The Promising Approach of Coronary Sinus Reducer in Patients with Refractory Angina

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**ABSTRACT**

Our systematic review aimed to investigate the theories and studies which evaluate the effectiveness of coronary sinus reducer “CSR” in patients with refractory angina. Chronic refractory angina is also a condition primarily due to severe coronary artery obstruction which is not properly controlled and is not subject to percutaneous or surgical revascularization by appropriate care. The coronary sinus reducer “CSR” has emerged as a therapeutic novel which is a strategy for patients with refractory angina. The CSR is a stainless steel, balloon expanding, hourglass shaping tool percutaneously inserted though right internal jugular vein in the coronary sinus. Upon implantation, it produces a regular lumen narrowing that enhances blood flow from coronary venous pressure to an ischemic myocardial layer by redistributing blood from subepicardial myocardium.

**Keywords:** Myocardium; Coronary sinus; Refractory angina; Coronary sinus reducer

**INTRODUCTION**

Refractory angina refers to long-lasting symptoms (for>3 months) due to established reversible ischemia in the presence of obstructive CAD, which cannot be controlled by escalating medical therapy with the use of second-and third-line pharmacological agents, bypass grafting, or stenting including PCI of chronic total coronary occlusion. Incidence is growing with more advanced CAD, multiple comorbidities and aging of the population. The quality of life of patients with refractory angina is poor, with frequent hospitalization and a high level of resource utilization. The number of potential treatment options is increasing, but the level of evidence in support of their safety and efficacy varies from non-existent (in the case of transmyocardiallaser application) to promising. RCTs with endpoints such as the severity and frequency of angina, as well as quality of life, are obviously needed along with safety metrics. Despite significant advances in revascularization techniques and agents used in pharmacological therapy, there is still a significant population suffering from RFA and the global prevalence is even increasing. Antiangular treatment and secondary risk-factor modification are the traditional approaches for this group of patients [1]. The coronary sinus Reducer is a novel technology designed to reduce disabling symptoms and improve quality-of-life of patients suffering from refractory angina. This review serves to update the clinician as to current evidence and future perspectives of the optimal utilization of this innovative technology [2]. The CSR is a stainless steel, balloon expanding, hourglass shaping tool percutaneously inserted though the right Internal jugular vein in the coronary sinus to achieve a controlled narrowing of the coronary sinus that may alleviate myocardial ischemia, possibly by redistributing blood from the less ischemic sub-epicardium to the more ischemic sub-endocardium, or by neoangiogenesis [3]. Increase of CS backward pressure to improve redistribution of myocardial blood flow into ischemic myocardial territories for the treatment of chronic angina was first conceived by Beck et al. The Reducer System, designed to fit the range of anatomies encountered in most patients, comprises the Reducer scaffold pre-mounted on a customized hourglass-shaped balloon catheter. When inflated, the expanded balloon gives the metal mesh its final configuration (Figure 1). In patients with advanced CAD, the normal sympathetically mediated constriction of sub-epicardial vessels favoring blood flow toward the subendocardial layers during exercise. Moreover, subsequent elevated left ventricular end-diastolic pressures compress sub-endocardial small vessels, further worsening ischemia. The chronic elevation of venous pressure following Reduce rimplantation should increase the backward pressure in the venules and capillaries, promoting...
blood redistribution and re-establishing the normal endocardial oepicardial blood flow ratio. In 2007, the first-in-man study of CS Reducer implantation in 15 patients with RAP reported no peri-procedural and 11 months major adverse cardiac events. The average CCS class was reduced at 1-year follow-up, with sustained effect at 3 years. Importantly, device patency was documented at 12 years in 10 patients with available follow-up. In the double-blind placebo-controlled COSIRA (Coronary Sinus Reducer for Treatment of Refractory Angina) trial randomizing 104 RAP patients in a 1:1 ratio to CS Reducer implantation or a sham procedure. Real-world data across several centers recently confirmed the safety and the efficacy of the procedure, with success rate exceeding 98%, no severe peri-procedural complications, and a consistent 70% to 85% rate of symptomatic responders at 1 and 2 year follow-up, further providing insights on potential cost-effectiveness). Beyond symptomatic efficacy, objective evidence of inducible ischemia reduction by dobutamine stress echocardiography and treadmill exercise test were recently reported as well as functional status benefits at the cardiopulmonary exercise test. Notably, initial studies with stress cardiac magnetic resonance following Reducer implantation demonstrating myocardial perfusion improvement accompanied by improved left ventricular function suggest this may be a pivotal effect underlying anginal symptoms reduction. Last, insights on Reducer impact on myocardial perfusion and symptoms in patients with refractory microvascular angina suggest high clinical efficacy in this population (currently lacking established non-pharmacological therapeutic option at the end).

Background of the disease

Angina is chest discomfort caused by myocardial ischemia without necrosis, and is further qualified by its precipitating factors, time course to relief, and clinical characteristics, such as radiation and quality. Clinically, angina may be further subdivided according to common usage, as follows: chronic “stable”, decubitus, nocturnal, refractory, unstable, microvascular, vasospastic, atypical, silent.

Refractory angina is stable chronic angina is termed refractory when it is not controllable by a combination of maximal antiangina medication, angioplasty or coronary artery bypass surgery, or in whom the risks are unjustified [6].

Pathophysiology

Myocardial energy (oxygen) balance: For over 40 years, it has been recognized that myocardial ischemia results from an imbalance between myocardial energy supply, from insufficient sources of oxygen and substrate (glucose, free fatty acids), and myocardial oxygen demand. 64 – 67 Usually this is simply referred to as an imbalance between myocardial oxygen supply and demand, but it should be clear that substrate supply, utilization, and enzymatic activities, along with other variables involved in intermediary metabolism and mitochondrial function, play a major role in the pathogenesis of myocardial ischemia in angina, acute coronary syndromes, and during reperfusion ischemic injury. The production of useable energy in the form of ATP is determined by the degree of oxidative phosphorylation (including nutrient supply) and oxygen availability; hence, the two are inexorably intertwined. Major determinants of myocardial oxygen demand are heart rate, blood pressure, and myocardial wall tension, in turn influenced by preload, afterload, and contractility. Since myocardial oxygen extraction from coronary arterial blood at rest is normally high, about 75% of arterial oxygen content, 68 adjustments in oxygen extraction cannot correct an imbalance. Physiological increases in myocardial oxygen needs are normally provided by rises in coronary blood flow [6].

METHODS AND RESULTS

This systematic review was performed according to the latest data and information collected from Pubmed, Google scholar in 2020 as well as the ESC new guidelines “European society of cardiology new guidelines in 2019” as a summary for this new approach of therapy. This review concentrates on the new methods and results emerged in 2020 about this approach.

Trials were underpowered according to the Esc guidelines of note, a patient-level pooled analysis of 304 patients included in three double-blind, cell therapy, placebo-controlled trials, among which was the RENEW trial, showed that the coronary sinus reducer device represent alternative options in patients with refractory angina, which is resistant after having exhausted all options for medical therapy and mechanical revascularization. Controlled coronary sinus narrowing with the implantation of a large stainless steel device increases coronary sinus pressure leading to improved perfusion in the LAD territory [3].

An international retrospective research was conducted on patients undergoing CSR implantation, separating them into 2 classes based on the presence or absence of CTO lesions. Baseline and clinical characteristics in the 2 groups were

![Figure 1: Expanded balloon gives the metal mesh its final configuration.](image-url)
analyzed. The primary outcome was the Canadian Cardiovascular variability. Class of the society (CCS) at 6-month follow-up. In the participating centers, 205 patients with refractory angina were treated consecutively with the study system between January 2014 and December 2018, 103 (50.2% of whom had a coronary angiogram CTO lesion and formed the CTO-group. Baseline Study population characteristics were well balanced between the 2 classes. In all cases CSR has been successfully inserted. In the CTO-group, the baseline CCS rating was 3 ± 0.5 versus 3.1 ± 0.6 in the non-CTO-group (p=0.45) and increased to 1.6 ± 0.9 versus 2 ± 1.1 (p<0.01) respectively. Significantly greater CCS class improvement in the CTO-group (1.4 ± 0.9 vs. 1.1 ± 1 respectively, p<0.01). Any improvement in the CCS class was reported in 79 (80.6%) CTO patients, whereas a significantly lower percentage (65 patients, 66.3%) of non-CTO patients reported CCS class benefits (p=0.03). In conclusions, patients with non-revascularized CTO lesions that suffer from refractory angina have a better response to CSR implantation than patients without CTOs. For such patients CSR implantation should be considered a legitimate CTO-PCI complementary therapy [7].

Between January 2014 and December 2018, 4 centers in the Netherlands, Belgium and Italy conducted another retrospective multicenter, international study analyzing data from patients undergoing CSR implantation. Patients were also divided into two groups according to the presence or absence of a CTO at the coronary angiogram of baseline. CTO has been identified as complete occlusion in any major coronary epicardial vessel or related side branches (reference vessel diameter 0.2-2.5 mm), with TIMI 0 in the distal segment and at Minimum age ≥3 months (as per clinical information or previous coronary angiograms). In patients with CABG experience, being located in a major epicardial branch without a patent graft leading to the distal tube, a CTO was considered. Both angiograms were reviewed by an independent, expert cardiologist to define the presence of CTO. Primary endpoint of this research is the increase in CCS class in the two sample groups as measured at 6 months after CSR implantation in the ambulatory clinic. Baselines, statistical analysis and full data concerning the effect of CSR implantation were shown in Figure 2 [7].

Gallone et al. record a case of improved myocardial function as assessed by strain imaging of cardiac magnetic resonance (CMR) following CS reducer implantation in patients with extreme 3-vessel disease suffering from angina refractory and heart failure. They, alongside symptomatic improvement. Demonstrate an increase in myocardial perfusion as well as an improved contraction of myocardial ischemic segments 4 months after implantation reduction using CMR dipyridamole stress test and systolic stress analysis. The current report by Gallone et al. is a follow-up to a recent CMR study published by the same group showing an improvement in stress myocardial perfusion and in resting ventricular5volumes function in19patients undergoing Reducer implantation. That analysis included important change in angina symptoms and 6-minute walk study, a small rise in the fraction of left ventricular ejection (LVEF) was observed (61 [IQR 47–71] to 66 [IQR 57–72]%).

The increase in LVEF was notably more pronounced in baseline patients with decreased LVEF (11.3 [IQR 6.5–54.5] vs. 3.8 [IQR 0.6–9.1] percent). That case report describes a significant increase in LVEF in a patient with reduced baseline LVEF (from 43% at baseline up to 66% after treatment).

### Table 1: Statistical analysis and full data concerning the effect of CSR implantation.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Population (n=205)</th>
<th>Patients with chronic total occlusion (n=103)</th>
<th>Patients without chronic total occlusion (n=102)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>10 (5%)</td>
<td>0 (0%)</td>
<td>10 (5%)</td>
<td>0.35</td>
</tr>
<tr>
<td>II</td>
<td>20 (10%)</td>
<td>1 (1%)</td>
<td>19 (10%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>12 (6%)</td>
<td>0 (0%)</td>
<td>12 (6%)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>18 (9%)</td>
<td>1 (1%)</td>
<td>17 (9%)</td>
<td></td>
</tr>
<tr>
<td>non-CCS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>10 (5%)</td>
<td>1 (1%)</td>
<td>9 (5%)</td>
<td>0.11</td>
</tr>
<tr>
<td>II</td>
<td>15 (7.5%)</td>
<td>1 (1%)</td>
<td>14 (7.5%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>15 (7.5%)</td>
<td>1 (1%)</td>
<td>14 (7.5%)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>19 (9.5%)</td>
<td>1 (1%)</td>
<td>18 (9.5%)</td>
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</table>

This study functionality Epicardium to subendocardial ischemic layer [8]. Giannini et al. also showed that flow redistribution after implantation of CS reduction could induce contractility improvement outside segments of significant perfusion deficiencies. The CMR strain study, first described in patients implanted with Reducer by Gallone et al. supports this observation by showing a global improvement in spatial contractility of Convenient LV segments in neither longitudinal, circumferential and radial directions. To this end, implantation of a CS reducer is not recommended in patients with Significant systolic heart failure (EF<30 per cent) that may require resynchronization therapy through 2 Sinus coronary. Meanwhile, with its effect on coronary and microvascular blood flow, Reducer implantation appears to have a multifaceted effect on LV systolic and diastolic function. Additional, more comprehensive studies are required to shed light on the processes that underlie this groundbreaking therapeutic alternative (Figure 3). Suggested effects of coronary sinus Reducer implantation on left ventricular function [9].
Another case was identified, and despite adequate medical therapy and prior surgical revascularization, a 38-year-old female with ALCAPA (anomalies left origin from pulmonary artery) presented with restricting exertional angina. She was diagnosed with ALCAPA at the age of 23, and the left coronary system originating from the left side component of the pulmonary artery could not be activated for direct anastomosis to the ascending aorta during surgery. Thus, with initial symptomatic change, she had a left internal mammary artery (LIMA) graft to the left anterior descending artery (LAD). At age 36, however, she experienced chronic chest pain secondary to LIMA graft failure and underwent a coronary artery bypass surgery with right internal mammary artery (RIMA) to the LAD and saphenous vein graft (SVG) to the obtuse marginal (OM). She established angina by crescendo a year later. A 12-lead electrocardiogram demonstrated non-dynamic lateral ischemic shifts (aVL, V5–6) and negative levels of serial high-sensitivity troponin I. She was taken into hospital for further investigation. Give-in that her angina had deteriorated in severity. No feasible strategy on PCI has been established. Given several anti-anginal medications (bisoprolol, amlodipine, isosorbide-mononitrate, nicorandil, and ranolazine), the patient complained that constant anginal pain lasted up to 30 minutes in rest and exertion (CCS Class 4). Her angina reduced her effort resistance dramatically. She often developed angina and presyncope, particularly at the gym during treadmill and bike. Her symptoms also impacted her quality of life - her Seattle). After a multidisciplinary team discussion. The CSR was deployed at 4 atmospheres and with no immediate complications achieved an excellent angiographic result. A Cardiac CT post-procedure showed sufficient CSR positioning (Figure 4a).

A myocardial perfusion scan revealed a decrease in ischemia five months after CSR implantation (4 per cent overall ischemic burden (Figure 4b). At first, her angina symptoms continued, but at clinic follow-up 8 months after CSR implantation, her angina had essentially (CCS 0).

The other case shows the use of CSR in a patient with RA to improve the angina symptoms and quality of life. In the US, it is estimated that between 600,000 and 1.8 million patients suffer from RA, with 75,000 new cases diagnosed every year [4]. In Europe the estimated incidence is 30,000–50,000 new cases per year [3]. The registry of OPTions In Myocardial Ischemic Syndrome Therapy (OPTIMIST) has suggested that mortality is no worse in patients with RA, emphasizing improvement of symptoms and quality of life as priorities for these patients [9]. The Coronary Sinus Reducer for Refractory Angina Treatment (COSIRA) trial, a randomized placebo-controlled trial, showed that implantation improved symptoms by two CCS levels in 35 per cent of patients com-matched with placebo control (p=0.02). The patient had refractory chest pain and recurring healthcare attendance. By definition, patients should have gone through a series of therapies as shown in this case – ideal medical therapy as well as redo bypass surgery on coronary
Our patient with left-sided ischemia met the CSR implantation indications agreed on through our multidisciplinary pathway. The treatment itself was uncomplicated, and the patient was released home the next day. Patients are recommended to take up to 6 months after CSR implantation in our centre before undertaking a major angina reduction. It is assumed that this amount of time will take to occur for the endothelialization of the stent, and to develop the stenosis and improvements in the perfusion. All patients receiving a CSR in the center undergo regular functional ischemia monitoring at 6 months after implantation to determine any changes in the ischemic burden. Usually patients need dual anti-platelet therapy 6 months after CSR implantation [9].

DISCUSSION

The Study was performed between September 2010 and December 2017 to assess the diagnosis of RAP at eight medical centers in Belgium, the Netherlands and Italy. This international longitudinal, observational, multicenter research included 215 consecutive patients who had implantation with reducer. Patients with extreme RA [Canadian Cardiovascular Society (CCS) classes 2 - 4] were diagnosed with reducer implantation beyond the full toleration of medical therapy and found not to be receptive to further percutaneous or surgical revascularization procedures. The procedural success in 211 (98.1 per cent) patients has been achieved. Implantation reducer was not reached in 4 patients as shown in this Figure 5 [10].

Another analysis showing that CPET was planned in patients with chronic refractory angina undergoing CSR implantation prior to the index procedure and at 6-month follow-up. Improvements in VO₂ max and in VO₂ at anaerobic threshold (AT) were the principal endpoints of this study. It also reported clinical incidents and symptom improvements. The research population was composed of a total of 37 patients [11]. The CSR implantation process was successful and in general without any complications. Important changes in VO₂ max (+0.97 ml/ kg/ min [+11.3%], 12.2 ± 3.6 ml/ kg/ min at baseline vs. 13.2 ± 3.7 ml/ kg/ min, p=0.026), and workload (+12.9 [+34%]; 68 ± 28 W vs. 81 ± 49W, p=0.05) were observed at follow-up CPET, with non-significant variations in VO₂ at AT (9.84 ± 3.4 ml/ kg/ min vs. 10.74 ± 3.05 ml/ kg/ min, p=0.06). The rating of the Canadian Cardiovascular Society (CCS) increased from an average of 3.2 ± 0.5 to 1.6 ± 0.8 (p<0.01), and substantial benefits were shown in all variables in the Seattle Angina Questionnaire [11].

A 78-year-old man was also diagnosed with refractory angina and no chance of surgical or percutaneous revascular was scheduled for coronary sinus Reducer NeovascInc (Richmond, Canada) implantation. In short, the coronary sinus Reducer stent restricts cardiac venous drainage with the purpose of transferring blood from nonischaemic to ischaemic territories supplied by narrowed or occluded coronary arteries. Using a 9 Fr straight guiding catheter and a guidewire Supra Core 35 (Chicago IL, USA) the procedure was performed via a right jugular venous entry. After the Reducer has made his way into the coronary sinus [6]. Reducer the expected location of inflation in the balloon. Coronary sinus, the guidance catheter was removed until the proximal stent mark and the balloon was inflated at 5bar pressure (Figure 6). Injection of the contrast medium via the leading catheter has demonstrated complete occlusion of the coronary sinus by the Reducer’s balloon. The delivery device was removed after balloon deflation, but it remained suddenly stuck in the stent that was pulled to the proximal portion of the coronary sinus. At first, the delivery system’s balloon was reinflated to optimize stent expansion in an attempt to attach it to the coronary sinus wall (Figure 7). The balloon remained attached to the stent, however, and was pulled to the ostium coronary sinus. The right femoral vein received a second venous access and a 12-Fr Flexor introducer (Cook Medical, Bloomington, IN, USA) was inserted in the right atrium (RA). A 15-mm Goose Neck Snare Medtronic (Minneapolis, MN, USA) has been advanced into the RA through this introducer. The Reducer balloon was reinflated at this point to avoid embolization of the stent, and the stent was retracted to the RA (Figure 8). The snare was then placed around the stent and tightened while the Reducer balloon was simultaneously deflated and the delivery system removed. It was removed by the 12-Fr introducer after the stent was snapped (Figure 9). A second Reducer was finally implanted in the coronary sinus in a more distal position and with a higher inflation pressure (6atm). Delivery system was withdrawn with no complications. This is the first case identified for percutaneous Reducer stent retrieval [12].

Figure 5: CCS Square and SAQ score variations after reducer implantations CCS and SAQ.

Figure 6: Reducer balloon inflation in the planned position.
In one of the randomized sham-controlled COSIRA trials, as well as in the available prospective non-randomized clinical evidence, 70–80% of patients with refractory angina tend to experience symptomatic re-running after reducer implantation. Konigstien et al. used dobutamine echocardiography 6 months after Reducer implantation to demonstrate improvement of the LV ejection fraction at stress and in the wall motion score index. Four months after Reducer implantation using cardiac MRI perfusion, Francesco Giannini et al. showed improvement in myocardial perfusion. The same group of investigators also showed improvement in left ventricular contractility (fraction of ejection and amount of strokes) using cardiac MRI [13]. We have also demonstrated improvement in cardiopulmonary stress test parameters.

Another international study which collects prospective and retrospective long-term data on subjects treated with the Reducer with refractory angina pectoris (CCS class 2-4). It is expected the study will enroll 400 subjects in up to 40 medical centres. Clinical evaluation including completion of the Seattle Angina Questionnaire (SAQ), EQ-5D-5L Score, CCS class evaluation, and objective assessment by treadmill ergometry, and 6-minute walk test (6MWT) [14].

A total of 207 patients (80 percent male, 68.0 ± 9.4 years) were enrolled in the prospective arm of which 159 were enrolled. No procedure or device-related significant adverse heart events were adjudicated for up to 2 years. At 6 and 24 months (p<0.0001), angina frequency (mean CCS class) decreased from 2.8 ± 0.6 at baseline to 1.8 ± 0.7 at 82% of patients improved by CCS grade 1 at 2 years and 31% improved by CCS grade 2. 71 per cent of patients had severe angina disabling (CCS class 3-4) at baseline. Only 13 per cent suffered from CCS class 3-4 at 2 years, representing an 81 per cent decrease in angina severity. At 6 and 12 months, the SAQ and EQ-5D-5L scores increased considerably. 6MWT increased the distance (from 327 ± 121 m at baseline to 377 ± 104 m and 359 ± 112 m at 6 months and 12 months respectively, p<0.01 for both). Exercise duration on treadmill increased from 370 ± 151 sec to 403 ± 165 sec 1 year following Reducer implantation (p<0.007).

CONCLUSION

This review indicates that the coronary sinus reducer “CSR” is considered a safe therapeutic novel for treatment of refractory angina resistant to medical and interventional therapies. It was performed on a small number of patients and it was underestimated in the new guidelines. In the future, we need further large randomized trials to further investigate the efficacy of this promising device.
REFERENCES