Feasibility and Short-Term Efficacy of Percutaneous Mitral Annular Reduction for the Therapy of Heart Failure–Induced Mitral Regurgitation

David M. Kaye, MBBS, PhD; Melissa Byrne, BSc, BApp Sc; Clif Alferness, BE; John Power, BVSc, PhD

Background—Mitral regurgitation (MR) frequently accompanies congestive heart failure (CHF) and is associated with poorer prognosis and more significantly impaired symptomatic status. Although surgical mitral valve annuloplasty has the potential to offer benefit, concerns about the combined surgical risk and possible effects on ventricular performance have limited progress. We evaluated the feasibility and short-term efficacy of a novel device placed in the coronary sinus to reduce MR in the setting of CHF.

Methods and Results—CHF and MR were induced in 9 adult sheep by rapid ventricular pacing for 5 to 8 weeks. A mitral annular constraint device was implanted percutaneously through the right internal jugular vein in the coronary sinus and great cardiac vein to create a short-term stable reduction (24.9±2.5%) in the mitral annular septal–lateral dimension as assessed echocardiographically. Right and left heart pressures and cardiac output were determined before and 15 minutes after device implantation. MR extent was examined echocardiographically and expressed as a ratio of left atrial area (MR/LAA). After device placement, MR was substantially reduced from an MR/LAA of 42+6% to 4±3% (P<0.01). In association, mean pulmonary wedge pressure was significantly reduced (26±3 to 18±3 mm Hg; P<0.01) and mean cardiac output significantly increased (3.4±0.3 to 4.3±0.4 L/min; P=0.01).

Conclusions—In this model of CHF, percutaneous placement of a mitral annular constraint device in the coronary sinus resulted in the short-term elimination or minimization of MR and was accompanied in the short term by favorable hemodynamic effects. (Circulation. 2003;108:1795-1797.)

Key Words: regurgitation ■ heart failure, congestive ■ catheterization ■ mitral valve

Mitral regurgitation (MR) frequently accompanies congestive heart failure (CHF). The precise mechanism is controversial and can relate to mitral annular dilatation or tethering of the leaflets secondary to progressive ventricular remodeling.1–3 Once established, MR plays a pivotal role in the pathophysiology of CHF. Several studies have shown that the presence of MR in patients experiencing CHF is associated with poor outcome.4,5 Although this observation could suggest that MR is merely a marker of CHF severity, it is also increasingly apparent that the development of MR hastens the progression of CHF.6,7 Although the precise mechanism for the relationship between the presence of MR and CHF progression remains somewhat uncertain, many potential mechanisms could be proposed. These include the hemodynamic overload imposed by MR per se, in addition to the activation of cardiac sympathetic nerves8 and proinflammatory cytokines such as tumor necrosis factor-α,9 which could also influence the outcome of CHF.10,11 The presence of functional MR in CHF also contributes substantially to the development of symptoms. During exercise, load-dependent increases in regurgitant fraction develop in conjunction with substantial elevations in pulmonary arterial pressures and blunted forward cardiac output responses.12

In CHF without primary valvular pathology, various therapeutic approaches have been used, including pharmacological and surgical approaches. To date, the full potential role of anatomic intervention on the mitral valve in CHF has been limited in most centers by virtue of the relatively high associated operative mortality rate.13 Nevertheless, recent data suggest that in patients with moderate to severe symptoms of CHF, surgical correction of MR can provide long-term benefit.14 Most typically, this is achieved by placement of an annuloplasty ring in an effort to reduce the mitral valve annulus and to improve coaptation of the valvular leaflets.

Given concerns about the mortality associated with primary mitral valve surgery in CHF, we have developed a...
strategy for the percutaneous insertion of a device placed in the coronary sinus (CS) and great cardiac vein that could be used to reduce MR in the setting of CHF.

Methods

Induction of Dilated Cardiomyopathy and MR

Pacemakers, reprogrammed for high-rate pacing, (Sigma, Medtronic Inc) and right ventricular pacing leads were implanted in 9 adult sheep. After recovery, animals were paced at 190 bpm for between 5 and 8 weeks until MR of at least moderate severity had developed as assessed by echocardiography (Cypress, Acuson).

Device Implantation and Hemodynamic Assessment

On the day of device implantation, the pacemaker rate was reduced below the underlying native rhythm. Approximately 30 minutes later, the animals were anesthetized with bolus propofol (4 mg/kg intravenously) followed by a continuous intravenous infusion of 15 mg/kg ketamine per hour and 30 mg/kg propofol per hour in conjunction with positive pressure ventilation. All animals were placed in the left lateral decubitus position and underwent transthoracic echocardiography. Left atrial cross-sectional area and mitral annular dimensions were measured in the parasternal long-axis view. The extent and area of the regurgitant jet was assessed using color Doppler echocardiography. A 9F introducer sheath was subsequently positioned in the right internal jugular vein. A flow-directed thermistor catheter (Swan-Ganz, Baxter-Edwards) catheter was positioned for the determination of pulmonary arterial pressures and cardiac output. An 8F guide sheath containing the device was subsequently placed in the CS and advanced along the great cardiac vein to the level of the anterior interventricular vein. A novel mitral annular constraint device (Figure) was then placed in the CS/great cardiac vein. The device is constructed of nitinol wire with distal and proximal anchors connected by an intervening cable. The distal anchor was first deployed from the guide sheath into the distal great cardiac vein and locked in position. Tension was then applied to the device such that there was a reduction in the underlying mitral annular diameter of ~25%. The tension was maintained while the proximal anchor was deployed into the body of the CS and locked in position. The echocardiographic and hemodynamic assessments were then repeated.

The investigation conforms with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 82-23, revised 1996).

Echocardiographic and Hemodynamic Effect of Mitral Annular Constraint

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Implantation</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral annular diameter, cm</td>
<td>4.17±0.14</td>
<td>3.24±0.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MR:LA area, %</td>
<td>41.9±6.4</td>
<td>41.1±2.8</td>
<td>0.003</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>3.4±0.3</td>
<td>4.3±0.4</td>
<td>0.01</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>26±3</td>
<td>18±3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PAP mean, mm Hg</td>
<td>31±2</td>
<td>25±2</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

MR:LA area indicates ratio of mitral regurgitant jet to left atrial area; PCWP, pulmonary capillary wedge pressure; and PAP, pulmonary artery pressure.

Statistical Methods

Data are presented as mean±SEM. Within-subject responses were analyzed using a paired t test. A probability value <0.05 was considered statistically significant.

Results

The CS was successfully cannulated in all cases, allowing placement of the annular support device in all cases. Before device placement, the mitral regurgitant jet area exceeded 20% of the left atrial area in all animals. After device positioning, there was a significant reduction in the mitral annular dimension and in the extent of MR (Table). Furthermore, MR was absent in 7 of the 9 animals, with only trivial MR in the remaining 2 animals. In conjunction, with the echocardiographic findings, the mean cardiac output increased significantly (Table), and this was accompanied by a significant short-term reduction in pulmonary capillary wedge pressure (Table). During the deployment period, no atrial or ventricular arrhythmias occurred and the arterial blood pressure remained unchanged (data not shown). No episodes of CS perforation or dissection occurred.

Discussion

Several studies now indicate an association between the presence of MR with poor outcome and worse functional status for patients with CHF. Although pharmacological15–17 and possibly biventricular pacing–based18 strategies have shown some capacity to alleviate MR in patients with CHF, their effect is usually incomplete. Although surgical approaches to the reduction of MR associated with CHF have been reported,13,19 concern persists in relation to the high mortality rate that accompanies surgery in patients with severe heart failure and in relation to concerns over the short-term hemodynamic effect of alleviating MR in the setting of a failing ventricle.

The present study was performed in a well-characterized model of CHF, in which the major cause of MR has been previously shown to be annular dilatation and subsequent loss of leaflet coaptation.1 As a corollary, further studies will focus on determining whether this novel approach is applicable to MR that accompanies other forms of cardiomyopathy, particularly that resulting from ischemic heart disease.

Study Limitations

In the present study, we only evaluated the short-term hemodynamic effects of percutaneous mitral annular reduction in an experimental model in which MR developed...
secondary to pacing-induced left ventricular dilatation. Accordingly, we cannot comment about the long-term efficacy of this therapy alone, or in comparison to medical or surgical therapy for heart failure–associated MR. In this study, we used a relatively short-term model of MR, and device deployment was accompanied by significant reductions in both wedge pressure and pulmonary artery pressure. In the setting of chronic severe MR, it is conceivable that chronic increases in the pulmonary vascular resistance could limit the reduction in pulmonary artery pressure. The significance of this remains unclear because chronic remodeling of the pulmonary vasculature could occur some time after reduction of MR. Nevertheless, the hemodynamic benefit that we observed in the present study resulted in a similar improvement in cardiac output as that seen chronically with surgical mitral annuloplasty.20

Conclusion
We have shown for the first time that placement of a mitral annular constraint device in the CS has the potential to substantially reduce MR in an experimental model of dilated cardiomyopathy. This was well tolerated in the short term and accompanied by favorable hemodynamic effects. Further detailed studies are required to evaluate the tolerability and effectiveness of this novel therapy on left ventricular function in the long term.

Acknowledgment
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References
7. Trichon BH, O’Connor CM. Secondary mitral and tricuspid regurgitation accompanying left ventricular systolic dysfunction: is it important, and how is it treated? Am Heart J. 2002;144:373–376.
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