Reinvention of an old concept for a new patient population

Coronary sinus reducer device for patients with refractory angina

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Summary

Although fascinating improvements in surgical, interventional and medical treatment of patients with coronary artery disease have been achieved, a growing number of patients present with refractory angina despite optimal treatment. Currently, different approaches are being investigated to reduce angina and to improve quality of life in these patients with "no options". Slowing of coronary venous drainage by implantation of a stent device that reduces the diameter of the coronary sinus is a promising approach, as demonstrated by a recent phase II trial. In this report we document the first implantation of this novel device at our institution in Switzerland, give a stepwise description of the implantation procedure and discuss the currently available literature with regard to the physiology and clinical indications for the so-called (coronary sinus) Reducer™ device.

Key words: refractory angina; intervention; coronary sinus; Reducer™

Introduction

A growing number of patients with end-stage coronary artery disease present with significant angina, but the ischaemic region is not accessible to standard interventional or surgical procedures, most commonly because of diffuse disease and/or occluded bypass grafts affecting flow at the level of the microcirculation. In these patients, symptomatic medical treatment with classical antianginal medications such as beta-blockers, calcium channel blockers and nitrates is advised, but may not be sufficient to control symptoms. Newer approaches, including novel pharmacological agents such as ranolazine, ivabradine or nicorandil, as well as nonpharmacological approaches, are currently being tested, but so far none have proved to be of significant benefit for the patients at risk in larger phase II trials.

Most recently, a surgical procedure from the 1950s was "reinvented" as a percutaneous option for refractory angina: restriction of the venous drainage of the heart by reducing the diameter of the coronary sinus, as initially described by Claude Schaeffer Beck in his seminal paper published in the *Journal of the American Medical Association* in 1955 [1]. Here, we report the first implantation of the new percutaneous, hourglass shaped Neovasc Reducer™ device (Neovasc Inc., Richmond, Canada, fig. 1A) at our institution in a patient with refractory angina of Canadian Cardiovascular society (CCS) class III.

Description of the case

Patient history

We report a 70-year-old male patient who presented with exercise-induced angina and dyspnoea for the past 2–3 years (CCS III, New York Heart Association [NYHA] II). He was otherwise free of complaints, specifically orthopnoea, nycturia or significant ankle swelling under his current medical regimen, which included bisoprolol 2.5 mg daily, ramipril 2.5 mg daily and nicorandil 10 mg twice daily. He is well-known at our clinic, with a long history of cardiovascular events. In 1976 and 1982 (aged 30 and 36 years, respectively) he suffered two myocardial infarctions, but it was not until 1991 that he had his first coronary artery bypass graft (CABG: vein-RCA, vein-RCX, LIMA-LAD). Eighteen years later, with the two venous bypasses occluded, newly diagnosed severe mitral regurgitation and persistent angina pectoris, the patient was scheduled for a re-do CABG (RIMA-RCA/RCX, 2009) combined with a mitral valve reconstruction including the implantation of a 32-mm Physio ring (Edwards LifeSciences, Irvine CA, USA). During the following years, the patient was regularly seen for routine check-ups with exercise testing. He underwent follow-up angiograms which demonstrated slow progression of the coronary artery disease as a cause of recurrent angina and non-sustained ventricular tachycardias (2010). Medical treatment with ranolazine for refractory angina was not tolerated, so he was switched to nicorandil. Also, he underwent implantation of a pacemaker because of bradycardic atrial fibrillation (2011). At his most recent check-up, a severely reduced ejection fraction of 30%

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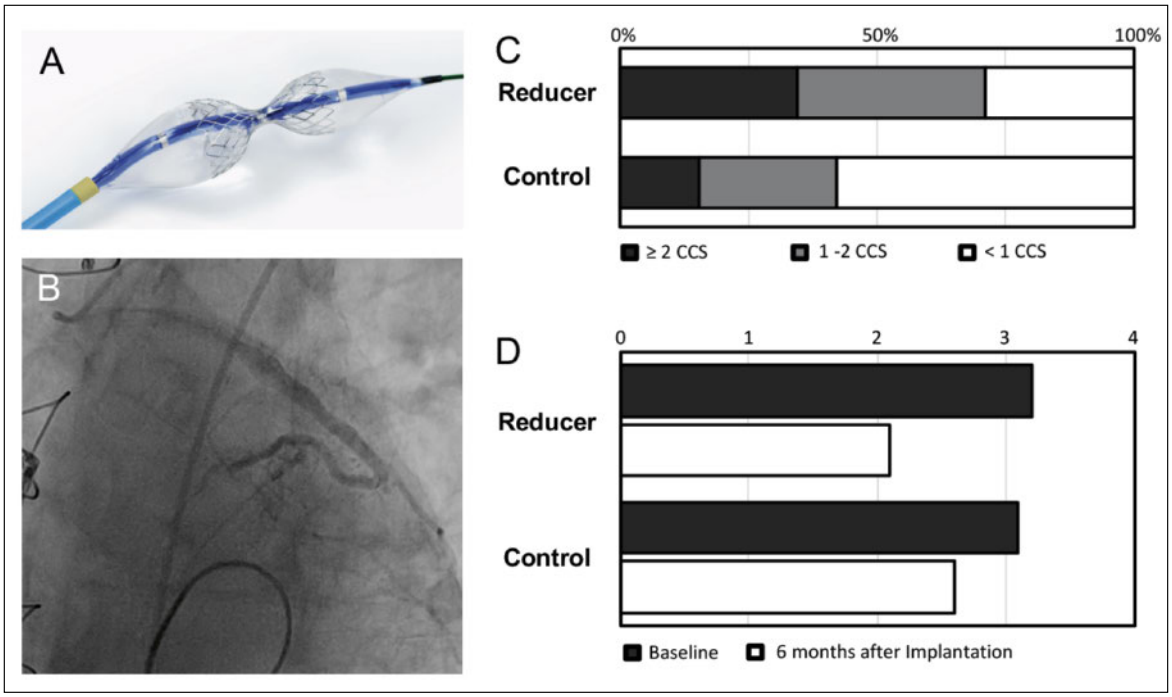

Figure 1: (A) The Reducer™ is an hourglass shaped device that is implanted into the coronary sinus (picture reprinted from [27]). (B) On the most recent angiogram, the bypasses to LAD, RCA and RIM were found to be patent. The anastomosis to the RCX, however, was chronically occluded. It was concluded that further coronary interventions including CTO revascularisation would not be beneficial in this patient. Improvement of angina by CCS class after CS Reducer™ implantation (modified from [25]). (C) Positive changes by ≥1 and ≥2 CCS classes were more frequently encountered in patients after Reducer™ implantation. (D) On average, the CCS class was reduced from 3.2 ± 0.4 at baseline to 2.1 ± 1.0 at 6 months of follow-up in the Reducer™ group, as compared with a reduction from 3.1 ± 0.3 to 2.6 ± 0.9 in the control group (p = 0.001).

was documented, with akinesia of the inferior, inferolateral and inferoseptal walls and an overall hypokinetic left ventricle. Ischaemia and viability were then both evaluated with ^{13}N-NH_3 positron emission tomography myocardial perfusion imaging (PET-MPI), which showed a reduction of coronary reserve and hyperaemic velocities corresponding to a significant ischaemia in the left anterior descending artery (LAD) region. Subsequent coronary angiography that the bypasses (LIMA-LAD, RIMA-RCA, and vein-RIM) were patent except for a previously known chronic occlusion of the jump to the circumflex artery (RCX), with occlusion both distal and proximal of the anastomosis (fig. 1B). Owing to the lack of antegrade or retrograde access, chronic total occlusion (CTO) revascularisation was not an option. At this point, with medical and traditional interventional methods being exhausted, an interdisciplinary meeting involving the treating cardiologists and cardiac surgeons took place, after which it was decided that the best course of therapy would involve the implantation of a Reducer™ device.

Stepwise description of the implantation of the device

We applied the device via the right internal jugular vein. A 9F sheath was introduced into the vein, and then a 5F multipurpose catheter was carefully placed deep in the main vessel of the coronary sinus (fig. 2A). Injection of contrast allowed us to visualise the anatomy of the coronary sinus in order to define and measure the most suitable position for the implantation of the device (fig. 2B). Then a Supra Core 35 guidewire was placed deep into the coronary sinus (fig. 2C) and intravenous heparin administered. A 9F straight guiding catheter was placed with a "mother and child technique" distal to the planned implantation site; then the 5F multipurpose catheter was retracted. Next, the Reducer™ inside the guiding catheter was advanced to the anticipated site of implantation (fig. 2D). Then the 9F guiding catheter was retracted to the third or proximal mark of the stent and the balloon was inflated with 4 and 6 bar pressure, while backed up with the guiding catheter (fig. 2E). Injection of contrast via the guiding catheter demonstrated full occlusion of the coronary sinus by the balloon of the Reducer™ (fig. 2F). The pressure was maintained for 30 seconds before the balloon was deflated. The guiding catheter was then

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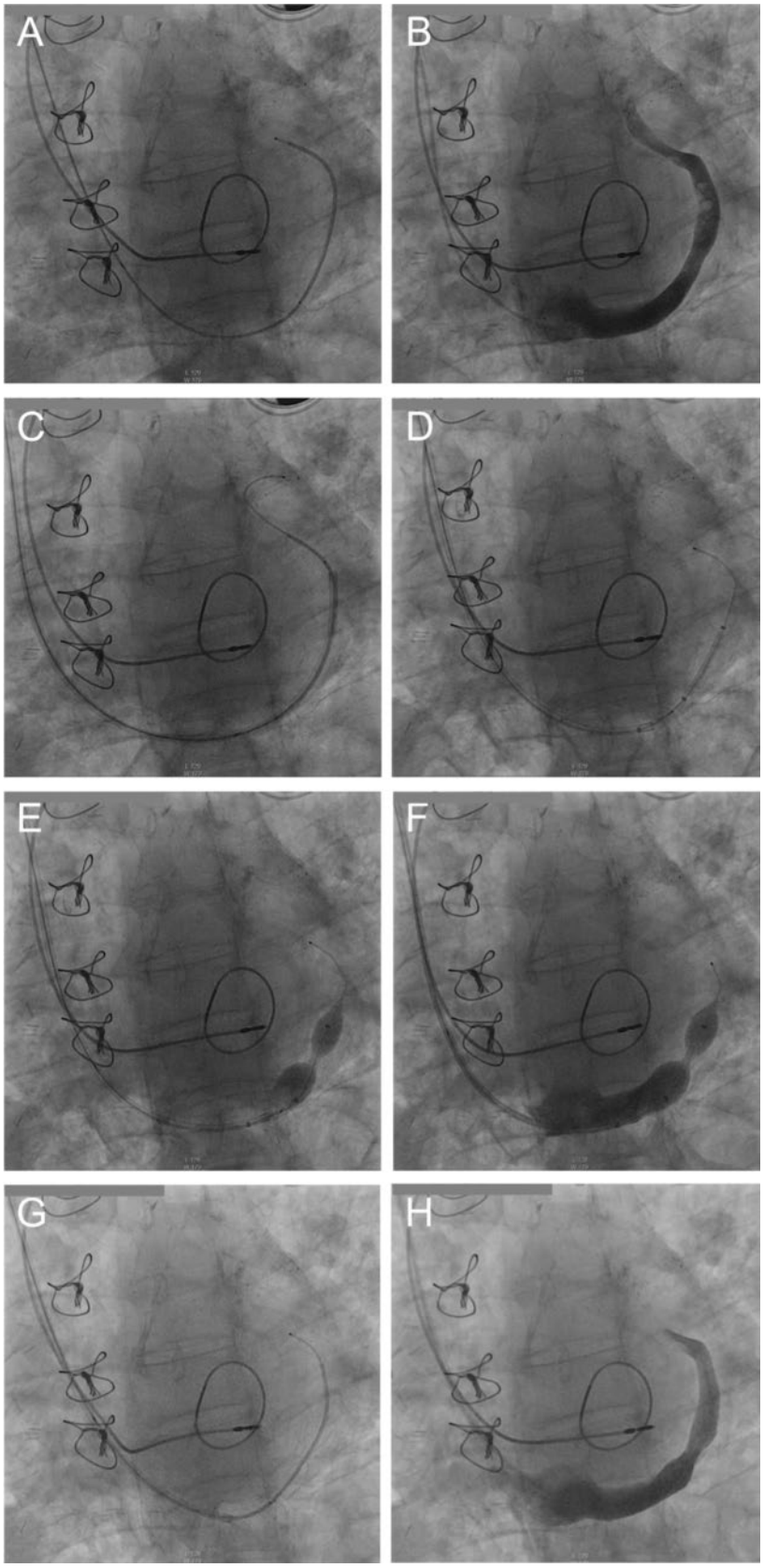

pulled back. Finally, a multipurpose catheter was passed through the Reducer™ (fig. 2G) and the coronary sinus was visualised by injecting contrast distal to the implanted device (fig. 2H).

Postinterventional course

The in-hospital course after the implantation of the device was completely uneventful. The patient remained asymptomatic at rest, with no significant laboratory or ECG changes on the day after the implantation. He was discharged and signed up for for clinical and imaging check up 8 weeks later. Clopidogrel 75 mg daily for 1 month was prescribed (in addition to phenprocoumon prescribed owing to atrial fibrillation). At the next check-up the patient presented with significantly reduced symptoms and was now able to climb three floors without angina or dyspnoea (CCS I, NYHA I).
Follow-up hybrid imaging with coronary computed tomography angiography and PET-CT demonstrated positioning of the Reducer™ in the coronary sinus (fig. 3A–D) and improvement in global quantitative hyperaemic flow from 0.83 to 1.08 ml/min/g 12 weeks after implantation. Most significantly, hyperaemic flow was improved in the LAD region from 0.89 to 1.31 ml/min/g. In addition, myocardial flow reserve increased from 1.61 to 1.82 globally (fig. 3E).

Discussion

In principle, the two main treatment options for ischaemia in coronary artery disease, percutaneous coronary intervention and CABG, both aim at increasing the coronary blood flow to the ischaemic myocardium by reopening or bypassing narrowed or occluded epicardial coronary arteries, respectively. This approach of increasing the inflow to the myocardium has been accepted as the gold standard of treatment in patients with coronary artery disease, particularly those with acute myocardial ischaemia. However, in the past a paradigmatically different approach has also been utilised to reduce ischaemia in territories supplied by narrowed or occluded coronary arteries, i.e., shifting blood from nonischaemic to ischaemic territories by reducing the outflow from the myocardium and thereby increasing coronary sinus pressure. Recently, safety and efficacy of a new percutaneous device embodying this initially surgical approach was reported. Here, we report the first implantation of this novel device at our institution.

Figure 2: Implantation of the coronary sinus (CS) Reducer in 8 steps. (A) Positioning of a multipurpose catheter in the CS. (B) Visualisation of CS anatomy and identification of optimal implantation site. (C) Placement of a guidewire deep into the CS. (D) Positioning of guiding catheter just distally to the planned implantation site. (E) Inflation of the Reducer™. (F) Demonstration of full CS occlusion by contrast injection. (G) Passage of a multipurpose catheter through the Reducer™. (H) Check angiography.

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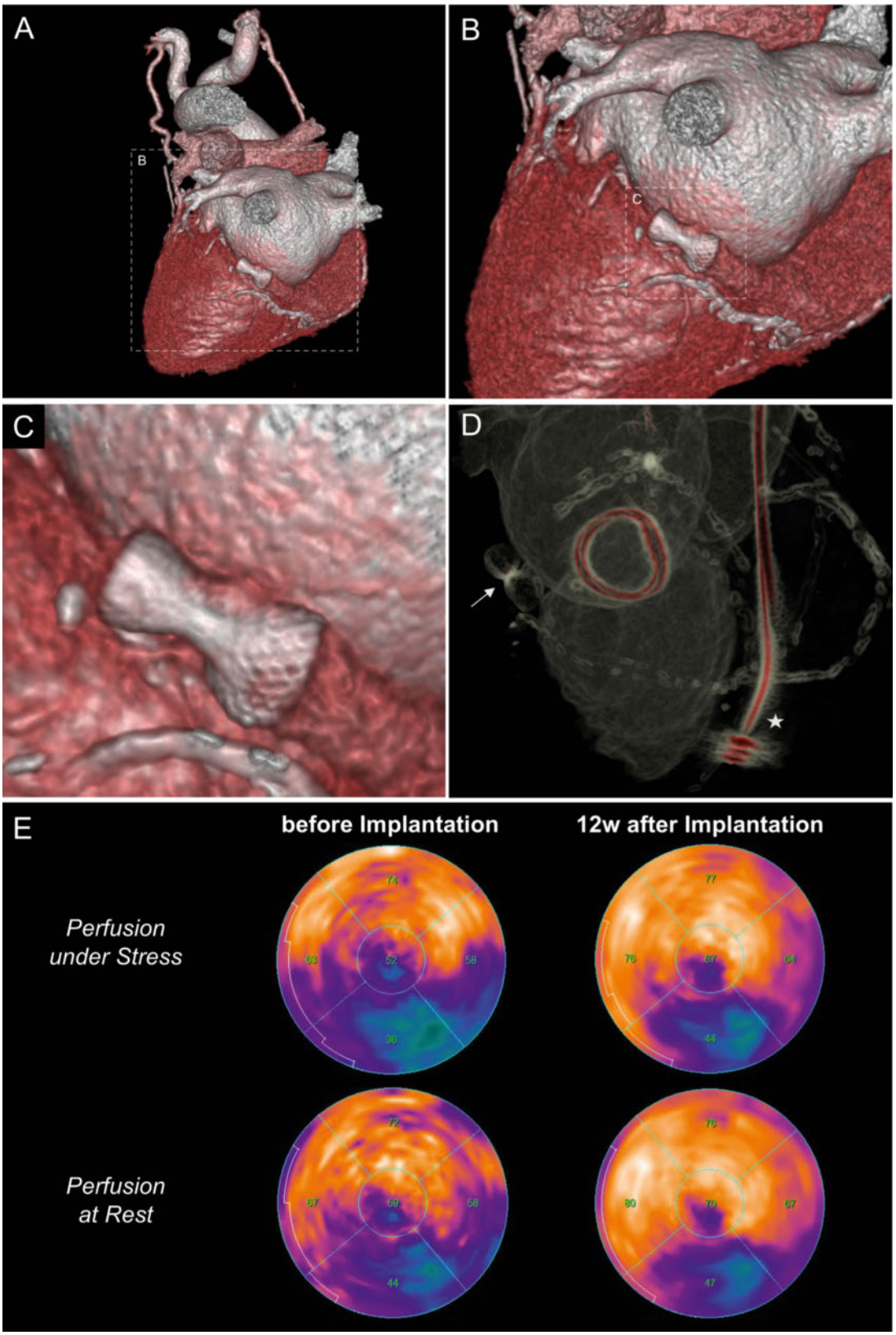

Figure 3: Coronary computed tomography angiography-derived 3D reconstruction of the Reducer™ in position and comparison of myocardial perfusion before and after implantation as assessed by ^{13}N-NH_3 positron emission tomography–myocardial perfusion imaging (PET-MPI). (A–D) The Reducer™ has an hour glass-like shape and is implanted deep in the coronary sinus (arrow). 3D reconstruction demonstrates the position in relationship to the implanted mitral valve ring (arrow heads) and pacemaker electrode (star). (E) Compared with the status before implantation, perfusion both at rest and under stress is considerably increased by the Reducer™ (yellow/orange: normal perfusion, purple: reduced perfusion).

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The subendocardial microvasculature and its contribution overall

The association between atherosclerosis of the large epicardial coronary arteries and myocardial ischaemia is well documented, and the severity of coronary artery disease is a determinant of survival. However, the epicardial arteries constitute only a subportion of the coronary arterial system, which also encompasses smaller vessels including prearterioles and intramural arterioles – the so called microvascular system or microvasculature. The ability of the microvasculature to respond to stimuli to decrease coronary resistance during episodes of increased demand is a major determinant of the coronary flow reserve (i.e., the change from basal coronary perfusion to maximal coronary vasodilation). Thus, even in angiographically normal arteries, ischaemia and reductions in coronary flow reserve may occur because of dysfunction of the microvasculature. In healthy subjects, exercise results in vasodilation of the epicardial and constriction of the subepicardial microcirculation mediated by selective sympathetic activation leading to increased subendocardial perfusion [2]. This compensatory mechanism appears to be defective in patients with coronary artery disease [3]. This leads to a rise in prearteriolar pressure when epicardial coronaries are critically stenosed, resulting in redistribution of blood from the subendocardial to the subepicardial layers of the left ventricle. Higher vascular resistance of subendocardial conduit vessels and subendocardial microcirculation are also suggested to play a role in the specific risk of the subendocardial layer for ischaemia.

Prevalence of refractory angina in patients withcoronary artery disease

Refractory angina was defined in the European Society of Cardiology guideline as "a chronic condition (>3 months) characterised by the presence of angina caused by coronary insufficiency in the presence of CAD which cannot be controlled by a combination of medical therapy, angioplasty, and coronary bypass surgery" [4]. It is estimated that the prevalence of refractory angina is about 6–14% among patients with coronary artery disease [5–7]. Data from the OPTIMIST program at Minneapolis Heart Centre (OPtions In Myocardial Ischemic Syndrome Therapy) demonstrated in a prospective cohort of 1200 patients that all cause mortality was relatively low in the first year (3.9%; 95% confidence interval [CI] 2.8–5.0) [8]. Compared with other patients with coronary artery disease, however, refractory angina is associated with lower quality of life [6, 9], higher rates of rehospitalisation [7] and higher medium-term mortality (28.4% at 9 years, 95% CI 24.9–32.0) [8].

Limitations of PCI and CABG in this patient population and currently available medications to improve this

The reasons for exclusion of patients with refractory angina from further interventions are – based on the data from Minneapolis – mainly collateral dependent myocardium (48%), diffuse coronary artery disease (47%), severely degenerated systemic vein grafts (35%), poor distal targets (20%), multiple coronary restenoses (11%), no graft conduits (4%) or a combination of these [8]. In addition, significant comorbidities (e.g., chronic kidney injury, cerebrovascular disease) alone or in combination with the patients age may limit the options of traditional revascularisation. Currently, anti-anginal medication and improvement of secondary risk factors are the mainstay of treatment in these patients, mostly with limited success. Besides standard antianginal medical treatment with beta-blockers, calcium channel blockers and nitrates, the following substances are available for patients with recurrence of symptoms despite maximal standard medication. Ranolazine has been demonstrated to reduce anginal symptoms and to improve exercise tolerance by inhibition of the late inward sodium channel, which prevents calcium overload and decreases diastolic tension. It is usually used as a substitute for or added to a beta-blocker, and its efficacy in patients with stable angina has been demonstrated in several randomised controlled trials (MARISA, CARISA, TERISA, ERICA and MERLIN-TIMI-36 trials) [10–13]. Perhexiline and trimetazidine promote a shift from fatty acid oxidation to glucose oxidation and thereby increase the metabolic efficacy of the myocardium and reduce anginal symptoms [14, 15]. By activating potassium channels, nicorandil promotes arterial and venous dilation and thereby improves coronary blood flow (IONA trial) [16]. Ivabradine, an inhibitor of a sinus pacemaker current, reduces the heart rate effectively. It may reduce angina in patients with CCS class II or higher on top of optimal medical therapy [17]. In addition, technical improvements in revascularisation of chronic total occlusions, particularly the expanded use of the retrograde approach and advanced re-entry techniques, have been able to reduce refractory anginal symptoms in a large proportion of patients (meta-analysis in [18]). Further approaches, including injections of bone-marrow derived stem cells [19], therapeutic angiogenesis [20] and spinal cord stimulation are currently being tested [18].

Mechanistic approach of the coronary sinus reducer and current indications

The principle behind the Reducer™ is the assumption that reduction of angina can be achieved via enhancing perfusion to the ischaemic myocardium by in-

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creasing pressure within the coronary sinus. In animal studies, occlusion of the coronary sinus has been shown to significantly reduce ischaemic damage and the size of myocardial infarctions by about 30% compared with sham-operated animals [21, 22]. Three main mechanisms have been identified as potential contributors to this phenomenon:

1. Elevation of the coronary sinus pressure increases the back pressure in the precapillary arteriolar system and thereby enhances the dilatation of the constricted subendocardial capillaries, which shifts coronary flow from the subepicardium to the subendocardium.
2. Coronary blood flow and myocardial contractility decrease in the infarcted myocardium, resulting in decreased regional perfusion pressure. When the coronary sinus pressure rises, this promotes a shift in blood flow within pre-existing collaterals from nonischaemic (high tissue pressure) to ischaemic (low tissue pressure) myocardium, specifically reducing subendocardial ischaemia [23]. This effect was observed with and without intact vasomotor tone, the later being induced by adenosine infusion [24].
3. Since the subendocardium is at significantly higher risk of ischaemia, coronary sinus occlusion reverses the subendocardial to epicardial blood flow ratio towards the subendocardium. In addition, early studies in pigs demonstrated that full occlusion or permanent constriction of the coronary sinus leads to neovascularisation (development of new collaterals) within the epicardial and intramyocardial layers of the heart.

Ultimately, all these mechanisms result in improved subendocardial perfusion, enhanced oxygen delivery, improved contractile function and reduction of anginal symptoms. In the COSIRA trial (phase II, COronary SInus Reducer for Treatment of Refractory Angina), 104 patients with refractory angina of CCS class III or IV and documented myocardial ischaemia were randomly assigned to implantation of a Reducer™ or a sham procedure [25, 26]. Improvement of at least two CCS classes 6 months after implantation was more frequent in the device group (35 vs 15%, p = 0.02; fig. 1C,D). In addition, quality of life, as assessed with the Seattle Angina Questionnaire, was significantly improved in patients with a Reducer™ compared with the control group. The device appeared to be safe, as adverse outcomes such as myocardial infarction or death did not appear to differ significantly between the groups ([25, 26], recently reviewed in [27]). As far as currently known, the coronary sinus reducer appears to remain patent for several years.

Ongoing studies

After the publication of the phase II COSIRA trial, currently ongoing studies involve the implantation of demonstrate reversible ischaemia (REDUCER trial, NCT01566175) as well as collection of long-term follow-up data after implantation (REDUCER-I trial, NCT02710435). The latter is a multinational trial involving more than ten centres across western Europe with prospective (implantation of new devices) and retrospective (implantation as part of the COSIRA trial or under a CE mark) investigation of long-term outcome. It is the aim to involve up to 400 patients and enrolment has been under way since December 2016 (estimated primary completion in September 2017). Classical endpoints will be analysed (reduction of CCS class, occurrence of major side effects, major cardiac adverse events) as well as changes in exercise tolerance and quality of life.

Conclusion

Patients with refractory angina constitute a significant part of all patients with coronary artery disease and suffer from reduced exercise tolerance and quality of life. With the number of these patients expected to grow further in the decades to come, new treatment strategies have to be developed to improve medical therapy in such patients with “no options”. Implantation of the Reducer™, despite being an interventional procedure, is easy to perform and safe. Obviously, long-term follow up data have to be awaited from currently ongoing trials. But it can be assumed that this approach will have a role in the future treatment of -patients with refractory angina due to microvascular malfunction.

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References
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