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Letters

RESEARCH LETTER

Coronary Sinus Narrowing Improves Right Ventricular Function

Right ventricular (RV) function affects outcome in coronary artery disease (CAD) patients.[1] Elevating coronary sinus (CS) pressure with the use of coronary Reducer device (Neovasc) was shown to improve subendocardial blood flow in the ischemic heart, alleviate ischemia and angina, and improve left ventricular (LV) function.[2,3] We tested whether in patients with refractory angina and ischemia, who are treated with Reducer implantation, the increased CS pressure will also improve RV performance.

We conducted a single-center, single-arm, open-labeled prospective study, enrolling consecutive patients with obstructive CAD and refractory angina despite optimal medical therapy, who were not candidates for revascularization procedures. All participants had objective evidence of reversible myocardial ischemia in technetium sestamibi scan, LV ejection fraction (LVEF) ≥35%, and no significant valvular disease. Primary pulmonary hypertension was excluded when appropriate.

All underwent full echocardiographic evaluation at baseline and 4 to 6 months following Reducer implantation. Impaired RV function was defined as the presence of ≥2 of the following: RV fractional area change (RV FAC) <35%, tricuspid annulus plane systolic excursion (TAPSE) <16 mm, peak systolic lateral tricuspid annular velocity (S') <10 cm/s and myocardial performance index (MPI) >0.44. All measurements were done in accordance with the American Society of Echocardiography Guidelines for the Echocardiographic Assessment of the Right Heart in Adults.[4] LVEF was evaluated using the Simpson method, and LV diastolic function was evaluated by integration of mitral inflow, left atrial volume index, tissue Doppler imaging of the mitral annulus, and peak tricuspid regurgitation velocity. Images were obtained in a steady state condition by expert technicians and cardiologists blinded to the study details using the same equipment (iE33, Philips Medical Systems). No changes in medical treatment were allowed for the first 6 months post-implantation. The study was approved by the Tel Aviv Medical Center institutional ethics committee, and all participants signed an informed consent (Use of the Neovasc Coronary Sinus Reducer System for the Treatment of Refractory Angina Pectoris in Patients With Angina Class 3-4 Who Are Not Candidates for Revascularization [Reducer]; NCT01566175).

Enrolled were 25 patients. Mean age was 67 ± 9 years, 84% men, mean CCS (Canadian Cardiovascular Society) 3.4 ± 0.8. Baseline RV dysfunction was present in 14 patients (56%). Patients with and without RV dysfunction had similar baseline characteristics in terms of age (66 ± 10.8 vs 68 ± 7.1 years; $P = 0.63$), sex (85% vs 88% men; $P = 1.00$), LVEF (48 ± 9.1% vs 49 ± 5.3%; $P = 0.64$), right coronary artery (RCA) involvement (4 vs. 4; $P = 1.00$), regional LV ischemic distribution, diastolic function, and cardiovascular risk profile. Following Reducer implantation, a similar degree of angina relief was observed in patients with and without RV dysfunction.

Improvement in RV function indices after Reducer implantation was shown in the entire cohort but reached statistical significance in the subgroup of patients with baseline RV dysfunction (S' 8 ± 1.2 cm/s to 9.5 ± 1.5 cm/s; $P = 0.01$; RV FAC 34.1 ± 5.4% to 36.7 ± 5.1%; $P = 0.033$; MPI 0.56 ± 0.07 to 0.49 ± 0.05; $P = 0.036$, and TAPSE from 15.8 ± 3.2 cm to 16.2 ± 2.9 cm; $P = 0.001$, before and after Reducer implantation, respectively) (**Figure 1**). The improvement in RV function was not associated with either LV systolic or diastolic function change (P for interaction = 0.6). However, lateral LV wall ischemia was associated with an improvement in several RV function indices (P for interaction = RV FAC 0.024, S' 0.011 cm/s, and MPI 0.008, respectively).

Though physiological differences in afterload, wall stress, and myocardial perfusion allow the RV to better recover from ischemic injury,[5,6] its function is jeopardized in the presence of ischemia. Our study demonstrates that in severe CAD patients, CS narrowing with the use of coronary Reducer may induce RV function recovery. These findings correlate with previous reports showing an improvement in LV function in similar patients.[3] However, the improvement shown in RV function in our study was not associated with LV systolic or diastolic function

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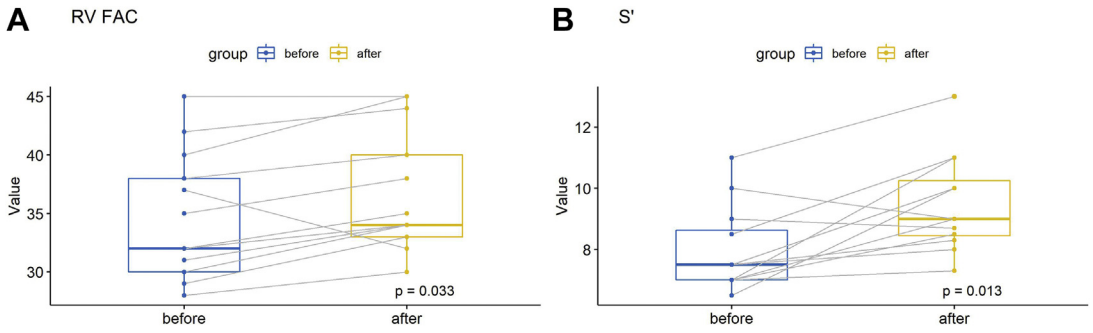
FIGURE 1 Coronary Reducer Implantation Effect on RV Function



Of 25 severe coronary artery disease patients, 14 had baseline RV dysfunction. Reducer implantation (known to ameliorate myocardial ischemia) was associated with an improvement in several RV function indices (eg, RV FAC improved from 34.1 ± 5.4% to 36.7 ± 5.1%; $P = 0.033$ and S' improved from 8 ± 1.2 cm/s to 9.5 ± 1.5 cm/s; $P = 0.01$), a finding that might contribute to patients' clinical stabilization. FAC = fractional area change; RV = right ventricular.

changes and implies that the RV may directly benefit from the improved myocardial perfusion induced by the Reducer device. Furthermore, RCA involvement in our cohort was not associated with the effect of Reducer on RV function, corresponding with a recent publication showing that the Reducer is effective also when a total occlusion of the RCA was found.[7] Small-vessel disease is prevalent in CAD patients, and though RV ischemia was not directly evaluated in our study, it might be presumed that increased CS pressure with the Reducer device induces dilatation of small resistant arterioles, causing redistribution of blood to ischemic RV subendocardium. This, in turn, may lead to improved myocardial function.

Our study is limited by its small size, the use of 2-dimensional echocardiography as a single method for RV function evaluation and the lack of direct assessment of RV ischemia. Therefore, our results should be seen as hypothesis-generating and warrant repeated investigation in a larger cohort and using other methods for evaluating RV ischemia and function. Nevertheless, our findings suggest that in this small group of severe CAD patients, coronary Reducer implantation was associated with RV function improvement, a result that might contribute to patients' clinical stabilization.

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REFERENCES

1. Haddad F, Doyle R, Murphy DJ, Hunt SA. Right ventricular function in cardiovascular disease, part II: pathophysiology, clinical importance, and management of right ventricular failure. *Circulation*. 2008;117:1717–1731.

2. Konigstein M, Giannini F, Banai S. The Reducer device in patients with angina pectoris: mechanisms, indications, and perspectives. *Eur Heart J*. 2018;39:925–933.

3. Tzanis G, Palmisano A, Gallone G, et al. The impact of the coronary sinus reducer upon left ventricular function in patients with refractory angina pectoris. *Catheter Cardiovasc Interv*. 2020;95:1104–1108.

4. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr*. 2010;23:685–713; quiz 786-8.

5. Lee FA. Hemodynamics of the right ventricle in normal and disease states. *Cardiol Clin*. 1992;10:59–67.

6. Laster SB, Ohnishi Y, Saffitz JE, Goldstein JA. Effects of reperfusion on ischemic right ventricular dysfunction. Disparate mechanisms of benefit related to duration of ischemia. *Circulation*. 1994;90:1398–1409.

7. Zivelonghi C, Verheye S, Timmers L, et al. Efficacy of coronary sinus reducer in patients with non-revascularized chronic total occlusions. *Am J Cardiol*. 2020;126:1–7.

RESEARCH LETTER

Changes in Blood Pressure Reactivity Against Physical Activity Evaluated by Multisensor-ABPM in Heart Failure Patients

The pathologic significance of blood pressure (BP) variability in patients with heart failure (HF) has not been fully elucidated. Although HF pathophysiology is known to involve cardiac function and autonomic nervous dysfunction, which may lead to a pathologic BP response to physical activity, assessment of the pathophysiology of HF remains challenging under an ambulatory condition. We previously described a patient with an increase in BP reactivity during physical activity after an improvement of cardiac function.[1] We propose the term "actisensitivity" to describe such BP reactivity in response to physical activity; this new aspect of BP variability can be evaluated using our recently developed device, a multisensor-ambulatory BP monitoring (ABPM) device (TM-2441, A & D Co) equipped with: 1) an actigraph that can detect physical movements in 3 directions using an accelerometer; 2) a thermometer; and 3) a barometer.[2] In the present study, actisensitivity is defined as the slope of the regression line that is calculated from 24-h ambulatory systolic BP (SBP) with the log-transformed value corresponding to the 5-minute average of physical activity just before each BP measurement (**Figure 1**).[1,2] In the present study, we prospectively assessed the changes in actisensitivity and ambulatory blood pressure (ABP) parameters between patients with and without improved cardiac function during the treatment of HF.

We assessed multisensor-ABPM data in 20 patients with diagnosed HF (mean age, 63.3 ± 14.1 years; male: 65%; ischemic heart disease: 15%; atrial fibrillation: 25%) just after initial or adjusted treatments, and reassessed the multisensor-ABPM data at follow-up from 6-12 months after tailored treatment. Second, we divided these patients into an improved (n = 11 patients) and a not-improved (n = 9) cardiac-function group; an increase in echocardiographic left ventricular ejection fraction (LVEF) of ≥10% as determined using the biplane method of disks was used as the cutoff.[3] We then compared the changes in actisensitivity and ABP parameters between the 2 groups. Multisensor-ABPM was measured automatically at 30-min intervals for 24 hours using an oscillometric method, and the daytime and nighttime were based on a diary. Patients were recruited during hospitalization or as outpatients. All examinations including multisensor-ABPM and echocardiography were measured in stable condition, ie, all patients could walk alone. Echocardiography was conducted within 1 month before and after the multisensor-ABPM measurements. This study was approved by the Institutional Review Board of the Jichi Medical University School of Medicine and informed consent was obtained from all participants.

LVEF at baseline and follow-up were 29.8% ± 7.2% and 44.9% ± 5.8% in the improved group (n = 11) and 40.8% ± 13.3% and 39.7% ± 12.5% in the not-improved group (n = 9), respectively. In the improved group, 24-hour and nighttime diastolic BP decreased at follow-up (24-hour BP at baseline vs follow-up: 115.5 ± 22.1/79.4 ± 16.4 mm Hg vs 113.7 ± 21.7/74.9 ± 13.0 mm Hg; $P = 0.606$ and $P = 0.040$ for SBP and diastolic BP, respectively; nighttime BP: 112.6 ± 21.6/78.8 ± 16.9 mm Hg vs 105.9 ± 20.8/69.6 ± 12.5 mm Hg; $P = 0.272$ and $P = 0.041$, respectively). These changes were not observed in the not-improved group. Parameters of ABP variability—ie, SD, coefficient of variation, and average real variability of SBP over 24 hours, daytime or nighttime—were not significantly different between baseline and follow-up in either group. Additionally, physical activity (G) did not change between baseline and follow-up in either group. However, the actisensitivity value tended to increase from baseline to follow-up in the improved group (1.0 ± 3.5 vs 4.5 ± 3.5; $P = 0.065$), but not in the not-improved group (3.2 ± 5.4 vs 2.0 ± 6.3; $P = 0.479$). The degree of changes in actisensitivity from baseline to follow-up tended to be higher in the improved group than the not-improved group (3.5 ± 5.6 vs −1.2 ± 4.8; $P = 0.059$). Moreover, in the overall patient group, the change of actisensitivity from baseline to follow-up was significantly related to the changes of LVEF ($r = 0.553$; $P = 0.011$) (**Figure 1**).

Although the present study was conducted in a small sample, to our knowledge this is the first study to prospectively observe the changes of ABP profiles and novel BP reactivity against physical activity actisensitivity in patients with HF using the new