Determinants of the Development of Mitral Regurgitation in Pacing-Induced Heart Failure

Masami Takagaki, MD; Patrick M. McCarthy, MD*; Marlene Goormastic, MPH**; Yoshie Ochiai, MD; Kazuyoshi Doi, MD; Michael W. Kopcak Jr, BA; Tomotsugu Tabata, MD†; Lisa A. Cardon, RDCS†; James D. Thomas, MD‡; Kiyotaka Fukamachi, MD

The pacing-induced heart failure model provides an opportunity to assess the structural and functional determinants of mitral regurgitation (MR) in dilated cardiomyopathy. This study aimed to evaluate MR to better understand the multitude of factors contributing to its development. Heart failure was induced by rapid ventricular pacing (230 beats/min) in 40 mongrel dogs. Left ventricular (LV) size and MR were evaluated echocardiographically. LV contractility was analyzed using a conductance catheter. MR increased to mild in 12 animals (regurgitant orifice area, 0.06±0.05 cm²), moderate in 15 (0.14±0.07 cm²), and severe in 13 (0.34±0.16 cm²). The grade of MR had an inverse relationships with Emax (the slope of the end-systolic pressure–volume relationship, p<0.01) and dE/dt (the slope of the maximum rate of change of pressure–end-diastolic volume [V̇ED] relationship, p<0.01) and positive relationships with V̇ED and end-diastolic cross-sectional areas and lengths (p<0.05) by univariate analysis. The dE/dt had an independently significant (p<0.01) relationship by multivariable logistic regression. Many factors influence the development of MR and because of its similarity to the clinical situation, this model can be used to investigate MR and heart failure, as well as new surgical therapies. (Circ J 2003; 67: 78–82)

Key Words: Contractility; Heart failure; Pacing; Mitral valve; Regurgitation

New surgical strategies for treating patients with heart failure include mitral valve repair alone, the Batista procedure, the Dor procedure, and the use of new heart-assist devices. Analysis of these effects of these therapies is complicated because the operations are designed in part to treat left ventricular (LV) dysfunction as well as mitral regurgitation (MR). A reliable experimental animal model of MR associated with heart failure is needed and although several models of experimentally induced MR have been reported to date, all are based on MR in normal ventricles.

The chronic rapid ventricular pacing model has frequently been used in dogs because it induces severe heart failure; the resulting clinical, echocardiographic, hemodynamic, and neurohormonal changes are very similar to those found in patients with dilated cardiomyopathy (DCM). Our hypothesis is that MR in this model is multifactorial and related not only to LV size and geometry, but also to cardiac performance, as shown in patients with functional MR. Few studies have reported these relationships, especially the factor of LV contractility. The purpose of this study was to evaluate MR in this model to better understand the multitude of factors that contribute to MR in patients with heart failure. This study was planned as the basis for further studies to evaluate new devices or surgical interventions that may affect MR as well as ventricular function.

Methods

Animal Preparation and Surgical Procedures

All animals received humane care in compliance with the Guide for the Care and Use of Laboratory Animals, prepared by the National Academy of Sciences and published by the National Institutes of Health (NIH publication 85-23, revised 1985), and institutional guidelines. A total of 40 mongrel dogs (body weight 26.0±1.4 kg) were anesthetized with intravenous thiopental (15 mg/kg) and isoflurane (0.5–2.5%). A bipolar, screw-in, transvenous pacing lead (Medtronic 4068, Medtronic Inc, Minneapolis, MN, USA) was inserted into the right ventricular apex and attached to a programmable pulse generator (Medtronic 8086, Medtronic Inc) inserted into a cervical pocket. Rapid ventricular pacing at a rate of 230 beats/min was started at a minimum of 2 days after surgery. Transthoracic echocardiographic studies were performed with the animal awake and the pacemaker off before and after induction of heart failure.

After 26.3±3.9 days of pacing, the animal was anesthetized in the same way as for the pacemaker implantation with the pacemaker off. A conductance catheter with 2 Millar pressure sensors (Model SPC-562, Millar Instruments, Houston, TX, USA) was inserted into the LV to acquire instantaneous pressure–volume loops for the terminal study. A 7.5Fr Swan-Ganz catheter was inserted into the pulmonary artery. A median sternotomy was performed, and the pericardium opened. A fluid-filled catheter was inserted into the left atrium. All hemodynamic data were recorded digitally at a sample rate of 200 Hz using the ‘PowerLab’ (AD Instruments Inc, Mountain View, CA, USA) data acquisition system. Cardiac output was
measured by the thermodilution method. An epicardial echocardiographic study was performed. The superior and inferior venae cavae were transiently occluded (bicaval occlusion) to obtain the LV pressure–volume loops under various preloads. The animal was then killed, and the heart was excised to measure the weight of the LV.

Echocardiographic Parameters

End-diastolic and end-systolic cross-sectional areas (cm²) in the short-axis view, both at the mitral annulus level (MAED and MAES) and the mid-papillary level (PAED and PAES), and end-diastolic (LED) and end-systolic (LES) LV length (cm) in the long-axis view were measured. End-diastolic volume (VED), end-systolic volume (VES), ejection fraction (EF), and LV shape index were calculated by the equations as shown:7,14

\[
V_{ED} (ml) = \frac{LED}{3} \times [MAED + (MAED + PAED)/2 + PAED/3]
\]
\[
V_{ES} (ml) = \frac{LES}{3} \times [MAES + (MAES + PAES)/2 + PAES/3]
\]
\[
EF (%) = \frac{(VED - VES)}{VED} \times 100
\]
\[
LV \text{ shape index} = 2 \times \frac{1}{[(PAED)/B]^{1/2}/LED}.
\]

The MR grade was ranked as mild, moderate, or severe on the Doppler echocardiogram and to support this semi-quantitative MR evaluation, the regurgitant orifice area (ROA) was measured as a quantitative MR parameter using the proximal isovelocity surface area.15,16 Maximal instantaneous regurgitant flow (Q_max) was calculated as Q_max = 2 × \(r^2 v_r\), where r is the maximal distance to the contour of velocity vr with a hemispheric contour assumed. The ROA was obtained by dividing maximal flow by the peak regurgitant velocity (vp) obtained by continuous-wave Doppler:

\[
ROA = \frac{Q_{max}}{vp}.
\]

LV Performance Analysis

The data analysis was performed using a custom-made visual basic program on Excel software (Excel 97 SR-1, Microsoft Corporation, CA, USA). The maximum and minimum rates of change of LV pressure (LV dP/dtmax and LV dP/dtmin) were determined from the LV pressure waveform. Catheter volumes were calibrated to an epicardial echocardiogram, using a 2-point calibration based on matching VES and VED.17 The upper left corners of the LV pressure–volume loops were connected by an iterative linear regression method, and the slope (Emax) of the end-systolic pressure–volume relationship (ESPVR) was obtained. It is known to be a load-independent index of LV contractility.18

We also evaluated the linear relations between LV dP/dtmax and VES, the slope of which (dE/dt) has also been reported to respond to changes in the contractile state.19

Statistical Analysis

All data are expressed as mean value ± SD. The changes of VED, VES, and EF at the terminal study were compared by paired t-test with those at baseline. The relationships between MR grade and the LV parameters were analyzed using analysis of variance. Multiple comparisons were done using Duncan’s multiple range test. A multivariable logistic regression model was also run to test for factors that were independently significant. All hemodynamic, echocardiographic, and LV performance parameters were entered into the analysis. The p values in the relationships between ROA and the LV parameters were provided based on Spearman correlations. Analysis was done using SAS statistical software (version 6.12, SAS Institute Inc, Cary, NC, USA). All data revealing a p value less than 0.05 were considered statistically significant.

Results

Transthoracic Echocardiographic Data Analysis

VED and VES at the terminal study (119.3±20.4 ml and 83.3±18.3 ml) were significantly greater compared with those at baseline (82.6±14.0 ml and 31.8±8.4 ml, p<0.0001). EF at the terminal study (30.5±7.7%) was significantly smaller than at baseline (61.7±6.0%, p<0.0001).

Relationships Between MR Grade and All Variables

In all 40 animals, MR was absent or trivial at baseline and became evident at the terminal study: mild in 12 (ROA 0.06±0.05 cm²), moderate in 15 (ROA 0.14±0.07 cm²), and severe in 13 dogs (ROA 0.34±0.16 cm²).

By univariate analysis, parameters related to LV contractility had a significant inverse relationship with MR grade.

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Fig. 1: Relationship between cardiac contractility and mitral regurgitation (MR). Cardiac contractility was significantly higher in the mild MR group than in the moderate and severe MR groups. *p<0.01 compared with moderate and severe MR groups. Emax, the slope of the end-systolic pressure–volume relationship; dE/dt, the slope of LV dP/dtmax–VED relationship.

Fig. 2: Representative pressure–volume loops during bicaval occlusion in mild and severe MR group. Each animal had a similar VEd before bicaval occlusion; however, the end-systolic pressure–volume relationship is totally different between these 2 animals. Open and closed circles show end-systolic points of each pressure–volume loop of the animal in the severe and mild MR group, respectively. The end-systolic pressure–volume relationship is expressed as linear regression lines of these points by an iterative linear regression method. LV, left ventricular; MR, mitral regurgitation; VEd, LV end-diastolic volume.
Ro A revealed a significant inverse relationship with Emax increased the risk of moderate or severe MR. Furthermore, by multivariable logistic regression. Lower dE/dt values were totally different. The dE/dt was also the only ship were totally different. The dE/dt was also the only grade of MR and end-systolic pressure-volume relation-

bicaval occlusion between these 2 did not differ so much, the grade of MR and end-systolic pressure-volume relationship were totally different. The dE/dt was also the only independently significant factor (p = 0.009) related to MR by multivariable logistic regression. Lower dE/dt values increased the risk of moderate or severe MR. Furthermore, ROA revealed a significant inverse relationship with Em max (p = 0.05) and dE/dt (p = 0.03).

Other hemodynamic parameters are shown in Table 1. LV dP/dtmax (p = 0.03) and LV end-diastolic pressure (p = 0.01) were significantly lower in the mild MR group than in the other 2 groups. Left atrial pressure (LAP) was significantly (p = 0.004) lower in the mild MR group than in the severe group. Transmittal pressure, defined as the average of the difference between LV pressure and LAP during the systolic phase, was significantly (p = 0.03) lower in the severe MR group than in the other 2 groups.

The relationship of MR to the epicardial echocardiographic parameters is shown in Table 2. V ED (p = 0.01) and PA ED (p = 0.03) were significantly smaller in the mild MR group than in the other 2 groups. LVED length (p = 0.04) was significantly less in the mild MR group than in the severe group. VES, MA ED, and LV shape index tended to be smaller in the mild MR group, but these differences were not statistically significant (p = 0.09, 0.06, and 0.11, respectively).

Discussion

LV contractility was significantly higher in the mild MR group than in the other 2 groups (Emax (p = 0.009) and dE/dt (p = 0.002)). Moreover, ROA, as a quantitative analysis of MR, showed significant inverse relationships with Emax (p = 0.05) and dE/dt (p = 0.03). The dE/dt was the only independently significant factor (p = 0.009) related to MR by multivariable logistic regression. These results led us to conclude that LV contractility was an important determinant of MR in this canine model.

The effect of contractility on MR has been reported in both valvulotomy performed animals and humans. Yoran et al clearly showed that angiotensin and volume infusion worsened MR with increased ROA. Moreover, no reoperation improved MR with decreased ROA. Kaul et al observed that incomplete mitral leaflet closure was the most common cause of MR in their patients; they found that only LV systolic function separated these patients from normal...
Determinants of MR

We cannot apply our findings directly to patients with functional MR, for the induction time to heart failure is totally different. MR that has developed slowly may be more strongly related to changes in LV size and geometry, as shown in previous studies.9–12 The short induction period in this canine model might not be long enough to induce the morphological dilatation observed in humans. Most recently, Yiu et al analyzed the data of functional MR patients and reported that excess valvular tenting and loss of systolic annular contraction were strongly associated with the MR.23 They have not investigated load-independent parameters for the LV contractility, and we have not analyzed the local LV remodeling or regional LV function. We need to analyze the clinical data to characterize the differences between this animal model and patients.

We also have to consider that this study was performed in an open chest condition. The considerable differences in LV size by epicardial echocardiography (open chest preparation) from those by transthoracic echocardiography (closed chest, conscious condition) were noted, as shown in our results. However, a linear correlation observed between ventricular volumes in these 2 conditions \( r = 0.804 \) supports that all the animals were similarly treated during these preparations. The effects on the relationship with MR could also be minimized. In addition, the resolution of the Doppler echocardiographic images was much better in open chest conditions compared with those in closed chests.

Finally, because \( V_0 \) for ESPVR was very negative in the severe MR case, there might have been some problems with absolute values of volumes. However, the calibration method of matching \( V_0 \)s and \( V_0 \)s is the only way that is theoretically reasonable in the presence of MR, unless we can measure the amount of MR precisely. Although it was impossible to validate this calibration in our data, the similar results in \( dV/dt \) support our conclusion.

Conclusion

The multifactorial development of MR includes the effects of change in LV contractility, size, and geometry. Because our results are similar to those found in patients, this canine model could be a good experimental model to investigate MR and heart failure, including how well new devices and surgical therapies correct the clinical condition.

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References


