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The effect of extracorporeal shockwave myocardial revascularization therapy to myocardial perfusion and function in indicated CABG-stable angina pectoris patients: case series

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Abstract. – OBJECTIVE: Many studies have found a beneficial effect of Extracorporeal Shockwave Myocardial Revascularization (ESMR) therapy for refractory angina patients. However, clinical studies ESMR therapy for indicated coronary artery bypass grafting (CABG)-stable angina pectoris (SAP) patients are limited.

PATIENTS AND METHODS: Four indicated CABG-SAP patients CCS class I-III reviewed in this study. All patients refuse to CABG procedure. Data of myocardial perfusion and function from medical records were collected.

RESULTS: After ESMR therapy, summed rest score was improved in patient 1 from 14 to 8, Patient 2 from 10 to 5, and Patient 3 from 6 to 4.

Summed stress score was improved in patient 1 from 31 to 19. Left ventricular ejection fraction was improved in patient 1 at rest from 59 to 67% and stress from 39 to 57%. The global longitudinal strain was improved in patient 1 from -16 to -20.9 and Patient 3 from -14.8 to -18.2. Diastolic dysfunction severity was improved in patient 2 and patient 3 from grade 2 to grade 1.

CONCLUSIONS: In our case series, ESMR therapy for indicated CABG-SAP patients might improve myocardial perfusion and function, especially for patients with a high ischemic burden.

Key Words:
Case series, Echocardiography, Extracorporeal shockwave therapy, Myocardial perfusion imaging, Stable angina.

Introduction

Coronary artery disease (CAD) remains the leading cause of adult mortality in Indonesia, with a proportion of 35% or 652 thousand annual deaths due to CAD[1]. Manifestation of CAD mainly divided into Acute coronary syndrome (ACS) and Stable angina pectoris (SAP). According to the current guidelines, SAP treatment mainly focuses on medical therapy and invasive revascularization using percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)[2]. However, studies in Indonesia[3] showed that a third of patients were fearful of undergoing this invasive procedure which significantly increases risk of patients' mortality.

Extracorporeal shockwave myocardial revascularization (ESMR) is a non-invasive procedure have beneficial to improve myocardial perfusion and function in refractory angina patients in many studies[4-7]. A recent randomized clinical trial[5] (RCT) of ESMR shows improvement in myocardial perfusion. Along with that finding, a recent meta-analysis[8] of 556 refractory angina patients shows significant improvement of left ventricular ejection fraction (LVEF). Using a different population approach, we retrospectively describe a case series of ESMR therapy's addition to treating indicated CABG-SAP patients who refused CABG therapy.

Patients and Methods

We reviewed records from four indicated CABG-SAP patients who completed nine sessions of ESMR therapy in Dr. Hasan Sadikin General Hospital, Bandung, Indonesia. We collect data in-

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Table I. Patients characteristics.

Variable	Patient#1	Patient#2	Patient#3	Patient#4
Sex	Male	Male	Male	Female
Age (years)	54	61	75	50
BMI (kg/m^2)	26.6	25.3	24.6	24.6
CAD history (years)	10	2	2	2
CCS Class	III	II	I	I
Coronary Stenosis				
LAD	Yes	Yes	Yes	Yes
LCX	Yes	Yes	Yes	Yes
RCA	Yes	Yes	Yes	Yes
LM	No	Yes	No	No
Risk Factor				
Non-modifiable				
History of Premature CAD in first- degree relatives	No	No	No	Yes
Modifiable				
Obesity	Yes	No	No	No
Hypertension	Yes	Yes	No	Yes
Hypercholesterolemia	No	No	Yes	No
Diabetes Mellitus	No	No	No	Yes
Smoking	No	Yes	Ex	Yes
Stress	Yes	No	No	No
Medical Therapy				
Antiplatelet	Yes	Yes	Yes	Yes
ACE-I	No	No	Yes	No
ARB	Yes	Yes	No	Yes
CCB	Yes	Yes	No	Yes
β-Blocker	Yes	Yes	Yes	No
Diuretics	No	Yes	Yes	Yes
Digitalis	No	No	No	No
Statin	Yes	Yes	Yes	Yes
Anticoagulant	No	No	No	No
Nitrate	Yes	Yes	Yes	Yes

ACE-I: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, BMI: body mass index, CAD: coronary artery disease, CCB: calcium channel blocker, CCS: the Canadian cardiovascular score, LAD: left anterior descending artery, LCX: Left Circumflex coronary artery, LM: left main, RCA: right coronary artery.

dicating myocardial perfusion and function before initiation of ESMR therapy and at follow-up after four months after ESMR therapy. The myocardial perfusion is measured using summed stress score (SSS) and summed rest score (SRS). The myocardial function is measured using rest and stress LVEF, global longitudinal strain (GLS), and diastolic function. Data from single-photon emission computerized tomography (SPECT) scan examination used to determine SSS, SRS, rest, and stress LVEF. Data from echocardiography used to determine GLS and diastolic function. The Ethical approval was obtained by the Ethical Committee of Dr. Hasan Sadikin General Hospital (No. LB.02.01/X.6.5/284/2020).

Clinical and demographic features of included patients are reported in Table I. Patients 2, 3, and 4 have been diagnosed with SAP in the last two years. However, patient 1 has been diagnosed from SAP for ten years with the Canadian cardiovascular society (CCS) class III. All patients have features of three-vessels-disease (3VD), although Patient 2 also has left-main-disease (LM disease). Only patient 4 have comorbid with diabetes. Patients 2 and 4 are actively smoking at the time of therapy. All patients have been taking optimal medical therapy for at least four weeks. No patients have a history of invasive revascularization. Patients are refused the CABG procedure and deemed to ESMR therapy.

ESMR therapy consisted of nine sessions over three months with three sessions per week. The first step of ESMR therapy is to determine the target zone using SPECT scan. ESMR was performed using a standard echocardiography transducer coupled with a shockwave generator fixated to the target zone. Low-intensity shockwaves (100 impulses/spot) were delivered to the target

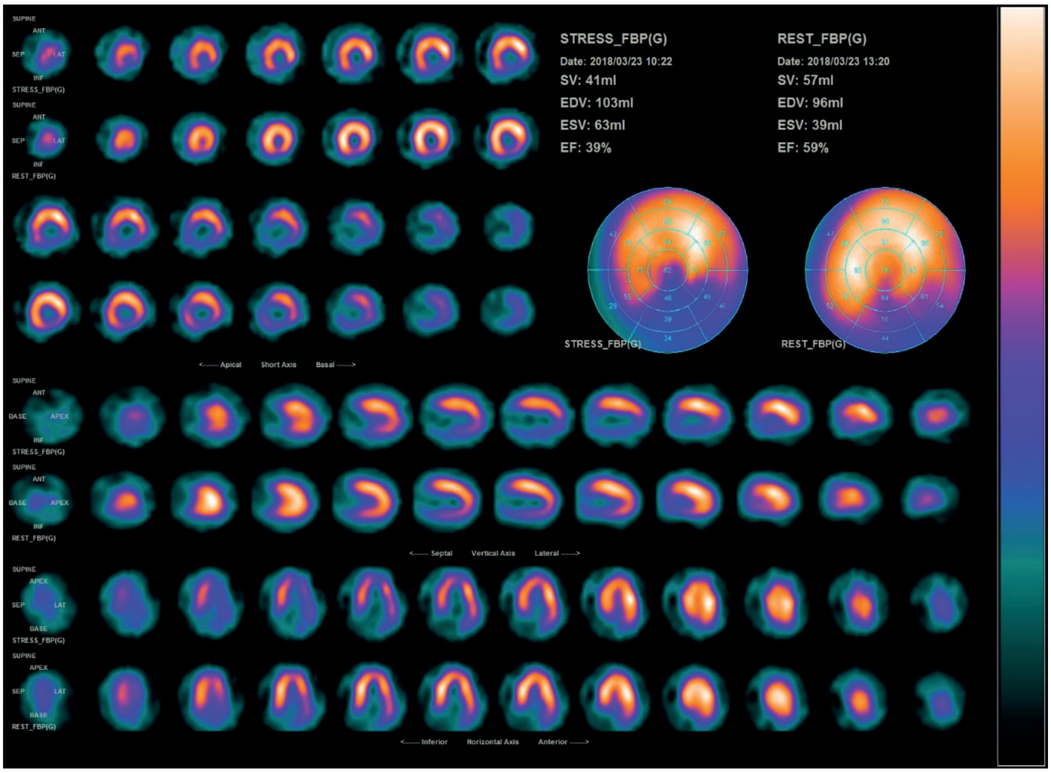

Figure 1. Patient 1 myocardial perfusion before ESMR therapy measured using SPECT scan.

spot when end-diastole. A shockwave applicator is used to calibrate and fixate the targeted area to the ischemic location. To completed nine sessions of therapy, the therapy was performed on the 1st, 5th, and 9th intervention week. During the 1st, 5th, and 9th intervention week, the shockwave was delivered to the left ventricle's basal, middle, and apical segments, respectively, for 30 minutes each session. A 3-week therapy-free interval was kept after the 1st, 5th, and 9th therapy week.

After four months of ESMR therapy, patient 1 demonstrated improved myocardial perfusion calculated as SRS from 14 to 8 and SSS from 31 to 19 (Figure 1 and Figure 2). Three patients demonstrated improvement of resting myocardial perfusion calculated as SRS. However, patient 4 demonstrated deterioration of SRS from 1 to 6. In the measurement of myocardial perfusion at stress, patients 2 and 4 demonstrated deterioration of SSS, from 10 to 5 and 8 to 16, respectively (Figure 3).

After four months of ESMR therapy, the myocardial function measured using rest and stress LVEF is improved in patient 1 but reduced in patient 4. Even though there is a reduction of resting LVEF, patient 2 demonstrated a better LVEF at stress than resting state after ESMR therapy (Table II).

Table II. Effect of ESMR to left ventricular ejection fraction.

	Left Ventricular Ejection Fraction (%)			
	Rest		Stress	
	Before ESMR	After ESMR	Before ESMR	After ESMR
Patient 1	59	67	39	57
Patient 2	60	55	57	57
Patient 3	44	44	36	34
Patient 4	85	59	70	48

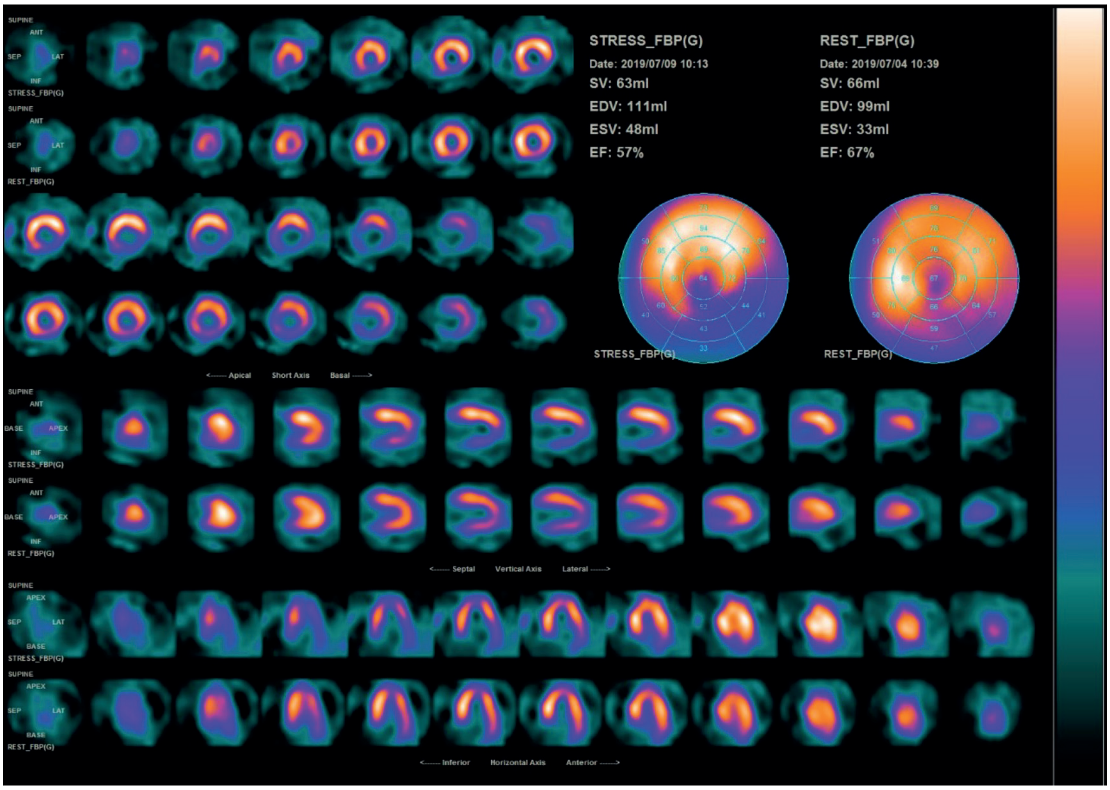

Figure 2. Patient 1 myocardial perfusion after ESMR therapy measured using SPECT scan.

When using GLS to measure myocardial function, there is improvement in patient 1 and 3 from -16 to -20.9 and -14.8 to -18.2. However, there is still evidence of myocardial function reduction measured by GLS in patient 4 after ESMR therapy -26.1 to -20.7 (Figure 4).

The measurement of LVEF and GLS were generally used to measure systolic function. We also evaluate the diastolic function after ESMR therapy. There is an improvement of diastolic function in patient 2 and 3 with baseline diastolic dysfunction grade 2 to diastolic dysfunction grade 1. However, there is no improvement of diastolic dysfunction in patient 1 and 4 with baseline diastolic dysfunction grade 1. There was no complication or cardiac event during ESMR therapy until the time of post-therapy evaluation.

Discussion

ESMR therapy works by stimulating angiogenic growth factors, including vascular endothelial growth factor (VEGF) and nitric oxide synthase (NOS). These factors will promote progenitor cell endothelial recruitment and neovascularization. This process increases collateral growth, myocardial remodeling, and left ventricular compliance[4,9,10].

Our case series found that neovascularization effect from ESMR therapy could improve myocardial perfusion and function in indicated CABG-SAP patients. In literature, there are limited studies that evaluate the use of ESMR therapy in indicated CABG-SAP patients. The use of ESMR on indicated CABG-SAP patients will provide a new clinical application to its previous use in refractory angina patients. Thus, for SAP patients that refused the invasive approach, this therapy could be a hope to improve their prognosis.

There are differences in the anatomical conditions in refractory angina and indicated revascularization-SAP patients. In indicated CABG-SAP patients, there is still significant epicardial stenosis causing a mismatch of oxygen demand in the myocardium, which can cause deteriorated myocardial mechanics. Whereas in refractory angina, the cause of decreased myocardial mechanics occurs due to various factors, such as microvascular disorders, vasospasm, and other factors beyond the presence of significant epicardial stenosis[11].

This case series measured myocardial mechanics through myocardial perfusion and myocardial function. The myocardial perfusion was measured using SPECT examination that evaluates radionuclide uptake in myocardial regions through coronary vessels. The SRS is the sum of the individual scores from the 17 segments of the polar map obtained during the resting state. In comparison, SSS was taken during stress to evaluate perfusion defects in myocardial regions[12]. The myocardial function was measured using rest and stress LVEF, GLS, and diastolic dysfunction. In clinics, LVEF is widely used to determine the pump function of the heart. In comparison, GLS and diastolic dysfunction are used to determine the prognosis of myocardial function.

This case series was conducted retrospectively, and biomarkers evaluation are not routinely conducted. Thus, the neovascularization effect could only be measured from the improvement of myocardial mechanics. *In vitro* studies found that ESMR therapy could stimulate neovascularization[13], further confirmed by Cai et al[14] that demonstrated a significant increase of VEGF and Interleukin-8 (IL-8) after ESMR therapy in refractory angina patients. A recent study by Sanchez et al[15] also demonstrated a significant increase of VEGF and other pro-angiogenic biomarkers concordance with myocardial mechanics improvement in refractory angina pectoris patients.

In our case series, ESMR therapy is best to improve myocardial perfusion and function in patient 1. This patient had the longest history of CAD and higher severity of CCS. In addition, this patient had no smoking history compared to the other patients. As demonstrated in previous trials and prospective cohort studies, ESMR therapy could improve myocardial perfusion, LVEF, and GLS in refractory angina pectoris patients[4,5,10]. Seeking patient characteristics, patient 1 having similar characteristics in patients studied in most previous studies with a long history of CAD, higher CCS class, and high ischemic burden.

We found a deterioration of myocardial perfusion and function at rest after ESMR therapy in patient 2. However, at stress, myocardial perfusion and function are preserved with slight improvement from baseline after ESMR therapy. The LM disease in patient 2 seems to reduce the beneficial effect of ESMR therapy. It is known that LM disease if left untreated, could burden myocardial perfusion and function way more[16]. However, ESMR therapy could still preserve myocardial perfusion and function in this patient.

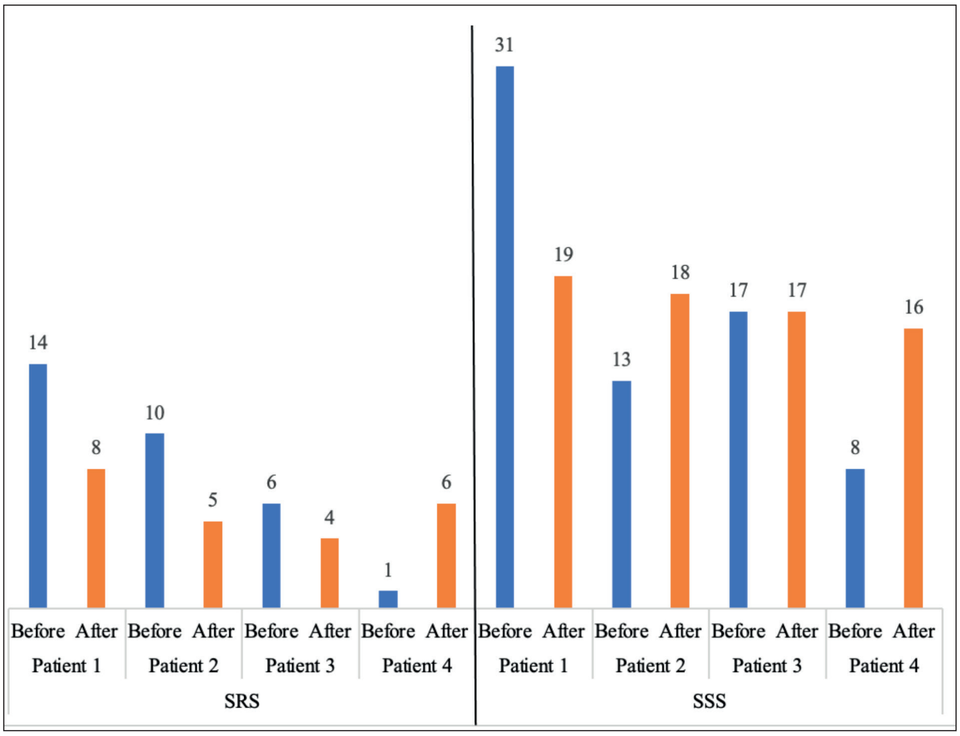

Figure 3. The Effect of ESMR therapy to myocardial perfusion using SPECT scan. SRS: Summed Rest Score, SSS: Summed Stress Score.

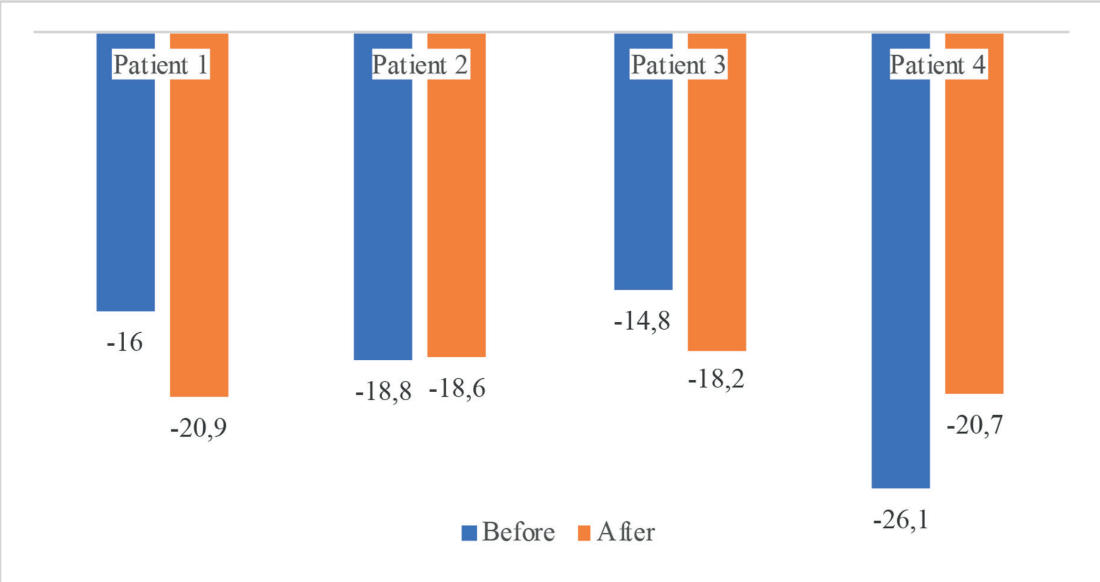

Figure 4. The effect of ESMR to Global Longitudinal Strain

The myocardial function measured as GLS is improved in patient 1 and 3. Unique findings are found in patient 3, which has a remarkable improvement in GLS over LVEF. This finding still indicating a good prognosis[17]. GLS value indicates sub-clinical myocardial dysfunction, which is more sensitive than LVEF to predict left ventricle function[18].

In patient 4, myocardial perfusion and function deteriorated even after ESMR therapy. Diabetes and current smoking could be significant risk factors that could reduce the beneficial effect of ESMR therapy. Diabetes and smoking activity are found to cause poor collateral growth and reduced myocardial perfusion[19-22]. This mechanism leads to an extensive fibrotic area of the cardiac muscle and deteriorating left ventricle function[20].

In the context of diastolic dysfunction, Duque et al[10] demonstrated that the reduction of diastolic dysfunction severity after ESMR therapy only occurred in 15% of the studied sample. In patient 2 and 3, the improvement of diastolic function is concordance with the improvement of myocardial perfusion at rest. Hence the diastolic function is more sensitive to ischemia than systolic function. Therefore, the improvement of diastolic function could indicate a good prognosis[23].

As the previous population studied is refractory angina patients that not amendable for invasive therapy. Therefore, novel results in our study using indicated CABG-SAP populations could give a preliminary view to study further. Our study has several limitations. Our study is retrospective, with only a small number of patients without a control group. Since variables measured are collected from records, we could not exclude the potential of the measurement bias. Due to the limitations above, therefore, there is some risk of bias to generalize this result.

Conclusions

This result from small case series indicates that ESMR therapy for indicated CABG-SAP patients could improve myocardial perfusion and function. The beneficial effect of this therapy is found mainly in CCS III patient with a high ischemic burden. However, this beneficial effect of ESMR therapy is not optimized in patients with several conditions, such as active smoking, diabetes, and LM disease.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgment

This study supported by Ulin General Hospital, Banjarmasin, Indonesia.

Ethics Approval

Ethical approval to report this case series was obtained from Dr. Hasan Sadikin General Hospital (No. LB.02.01/X.6.5.284/2020).

Informed Consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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