II: Spezielle Herzschrittmachertherapie ICD-, CRT- und CCM-Therapie*
17.09.2020	*Modul III: Revision bei kardialen elektronischen Rhythmusimplantaten*

Fähigkeiten und Interessen:

Persönliche Fähigkeiten :

- Dynamisch, Eigenmotivation, Selbst Lernender und harter Arbeiter.
- Hervorragende schriftliche und mündliche Kommunikationsfähigkeit.
- Gute Protokolle folgender und Laborarbeit.
- Fähigkeit, unter Druck zu arbeiten.
- Fähigkeit zur individuellen oder innerhalb von Gruppen Arbeit.
- Gute Führung und höhe Führungsqualitäten.
- Entscheidungsfindung und Problemlösung.

EDV-Kenntnisse :

- Erfahrung im Orbis sowie SAP
- Experter Microsoft Office-Suite.
- Programmiersprache C # (Microsoft Visual Studio).
- Web - Design (PHP , HTML , XML, Javascript , CSS, Flash).
- Microsoft SQL und MySQL- Datenbanken Implementierung und Wartung.
- Hardware Wartung.
- Aufbau von Netzwerken.