

# Relationship Between Systolic and Diastolic Function with Improvements in Forward Stroke Volume Following Reduction in Mitral Regurgitation

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## Abstract

Efforts to improve mitral regurgitation (MR) are often performed in conjunction with coronary revascularization. However, the independent effects of reduced MR area (MRa) are difficult to quantify.

Using a previously developed cardiovascular model, ventricular contractility (elastance 1-8 mmHg/ml) and relaxation (tau: 40-150 msec) were independently adjusted for 4 grades of MR orifice areas (0.0 to 0.8 cm<sup>2</sup>). Improvements in forward stroke volume (fSV) were determined for the permutations of reduced MRa.

For all conditions, LV end-diastolic pressure and volumes ranged from 7.3-24.2 mmHg and 64.8-174.3 ml, respectively. Overall, fSV ranged from 36.0 - 89.4 (mean: 64.2±12.8) ml, improved between 6.4 and 35.3% (mean: 15.6±8.1%), and was best predicted by ( $r=0.97$ ,  $p<0.01$ ):  $\% \Delta(fSV) = 34 [MRa_{initial}] - 46 [MRa_{final}] - 0.5[elastance]$ .

Reduced MRa, independent of relaxation and minimally influence by contractility, yield improved fSVs.

## 1. Introduction

Chronic mitral regurgitation, particularly in the setting of ischemic heart disease, is independently associated with a poor long-term prognosis. Both the effective regurgitant orifice area and the regurgitant volume have been shown to be the strongest inverse predictors of survival [1]. While there is considerable clinical interest in correcting MR and reducing the accompanying symptoms and potential long-term complications, early attempts at surgical correction with valve replacement were associated with an unacceptably high morbidity and mortality. Consequently, management has been either predominantly medical or, in eligible patients with end-stage heart disease, cardiac transplantation. With advances in surgical techniques and a broader understanding of the pathophysiology of end-stage heart disease, recent reports have suggested surgical treatment of chronic mitral regurgitation at the time of myocardial revascularization can be performed with minimal additional morbidity and/or mortality [2]. However, the

independent effects and potential benefits of surgical reduction in mitral regurgitant orifice areas in these high-risk patients are difficult to quantify.

Advances in numerical modeling of the cardiovascular system allow for exploring complex changes in physiology in a manner that would otherwise be clinically impossible. We sought, using a previously developed and clinically verified numerical model of the cardiovascular system, to better understand the relationship between reductions in mitral regurgitation and the effects on forward stroke volume and other commonly used parameters of cardiac function – namely ejection fraction, end-diastolic pressures and volumes.

## 2. Methods

### 2.1. Numerical modeling

A numerical model of the cardiovascular system was developed based upon fluid dynamics concepts and previous research describing the mathematical relationships of cardiac chamber (atrial and ventricular) systolic and diastolic pressure-volume curves. Our model, written in the LabVIEW (National Instruments, Austin, TX, USA) programming environment, is a lumped parameter, closed-loop model that consist of 24 first order differential equations. These equations are solved iteratively using the fourth-order Runge-Kutta method and results in instantaneous (5 msec intervals) pressures (Equation 1), volumes (Equation 2), and flows (Equation 3) through the heart and cardiovascular system.

$$\text{Equation 1: } \frac{dP_i}{dt} = \frac{(Q_{i-\frac{1}{2}} - Q_{i+\frac{1}{2}})}{C_i}$$

$$\text{Equation 2: } \frac{dV}{dt} = Q_{in} - Q_{out}$$

$$\text{Equation 3: } \frac{dQ_j}{dt} = \frac{P_{j-\frac{1}{2}} - P_{j+\frac{1}{2}} - r_j(Q_j)}{m_j}$$

**Equation Legend:**

C = Compliance            i = Chamber node  
 P = Pressure                j = Flow node  
 Q = Flow                    m = Inertial term  
 V = Volume                 t = time  
 r = Resistance term

The pulmonary and systemic venous and arterial systems were modeled with a linear pressure/volume relationship and compliance.

For the active cardiac chambers, systolic and diastolic pressure/volumes relationships were modeled independently with a chamber specific activation function.

A linear pressure/volume relationship and constant elastance was used for the atria. For the ventricles, a linear P/V relationship was used for systole, whereas diastole was modeled with a rising mono-exponential function above and a negative exponential equation below an equilibrium volume.

Experimentally obtained and clinically verified values for left atrial and ventricular systolic and diastolic parameters were used as constants [3].

The mitral valve was modeled as an orifice defined by an effective orifice area, a resistance to flow, and inertance parameters independently for both the forward (diastolic filling) and reverse (mitral regurgitation) direction of blood flow.

To explore the effects of reductions in mitral regurgitant orifice areas on stroke volume, ventricular contractility (elastance 1-8 mmHg/ml) and the time constant of relaxation (tau: 40-150 msec) were independently adjusted for each of 4 grades of MR orifice areas (0.0 to 0.8 cm<sup>2</sup>). Regurgitant orifice area was modeled based upon areas commonly encountered clinically as described using semi-quantitative echocardiographic techniques (Table 1) [4]. To increase the utility of our findings to clinical practice, these parameters were specifically chosen with emphasis on impaired LV systolic and diastolic function.

Table 1: Echocardiographic Grading of Mitral Regurgitation and Effective Orifice Areas

Echo Grade	Regurgitant Area	Modeled Area
0-1+	<0.1 cm <sup>2</sup>	0.0 cm <sup>2</sup>
2+	0.1 - 0.25 cm <sup>2</sup>	0.2 cm <sup>2</sup>
3+	0.25 - 0.5 cm <sup>2</sup>	0.4 cm <sup>2</sup>
4+	> 0.5 cm <sup>2</sup>	0.8 cm <sup>2</sup>

One hundred conditions were modeled with relative improvements in forward stroke volume (fSV) determined for different permutations of reduced MR areas. Step-wise multivariate regression analysis was used to determine the predictors of optimal stroke volume improvements.

**3. Results**

Table 2 summarizes the wide range of hemodynamics obtained through numerical modeling.

Table 2: Model Data Summary

	Min - Max	Average ± Std
<b>Left Atrial</b>		
Pressure-mean	8.46 - 25.1	16.86 ± 3.96
Pressure-max	14.7 - 40.1	26.64 ± 6.03
Pressure-min	4.17 - 16.36	10.46 ± 3.02
Volume-mean	53.9 - 141.5	97.89 ± 20.7
Volume-max	83.3 - 180.6	133.54 ± 25.3
Volume-min	27.6 - 68.8	50.60 ± 9.89
<b>Left Ventricular</b>		
Ejection Fraction (%)	0.53 - 0.68	0.62 ± 0.04
Pressure-max	59.4 - 141.2	97.41 ± 22.0
Pressure-min	3.00 - 20.52	11.42 ± 4.45
Pressure-mean	25.5 - 46.78	35.34 ± 5.32
Volume-max	78.9 - 174.2	140.63 ± 21.8
Volume-min	18.2 - 100.3	41.32 ± 22.7
End-diastolic pressure	7.33 - 24.24	15.09 ± 3.97
End-diastolic volume	64.7 - 174.2	135.68 ± 26.3
Ejection Fraction	0.18 - 0.76	0.71 ± 0.13
Stroke Volume	35.9 - 89.41	64.19 ± 12.7
Regurgitant Volume	0.00 - 8.00	3.61 ± 2.95
<b>Systemic Pressures</b>		
Mean	49.3 - 99.96	73.26 ± 13.2
Systolic	60.4 - 120.3	89.90 ± 15.8
Diastolic	39.2 - 78.34	57.83 ± 10.2

Note: All pressures are in mmHg and volumes are in ml.

**3.1. Effects of reduction in mitral regurgitant orifice areas**

Stepwise and multivariate regression analysis demonstrated that the strongest predictors of the relative improvement in forward stroke volume was defined by the following equation:

$$\% \Delta fVS = (34.0 [\text{initial MR area}] + (-46.0 [\text{final MR area}] + (-0.46 [\text{elastance}]) - 4.9$$

By using the above equation, a strong correlation (r=0.97, p < 0.001) was observed between the predicted and the actual, model derived, percent improvement in forward stroke volume for all permutations of reductions in mitral regurgitant orifice areas (Figure 1).

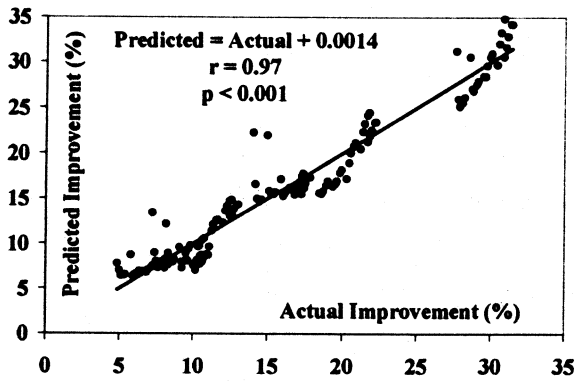


Figure 1: A strong correlation is observed between the actual and predicted improvement in forward stroke volume when using the equation derived from multivariate regression analysis

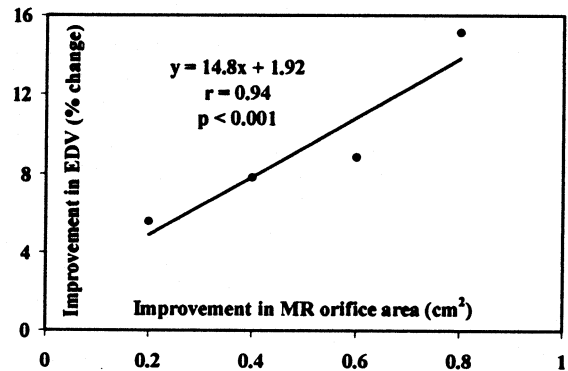


Figure 3: Reduction in mitral regurgitant (MR) orifice areas correlated linearly with improved end-diastolic volume (EDV)

When considering the minimal influence of elastance, overall, a strong relationship was observed between the reduction in mitral regurgitant orifice area and the improvement in forward stroke volume (Figure 2).

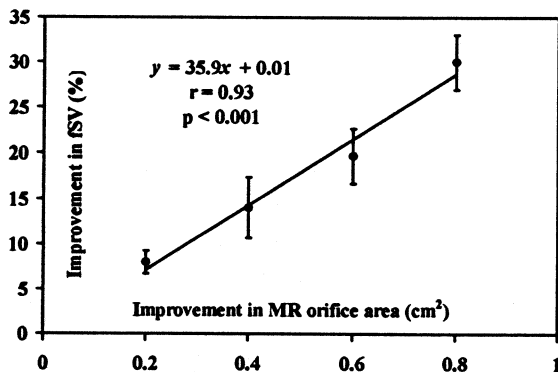


Figure 2: Reduction in mitral regurgitant (MR) orifice areas correlated linearly with improved forward stroke volume (fSV)

In addition to improvements in forward stroke volume, numerical modeling also demonstrated the physiologic benefits of reduction in MR orifice areas – namely improvements in more favorable end-diastolic volumes (Figure 3), end-diastolic volumes (Figure 4), and left ventricular ejection fraction (Figure 5).

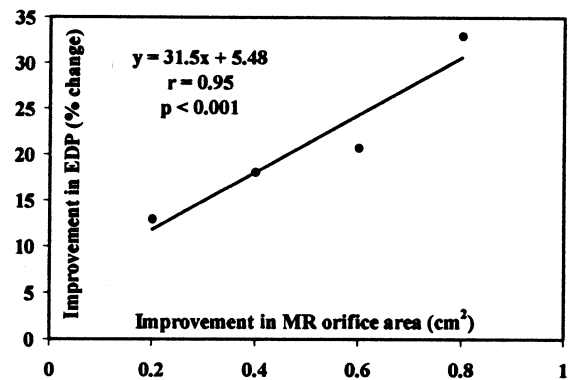


Figure 4: Reduction in mitral regurgitant (MR) orifice areas correlated linearly with improved end-diastolic pressure (EDP)

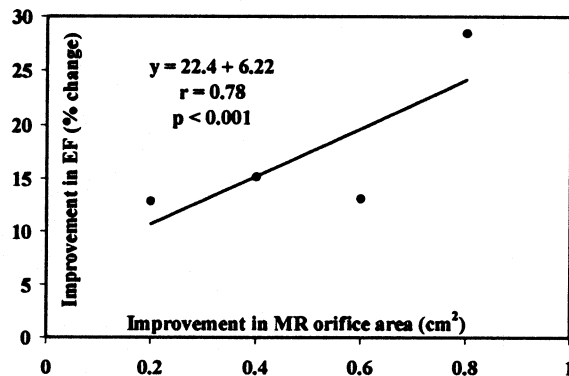


Figure 5: Reduction in mitral regurgitant (MR) orifice areas correlated linearly with improved ejection fraction (EF)

## 4. Discussion

Previously, we have shown that numerical modeling has been beneficial in broadening our understanding of complex cardiovascular physiologic relationships [5,6]. A significant benefit of modeling is that it allows for exploring the effects of wide ranging in physiologic perturbations in a manner that may not be suitable or possible for *in situ* experimentation.

We have demonstrated through sophisticated numerical modeling that reductions in mitral regurgitant orifice areas are linearly associated with an increased forward stroke volume – with an increase that is directly related to the degree of MR reduction. Furthermore, we have also shown that reductions in MR area is also associated with more favorable left ventricular hemodynamics, namely a reduction in end-diastolic volume, pressure, and improve ejection fraction. We also demonstrated through multivariate analysis that such physiologic improvements are predominately a function of the initial and final regurgitant orifice areas and are minimally influenced by diastolic relaxation ( $\tau$ ) or systolic elastance.

Bolling and colleagues, in 16 patients with end-stage dilated cardiomyopathy and severe MR, demonstrated significant improvements in clinical performance and hemodynamics [7]. All patients underwent mitral valve annuloplasty. Post-repair intra-op TEE demonstrated no MR in 12 with trivial to mild in the remaining 4. Significant improvements were observed in EDV ( $335 \pm 107$  to  $307 \pm 103$ ), ESV ( $227 \pm 101$  to  $237 \pm 98$ ) and stroke volume ( $58 \pm 13$  to  $70 \pm 21$ ). These benefits were associated with a corresponding improvement in NYHA functional class from  $1.8 \pm 0.4$  to  $3.9 \pm 0.2$ .

More recently, Chen and Adams, in 79 patients with ischemic cardiomyopathy undergoing mitral valve repair, have shown significant improvements in ejection fraction ( $24.3 \pm 4.5\%$  to  $32.3 \pm 8.9\%$ ,  $p < 0.001$ ) and NYHA functional class ( $1.60 \pm 0.86$  to  $3.18 \pm 0.65$ ,  $p < 0.001$ ) [8]. These findings are consistent with our model derived 10-20% improvement in ejection fraction. Furthermore, these results were obtained with acceptable 1, 2, 3, 4, and 5-year actuarial survivals (65%, 53%, 38%, 23%, and 11%).

A primary motivating factor in this study is that human data is both limited and difficult to acquire. Few studies have explored the hemodynamic benefits of reduction of MR, particularly in patients with impaired ventricular function - the very patient population that theoretically may benefit the most from aggressive surgical therapy.

## Acknowledgements

Supported by Grant 93-13880 from the American Heart Association, Greenfield, TX, Grant 1R01HL56688-01A1, National Heart Lung and Blood Institute, Bethesda, MD, Grants NCC9-58 and NCC9-60, National Aeronautics and Space Administration, Houston, TX. Dr. Firstenberg is supported in part by a grant from *The Lancet*.

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