Coronary artery disease

The Reducer device in patients with angina pectoris: mechanisms, indications, and perspectives

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Despite available pharmacological and interventional therapies, refractory angina is a common and disabling clinical condition, and a major public health problem, which affects patients’ quality-of-life, and has a significant impact upon health care resources. Persistent angina is common not only in patients who are not good candidates for revascularization, but also in patients following successful revascularization. Clearly, there is a need for additional treatment options for refractory angina beyond currently available pharmacological and interventional therapies. It is of pivotal importance, in this condition, to practice a patient-centred health assessment approach, measuring success of a new therapy by its effects on patients’ symptoms, functional status, and quality-of-life, rather than hard clinical endpoints as used in clinical studies. 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.

Introduction

Chronic angina pectoris, refractory to medical and interventional therapies, is a common and disabling medical condition, and a major public health problem that affects millions of patients worldwide.1–3 Refractory angina is common not only in patients who are not good candidates for revascularization, but also in patients following successful revascularization. In such cases, in which angina persists following revascularization, the term often used is ‘persistent angina’. The prevalence of persistent angina is as high as 25% after 1 year, and up to 45% after 3 years following revascularization.4

Refractory angina might be the presenting symptom of a wide range of clinical entities, including obstructive coronary artery disease (CAD), microvascular disease with patent epicardial coronary arteries, hypertrophic cardiomyopathy, and left ventricular diastolic dysfunction. In patients with obstructive CAD, refractory angina can be due to any degree of disease severity within the wide spectrum between a single discrete coronary branch occlusion and a diffuse severe CAD.

The long-term mortality of patients with refractory angina is not inferior to that of other patients with stable/chronic ischaemic heart disease.5 Therefore, the goal of therapy for these patients should be directed primarily at improving quality-of-life and chest pain relief rather than extending their lifespan.4

In current daily practice in the catheterization laboratory, as well as in clinical trials of coronary interventions, success is measured by the rates of death, myocardial infarction, target vessel revascularization, and by the success or failure of new devices. It is remarkable that we almost never assess what reflects success from the patients’ perspective, which is reduction of disabling symptoms and improvement of quality-of-life. At present, both health care professionals and the public need higher awareness for the clinical significance of chronic angina, as it carries important implications for patient health. Chronic angina is associated with an increased risk of both
cardiovascular hospitalizations and significant healthcare costs. The use of patient-centred health status approach, which measures patients’ symptoms, function, and quality-of-life, can identify patients who are most likely to benefit from intensified disease management, and utilization of novel therapeutic technologies.6

In this context, the coronary sinus Reducer is a novel technology designed to improve quality-of-life and functional capacity by reducing angina burden. The clinical utilization of this device-based therapy for refractory angina continues to grow, with very encouraging clinical evidence to support its safety and efficacy.7–12

**Refractory angina**

Chronic refractory angina pectoris is a common clinical entity. According to the 2013 European Society of Cardiology Guidelines on the management of stable CAD2 an increase in the prevalence of angina is expected as the population continues to age, with no discrimination between males and females.

Patients with disabling symptoms of angina [Canadian Cardiovascular Society classification (CCS class) II–IV] despite optimal medical and interventional therapies for more than 3 months, and with objective evidence of myocardial ischaemia, are classified as having refractory angina.13 They often have poor quality-of-life, and experience limitations in their ordinary daily physical activities.14,15 These patients are often labelled as ‘no option’ patients.

The presence of chronic angina per se is not necessarily associated with worse clinical outcome. Prognosis is determined by the nature and severity of the underlying disease.

Patients with chronic angina are either unsuitable for revascularization or continue to suffer from angina following successful or unsuccessful revascularization procedures. Revascularization eliminates angina symptoms in only about two-thirds of patients with stable CAD, independently of the choice of revascularization procedure (PCI or CABG), and of the use of drug-eluting stents. Randomized clinical trials,16–19 registry data,20 and meta-analysis21 have consistently shown that about 30% of patients revascularized for stable CAD continue to experience anginal symptoms.

There is a strong correlation between the prevalence of angina and healthcare resources utilization. This association is reflected by increased hospitalizations and revascularization procedures, and by a higher number of sick leaves among patients who are still actively working.6,22,23 In addition, refractory angina is associated with considerable psychological morbidity and depression.24

A considerable number of therapeutic strategies have been investigated over the years to treat refractory angina pectoris. Currently, according to the 2013 ESC guidelines for the treatment of patients with stable CAD,2 Ivabradine, Nicorandil, and Ranolazine should be considered for the treatment of refractory angina (IIa recommendation). Non pharmacological therapies include enhanced external balloon counter pulsation (EECP) (IIa recommendation), transcutaneous electric nerve stimulation (TENS) and spinal cord stimulation (SCS) (IIb recommendation). Myocardial laser revascularization techniques, either surgical or percutaneous, are no longer recommended by the ESC guidelines.

Clearly, there is a need for additional treatment options for refractory angina beyond currently available pharmacological and interventional therapies.

### The concept of coronary sinus narrowing and its presumed antianginal effect

Augmentation of coronary sinus (CS) pressure for the treatment of chronic angina is a long-standing concept. In the 1950’s and 1960’s Claude Beck performed a surgical narrowing of the CS to achieve redistribution of myocardial blood flow into ischaemic territories of the myocardium with remarkable success.25,26 In an open chest surgery, he created a 60–70% narrowing of the CS to achieve a 3 mm residual lumen diameter, in patients suffering from severe disabling angina. This procedure was associated with significant relief of angina symptoms, improved functional class, and reduced 5-year mortality rate. Beck’s studies have been duplicated by other surgeons with positive outcomes.26,27

Non-surgical methods to elevate CS pressure have been also investigated over the years. Mohl and colleagues28,29 used a closed loop CS balloon system to automatically occlude and release the CS, and continuously monitor CS pressure. More recently, Pressure-controlled Intermittent Coronary Sinus Occlusion (PICSOC®) was approved for treatment of acute coronary syndrome, heart failure, and cardiac surgery patients. In fact, intermittent CS occlusion has been shown to provide myocardial salvage during coronary artery occlusion, reducing myocardial ischaemia severity and infarct size.30–33

In the healthy heart, blood flow in the subendocardial myocardium is normally higher than in the subepicardial layers of the myocardium. Moreover, during exercise and increased demand, a physiologic compensatory mechanism causes selective sympathetically mediated vasoconstriction with increased resistance to flow in subepicardial vessels, favouring subendocardial perfusion and allowing an appropriate augmented contractility. However, in the presence of a significant epicardial coronary artery stenosis, this compensatory mechanism becomes dysfunctional and the transmural myocardial perfusion is redistributed towards the subepicardial layers of the left ventricle. The normal ratio between subendocardial and subepicardial blood flow is significantly reduced, reflecting shifting of blood from the higher resistant subendocardial blood vessels to the less resistant subepicardial blood vessels. Thus, the perfusion of the subendocardium during stress becomes compromised, causing ischaemia, impaired contractility, elevated left ventricular end diastolic pressure (LVEDP), with consequent angina symptoms and shortness of breath.34

Elevated LVEDP exerts an external pressure on the subendocardial capillaries and arterioles, which further increases the resistance to flow, contributing to the viscous cycle of subendocardial ischaemia.

Elevating backward pressure in the coronary venous system, results in a slight dilatation of the diameter of arterioles that leads to a significant reduction to vascular resistance in the subendocardium. Consequently, blood flow in the ischaemic subendocardial layers of the myocardium is enhanced, contractility improves, and LVEDP decreases. Thus, the result of the decreased subendocardial vascular resistance is redistribution of blood from the less ischaemic subepicardium to the more ischaemic subendocardium, which will lead to symptom relief.25,36
Overview of the Reducer

The Reducer is a stainless-steel mesh designed to create a focal narrowing in the lumen of the coronary sinus (CS) to generate a pressure gradient across it. The Reducer System comprises the Reducer device pre-mounted on a customized hourglass shaped balloon catheter. When inflated, the expanded balloon gives the metal mesh its final hour glass configuration. The narrowing within the CS, and the pressure gradient across the device are established 4–6 weeks after implantation, when the metal mesh should be covered by tissue ingrowth.

In the presence of myocardial ischaemia, the device is intended to improve perfusion to ischaemic territories of the myocardium by forcing redistribution of blood from the less ischaemic subepicardium to the more ischaemic subendocardium, thus alleviating the symptoms of angina.

The Reducer is implanted percutaneously via the right jugular vein into the CS. The semi-compliant delivery balloon is available in one single size, and the final expanded diameters are dependent on the inflation pressure (Figure 1).

The Reducer is designed to fit the range of anatomies encountered in most patients, and it is compatible with CS diameters of 9.5–13 mm at the proximal implant site. The proximal and distal portions of the device are configured to different diameters, based on balloon expansion, allowing the device to conform to the tapered configuration of the anatomy of the CS, with the centre narrowing consistently 3 mm in diameter (Table 1).

Implantation is performed with an intentional 10–20% oversizing of both wide ends of the device. Oversizing is important and helps to achieve two goals: (1) to anchor into the elastic vessel wall to help prevent migration and (2) to trigger a process of injury-induced tissue proliferation, which within 4–6 weeks after implantation should cover the gaps between the metal struts to establish the pressure gradient across the narrow centre of the device. Importantly, since the narrow central part of the device is not in direct contact with the vessel wall, and does not cause any vessel wall injury, there is no trigger for tissue growth at this point, and therefore, the vessel lumen at the centre of the device remains patent. If a central narrowing is observed in the immediate post implantation angiography, it is likely the result of spasms of the CS’s thin wall onto the metal mesh.

As the Reducer is a stainless-steel mesh, the central narrowing can be easily dilated if needed, using a 5–8 mm balloon, at any time after implantation.

Implantation techniques and considerations

Following pre-treatment with aspirin and clopidogrel, under local anaesthesia and ultrasound guidance, a 9F introducer sheath is inserted into the right internal jugular vein.

In a left anterior oblique (30°) angulation, the CS is engaged with a diagnostic multipurpose catheter. After confirming that the catheter tip is in the lumen of the main vessel, venography is performed to size the CS, locate side branches, and identify the preferred site for device implantation. The ideal location for implantation is usually about 2–4 cm distal to the CS ostium, where the CS diameter is between 7–13 mm, avoiding side branches. The selected site for implantation is landmarked by bony markers (vertebrae, inter-vertebral space). A wire is then advanced within the multipurpose catheter deep into the CS, and the diagnostic catheter is removed. After intravenous administration of 70 u/kg of unfractionated heparin, the Reducer system inside a 9F guiding catheter is advanced over the guide wire into the CS. The guiding catheter is withdrawn, exposing the Reducer, which is held in the landing zone previously identified. The balloon is inflated to 4–6 atm to achieve 10–20% oversize of the Reducer. While the balloon is fully inflated, a small amount of contrast is injected through the guiding catheter to verify sufficient oversizing (Figure 2).

Balloon retrieval into the guiding catheter is performed with caution to avoid device displacement. This is achieved by allowing the tip of the guiding catheter to move forward into the narrow neck of the Reducer and support the Reducer while the balloon is safely pulled back into the guiding catheter (Figure 3). The final venography confirms correct position of the scaffold and excludes complications.
Following Reducer implantation a duel antiplatelet therapy with aspirin and clopidogrel is recommended for 6 months.

Potential complications of the procedure include dissection or perforation of the CS, migration of the device, especially if the diameter of the CS at the site of implantation is >13 mm or in cases of insufficient oversizing. Thrombotic occlusion is theoretically possible; however, no such cases have been reported so far.

Pre-clinical studies

Pre-clinical experiments to evaluate the feasibility, safety, and efficacy of Reducer implantation in swine models with and without myocardial ischaemia have demonstrated that narrowing of the CS with the Reducer is feasible, safe, and reduces the extent and severity of ischaemia.

Overall, procedural success rate was 100% (n = 34), with no short- or long-term complications. Among the safety/feasibility arm, all CS Reducers were patent at the time of sacrifice. Microscopic evaluation of the coronary sinuses harvested between 1 and 6 months following implantation revealed optimal local tissue toleration (no to very low foreign body response) and favourable healing characteristics (fully endothelialized, mature, and stable neointima with no residual fibrin). The deployment characteristics of the Reducer resulted in over-distension of the proximal and distal ends and deep embedding of the metal struts within the sinus wall. There was compensatory neointima proliferation that restored vessel wall integrity and maintained lumen patency. Conversely, the central part of the device showed under-sizing and malapposition, where the centre part of the Reducer was free in the vascular lumen or partially attached to the wall by mature neointima. Struts malapposition did not produce any

### Table 1  Reducer Compliance Chart—Lists the typical outer diameter (OD) of the Reducer at the defined locations when inflated to the indicated pressures (atm)

<table>
<thead>
<tr>
<th>Pressure (atm)</th>
<th>D 1-proximal diameter (mm)</th>
<th>D-neck diameter (mm)</th>
<th>D 2-distal diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>12.0</td>
<td>3.0</td>
<td>9.6</td>
</tr>
<tr>
<td>3</td>
<td>12.7</td>
<td>3.0</td>
<td>10.2</td>
</tr>
<tr>
<td>4—Nominal</td>
<td>13.3</td>
<td>3.0</td>
<td>10.7</td>
</tr>
<tr>
<td>5</td>
<td>13.6</td>
<td>3.0</td>
<td>11.1</td>
</tr>
<tr>
<td>6—Rated burst</td>
<td>13.9</td>
<td>3.1</td>
<td>11.5</td>
</tr>
</tbody>
</table>

**Figure 2** Left: Angiography of the coronary sinus in left anterior oblique (LAO) 30° using a diagnostic 6 F multipurpose catheter from the left internal jugular vein. Middle: Contrast injection through the guiding catheter while the balloon is fully inflated, to ensure sufficient oversizing of the Reducer. Right: final angiography of the coronary sinus (CS) demonstrating oversizing of both distal and proximal ends of the Reducer with a central narrowing.
Patients suffering from disabling chronic angina seek for new therapeutic options and usually have high expectations for clinical benefit. In this population, a clinical trial to evaluate the efficacy of a new therapy is particularly at risk of bias when a subjective outcome such as pain is the primary endpoint. In fact, placebo treatment alone can give a substantial improvement in angina symptoms and in exercise duration. For this reason, the COSIRA trial was designed to eliminate both patient and investigator biases in the interpretation of outcome endpoints by using a sham intervention control arm.

Clinical reports describing current experience with the CS Reducer from centres in which the Reducer is routinely utilized describe favourable results, with angina relief in most patients treated, and no device-related adverse events. In a small registry study including 23 patients undergoing Reducer implantation, significant improvement in objective parameters of ischaemia, such as exercise duration, wall motion score index, and summed stress score were observed.

The effect of the CS Reducer on myocardial perfusion has also been assessed by measuring myocardial perfusion reserve index (MPRI) using perfusion dipyridamole cardiac magnetic resonance (CMR). Among 15 patients undergoing Reducer implantation with baseline rest-stress cardiac magnetic resonance and 4-month follow-up, global MPRI increased from 1.46 ± 0.40 to 1.80 ± 0.78, (Unpublished data, Figures 5 and 6).

Currently, a multi-centre observational clinical study is undergoing in Europe (REDUCER-I-NCT02710435). Patients with chronic refractory angina pectoris classified as CCS grade II–IV despite optimal medical therapy with objective evidence of myocardial ischaemia, and limited or no options for revascularization are being enrolled. Enrolment will include 400 patients at up to 40 centres internationally, with clinical follow-up to 5 years. Enrolment to date is approaching 100 patients. Preliminary results indicate that among patients who completed 6 months follow-up 81% (39/48) experienced improvement of at least 1 CCS class following Reducer implantation, while 46% (22/48) reported an improvement of ≥2 CCS classes. Moreover, 6-min walk test was increased from a mean of 296.9 ± 147.4 to 365.2 ± 121.3 following Reducer implantation (unpublished data, Table 2).

A phase III multicentre, randomized, double-blind, sham-controlled trial (COSIRA-II) is planned in the USA and Canada.
Patient selection and screening

Patients with stable effort induced angina CCS class II to IV, treated with maximally tolerated guideline-directed medical therapy, who demonstrate objective evidence of myocardial ischaemia in the distribution of the left coronary artery, and who are deemed unsuitable for revascularization, are good candidates for Reducer implantation. Those who continue to suffer from angina following failed or successful revascularization procedures might also benefit from this therapy.

Patients in whom angina is related only to ischaemia arising from the right coronary artery (RCA) are less likely to improve following Reducer implantation, as the insertion of the vein draining the RCA territory (middle cardiac vein) into the CS is next to the ostium of the CS. The preferred site for Reducer implantation is more distal into the CS, about 2 cm away from the ostium and therefore, the pressure gradient created by the narrowing would likely not affect the middle cardiac vein.

In patients in which the CS diameter is >13 mm, implantation of the Reducer is contraindicated as it may result in migration of the device.

Symptoms of exertional dyspnoea in patients with severe left ventricular systolic dysfunction are unlikely to resolve or improve after Reducer implantation, unless myocardial dysfunction is secondary to myocardial ischaemia. Also, in patients with severe systolic heart failure (EF < 30%) that may need resynchronization therapy and implantation of CRT lead in the coronary sinus, Reducer implantation is not advisable.

In patients experiencing an acute cardiac event, or in patients who have recently undergone a cardiac interventional procedure (PCI, heart surgery, or pacemaker implantation), it is recommended to wait at least 3 months to determine clinical symptoms and clinical stability prior to consideration of Reducer implantation (Table 3).
The non-responders

In the randomized controlled COSIRA trial, as well as in the non-randomized clinical data, it appears that 70–80% of patients with refractory angina experience a symptomatic relief following Reducer implantation. Several factors, related to patient’s selection, anatomy and pathophysiology, might explain the 20–30% rate of non-responders. Such factors are: angina due to ischaemia arising from the territory of the right coronary artery; exertional shortness of breath secondary to heart failure and not to ischaemia; incomplete tissue coverage of the metal struts with inadequate pressure gradient across the device; a well-developed alternative venous drainage of the myocardium into the right ventricle (the Thebesian venous system); or non-angina chest pain.

Conclusions and towards the future

Current treatment options for refractory angina are exhausted with less than optimal results. Clearly, there is an unmet need for treating patients with refractory angina. Further research is needed to identify the subset of patients who would benefit most from Reducer implantation.

Table 2  Results of clinical studies

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Design</th>
<th>Number of patients implanted</th>
<th>Successful implantation</th>
<th>CCS class pre implantation</th>
<th>CCS class post implantation</th>
<th>Treatment responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Banai et al.</td>
<td>2007</td>
<td>Open label</td>
<td>15</td>
<td>15/15</td>
<td>3.07</td>
<td>1.64</td>
<td>12/15 (80%)</td>
</tr>
<tr>
<td>Königstein et al.</td>
<td>2014</td>
<td>Registry</td>
<td>23</td>
<td>21/23</td>
<td>3.3</td>
<td>2</td>
<td>16/20 (80%)</td>
</tr>
<tr>
<td>Verheye et al.</td>
<td>2015</td>
<td>Double blind sham controlled</td>
<td>52/104</td>
<td>50/52</td>
<td>3.2</td>
<td>2.1</td>
<td>37/52 (71%)</td>
</tr>
<tr>
<td>Giannini et al.</td>
<td>2016</td>
<td>Registry</td>
<td>50</td>
<td>50/50</td>
<td>3.3</td>
<td>2.0</td>
<td>35/50 (70%)</td>
</tr>
<tr>
<td>Reducer-1</td>
<td>2017</td>
<td>Registry</td>
<td>94</td>
<td>92/94</td>
<td>2.9</td>
<td>1.6</td>
<td>39/48b (81%)</td>
</tr>
</tbody>
</table>

Unpublished data.

bPatients completed 6 months follow-up.

Table 3  Patients selection

<table>
<thead>
<tr>
<th>Good candidates for the Reducer</th>
<th>Not good candidates for the Reducer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic stable angina (&gt;3 months), CCS class 2–4, despite maximally tolerated guidelines directed medical therapy</td>
<td>Chest pain due to a non-coronary origin (significant valvular disease, heart failure, or non-cardiac chest pain)</td>
</tr>
<tr>
<td>Objective evidence of reversible ischaemia</td>
<td>No evidence of inducible ischaemia</td>
</tr>
<tr>
<td>Ischaemia in the territory of the left coronary artery system (left main, left anterior descending and left circumflex arteries)</td>
<td>Ischaemia only in the territory of the right coronary artery</td>
</tr>
<tr>
<td>LVEF&gt;30%</td>
<td>LVEF &lt;30% or heart failure with NYHA class 3–4</td>
</tr>
<tr>
<td>Mean RA pressure &lt;15mmHg</td>
<td>Mean RA pressure &gt;15 mmHg</td>
</tr>
<tr>
<td>Pacemaker electrodes in the RA implanted &gt;3 months</td>
<td>Pacemaker electrode in the RA implanted &lt;3 months</td>
</tr>
<tr>
<td></td>
<td>CRT electrode in the coronary sinus</td>
</tr>
<tr>
<td></td>
<td>Recent (&gt;3 months) acute coronary syndrome, PCI or CABG surgery</td>
</tr>
</tbody>
</table>
these patients, and novel therapeutic options for this group of patients would be welcomed.

It is of pivotal importance, in this condition, to practice a patient-centred health assessment approach, measuring success of a new therapy by its effects on patients’ symptoms, functional status, and quality-of-life, rather than hard clinical endpoints as used in clinical studies. The coronary sinus Reducer is a new technology designed to reduce disabling symptoms and improve quality-of-life of patients suffering from refractory angina.

At present, accumulating evidence supports the clinical benefit of the Reducer in significantly alleviating symptoms of angina in 70–80% of patients with obstructive CAD who are not candidates for revascularization. Appropriate patient selection and referral to specialized centres are important to maximise efficacy of this treatment and improve success rates.

Identifying other patient populations who might benefit from utilization of this therapeutic technology is the next goal. It is still to be investigated if patients with other chronic cardiac conditions characterized by angina and subendocardial ischaemia, such as microvascular angina, diastolic dysfunction, hypertrophic cardiomyopathy, and chronic total occlusion might also benefit from this innovative therapy.

While the Reducer’s clinical efficacy on reducing angina burden is apparent, studies utilizing objective methods of assessment of myocardial ischaemia (PET, perfusion CMR) in larger cohorts are required, due to the large placebo effect reported related to novel therapies in this specific patient population.

Supplementary material

Supplementary material is available at European Heart Journal online.

Conflict of interest: Shmuel Banai is the Medical Director of Neovasc Inc. All other authors, Dr Konjestin and dr Giannini have no conflict of interest.

References


Coronary sinus Reducer for refractory angina


