

Coronary Sinus Reducer Stent for the Treatment of Chronic Refractory Angina Pectoris

A Prospective, Open-Label, Multicenter, Safety Feasibility First-in-Man Study

Shmuel Banai, MD,* Shmuel Ben Muvhar,† Keyur H. Parikh, MD,‡ Aharon Medina, MD,§ Horst Sievert, MD,|| Ashok Seth, MD,¶ Jonathan Tsechori, MD,* Yoav Paz, MD,* Ami Sheinfeld, MD,# Gad Keren, MD*

Tel Aviv, Or Yehuda, Jerusalem, and Ramat Gan, Israel; Ahmedabad and New Delhi, India; and Frankfurt, Germany

Objectives

This study sought to evaluate the safety of the Coronary Sinus Reducer (Neovasc Medical, Inc., Or Yehuda, Israel) as a potential alternate therapy for patients with refractory angina who are not candidates for conventional revascularization procedures.

Background

Increased coronary sinus (CS) pressure can reduce myocardial ischemia by redistribution of blood from nonischemic to ischemic territories. The Coronary Sinus Reducer is a percutaneous implantable device designed to establish CS narrowing and to elevate CS pressure. In preclinical experiments, implantation of the Reducer was safe and was associated with improved ischemic parameters. In the present study, the safety and feasibility of the Coronary Sinus Reducer was evaluated in patients with refractory angina who were not candidates for revascularization.

Methods

Fifteen coronary artery disease patients with severe angina and reversible ischemia were electively treated with the Reducer. Clinical evaluation, dobutamine echocardiography, thallium single-photon emission computed tomography, and administration of an angina questionnaire were performed before and 6 months after implantation. Cardiac computed tomography was performed 2 days and 6 months after implantation.

Results

All procedures were completed successfully. No procedure-related adverse events occurred during the periprocedural and the follow-up periods. Angina score improved in 12 of 14 patients. Average Canadian Cardiovascular Society score was 3.07 at baseline and 1.64 at follow-up ($n = 14$, $p < 0.0001$). Stress-induced ST-segment depression was reduced in 6 of 9 patients and was eliminated in 2 of these 6 ($p = 0.047$). The extent and severity of myocardial ischemia by dobutamine echocardiography and by thallium single-photon emission computed tomography was reduced ($p = 0.004$ [$n = 13$] and $p = 0.042$ [$n = 10$], respectively).

Conclusions

Implantation of the Coronary Sinus Reducer is feasible and safe. These findings, along with the clinical improvement observed, support further evaluation of the Reducer as an alternative treatment for patients with chronic refractory angina who are not candidates for coronary revascularization. (J Am Coll Cardiol 2007;49:1783-9)

© 2007 by the American College of Cardiology Foundation

The increasing number of coronary revascularization procedures along with improved drug and device therapies has greatly increased the life expectancy of patients with coronary artery disease (CAD). However, there are still a

considerable number of patients who remain severely disabled by chronic refractory angina pectoris. This group of patients is rapidly growing because of the improvement of cardiovascular care provided. It is estimated that 5% to 10% of patients with angina pectoris have refractory angina. Those in this group of no-option patients often have severe diffuse CAD and are not candidates for further revascularization by coronary artery bypass graft (CABG) surgery or percutaneous coronary intervention (PCI) (1,2). The estimated 1- and 3-year mortality rates for these patients are 1% to 5%, and up to 24%, respectively (2-7).

A considerable number of therapeutic strategies for treating severe chronic angina have been investigated (8,9). All

From the *Cardiology Department, Tel Aviv Medical Center, Tel Aviv, Israel; †Neovasc Medical, Inc., Or Yehuda, Israel; ‡The Heart Care Clinic/SAL Hospital, Ahmedabad, India; §Bikur Cholim Hospital, Jerusalem, Israel; ||Cardio Vascular Center Frankfurt, Sankt Katharinen, Frankfurt, Germany; ¶Max Devki Devi Heart and Vascular Institute, New Delhi, India; and the #Sheba Medical Center, Ramat Gan, Israel. The research and development of the Coronary Sinus Reducer stent were done by Neovasc Medical, Inc. Drs. Banai and Keren are active consultants and Shmuel Ben Muvhar is the Chief Executive Officer of Neovasc Medical, Inc.

Manuscript received September 22, 2006; revised manuscript received January 2, 2007, accepted January 2, 2007.

Abbreviations and Acronyms

- CABG** = coronary artery bypass graft
- CAD** = coronary artery disease
- CCS** = Canadian Cardiovascular Society
- CS** = coronary sinus
- CT** = computed tomography
- PCI** = percutaneous coronary intervention
- SPECT** = single-photon emission computed tomography

have only limited feasibility, and none of these approaches has become a widely used therapy. In the setting of obstructive CAD, increased coronary sinus (CS) pressure can lead to redistribution of collateral blood flow from nonischemic into ischemic territories of the myocardium. Such redistribution of arterial blood significantly reduces myocardial ischemic damage and infarct size (10-15).

The Coronary Sinus Reducer (Neovasc Medical, Inc., Or Yehuda, Israel) is a stainless steel balloon-expandable stent specially designed to establish a narrowing of the CS, which is the final pathway of the cardiac venous drainage, and to increase coronary venous pressure. The Reducer is implanted by a percutaneous transvenous approach. In a set of preclinical experiments, we have shown that implantation the Coronary Sinus Reducer is feasible and safe. In ischemic hearts, implantation of the Reducer was associated with reduced mortality and improved ischemic parameters. Our hypothesis is that in patients with CAD and refractory angina who are not candidates for conventional revascularization procedures, elevating CS pressure with the Reducer might enhance perfusion to ischemic territories of the myocardium and improve their symptoms. As a first step in the evaluation of the Coronary Sinus Reducer as a potential alternative therapy for patients with refractory angina who are not candidates for revascularization, a first-in-man study was conducted.

Methods

This was a multicenter, nonrandomized, open-label prospective study that evaluated the safety and feasibility of the Coronary Sinus Reducer. All patients received the intended therapy. The study was conducted at 3 sites in Germany and in India.

Patients. Patients were eligible for inclusion in the study if they had a history of CAD with refractory angina (Canadian Cardiovascular Society [CCS] class II to IV) despite optimal medical therapy, objective evidence of reversible myocardial ischemia, and ejection fraction >30%. All patients were considered unacceptable candidates for PCI or CABG. All were treated electively with implantation of the Coronary Sinus Reducer.

INCLUSION CRITERIA.

1. Symptomatic CAD with refractory angina defined as CCS class II to IV, despite medical therapy.
2. Patients with CAD who were either not amenable to or were at high risk for CABG or PCI.

3. Reversible myocardial ischemia, determined by perfusion scan and/or by dobutamine echocardiography.
4. Left ventricular ejection fraction $\geq 30\%$.

EXCLUSION CRITERIA.

1. Recent (within 3 months) myocardial infarction.
2. Recent (within 7 months) PCI or CABG.
3. Severe arrhythmias, including chronic atrial fibrillation.
4. Decompensated heart failure.
5. Severe valvular heart disease.
6. Pacemaker or other CS electrode.
7. Mean right atrial pressure ≥ 15 mm Hg.
8. Patients who had undergone tricuspid valve replacement or repair.

The device. The Reducer is a stainless steel balloon-expandable stent designed to establish narrowing of the CS (Fig. 1). The diameter at its mid portion is 3 mm, and it can reach a diameter of 7.0 to 13.0 mm at both ends using inflation pressure of 2 to 4 bars. The Reducer is introduced into the CS through the right internal jugular vein.

In case it is necessary to remove the narrowing from the CS, balloon inflation to a pressure of 8 bars will completely open the Reducer, which will then attain a tubular shape.

Study end points. PRIMARY END POINT: SAFETY. The primary end point in this study was the absence of any major adverse cardiac events related to the procedure during 6 months of follow-up. An adverse event was defined as death, myocardial infarction, perforation of the CS, CS occlusion, or need for urgent dilatation of the Reducer.

SECONDARY END POINT: TECHNICAL SUCCESS. The secondary end point was successful delivery and deployment of the Reducer in the CS, as assessed by angiogram and/or by computed tomographic (CT) angiography.

Follow-up. Each patient underwent a full clinical evaluation, stress test, radionuclide perfusion study with single-photon emission computed tomography (SPECT), and/or

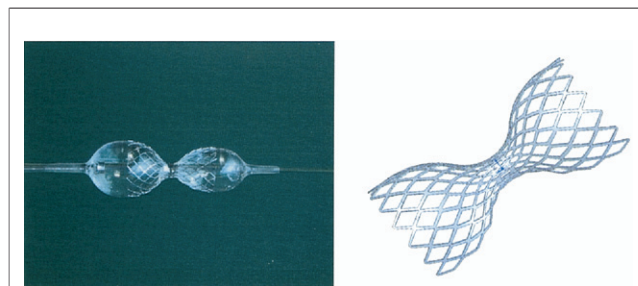


Figure 1 Coronary Sinus Reducer Stent: A Stainless Steel Balloon-Expandable Stent

(Left) The Reducer stent on the inflated designated balloon. (Right) The Reducer stent.

dobutamine echocardiography at baseline (before implantation of the Reducer) and 6 months later. Dobutamine echocardiography and thallium SPECT studies were analyzed by core laboratories.

DOBUTAMINE ECHOCARDIOGRAPHY. An 18-segment quantitative analysis was used. The wall motion of each segment was graded according to a score (0 = not scored, 1 = normal, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic, 5 = aneurysmatic). The summed scores of myocardial contractility during peak dobutamine infusion at baseline and after 6 months were compared. A medically significant change was defined as a change of 1 score or more in at least 2 segments.

MYOCARDIAL PERFUSION IMAGING. A 20-segment semi-quantitative visual analysis and an automated quantitative analysis were used. A qualitative comparison between stress and rest redistribution images at baseline and at 6-month follow-up was made by the calculation of a defect extent score. The score was derived from the number of abnormal segments among those evaluated. A medically significant change was defined as a difference of at least 4 points in the total score.

CARDIAC CT ANGIOGRAPHY. The CT angiographies at 1 to 3 days of Reducer implantation and at 6 months were compared to evaluate the exact placement and patency of the Reducers.

QUALITY OF LIFE AND ANGINA CLASS. The Seattle Angina Questionnaire for assessing quality of life and angina class was completed at baseline and at 3 and 6 months of follow-up.

REDUCER STENT IMPLANTATION PROCEDURE. Treatment with aspirin 100 mg/day and clopidogrel 75 mg/day was started 1 week before implantation. Under fluoroscopic guidance, a preshaped guiding sheath was introduced into the CS through a right internal jugular vein. After CS pressure was recorded, angiography was performed. The dimensions of the proximal segment of the CS were measured using quantitative coronary angiography. The optimal site for implantation was chosen according to the vessel diameters and to avoid side branch bifurcation. The Reducer, crimped on a balloon, was then inserted over the wire into the CS, positioned at the desired site, and implanted by inflating the balloon. Postimplantation angiography was performed to ensure appropriate implantation, patency, and appropriate reduction of the lumen's diameter, and to ensure lack of migration of the Reducer, thrombosis within the Reducer or the CS, and perforation or dissection of the CS (Fig. 2).

Statistical analysis. The baseline and follow-up measurements were compared using the one-sided Wilcoxon signed rank test; $p < 0.05$ was considered statistically significant.

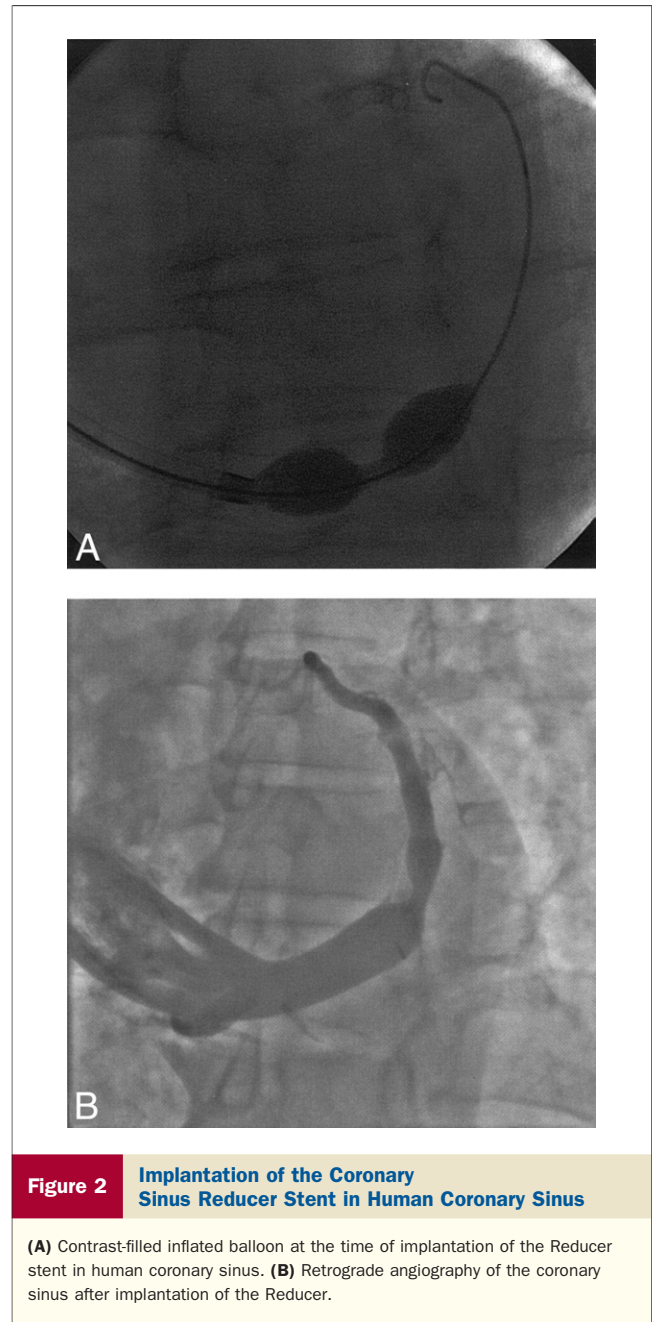


Figure 2 Implantation of the Coronary Sinus Reducer Stent in Human Coronary Sinus
(A) Contrast-filled inflated balloon at the time of implantation of the Reducer stent in human coronary sinus. (B) Retrograde angiography of the coronary sinus after implantation of the Reducer.

Results

Patients. From October 2004 to July 2005, a single Reducer was implanted in the CS of 15 patients at 3 medical centers. All had proven CAD, evidence of reversible myocardial ischemia by dobutamine echocardiography, and/or thallium SPECT, and all suffered from refractory angina. The clinical characteristics of the patients are presented in Table 1.

One patient who was included in the safety/feasibility analysis was excluded from the quality of life/angina score analysis as well as from the stress and perfusion test analyses. This patient continued to suffer from severe angina after implantation of the Reducer. His cardiac CT angiography showed a diseased saphenous vein graft that was missed

Table 1 Clinical Characteristics of the Patients	
Characteristic	n
Male	12
Female	3
Age (yrs)	50-80 (mean 65)
S/P myocardial infarction	4
S/P percutaneous coronary intervention	6
S/P coronary artery bypass graft	3
Hypertension	10
Hyperlipidemia	5
Diabetes	1
Angina class	
CCS 2	1
CCS 3	12
CCS 4	2
Number of diseased vessels	
1	3
2	6
3	6

CCS = Canadian Cardiovascular Society; S/P = status post.

during his baseline coronary angiogram. The obstructive saphenous vein graft lesion was treated with a stent, and the patient's symptoms improved significantly.

Primary and secondary end points. All implantation procedures were completed successfully. All patients were discharged from the hospital 1 to 2 days later without clinical complications. No major adverse cardiac events had occurred during the periprocedural period or during the follow up period of 10 to 12 months (mean follow-up 11 ± 1.03 months).

Additional evaluation. CT ANGIOGRAPHY. In 12 patients, CT angiography was performed. All Reducers were patent, well positioned, and located at the exact site of deployment with no evidence of migration. The mean diameters of the Reducers as measured in the postimplantation multislice CT were: proximal 11 ± 2 mm, distal 7.2 ± 1 mm, and mid 3.0 ± 0.2 mm (Fig. 3).

ANGINA SCORE. Angina score improved significantly 6 months after implantation. The CCS class was lower after 6 months in 12 of the 14 patients and remained constant in 2. The average CCS class for the 14 patients was 3.07 at baseline and 1.64 at follow-up (p < 0.0001). The individual and per-the-group changes in CCS class are outlined in Figures 4A and 4B. Most patients reported improvement in quality of life and reduction in anginal symptoms only several weeks after implantation of the Reducer, and not immediately after implantation.

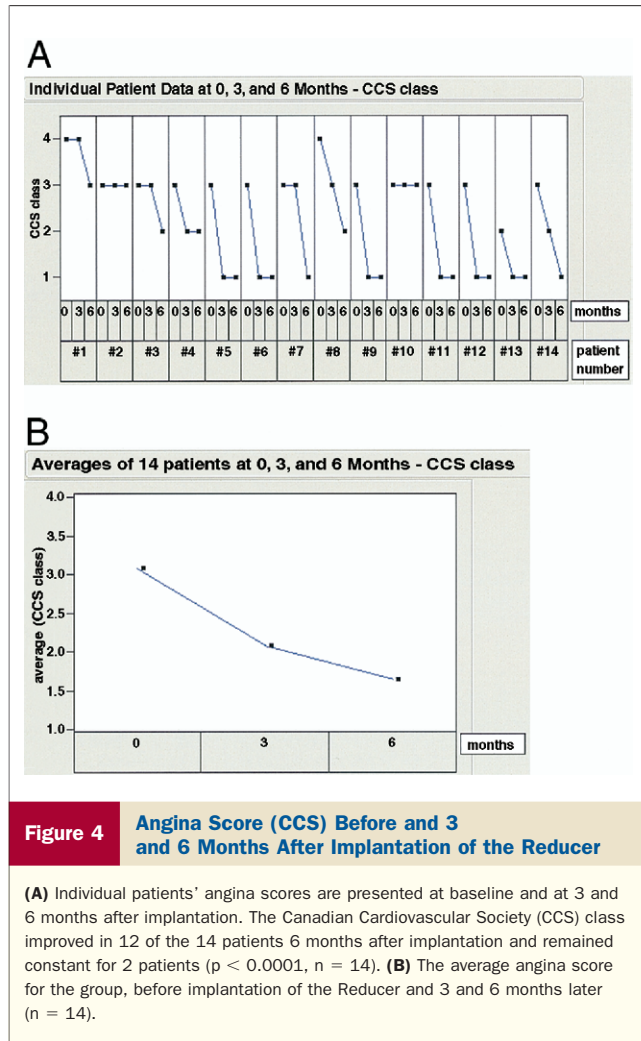
ST-SEGMENT DEPRESSION DURING EXERCISE STRESS TEST. Of the 11 patients in whom electrocardiographic tracings at baseline and at the 6-month stress test were of good technical quality, transient ST-segment depression was documented during the baseline exercise stress test in 9. At 6-month follow-up, ST-segment depression was lower in 6 of these 9 patients, and was no longer present in 2 of the 6. One patient had a higher ST-segment depression at 6 months. The average ST-segment depression for the 9 patients was 2.00 mm at a mean heart rate of 117 beats/min at baseline and 1.22 mm at a mean heart rate of 124 beats/min at follow-up (p = 0.047) (Fig. 5). In 9 of the 11 patients, exercise duration and peak heart rate increased at the 6-month follow-up stress test compared with baseline. For the whole group, the average double product and exercise duration were unchanged 6 months after implantation compared with baseline (18,675 at baseline vs. 20,365 at 6 months [p = 0.18] and 7.08 at baseline vs. 6.79 at 6 months [p = 0.59], respectively).

DOBUTAMINE ECHOCARDIOGRAPHY. In 13 of the 14 patients, dobutamine echocardiography data were of good technical quality. In 8 of these 13 patients there was a medically significant improvement (a change of 1 score or more in at least 2 segments) when the stress images at baseline and 6 months were compared. The average score of all 18 segments was lower at 6 months (baseline 25.08, 6



Figure 3 Cardiac Computed Tomographic Angiography of Human Hearts After Implantation of the Coronary Sinus Reducer Stent

(A) Three-dimensional reconstruction of the posterior aspect of the heart. The Reducer stent implanted at the proximal segment of the coronary sinus is clearly seen. (B, C) Longitudinal section of the coronary sinus. The proximal and distal diameters of the Reducer perfectly match the funnel-shaped coronary sinus.



months 1.08, difference 4.00; $p = 0.004$) (Fig. 6). Of the remaining 5 patients, 3 had a higher total score at 6 months than at baseline and 2 had a lower score; the differences were relatively small, and all 5 had low baseline values.

THALLIUM SPECT PERFUSION STUDIES. In 10 patients SPECT images were of good technical quality at baseline and 6 months. In 4 of the 10 patients there was a medically significant reduction in the extent and/or severity of myocardial ischemia as measured by the total score. Among the remaining 6 patients, the SPECT images were unchanged in 5 and worsened in 1 patient at 6 months. The average score for the group was 12.6 at baseline and 9.6 at 6 months, $p = 0.042$ ($n = 10$).

Discussion

This is the first human experience with the implantation of Coronary Sinus Reducer. The absence of adverse events for up to 12 months of follow-up suggests that the implantation of the Reducer is feasible and safe. The present safety/feasibility study is the first step in the clinical evaluation of

the Coronary Sinus Reducer as a possible treatment for patients with refractory angina.

The majority of patients suffering from CAD can be adequately treated by drug therapy and by revascularization. Improved drug therapy and the refinement of revascularization techniques have greatly increased the life expectancy and improved quality of life for these patients in the last few decades. Nevertheless, despite an increasing number of coronary interventions over recent years, there are still a considerable number of patients suffering from chronic refractory angina pectoris. The percentage of these no-option patients is not known exactly, but has been suggested to be 30 per million inhabitants per year; other estimates are 2.5% to 5% of coronary angiography procedures (1,8). The group of no-option patients includes those who have angina despite optimal medical therapy. These patients may not have been offered PCI or CABG because of the severe diffuse nature of their coronary disease, or these patients may continue to experience severe angina after CABG and PCI.

A considerable number of therapeutic strategies for treating refractory angina have been investigated, none of which has become an accepted and widely used tool in today's clinical practice. Elevated coronary venous pressure achieved by narrowing of the CS as a therapeutic approach for patients with disabling angina was first described and used by Beck and Leighninger in 1955 (16,17).

Elevating CS pressure using intermittent CS occlusion and pressure-controlled intermittent CS occlusion have been described to be effective in salvaging ischemic myocardium in several experimental models of coronary artery

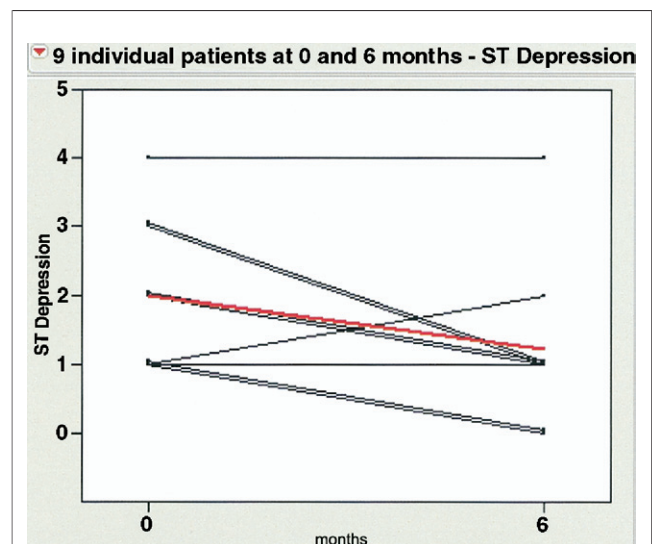
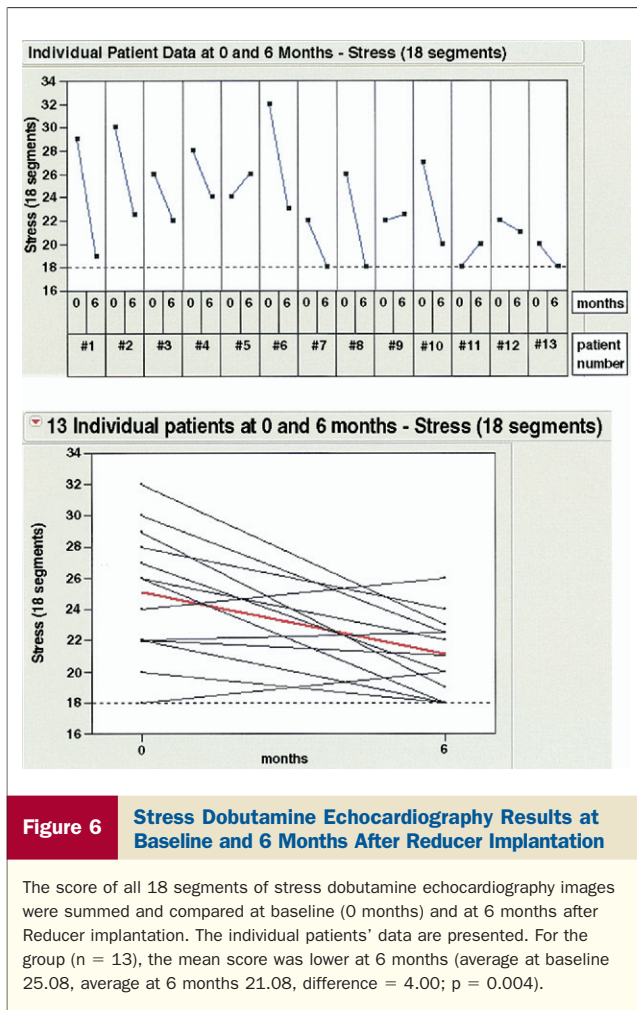


Figure 5 **Exercise-Induced ST-Segment Depression Before and 6 Months After Implantation**

Transient ST-segment depression was present during the baseline stress test in 9 patients. At 6-month follow-up, ST-segment depression was lower in 6 patients and was no longer present in 2 of the 6. For ST-segment depression, the average for the 9 patients was 2.00 mm at baseline and 1.22 mm at follow-up ($p = 0.047$).



occlusion (18,19); however, the modes of action of these interventions remain speculative. The CS pressure elevation enhances coronary collateral flow and reduces subendocardial ischemia, with a positive correlation between the elevated CS pressure and the changes in collateral blood flow from nonischemic to ischemic territories of the myocardium (11).

Clinical application of CS interventions during the early reperfusion period has shown improvement in regional myocardial function and salvaging of ischemic myocardium, especially by limiting the infarct from its border (13,14,20–22).

Few pathophysiological mechanisms are proposed to explain the anti-ischemic effects of elevated CS pressure: first, the opening of pre-existing collateral vessels between normally perfused and ischemic segments of the myocardium; and second, reversal of the endocardial/epicardial blood flow ratio in favor of the endocardium with an increase in endocardial blood flow (10). In the long run, the potential for formation of new blood vessels also has been suggested.

Significant stenosis of an epicardial coronary artery is associated with decreased myocardial perfusion and acti-

vation of compensatory mechanisms to overcome this limitation. Distal vessels dilate, and pre-existing collateral connections are opened and develop over time into significant vessels that transmit blood from normally perfused territories to ischemic regions. New coronary collaterals develop over time as well. Previous studies with an increase in CS pressure have shown clearly that the coronary collateral circulation is enhanced in a significant way by this intervention.

Furthermore, the subendocardium is more vulnerable to ischemic damage than the midmyocardium or subepicardium. Epicardial coronary stenoses are associated with reduction in the subendocardial-to-subepicardial flow ratio. This mechanism, which has been demonstrated in multiple experiments, is explained by the high intramyocardial forces acting on vessels in the subendocardium. This high intramyocardial force does not enable the vasodilatory response of the vascular system to fully compensate for the decrease in coronary perfusion caused by the stenosis. The Coronary Sinus Reducer, by increasing backpressure into the precapillary arteriolar system, will facilitate dilatation of the constricted subendocardial capillaries. Any change in the diameter of these vessels will be more pronounced than the changes taking place in the already-dilated vessels in the epicardial territory, thereby facilitating the directional changes in flow toward the subendocardial segments (10–12,14). Improved capillary perfusion in the subendocardium of the ischemic territory will improve contractility and increased oxygen consumption (15).

Our hypothesis is that in the setting of obstructive CAD, by increasing CS pressure, perfusion of the myocardium in ischemic areas will be enhanced and consequently hemodynamic parameters and symptoms of angina will improve. To test the validity of our hypothesis we have conducted a set of preclinical experiments followed by this first-in-man study.

Preclinical experiments have shown that implantation of the Coronary Sinus Reducer in pig hearts was feasible and safe and carried no short- or long-term complications. No short- or long-term complications were observed during follow-up of up to 1 year. The mean pressure gradient measured across the reducers was 3.71 ± 1.75 mm Hg immediately after implantation and 2.83 ± 1.47 mm Hg 6 months later. In a pig model of reversible myocardial ischemia, implantation of the Reducer was associated with reduced mortality and improved ischemic parameters.

The present study has shown that the use of this new technique to establish a narrowing of the CS is feasible and safe. Whether or not the reduction in CS diameter and the increased CS pressure will subsequently improve collateral blood flow into ischemic territories of the myocardium, reduce ischemia, and improve symptoms of angina is still to be proven in a larger clinical study designed and powered to prove efficacy.

Refractory angina is a chronic condition with little change over time. In the present study, 6 months after implantation of the Coronary Sinus Reducer, angina score improved in 12

of 14 patients, stress-induced ST-segment depression was reduced in 6 of 9 patients and was eliminated in 2 of the 6, the severity of dobutamine-induced myocardial ischemia was significantly reduced in 8 of 13 patients, and in 4 of 10 patients the extent and severity of myocardial ischemia was reduced by thallium SPECT. Although not designed and not powered to prove efficacy, the improvement in subjective and objective ischemic parameters observed might reflect the potential efficacy of this device in the treatment of refractory angina. It should be emphasized that until a randomized placebo-controlled trial is conducted, it can not be ruled out that the subjective improvement observed is not attributed to a placebo effect. Such a placebo effect has been reported in many refractory angina trials.

Conclusions

In this open-label, multicenter, nonrandomized, prospective study, the use of percutaneous transvenous implantation of the Coronary Sinus Reducer in patients with refractory angina was found to be safe and feasible. These findings, along with the clinical improvement observed, support further evaluation of the Coronary Sinus Reducer in a randomized placebo-controlled trial, as an alternative tool for treating patients with refractory angina who are not candidates for or are at high risk for revascularization.

Reprint requests and correspondence: Dr. Shmuel Banai, Interventional Cardiology, Tel Aviv Medical Center, 6 Weizman Street, Tel Aviv, Israel. E-mail: banais@netvision.net.il.

REFERENCES

1. Mannheim C, Camici P, Chester MR, et al. The problem of chronic refractory angina. *Eur Heart J* 2002;23:355-70.
2. McNab D, Khan SN, Sharples LD, et al. An open label, single center, randomized trial of spinal cord stimulation vs. percutaneous myocardial laser revascularization in patients with refractory angina pectoris: the SPiRiT trial. *Eur Heart J* 2006;27:1048-53.
3. Salem M, Rotevatn S, Stavnes S, Brekke M, Vollset SE, Nordrehaug JE. Usefulness and safety of percutaneous myocardial laser revascularisation for refractory angina pectoris. *Am J Cardiol* 2004;93:1086-91.
4. Aaberge L, Rootwelt K, Blomhoff S, Saatvedt K, Abdelnoor M, Forfang K. Continued symptomatic improvement three to five years after transmyocardial revascularisation with CO₂ laser: a late clinical follow-up of the Norwegian randomised trial with transmyocardial revascularisation. *J Am Coll Cardiol* 2002;39:1588-93.
5. Schoefield PM, Sharples LD, Caine N, Burns S, Tait S. Transmyocardial laser revascularisation in patients with refractory angina: a randomised controlled trial. *Lancet* 1999;353:519-24.
6. Leon MB, Kornowski R, Downey WE, et al. A blinded, randomised, placebo-controlled trial of percutaneous laser myocardial revascularisation to improve angina symptoms in patients with severe coronary artery disease. *J Am Coll Cardiol* 2005;46:1812-19.
7. Oesterle SN, Sanborn TA, Ali N, et al. Percutaneous transmyocardial laser revascularisation for severe angina: the PACIFIC study. *Lancet* 2000;356:1705-8.
8. Nordrehaug JE, Salem M. Treatment of chronic refractory angina pectoris—light at the end of the tunnel? *Eur Heart J* 2006;27:1007-9.
9. DeJongste MJL, Tio RA, Foreman RD. Chronic therapeutically refractory angina pectoris. *Heart* 2004;90:225-30.
10. Ido A, Hasbe N, Matsuhashi H, Kikuci K. Coronary sinus occlusion enhances coronary collateral flow and reduces subendocardial ischemia. *Am J Physiol Heart Circ Physiol* 2001;280:H1361-7.
11. Sato M, Saito T, Mitsugi M, et al. Effects of cardiac contraction and coronary sinus pressure elevation on collateral flow. *Am J Physiol* 1996;271:H1433-40.
12. Rouleau JR, White M. Effects of coronary sinus pressure elevation on coronary blood flow distribution in dogs with normal preload. *Can J Physiol Pharmacol* 1985;63:787-97.
13. Syeda B, Schukro C, Heinze G, et al. The salvage potential of coronary sinus intervention: meta-analysis and pathophysiologic consequences. *J Thorac Cardiovasc Surg* 2004;127:1703-12.
14. Mohl W, Glogar DH, Mayr H, et al. Reduction of infarct size induced by pressure-controlled intermittent coronary sinus occlusion. *Am J Cardiol* 1984;53:923-8.
15. Dijkman MA, Heslinga JW, Sipkema P, Westerhof N. Perfusion-induced changes in cardiac contractility depend on capillary perfusion. *Am J Physiol Heart Circ Physiol* 1998;274:H405-10.
16. Beck CS, Leighninger DS. Scientific basis for the surgical treatment of coronary artery disease. *JAMA* 1995;159:1264-71.
17. Wising PJ. The BECK-I operation for angina pectoris: medical aspects. *Acta Med Scand* 1963;174:93-8.
18. Aldea GS, Zhang X, Rivers S, Shemin RJ. Salvage of ischemic myocardium with simplified and even delayed coronary sinus retroperfusion. *Ann Thorac Surg* 1996;62:9-15.
19. Ikeoka K, Nakagawa Y, Kawashima S, Fujitani K, Iwasaki T. Effects of intermittent coronary sinus occlusion on experimental myocardial infarction and reperfusion hemorrhage. *Jpn Circ J* 1990;54:1258-73.
20. Mohl W, Kajgana I, Bergmeltser H, Rattay F. Intermittent pressure elevation of the coronary venous system as a method to protect ischemic myocardium. *Interactive Cardiovasc Thorac Surg* 2005;4:66-9.
21. Berland J, Farcot JC, Barrier A, Dellac A, Gamra H, Letac B. Coronary venous synchronized retroperfusion during percutaneous transluminal angioplasty of left anterior descending coronary artery. *Circulation* 1990;81:IV35-42.
22. Incurvati RL, Tauberg SG, Pecora MJ, et al. Clinical application of coronary sinus retroperfusion during high-risk percutaneous transluminal coronary angioplasty. *J Am Coll Cardiol* 1993;22:127-34.