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Extracorporeal shockwave myocardial therapy is efficacious in improving symptoms in patients with refractory angina pectoris – a multicenter study

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Abstract

Objective—Medically refractory angina remains a significant health concern despite major advances in revascularization techniques and emerging medical therapies. We aimed to determine the safety and efficacy of extracorporeal shockwave myocardial therapy (ESMT) in managing angina pectoris.

Methods—A single-arm multicenter prospective study was designed aiming to determine the safety and efficacy of ESMT. Patients of functional Canadian Cardiovascular Society class II–IV, despite stable and optimal medical management, with documented myocardial segments with reversible ischemia and/or hibernation on the basis of echocardiography/single-photon emission computerized tomography (SPECT) were enrolled from 2010 to 2012. A total of 111 patients were enrolled, 33 from Indonesia, 21 from Malaysia, and 57 from Philippines. Patients underwent nine cycles of ESMT over 9 weeks. Patients were followed up for 3–6 months after ESMT treatment. During follow-up, patients were subjected to clinical evaluation, the Seattle Angina Questionnaire, assessment of nitrate intake, the 6-min walk test, echocardiography, and SPECT.

Results—The mean age of the population was 62.9 ± 10.9 years. The summed difference score on pharmacologically induced stress SPECT improved from 9.53 ± 17.87 at baseline to 7.77 ± 11.83 at follow-up ($P = 0.0086$). Improvement in the total Seattle Angina Questionnaire score was seen in 83% of patients ($P < 0.0001$). Sublingual nitroglycerin use significantly decreased

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Conflict of interest

There are no conflicts of interest.

(1.14 ± 1.01 tablets per week at baseline to 0.52 ± 0.68 tablets per week at follow-up; $P = 0.0215$). There were no changes in left ventricular function on echocardiography (0.33 ± 9.97 , $P = 0.93$). The Canadian Cardiovascular Society score improved in 74.1% of patients.

Conclusion—This multicenter prospective trial demonstrated that ESMT is both a safe and an efficacious means of managing medically refractory angina.

Keywords

angina pectoris; coronary artery disease; extracorporeal shockwave myocardial revascularization

Background

Medically refractory angina is a significant health concern despite advances in revascularization techniques and emerging medical therapies [1]. Myocardial ischemia may cause chest pain, reduced exercise tolerance, arrhythmia, heart failure, or sudden cardiac death. Medical treatment, percutaneous coronary intervention, and coronary artery bypass grafting are all options considered in the management of patients with chronic coronary artery disease [2]. There is a subset of patients with angina despite the use of alternate therapeutic modalities who are not candidates for revascularization. These patients with chronic refractory angina have limited treatment options [3]. Emerging technology including neurostimulator implantation, laser revascularization, and gene/cell therapy in an effort to promote angiogenesis may be considered; however, these therapies are invasive, expensive, and have yet to be proven as clinically efficacious and feasible [3–6].

Extracorporeal shockwave therapy (ESMT) is a new, angiogenesis-based option in patients with refractory angina pectoris [7–9]. Shockwave therapy is used routinely in the orthopedic setting, as well as for the treatment of renal stones by urologists in the form of lithotripsy [10, 11]. ESMT has since been recognized as a new, non-invasive treatment modality that may alleviate symptoms of refractory angina through improvement of myocardial perfusion [12,13].

Shockwave therapy acts by inducing shear stress and myocardial angiogenesis [14]. The exact mechanism by which shockwave therapy promotes angiogenesis is unknown; however, it is thought to be mediated through vascular endothelial growth factor (VEGF) and endothelial nitric oxide synthase [13,15]. In patients with no revascularization options, inducing angiogenesis has the potential to improve contractility of the hibernating myocardium and further improve symptoms and outcomes in patients with chronic ischemic heart disease [13]. Upregulation of nitric oxide production *in vitro* with shockwave therapy may also promote angiogenesis [15].

In the animal model, shockwave therapy has been described as both safe and efficacious. It has been shown to improve both myocardial perfusion and left ventricular ejection fraction (LVEF) [12,13]. Several small human studies have also suggested that ESMT is both safe and potentially clinically efficacious in the management of chronic refractory angina [1,7,16]. In our multicenter study, we aimed to test the hypothesis that ESMT improves myocardial ischemia and functional status in patients with chronic refractory angina.

Methods

Study design

This study was designed as a multicenter prospective, single-arm study aimed at determining the efficacy and safety of ESMT. Three centers were involved, St. Luke's Medical Center (Manila, Philippines), Haparan Kita National Cardiovascular Center (Jakarta, Indonesia), and University of Malaya Medical Center (Kuala Lumpur, Malaysia). The study was sponsored by Medispec, who provided machinery. The sponsors were not involved in data collection or data analysis. The first and corresponding authors at Mayo Clinic were responsible for designing the study, compilation of data, analysis, and writing of the manuscript.

Patient selection

Patients were recruited from January 2010 to December 2012. Patients older than 20 years of age with documented ischemic heart disease who had been evaluated by a cardiologist and were deemed unsuitable for conventional methods of revascularization were included. All patients were thought to be maximized on medical therapy by their primary cardiologist. Patients were classified as belonging to functional Canadian Cardiovascular Society (CCS) class II–IV, despite stable and optimal medical management for at least 6 weeks before enrollment, with documented myocardial segments with reversible ischemia and/or hibernation on the basis of echocardiography/single-photon emission computerized tomography (SPECT). All patients had no acute clinical event at least 3 months before enrollment. Exclusion criteria were occurrence of acute myocardial infarction less than 3 months before enrollment, intraventricular thrombus, malignancy in the area of treatment, life expectancy less than 12 months, chronic lung disease, endocarditis, pericarditis, or pregnancy. All patients were maximized on their medication regimen before enrollment and remained on a stable medication regimen during the study.

Myocardial ischemia detection

Patients underwent technetium sestamibi myocardial perfusion at resting state and after stress induced by dipyridamole to identify areas of ischemia [17]. The left ventricle was divided into 17 segments. Segments were assessed on the short, horizontal long, and vertical long axes and the summed stress score (SSS) and summed rest score were determined. A high score correlated with worse perfusion. Ischemic areas on SPECT were correlated with echocardiographic segments in a 16-segment echocardiographic model to plan treatment each week, starting from the border zone to the center of the ischemic area.

Stress images were read by a single blinded reader at each site, but not in a core lab.

Study protocol

The study was conducted in three main phases. During the pretreatment phase, the patient underwent pretesting to determine eligibility and identify ischemic areas for treatment. At baseline, the patients also underwent SPECT. During the treatment phase, ischemic areas were treated with shockwaves using an ultrasound device for guidance (Fig. 1). During the

post-treatment phase, the patients enrolled were evaluated at 3 to 6 months after treatment to determine the safety and efficacy of ESMT treatments.

Each patient underwent nine treatment sessions over a 9-week period during the treatment phase – that is, during weeks 1, 5, and 9. Each week the patients underwent three treatments on alternate days, with less than 1000 shocks per treatment session.

Baseline parameters

On initial evaluation, the patients were subjected to comprehensive medical evaluation with ECG, scoring by CCS classification, the exercise test, Seattle Angina Questionnaire (SAQ), assessment of the medication regimen, baseline SPECT, identification of myocardial segments with reversible ischemia and/or hibernation ischemia by stress echocardiography, and identification of myocardial segments with decreased perfusion. Stress SPECT obtained no more than 3 months before enrollment was also reviewed. In addition, Doppler images, nitrate medication intake, stability of the medication regimen, and time to angina were also assessed during the initial visit.

Endpoints

Safety endpoints included the incidence of adverse events, patient complications, and the level of troponin T after each treatment session. ECGs were monitored continuously for associated changes throughout treatment. The efficacy of ESMT was defined by several endpoints, including change in SPECT score, ejection fraction, SAQ score, and maximal exercise time using the Bruce protocol or the modified Bruce protocol. Patients were also asked about medication use and specifically the number of nitroglycerin tablets consumed per week.

Follow-up

Patients were followed up at 3 and 6 months after ESMT treatment, at which time they were subjected to complete clinical evaluation, SAQ, assessment of nitrate intake, the 6-min walk test, echocardiography, and SPECT.

Statistical analysis

Continuous variables were expressed as mean $\pm$ SD, whereas categorical variables were expressed as percentages. Parametric and nonparametric tests were used to analyze variables with normal and abnormal distributions, respectively, whereas the χ^2 -test was used to compare categorical variables. *P*-values less than 0.05 were considered statistically significant. Statistical analysis was carried out by a doctorate in statistics using JMP.

Results

ESMT was well-tolerated by patients, without any complaints of discomfort. There were no major adverse cardiovascular events reported. Baseline characteristics are summarized in Table 1. A total of 111 patients were enrolled in the study, 33 from Indonesia, 21 from Malaysia, and 57 from Philippines. The mean age of the population was 62.9 ± 10.9 years, ranging from 41 to 86 years. The population was 83.8% male. The average BMI was 23.9

$\pm 6.0 \text{ kg/m}^2$. Of the patients, 77% had a history of hypertension, 76% reported a history of three-vessel disease, 48% had a history of myocardial infarction, and 36% had congestive heart failure. A history of stroke was reported in 13.3% and a history of peripheral vascular disease was reported in 7.8% of patients. Of the total number of patients enrolled, 45.0% had a history of smoking, 51.4% had a history of diabetes, and 86.0% had a history of dyslipidemia. About one-third of patients had undergone coronary artery bypass grafting previously. β -Blockers were consistently used by 91.9% of patients, whereas 60.8% used calcium-channel blockers daily and 66.7% used ACE inhibitors on a regular basis.

Figure 2 summarizes the results of pharmacologically induced SPECT. Baseline SSS improved from 26.49 ± 19.38 to 23.88 ± 19.90 ($P < 0.05$). There was no change in the mean summed rest score from baseline to follow-up. (16.62 ± 17.77 vs. 15.82 ± 15.28 , $P = 0.87$). The summed difference score improved from 9.53 ± 17.87 at baseline to 7.77 ± 11.83 at follow-up ($P < 0.01$). Overall, 64% of patients had improvement in the summed difference score at follow-up, and 60% in the SSS.

Figure 3 depicts the maximal exercise time. The maximal exercise time improved at follow-up, estimated using the Bruce protocol (252.1 ± 51.6 vs. 313.5 ± 164.3 s, $P = 0.008$) and the modified Bruce protocol (457.0 ± 146.8 vs. 606.0 ± 126.4 s; $P < 0.001$). Of the patients, 62% showed greater than 10% improvement in their exercise time according to the modified Bruce protocol or the Bruce protocol. According to the Bruce protocol, 52% showed greater than 10% improvement in the maximal exercise time, and 79% showed greater than 10% improvement according to the modified Bruce protocol.

The SAQ was used to assess changes in symptoms. Of the patients, 83% showed an improvement in the total SAQ score, with significant improvements in individual scores, including improvement in physical limitation, anginal stability, treatment satisfaction, and quality of life ($P < 0.0001$). The total SAQ score improved significantly from baseline to follow-up [317.4 ($253.2, 365.8$) vs. 390 ($333.8, 413.6$), $P < 0.0001$]. Sublingual nitroglycerin use was significantly reduced at follow-up (1.14 ± 1.01 to 0.52 ± 0.68 tablets per week, $P = 0.02$; Fig. 4).

Echocardiography revealed no significant changes in overall LVEF ($0.33 \pm 9.97\%$, $P = 0.93$). The CCS score improved in 74.1% of patients. Of the patients, 70.4% had a one-point increase in the CCS score, whereas 3.7% had a two-point increase in the CCS score. Of the patients, 24.1% had no change in the CCS score at follow-up.

Discussion

In our multicenter, single-arm prospective study aiming to determine the safety and efficacy of ESMT in patients with chronic ischemic heart disease, we found that ESMT is safe, clinically feasible, and successful in improving myocardial perfusion by SPECT, increasing exercise time, and reducing the CCS score, the SAQ score, and nitrate use. Our findings extend those of other studies that have suggested a potential role for ESMT in the management of patients with chronic refractory angina.

Refractory angina is associated with excessive chest pain, but not significant cardiac mortality, with a rate as low as 2% per year [18,19]. For this reason, novel symptom-driven treatments such as ESMT may have utility in the appropriate management of refractory angina.

The mechanism by which ESMT exerts its effect appears to be multifactorial. The shockwave is thought to exert a shear-stress effect [14,20]. VEGF mRNA expression may be enhanced by shockwave therapy, in addition to acceleration of bone marrow cell differentiation into endothelial cells [21]. ESMT can thus induce angiogenesis and abate inflammation [13,22,23]. ESMT may also increase circulating endothelial progenitor cells and chemokines that home endothelial progenitor cells to ischemic areas, and may thus be associated with a reduction in inflammation, oxidative stress, and fibrosis [7,13,22,24]. Previous studies have suggested that physiologic responses to ESMT are integral to explaining the improved myocardial perfusion seen with ESMT administration.

Our results are supported by several animal studies that have reported a potential beneficial effect of ESMT therapy. Fu and colleagues randomized male mini-pigs into two groups of myocardial infarction to no shockwave therapy and shockwave therapy at 3 months after myocardial infarction and found preserved LVEF and a lower left ventricular end systolic dimension in pigs receiving shockwave therapy. ESMT has also been associated with neovascularization in joints, with the early release of angiogenesis-mediating growth and proliferation factors such as VEGF, which allows improved blood supply and tissue regeneration [1,25]. In-vitro studies have suggested that low-energy shockwaves may increase endothelial nitric oxide synthase activity and increase the production of intracellular nitric oxide, potentially explaining the beneficial effects of shockwave therapy seen up to 4 weeks after treatment [1,26,27]. ESMT is administered at 10% of the energy of lithotripsy, and even at such low concentrations, ESMT has been shown to promote angiogenesis and improve cardiac function safely in the animal model [13].

Our study extends the findings of previous studies, which have suggested that ESMT may be safe and efficacious in small groups of patients [1,7,9,12,13,16,28]. This is at present the first and largest international multicenter study showing that ESMT decreases nitroglycerin consumption, increases myocardial perfusion on SPECT, improves CCS scores, and increases exercise capacity. Our study is supported by smaller ones, such as that by Fukumoto *et al.* [7], which reported that ESMT was safe and associated with improved symptoms, reduced nitroglycerin use, and improved myocardial perfusion 12 months after treatment. Yang and colleagues conducted a double-blind randomized controlled trial of 25 patients and reported findings similar to ours including improved exercise time, SAQ scores, and nitroglycerin usage. Theirs was a small subset of selected patients, and our results further these findings using a multicenter model with a larger, more diverse population [29]. This therapy has also been studied in patients with heart failure. Peng and colleagues [30] studied 50 patients with ischemic heart failure with a low LVEF and found improved symptoms after randomization to shockwave therapy, as did Vasyuk *et al.* [31], who studied 24 patients with LVEF less than 40% and found improved symptoms and SPECT scores at follow-up. Zuoziene *et al.* [32] tested the effect of ESMT on anginal symptoms in another study of patients with end-stage coronary artery disease and found significant improvement

in CCS score and the use of nitroglycerin. SPECT showed improvement of myocardial stress in 75% of the treated patients. As in other studies, no complications or adverse events were observed [1]. Cassar *et al.* [33] in a multicenter study based in the USA also reported improved symptoms with shockwave therapy, but did not report any change in myocardial perfusion. Most recently, the CELLWAVE trial studied similar patients with ischemic cardiomyopathy who had received bone marrow-derived stem cells and ESMT and found a significant improvement in left ventricular function at 4 months [34]. The primary focus of our study was angina and the management of its symptoms, as opposed to treatment of heart failure with ESMT. Most importantly, the multicenter nature of our study and the larger number of patients further increases its significance in suggesting ESMT as a clinically efficacious therapy for refractory angina. We present a large, diverse patient population that has shown both clinical and diagnostic responses to therapy. We thus find that our results of improved myocardial perfusion and anginal symptoms are important, especially as they are supported by previous studies. We did not see significant improvement in ejection fraction; this may be due to inherent variations in study design such as length of time of follow-up as well as modality of imaging used [1]. Our study thus furthers the growing body of literature suggesting efficacy and feasibility of shockwave therapy in the treatment of anginal symptoms. We present the largest and first international multicenter study that explores the potential benefits of shockwave therapy in a diverse patient population.

ESMT has several advantages over other emerging therapies for refractory angina. First, its noninvasive nature makes it superior to other therapies thought to potentially improve anginal symptoms such as trans-myocardial laser revascularization and gene or cell therapy [2,35,36]. Surgical or interventional treatments of refractory angina may not provide optimal results and subject the patient to risk. Second, the therapeutic effect of ESMT is controlled, with localized precise administration of shockwaves to a particular ischemic region under echocardiographic guidance. Ease of administration is also an important advantage that ESMT has over other novel therapies. The therapy requires a mean of 20 min per session, can be performed in the outpatient setting, and is easily repeatable as the symptoms or disease progresses. Finally, perhaps the most compelling advantage of ESMT is its safety. As in previous studies, we did not observe any adverse effects from ESMT [1,12,13,16].

Our study has several strengths and some inherent limitations. First and foremost, our study is the largest multicenter trial designed to study the safety and efficacy of ESMT. Second, to our knowledge, this is the largest study using ESMT for patients with chronic angina. Our large study population and collaborations with multiple centers increase the credibility of our results. One of the major limitations of the current study, however, is the lack of a sham arm, making it difficult to exclude the partial placebo effect. Improvement in symptoms with ESMT is correlated with improvement in SPECT, thus providing internal validation for our results. In addition, the present study does not allow dose dependency conclusions, and dose-dependent effects would need to be confirmed in a large multicenter trial with varying doses of shockwave therapy.

Conclusion

In our multicenter single-arm prospective study, we report both safety and efficacy of ESMT. ESMT appears to be beneficial in improvement of both myocardial perfusion and symptoms of angina. Larger randomized controlled studies are required to further evaluate the efficacy of ESMT.

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Patient under
electrocardiographic monitoring

Receives, in the ischemic zones localized with
ultrasound guidance, the shockwaves produced by the
generator that is attached to the chest wall

At each session, the cardiac shockwave therapy is applied to the border of the ischemic area
to potentially induce neovascularization from the healthy region to the ischemic area

Fig. 1.

The means by which extracorporeal shockwave myocardial revascularization is administered. The patient is placed under electrocardiographic monitoring and shockwaves are produced by a generator attached to the chest wall; they are administered at the ischemic border zone by echo-guided localization in an effort to induce neovascularization from the healthy myocardium to the ischemic myocardium.

Fig. 2.

Depicts a significantly decreased summed rest score (SRS) and summed stressed score (SSS) after 4–6 months of follow-up after extracorporeal shockwave therapy. SDS, summed difference score; SPECT, single-photon emission computerized tomography. * $P<0.05$.

Fig. 3.
Maximal exercise time improved with extracorporeal shockwave myocardial therapy.

Fig. 4.

Depicts significantly reduced nitroglycerin use on follow-up 4–6 months after the administration of extracorporeal shockwaves. * $P<0.05$.

Table 1

Baseline characteristics

Variable	Mean $\pm$ SD/ <i>n</i> (%)
Age (years)	62.9 $\pm$ 10.9
Sex	
Male	98 (83.7)
Female	18 (16.2)
BMI	23.9 $\pm$ 6.0
Hypertension	86 (77.4)
History of myocardial infarction	44 (48.9)
Heart failure	36 (40.0)
Cerebrovascular disease	12 (13.3)
Peripheral vascular disease	7 (7.8)
Smoking	50 (45.0)
Kidney disease	4 (4.4)
COPD	5 (5.6)
Type 2 DM	57 (51.4)
Hyperlipidemia	49 (86.0)
Previous PCI	32 (29.4)
Previous CABG	34 (31.2)
β -Blocker use	79 (91.9)
Calcium-channel blocker use	45 (60.8)
ACE inhibitor	38 (66.7)
Nitrate use	70 (88.6)
Aspirin use	71 (96.0)
Antiplatelet agent	62 (70.0)

ACE, angiotensin-converting enzyme; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus.