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The beneficial effect of extracorporeal shockwave myocardial revascularization: Two years of follow-up

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ABSTRACT

Objectives: Despite the advancements achieved by revascularization technique and pharmacological therapies, the number of patients with refractory angina (RA) is still high, carrying together a poor prognosis. Experimental data and small clinical studies suggest that the use of extracorporeal shockwave myocardial revascularization (ESMR) might improve symptoms of angina in patients with RA. The aim of our study is to evaluate the efficacy of cardiac shock wave therapy in a long term follow-up of patients with coronary artery disease (CAD) otherwise not suitable for revascularization.

Methods: We performed a prospective study enrolling patients with RA despite optimal medical therapy and without indication for further PCI or CABG. Characteristics such as angina class scores (CCS class score), nitroglycerin consumption and hospitalization were compared at baseline and 1, 6 and 12 months after ESMR therapy.

Results: We enroll 72 patients with a mean age of 74.6 ± 14.7 years. We treated 440 echocardiographical segments of ischemical myocardium. During the longest published follow-up (2.88 ± 1.65 years, range 0.63–6.11) there was a significant reduction of medium CCS class score (from 2.78 ± 0.67 to 1.44 ± 0.6; $p = 0.0002$), nitroglycerin consumption (67% vs 21%; $p < 0.001$) and hospitalization rate (40% vs 18%; $p < 0.03$).

Conclusion: Our study confirms the beneficial effect of ESMR therapy on cardiac symptoms and the possibility to reduce hospitalizations in patients with refractory angina also in a long term follow up. It supports a role for ESMR as a non-invasive therapeutic 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 are reduced and conventional medical therapy is frequently inadequate 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, the reduction of hospitalizations and the restoration of normal activities [1]. Despite the improvements in invasive and pharmacological therapies achieved by the medical community, up to 26% of patients still experience symptoms [2–6].

Other treatment has been proposed such as transmyocardial laser revascularization during CABG. Newer approaches such as gene therapy promoting angiogenesis and stem cell transplantation failed or are still in a pre-clinical stage and are invasive in nature. [7–9].

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 relatively new non-invasive treatment that had yet demonstrated to improve myocardial perfusion and to reduce symptoms of myocardial ischemia, through the application of low energy shockwaves (SW), i.e. special acoustic waves that can be targeted and focused on a selected area of the heart under echocardiographic guidance [12–13].

Low-energy extracorporeal shock-wave therapy (ESWT) has been initially developed as a treatment standard or alternative therapy for a variety of orthopedic and soft tissue diseases [14,15]. The observed immediate increase in blood flow due to local vasodilation and the formation of new capillaries in the treated tissue [16,17] have led to its application as a therapy for patients with RA. Shock waves consist of acoustic energy produced by a wave generator 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; using an electrocardiographic R-wave gating SW are then delivered through the applicator to the border of the ischemic area in order to induce neovascularization from the healthy area to the ischemic one. Several treatment sessions are required.

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Despite it is not fully understood how it works, there are two main mechanisms proposed: first off, immediate vasodilatation then the induction of neovascularization, the latter most likely accounting for the observed long term effects.

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

2. Methods

The study was approved by our institutional ethic committee and an informed consent was obtained from all participants prior to inclusion.

2.1. Patient selection

Entry criteria included age > 18 years, documented history of CAD with at least three months of refractory angina, coronary disease not amenable for revascularization, as was determined by an interventional cardiologist and cardiac surgeon. All patients enrolled should be on top of medical therapy, intended as stable maximal tolerated therapy, for at least 6 weeks before enrollment without significant symptoms improving.

Patients were excluded if they had a history of myocardial infarction or unstable angina within previous 3 months, active acute myocarditis, pericarditis, or left ventricular thrombus, significant valve disease, cardiac malignancies, 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 without adequate chest acoustic window.

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) were recorded and compared at baseline and 1 year after ESMR therapy between the groups.

2.1.1. The Cardiac Shock Wave Therapy (CSWT): Treatment protocol

The CSWT was applied with a commercially available cardiac shock wave generator system (Cardiospect™, Medispec, Germantown, MD) under echocardiographic guidance. The initial step of ESMR is to locate the ischemic region of interest after which, a full cardiac cycle is recorded with echocardiographic system. These measurements are calibrated into the shockwave applicator head to ensure the position of the focal treatment zone on the ischemic zone and shockwaves were then applied.

The ischemic area of interest was divided into 3 zones, corresponding to the three weeks of treatments. The treatment was divided into three sessions with 3 treatments for week every 4 weeks. Each treatment for each target spot consisted of 100 pulses gated by R wave trigger. Up to 10 target spots (total of 1000 pulses) were treated at each individual session. We applied a low energy of shockwaves (0.09 mJ/mm^2, ≈10% of the energy for the lithotripsy treatment. Each session lasted about 20 min.

During the treatment symptoms and vital signs were continuously monitored.

2.1.2. Endpoints

The endpoints were to examine the effects of ESMR application evaluating angina class scores (CCS class score), nitroglycerin consumption (number of single doses of sublingual nitrates) and hospitalization at 1, 6, 12 months after shock wave therapy,

2.1.3. Statistical analysis

Data are expressed as percentages for discrete variables and mean ± SD for continuous variables. Variables with normal distribution have been analyzed using parametric tests while variables with a non-normal distribution have been analyzed using non-parametric tests; categorical variables and proportions have been compared with the chi-square test; p values< 0.05 are considered statistically significant. Comparisons have been performed between the baseline and follow up. All the statistical analyses have been performed using SPSS Software, version 20.0.

3. Results

72 patients were enrolled in the treatment group between November 2009 and October 2016. The treatment was well tolerated: without any adverse effects. Globally we treated with SW therapy 440 echocardiographic cardiac segments (corresponding to a media of 6.1 segment per patient).

The mean age of the patients was 74.6 ± 14.7 years. The baseline characteristics are displayed in Table 1. While writing 3 patients had a total follow up of more than 6 years, 9 had it between 5 and 6 year, 5 between 4 and 5, 13 between 3 and 4, 8 between 2 and 3, 23 between 1 and 2, while 8 patients had less than 1 year of follow-up: mean follow up was 2.88 ± 1.65 years (range 0.63–6.11). After SW treatment patients usually experiment a slow improvement of symptoms during the first months. During the follow-up we had 13 patients needing ED access for symptoms (18%), of whom 8 (11% of total population) were recognized as NSTE-ACS. No patient had STEMI. Four patients died for non cardiovascular disease (2 neoplasms, 1 septic shock and 1 severe bleeding). Finally 2 of the symptomatic patients need to be treated again with SW therapy because of recurrent angina, with one of them receiving intracoronary stem cell therapy five years after enrollment in our study.

Clinical follow-up demonstrated a significant improvement in CCS class score with classes distribution reported in Table 2, Fig. 1, and a significant improvement of NYHA class score (see Fig. 2).

Before treatment 62% of patients used nitrates as oral spray or sublingual tablets because of unexpected symptoms (a mean of 7 ± 3 nitroglycerin intakes/month, with 5 patients taking it everyday, 7 patients almost 1 time per month and the others usually 1 times per week). This proportion decreased in the first month following treatment, to only 24% patients still consumed occasionally (9 patients 1 time per month, 1 patient almost each week and the others less than 1 time per months) these drugs at the end of the 1 year follow-up ($p = 0.02$, Fig. 3).

Table 1
Patients characteristics; values are expressed as mean ± standard deviation for age and as number of patients (percentage) for the other parameters.

Age (years)	74.6 ± 14.7
Female gender	15 (21%)
Prior IMA	28 (39%)
Prior PCI	58 (80%)
Prior CABG	30 (42%)
Prior ICTUS	11 (15%)
Hypertension	71 (98%)
Hypercholesterolemia	68 (94%)
Active smoker	8 (11%)
Previous smoker	19 (26%)
Diabetes	25 (35%)
Family history	45 (63%)
CKD	18 (25%)
Therapy	
Beta-blockers	65 (90%)
Nitrates	53 (73%)
ACE-i	39 (54%)
ARB	31 (43%)
Acetylsalicylic acid	65 (90%)
Calcium antagonist	43 (60%)
Statins	61 (84%)
Ranolazine	26 (36%)

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