

Journal für **Kardiologie**

Austrian Journal of Cardiology

Österreichische Zeitschrift für Herz-Kreislauserkrankungen

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Mayr A, Theurl M, Schreinlechner M

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Journal für Kardiologie - Austrian

Journal of Cardiology 2019; 26

(11-12), 328-331

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Safety and Efficacy of Cardiac Shockwave Therapy in Patients undergoing CABG surgery

F. Nägele¹, L. Pölzl¹, J. Hirsch¹, M. Graber¹, D. Lobenwein¹, M. Mitrovic², A. Mayr³, M. Theurl⁴, M. Schreinlechner⁴, M. Pamminer³, C. Dorfmueller⁵, M. Grimm¹, C. Gollmann-Tepeköylü¹, J. Holfeld¹

¹University Clinic of Cardiac Surgery, Medical University of Innsbruck; ²Clinical Trial Center, Medical University of Innsbruck; ³University Clinic of Radiology, Medical University of Innsbruck; ⁴University Clinic of Internal Medicine III, Medical University of Innsbruck; ⁵Heart Regeneration Technologies GmbH, Innsbruck, Austria

Introduction

Despite of modern revascularization techniques, coronary artery disease (CAD) remains a severe socio-economic burden as it still accounts for the majority of chronic heart failure patients not only in industrialized nations but worldwide. Ischemic heart disease and subsequently, chronic heart failure is the number one cause of death worldwide and has risen from 6.5 Mio per year in 2000 to nearly 9 Mio per year in 2016 [1]. 5-year mortality rates are as high as 50%, even with modern drug and device therapy [2]. Numerous studies, across a range of modalities, have clearly shown that most patients with ischemic heart disease suffer from reduced left ventricular ejection fraction (HFrEF). In general, transmural infarction accounts for this myocardial dysfunction as contractile myocardium is replaced by fibrotic scar tissue upon coronary artery obstruction. Not all patients who are suffering from HFrEF have clinical or imaging evidence of acute infarction, and function is commonly impaired in myocardial segments that still show preserved metabolic activity surrounding the fibrotic area. These peri-infarction zones are also known as “hibernating myocardium”. Shahbudin Rahimtoola was the first to describe the theory of an adaptive functional down-regulation of ischemic myocardium to reduce oxygen demand and thereby prevent myocyte necrosis, namely hibernation,

in 1985 [3]. Three decades later, this attractive pathophysiological target in heart failure of dysfunctional myocardium that could be “switched back on” to reverse this fatal disease remains to be fully exhausted. Currently available therapeutic options, including (stem) cell therapy, gene therapy, cellular reprogramming, or tissue engineering, remain purely experimental.

Further, it has been discovered that some pioneering stem cell trials have unexplained discrepancies that drive doubt over their validity. In a systemic exploration, it could even be shown that clinical studies with progressively higher effects on ejection fraction upon stem cell therapy tend to show gradually more discrepancies [4]. Thus, there is an urgent clinical need for new options to target hibernating myocardium and thereby alleviate the symptoms, progression, mortality, and cost of heart failure (Fig. 1–3).

Shock wave therapy

Shockwaves are naturally occurring, specific types of sound pressure waves initiated by a sudden release of energy, e.g. thunder when lightning. For more than 30 years, shockwaves are used in clinical routine to disintegrate kidney stones, a procedure called lithotripsy. At low energy levels shockwaves

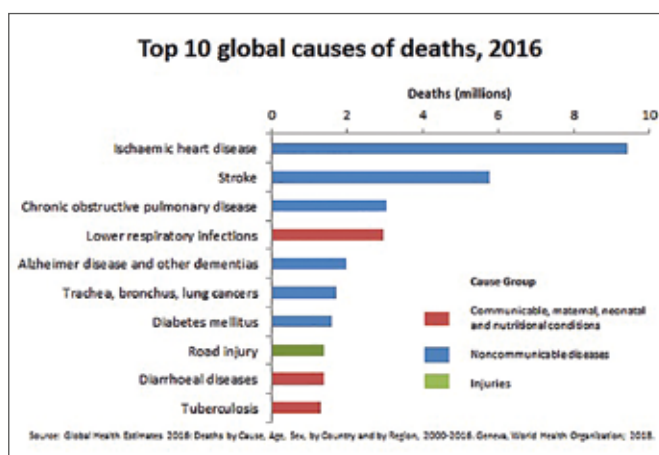


Figure 1. Top 10 global causes of death (WHO 2016). From [1], Creative Commons licence CC-BY-NC-SA 3.0 IGO.

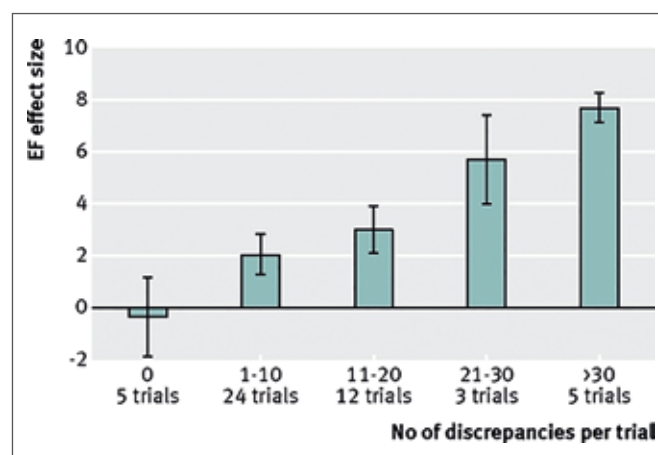


Figure 2. Discrepancy count is related to effect size in bone marrow stem cell therapy trials. From [4], Creative Commons licence CC-BY-NC.

were shown to have a regenerative effect on non-healing bone fractures, chronic tendon pathologies (e.g. tendonitis calcarea and heel spur) as well as in wound healing disturbances [5]. In some orthopedic and traumatologic indications shockwave therapy is considered the gold standard for treatment and in part reimbursed by public health insurance.

Although impressive effects of shockwave therapy were shown in numerous clinical trials and the indications in the daily clinical routine were continuously broadened, the underlying working mechanism remained largely unknown. Our group started working on elucidating the mechanisms of those regenerative effects with a particular interest in cardiac regeneration already in 2005. Numerous pre-clinical experiments in small and large animals showed encouraging results [6–8].

In animal models of acute and chronic ischemia shockwave therapy was shown to exert a marked improvement of left ventricular ejection fraction [7, 8]. An increased number of capillaries and arterioles within the hibernating myocardium was found as well as upregulation of pivotal angiogenic growth factors, such as VEGF and PlGF [8, 9]. Besides the outgrowth from existing vessels (angiogenesis) even de-novo vessel formation from endothelial progenitor cells recruited from bone marrow could be observed [8]. Ongoing studies further show a clear hint that transdifferentiation of cardiac fibroblasts towards endothelial cells may as well be involved.

The translation of the physical stimulus of shockwaves to a biological signal (“mechanotransduction”) is induced by a mechanical release of specific microvesicles from treated cells [6]. These so-called Exosomes carry proteins, enzymes, amino acids and other substances that lead to a stimulation of Toll-like receptor 3 (Tlr3). This receptor is part of the innate immune system and its signaling leads to the release of inflammatory cytokines which via the Akt/ERK pathway stimulate angiogenesis and vasculogenesis. The effect of shockwave therapy is completely abolished in mice lacking Toll-like receptor 3 (Tlr3^{-/-}) [10].

The fact that shockwaves indirectly stimulate a highly conserved innate immune receptor may explain why this new therapy is extremely powerful and at the same time shows no side-effects. In contrast to (stem) cell or gene therapy approaches shockwave therapy stimulates endogenous effects without adding or applying any foreign agent to the organism (Fig. 4, 5).

■ CAST-Trial

The mentioned preclinical findings provided the basis for translation into a clinical setting. In a first-in-man pilot study, ten patients with severe left ventricular dysfunction due to a post-infarctional transmural scar and an indication for CABG were treated with direct epicardial SWT in addition to standard CABG surgery. Direct cardiac shock wave therapy could successfully be performed in all patients. There were no severe side effects observed neither upon treatment

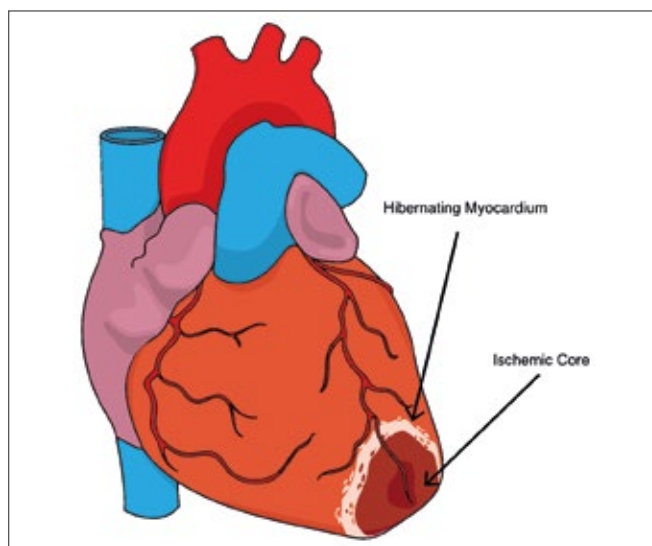


Figure 3. Hibernating myocardium shows reduced blood flow and contractile dysfunction, in the absence of acute ischemia or significant fibrosis. © J. Holfeld.

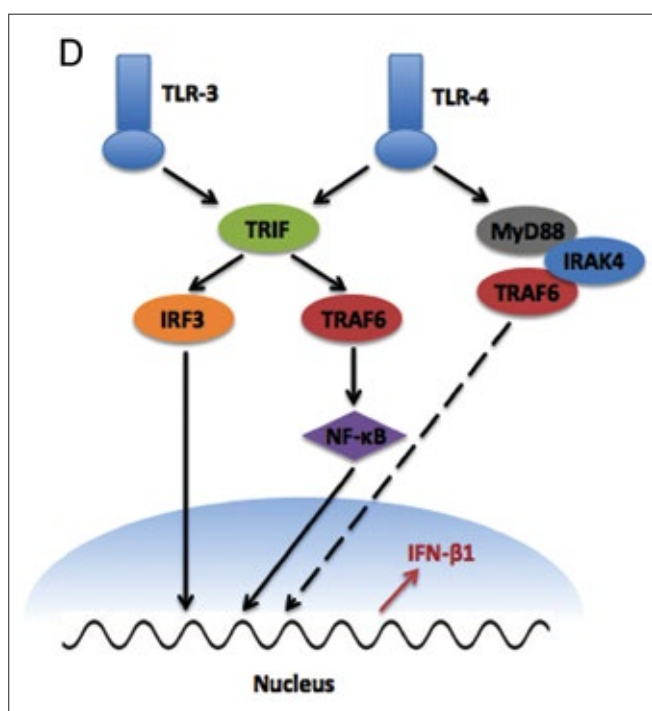


Figure 4. TLR3 and TLR4 signalling pathways both involve TRIF. TLR3 involves IRF3 and TRAF6, while TLR4 acts via MyD88 signalling as well. From [10], by permission of Oxford University Press.

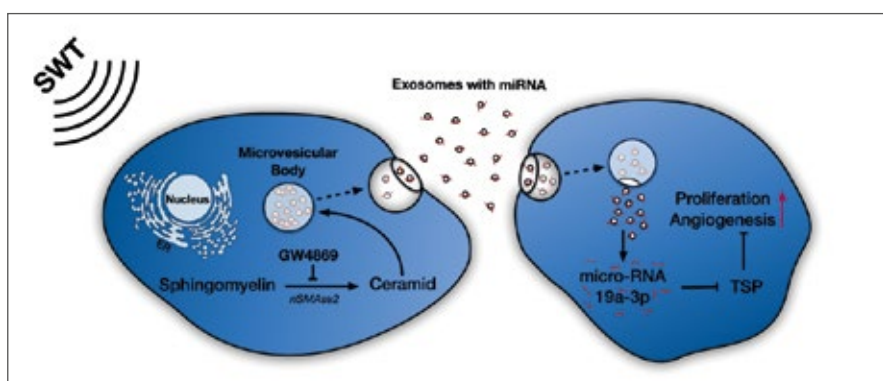


Figure 5. Suggested mechanism of angiogenic SWT effects. From [6], by permission of Oxford University Press.

(intraoperative arrhythmias, cardiac hematoma formation, lacerations with causal relation to shock wave therapy), nor in the six-month follow-up period. Hence, this first-in-men application proved safety and feasibility of the new therapy and the underlying medical device (study unpublished). We therefore hypothesized that direct cardiac SWT is a safe and feasible adjunctive therapy to CABG, in particular for patients with large areas of dysfunctional myocardium due to ischemia. Up to date, no published data on direct cardiac SWT in humans exist. The CAST trial (ClinicalTrials.gov Identifier: NCT03859466) is a prospective, single-blind, randomized controlled, single-center study assessing the efficacy and safety of cardiac shockwave therapy adjunctive to CABG. 80 male or female patients above 21 and under 80 years of age with reduced left ventricular function ($LVEF \leq 40\%$) and regional left ventricular wall motion abnormalities undergoing primary



Figure 6. Intra-operative shockwave therapy during coronary artery bypass surgery. Saline is used as a coupling medium between the shockwave applicator and the myocardium.

CABG are randomly assigned in a 1:1 ratio to receive additional cardiac SWT (intervention group; 40 patients) or CABG surgery alone (control group; 40 patients).

The CAST trial is a monocenter, prospective, randomized controlled, single-blind study.

The following null-hypothesis will be tested: There will be no difference in LVEF between the two study groups one year after treatment.

Alternative hypothesis: There will be a significant increase of the primary endpoint LVEF in the shockwave group compared to the control group one year after treatment.

Inclusion Criteria	Exclusion Criteria
- Male or female patients above 21 and under 80 years of age undergoing primary coronary artery bypass grafting. - Patients have to present with reduced left ventricular function defined as $LVEF \leq 40\%$. - Patients have to present with regional left ventricular wall motion abnormalities. - Patients have to give written informed consent to participate in the study.	- Significant concomitant aortic valve disease in need of surgical treatment (except significant aortic valve disease not detected in preoperative cardiac ultrasound that is detected intra-operatively). - Serious radiographic contrast allergy. - Patients in cardiogenic shock. - Patients with a contraindication for cardiac MRI. - History of significant ventricular arrhythmias, except arrhythmias associated with MI. - Present co-morbidity which reduces life expectancy to less than 1 year. - Presence of ventricular thrombus. - Presence of a cardiac tumor. - Pregnancy.

The duration of the planned recruitment phase consists of 24 months. The Study will end 12 months after inclusion of the last patient. The duration of SWT for each patient is approximately 15 minutes (Fig. 6)

Conclusion

Currently, there is no therapeutic treatment option for chronic heart failure available. Doubts over stem cell therapies are increasing and further strategies remain purely experimental e.g. gene therapy. Shockwave therapy has been in medical routine use for over 30 years and is tested in millions of patients with various indications. It is proven to be safe and does not cause any (long-term) side effects. Our study group was able to elucidate

in-vitro mechanistic data, necessary to perform small animal mechanistic and efficacy studies which were then expanded to large animal efficacy and feasibility studies. A first-in men clinical pilot trial of cardiac shockwave therapy adjunctive to CABG surgery has already been successfully performed. In the currently ongoing CAST-trial we are evaluating on safety and feasibility of cardiac shockwave therapy in a monocenter RCT fashion.

www.cast-trial.com

References:

1. WHO. The top 10 causes of death. <https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death> (2018) (last seen 28.10.2019) .
2. Ryan MJ, Perera D. Identifying and managing hibernating myocardium: What's new and what remains unknown? *Curr Heart Fail Rep* 2018; 15: 214–23.
3. Rahimtoola SH. The hibernating myocardium. *Am Heart J* 1989; 117: 211–21.
4. Nowbar AN, et al. Discrepancies in autologous bone marrow stem cell trials and enhancement of ejection fraction (DAMASCENE): weighted regression and meta-analysis. *BMJ* 2014; 348: g2688.
5. Schaden W, et al. Extracorporeal shock-wave therapy (ESWT) – First choice treatment of fracture non-unions? *Int J Surg* 2015; 24: 179–83.
6. Gollmann-Tepeköylü C, et al. miR-19a-3p containing exosomes improve function of ischaemic myocardium upon shock wave therapy. *Cardiovasc Res* 2019; [E-pub ahead of print].
7. Tepeköylü C, et al. Shockwaves prevent from heart failure after acute myocardial ischaemia via RNA/protein complexes. *J Cell Mol Med* 2017; 21: 791–801.
8. Gollmann-Tepeköylü C, et al. Shock wave therapy improves cardiac function in a model of chronic ischemic heart failure: Evidence for a mechanism involving vegf signaling and the extracellular matrix. *J Am Heart Assoc* 2018; 7: e010025.
9. Holfeld J, et al. Epicardial shock-wave therapy improves ventricular function in a porcine model of ischaemic heart disease. *J Tissue Eng Regen Med* 2016; 10: 1057–64.
10. Holfeld, J. et al. Toll-like receptor 3 signalling mediates angiogenic response upon shock wave treatment of ischaemic muscle. *Cardiovasc Res* 2016; 109: 331–43.

Correspondence to:

Johannes Holfeld, MD

University Clinic of Cardiac Surgery, Medical University of Innsbruck

Innrain 52, 6020 Innsbruck, Austria

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