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Review

Shockwave therapy of the heart

Johannes Holfeld*, Daniela Lobenwein, Can Tepeköylü, Michael Grimm

Dept. of Cardiac Surgery, Innsbruck Medical University, Austria

HIGHLIGHTS

- Shockwave therapy of the heart improves heart function after myocardial infarction.
- Shockwave therapy induces angiogenesis and vasculogenesis in infarcted myocardium.
- Shockwave therapy modulates inflammation.

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1. Introduction

Ischemic heart disease represents a collective term for a continuous disease pathophysiology, ranging from acute myocardial infarction to congestive and chronic heart failure. According to the World Health Organization (WHO) and its Global Burden of Disease study 2010 ischemic heart disease represents the most common cause of death and disability-adjusted life years (DALY) worldwide [1]. Due to demographic changes in developed countries with an increase in life expectancy and a changing, more Western lifestyle in threshold countries, the number of patients suffering from ischemic heart disease is expected to rise dramatically in the future, presenting a major challenge for health care systems [1].

2. Myocardial infarction

2.1. Definition, risk factors

Myocardial infarction (MI) occurs due to insufficient oxygen supply of the heart muscle, in the majority of cases because of coronary artery disease [2]. This leads to a severe injury of the affected myocardium [2,3]. Family history of MI, smoking, hypertension, high blood cholesterol levels, as well as overweight and diabetes are main risk factors that contribute to the development of myocardial infarction [1,4].

2.2. Pathophysiology

Insufficient blood supply of the myocardium causes heart attack and myocardial infarction [3]. Myocytes die from hypoxic conditions, become necrotic and release their enzymes, which can be measured in the patient's blood as biomarkers for MI. Lost myocytes get replaced by fibrous tissue and lead to establishment of an infarction scar, comparable to scars after wound healing [3]. Scar tissue does not have the same contractile properties as healthy myocardium and therefore leads to a decrease of heart function by means of left ventricular ejection fraction. Finally, about 50 percent of patients suffering from myocardial infarction develop heart failure with a long-term significantly impaired heart function. This not only dramatically compromises quality of life of those patients but represents a severe socio-economic health burden due to the need of repeated hospitalization of heart failure patients.

Besides optimized drug therapy, revascularization is the gold standard after MI. Performed either via percutaneous intervention and stent implantation or as coronary artery bypass graft surgery (CABG) it is still limited by non-viable myocardium.

3. Regeneration of infarcted myocardium

Three main approaches exist in cardiovascular research focusing

* Corresponding author. Department of Cardiac Surgery, Innsbruck Medical University, Anichstraße 35, 6020 Innsbruck, Austria.
E-mail address: johannes.holfeld@i-med.ac.at (J. Holfeld).

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on the regeneration of infarcted myocardium. This involves (stem) cell therapy, gene therapy and tissue engineering [5–7]. However, none of them has yet gained broad clinical use as of low efficiency, severe side effects, ethical concerns or technical challenges in application.

Due to the low clinical feasibility of these current treatment possibilites, there is an urgent need for new treatment approaches to regenerate ischemically damaged myocardium. The main target for new regeneration therapies is the so-called "hibernating myocardium" or peri-infarction zone, whose function could potentially be restored by regenerative mechanisms and increased blood supply Fig. 1.

3.1. Angiogenesis

Angiogenesis is defined as the sprouting of capillaries from pre-existing vessels [11,12]. Briefly, angiogenesis starts with the release of proangiogenic chemokines and growth factors such as Vascular Endothelial Growth Factor (VEGF) due to various stimuli, of which the most potent is hypoxia itself being represented by an increase of HIF1α (Hypoxia inducible factor 1 alpha). As a consequence, endothelial cells that previously formed the intimal layer of the vessel, begin to sprout and migrate along a chemokine gradient in the surrounding tissue [13,14]. In order to maintain vessel integrity and reach stabilization of newly formed capillaries, endothelial cells recruit and interact with vessel covering pericytes. Maturation of vessels from capillaries to arterioles is mainly triggered by Placental Growth Factor (PlGF) [11,13].

3.2. Postnatal vasculogenesis

Postnatal vasculogenesis is defined as the *de novo* development of vessels, mainly formed of circulating endothelial progenitor cells (EPCs) and vascular progenitor cells [15,16]. EPCs as well as vascular progenitor cells derive from stem cells of the bone marrow. The most important chemoattractant for the mobilization and recruitment of EPCs is Stromal cell derived factor-1 (SDF-1) that is bound to the C-X-C chemokine receptor type 4 (CXCR-4) on EPCs [16]. SDF-1 is upregulated in ischemic tissues. Therefore it is hypothesized that induction of vasculogenesis could be a therapeutical strategy in the setting of peripheral as well as coronary artery [17].

4. Cardiac shock wave therapy

4.1. Extracorporal shock wave therapy

Shock Wave Therapy (SWT) was proven beneficial for regeneration of soft tissue disturbances, such as chronic tendinopathies, muscular pathologies, non-healing diabetic ulcers and non-union fractures. The question arose whether these regenerative effects could possibly be achieved in ischemic myocardial tissue as well. Shock wave therapy has been used for lithotripsy in much higher energies than applied on soft tissue or myocardium for more than 30 years. To-date no severe side effects could be observed, and SWT is therefore seen as a safe technology.

4.2. ESWT in the experimental setting

First experiments applying extracorporal SWT in a porcine model of chronic heart ischemia showed a significantly higher number of vessels, as well as a significant improvement of systolic function in the animals of the SWT group compared to the control group [18].

4.3. ESWT in the clinical setting

Following this a clinical trial using extracorporal SWT in patients with coronary artery disease suffering from angina symptoms, who had no indication for PCI or CABG treatment, was performed [19]. Patients enrolled in the study reported a significant improvement in angina symptoms and an increased myocardial blood flow was measured in the SWT group [19]. Extracorporeal cardiac shockwave therapy today is applied in a repeated manner (2–3 applications per week, 9 applications in general) ultrasound guided from a subxyphoidal position. Thereby, its strength is the reduction of angina symptoms, whereas a significant increase in left ventricular ejection fraction could not be shown.

4.4. Modes of delivery of ESWT to myocardium

Extracorporeal cardiac SWT bares the risk of potential lung injury and is limited to certain areas of the heart because lungs, sternum and ribs open a quite small acoustic window to the heart. Therefore, direct epicardial shock wave therapy (DESWT) was developed. Extracorporeal cardiac shock wave therapy bares the risk of lung injury, whereas direct epicardial cardiac shock wave therapy prevents this possible complication. Apart from that no clinical procedural complications have been reported. It has shown promising results in pre-clinical studies and a clinical pilot trial, thereby applied during coronary artery bypass graft surgery (CABG). The benefit of DESWT is the accessibility of the whole heart and its efficacy showing marked functional improvement of the heart (LVEF) without need for repeated application. However, the surgical access is still very invasive and DESWT can therefore be used for CABG patients only [20,21]. Nevertheless, the impressive effects and the advantages of whole heart treatment urge us to further develop this technique being thought to get minimally-invasive in future days.

5. Mechanisms

Although shock waves are in broad clinical use for more than 30 years now and have been applied in a wide variety of bone and soft tissue indications, the exact working mechanism remains largely unknown. Early evidence was found for angiogenesis [22]. Some years later vasculogenesis could be proven [23] Fig. 2. However, the exact mechanism of mechanotransduction, as the link between shock wave therapy application and molecular mechanisms, still needs to be elucidated. Mechanotransduction means the translation of the physical stimulus to a biological response. At the example of direct epicardial application, the following sections aims to illustrate the evolving knowledge of molecular mechanisms of cardiac shock wave therapy. Moreover, SWT appears to initiate the same mechanisms in each tissue, rendering new findings in these pathways interesting for all applications of SWT.

5.1. Angiogenesis in rodent model

In order to investigate these biological mechanisms more thoroughly and test whether these effects also could be observed with direct epicardial shock wave therapy (DESWT), we conducted a rodent animal model of chronic heart ischemia. 8- to 10-week-old Sprague–Dawley rats underwent left anterior deschending coronary artery (LAD) ligation. Animals in the treatment group received 4 weeks after the procedure 300 shock wave impulses to the left ventricular anterior wall by using a CardioGold® SWT system with a specially designed applicator (TRT Llc, Woodstock, Georgia, USA). CardioGold® uses a parabolic reflector that allows treatment of a target area with a diameter of 0.5–0.7 mm and a penetration depth

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of 1–1.5 cm. However, device as well as applicator are not on the market and were designed for experimental use only. The used energy flux density (0.38 mJ/mm^2) and the cumulative treatment dose are based on our experience with the treatment of acute and chronic wounds, as well as diabetic and vascular ulcers.

Histologic analysis revealed significantly more vital cells and more vWF positive endothelial cells in the left ventricular anterior wall of treatment animals compared to controls. Both of this results indicated angiogenesis. Vessel counting showed higher numbers of vessels in the anterior wall of treatment animals of every size including large vessels >20 μm that could even be arterioles. This increased microvascular density may be one key factor for improved functional outcome of these animals [20].

In addition up-regulation of mRNA expression of the angiogenetic growth factors VEGF and PlGF was observed 24 h, 48 h and 7 days after DESWT in the treatment group compared to controls. Both are a well-known promotors of angiogenesis. Both have been shown to improve regional blood flow when injected directly into ischemic myocardium. PlGF reportedly amplifies the angiogenetic activity of VEGF and stimulates the maturation of vessels through coverage with smooth muscle cells. This leads to stabilization and durability of new vessels [20].

5.2. Proof of concept in a porcine model

In order to validate the efficacy, feasibility and safety of direct epicaridal shock wave therapy and to further investigate the biological mechanism in a close to human setting, a porcine animal model of chronic heart ischemia was performed [21]. Pigs underwent LAD ligation, followed by thoracotomy and epicardial SWT 4 weeks after ligation in the SWT group. In animals of the treatment group, a total of 300 shock wave impulses (energy flux density of 0.38 mJ/mm^2) were applied to the cardiac anterior wall including the infarction scar as well as the peri-infarction area using the CardioGold® SWT system An identical procedure without application of SWT was performed in the control group. In order to investigate the effects of SWT on healthy myocardium, a third group was studied (SWT only): thoracotomy without LAD ligation (sham operation) and 6 weeks later, re-thoracotomy with SWT treatment to healthy non-infarcted myocardium.

Baseline left ventricular ejection fraction was comparable between the treatment and control group. Four weeks after LAD ligation (before re-operation with or without SWT) LVEF was decreased in treatment and control animals compared with baseline values. Six weeks after SWT LVEF significantly improved in the treatment group. Left ventricular function remained impaired in the control group 6 weeks after treatment.

With regard to regional wall motion we echocardiographically observed a conversion of dyskinetic to akinetic areas in the treatment group as a structural prerequisite for improvement of LVEF. In addition quantitative histologic analysis of the left ventricular anterior wall revealed a significantly higher number of vessels that were larger in diameter, indicating a higher micro-vascular density in the treatment group compared to the control group 6 weeks after treatment. Moreover higher numbers of vWF-positive endothelial cells as well as more vital cells in the anterior heart wall were observed in the treatment group compared to the control group 6 and 8 weeks after treatment.

5.3. Vasculogenesis in rodents

Small animal studies showed that SWT was able to recruite injected exogenous endothelial progenitor cells to ischemic tissue. We wanted to investigate whether SWT also could attract endogenous bone-marrow derived endothelial progenitor cells [24]. Therefore we performed a rodent animal model of chronic hind limb ischemia by excision of the femoral vessels. Three weeks after surgery, animals in the treatment group received SWT to ischemic muscles.

Flow cytometry analysis of peripheral blood revealed a significantly higher number of CD31/34 positive cells 24 h after SWT compared to untreated controls. Interestingly, one week after treatment the number of circulating progenitors was still elevated whereas 6 weeks later no difference between treatment and control animals could be observed. This elevation of circulating EPCs over the time indicates an early mobilization of EPCs having its peak after 24 h and lasting about 1 week. At later time points these cells obviously may already have been migrated to the target muscle as shown at 6 weeks after SWT.

Hypoxia inducible factor 1α (HIF-1α) plays a crucial role in the regulation of stromal cell-derived factor 1 (SDF-1). SDF-1 itself serves as one of the most potent chemoattractants for recruitment of EPCs from bone marrow. Significantly increased mRNA levels of HIF-1α and SDF-1 were found in treated muscles compared to untreated controls. At the same time SDF-1 receptor CXCR-4 was upregulated significantly. Vascular endothelial growth factor (VEGF) was as well upregulated in both the treatment and the control group 24 h after SWT. However, this level remained to be significantly higher after 6 weeks in the treatment group compared to controls. VEGF not only is well known as the pivotal angiogenic growth factor, but also for its major chemoattractive effect towards EPCs.

Immunohistochemical staining for CD31 positive cells revealed significantly higher numbers of endothelial cells in SW treated muscle after which contribute to new vessel formation.

Significantly higher numbers of proliferating cells were found in the treatment group shown by PCNA staining. Besides the hypothesis of endothelial progenitor recruitment this indicates additional vessel sprouting in parallel.

Blood perfusion of hind limbs was measured by laser Doppler perfusion imaging 6 weeks after treatment. Significant improvement could be observed in the treatment group.

5.4. Modulation of inflammation

The pathophysiology of myocardial infarction represents tissue necrosis accompanied by an inflammatory reaction that finally

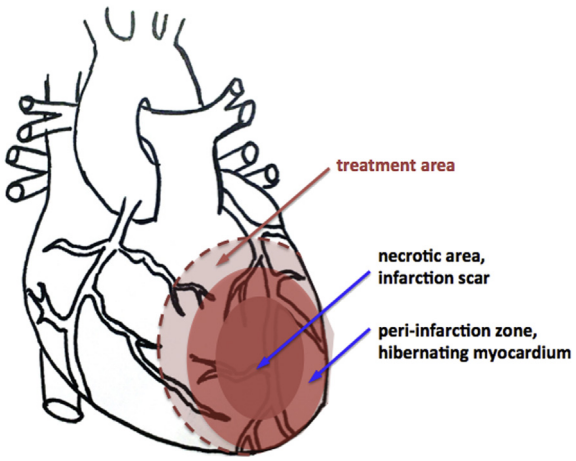

Fig. 1. Schematic drawing depicting the central necrotic area of a myocardial infarction representing the non-viable infarction scar. This is surrounded with the peri-infarction zone consisting of the so-called hibernating myocardium. It is chronically undersupplied with blood and thereby oxygen as well as nutrients. This area can be recovered by shock wave treatment leading to improved heart function.

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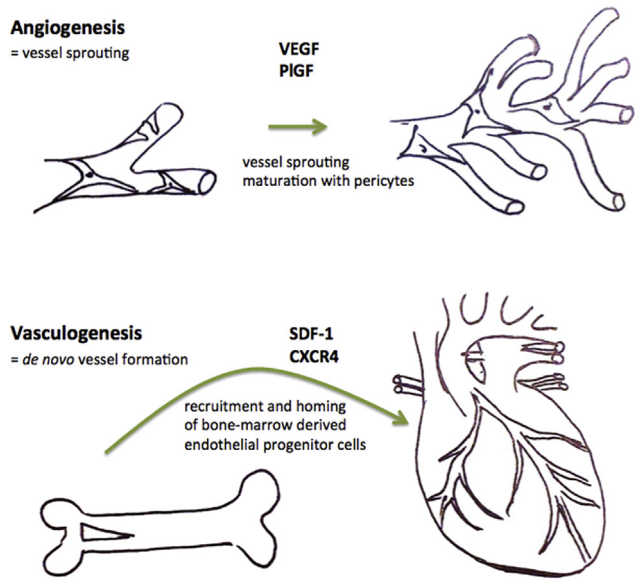

Fig. 2. Angiogenesis and vasculogenesis appear to be the pivotal effects of shockwave therapy leading to healing and regeneration of harmed tissue. Angiogenesis is mainly mediated by growth factors VEGF and PlGF whereas vasculogenesis depends on the SDF-1/CXCR4 axis.

leads to fibrose tissue and scar formation. Angiogenesis as well as wound healing depend on inflammation in a specific timely manner. Moreover angiogenesis and inflammation are not only related processes, they are also capable of influencing and potentiating each other. Thereby, it is noteworthy to recognize that neither initiation nor suppression of inflammation is the sole effect induced by shock wave therapy and neither of it is solely positive for tissue regeneration. The clue is modulation of inflammation in an at least bi-phasic manner over time in order to create the milieu for regeneration [25].

Our experiments showed a significant activation and increased expression of Toll-like Receptor 3 (TLR3), a receptor that is part of the innate immune system and responsible to recognize nucleic acids. We detected enhanced expression of TLR3 and of the transporter protein for nucleic acids cyclophilin B, of pro-inflammatory cytokines cyclophilin A and interleukin-6 and of anti-inflammatory interleukin-10 in a time-dependent manner. No changes were found in the expression of vascular endothelial cell adhesion molecule. We thereby have been able to show that SWT modulates inflammation via the TLR3 pathway. The interaction between interleukin 6 and IL-10 in TLR3 stimulation can be schematically seen as a three-phase regulation over time [25].

6. Conclusion

The number of patients suffering from ischemic heart disease will dramatically increase within the next years, representing an enormous problem to healthcare systems. Current treatment strategies fail to regenerate ischemic myocardium, and offer therefore only symptomatic relief. Shock wave therapy was shown to induce regeneration in various tissues, amongst others also in ischemic myocardium. There is increasing knowledge about the mechanism of shockwave therapy, such as angiogenesis, growth factor release, NO release and many others. Although in many publications referred to as mechanisms of shockwave therapy this term appears to be misleading as the real working mechanism, the so-called mechanotransduction, fully remains to be elucidated. To our knowledge today the mechanism seems to be closely related to Toll-like receptor 3 stimulation on endothelial cells, which our group discovered in recent experiments [25,26].

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Author contribution

All stated authors contributed in writing this review paper.

Conflicts of interest

None.

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