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RESEARCH CORRESPONDENCE

First Experience With the Coronary Sinus Reducer System for the Management of Refractory Angina in Patients Without Obstructive Coronary Artery Disease

The Coronary Sinus (CS) Reducer (Neovasc Inc., Richmond, British Columbia, Canada) is a percutaneous device implanted in the CS to create a controlled narrowing of the lumen leading to an increase in coronary venous pressure, capillary and arteriolar dilatation, and restoration of the endocardial/epicardial blood flow ratio typically impaired in ischemic myocardium. A single randomized clinical trial and several observational studies have demonstrated Reducer safety and efficacy in patients with obstructive coronary artery disease and refractory angina, who are not candidates for revascularization (1–3). Recurrent angina following successful percutaneous coronary interventions (PCI) is common: a focused analysis of the SYNTAX trial reported a prevalence of recurrent angina of 28.5% at 1 year and 25.9% at 5 years after PCI (4). In particular, patients with refractory angina and evidence of myocardial ischemia despite optimal medical therapy and angiographically successful percutaneous revascularization frequently present to clinicians (5). Coronary microvascular dysfunction seems to be the underlying pathophysiological mechanism.

Because no data are available with regards to Reducer performance in this patient group, we address this issue with this preliminary study.

Between 2015 and 2016 all patients referred to 2 Italian institutions (San Raffaele Hospital, Milan, Italy; ASST Bergamo Est, Bolognini Hospital, Seriate, Italy) undergoing coronary angiography because of chronic stable angina (Canadian Cardiovascular Society [CCS] class 3 to 4) with noninvasive evidence of myocardial ischemia despite optimal medical therapy (OMT) were screened.

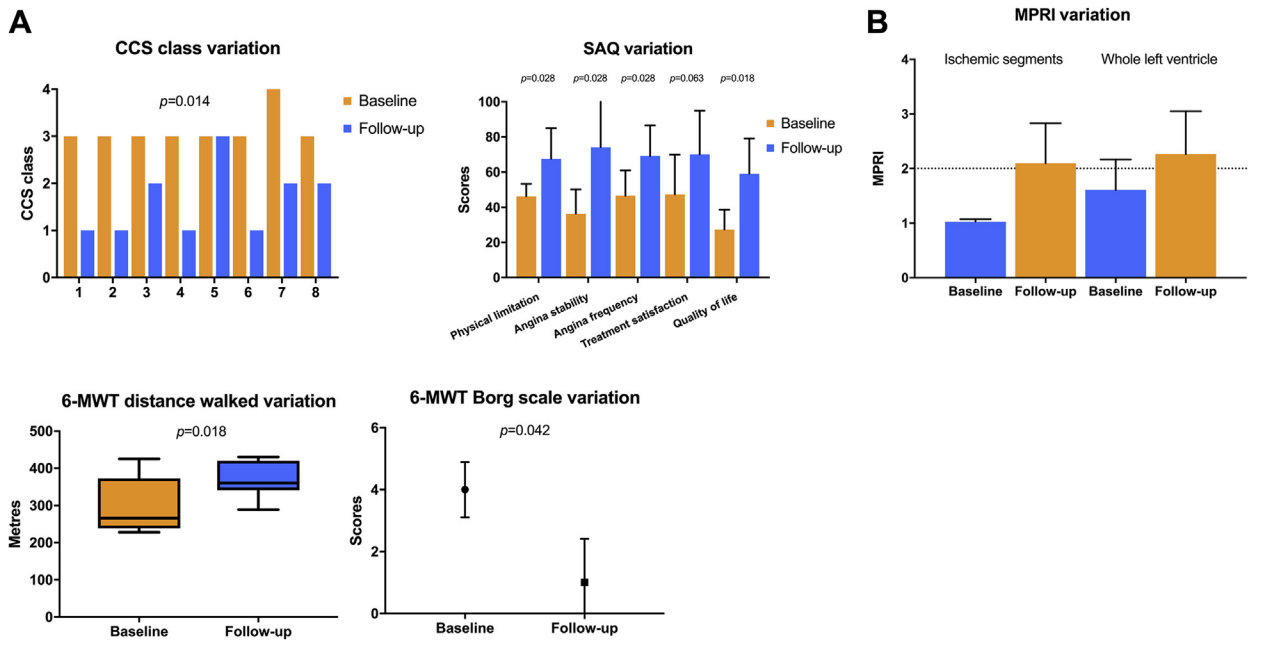
Eight patients with evidence of complete revascularization and nonobstructed epicardial coronary arteries (absence of coronary plaques, <50% narrowing in all epicardial coronary arteries, or a negative intracoronary fractional flow reserve test in case of intermediate lesions) underwent compassionate CS Reducer implantation for the treatment of microvascular angina. All patients had previously undergone at least 1 PCI.

Four (50%) patients were women. Median age was 61.5 years (range 50 to 68 years). Seven patients were in CCS class 3, and 1 was in class 4 despite OMT (median number of anti-ischemic drugs used was 3; range 2 to 4). Median left ventricle ejection fraction was 58.0% (interquartile range [IQR]: 55.0% to 61.5%).

No cases of death, need for coronary angiography/PCI, or hospitalization for angina were noted during the follow-up period. Median CCS class improved from 3.0 (3 to 4) to 1.5 (1 to 3) ($p = 0.014$) (**Figure 1A**). At 1 year, this benefit was maintained for 3 of the 5 patients assessed. Discontinuation of at least 1 antianginal agent was possible in 3 of 8 (37.5%) patients.

A significant improvement in most of the questionnaire domains of the Seattle Angina Questionnaire was observed. Physical limitation improved from 46.0 (IQR: 40.5 to 53.3) to 64.0 (IQR: 53.0 to 80.0) ($p = 0.028$), angina stability from 40.0 (IQR: 21.3

FIGURE 1 Baseline and 4-Month Follow-Up Endpoints



(A) Reduction in angina symptoms, improved exercise tolerance, and quality of life. **(B)** Perfusion stress cardiac magnetic resonance studies with MPRI calculation. Note the increment in the mean MRPI of the ischemic segments and in the mean MPRI of the left ventricle after treatment. 6-MWT = 6-min-walk test; CCS = Canadian Cardiovascular Society; MPRI = myocardial perfusion reserve index; SAQ = Seattle Angina Questionnaire.

to 43.0) to 80.0 (IQR: 58.0 to 100.0) ($p = 0.028$), angina frequency from 47.0 (IQR: 33.0 to 58.0) to 66.0 (IQR: 56.0 to 80.0) ($p = 0.028$), treatment satisfaction from 40.0 (IQR: 26.8 to 73.3) to 75.0 (IQR: 66.0 to 82.0) ($p = 0.063$), and quality of life from 26.5 (IQR: 17.8 to 39.0) to 56.0 (IQR: 53.0 to 60.0) ($p = 0.018$).

At the 6-min-walk test, the distance walked increased from 266 m (IQR: 238.5 to 372.8 m) to 360 m (IQR: 341 to 420 m) ($p = 0.018$) and the Borg scale scores reduced from 4.0 (IQR: 3.0 to 5.0) to 0.0 (IQR: 0.0 to 2.5) ($p = 0.042$) (Figure 1A).

A subgroup of 3 patients underwent dipyridamole stress cardiac magnetic resonance with myocardial perfusion reserve index (MPRI) calculation to objectively measure the effect of Reducer implantation.

MPRI of the ischemic segments significantly increased after Reducer implantation in all 3 patients. Mean MPRI of the ischemic segments increased after Reducer implantation, rising from 1.00 to 2.06 in Patient #1 ($p = 0.023$), from 1.08 to 1.38 in Patient #4 ($p = 0.004$), and from 1.00 to 2.85 in Patient #5 ($p = 0.052$). Mean left ventricular MPRI showed an absolute increase at follow-up from 2.25 to 3.08 in Patient #1 ($p = 0.028$), from 1.25 to 1.51 in Patient #4 ($p = 0.004$), and from 1.33 to 2.20 in Patient #5 ($p < 0.001$). Figure 1B shows mean MPRI improvement in patients with available dypiridamole cardiac magnetic resonance before and after Reducer implantation.

This preliminary experience suggests that CS Reducer is safe and may have a role in the management of patients presenting with refractory angina, in spite of complete epicardial revascularization with PCI and OMT. Its use was associated with a reduction in CCS angina class, angina burden, and increasing quality of life and exercise tolerance. Reducer system is particularly appealing in this setting, because it has the unique sustained biologic effect of normalizing subendocardial to subepicardial blood flow ratio, typically compromised in such patients. In a subgroup of patients, Reducer use was further found to objectively improve the MPRI. Larger studies with longer-term follow-up are warranted to build on these findings and to further investigate the role of this promising novel therapy in this challenging patient subgroup.

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