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# Ex Vivo Study of Altered Mitral Apparatus Geometry in Functional Mitral Regurgitation

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## ABSTRACT

**Background:** Functional mitral regurgitation (FMR) in patients with ischemic or nonischemic cardiomyopathy has been related to several overlapping factors. In vivo, these factors are very difficult to study independently of dynamic processes, such as ventricular wall motion or annular contraction. We developed an ex vivo left ventricular model that allows independent variations of annular size, papillary muscle (PM) position, and transvalvular pressure. We tested the hypothesis that FMR is a consequence of an altered balance of the tethering and coapting forces acting on leaflets.

**Methods:** Measurements were made on 4 excised porcine valves under physiological pressures and flows. Testing was done by systematically varying annular size and PM position. We evaluated 3 annulus sizes (normal, 15% dilation, and 25% symmetric dilation) by sequentially displacing PMs in lateral, posterolateral, and apicoposterolateral positions.

**Results:** Our results show that annular dilation is a major determinant of mitral regurgitation. Displacement of PMs also affects the regurgitant flow, but to a much lesser degree. Apical and posterolateral PM displacement increases regurgitant flow to a higher degree than isolated lateral or posterolateral displacement. Increased transvalvular pressure decreases regurgitant flow for any given geometric configuration of the mitral valve (MV).

**Conclusion:** Clinically observed pathologic configurations of the MV can be accurately reproduced ex vivo by altering the tethering and coapting forces acting on mitral leaflets. Our results support the mechanism of mitral regurgitation in which increased tethering forces and decreased coapting forces acting on the leaflets create the regurgitant orifice.

## INTRODUCTION

The increased popularity of mitral valvuloplasty has brought about the need for a better understanding of the functional anatomy of the mitral apparatus. The mitral apparatus is a complex 3-dimensional structure composed of an annulus, anterior and posterior leaflets, chordae tendinae, papillary muscles (PMs), and the underlying left ventricular myocardium. All components of the mitral apparatus need to function synergistically to effectively control the blood flow from the left atrium to the left ventricle. A malfunction of any of the components may produce valvular dysfunction (stenosis or insufficiency) and thereby compromise cardiac function.

Functional mitral regurgitation (FMR) is a common complication in patients with ischemic or nonischemic cardiomyopathies. Although it has been thoroughly studied in the last decade, the precise mechanisms of FMR remain to be fully elucidated. It has been related to several overlapping factors: an altered force balance on mitral cusps caused by displacement of PM and/or annular attachments that restrict adequate leaflet coaptation, as well as global ventricular dysfunction with a reduction in the transvalvular pressure for closing the leaflets [He 1997; Nielsen 1999; Espino 2007].

In vivo, these overlapping factors are very difficult to study independently of dynamic processes, such as ventricular wall motion or mitral annular contraction [He 1997]. We developed an ex vivo model of the left ventricle to evaluate the effect of annular size, PM position, and transvalvular pressure on mitral regurgitant flow.

## METHODS

### *Specimens*

Mitral valves (MVs) were dissected together with intact chordae tendinae and PM from porcine hearts obtained from a local abattoir. Porcine hearts were chosen because they proved to be an established geometrical model of a human heart [Kunzelman 1994]. Septolateral and intercommissural diameters of each valve were measured with a digital caliper (Tresna model EC16; Guilin, China) prior to dissection. After dissection from the heart, each valve was first fixed in 2% formalin solution for 10 minutes and then stored in a saline solution at 4°C until tested in a model. All tests were carried out <24 hours after the valves were harvested.

Prior to testing, running Prolene 3-0 suture (Ethicon, Somerville, NJ, USA) was used to sew a valvular annulus to a 2-mm-thick rubber disc by a 10-mm-wide strip of atrial muscle. Eight interrupted pledgeted Ti-cron 2-0 sutures (United States Surgical Corporation, Norwalk, CT, USA) were also placed on the ventricular side of the annular

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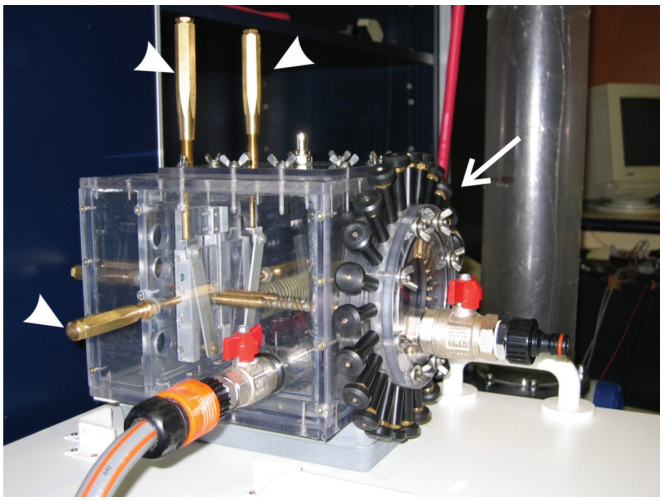

Figure 1. The test chamber. The papillary muscle guiding system (arrowheads) and the annular-dilation guiding system (arrow) are indicated.

circumference and fixed to the annular-dilation guiding system. The mitral annulus was thus suspended and supported by pledgeted sutures in a desired configuration and thereby prevented from changing shape once the test chamber was pressurized. The precise anatomic D shape of the annular attachment on the rubber disc was determined with the MV sizers (Medtronic, Minneapolis, MN, USA) commonly used by surgeons when they perform MV annuloplasty. To prevent possible para-annular leaks, we coated the juncture line between the annulus and the rubber with a thin layer of nonacidic liquid silicone gel.

PMs were sewn on 2 L-shaped metal parts, each with ten 1-mm holes and a spherical groove. These metal parts were used for fixation on the PM-guiding system. To avoid tissue slipping, we wrapped PMs in 0.1-mm-thick soft rubber for support before stitching them to the metal parts.

### *Model Overview*

The measurements were made in a left ventricle model (Figure 1) that was designed specifically for this study. The 2 main components of the model are the water turret used for pressurizing the fluid and the test chamber that holds the valve. The 2 components are linked together with a reinforced rubber tube. Regular water was used to conduct these initial experiments.

**Test chamber.** The test chamber was made out of 8-mm-thick Lexan® and was designed for controlled manipulation of the mitral apparatus—annular dilation and PM displacement—over a range of clinically encountered configurations.

The rubber disc with a sewn-in valvular annulus and the annular-dilation guiding system was mounted to the front wall of the test chamber with 8 holding screws and a 50-mm-thick Lexan spacer. The annular-dilation guiding system was used to change the shape of the mitral annulus by pulling on the Ti-cron sutures. With this system, any desired annular dilation (symmetric or asymmetric) could be achieved (Figure 1).

Two separate sets of guiding systems were mounted inside the test chamber to enable independent lateral, anteroposterior, and apical displacement of both PMs in a 4-cm radius. PMs were attached to the guiding systems simply by attaching the L-shaped metal parts on a swivel joint at the tip of a guiding system. Initially, the PMs were placed in a baseline position that was determined by aligning the tips of the PMs with the coaptation line of the cusps and allowing the leaflets to coapt without any prolapse or apical displacement 5 mm below the annular plane. PMs were then displaced to a desired configuration with PM-guiding systems. Once the valve was mounted, the test chamber was flooded and vented of residual air.

**Water turret**. The water turret was 2.5 m high and also made of Lexan. Its main component was a basal portion with computer-controlled inflow and outflow valves and a connection for a flowmeter (Optiflux 5000 DN4; Krohne Messtechnik, Duisburg, Germany) continuing to a reinforced rubber tube that connected the water turret to a test chamber. The water turret was used to pressurize the water (pressure range, 0-200 mm Hg). A pressure transducer (Peramic CER-8000 B; Klay Instruments, Dwingeloo, the Netherlands) was used to measure the pressure in the test chamber at the level of the MV. The desired pressure was achieved by manipulating the inflow valve (which was connected to the high-pressure water source) and the outflow valve.

**Computer program.** For this study, we designed a special computer program that enabled us to completely automate the experiments and to acquire data in real time. Via a negative-feedback loop, the program was used to control the inflow and outflow valves on the water turret to ensure stable pressure at the level of the MV, regardless of the actual regurgitation. The program also collected data from the flowmeter and the pressure transducer. Data were acquired at a sampling rate of 128 Hz and digitized with a 12-bit analog-to-digital converter. The program is designed for Microsoft Windows (Redmond, WA, USA) and can be run on any personal computer.

### *Experimental Protocol*

The initial experiments were carried out in order to commission the left ventricular model, which we developed specifically for ex vivo studies of the mitral apparatus. Measurements of mitral regurgitant flow were made on 4 porcine valves under static physiological pressures (transmitral pressure, 40-140 mm Hg, at increments of 15 mm Hg). Experiments were performed by systematically varying annular size and PM position. We evaluated 3 annular sizes (normal, 20% symmetric dilation, and 35% symmetric dilation). Computer camera snapshots were used to accurately determine mitral annular geometry and diameters. For each annulus size, PMs were sequentially studied in one of 3 positions (lateral, posterolateral, or apicoposterolateral displacement); we used 2 amplitudes for each displacement, 5 mm and 10 mm.

Our preliminary tests showed that up to 10 measurements could be performed safely and reproducibly on a single valve. We did not exceed this limit for any of the 4 valves tested in our study.

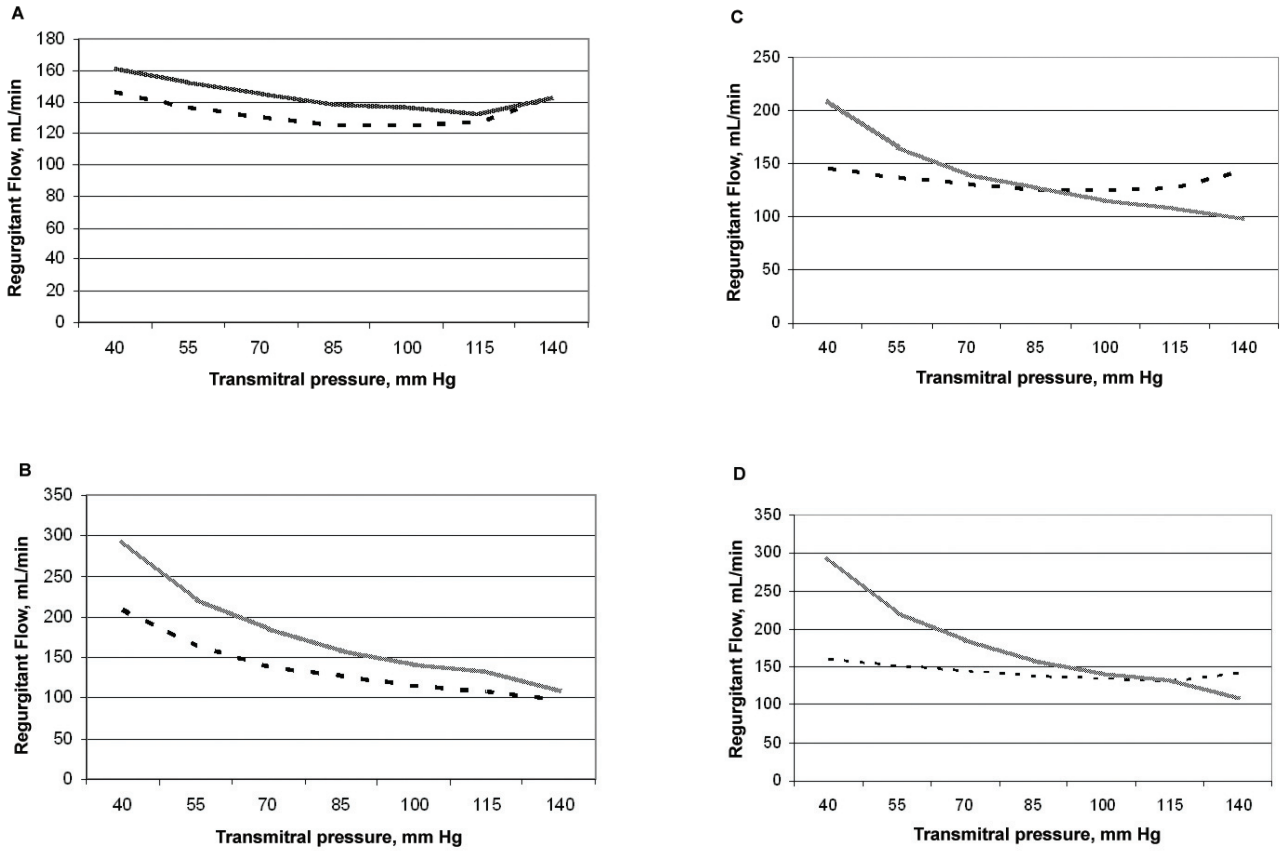


Figure 2. Pressure-flow relationship for different configurations of the mitral valve. The effect of papillary muscle (PM) position on regurgitant flow for a given mitral annular dilation is demonstrated: A, 15% dilation/5-mm PM displacement (dashed line) and 15% dilation/10-mm PM displacement (solid line). B, 25% dilation/5-mm PM displacement (dashed line) and 25% dilation/10-mm PM displacement (solid line). PM displacement does affect mitral regurgitation, but to a lesser extent than mitral annular dilation: C, 15% dilation/5-mm PM displacement (dashed line) and 25% dilation/5-mm PM displacement (solid line). D, 15% dilation/10-mm PM displacement (dashed line) and 25% dilation/10-mm PM displacement (solid line). These data also show that when significant tethering forces are exerted on mitral leaflets, every change in mitral geometry is reflected as a significant change in regurgitant flow. For the purpose of clarity, the data in these figures represent hemodynamic changes recorded for a single valve; however, they are representative of the data obtained for all the valves tested.

Overstretching of the specimens sometimes led to structural damage, such as disruption of the sutures, tearing of the annulus, rupture of the chordae or tearing of the PMs. No further tests were performed on the MV if such damage occurred.

## RESULTS

### *Mitral Annular Dilation*

In our series of experiments, increasing the mitral annular diameters (symmetrical dilatation of the annulus) led to increased regurgitant flows (Figure 2), regardless of the PM position.

### *PM Position*

PM displacement was demonstrated to affect regurgitant flow, but to a lesser degree than annular dilation. In the normal annulus configuration, PM manipulations did not produce regurgitant flow. In the 20% and 35% annular dilation configurations, apicoposterolateral PM displacement increased regurgitant flow to a higher degree than isolated lateral or posterolateral displacement (Figure 2).

We also demonstrated that the effect of PM displacement on regurgitant flow increases with annular dilation: The same PM displacement had a more pronounced effect on regurgitant flow with the 25% annular dilation than with the 15% annular dilation.

### *Transmitral Pressure Gradient*

Increasing the transmitral pressure gradient invariably led to an exponential decrease in regurgitant flow. This effect was observed independently of the annular configuration or the PM position (Figure 2).

Because the primary focus of this study was a proof of concept and because a small number of valves were tested, we have not performed a statistical analysis of our data at this

time. Although the absolute values of regurgitant flow for the same MV configuration were somewhat different for the 4 valves, the trends were the same for all valves. These data are summarized in Figure 2.

## DISCUSSION

FMR occurs as a consequence of regional or global left ventricular dysfunction, despite a structurally normal mitral apparatus. FMR is a common complication in patients with ischemic heart disease or a nonischemic cardiomyopathy. FMR has been shown to increase the long-term risk for adverse events and mortality after surgical valve repair [Blondheim 1991; Tahta 2002].

Several overlapping geometric and hemodynamic factors have been proposed to contribute significantly to the occurrence and severity of FMR, namely dilation of the mitral annulus, tethering of the leaflets by displaced PMs, and ventricular dysfunction through the diminished transmitral pressure to close the leaflets [He 1997; Nielsen 1999; Espino 2007].

Several investigations found evidence to support the leaflet-tethering hypothesis [He 1997; Komeda 1997; Otsuji 1997; Nielsen 1999; Espino 2007]. Interestingly, overlap in mitral annular size has been demonstrated between patients with and without FMR, thus suggesting that other mechanisms apart from mitral annular dilation (such as PM displacement) also play an important role in FMR [Chandraratna 1981; Otsuji 2002]. Left ventricular dilation and left ventricular contractile dysfunction have also been proposed as significant determinants of FMR [Kono 1992; He 1997; Hung 1999].

These mechanisms are very difficult to study, however, and cannot be tested independently in vivo. Few instruments are currently available to test the function of the mitral apparatus ex vivo, mainly because of the technical difficulties involved. To evaluate the effect of annular size, PM position, and transvalvular pressure on FMR, we developed an ex vivo left ventricular model.

Our initial results agree with previously published data and demonstrate that mitral annular dilation is a primary determinant of FMR. Apical and posterolateral PM displacement was shown to increase the regurgitant flow, but to a much lesser extent than annular dilation. In addition, we have shown that an increased transmitral pressure gradient decreased the regurgitant flow for any given geometric configuration of the mitral apparatus (Figure 2).

These results support the mechanism of mitral regurgitation in which increased tethering forces and decreased coapting forces acting on the leaflets are responsible for the creation of the regurgitant orifice and therefore mitral regurgitation.

Any clinical implications of our model must be drawn cautiously. FMR is not a homogeneous entity and can be affected by a wide spectrum of changes, such as global left ventricular dilation, local bulging of the left ventricular wall, left ventricular contractile dysfunction, and changes in mitral annular shape—all of which can affect the geometric relations between different components of the mitral apparatus and thus influence regurgitant flow [He 1997]. FMR can also change significantly with the use of inotropic drugs or loading conditions. The basic interactions between different components of the mitral apparatus remain unchanged, however, and are based on the equilibrium between tethering forces (relationship between annular and PM attachments) and opposing coapting forces (transvalvular pressure).

Our study also suggests that clinically observed pathologic configurations of the MV can be accurately reproduced and studied ex vivo through alteration of the tethering and coapting forces acting on mitral leaflets.

A minor limitation of our study was the use of regular water as a blood surrogate. Given that the current system is an open one (the redundant fluid is discarded), it would not have been feasible to use 0.9% saline or any other blood surrogate. We are, however, already designing a closed, pulsatile ex vivo left ventricular model that will permit us to use a more appropriate surrogate for blood. It will also permit us to better evaluate the dynamic changes of the MV apparatus under different pathomorphologic conditions.

## CONCLUSION

The model we have described enabled us to independently test the mechanisms involved in FMR, both separately and in combination, to demonstrate the multifactorial etiology of FMR. Our preliminary data show that mitral annular dilation is a foremost culprit in FMR. PM displacement and the transmitral pressure gradient also were shown to influence the regurgitant flow, but to a lesser extent. Further studies are warranted to further clarify the pathophysiological mechanisms involved in FMR and to closely analyze their interaction on the different levels of the mitral apparatus.

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