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The beneficial effect of extracorporeal shockwave myocardial revascularization in patients with refractory angina

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ABSTRACT

Objectives: The incidence of patients with refractory angina (RA) is increasing. Medical therapy for RA is limited and prognosis is poor. Experimental data suggest that the use of Extracorporeal shockwave myocardial revascularization (ESMR) may contribute to angiogenesis and improve symptoms of angina in patients with RA. Purpose of our study is to determine the efficacy of cardiac shock wave therapy (ESMR) in the management of patients with nonrevascolarized coronary artery disease (CAD).
Methods: We performed a prospective cohort study to examine the efficacy of ESMR applcation in patients with RA despite optimal medical therapy, not suitable for further PCI or CABG. Characteristics such as angina class scores (CCS class score), nitroglycerin consumption and hospitalization rate among cases (patients with RA who received ESMR) and controls (patients with RA who did not receive ESMR) were compared at baseline and 6 months after ESMR therapy. In patients receiveing d ESMR the effect of on cardiac perfusion was assessed.
Results: There were 43 patients in the case group and 29 patients in the control group. The mean age of the patients was 70 ± 9.5 years in the case group and 71 ± 5.3 years in the control group. Other characteristics (diabetes, coronary artery bypass graft, percutaneus coronary intervention, baseline CCS class score) were similar in both groups. There was a significant improvement in CCS class score (1.33 ± 0.57 in cases and 1.92 ± 0.69 in controls; $p = 0.0002$), nitroglycerin consumption (20% in case cases, and 44.8% in controls; $P < 0.03$) and hospitalization rate significantly reduced (13.9% in case cases, and 37.9% in controls; $P < 0.03$). The patients who received ESMR, there was a significantly improvement in myocardial perfusion after 6 months with a 33% relative reduction of summed stress score (SSS) ($p = 0.002$).
Conclusion: This case control study demonstrates the beneficial effect of ESMR therapy on cardiac symptoms, myocardial perfusion and reduced hospitalization in patients with refractory angina. Ther current study supports a role for ESMR as a non-invasive therapuetic option for patients with RA.

1. Introduction

Refractory angina in patients without revascularization options (RA) is a growing clinical concern,. The prognosis and the quality of life in these patients is reduced and conventional medical therapy is frequently inadeguate for symptom relief. According to the last ACC/AHA guidelines on the management of chronic stable angina, the goal of the treatment should be the elimination of chest pain reduce hospitatlizations, cost and the restoration of normal activities [1]. Despite the continued growth in myocardial revascularization most patients continue to require antianginal drugs; furthermore, despite both revascularization and optimal pharmacotherapy, up to 26% of patients still experience limiting symptoms [2–5].

Previous studies showed other modalities of treatment such as transmyocardial laser revascularization during CABG with proved reduction of symptoms in patients with diffuse coronary disease not amenable to conventional revascularization. Newer approaches such as gene therapy promoting angiogenesis and stem cell transplantation so far failed or are still at in a pre-clinical stage and are invasive in nature [6–9].

Shockwave therapy has been used in the last decades in other medical fields such urology and in the treatment of several orthopedic settings [10,11]. Extracorporeal Shockwave Myocardial Revascularization therapy (ESMR) is a new non-invasive treatment that may improve myocardial perfusion and reduce symptoms of myocardial ischemia, through the application of shockwaves (SW), i.e. special acoustic waves that can be targeted and focused on a selected area of the heart under echocardiographic guidance [12].

High-energy extracorporeal shock-wave ther- apy (ESWT) was introduced for medical use 30 years ago as a treatment for ureteral

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stones [13]. ESWT has changed the treatment of uro- lithiasis, and even today remains the primary treatment for most uncomplicated upper urinary tract calculi [14]. The 'destroyer-use' of high-energy SWs is different from the more recent 'regenerative-use' of low-energy SWs. Low-energy ESWT has been developed as a treatment standard or alternative therapy for a variety of orthopaedic and soft tissue diseases [15,16]. The observed immediate increase in blood flow due to local vasodilation and the formation of new capillaries in the treated tissue [17,18] has led to one of its more promising application in cardiovascular medicine as a possible therapy for patients with refractory angina. Shock waves consist of acoustic energy that can be transmitted in a liquid medium and focused with precision of several millimeters to any intended treatment area inside the body. The energy density describes the maximum amount of acoustical energy which is transmitted per pulse, and varies among different uses of shock waves, from 0.09 mJ/mm^2 in cardiology up to 0.9–1.8 mJ/mm^2 in lithotripsy.

Shock waves can be artificially generated by discharge of a high voltage spark under water. Cardiac shock wave therapy (ESMR) is performed using a generator system designed to address the clinical anatomical requirements of the chest cavity. A cardiac ultrasound imaging system is used to locate the treatment area with documented ischemia. Shock waves are then delivered via a special applicator through the anatomical acoustic window to the treatment area under electrocardiographic R-wave gating. Several treatment sessions are required. At each session, shock waves are delivered to the border of the ischemic area, to potentially induce neovascularization from the healthy area to the ischemic area.

The precise mechanisms remain to be elucidated, two major effects may contribute to the previous observations: immediate vasodilatation, and the induction of neovascularization in the treated tissue, which most likely accounts for the observed longterm effects. It has been described that shock wave may induce tissue cavitation, generating highly localized physical forces which could produce localized stress on cell membranes. This would lead to a variety of biochemical effects including: shear stress on cell membranes [19], hyperpolarization and Ras acti- vation [20], an increase in nitric oxide synthesis [21–23], an upregulation of VEGF, its recep- tor Flt-1 and PGF [24–26], in addition to an enhance expression of stromal-derived factor-1 [27]. Another potential cellular mechanism may involve the recruitment of progenitor cells to the site of the ischemia undergoing ESMR [28–29]. Thus, we can conclude that there are probably multiples angiogenic pathways involved in the beneficial effects of ESMR.

The purpose of our study is to determine the efficacy of cardiac shock wave therapy as an adjunct therapy in the management of patients with refractory angina compared to standard therapy.

Our study can be considered an extension of a previous multicenter study performed by the group at the Mayo Clinic, in which, however, there was no control group [30].

2. Methods

The study was approved by the institutional review board, and informed consent was obtained from all participants prior to inclusion.

2.1. Patient selection

Entry criteria included age > 18 years, documentated history of CAD with at least three months of refractory angina, coronary disease not amenable for revascularization, as was determined by an interventional cardioogust and cardiac surgeon and stable maximal medical therapy for at least 6 weeks.

Patients were excluded if they had a history of myocardial infarction or unstable angina within previous 3 months, active acute myocarditis, periarditis, or left ventricular thrombus, significant valve disease, cardiac malignanancyies, chronic pulmonary disease (included emphysema and pulmonary fibrosis), endocarditis, and pregnancy.

The options were discussed with each patient in order to exclude any options of revascularization and to reject patients with a non-adequate chest acoustic window.

72 patients were included in the prospective study, 43 patients in the treatment group; patients who received ESMR and 29 patients in the controls group, patients who did not receive ESMR. Clinical and demographic characteristics such as angina class scores (CCS class score), nitroglycerin consumption (consuming nitrates occasionally as oral spray or sublingual tablets) and hospitalization rate (presentation to the emergency room or hospital admissions) among cases and controls were recorded and compared at baseline and 6 months after ESMR therapy between the groups. In all 72 patients we also evaluated the improvement in cardiac perfusion as the reduction in single-photon emission computed tomography (SPECT) summed stress score (SSS) and summed rest score (SRS) at baseline. In patients who received shock wave therapy we also evaluated the improvement in cardiac perfusion (SPECT) summed stress score (SSS) and summed rest score (SRS) at 6 months. The control group was composed of patients who met the inlusin/excusion cretiria but for for different reasons could not undergo the treatment (poor acoustic window, declined to participate, and 2 patiens with absence of significant inducible ischemia at SPECT). The two patients with myocardial ischemia are not significant, however, were included in the control group because they still had a small positive scintigraphy; we decided not to treat them because the territory was not extended to at least two myocardial segments.

This study is not randomized, but case–control study. We followed the patients treated and those who were excluded from treatment, to see if there were any differences in follow-up between the two groups. The two groups (although numerically different) were, however, uniform.

2.2. Single-photon emission computed tomography (SPECT)

All patients underwent a single-photon emission computed tomography (SPECT) at the start of treatment and the 43 patients treated with shock wave therapy after 6 months. The 29 patients who did not receive the shock waves not performed SPECT control after 6 months for ethical questions. All images were acquired and processed according to the American Society of Nuclear Cardiology guidelines using either single-day or 2-day (depending on body weight) stress/rest–technetium-99 m sestamibi. Imaging was started 60 min after the tracer injection at rest or exercise. Identical doses of the tracer were used for the baseline and follow-up studies. All raw data of gated SPECT images (2 sets per patient before and 2 sets for patient after 6 months) were reconstructed using standard back-projection and identical filtering (Butterworth filter with a critical frequency of 0.4 cycles/s, order 5). Motion correction was applied before image reconstruction if >1 pixel of x or y axis deviation was observed over the 180° acquisition. No attenuation correction was used.

Quantitative SPECT was performed using a previously validated automated program that determines the extent and severity of LV perfusion defect size and the extent of reversible (ischemia) or fixed (scar) perfusion defects. Severity of ischemia was calculated as the percentage of count improvement toward normal values within ischemic pixels and defined as minimal (0–25% improvement), moderate (2–50% improvement), or marked (>50% improvement).

In addition, the automated program was used to derive the summed stress score, summed rest score, and summed difference score (SDS) based on conventional 17-segment model. The program assigned a score of 0 to 5 to each segment based on activity level: 0 = normal and 5 = absent. All data reported here are based on automated analysis of the data. In addition to perfusion data, the LV ejection fraction, end-diastolic volume, and end-systolic volume were measured from the gated SPECT as previously described.

At the conclusion of the protocol, the images were again interpreted side by side in a blinded fashion by 1 reader to qualitatively grade the perfusion pattern as improved, worsened, or no change.