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The impact of coronary sinus narrowing on diastolic function in patients with refractory angina

Yishay Szekely, Yan Topilsky, Samuel Bazan, Miri Revivo, Shmuel Banai, Maayan Konigstein *

Department of Cardiology, Tel Aviv Medical Center and Sackler School of Medicine, Tel Aviv University, Israel

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ABSTRACT

Objective: Evaluating the impact of Coronary sinus (CS) narrowing on diastolic function.
Background: Narrowing of the CS is an emerging therapy for refractory angina pectoris, improving perfusion to the ischemic subendocardium and relieving ischemia and angina. It was speculated that increased CS pressure might cause interstitial myocardial edema and diastolic dysfunction.
Methods: Prospective assessment of diastolic function was performed at baseline and 6 months following CS Reducer implantation in consecutive patients treated for refractory angina. Diastolic function assessment included left atrial volume, early transmitral filling peak velocity (E wave), E wave deceleration time (DT), transmitral atrial wave velocity (A wave), and early diastolic velocity of the septal (e′ septal) and lateral (e′ lateral) aspects of the mitral annulus.
Results: Twenty-four patients with chronic refractory angina and proven myocardial ischemia (mean age 69.3 ± 10.9 years) were included in the analysis. A wave velocity, E/A ratio, E wave DT and left atrial volume did not significantly change 6 months following Reducer implantation ($p > 0.1$ for all comparisons). A non-significant decrease in E wave velocity (80.5 ± 22.3 cm/s vs. 75.7 ± 17.5 cm/s, $p = 0.19$) and non significant increase in e′ septal and lateral (5.28 ± 1.54 cm/s vs. 5.30 ± 1.71 cm/s, $p = 0.95$ and 8.26 ± 1.85 cm/s vs. 8.46 ± 2.07 cm/s, $p = 0.69$, respectively) led to a non-significant decrease in E/e′ average ratio (12.6 ± 5.7 vs. 11.4 ± 3.3, $p = 0.24$). Mean diastolic function class significantly decreased following Reducer implantation from 1.5 ± 0.66 to 1.17 ± 0.76 ($p = 0.008$).
Conclusion: Coronary sinus narrowing in patients with myocardial ischemia and refractory angina does not adversely affect diastolic function and may actually improve it.

What is already known about this subject?

Coronary sinus narrowing is an emerging therapy for refractory angina pectoris. This procedure was speculated to cause interstitial myocardial edema and diastolic dysfunction.

What does this study add?

Coronary sinus narrowing in patients with myocardial ischemia and refractory angina does not adversely affect diastolic function and may actually improve it.

How might this impact on clinical practice?

This will encourage treating patients with refractory angina with coronary sinus narrowing without the concern of diastolic function deterioration. Furthermore, future studies might evaluate the use of this therapy for heart failure with preserved ejection fraction, a disease with a true unmet need of novel therapies.

1. Introduction

Chronic angina refractory to medical and interventional therapies is a disabling clinical condition and a major public health problem [1,2]. The prevalence of chronic angina is high not only in patients who are not candidates for revascularization, but also in patients following successful revascularization [3,4].

Current treatment options for refractory angina are exhausted with less than optimal results, and clearly, there is an unmet need for treating these patients more effectively. Percutaneous narrowing of the coronary sinus (CS) using the Reducer device has emerged as a safe and effective therapy to reduce disabling symptoms and improve quality of life in patients suffering from refractory angina. The clinical benefit of the Reducer has been demonstrated in a randomized sham-controlled trial as well as in non-randomized trials and registries. Published data support the clinical benefit of this therapy in alleviating symptoms of angina, improving exercise capacity and quality of life, and reducing myocardial ischemia in patients with refractory angina who are not good candidates for revascularization [5–13].

* Corresponding author at: Department of Cardiology, Tel-Aviv Medical Center, 6 Weizmann St., Tel-Aviv, Israel.
E-mail address: maayan.konigstein@gmail.com (M. Konigstein).

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The impact of CS narrowing on diastolic function has not been previously evaluated. It has been speculated by physicians that were introduced to this novel technology, that CS narrowing and the consequent elevated venous pressure, might cause interstitial stasis and edema within the myocardium, potentially leading to left ventricular diastolic dysfunction. On the other hand, reduction of myocardial ischemia by the Reducer may lead to improvement in diastolic function. We therefore aimed to evaluate the impact of CS narrowing on diastolic function, in patients with refractory angina and evidence of myocardial ischemia.

2. Methods

2.1. Study design

The data for the present analyses were collected prospectively, in a single center, open-label registry study, conducted at the Tel Aviv Medical Center, Tel Aviv, Israel. The study was approved by the national and the local institutional ethics committees. All participants signed a written informed consent for participation in the study.

2.2. Patients

Study population included 32 consecutive patients suffering from refractory angina who were treated with CS Reducer implantation and underwent echocardiographic evaluation of diastolic function at baseline and 6 months post procedure. Enrolled to the registry were patients suffering from severe disabling angina despite maximally tolerated medical therapy - Canadian Cardiovascular Society (CCS) class 2–4. All were deemed non-candidates for surgical or percutaneous coronary revascularization, as their last coronary angiography prior to the procedure revealed obstructive disease in epicardial vessels deemed too small for intervention, and/or had diffuse disease, chronic total occlusions or diffuse in-stent re-stenosis. All of them had no clear target for repeat revascularization, weather percutaneous or surgical.

All patients had objective evidence of myocardial ischemia of the left coronary arteries territory (by perfusion scan and/or by dobutamine echocardiography). All patients received maximally tolerated medical therapy as prescribed by the treating cardiologist that was unchanged during the study period. Importantly, as a national referral center, we left the decision upon medical treatment to the discretion of the referring cardiologist, before as well as after the procedure. Excluded were patients with one or more of the following: recent (within 3 months) myocardial infarction, percutaneous coronary intervention (PCI) or coronary arterial bypass grafting (CABG), life threatening rhythm disorders, ejection fraction (EF) <30% or clinically decompensated heart failure, severe valvular heart disease, patients who may be candidates for cardiac resynchronization therapy, and patients with a mean right atrial pressure higher than 15 mm Hg.

In seven patients, echocardiographic evaluation of diastolic function was incomplete or suboptimal. In addition, one patient experienced deterioration of aortic valve stenosis (from mild-moderate to severe) during the follow-up period. These patients ($n = 8$) were excluded from the final analysis.

CCS class of all patients was evaluated at baseline and 6 months following Reducer implantation by 2 cardiologists.

2.3. The CS Reducer device

The Reducer and the procedure were formerly described in detail elsewhere [12,14,15]. Briefly, it is a stainless steel, balloon expandable, hourglass shaped mesh, introduced into the CS through the right internal jugular vein. A few weeks following implantation, the Reducer struts are covered with tissue, and then, the narrowing is established, and a pressure gradient is generated. The diameter at the narrowed mid-portion of the Reducer is 3 mm, and it can reach diameters of 7–13 mm at both ends using inflation pressure of 2 to 4 bars.

2.4. Echocardiographic assessment of diastolic function

Early (E) and atrial (A) trans-mitral flow velocities, and early diastolic mitral annular velocity (e′) were measured in the apical 4-chamber view. Early trans-mitral filling peak velocity (E wave), E wave deceleration time (DT) and trans-mitral atrial wave velocity (A wave) were obtained with a pulsed-wave Doppler by placing the sample volume at the tip of the mitral valve leaflets. The e′ was measured from septal and lateral annulus. The ratio of peak E to peak e′ (septal, lateral and average) was calculated (mitral E/e′ ratio) from the average of at least 3 cardiac cycles. Left atrial (LA) volume was calculated using the biplane area length method at end systole. Diastolic function was assessed by integrating measurements of the mitral inflow, systolic pulmonary pressure, LA volume index, Doppler tissue imaging of the mitral annulus and peak tricuspid regurgitation (TR) velocity, based on recent guidelines [16]. According to these guidelines, left ventricular diastolic dysfunction is present when >2 of the following parameters meet their cutoff values-septal e′ < 7 cm/s or lateral e′ < 10 cm/s, average E/e′ ratio > 14, LA maximum volume index > 34 ml/m^2, and peak TR velocity > 2.8 m/s. We then calculated the E/A ratio and integrated it with the former specified measurements, classifying the patients into four categories: normal diastolic function = 0, impaired relaxation = 1, pseudo-normal = 2 and restrictive pattern = 3, using the same guidelines.

Echocardiographic evaluation was performed at baseline (during a 30-day period before the procedure) and 6 months following the procedure, by technicians and echocardiologists who were blinded to the study protocol, and unaware of the time point of the test in relation to treatment.

2.5. Statistical analysis

Descriptive results are expressed as mean value ± standard deviation (SD) for continuous variables and as percentages for categorical variables. Differences from baseline to 6-month parameters were compared by use of a paired t-test. All of the analyses were considered significant at a two-tailed p-value of <0.05. Statistical analyses were performed with the SPSS statistical package (SPSS, Chicago, IL).

The authors had full access to the data and take responsibility for their integrity. All authors have read and agreed to the manuscript as written.

3. Results

3.1. Baseline and follow-up clinical evaluation

Study population consisted of 24 patients (69.3 ± 10.9 years, 92% males). All had history of previous revascularization procedures, 19 patients (79%) had previous CABG surgery, and all had at least one previous PCI (median: 4 PCIs, range: 1–24 PCIs). Mean EF was 48 ± 6.9% (range: 35%–60%). Baseline clinical characteristics and medical therapy of the study population are presented in Table 1. Mean baseline CCS class was 3.4 ± 0.6 (CCS class II: 1 (4%) patient; class III: 13 (54%) patients; class IV: 10 (42%)). All had objective evidence of myocardial ischemia in the territory of the left coronary artery system (left anterior descending and left circumflex arteries) by dobutamine stress echocardiography and/or dipyridamole myocardial perfusion scan. There was no change in medical treatment prescribed at baseline, post procedure and during follow up.

Overall, 21/24 (88%) patients reported relief of symptoms expressed as at least 1 CCS class improvement following the procedure, and 12/24 (50%) reported improvement of at least 2 CCS classes. Six months following Reducer implantation, mean angina score expressed by CCS class decreased from 3.4 ± 0.6 to 1.9 ± 1 ($p < 0.0001$) (Fig. 1 A and B).

Table 1
Baseline clinical characteristics and medical therapy of the study population ($n = 24$).

Clinical characteristics	
Age, years (mean ± SD)	69.3 ± 10.9
Male gender	22 (92%)
Weight, kg (mean ± SD)	85.2 ± 20.9
Height, cm (mean ± SD)	165.6 ± 14.6
Diabetes mellitus	16 (67%)
Hypertension	20 (83%)
Hypercholesterolemia	24 (100%)
Smoking history	18 (75%)
Family history of ischemic heart disease	12 (50%)
Peripheral vascular disease	3 (12.5%)
Previous stroke/TIA	5 (21%)
Previous MI	11 (46%)
Previous PCI	24 (100%)
Number of PCI, median (range)	4 (1–24)
Previous CABG	19 (79%)
Estimated LVEF, %, mean ± SD (range)	48 ± 6.9 (35%–60%)
eGFR, ml/min/1.73 m^2 (mean ± SD)	91 ± 39.5
Medical treatment	
Beta blockers	20 (83%)
Calcium channel blocker	4 (17%)
ACE inhibitor/ARB	10 (42%)
Nitrates	17 (71%)
diuretics	5 (21%)
Aspirin	21 (88%)
Clopidogrel	17 (71%)
Warfarin	3 (12.5%)
Statins	21 (87.5%)
Ivabradine	0

ACE- angiotensin converting enzyme, ARB- angiotensin receptor blocker, CABG- coronary arterial bypass grafting, eGFR- estimated glomerular filtration rate, LVEF- left ventricle ejection fraction, MI- myocardial infarction, PCI- percutaneous coronary intervention, TIA- transient ischemic attack.

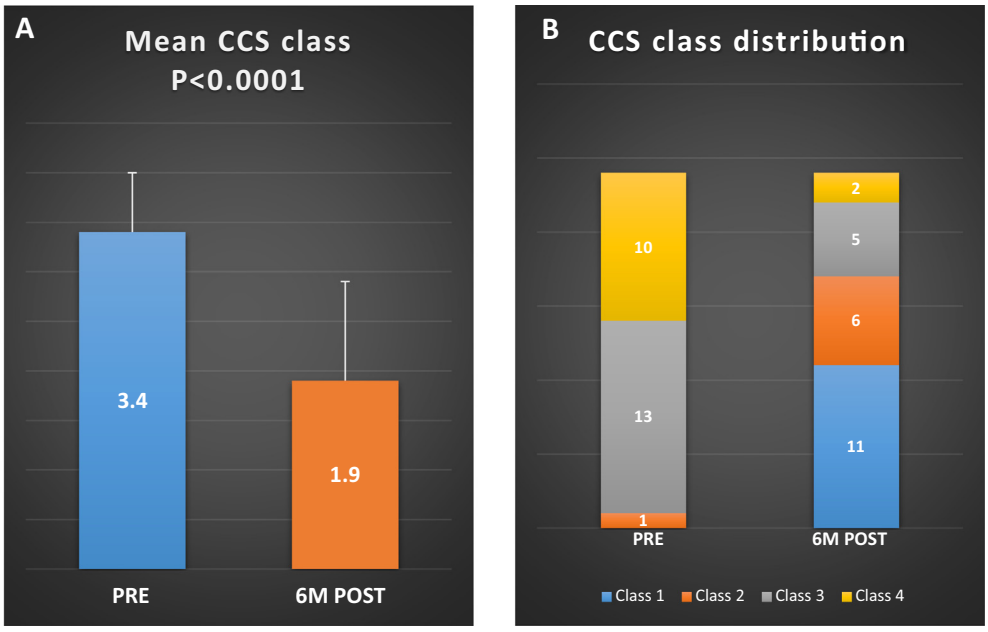

Fig. 1. CCS class following Reducer implantation. (1A) Mean CCS class at baseline and 6 months following Reducer implantation. (1B) Distribution of CCS classes at baseline and 6 months following Reducer implantation.

3.2. Baseline and follow-up diastolic function evaluation

Echocardiographic diastolic parameters at baseline and follow-up are presented in Table 2 and Fig. 2. A small non-significant decrease in E and A wave velocities (80.5 ± 22.3 cm/s vs. 75.7 ± 17.5 cm/s, $p = 0.19$ and 77.6 ± 17.5 cm/s vs. 74.8 ± 20, $p = 0.42$, respectively) was noted, with almost unchanged E/A ratio (1.02 ± 0.3 vs. 1.05 ± 0.4, $p = 0.71$). There was also a non-significant change in E wave DT and left atrial volume. The aforementioned decrease in E wave velocity along with a small, non-significant increase in e′ septal and lateral (5.28 ± 1.54 cm/s vs. 5.30 ± 1.71 cm/s, $p = 0.95$ and 8.26 ± 1.85 cm/s vs. 8.46 ± 2.07 cm/s, $p = 0.69$, respectively), led to a non-significant decrease in E/e′ average ratio (12.6 ± 5.7 vs. 11.4 ± 3.3, $p = 0.24$). However, mean diastolic dysfunction category significantly improved following Reducer implantation, from 1.5 ± 0.66 at baseline to 1.17 ± 0.76 at follow up ($p = 0.008$).

Table 2
Diastolic function at baseline and 6 months following Reducer implantation.

Parameter	Baseline	6 months follow-up	*p* value
Diastolic function category			
Mean ± SD	1.5 ± 0.66	1.17 ± 0.76	0.008
Normal diastolic function	1 (4%)	4 (17%)	
Impaired relaxation	11 (46%)	13 (54%)	
Pseudo-normal	11 (46%)	6 (25%)	
Restrictive pattern	1 (4%)	1 (4%)	
Echocardiographic diastolic parameters			
E wave (cm/s)	80.5 ± 22.3	75.7 ± 17.5	0.19
A wave (cm/s)	77.6 ± 17.5	74.8 ± 20	0.42
E/A ratio	1.02 ± 0.3	1.05 ± 0.4	0.71
e′ septal (cm/s)	5.28 ± 1.54	5.30 ± 1.71	0.95
e′ lateral (cm/s)	8.26 ± 1.85	8.46 ± 2.07	0.69
E/e′ ratio- lateral	10.7 ± 4.3	9.4 ± 2.7	0.37
E/e′ ratio- septal	16.5 ± 7	14.7 ± 5.1	0.17
E/e′ ratio- average	12.6 ± 5.7	11.4 ± 3.3	0.24
Left atrial volume (ml)	79.6 ± 28.9	83.3 ± 27.6	0.49
Deceleration time (ms)	208 ± 52	202 ± 40	0.63

Values presented as mean ± SD.

4. Discussion

The purpose of the present study was to evaluate the impact of CS narrowing on diastolic function in patients with myocardial ischemia and refractory angina treated with CS Reducer implantation. The main finding of the present analysis is that CS narrowing does not adversely affect diastolic function and may actually lead to improvement in diastolic function in patients undergoing this procedure.

The anti-ischemic and anti-anginal effects of CS narrowing that have been demonstrated in previous studies is attributed to the elevated backward pressure in the coronary venous system, forcing redistribution of blood to the ischemic subendocardial layers, thus normalizing the endocardial/epicardial blood flow ratio via arteriolar dilatation and reduced vascular resistance [17].

Following the introduction of the Reducer into clinical practice, concerns have been raised by clinicians that CS narrowing, and the consequent elevated venous pressure, might lead to interstitial stasis and edema, with consequent reduction in myocardial perfusion pressure, and aggravation of subendocardial ischemia. Both interstitial edema and subendocardial ischemia can lead to myocardial stiffening and impaired relaxation resulting in diastolic dysfunction [18]. However, as perfusion pressure within the subendocardial myocardium is determined mainly by the left ventricular end diastolic pressure and not so much by the coronary venous pressure [19,20], it is unlikely that elevated venous pressure will lead to a meaningful reduction in myocardial perfusion pressure. Moreover, it was clearly shown in preclinical [17,21,22], as well as clinical trials [8] that CS pressure elevation significantly improved myocardial perfusion and lessened myocardial ischemia.

Here we report, for the first time, that CS narrowing does not lead to worsening in diastolic function parameters in patients with myocardial ischemia and refractory angina.

The fact that there was no sign of worsening in diastolic parameters in our study, indicates that CS narrowing probably does not lead to interstitial stasis and edema. Moreover, a significant improvement in mean diastolic dysfunction category was noted, probably reflecting the result of several positive trends in specific echocardiographic diastolic parameters. In fact, the non-significant reduction in E wave

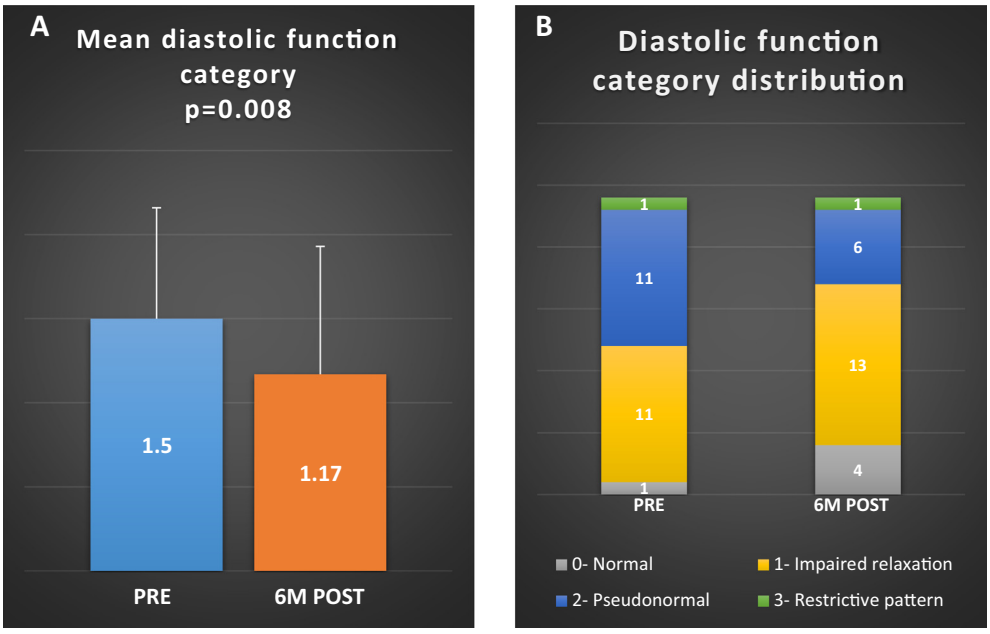

Fig. 2. Echocardiographic parameters of diastolic function at baseline and 6 months following Reducer implantation. (2A) Mean diastolic function category at baseline and 6 months following Reducer implantation. (2B) Distribution of diastolic function categories at baseline and 6 months following Reducer implantation.

velocity, along with a non-significant increase in e′ septal and lateral, led to a lower mean E/e′. These findings may be explained by improved subendocardial perfusion which leads to improved subendocardial contractility and left ventricle compliance with a consequent reduction in LV end diastolic pressure. Additional support for this hypothesis is found in studies showing that impaired coronary microvascular function is highly prevalent in patients with heart failure with preserved ejection fraction (HFpEF), a fact that may signal microvascular dysfunction as a therapeutic target in HFpEF [23–25]. Since coronary microvascular dysfunction is considered one of the pathophysiologic factors in HFpEF, a future perspective could be to further evaluate the impact of coronary sinus narrowing on outcomes of patients suffering from HFpEF, non-obstructive CAD and coronary microvascular dysfunction, proved by invasive or non-invasive methods (e.g. by measuring coronary flow reserve). In fact, promising data regarding the clinical benefit of Reducer implantation in patients without obstructive coronary disease has already been reported [26].

Importantly, while modification of medical treatment prescribed to the patients following the procedure could have masked diastolic dysfunction caused by CS narrowing, the fact that there was no change in medical treatment during follow-up period further establishes our conclusions.

4.1. Limitations

We acknowledge several limitations of this study. First, the study includes a small number of patients with a distinct male predominance. Moreover, some patients participating in the registry had incomplete echocardiographic diastolic evaluation and therefore were excluded from the present analysis. Second, CCS evaluators were not blinded to treatment, potentially leading to a certain bias. Finally, there was no cardiac MRI available for a more accurate evaluation of myocardial edema.

5. Conclusions

Coronary sinus narrowing does not impair diastolic function. Along with its already proven beneficial aspects, coronary sinus Reducer implantation might improve diastolic function by improving subendocardial perfusion. Larger studies, using a wider variety of modalities in the assessment of diastolic function, such as BNP and NT-proBNP measurement [27] or cardiac MRI [28], are required to further establish this finding.

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Author disclosures

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