Effectiveness and Safety of Extracorporeal Shockwave Myocardial Revascularization in Patients With Refractory Angina Pectoris and Heart Failure

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Extracorporeal shockwave myocardial revascularization (ESMR) is a therapy for refractory angina pectoris. Our aim was to assess the efficacy and safety of ESMR in the management of patients with stable coronary artery disease (CAD) and heart failure as well as its effects on inflammation and angiogenesis. In this single-arm prospective trial, we included 48 patients with CAD, myocardial ischemia assessed by radionuclide imaging, echocardiographic evidence of left ventricular systolic dysfunction and without revascularization options. Changes in angina grading score, myocardial perfusion, left ventricular ejection fraction, and six-minute walk test after ESMR therapy were used for efficacy assessment. Changes of inflammation and angiogenesis biomarkers were also evaluated. ESMR therapy was performed using a commercially available cardiac shockwave generator system (Cardiospec; Medispec). After 9 weeks of ESMR therapy, a significant improvement was found regarding the initial angina class, severity of ischemia, left ventricular ejection fraction, and six-minute walk test in most patients. No deleterious side effects after treatment were detected. Regarding biomarkers, endothelial progenitor cells and angiopoietin-3 were significantly increased whereas IL-18 and TGF-β were significantly decreased after ESMR in the total group. Notably, VEGF, IL-1ß, and lipoxin A4 levels were significantly increased only in patients with myocardial ischemia improvement. In conclusion, ESMR therapy is safe and effective in most but not all patients with CAD and heart failure. ESMR is associated with increased markers of angiogenesis and decreased markers of inflammation. Myocardial ischemia improvement after ESMR is associated with increased markers of angiogenesis and pro-resolving mediators. **(Am J Cardiol 2021;144:26−32)**

Extracorporeal shockwave myocardial revascularization (ESMR) provided by an echocardiography-based device for shockwave therapy directed to the myocardial ischemic-target area is one of the noninvasive treatment options for refractory angina pectoris.[1−4] This therapy could enhance myocardial angiogenesis in the border of the infarcted myocardium, thus suppressing the progression of left ventricular (LV) remodeling and improving prognosis.[1−4] Experience with this therapy is increasing and controlled clinical studies[5−7] and a meta-analysis[8] have indicated its effectiveness in refractory angina. Shockwaves induce localized stress on cell membranes that resemble shear stress[1−4]; however, the molecular mechanism by which shockwaves and shear stress promote neovascularization and improves cardiac function has not been fully determined.[1,3,4] The purpose of our study was to assess the efficacy and safety of ESMR in the management of patients with coronary artery disease (CAD) and heart failure (HF) and who were not candidates for interventional or surgical treatment at our institution, as well as to measure the potential effects of ESMR on inflammation and angiogenesis.

Methods

We designed a single-arm prospective trial to assess the efficacy and safety of ESMR in patients with CAD and HF. This research complies with the ethical standards of the Declaration of Helsinki and was approved by our Institutional Research Board and Ethics Committee. All participants signed an informed consent form to participate in the

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study. We included patients with chronic myocardial ischemia and echocardiographic evidence of LV systolic dysfunction who were followed at our heart failure clinic, were on antianginal therapy, and were not candidates for further revascularization options. Patients were eligible if they met the following criteria: (1) older than 30 years of age; (2) persistent angina or evidence of refractory LV systolic dysfunction despite medical therapy; (3) evidence of ischemia in the myocardial perfusion stress test by radionuclide imaging; (4) more than 1 month after acute myocardial infarction (AMI); (5) history of percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG) at least 6 months before enrollment; (6) Finally, to be included patients had to be in sinus rhythm. Patients were excluded from the study if they met any of the following criteria: (1) intracardiac thrombus; (2) evidence of acute myocarditis, pericarditis, or endocarditis; (3) severe valvular disease or history of metal valve replacement surgery; (4) evidence of implantable cardiac devices; (5) arrhythmia with a rate <40 beats/min or >120 beats/min; (6) skin ulceration or infection in the treatment area.

Before ESMR therapy, all the patients underwent a thorough evaluation that included medical history recording, with particular emphasis in angina grading according to the Canadian Cardiovascular Society classification (CCS),[9] physical examination, 12-lead electrocardiogram (ECG), myocardial perfusion stress test by radionuclide imaging, transthoracic echocardiography, six-minute walk test (6MWT), and blood sampling for biomarker measurements. The whole evaluation was repeated after ESMR treatment. To trace the ischemic areas and their severity and to localize the infarcted areas before and after treatment, image analysis of myocardial perfusion at rest and stress, and transthoracic echocardiography were conducted in each patient.

The protocol for perfusion analysis has been described elsewhere.[27] The myocardial perfusion status was scored qualitatively according to the radiotracer uptake as follows: 0 = normal; 1 = mildly reduced; 2 = moderately reduced; 3 = severely reduced; and 4 = absent radiotracer uptake.[28] The perfusion defect (score 1−4) was considered fixed when no differences were found between the rest and stress scores, whereas the reversible defect was defined as a segment with a higher score on stress images. Ischemia was defined as a change in one or more grades between the rest and stress images. Interpretation of tomographic images was performed by consensus by 2 experienced observers unaware of other patient data.

ESMR therapy was applied using a commercially available cardiac shockwave generator system under echocardiography guidance (Cardiospec; Medispec. Germantown, Maryland) and ECG monitoring according to the protocol.[10] Briefly, the patient was positioned and connected with the ECG monitor, and a shockwave applicator membrane and an ultrasound probe were used to select the target area based on the ischemic areas identified on the myocardial perfusion stress radionuclide imaging. The target area was divided into 5 segments with an 8-mm distance between them. A dose of up to 100 shocks was delivered to each treatment zone (in each session, the patient received 500 shots). Three treatment sessions on alternate days (at weeks 1, 5, and 9) with a total of 9 treatment sessions over 9 weeks were given to each patient.

Before and at the end of ESMR therapy, serum levels of tumor necrosis factor (TNF), interleukin-1β (IL-1β), IL-6, IL-8, IL-10, IL-18, interferon-γ (IFN-γ), stromal cell-derived factor-1 (SDF-1), IFN-γ-induced protein-10 (IP-10), macrophage inflammatory protein α (MIP-1α) and β (MIP-1β), monocyte chemo-attractant protein-1 (MCP-1), matrix metalloproteinase-2 (MMP-2), MMP-3 and MMP-9 were measured using ProcartaPlex panels (ThermoFisher Scientific, Vienna, Austria) on the MAGPIX system (Luminex, Austin, Texas). Transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), endothelin-1 (ET-1; R&D, Minneapolis, MN, USA), lipoxin A4 (LxA4; Cloud-Clone, Houston, Texas), resolvin D2 (RvD2; Cayman, Ann Arbor, Michigan), and angiopoietin-3 (AdipoGen, Liestal, Switzerland) were measured by ELISA. Endothelial progenitor cells (EPCs) were characterized by flow cytometry using a modification of the ISHAGE protocol[29] (Supplementary material).

Data were verified for normal distribution with the Kolmogorov-Smirnov test. Categorical data were summarized as frequencies and percentages. Continuous variables were reported as medians with interquartile ranges (IQRs). Significant differences before and after treatment were assessed using Chi-square or Fisher's exact test (categorical variables) or the Kruskal-Wallis or Mann-Whitney U test (continuous variables) as appropriate.

For the analysis of circulating biomarkers, the Wilcoxon signed-rank test was used to compare paired samples, whereas the Mann-Whitney U test was used to compare independent samples. One-tailed tests were used because our hypothesis was specific to the direction of the change between groups (or times), indicating the alternative hypothesis was specifically that group A is higher (or lower) than group B, whereas the null hypothesis was that both groups are equal. A p-value <0.05 was considered significant. Data were analyzed using SPSS 17.0 (SPSS, Chicago, Illinois) and GraphPad v6.0 (GraphPad, Inc., San Diego, California) statistical software.

Results

Forty-eight patients with CAD and HF and no revascularization options were enrolled. The demographic, clinical, functional, and treatment characteristics are shown in Table 1. Most patients were male (median age: 65.5 [56.2 to 71.5] years) with a history of AMI. The median time between the previous AMI and ESMR therapy was 21.3 (7.1 to 46.4) months. Dyslipidemia, diabetes, and hypertension were the predominant risk factors. Most patients were classified as having CCS II and III angina grading. By stress radionuclide imaging, ischemia was predominant in the anterior, septal, and inferior walls, and the severity was considered moderate-severe in most cases. From the functional point of view, all patients had a low left ventricular ejection fraction (LVEF) and a limited exercise capacity.

The effects of ESMR treatment on clinical, stress radionuclide and functional variables are shown in Table 2. After 9 weeks of ESMR therapy, a significant improvement was found in angina class grading and severity of ischemia in

Table 1
Baseline demographics and characteristics (n = 48)

Variable	
Age (years), median (IQR)	65.5 (56.2-71.5)
Men,	45 (94%)
Diabetes mellitus	27 (56%)
Hypertension	25 (52%)
Smoking	17 (35%)
Dyslipidemia	28 (58%)
Previous acute myocardial infarction	46 (96%)
Time between last AMI and ESMR (months) median (IQR)	21.3 (7.1-46.4)
Previous coronary artery bypass grafting	8 (17%)
CCS Angina class	
Class II	22 (46%)
Class III	21 (44%)
Class IV	5 (10%)
Ischemia location by stress radionuclide imaging	
Anterior	6 (12.5%)
Septal	19 (40%)
Lateral	6 (12.5%)
Inferior	17 (35%)
Ischemia severity by stress radionuclide assessment	
None	1 (2.1%)
Mild	11 (23%)
Moderate	22 (46%)
Severe	14 (29%)
LVEF, %, median (IQR)	35 (26-45)
6MWT (meters) median (IQR)	394 (350-448)
Treatment	
Statins	38 (79%)
Aspirin	35 (73%)
Beta-blockers	35 (73%)
ACE inhibitors/ARAs	32 (67%)
Nitrates	29 (60%)

ACE = angiotensin converting enzyme; AMI = acute myocardial infarction; ARAs = Angiotensin receptor antagonists; CCS = Canada Cardiovascular Society; LVEF = left ventricular ejection fraction; 6MWT = 6-min walk test.

the group (Figure 1), as well as a statistically significant functional improvement, as assessed by LVEF and the 6MWT. An example of ischemia improvement is shown in Figure 2.

Table 2
Effect of ESMR treatment on selected clinical, stress radionuclide, and functional variables

Variable	Before (n = 48)	After (n = 48)	p Value
CCS Angina class			
I	0	33 (68.8%)	<0.001
II	22 (45.8%)	14 (29.2%)	
III	21 (43.8%)	1 (2.1%)	
IV	5 (10.4%)	0	
Ischemia severity by stress radionuclide assessment			
No-ischemia	1 (2.1%)	8 (16.7%)	0.003
Mild	11 (22.9%)	21 (43.8%)	
Moderate	22 (45.8%)	12 (25%)	
Severe	14 (29.2%)	7 (14.6%)	
Functional			
LVEF, %	35 (26-45)	36.5 (27.2-47.5)	0.001
6MWT, meters	394 (350-448)	421.5 (388.5-487.5)	0.004

CCS = Canada Cardiovascular Society; LVEF = left ventricular ejection fraction; 6MWT = 6-min walk test.

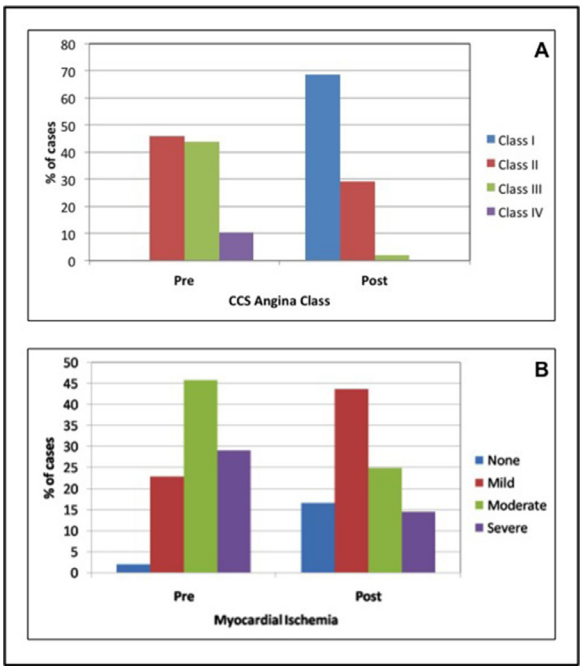

Figure 1. Changes in the angina class *(A)* and severity of myocardial ischemia *(B)* after ESMR therapy in the total group (n = 48). There was a significant improvement in both the angina class and ischemia severity after treatment ($p < 0.05$).

However, angina did not change in 7 (14.5%) patients and ischemia improvement was not detected in 22 (45.8%) patients. Likewise, LVEF did not change in 14 (29%) patients and worsened in 6 (12.5%) patients, and the 6MWT improved in 26 (54.1%) patients and remained unchanged or decreased in 22 (45.8%). No deleterious side effects in terms of rhythm abnormalities, worsening of the clinical evidence of heart failure, or embolic events were detected after treatment. After treatment, LVEF improvement was present in 69.2% of the patients with ischemia improvement. However, angina class, and 6MWT improved in a significant proportion of patients without myocardial ischemia improvement (Table 3).

Assessment of circulating biomarkers before and after ESMR therapy could be performed in approximately half of the patients, and the results are shown in Figure 3. In general, after treatment with ESRM, a significant increase was found in the number of circulating progenitor cells and in the serum angiopoyetin-3 levels. Other markers of angiogenesis, such as VEGF and ET-1, did not change (data not shown). The levels of IL-18 were decreased significantly after ESMR therapy, whereas other inflammation biomarkers such as IFN-γ, TNF, IL-6, IL-1β, and IL-10 did not show significant differences (data not shown). Regarding chemokines, we observed no significant differences in the serum levels after ESMR therapy. Similarly, significant differences were not found either in the levels of pro-resolving mediators LxA4 and RvD2 or in the levels of soluble MMPs (data not shown). Conversely, serum TGF-β levels showed a significant decrease after the administration of ESMR therapy (see also Figure 3).

Improvement in myocardial ischemia was detected in 26 of the 48 patients, and this improvement was significant

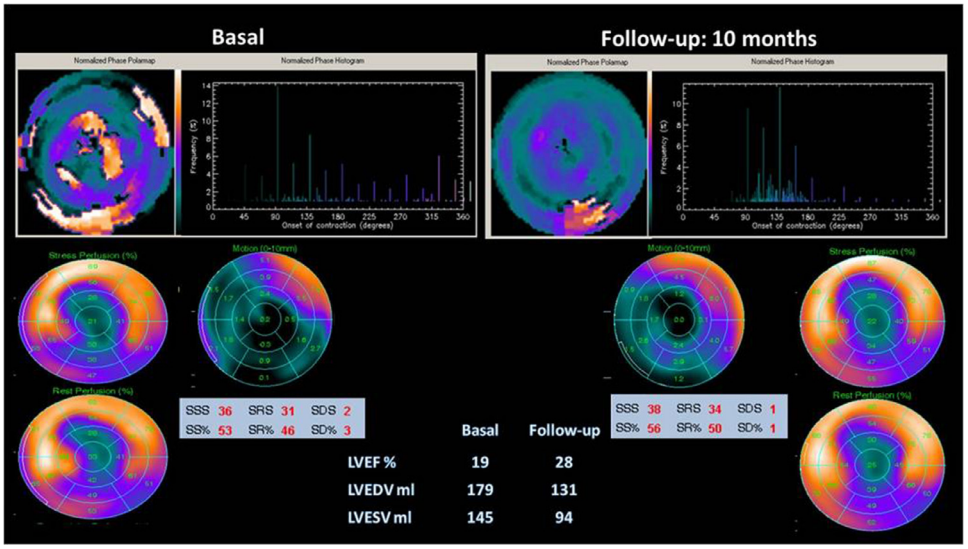

Figure 2. Improvement of myocardial ischemia after ESMR therapy. On the left images, the baseline myocardial perfusion study showed the following: (1) infarction of the apex and anteroseptal region without residual ischemia; (2) infarction of the inferior wall and inferoseptal and inferolateral region with minimal residual ischemia. The SDS was quantified in 3%. Important intraventricular asynchrony was identified. On the follow-up study at 10 months post-treatment (right images), a slight improvement in perfusion was observed around the peri-infarct area of the inferior wall, with a decrease in SDS up to 1%. Additionally, there was discrete improvement in the systolic function of the left ventricle (movement and increase in LVEF) and intraventricular asynchrony (bandwidth is decreased).

(69%) in the diabetic population. Age, gender, and other risk factors were not significantly different between the patients with and without improvement of ischemia after ESMR therapy (Table 3). Data on the circulating biomarkers of 14 patients in whom myocardial ischemia improved and those of 8 patients in whom ischemia worsened (or did not improve) after ESMR therapy was available for analysis. As indicated in Figure 3, an increase in the levels of LxA4, VEGF, and IL-1β was observed in patients with improvement in myocardial ischemia, whereas these analytes were decreased in those patients in whom ischemia did not change or deteriorated. There were no other differences associated with an improvement in myocardial ischemia (data not shown).

Table 3
Clinical variables at baseline and after the procedure associated with ischemia improvement in the total population

Variable, n (%) or median (IQR)	Improvement of ischemia		p Value
	Yes = 26 (54%)	No = 22 (46%)	
At baseline			
Age (years)	67 (58-75.2)	61.5 (55.5-68.5)	0.115
Men	24 (92%)	21 (95.5%)	0.654
Diabetes mellitus	18 (69%)	9 (41%)	**0.049**
Hypertension	16 (61.5%)	9 (41%)	0.154
Smoking	7 (27%)	10 (45.5%)	0.181
Dyslipidemia	17 (65%)	11 (50%)	0.281
Previous AMI	25 (96%)	21 (95.5%)	0.904
Prior CABG	5 (19%)	3 (14%)	0.604
Postprocedure			
Angina pectoris improvement	17 (67.4%)	12 (54.5%)	0.444
6MWT improvement	11 (42.3%)	15 (68.2%)	0.073
LVEF improvement	18 (69.2%)	10 (45.5%)	0.096

Significant differences are marked in bold.

AMI = acute myocardial infarction; CABG = coronary artery bypass grafting; LVEF = left ventricular ejection fraction; 6MWT = six-min walk test.

Discussion

The results of this prospective study confirmed and extended previous clinical experiences regarding the safety and efficacy of ESMR therapy in the setting of CAD and HF symptoms.[5–8,11] They also provided insightful perspectives regarding potential mechanistic explanations for efficacy.

ESMR is a safe procedure. All the patients completed the 9-week protocol, and, as in other clinical studies,[5–8,11] we observed no significant procedure-related complications after therapy. The absence of significant damage to myocardial ultrastructures has been demonstrated experimentally.[12] Regarding efficacy, most patients in our study improved their main limiting symptom of angina (Figure 1). The clinical and functional benefits of ESMR have been already demonstrated.[5–8,11]

By evaluating other more objective and robust end points, such as myocardial ischemia or LVEF changes, however, we found that not all patients improved. Ischemia improvement was not detected in almost half (46%) of the patients. Likewise, LVEF did not change in 29% or even worsened in 12.5% of the patients. Accordingly, ESMR is a useful intervention but not all patients respond. Using another methodology for assessment, such as magnetic resonance imaging, marginal or absence of improvement in myocardial ischemia or in ventricular mechanics after ESMR, has also been reported,[30] suggesting the need for more in vitro, animal, and human studies to unravel the exact mechanisms of improvement after shockwave treatment. In our study, improvement in myocardial ischemia does not necessarily translate in improvement in other

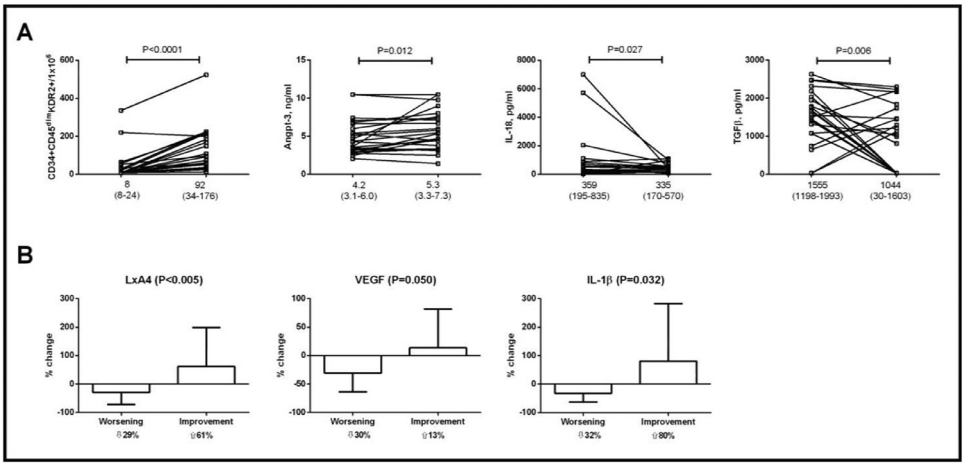

Figure 3. Changes in the circulating biomarkers after ESMR therapy. ***(Panel A)*** The median levels of biomarkers that changed significantly are presented before *(first column)* and after *(second column)* ESMR therapy. The number of endothelial progenitor cells and concentration of angiopoietin-3 (Angpt-3) increased significantly, while the serum levels of interleukin 18 (IL-18) and transforming growth factor β (TGF-) decreased after ESMR therapy. The values denote medians (interquartile range). ***(Panel B)*** Biomarkers associated with the improvement of myocardial ischemia after ESMR therapy. Patients who showed an improvement in myocardial ischemia after ESMR therapy also showed a significant increase in the percentage of change (before/after) of lipoxin A4 (LxA4), vascular endothelial growth factor (VEGF) and interleukin 1β (IL-1β) compared with those in whom myocardial ischemia worsened. The columns indicate the average percentage change, while the whiskers represent $\pm$1 standard deviation.

meaningful variables. As shown in Table 3, improvement in LVEF tends to correlate with myocardial ischemia improvement. However, improvement of angina in patients without improvement in myocardial ischemia might be the result of a placebo effect. Likewise, improvement in walking distance could be result of a training effect.

Earlier in vitro and animal studies suggested angiogenic and inflammation modulatory effects after ESMR to explain improvement in the ventricular function in ischemic heart failure. Animal studies have suggested that ESMR promotes angiogenesis in the ischemic myocardium by VEGF mRNA expression, endothelial cell proliferation, and endothelial nitric oxide synthase expression.[1,2] By modifying inflammation and enhancing angiogenesis in the border zone of infarcted myocardium, the progression of LV abnormal remodeling could be suppressed.[1,2,4] In vitro and animal studies have confirmed the roles of inflammation, adhesion signaling, and attenuation of cardiomyocyte apoptosis as important mechanisms for improvement after ESMR.[13–15] Animal studies demonstrated a positive effect on LVEF improvement that could be explained by angiogenesis induced by the stimulation of VEGF receptors.[14,15]

The molecular mechanisms of shockwave-induced angiogenesis remain unclear because human studies are scarce. In an interesting translational study of 26 patients with refractory angina pectoris, Cai et al[16] showed that EPC proliferation, mediated by VEGF and IL-8 secretion, may be among the potential mechanisms associated with myocardial improvement after ESMR therapy. Importantly, efficacy was evaluated exclusively based on clinical parameters (CCS angina improvement, functional class, the 6MWT, and nitroglycerin use). An objective assessment using myocardial perfusion and/or LVEF changes after ESMR therapy was not evaluated. Furthermore, no attempt was made to correlate changes in biomarkers with the improvement of the clinical variables.

ESMR therapy in our study was associated with an increase in proliferation markers (EPCs and angiopoietin-3), a decrease in proinflammatory markers (IL-18) and a decrease in profibrotic markers (TGF-) in the group as whole, findings that are in agreement with the postulated inflammation modulation and enhanced angiogenesis mediated by cardiac progenitor cell recruitment after ESMR.[17–19] The mobilization and importance of EPCs in remodeling and repair after AMI and in tissue repair in ischemic cardiomyopathy has been emphasized.[20,21] Likewise, the decrease in TGF- could be involved in LV remodeling and functional improvement shown after ESMR.[22]

Ischemia improvement was more frequent in the diabetic population, a finding that demands a deeper future evaluation in patients with diabetic cardiomyopathy. In contrast, ischemia improvement in our study was associated with an increase in VEGF, IL-1, and LxA4. Changes in pro-resolving mediators such as LxA4 after ESMR in the setting of CAD have not been previously described; however, its role in the inflammation resolving response leading to improved ventricular function after AMI has been established.[23,24]

Perhaps the elevation of IL-1β as a factor associated with the improvement of myocardial ischemia is not surprising because the role of IL-1β in the dual regulation of inflammatory and angiogenic pathways is well established (IL-1 is also called hemopoietin-1 due to its proangiogenic effects).[25,26] IL-1 receptor signaling mediates angiogenesis indirectly through its ability to induce the expression of VEGF. Indeed, IL-1β induces hypoxia-inducible factor-1α (HIF-1α), which mediates angiogenesis through its target gene VEGF.[26] Additionally, various reports have shown that IL-1β drives the transcription of VEGF and its receptor (VEGFR2) into cardiac myocytes and endothelial cells, indicating that an important role for IL-1β signaling is likely to enhance the biology of VEGF.[22]

We propose that ESMR therapy mobilizes EPCs from the bone marrow into the circulation and increases the production of angiogenic factors (angiopoietin) while decreasing fibrosis (TGF-β) and systemic inflammation (IL-18). However, ESMR therapy would improve myocardial ischemia only in those patients who can successfully accommodate EPCs in the myocardial tissue (due to mechanisms dependent on angiopoietin and other adhesion molecules); once established in the myocardium, these EPCs could facilitate the production of IL-1β, thus inducing VEGF-mediated angiogenesis.

Our study has some limitations. First, the study did not have a control (placebo) group. Second, there were a small number of patients in whom biomarker was evaluated, and our results need further confirmation. Third, the baseline medical treatment was dictated by treating cardiologist and it was not modified. How these medications may impact our results remains to be established. Fourth, the diabetic population was not completely assessed. Our study was not designed with this purpose, and the limited number of samples from diabetic patients precluded further analysis of the biomarker response in this population.

In conclusion, ESMR therapy is safe and effective in most but not all patients with CAD and HF. ESMR is associated with increased markers of angiogenesis and decreased markers of inflammation in the total group. However, myocardial ischemia improvement after ESMR is associated with increased markers of angiogenesis and pro-resolving mediators.

Authors' Contributions

Carlos Martínez: Conceptualization, Methodology; Francisco Azar: Conceptualization, Methodology; Héctor González-Pacheco: Visualization, Investigation, Writing-Reviewing and Statistic analysis; Luis M Amezcua-Guerra: Data curation, Writing- Original draft preparation and Writing- Reviewing; Felipe Massó: Visualization, Investigation; Ricardo Marquez-Velasco: Investigation; Rafael Bojalil: Investigation; Isabel Carvajal: Investigation; Erick Alexanderson: Investigation; Salvador Hernandez: Investigation; Araceli Paez-Arenas: Visualization, Investigation; Enrique López-Mora Investigation; Alejandra Venegas: Data curation; Malinalli Brianza-Padilla: Investigation; Rodrigo Gopar-Nieto: Investigation; Julio Sandoval Conceptualization, Methodology, Writing- Original draft preparation

Disclosures

The authors declare no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.12.065.

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