

Narrowing of the Coronary Sinus

A Device-Based Therapy for Persistent Angina Pectoris

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Abstract: Alongside the remarkable advances in medical and invasive therapies for the treatment of ischemic heart disease, an increasing number of patients with advanced coronary artery disease unsuitable for revascularization continue to suffer from angina pectoris despite optimal medical therapy. Patients with chronic angina have poor quality of life and increased levels of anxiety and depression. A considerable number of innovative therapeutic modalities for the treatment of chronic angina have been investigated over the years; however, none of these therapeutic options has become a standard of care, and none are widely utilized. Current treatment options for refractory angina focus on medical therapy and secondary risk factor modification. Interventions to create increased pressure in the coronary sinus may alleviate myocardial ischemia by forcing redistribution of coronary blood flow from the less ischemic subepicardium to the more ischemic subendocardium, thus relieving symptoms of ischemia. Percutaneous, transvenous implantation of a balloon expandable, hourglass-shaped, stainless steel mesh in the coronary sinus to create a fixed focal narrowing and to increase backwards pressure, may serve as a new device-based therapy destined for the treatment of refractory angina pectoris.

Key Words: angina pectoris, refractory angina, persistent angina, coronary sinus, reducer

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Persistent or refractory angina pectoris is a common and disabling medical entity. The prevalence of persistent angina continues to grow despite the advancements in interventional and medical therapies for ischemic heart disease. It is estimated that up to 25% of patients continue to have angina pectoris at 1 year, and up to 45% at 3 years after successful revascularization. These patients experience limitations in their ability to perform ordinary physical activities.

Augmentation of blood pressure within the coronary sinus (CS) for the treatment of chronic angina is a long standing concept.^{1,2} Elevating CS pressure may alleviate myocardial ischemia by forcing redistribution of coronary blood flow from the less ischemic subepicardium to the more ischemic subendocardium, with consequent dilatation of the capillaries and arterioles' diameters and reduction in the resistance to flow in the subendocardial arterioles. The result of this process is an enhancement of blood flow to the ischemic subendocardial layers of the myocardium, which will

improve contraction, reduce left ventricular end-diastolic pressure, and lead to symptoms relief.

In this review, we describe the clinical entity of persistent/refractory angina pectoris, its epidemiology, and available treatment options, and review the accumulating evidence regarding the feasibility, safety, and efficacy of interventions to narrow the CS as a potential novel therapy for chronic angina.

PERSISTENT ANGINA PECTORIS

Persistent or refractory angina pectoris refers to patients with Canadian Cardiovascular Society (CCS) grade II–IV angina, who have objective evidence of myocardial ischemia despite optimal medical therapy, and who are not candidates for revascularization. Patients with persistent angina have poor quality of life as they are disabled by their symptoms, and experience limitations in their ability to perform ordinary physical activities.³

Persistent angina pectoris is a major clinical challenge in contemporary cardiovascular medicine. Despite the remarkable progress in the treatment of ischemic heart disease, a growing number of patients who suffer from advanced coronary artery disease not amenable for revascularization continue to experience debilitating angina despite optimal medical therapy.⁴ These patients are often labeled as “no option” patients.

Even with the utilization of newest technologies, such as drug eluting stents or the bioresorbable scaffolds, postrevascularization angina is still a major problem. In most trials, up to 25% of patients continue to have angina pectoris at 1 year, and up to 45% at 3 years from the percutaneous coronary intervention (PCI).⁵

Limited data exist regarding the natural history and predictors of mortality for patients with refractory angina. A retrospective study from the Cleveland Clinic in 500 consecutive patients undergoing cardiac catheterization found that 1-year mortality among this population was 17%.⁶ However, a more recent report from a dedicated clinic for refractory angina⁷ has shown that in contrast to what was previously reported, despite the disabling symptoms, the life expectancy of patients with persistent angina is not significantly inferior to that of other patients with stable/chronic ischemic heart disease. It is therefore now well accepted that the goal of therapy of persistent angina should be directed mainly at improving these patients' quality of life rather than extending their lifespan.⁵

Epidemiology

Persistent angina pectoris is a common clinical entity. According to the 2013 European Society of Cardiology Guidelines on the management of stable coronary artery disease,⁸ an increase in occurrence of angina is reported with age in both sexes. It is estimated that there are as many as 525,000 patients suffering from angina in the EU and US, classified each year as having no revascularization options. The reasons for “no revascularization” include the presence of chronic total occlusion, diffuse disease, collateral-dependent myocardium, multiple restenosis, poor target vessels, and comorbidities.⁹ In addition, there are well over 500,000 other patients who have undergone either PCI or coronary bypass graft but continue to suffer

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from angina, which brings the total number of patients that could potentially benefit from new angina therapies to over 1 million annually.^{3,6} The incidence of patients suffering from angina 1 year after a successful PCI is surprisingly high and exceeds 20% of the patients treated with drug eluting stents.¹⁰⁻¹²

Treatment Options

Current treatment options for refractory angina focus on medical therapy and secondary risk factor modification.⁸ Additional approaches, such as cognitive behavioral therapy programs, may also be effective.¹³

A considerable number of therapeutic modalities for the treatment of severe chronic angina have been investigated over the years. These modalities include transcatheter electric nerve stimulation and spinal cord stimulation,¹⁴⁻¹⁶ left stellate ganglion blockade,¹⁷ endoscopic thoracoscopic sympathectomy,¹⁸ enhanced external balloon counter-pulsation,¹⁹⁻²³ and finally, myocardial laser revascularization.²⁴⁻³² Despite extensive studies conducted to evaluate the efficacy of these strategies, most studies have failed to demonstrate an advantage over conservative treatment, placebo or sham procedure in randomized controlled trials, and none of these alternative therapeutic options has become a standard of care for refractory angina.

Alternative approaches aimed at achieving therapeutic angiogenesis through gene or progenitor cell therapy remain under active investigation,³³⁻³⁶ but are not considered part of a routine therapy.

THE CONCEPT OF NARROWING THE CORONARY SINUS

In the 1950s and 1960s, Claude Beck performed a surgical narrowing of the CS to achieve redistribution of myocardial blood flow into ischemic territories of the myocardium with remarkable success.² Using open chest surgery in patients with severe disabling angina, he created a 60–70% narrowing of the CS to achieve a 3 mm residual lumen diameter. This procedure was associated with significant relief of angina symptoms, improved functional class, and reduced 5-year mortality rate.

A comparative study of 185 patients at the Cleveland Clinic showed that long-term mortality in the group of patients treated as per Beck's procedure (13%) was significantly lower compared with the 30% mortality rate observed in the control group.³⁷ Furthermore, in the surgical group, 90% of patients reported complete or significant relief of their symptoms as measured by reduction of pain and need for medications. The portion of patients fit for work also doubled in the treatment group from 45% before the intervention, to 90% as determined by patient self-report at follow-up. Beck's preclinical and clinical work suggested that the success of the "Beck 1" procedure was likely driven by elevated CS pressure triggering protective mechanisms that improved perfusion of ischemic territories of the myocardium. Beck's studies have been duplicated by numerous other surgeons with equally positive results.^{2,38} The Beck 1 procedure was used for the treatment of patients with angina pectoris in the 1950s and 1960s, and then became neglected when bypass surgery became mainstream therapy.

The Presumed Antianginal Effect of Increased Pressure Within the Coronary Sinus

In the healthy heart, blood flow in the subendocardial myocardium is normally higher than in the subepicardial layers of the myocardium. During exercise and increased demand, selective sympathetically mediated vasoconstriction of subepicardial vessels occurs as a physiologic compensatory mechanism, which further supports subendocardial perfusion and allows for an appropriate rise in contractility. In the presence of a significant epicardial coronary artery stenosis, this compensatory mechanism becomes dysfunctional and

the normal subendocardial to subepicardial blood flow ratio is significantly reduced, reflecting redistribution 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 ischemia, impaired contractility, elevation of left ventricle end diastolic pressure, with consequent angina symptoms and shortness of breath.³⁹

Elevated left ventricular end diastolic pressure exerts an external pressure on the subendocardial capillaries and arterioles which further increases the resistance to flow and ischemia in the subendocardium. The antianginal effect of elevated pressure in the CS remains speculative, but there is substantial evidence that the heightened CS pressure causes backwards pressure elevation in the venules and capillaries,^{40,41} which will result in dilatation of the capillaries and arterioles' diameter and reduction in the resistance to flow in the subendocardial arterioles. As a consequence, the abnormal subepicardial to subendocardial blood flow ratio may be restored to normal values.⁴⁰ In response to a CS pressure elevation, the blood flow to the ischemic subendocardial layers is enhanced, resulting in improved contractility and reduced left ventricular end diastolic pressure, which will further reduce subendocardial resistance, thus breaking the "vicious cycle" of ischemia.^{1,42}

Methods of Increasing Coronary Sinus Pressure

Nonsurgical methods to elevate CS pressure have been investigated. Mohl et al⁴³ successfully used a closed loop CS balloon system to automatically occlude and release the CS and continuously monitor CS pressure, but the need for prolonged use of an in-dwelling balloon catheter in the CS precluded its adaptation for routine clinical use. Recently, pressure-controlled intermittent coronary sinus occlusion (PICSO) was approved for the treatment of acute coronary syndrome, heart failure, and cardiac surgery patients based on the same principles and mechanism of action as the CS Reducer.⁴⁴⁻⁴⁸

THE CORONARY SINUS REDUCER

The Reducer System (Neovasc Inc, Richmond, BC, Canada) is a CE-marked endoluminal, balloon-expandable stainless steel hourglass-shaped metal mesh. The device is percutaneously implanted in the CS to create a focal narrowing leading to an increase in CS pressure. The device is introduced into the CS via a right internal jugular vein catheterization.

The over-the-wire balloon catheter has a unique hourglass shape. The proximal and distal portions of the balloon have different diameters to conform to the taper typically encountered in the CS. The semicompliant balloon is available in one single size, designed to fit the range of anatomies encountered in most patients. Its final expanded diameters are dependent on the inflation pressure (Fig. 1).

The device is implanted in the CS with a slight oversizing to achieve a 1.1:1.0 Reducer to CS diameter ratio. Oversizing of the implanted device aims to achieve 2 goals: first, it anchors the device into the vessel wall to help prevent migration; second, both ends of the device trigger and initiate a process of injury-induced tissue growth which within 3–6 weeks after implantation will cover the mesh struts, and will establish the pressure gradient across the narrowed center of the device (Figs. 2 and 3).

Immediately following implantation, blood will continue to flow through the mesh, and there will be no pressure gradient across the device. Only after several weeks, when tissue ingrowth covers the metal mesh, a narrowing with a pressure gradient across the central narrowed portion of the device will be established. Importantly, since the narrow central part of the mesh is not in direct contact with the CS wall and does not cause any vessel wall injury, the trigger for tissue growth will be much weaker at this point, and therefore the vessel lumen at the center of the device remains patent (Fig. 4).

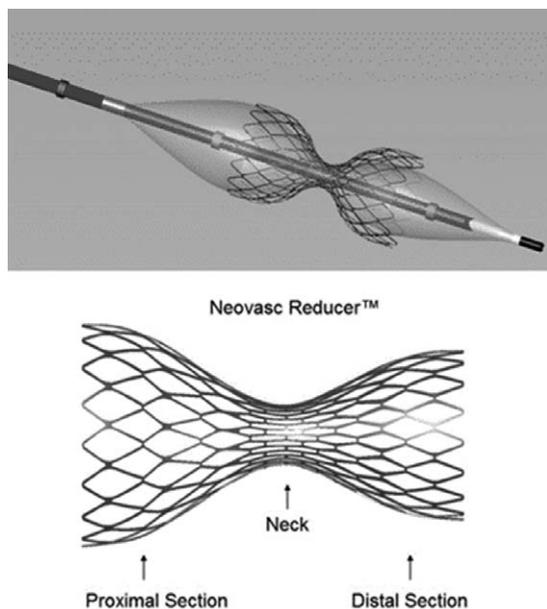


FIGURE 1. The Reducer is a stainless steel balloon expandable laser cut mesh. The semicompliant balloon is available in one single size, designed to fit the range of anatomies encountered in most patients. Its final expanded diameters are dependent on the inflation pressure. While the final diameters of the 2 distal ends of the Reducer depend on the inflation pressure of the balloon, the narrowed center segment of the Reducer will always be 3 mm in diameter.

Preclinical Experiments

CS narrowing devices were implanted in 34 pigs with and without myocardial ischemia.⁴⁹ Mean pressure gradient across the

narrowing at 6 months was 2.83 ± 1.47 mm Hg. Implantation of the device was associated with reduced mortality and improved myocardial ischemia in pigs with myocardial ischemia.

Clinical Studies

A first-in-man (FIM) nonrandomized clinical study with the Reducer System, including a long-term surveillance study, provided the initial indication for safety and feasibility of the device.⁵⁰ Fifteen patients were enrolled in 3 medical centers. The CS narrowing device was successfully implanted in all 15 candidates and all were discharged without clinical complications. No major adverse events occurred during the procedure or during follow-up. At 6 months follow-up, an improvement in angina score, a reduction in exercise stress test-induced ST-segment depression and a reduced dobutamine-induced myocardial ischemia were observed in the majority of these patients. At the 3-year follow-up, there were no deaths, MI, or adverse events attributable to the device.⁵¹

Computed tomography angiography revealed that the devices were patent and located at the exact site of deployment with no evidence of migration or occlusion. The improvement in angina score and in ischemia severity as demonstrated by dobutamine echo, thallium SPECT, and stress test results that were observed at 6 months were maintained through the 3-year follow-up. These findings supported further evaluation of the clinical efficacy of the device as an alternative tool to treat patients with chronic refractory angina.

Following the FIM study, a randomized, double-blind, sham-controlled, multicenter clinical trial, The Coronary Sinus Reducer for Treatment of Refractory Angina (COSIRA), was conducted to test the safety and efficacy of the CS reduction.⁵² Subjects with CCS class 3–4 angina ($n = 104$) and objective evidence of myocardial ischemia, who were not candidates for revascularization, were randomized to Reducer implantation or a sham procedure in 11 international clinical centers. The primary endpoint was an improvement of 2 CCS grade or more at 6 months. The primary endpoint was achieved in 35% (18/52) of the treatment group versus 15% (8/52) of the sham-control group ($P = 0.02$). Narrowing of the CS was associated with a greater angina relief (≥ 1 CCS grade improvement) in 71% (37/52)

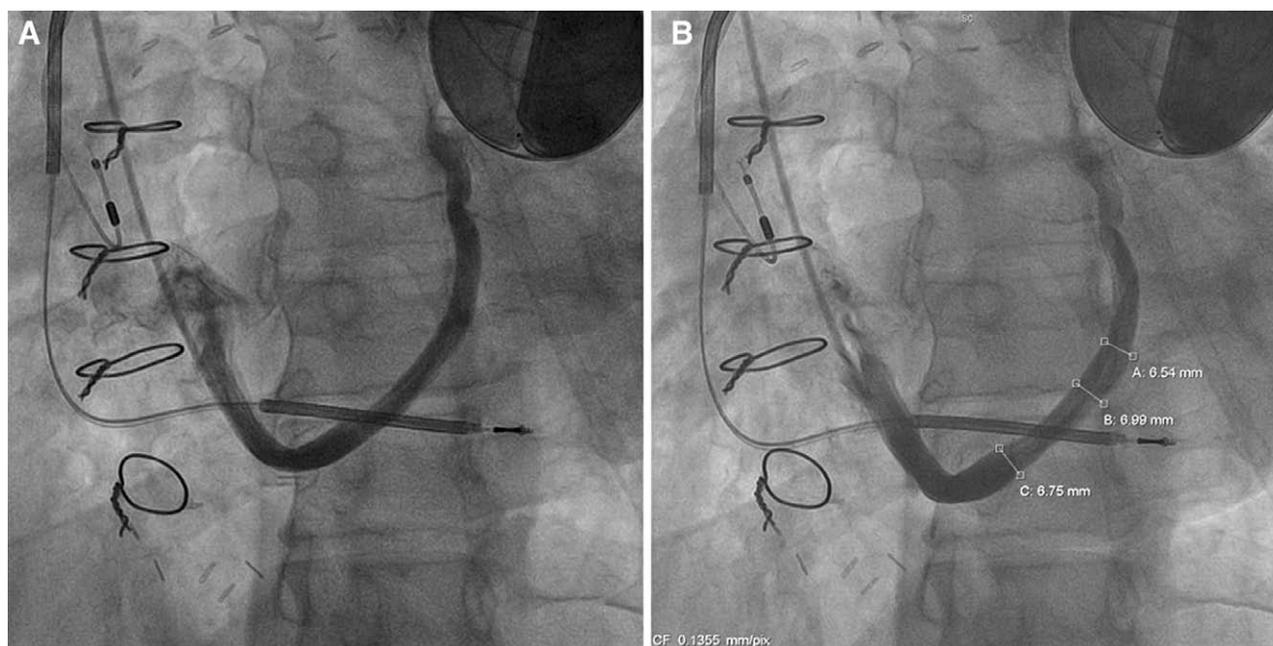


FIGURE 2. A, Angiography of the coronary sinus in left anterior oblique 30° using a diagnostic 6F multipurpose catheter from the right internal jugular vein. B, Quantitative coronary analysis to estimate the diameters of the coronary sinus at the planned site of implantation.

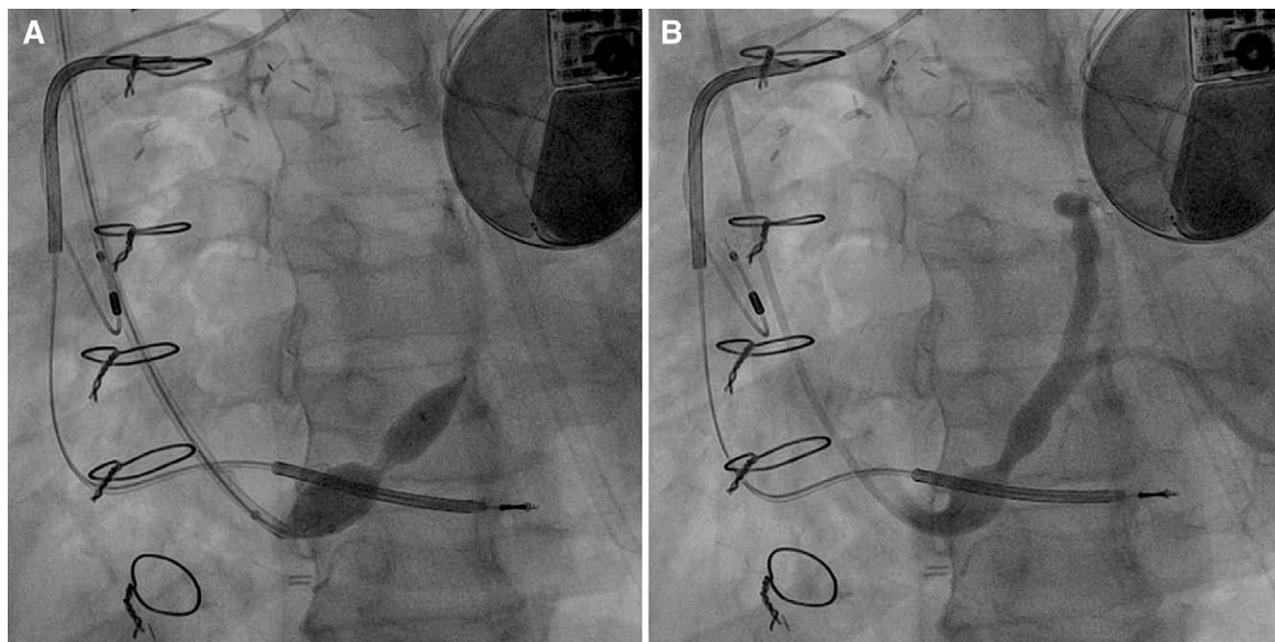


FIGURE 3. A, Implantation of the Reducer. B, Postimplantation angiography demonstrates the implanted Reducer with intentional slight oversizing of both distal ends of the device, and the central narrowing. At this stage, the central narrowing seen is due to spasm of the coronary sinus on the Reducer.



FIGURE 4. CT images of the Reducer in the coronary sinus. A, Longitudinal cross section of the device with blood flows through the narrowed center. B, Measurements of the different diameters of the Reducer after implantation. C, View into the implanted Reducer.

versus 42% (22/52) in the sham control ($P = 0.003$). Quality-of-life as measured by the Seattle Angina Questionnaire was significantly improved in the treatment group compared with the sham-control group (17.6 vs. 7.6 points improvement, respectively; $P = 0.03$).

The COSIRA clinical trial demonstrated that implantation of a device to narrow the CS significantly improved symptoms and quality-of-life in refractory angina subjects unsuitable for revascularization. Importantly, the CS Reducer appeared safe as no difference in the rate of adverse events was observed between the treatment and the sham control groups during the study period, and no device-related complications were reported.

Patients suffering from chronic angina despite optimal medical therapy seek for alternative novel therapeutic options and usually have

high expectations for clinical benefit. When a patient's stress is high, the placebo effect is greater.^{53,54} 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.⁵⁵ It has been argued that devices and invasive procedures trigger a greater placebo effect than do pills,⁵⁶ however, placebo treatment alone can give a substantial improvement in angina symptoms and in exercise duration.⁵⁷ In previous studies examining the effect of laser myocardial revascularization to improve angina symptoms, a pronounced placebo effect was noted, resulting in a 30% improvement in exercise duration and angina symptoms in the control group of patients.²⁸ For these very reasons, the COSIRA trial was designed to eliminate both patient and investigator biases in the interpretation of outcome end points by using a sham intervention control arm.⁵⁸

Any degree of angina relief (≥ 1 CCS class) was observed in more than 42% of the sham-controlled group, and ≥ 2 CCS class improvement was observed in 15% of the control group of patients. Nevertheless, the degree of angina relief achieved in the patients treated with the CS Reducer was significantly greater than the significant placebo effect observed.

The CS narrowing device is currently in use in several clinical centers in Europe and Canada. The results of treatment with this device in 21 refractory angina patients from 2 of these medical centers were recently reported.⁵⁹ No device-related adverse effects had been observed during the procedure or the follow-up period. In the majority of patients, symptoms of angina improved significantly concomitantly with improvement in objective parameters of ischemia.

A multicenter observational clinical study is currently under way in Europe.

Patients with chronic refractory angina pectoris classified as CCS grade II, III, or IV despite attempted optimal medical therapy, that have objective evidence of myocardial ischemia and limited or no options for revascularization, are being enrolled.

A phase III randomized controlled trial is planned in the US, Canada, and Europe.

CONCLUSION

Persistent angina pectoris is a common and disabling medical entity and its prevalence continue to grow despite the advancements in interventional and medical therapies for ischemic heart disease. Augmentation of blood pressure within the CS for the treatment of chronic angina is a longstanding concept that has been casted into the new CS narrowing device. The accumulating evidence regarding the feasibility, safety, and efficacy of the Reducer as a device-based therapy for chronic angina justifies further use and evaluation of this therapeutic strategy destined for patients who until now were considered as “no option patients.”

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