

Coronary Sinus Annuloplasty for Mitral Regurgitation

A look at several devices with the ability to reduce functional mitral regurgitation.

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The term *functional mitral regurgitation* (MR) is used to describe leaking of the mitral valve as a secondary process, that is, not due to inherent abnormalities in the mitral valve apparatus. This may occur in patients with dilated cardiomyopathies due to dilation of the mitral annulus, as well as from other mechanisms such as tenting of the papillary muscle in patients with an ischemic etiology of their cardiomyopathy. There is some looseness to the use of the term, as it sometimes, but not always, includes ischemic MR.

Additionally, secondary MR due to an ischemic etiology may or may not be associated with global left ventricular dilation, or may exclusively be due to papillary muscle tethering or dysfunction. However, studies looking at functional MR in association with a nonischemic dilated cardiomyopathy, an ischemic cardiomyopathy, or a combination of the two, have all identified that functional MR is associated with increased mortality,¹⁻⁵ worsening hemodynamic parameters,^{3,6} and a higher likelihood of symptomatic congestive heart failure, as well as poorer functional classification.³ These less favorable clinical parameters have even been shown to be present when the MR is mild. Additionally, it is likely that the presence of resting MR is just the tip of the iceberg because several studies have shown that patients whose functional MR worsens with exercise are more

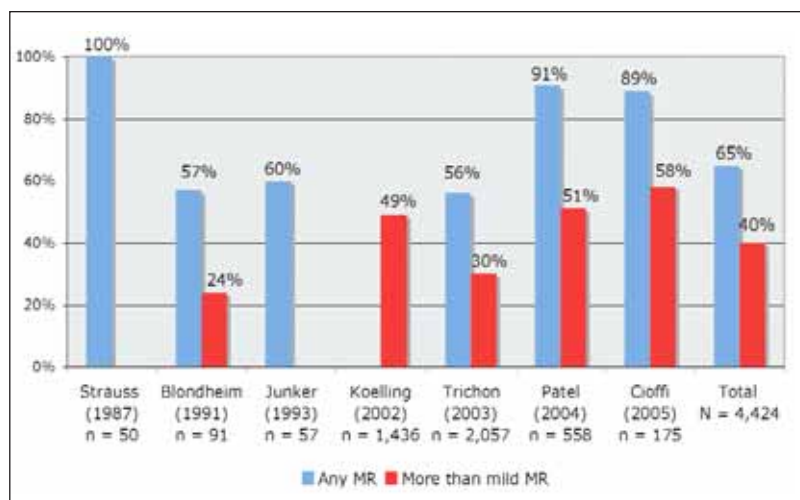


Figure 1. Prevalence of functional MR in patients with congestive heart failure.

likely to have symptoms and a worsened prognosis compared to those whose MR does not worsen with exercise.⁷⁻¹¹

Functional MR is surprisingly common, occurring in approximately 65% of patients with dilated cardiomyopathies, with more than 40% having more than mild MR (Figure 1).^{1-6,12,13} Because congestive heart failure is so prevalent, the incidence of functional MR may therefore be estimated as being perhaps 10 times greater than the incidence of organic mitral or aortic valve disease.¹⁴⁻¹⁶

However, functional MR is underappreciated in patients with congestive heart failure and/or cardiomyopathy. Part of the reason for this is likely due to a lack

of therapeutic options. Classic hemodynamic theory suggests that in the failing left ventricle, MR acted as a “pop-off,” and that closing the pop-off by surgically repairing the MR would lead to further left ventricular failure.¹⁷ Bolling and others¹⁸⁻²⁰ have discounted this theory by showing that there can be hemodynamic benefits by reducing the volume overload resulting from MR. This can be accomplished surgically by placing an undersized ring into the mitral annulus, reducing annular size, and improving leaflet coaptation. However, this therapy has not yet been assessed by a prospective, controlled, randomized trial using carefully defined end-points, and therefore, has not become the standard of care (or supported by guidelines) for patients with symptomatic functional MR, with the exception that it is commonly performed when patients are undergoing coronary artery bypass graft surgery to treat an ischemic etiology of cardiomyopathy.²¹

DEVICE TECHNOLOGY

Part of the reluctance to surgically treat the mitral valve of patients with functional MR is the recognition that these patients are at high surgical risk given their underlying cardiomyopathy. Therefore, it is attractive to consider a less-invasive therapy to treat the functionally incompetent mitral valve. There is a great variety of innovative therapies that have been proposed. Several of these have taken advantage of the close anatomical relationship of the coronary sinus/great cardiac vein to the posterior mitral annulus (Figure 2). Blood that supplies the heart via the coronary arteries returns to the venous system by way of venous drainage, which coalesces into the great cardiac vein. This vein lies in the posterior atrioventricular groove between the left atrium and left ventricle. The great cardiac vein becomes the coronary sinus, which drains into the right atrium. The great cardiac vein/coronary sinus is located slightly more on the atrial side of the atrioventricular groove, which is slightly superior to the mitral annulus. Several therapeutic approaches have proposed placing a device within the coronary

sinus/great cardiac vein to place some force on the mitral annulus, reduce the septal-lateral diameter of the mitral annulus, and/or cinch the mitral annulus. One of these therapies, the P3 system (Ample Medical, Inc., Foster City, CA),²² has stopped investigations, but three other companies have ongoing clinical research programs evaluating the Monarc device (Edwards Lifesciences, Irvine, CA), the Percutaneous Transmitral Annuloplasty (PTMA) device (Viacor, Inc., Wilmington, MA), and the Carillon Mitral Contour System (Cardiac Dimensions, Inc., Kirkland, WA).

Some of the considerations that each company has faced in evaluating this therapy include: how to get the device to provide tension on the system without slipping or fracturing; what is the force and degree of tension applied to the mitral annulus and how does that relate to efficacy in reducing MR; and how to avoid compromising coronary arteries that also run in the atrioventricular groove, specifically, the circumflex coronary artery and its branches. Although the various companies addressed these issues somewhat differently, they

each have required device iterations upon initially testing the devices in humans. Much of the data that are available at this time reflect the early evaluations of these therapies, while investigators are exploring early safety and efficacy, and identifying needs for device improvements. Therefore, the available data may be viewed as hypothesis-generating, providing information that justifies further study.

The Monarc device²³ is composed of two self-expanding nitinol stents with a connecting bridge. Within the bridge are dissolvable spacers. At body temperature, the spacers slowly dissolve, leading to a foreshortening of the bridge and creating a reductive force on surrounding structures. The distal stent is designed to be placed within the anterior interventricular vein, which is the tributary vessel of the great cardiac vein that is furthest from the coronary sinus, running near the ventricular septum. The proxi-

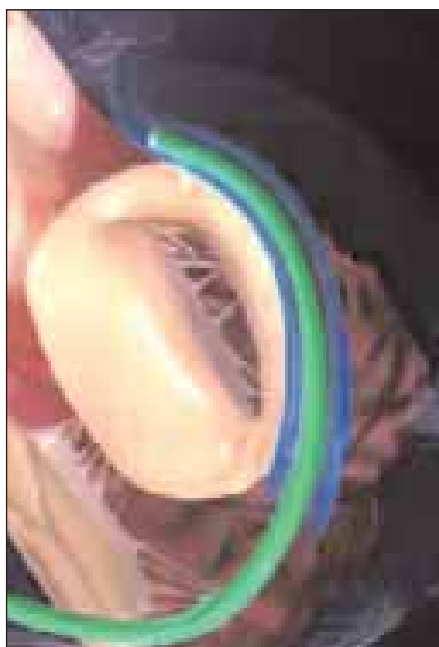


Figure 2. Schematic of the relationship of the coronary sinus/great cardiac vein to the posterior annulus of the mitral valve. In this schematic, a catheter (which may enter from the internal jugular or subclavian veins) has been placed into the coronary sinus and advanced into the great cardiac vein nearly to the anterior interventricular vein (the termination of the great cardiac vein).

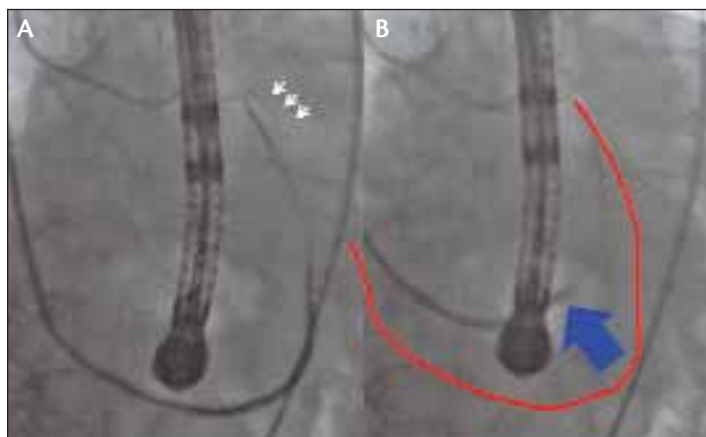


Figure 3. The Carillon device has been placed in the coronary sinus with a distal anchor (white arrows) deployed in the distal part of the great cardiac vein (A). After tension has been applied, the cinching force (blue arrow) directed to the posterior mitral annulus may be appreciated (B). The red line in part B is a recreation of the device curvature seen in part A before tension was applied. After tension was applied, a proximal anchor was deployed to maintain the tension. After this has been done, the efficacy and safety of the device can be assessed and the device released.

mal stent is placed in the coronary sinus. Thus, as the spacers in the connecting bridge dissolve, a foreshortening force is created with the intention of cinching the mitral annulus.

The PTMA device²⁴ is composed of a catheter that is placed via the right subclavian vein through the coronary sinus/great cardiac vein into the anterior interventricular vein distally, with the proximal aspect left in a pocket next to the subclavian vein, similar to a pacemaker. One to three stiffening rods can be placed into this catheter to push the great cardiac vein in, thereby reducing the septal lateral diameter. The decision about how many stiffening rods to place may be made based on efficacy, as well as the impact on coronary arteries.

The Carillon Mitral Contour System is composed of two self-expanding nitinol stents with a titanium curvilinear bridge. It is placed via the right internal jugular vein, with the distal anchor placed in the great cardiac vein. Manual tension is then applied, with delivery of a proximal anchor into the coronary sinus (Figure 3). This device is recapturable and removable until it is released, which may be done if there is inadequate efficacy in reducing MR, or if there is coronary artery compromise.

STUDY RESULTS

The Monarc device was tested in the EVOLUTION I study, which was a feasibility study. This study was not designed to formally address clinical efficacy endpoints,

although some data are available in a subset of patients. In the 72 patients enrolled, 59 received implants, with anatomic reasons limiting implants in the rest. All the patients had cardiomyopathy with 2–4+ MR, with 57% symptomatic. The results of the first five patients were published because this demonstrated proof of efficacy.²⁵ Four of these five patients received a device, and reduction in MR was seen in three of the four patients acutely. In these three patients, bridge separation occurred with return of MR. Thus, this therapy demonstrated effectiveness when the device was intact, and showed a lack of efficacy with loss of integrity. The device has since been redesigned to avoid separations. Data have recently been presented on 2-year efficacy in a subset of patients with available data. In 21 patients, the MR grade was reduced from a mean of 2.3 to 1.9 at 2 years ($P = .1$), and in 24 patients, the New York Heart Association (NYHA) classification was reduced from 2.7 to 2 at 2 years ($P = .002$). Using quantitative assessments of MR, there appeared to be little

deterioration from 1 to 2 years. A larger clinical study, EVOLUTION II, has been initiated in Europe.

The PTMA device has primarily been tested acutely, with only a few patients receiving a permanent implant. However, several patients have received a device with immediate reduction in MR.²⁶ In the few patients with permanent implantation, a reduction in mitral annular dimensions was demonstrated and persisted without change over several months. A finalized version of this device is now being tested in Europe in the PTOLEMY II registry.

The Carillon Mitral Contour System has been studied in the European AMADEUS study.²⁷ This study looked at symptomatic patients with dilated (ischemic and nonischemic) cardiomyopathy, depressed left ventricular ejection fraction, and 2–4+ MR as assessed by an echocardiographic core lab. Implantation of the Carillon device was attempted in 48 patients, with 29 receiving implants. Reasons for nonimplantation included distal anchor slipping of an early version of the device (resolved with minor redesign), inability to access the coronary sinus/great cardiac vein, insufficient reduction in MR, and/or coronary artery compromise. Although coronary arteries were crossed in 84% of cases, coronary artery compromise limited implantation in 15%. There were three non-ST-elevation myocardial infarctions in this study. In one, the event was clinically relevant, but no clear obstruction was observed. This

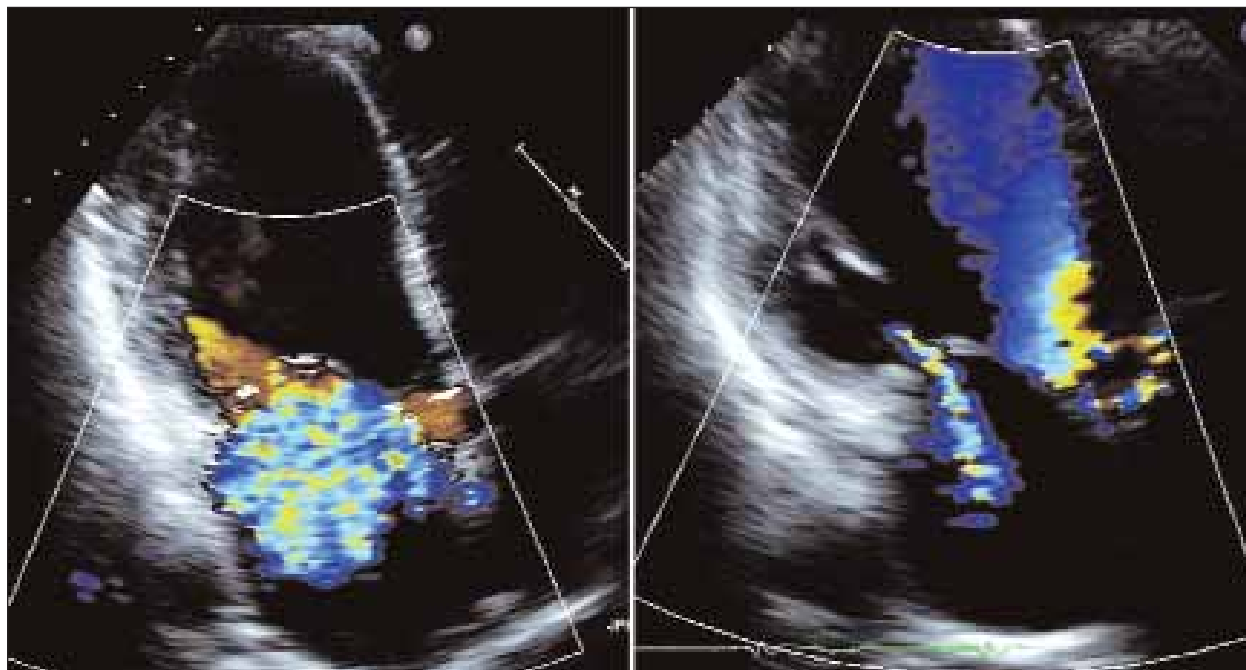


Figure 4. Color Doppler echocardiograms before (right) and 1 month after (left) implantation of a Carillon device, demonstrating a marked decrease in MR.

patient developed worsening renal failure and died 3 weeks later; this was the only procedural (within 30 days) death of the study. The overall 30-day major adverse event rate was 13%, which appears to be acceptable because in this high-risk cohort, there is a > 20% predicted 1-year mortality rate, and half of the complications were related to vascular access. It is of note that a subsequent European study (TITAN) has completed enrollment, and there was only one 30-day complication in the 53 patients enrolled, providing a major adverse event rate of < 2%.

In AMADEUS, efficacy was assessed using a variety of modalities. MR was assessed by a core lab using quantitative assessments. Overall, in AMADEUS, there was a 27% quantitative reduction in MR (Figure 4). Clinical parameters improved as well. At baseline, 88% of patients were in NYHA class III or IV, whereas at 6 months, only 12% of patients receiving an implant were in NYHA class III or IV. There were marked improvements in functional capacity, as assessed by 6-minute walk tests, as well as in quality-of-life tests.

CONCLUSION

Several devices using the coronary sinus access as a means to reduce mitral annular dimensions have demonstrated the ability to reduce functional MR and the proof-of-concept that this approach is feasible. Ongoing studies are being performed to further assess

the safety and efficacy of this approach. Early evaluations have been favorable, with meaningful clinical impact justifying further trials. A pivotal randomized trial of the Carillon Mitral Contour System is currently under design, comparing a treated group to a control group of patients. ■

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