

Percutaneous Transvenous Mitral Annuloplasty Initial Human Experience With a Novel Coronary Sinus Implant Device

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Background—We assessed the safety and feasibility of permanent implantation of a novel coronary sinus mitral repair device (PTMA, Viacor Inc).

Methods and Results—Symptomatic (New York Heart Association class 2 or 3) patients with primarily functional mitral regurgitation (MR) were included. A diagnostic PTMA procedure was performed in the coronary sinus venous continuity. MR was assessed and the PTMA device adjusted to optimize efficacy. If MR reduction (≥ 1 grade) was observed, placement of a PTMA implant was attempted. Implanted patients were evaluated with echocardiographic, quality of life, and exercise capacity metrics. Nineteen patients received a diagnostic PTMA study. Diagnostic PTMA was effective in 13 patients (MR grade 3.2 ± 0.6 reduced to 2.0 ± 1.0), and PTMA implants were placed in 9 patients. Four devices were removed uneventfully (7, 84, 197, and 216 days), 3 for annuloplasty surgery due to observed PTMA device migration and/or diminished efficacy. No procedure or device-related major adverse events with permanent sequela were observed in any of the diagnostic or implant patients. Sustained reductions of mitral annulus septal-lateral dimension from 3D echo reconstruction dimensions were observed (4.0 ± 1.2 mm at 3 months).

Conclusions—Percutaneous implantation of the PTMA device is feasible and safe. Acute results demonstrate a possibly meaningful reduction of MR in responding patients. Sustained favorable geometric modification of the mitral annulus has been observed, though reduction of MR has been limited. The PTMA method warrants continued evaluation and development. (*Circ Cardiovasc Intervent.* 2009;2:277-284.)

Key Words: annuloplasty ■ coronary sinus ■ heart failure ■ mitral valve ■ regurgitation

Mitral regurgitation (MR) frequently accompanies heart failure.¹⁻³ Although discrete leaflet pathology may induce pure MR and heart failure, often MR is functional and occurs without leaflet abnormalities. Functional MR is a consequence of ventricular geometric distortion, annular dilatation, and frequently tethering of the leaflets⁴ and may precipitate or accelerate ventricular enlargement, annular dilation, and heart failure symptoms.⁵ In a graded fashion, MR is an independent predictor of morbidity and mortality in patients with ischemic heart disease and heart failure.^{6,7} MR clinical presentation is also frequently dynamic and exaggerated by exertion, thus leading to underassessment of the disease state severity by echocardiography performed at rest.⁸⁻¹²

Current therapeutic interventions to limit the impact of MR include both medical and surgical therapies.^{13,14} Surgical valve repair is performed via placement of an annuloplasty

ring and/or mitral leaflet-subvalvular apparatus repair or mitral valve replacement.^{15,16} Current guidelines encourage surgical therapy for patients with symptoms, atrial fibrillation/arrhythmias, pulmonary hypertension, or changes in left ventricular function.^{17,18} Many patients who might otherwise benefit from treatment are excluded because they are unsuitable for such highly invasive open chest surgery due to the associated surgical morbidity and mortality.^{19,20} Similarly, many patients with mild MR at the time of surgical revascularization progress to significant MR after coronary artery bypass grafting.²¹

Various investigators have proposed less invasive repair techniques to interrupt the natural history of MR in ischemic heart disease and heart failure.²²⁻²⁴ Current efforts include approaches to directly clip²⁵ the mitral leaflets or modify the mitral annulus via the coronary sinus^{26,27} and various other

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Table 1. Summary of PTMA Implant Feasibility Cases Grouped by Device and Protocol Evolution

Case Group	Dates	Procedures (n=29 in 27 Patients)	PTMA Diagnostic	PTMA Implants*	Design/Protocol Changes
1	April to May 2006	3	1	1	Initial device
2	September 2006 to January 2007	9	6†	1	Enhanced Nitinol fatigue properties CT screening/selective rendering analysis Additional PTMA device stiffness profiles
3	March to June 2007	11	8	5	0.025-in OTW implant configuration Increased stiffness PTMA rods Implants placed just distal of CSO
4	September to November 2007	6	6‡	2	0.035-in OTW implant; more trackable tip Reduced size, adjustable implant hub More proximal implant position target: CSO engagement

CT indicates computed tomography; OTW, over the wire; CSO, coronary sinus orifice.

*All implanted patients first underwent a PTMA diagnostic procedure immediately preceding the PTMA implant.

†Two patients receiving successful diagnostic PTMA evaluations in group 2 were implanted in later procedures with improved devices, one each in groups 3 and 4.

‡Two PTMA diagnostic evaluation patients in group 4 are active candidates for future PTMA implants.

novel techniques.²⁸ Preliminary data in both animal models and initial, temporary human studies have demonstrated the potential of the PTMA device (Viacor Inc, Wilmington, Mass) and the method to reduce the mitral annular septal-lateral dimension and limit MR.^{29,30} This report describes initial results and procedure revisions in an intention-to-implant feasibility study.

Methods

Study Design

Patients were enrolled in 4 European and 1 Canadian institution between April 2006 and November 2007. The protocol was approved by national regulatory bodies and local ethics committees. New York Heart Association functional class 2 to 3 patients with heart failure were screened for possible participation based on medical history and echocardiographic findings. Eligible patients included those with moderate to severe functional MR, graded 2+ to 4+, and a left ventricular ejection fraction of 20% to 50%. Contraindications to PTMA included organic mitral valve disease, leaflet prolapse, significant renal dysfunction (Cr >2.3 mg/dL), presence of a proximal coronary circumflex stent, and a left dominant coronary circulation. Preprocedure evaluation included transthoracic echocardiography with 3D imaging of the mitral annulus, 6-minute walk, and quality-of-life survey. The study's primary end point was safety (30-day major adverse cardiac event).

PTMA Device Description

The Viacor PTMA system uses 2 primary structural elements: a multilumen PTFE (Teflon) PTMA catheter and Nitinol (nickel-titanium alloy) PTMA treatment rods. The PTMA catheter is provided in both diagnostic and implant versions. The PTMA system has been described previously.³¹ The PTMA implant device incorporates an integral proximal titanium access hub to facilitate the delivery and fix the position of the PTMA rods within the implant system. The implant differs from the diagnostic device in that the treatment section of the implant is fitted with an integral, nonabsorbable external polyester surgical suture winding to enhance the stability of the PTMA implant system. The diagnostic and implant PTMA rods are equivalent; each is formed from a single Nitinol wire that is profiled to provide precise, incremental application of stiffness to the posterior mitral annulus and thus reduce the septal-lateral dimension of the valve, improve leaflet coaptation, and reduce MR.

Procedure

Interventional device placement was performed in the cardiac catheterization laboratory after induction of general anesthesia. Transesophageal echocardiography (TEE) was used to measure quantitative procedural baseline MR and the septal-lateral annular dimension. For the most recent 15 patients enrolled in the study, a contrast enhanced, multidetector computed tomography (MDCT) scan was obtained before the procedure, and the dataset selectively rendered (M2S, West Lebanon, NH) and reviewed from the perspective of standard fluoroscopic viewing angles, both before the catheterization procedure and then continuously throughout the case in matched viewing angles. Arterial access was obtained for coronary angiography by standard techniques. Percutaneous venous access was obtained via the right or left subclavian vein. Access to the coronary sinus was established using standard 8F coronary sinus (CSG) sheaths (St Jude Apeel or Biotronik ScoutPro). After occlusive venography to demonstrate course and patency of the venous anatomy in multiple fluoroscopic views, a guide wire was advanced into the descending anterior interventricular vein. If the descending anterior interventricular vein could not be accessed, the case was terminated.

The Viacor 7F, 3-lumen PTMA diagnostic multilumen catheter was advanced over a 0.025-in or, in later cases, 0.035-in guide wire through the CSG sheath and into the coronary sinus under fluoroscopic guidance. The PTMA catheter was advanced until the distal radio-opaque marker was observed to have advanced 2 to 3 cm past the great cardiac vein into the anterior interventricular vein. PTMA diagnostic rods were progressively inserted into the PTMA diagnostic catheter to increase and adjust the treatment effect on the mitral annulus as observed by TEE with hemodynamic manipulation as needed to standardize arterial blood pressure during anesthesia. Up to 3 PTMA treatment rods were placed simultaneously within the PTMA catheter. Rods of various stiffness and design were used to apply stiffnesses of 100 to 600 g/cm selectively to the P2 segment of the mitral valve Angiographic, ECG and echocardiographic parameters were continuously monitored and recorded. Ultimate device size and position was determined by maximal reduction in the mitral annular dimensions with accompanying reduction in MR. If no treatment effect was observed via TEE with diagnostic PTMA, the devices were withdrawn and the patient was recovered. If treatment benefit was noted, and angiography verified no impingement on coronary circulation or PTMA device instability, the diagnostic catheter was exchanged for the implant PTMA catheter and rods. To conclude the implant procedure, the titanium PTMA implant hub was closed, sutured to subclavian fascia, the skin closed, and the patient was recovered.

Table 2. Clinical Features of Patients (n=27)

	n	%
Age, y	70.4±9.4	
Age>70 y	14	52
Male gender	15	56
Ischemic	16	59
Nonischemic	11	41
Hypertension	5	19
Previous CABG	10	37
Previous PCI	8	30
Obstructive lung disease	5	22
Atrial fibrillation	10	37
NYHA functional class III	20	74
NYHA functional class II	7	26
BSA>1.85 (m ²) (1.87±0.19)	14	52

CABG indicates coronary artery bypass graft; PCI, percutaneous coronary intervention; BSA, body surface area; NYHA, New York Heart Association.

Postprocedural Evaluation

Patients continued the standard medical care for heart failure without protocol directed changes. Echocardiography, clinical examination, and laboratory assessments were performed at 24 hours post-implantation and at ≈14, 30, 180, and 360 days. Three-dimensional geometric tracing of the mitral valve annulus at end diastole from echocardiographic volume datasets was performed using Tomtec 4D Cardio-View (Tomtec Imaging Systems, GmbH, Germany) software to assess changes in mitral annular geometry. Quality of life and exercise tolerance were performed at 30 and 180 days. Echocardiography was evaluated both by the enrolling centers and by the echocardiography core laboratory (Cleveland Clinic, Cleveland, Ohio). Quantitative echocardiography of TEE procedural images was also performed by the enrolling centers during and after procedures.

Results

Feasibility cases were conducted in 4 groups beginning in April 2006 and continuing through November 2007 as summarized in Table 1. Although the trial design and device description remained essentially constant, each successive group of cases incorporated incremental technical enhancements in the device itself and procedure sequence reflective of first-in-man case experience with a new therapeutic device. In case groups 1, 2, and 3, the stiffness and fatigue properties of the Nitinol PTMA devices were modified to more optimally match the requirements of the human anatomy. During case groups 2, 3, and 4, changes to both the diagnostic and

Table 3. Baseline Echocardiographic Features of Patients (n=27)

LV ejection fraction, %	35.6±10.4
LV end-diastolic volume, mL	108.9±51
LV end-systolic volume, mL	161.1±57
LV end-diastolic diameter, mm	58.2±8.3
Mitral annular dimension A-P diastolic, mm	30±4.6
Mitral annular dimension A-P systolic, mm	35±4.5
Effective regurgitant orifice, cm ²	0.21±0.12
Regurgitant volume, mL	32.5±190

LV indicates left ventricular; A-P, anteroposterior.

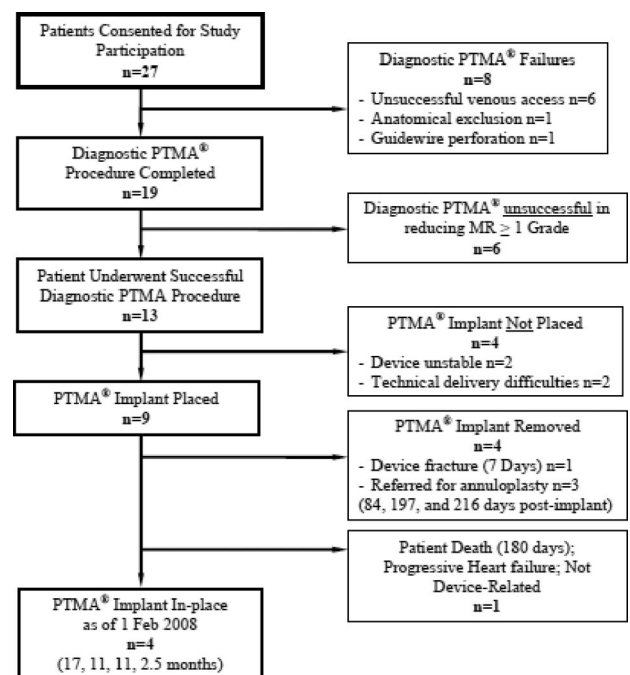
Table 4. Procedure Major Adverse Cardiac Event and Significant In-Hospital Complications (4 of 27 Patients, 29 Procedures)

	n	Procedure %
Death	0	0
MI	0	0
Stroke	0	0
Tamponade	0	0
Emergent surgery	0	0
Subclavicular hematoma	1	3
Pneumonia	1	3
Transient renal dysfunction	1	3
PTMA implant device fracture/removal	1	3
Circumflex stent implantation	1	3
Pericardial effusion (CS access related; no PTMA)	1	3

MI indicates myocardial infarction; CS, centrum semiovale.

implant devices were made to improve the guide wire trackability of the distal tip to improve access to the descending anterior interventricular vein. Finally, in group 4, the implant system was modified to permit up to 15 mm of linear adjustment of the position of the PTMA rods within the implant system via an adjustable proximal hub.

Clinical features of the 27 patients (29 procedures) evaluated for PTMA are shown in Table 2. Age was 70.4±9.4 years. Fifteen (56%) of the patients were men. Sixteen patients (59%) had an ischemic etiology of heart failure and 10 (37%) had undergone a prior coronary artery bypass grafting procedure. Baseline echocardiographic features are shown in Table 3. In the entire cohort, the left ventricular ejection fraction was 35.6±10.4% with an left ventricular end-diastolic diameter of 58.2±8.3 mm. The effective regurgitant orifice area was 0.21±0.12 cm².

**Figure 1. Procedural features and course.**

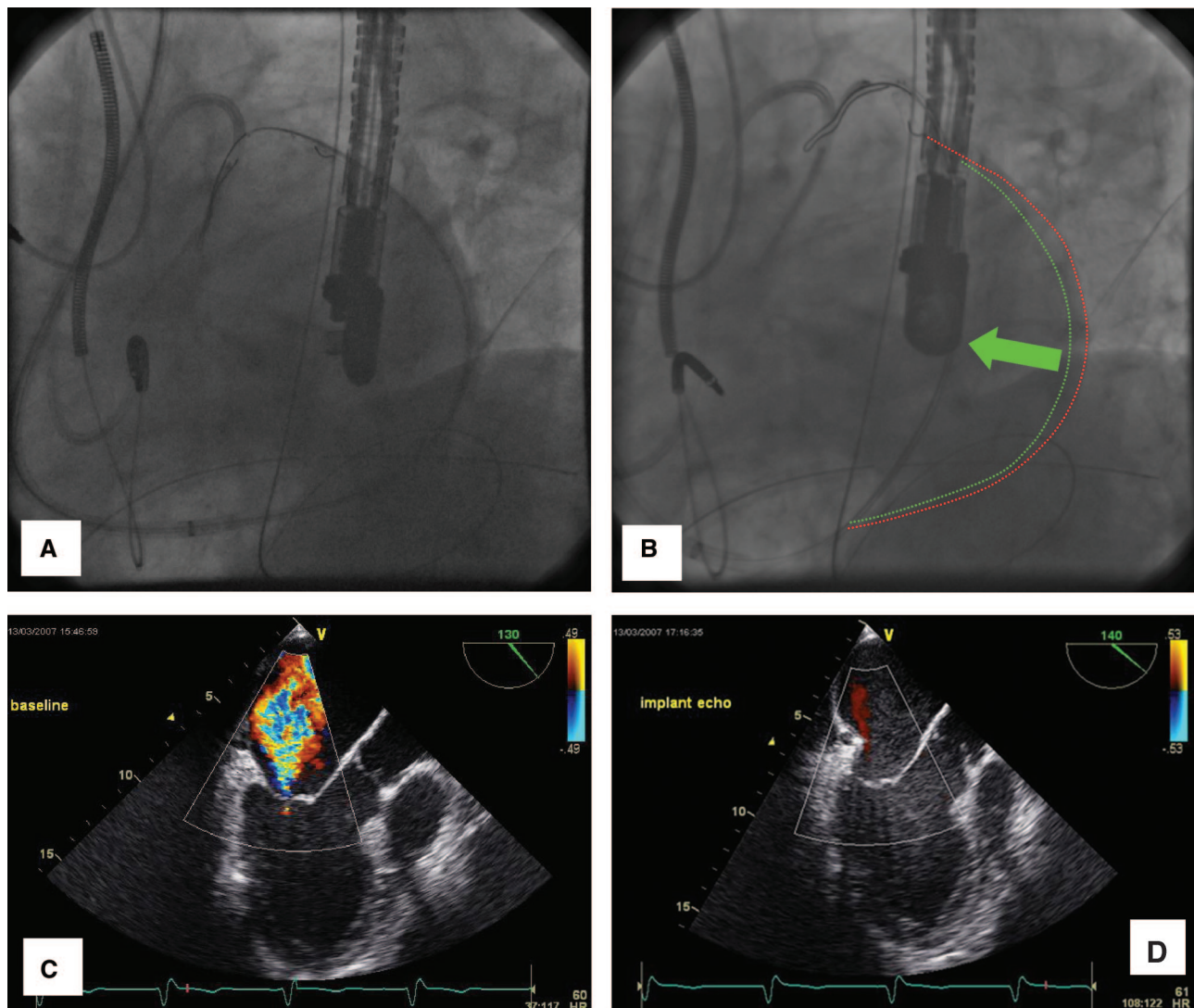


Figure 2. Fluoroscopic images recorded from a left anterior oblique caudal angulation showing the initial PTMA catheter placement without treatment devices (A) and after introduction and optimal positioning of the PTMA Nitinol treatment stiffening rods (B). Echocardiographic images from procedural TEE show a midesophageal long-axis view at procedure baseline (C) and with the PTMA implant device in place (D).

Procedural major adverse cardiac events and significant in-hospital complications are listed in Table 4. None of the device or procedure-related events resulted in permanent sequela. Several events are notable. After placement of the first implant, protocol driven angiography at 60 minutes postimplant suggested a possible circumflex abnormality directly adjacent to the PTMA device without reduction in TIMI grade flow. Intravascular ultrasound was performed. During and subsequent to intravascular ultrasound abrupt vessel closure ensued with ST elevation. The vessel was treated with stent implantation without further clinical event or myonecrosis. In all subsequent cases, including during both diagnostic and implant PTMA, there have been no observations of similar abnormalities or arterial impingement. The one noted event of device fracture and removal also occurred in the first implanted patient. The device was observed via x-ray to have suffered an internal fracture resulting in loss of treatment effect as observed by echo. The

device was percutaneously removed uneventfully under fluoroscopic observation and local anesthesia. The single episode of pericardial effusion occurred during attempts to access the coronary sinus with a commercially available guide wire. The PTMA device was not introduced, pericardiocentesis was performed, and the procedure terminated. Patient recovery was uneventful.

Procedural features and course are shown in Figure 1. A total of 29 catheterization laboratory procedures have been performed in 27 patients. This figure represents the cumulative PTMA experience with the design iterations of the PTMA intention-to-implant device. Anatomy or technical failure to place the diagnostic PTMA device occurred in 29.6% of patients prompting multiple changes in the PTMA device and technique (Table 1). The overall success rate of diagnostic PTMA occurred in 13 of 27 patients (48%). With successful placement of the PTMA diagnostic device, MR was successfully reduced in 13 of 19 patients (68%). Learn-

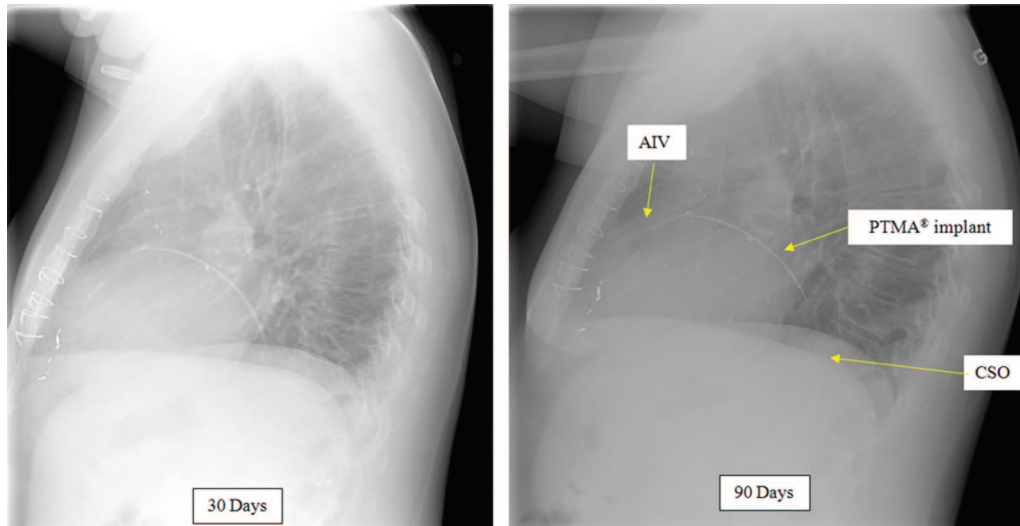


Figure 3. Lateral x-rays taken at 30 and 90 days showing position and shape of the PTMA implant device.

ing curves with both technique and imaging were demonstrated through the improved percentage of cases with successful access and PTMA diagnostic procedures. The diagnostic PTMA procedure time was 138 ± 42 minutes for the entire cohort of patients. The implant PTMA procedure required 35 ± 38 minutes. In 2 patients, the PTMA implant was performed in a procedure separate from a successful diagnostic PTMA demonstrating efficacious reduction in MR. The overall 30-day success rate of implanted PTMA was 8 of 13 (62%) (Table 2).

Sample case fluoroscopic and echocardiographic images are shown in Figure 2. The impact of the device on the mitral annulus can be clearly seen with TEE echocardiography and guides successful placement of the rods. A lateral x-ray of a PTMA implant at 30 and 90 days is shown in Figure 3 demonstrating device stability. Despite efficacious diagnostic PTMA and implant placement, 2 devices migrated sufficiently to be readily observed via echo and x-ray. One of the devices was observed via echo and chest x-ray to have partially dislodged proximally from the coronary sinus, whereas another was observed to have migrated distally within the coronary sinus and great cardiac vein. Along with a third patient with minimal efficacy, all 3 devices were removed by percutaneous approach, and the patients subsequently underwent annuloplasty surgery.

Acute echo results as observed by TEE in 13 patients undergoing diagnostic PTMA with all iterations of the PTMA system are shown in Figure 4. Core laboratory echo composite MR grade progression for the implanted patients from baseline through the latest available follow-up study is shown in Figure 5, including patients who subsequently underwent device removal and surgical mitral valve repair. Figure 6 demonstrates sustained effective remodeling and reduction of the mitral annulus via tracing of the mitral annulus from 3D echo datasets.

Discussion

This report summarizes the first-in-man clinical experience with the PTMA device and the progression of design modi-

fications to improve clinical success and durability in small cohorts of patients. In contrast to other coronary sinus devices using active fixation with stents or other tissue anchors, the PTMA method is based on the application of an elastic bending deformation without the use of discrete anchors or stents. The method is intended to atraumatically diffuse the remodeling forces over the maximum available length of the

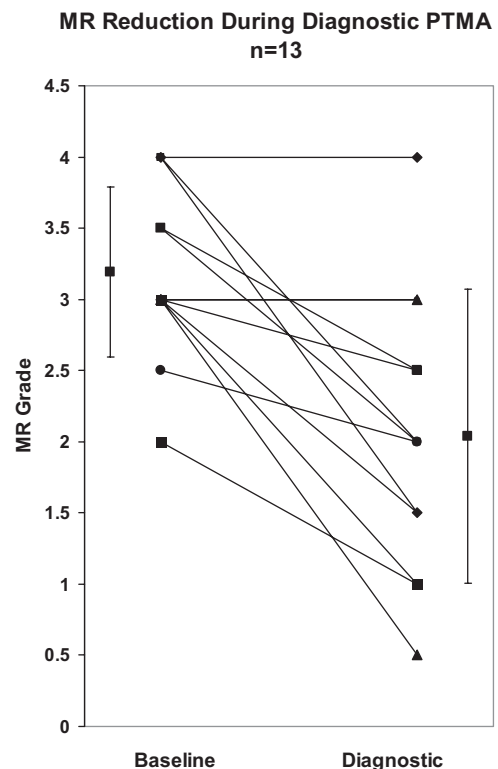


Figure 4. Baseline (MR grade 3.2 ± 0.6) and best diagnostic procedure result (2.0 ± 1.0) for 13 of the 19 diagnostic PTMA cases. In the remaining 6 cases, TEE data were unavailable or unusable, primarily due to either image quality or hemodynamic variations; in 4 of the 6 cases, PTMA was considered ineffective, and in the remaining 2 cases, only modest impact on MR was observed.

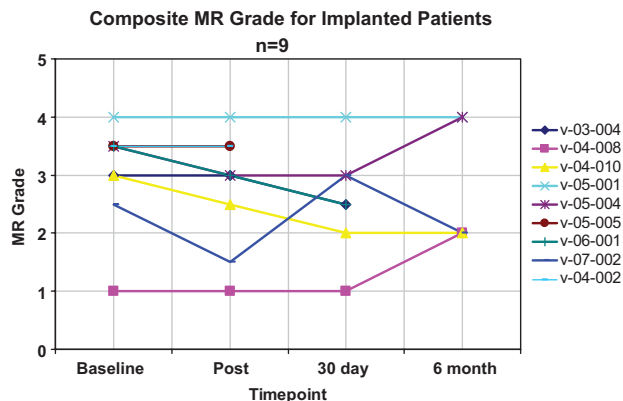


Figure 5. Core laboratory composite TTE echo grading for the 9 patients receiving PTMA implants. Patient v-04-008 was graded 2 to 3+ baseline by center-administered TEE examination. PTMA implants in patients v-07-002, v-05-004, and v-05-005 were uneventfully removed percutaneously before annuloplasty surgery. In patients v-07-002 and v-05-005, the PTMA device was observed via echo and fluoroscopy to have migrated out of the implanted position within the venous continuity.

coronary venous continuity so as to minimize the likelihood of arterial impingement or tissue erosion. Given the known geometric complexities of the relevant mitral anatomy, the PTMA clinical and technical approach is intended to allow for iterative observation, learning, and device development. Deflection of the device and the anatomy can be observed via echocardiography and fluoroscopy, combined with MDCT data, providing quantified input data to guide improvement of the device characteristics. These principles have been extensively modeled in relevant, though imperfect, animal models.^{29,30}

Procedural and Implant Considerations

As has been previously reported, coronary venous anatomy and the adjacent mitral apparatus are highly variable.^{32,33} The primary end point for this feasibility study is safety; procedure decisions were thus taken with considerable caution. As the device is removable at any point, in the event of clinical uncertainty, procedures were discontinued and no implant devices placed.

Variability in the anatomy of the coronary venous system, including tortuosity and narrow diameters, and also the

structural interrelation with the mitral apparatus, was appreciated to impact both deliverability and stability of the PTMA device. Retrograde venography is limited in its utility in reliably guiding anterior vein subselection. Multidetector computed tomography utilization in screening to demonstrate continuity of the coronary venous system and coregistration with fluoroscopic images improved technical success and proved a valuable asset to the procedure.^{34,35} Successive device iterations improved PTMA device deliverability, particularly the most recent change to 0.035-in guide wire compatibility on the diagnostic and implant devices.

The implants that have achieved stable results chronically as shown in Figure 6 were placed somewhat distal of the CSO, thus sacrificing maximum geometric efficacy for chronic stability. Current device improvements are directed toward adjusting the stabilizing properties of the PTMA system to facilitate increased geometric efficacy with a stable device.

Arterial impingement with coronary sinus mitral repair devices has been a significant concern raised by multiple authors.^{23–27,32} We have only experienced the one described event treated with circumflex stenting. No evidence of arterial impingement was observed in any of the subsequent cases in this cohort. This result may be due to the design of PTMA device, which is exerting generally diffuse and outboard pressure in the vicinity of typical circumflex coronary cross-over. Given the close relationship and highly variable nature of the venous and arterial courses and the close proximity and significant elastic stiffness of the PTMA device, possible arterial interaction will continue to be carefully evaluated both during screening diagnostic and interventional procedures.

PTMA requires successful long-term engagement of the coronary venous continuity relying on the structural integrity of the PTMA nitinol rods and anatomic stability of the PTMA device for long-term effect. Initial results from other mitral annular remodeling devices have highlighted the concerns regarding the durability challenges for structural implants placed in the coronary venous continuity,²⁶ as have the results for surgical annuloplasty^{36,37} and biventricular pacing.^{38,39} The first PTMA implant was accompanied by Nitinol fracture within the first 72 hours requiring explant. Fatigue and design properties of the Nitinol were modified as were the durability

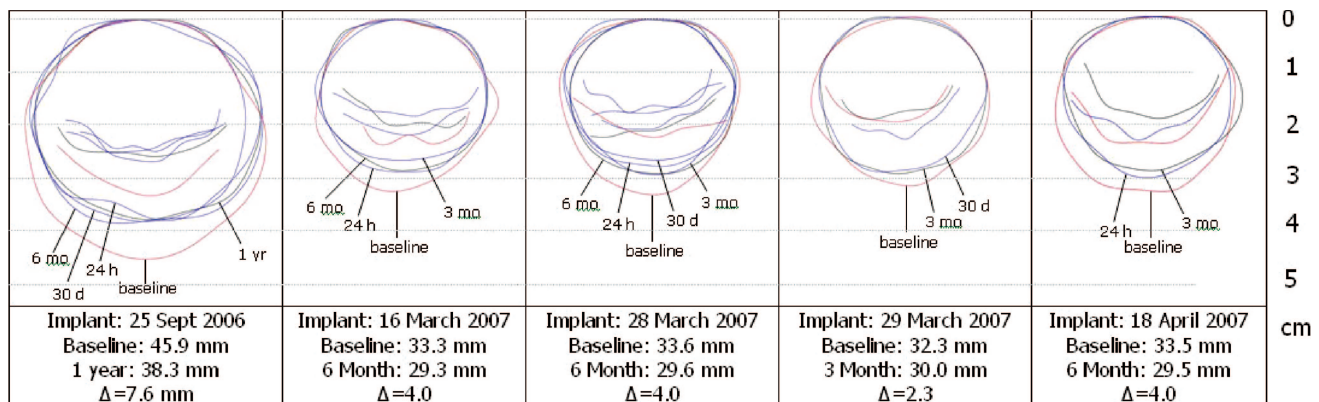


Figure 6. Core laboratory tracings of the mitral annulus and leaflet line of coaptation from 3D echo data sets recorded at preprocedure baseline and follow-up time points noted from patients with PTMA implants still observed by x-ray to be in place. Actual tracings are full 3D datasets that also capture full contour information (eg, the “saddle shape” character of the annulus).

test criteria and implant procedures. Subsequent long-term implants have not evidenced any structural failures.

Evidence for Effect

In this initial series, particularly in cases where the patient characteristics and device placement were favorable, significant acute geometric reductions of mitral annular septal-lateral dimension and associated MR have been observed. Surgical experience suggests that a septal-lateral annular reduction of at least 8 mm is typically required for a successful repair in a straightforward case.^{28,40} Multiple cases in this series have acutely demonstrated corrections of this magnitude (Figure 3). However, the aggregate sustained reduction of the septal-lateral dimension of the mitral annulus (Figure 6) has been less than the typical surgical correction. Not surprisingly, the associated late reductions of MR have been similarly modest. Further examination of the clinical efficacy of this anatomic effect as correlated to MR, chamber volumes, and clinical outcomes requires further study because the clinical efficacy of a partial correction may have limited benefit in a broad range of patients. Thus, speculation as to the clinical impact of the PTMA device in its early form is premature.

Study Limitations

The number of patients enrolled so far has been small and the iterative nature of the investigation limits the generalizability of the results. The protocol and device continues to undergo fundamental improvements. Long-term efficacy and safety remain unknown, including implications for subsequent procedures such as cardiac pacing and retrograde cardioplegia, although successful mitral annular surgery after PTMA implant demonstrates PTMA does not appear to limit surgical options for patients.

Conclusions

This initial case series suggests that it is feasible and safe to access and geometrically modify the mitral annulus with this fully reversible, implantable coronary sinus device. The initial safety results are acceptable. The magnitude of treatment effect observed in implanted patients likely must be increased to provide a significant clinical benefit for a meaningful subgroup of patients. This experience warrants further investigation to optimize treatment effect and elucidate the clinical impact on patients with functional MR.

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Disclosures

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