

Evaluation of left ventricular systolic and diastolic regional function after enhanced external counter pulsation therapy using strain rate imaging

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Received 16 January 2008; accepted after revision 25 May 2008; online publish-ahead-of-print 21 June 2008

KEYWORDS

EECP;
Tissue Doppler imaging;
Ventricular function;
Coronary artery disease

Aims Enhanced external counter pulsation (EECP) is a non-invasive and non-pharmacological therapy for patients with symptomatic coronary artery disease (CAD). There are, however, insufficient data to support the effectiveness of EECP in improving the myocardial mechanical properties of patients with refractory stable angina. We aimed to assess the effects of EECP on myocardial mechanical properties and cardiac functions in CAD patients not eligible for surgical or percutaneous revascularization procedures.

Methods and results Twenty patients in New York Heart Association (NYHA) functional Class III and IV angina were evaluated. The mean age of the patients was 63 ± 9 years, and 65% were male. A comprehensive echocardiographic study including an evaluation of the tissue Doppler-based parameters of systolic and diastolic functions was performed before and after the termination of the protocol. EECP was carried out 1 h per day, 5 days per week, for 7 weeks. EECP resulted in a significant increase in peak late diastolic transmitral inflow velocity (0.75 ± 0.14 vs. 0.83 ± 0.20 m/s, $P < 0.05$), propagation velocity (42.35 ± 6.25 vs. 46.00 ± 5.68 cm/s, $P < 0.05$), peak early diastolic velocity of mitral annulus (5.35 ± 1.79 vs. 5.95 ± 1.10 cm/s, $P < 0.05$), peak systolic velocity (2.51 ± 0.28 vs. 2.67 ± 0.26 , $P < 0.05$), and early diastolic velocity (3.24 ± 0.18 vs. 3.52 ± 0.26 cm/s, $P < 0.01$) of all middle segments, peak late diastolic velocity of all basal (4.48 ± 0.58 vs. 4.75 ± 0.70 cm/s, $P < 0.05$) and middle segments (2.82 ± 0.66 vs. 3.25 ± 0.46 cm/s, $P < 0.01$), peak systolic strain rate of all basal (0.76 ± 0.07 vs. 0.99 ± 0.08 1/s, $P = 0.001$) and middle segments (0.75 ± 0.09 vs. 0.94 ± 0.09 1/s, $P < 0.001$), peak systolic strain of basal (11.64 ± 1.51 vs. $13.97 \pm 1.52\%$, $P < 0.01$) and middle segments (11.81 ± 1.15 vs. $13.73 \pm 1.57\%$, $P < 0.001$), and left ventricular (LV) ejection fraction (40.25 ± 12.72 vs. $46.25 \pm 12.97\%$, $P < 0.001$). There was also a significant decrease in the ratios of transmitral E/A (0.92 ± 0.41 vs. 1.08 ± 0.46 , $P < 0.05$) and E/Ea (12.61 ± 4.22 vs. 15.44 ± 6.96 , $P < 0.05$) after EECP therapy. A significant reduction in NYHA angina class (≥ 1 angina class) was seen in the patients, who completed treatment.

Conclusion EECP therapy seemed to improve both regional and global LV systolic and diastolic functions in patients with chronic angina pectoris.

Coronary artery disease (CAD) is a leading cause of death and disability worldwide. Chronic myocardial ischaemia resulting from CAD can cause stable angina and interfere with ordinary activities.¹ Treatment of CAD consists of medical and invasive surgical and non-surgical coronary interventions.² However, there are patients who are not suitable candidates for coronary interventions and are symptomatic despite aggressive

medical treatment.^{3,4} The search for alternative therapies for this subgroup of patients has recently yielded some new treatment modalities such as enhanced external counter pulsation (EECP).⁵ EECP is a non-invasive, outpatient therapy for the treatment of chronic angina pectoris patients who have not responded to pharmacotherapy and are not candidates for surgical or percutaneous revascularization procedures, e.g. angioplasty and coronary bypass surgery.^{6,7} The haemodynamic effects of EECP are similar to those of intra-aortic balloon pumping⁸ (IABP) but in contrast to IABP, EECP provides

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long-lasting increase in the coronary blood flow.^{9,10} EECP has been demonstrated to be effective in some disorders¹¹ inasmuch as it boosts myocardial perfusion, enhances dipyridamole-induced coronary vasodilatation, and increases the time to 1-mm ST-segment depression, which can ultimately reduce both angina and myocardial ischaemia in patients not responding to medical and surgical therapy.¹² Be that as it may, the exact mechanism whereby EECP exerts its favourable effects has hitherto remained unclear,¹¹ and there is insufficient evidence to support the effectiveness of EECP treatment in myocardial function.⁶

Strain rate imaging has been derived from regional velocity gradients within the myocardium aligned along the Doppler beam.^{13,14} Strain rate measures the rate of the deformation of a tissue segment, and peak systolic and diastolic strain rate represents the maximal rate of deformation in systole and diastole. Strain is obtained by integrating strain rate over time and represents the deformation of a tissue segment over time, and end-systolic strain represents the magnitude of peak deformation in systole. A spatial map of longitudinal deformation within the myocardium can be obtained with this method.

The present study sought to evaluate the effects of EECP therapy on both global and regional left ventricular (LV)

systolic and diastolic functions of intractable angina patients not amenable to medical treatment or percutaneous revascularization procedures.

Methods

Study patients

We studied 20 patients, comprising 13 men and 7 women aged between 45 and 78 years (mean 63 ± 9 years), with severe anginal symptoms secondary to chronic CAD, none of them were candidate for revascularization therapy. The majority of patients (90%) had multi-vessel disease. The inclusion criteria were New York Heart Association (NYHA) Class III or IV angina despite aggressive pharmacotherapy. All medications (except for TNG PRN) remained unchanged. We excluded the patients with poor strain/strain curves in more than two segments. The patients were questioned about any adverse reaction and improvement of angina. All the subjects were studied after written informed consent had been obtained in accordance with the regulations of the ethics committee of Shaheed Rajaie Cardiovascular Medical and Research Center, Tehran, Iran.

Study protocol used for EECP treatment

The EECP device (*Figure 1*) consists of three paired pneumatic cuffs applied to the lower extremities (Vasomedical, Westbury, NY, USA). Patients are typically treated for a 1-h daily programme for a total of 35 sessions over 7 weeks. Three sets of pneumatic cuffs, wrapped around the patient's calves, lower thighs, and upper thighs (*Figure 2*). The cuffs are inflated sequentially at the onset of diastole, and 300 mmHg of external pressure is applied during diastole. At the onset of systole, the external pressure in the cuffs is released, producing a decrease in systolic pressure. A computer-controlled pneumatic system with a display console is used to inflate and deflate the series of compressive cuffs, and inflation and deflation are triggered by events in the cardiac cycle through microprocessor-interpreted electrocardiography signals. The compression is triggered by the electrocardiographic R-wave, with the delay being adjusted until the induced retrograde pulse wave enhances the cardiac output as reflected by an optimally augmented blood pressure and blood flow wave during cardiac diastole.^{15,16} A finger plethysmogram is utilized throughout treatment to monitor diastolic and systolic pressure wave forms (*Figure 1*).⁶



Figure 1 Enhanced external counter pulsation device.

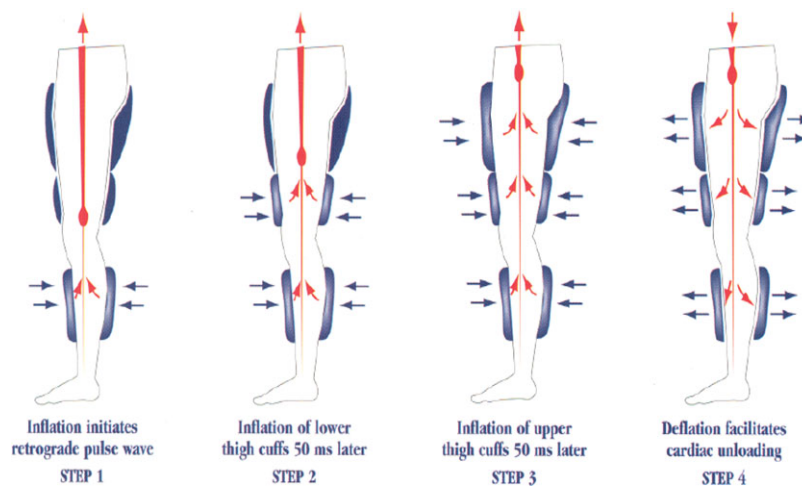


Figure 2 Mechanism of EECP. Schematic of EECP showing sequential cuff inflation and deflation. EECP induced by successive compression of cuffs wrapped around the calves, thighs, and buttocks. Rhythmical, 250-mmHg compression during diastole is optimized by adjusting the delay between the electrocardiographic R-wave and the compression onset until a finger-plethysmographic pulse curve shows a blood pressure augmentation during diastole above systolic blood pressure values.

Echocardiography examinations

Echocardiography examinations were done before and after EECP using Vivid seven digital ultrasound scanner equipment with an ergonomically designed multi-frequency M3S transthoracic sector transducer and tissue velocity imaging facility.

LV systolic and diastolic function parameters were measured. LV diastolic function was assessed via conventional PW Doppler of the mitral inflow including early (E) and late (A) transmitral diastolic velocities, E/A ratio, isovolumetric relaxation time (IVRT), deceleration time (DT), A-wave duration, E/Ea ratio, propagation velocity, pulmonary veins flow velocities, and peak filling rate. IVRT was recorded as the interval between aortic valve closure and mitral valve opening. Greyscale images were recorded in second harmonic mode with 1.7 MHz as transmit frequency. LV ejection fraction (LVEF) was assessed via eyeball evaluation and via Simpson's method if accurate endocardial border detection was possible.¹⁷

Tissue Doppler, strain, and strain rate imaging and data analysis

Colour Doppler myocardial imaging (CDMI) from the interventricular septum, lateral, anterior, inferior, anteroseptal, and posterior walls were recorded using the apical 4-, 2-, and 3-chamber views with the subjects in left lateral decubitus position according to the recommendations of the American Society of Echocardiography,¹⁸ pre- and post-EECP treatment. All data sets were acquired over three consecutive heartbeats at high frame rate (130–180 frames/s) using a 2.4 MHz transducer. In all acquisitions, the 2D-sector angle was minimized to attain a high frame rate, and the pulse repetition frequency was adjusted in order to avoid aliasing. Aortic valve opening and closing times and also mitral valve opening and closing times were measured using systolic aortic blood flow and diastolic mitral blood flow recording via pulsed Doppler with the sample volume placed at the level of the aortic annulus and mitral valve tip, respectively. The digital cine-loops raw data sets containing both grey scale and tissue velocity imaging information were stored in the scanner memory for off-line analysis. After the completion of the echocardiographic examinations via CDMI, the raw data were analysed off-line using the Vivid seven system to obtain regional myocardial velocity, strain, and strain rate imaging profiles in all LV base and mid segments in the myocardial location using an 8×4 region of interest (ROI). Information on a total of 12 base and mid segments throughout the 3 end-expiratory beats was recorded and analysed for each patient. The following data were measured in each patient pre- and post-EECP treatment within 1 week and the results were averaged: peak systolic velocity (S-wave), peak early (E-wave) and late (A-wave) diastolic velocities, end-systolic strain, peak systolic strain rate (Figure 3), and also peak early (Ea) and late (Aa) diastolic annular velocities.

Statistics

Statistical analysis was conducted using SPSS software package version 13 (SPSS Inc., Chicago, IL, USA). Data were expressed as mean \pm SD. Data were tested for normal distribution with the Kolmogorov-Smirnov test. The comparison of the differences between the pre- and post-EECP groups was performed using the paired samples *t*-test. The multiple comparisons were performed with the ANOVA, and the comparison of the differences between base and mid segment for the percentage of improvement was performed with the independent samples *t*-test. A difference was considered significant when the *P* < 0.05. Intra-observer variability was assessed for peak systolic velocity, end-systolic strain, and peak systolic strain rate. Two segments were selected from each patient randomly (total of 40 segments), and two measurements were taken using the tissue velocity, strain, and strain rate methods on the same segments. Intra-observer variability was defined as the

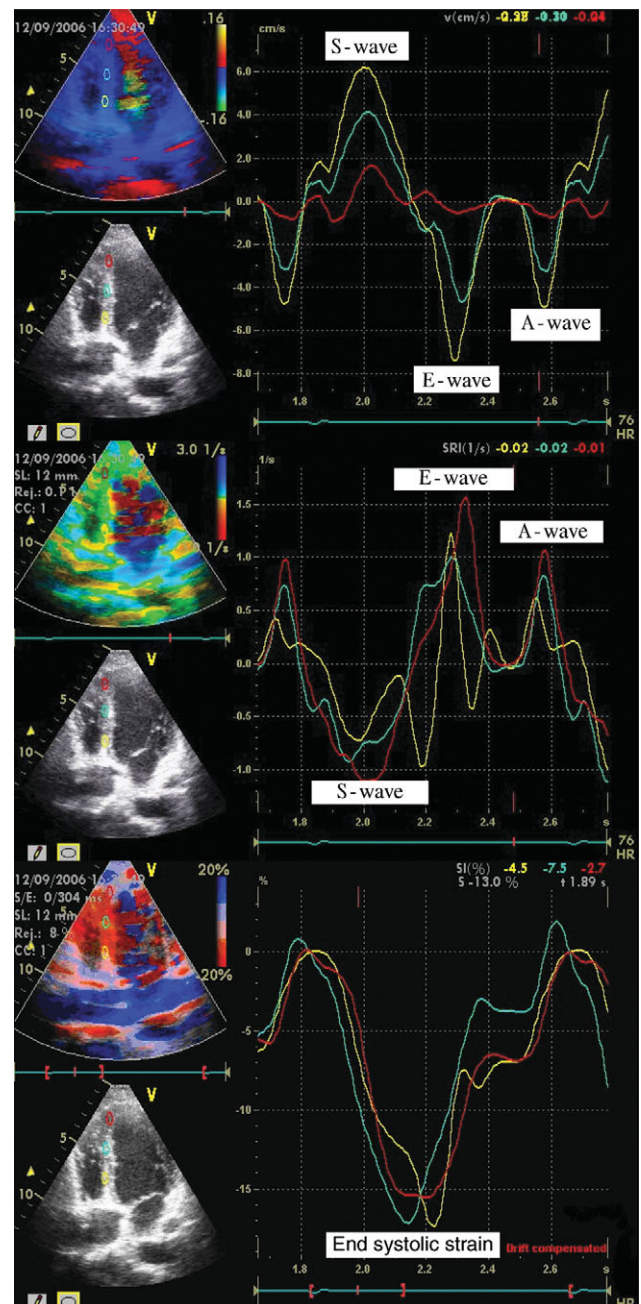


Figure 3 Example of ventricular septum tissue Doppler imaging: derivation of velocity (top), strain rate (middle), and strain (bottom) from tissue Doppler data at basal septum (yellow), mid septum (green), and apical segment (red). The series of velocity and strain rate curves comprising systolic [S] and early and late diastolic [E and A, respectively] components.

differences between the measurements and expressed as a percentage error of the means.

Results

Systolic function, diastolic function, and mitral annulus measurements

The mean values of the echocardiographic data of systolic and diastolic functions pre- and post-EECP treatment are presented in *Table 1*. EECP therapy caused a significant

Table 1 Comparison of transmitral inflow velocity, pulmonary flow velocity and tissue Doppler data of mitral annulus (mean absolute \pm SD) pre-and post-EECP

	Pre-EECP	Post-EECP	P-value
Transmitral spectral Doppler			
E-velocity, m/s	0.77 \pm 0.28	0.75 \pm 0.27	NS
A-velocity, m/s	0.75 \pm 0.14	0.83 \pm 0.20 ^a	0.030
DT _E , ms	224.20 \pm 97.63	212.70 \pm 62.49	NS
IVRT, ms	99.35 \pm 27.03	97.62 \pm 25.14	NS
VP, cm/s	42.35 \pm 6.25	46.00 \pm 5.68 ^a	0.012
A _m dur	145.30 \pm 15.06	135.50 \pm 32.01	NS
E/A ratio	1.08 \pm 0.46	0.92 \pm 0.41 ^a	0.037
Pulmonary spectral Doppler			
PVs, cm/s	51.35 \pm 13.06	56.60 \pm 17.96	NS
PVd, cm/s	44.85 \pm 19.68	41.35 \pm 13.74	NS
A _p dur, ms	110.39 \pm 49.06	123.90 \pm 13.74	NS
Mitral annulus tissue Doppler			
Ea-velocity, cm/s	5.35 \pm 1.79	5.95 \pm 1.10 ^a	0.036
Aa-velocity, cm/s	6.85 \pm 2.16	6.75 \pm 1.37	NS
E/Ea ratio	15.44 \pm 6.96	12.61 \pm 4.22 ^a	0.021
Left ventricular systolic function			
LVEF, %	40.25 \pm 12.72	46.25 \pm 12.97 ^a	0.000

^aThe mean difference was significant at the 0.05 level, NS, not significant; E-velocity, transmitral inflow peak E velocity; A-velocity, transmitral inflow peak A velocity; DT_E, deceleration time of transmitral flow E; IVRT, isovolumic relaxation time; VP, velocity of propagation; A_mdur, mitral A-wave duration; PVs, pulmonary peak systolic velocity; PVd, pulmonary peak diastolic velocity; A_pdur, pulmonary A-wave duration; Ea-velocity, mitral annulus peak early diastolic velocity; Aa-velocity, mitral annulus peak late diastolic velocity; LVEF, left ventricular ejection fraction.

improvement in LV diastolic function including increased late diastolic transmitral inflow velocity (0.75 \pm 0.14 vs. 0.83 \pm 0.20 m/s, $P < 0.05$), propagation velocity (42.35 \pm 6.25 vs. 46.00 \pm 5.68 cm/s, $P < 0.05$), and LV systolic function in terms of LVEF (40.25 \pm 12.72 vs. 46.25 \pm 12.97 cm/s, $P < 0.05$) (Table 1).

Peak systolic and diastolic velocity results

The results of the mean and SDs of the peak systolic (S), peak early diastolic (E), and peak late diastolic (A) velocity measurements from the base and mid segments of the ventricular septum, lateral, anterior, inferior, antero-septal, and posterior walls and also a comparison of the results pre- and post-EECP therapy are presented in Figure 4. EECP therapy brought about a significant increase in peak systolic velocities in the entire LV base and mid segments ($P < 0.05$) except for the lateral base, inferior base, posterior base, and mid segments (PV = NS). For peak early diastolic velocities, EECP therapy produced a significant increase in the entire base and mid segments ($P < 0.05$) except for the lateral and anterior wall base segments (PV = NS). Additionally, EECP therapy caused a significant increase in peak late diastolic velocities in all the segments ($P < 0.05$) except for the septum base, lateral base, posterior wall base, and mid segments (PV = NS).

Strain and strain rate results

The results of the mean and SDs of the end-systolic strain and peak systolic strain rate measurements from the base

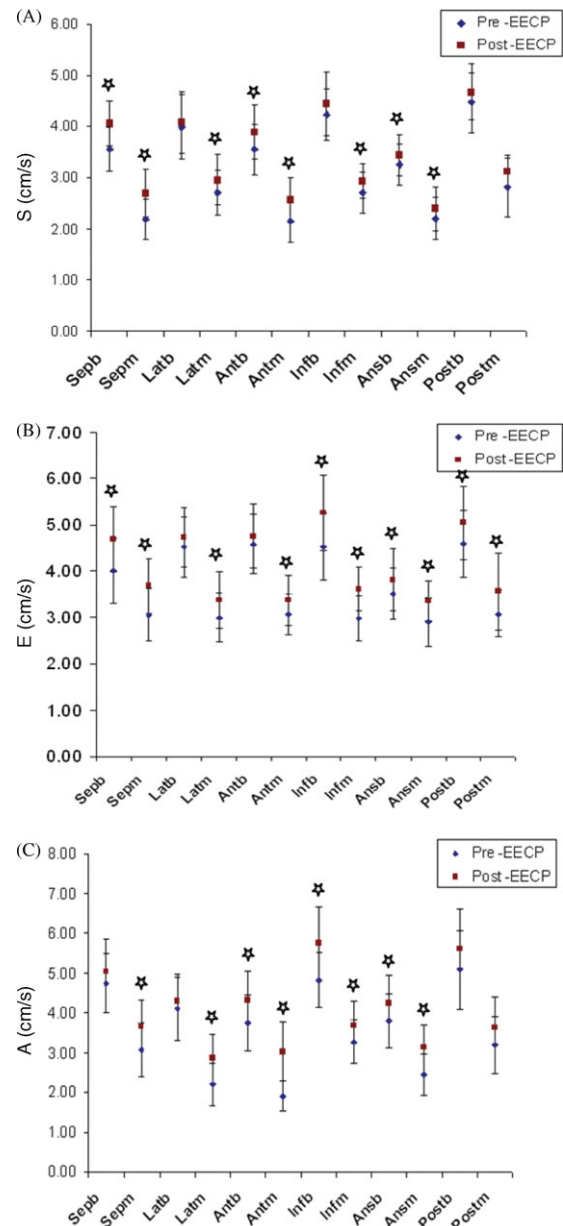


Figure 4 Comparison of peak systolic velocity (A), peak early (B), and late diastolic velocity measurements (C) (mean absolute \pm SD) pre- and post-EECP therapy presented for all left ventricular base and mid segments separately. Asterisks show that there are significant differences between the means (PV < 0.05). S, peak systolic velocity; E, peak early diastolic velocity; A, peak late diastolic velocity; Sepb, basal segment of septum; Sepm, middle segment of septum; Latb, basal segment of lateral wall; Latm, middle segment of lateral wall; Antb, basal segment of anterior wall; Antm, middle segment of anterior wall; Infb, basal segment of antero-septal wall; Infm, middle segment of inferior wall; Ansb, basal segment of antero-septal wall; Ansm, middle segment of antero-septal wall; Postb, basal segment of posterior wall; and Postm, middle segment of posterior wall.

and mid segments of the ventricular septum, lateral, anterior, inferior, antero-septal, and posterior walls and also a comparison of the results pre- and post-EECP therapy are presented in Figure 5.

EECP therapy resulted in a significant increase in the end-systolic strain of the entire base and mid segments

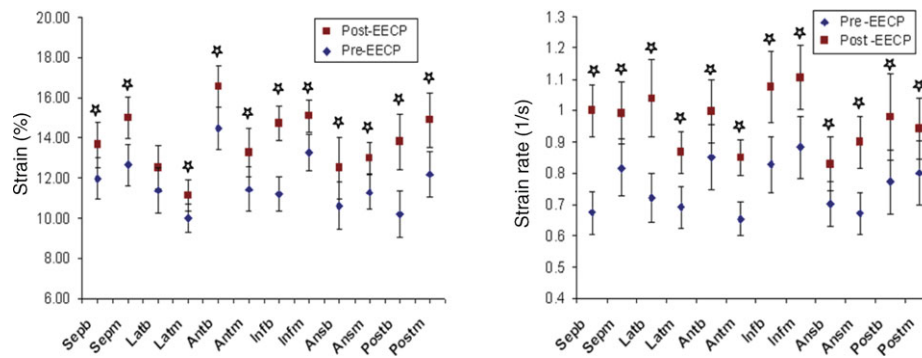


Figure 5 Comparison of strain (left) and strain rate (right) measurements (mean \pm SD) pre- and post-EECP therapy presented for all LV base and mid segments separately. Asterisks show that there are significant differences between the means ($P < 0.05$).

Table 2 Comparison of TDI, Strain and Strain rate measurements pre and post EECP (with mean absolute and standard deviation)

	Pre-EECP	Post-EECP	<i>P</i> -value
Tissue Doppler velocity			
S-base, cm/s	3.86 \pm 0.47	3.93 \pm 0.38	NS
S-mid, cm/s	2.51 \pm 0.28	2.67 \pm 0.26 ^a	0.045
E-base, cm/s	4.43 \pm 0.47	4.64 \pm 0.48	NS
E-mid, cm/s	3.24 \pm 0.18	3.52 \pm 0.26 ^a	0.008
A-base, cm/s	4.48 \pm 0.58	4.75 \pm 0.70 ^a	0.011
A-mid, cm/s	2.82 \pm 0.66	3.25 \pm 0.46 ^a	0.009
End-systolic strain			
Basal segments, %	11.64 \pm 1.51	13.97 \pm 1.52 ^a	0.002
Middle segments, %	11.81 \pm 1.15	13.73 \pm 1.57 ^a	0.000
Peak systolic strain rate			
Basal segments, 1/s	0.76 \pm 0.07	0.99 \pm 0.08 ^a	0.001
Middle segments, 1/s	0.75 \pm 0.09	0.94 \pm 0.09 ^a	0.000

^aThe mean difference was significant at the 0.05 level, NS, not significant differences; S-base, peak systolic velocity of basal segments; S-mid, peak systolic velocity of middle segments; E-base, peak systolic velocity of basal segments; E-mid, peak systolic velocity of middle segments; A-base, peak systolic velocity of basal segments; A-mid, peak systolic velocity of middle segments.

($P < 0.05$) except for the lateral base segment. There was also a significant increase in the end-systolic strain rate of the entire base and mid LV segments ($P < 0.05$).

Mean systolic and diastolic peak velocity, strain, and strain rate per region (basal and middle of the 12 LV segments) and SD were all calculated separately. These results are depicted in *Table 2*.

There was a significant reduction in NYHA anginal class (≥ 1 angina class) for all the patients who completed treatment.

Repeatability results

The mean differences for the intra-observer variability were 5.2, 4.7, and 6.2% for peak systolic velocity, end-systolic strain, and peak systolic strain rate, respectively.

Discussion

Treatment of patients with refractory angina pectoris still continues to pose a challenge to the medical community. EECP has emerged in recent years as a non-invasive, well-tolerated

therapeutic option for CAD patients with refractory angina not amenable to standard revascularization procedures.¹⁹ Indeed, prospective clinical trials and large treatment registries have shown major reductions in anginal symptoms and improvements in objective measures of myocardial ischaemia in response to EECP in patients with symptomatic CAD.² More recent studies have demonstrated the potential role of EECP in heart failure management inasmuch as it improves quality of life and reduces symptoms.⁶

EECP treatment is associated with an immediate increase in the blood flow in multiple vascular beds including the coronary arterial circulation¹⁰ and causes acute changes in haemodynamics including an increase in preload and a decrease in afterload.¹⁰ Several published studies, designed to assess objective evidence of improvement in myocardial perfusion²⁰ and beneficial haemodynamic effects, showed better various organ systems perfusion^{21,22} and LV diastolic filling after EECP treatment^{23,24} and, accordingly, recommended this modality as initial revascularization treatment for angina refractory to medical therapy.²⁵ The sudden drop in intra-aortic pressure unloads the LV during systole, thus reducing the work of the ventricle in ejecting blood and reducing oxygen requirements of the cardiac muscle.^{2,26} However, there have been no reports demonstrating the quantitative regional function of myocardial contractility.

The present study is the first study on regional and global LV systolic and diastolic functions in patients treated with EECP for chronic stable refractory angina pectoris. In addition to examining the motion of LV segments, which are susceptible to tethering to the adjacent tissue, we measured myocardial motion relative to the adjacent myocardium using strain and strain rate curves. A comparison of the tissue velocity, strain, and strain rate measurements pre- and post-EECP for each segment is presented in *Figures 4 and 5*. In the present study, total alteration (calculated for each parameter by averaging all LV base and mid segments, *Figure 6*) showed that there was a higher significant alteration in strain rate when compared with the strain and velocity measurements ($P < 0.05$). There was no significant difference between the total alterations of peak systolic and early and late diastolic velocities statistically. The results of total alteration and also alteration in LV walls are presented separately for each measured parameter in *Figure 6*. As regards which base or mid segments have better function after EECP, our statistical comparisons showed that there was no significant difference between

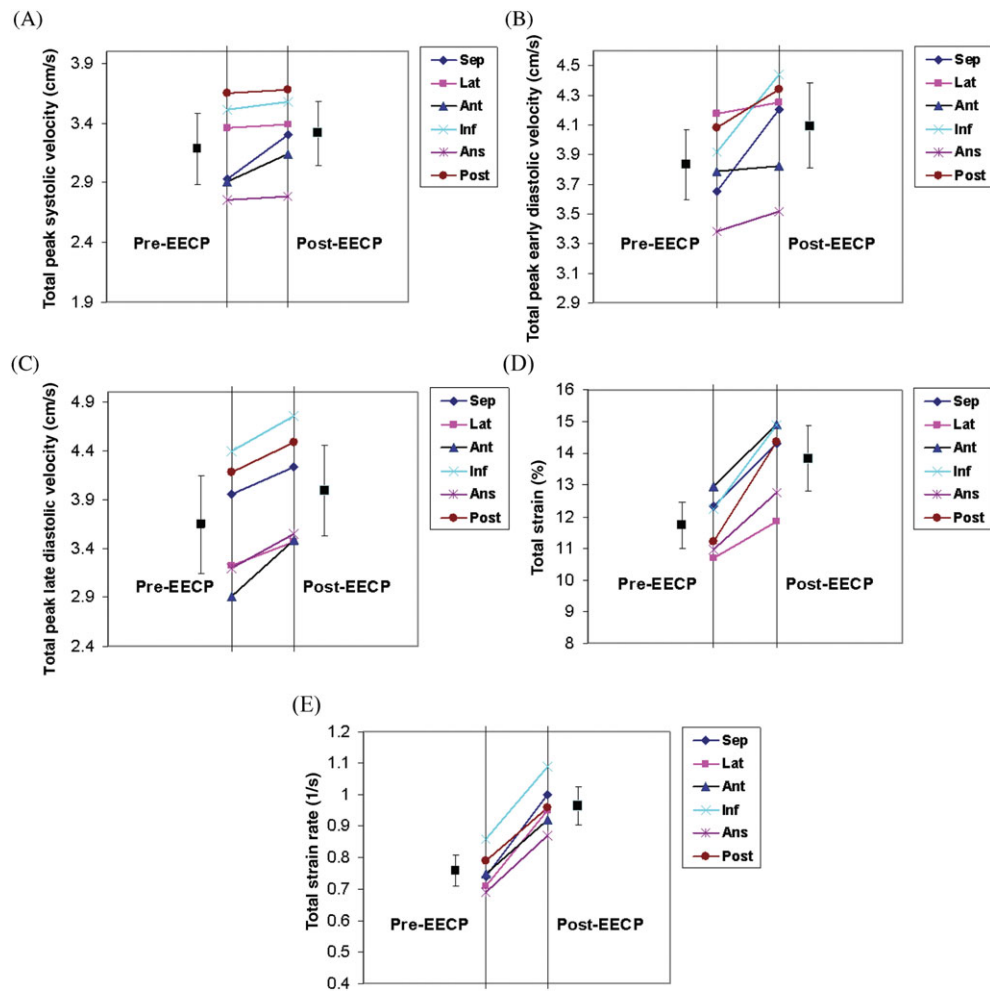


Figure 6 Comparison of total peak systolic velocity (A), total peak early diastolic velocity (B), total peak late diastolic velocity (C), total end-systolic strain (D), and total peak systolic strain rate (E) measurements, pre- and post-EECP therapy (mean \pm SD). The middle lines show alteration of the parameters for each wall separately. Total values calculated by average of all LV base and mid segments. Sep, septum wall; Lat, lateral wall; Ant, anterior wall; Inf, inferior wall; Ans, anteroseptal wall; Post, posterior wall.

base and mid improvement for the velocity, strain, and strain rate measurements.

In a study by Urano *et al.*²⁷ in patients with stable refractory angina, EECP treatment did not alter systolic LV function, but it did significantly improve the parameters of ventricular diastolic function. Arora *et al.*²⁸ did not see a difference in these parameters but reported significant differences in LV systolic function between pre- and post-EECP therapy measurements. We, however, saw significant differences in transmitral spectral late diastolic velocity, propagation velocity, and E/A ratio for diastolic ventricular function and also significant differences in LV systolic function by LVEF measurement.

Given the findings of this study, EECP can benefit patients suffering from CAD by improving global and regional LV systolic and diastolic functions according to velocity, strain, and strain rate imaging.

Study limitations

In this retrospective, non-randomized study, we evaluated the immediate effects of EECP treatment within 1 week after the completion of treatment for a relatively small number of patients in NYHA Class III and IV angina. The long-term effects

of EECP therapy on myocardial function, however, require further studies with larger sample populations and control groups if possible persistent improvements in myocardial function after EECP therapy are to be better documented.

In this study, we encountered some technical limitations. Velocity, strain, and strain rate measurements are angle-dependent and the angle between the ultrasound beam and LV axis must be small.²⁹ We manipulated the transducer position to make the Doppler beam as parallel as possible to the LV long-axis. Also, the velocity-regression technique has a number of potential pitfalls. For instance, strain rate curves are sensitive to signal noise and the quality of these curves may vary depending on the care used in obtaining the underlying velocity data.^{10,30} To minimize these disadvantages, we measured and averaged the parameters of three consecutive cardiac cycles.

Conclusions

The present study showed the beneficial effects of EECP on both regional and global functions of the myocardium. EECP improved systolic and diastolic parameters and caused significant alterations in longitudinal systolic and diastolic

myocardial functions as assessed by colour tissue Doppler imaging in patients with chronic angina pectoris. EECP is an effective, non-invasive therapy for CAD.

Acknowledgements

We wish to thank all the nursing staff involved in the administration of EECP treatment at Shaheed Rajaei Cardiovascular Medical and Research Center. Many thanks are also due to Hassan Moladoust for his valuable advice.

Conflict of interest: none declared.

Funding

This work was totally funded by Shaheed Rajaie Cardiovascular Medical and Research Center.

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