A Prospective Study of Predicting Factors in Ischemic Mitral Regurgitation Recurrence After Ring Annuloplasty

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Background. Ischemic mitral regurgitation (IMR) is a complex lesion to repair, and its successful management requires an understanding of its mechanism and severity. Ring annuloplasty, currently the surgical treatment of choice for IMR, has failure rates as high as 30% in patients with functional IMR. We sought to study the variables that can predict IMR recurrence after ring annuloplasty.

Methods. This is a prospective study of 114 patients with 3+ to 4+ IMR who underwent coronary artery bypass grafting and mitral valve annuloplasty with acceptable results at an approximately 2-year follow-up. Variables were compared in a failure group, comprising patients with 2+ or higher MR and a nonfailure group, consisting of those with less than +2 MR.

Results. There were five postoperative in-hospital deaths. During follow-up, 14 patients died and 95 patients

C hronic ischemic mitral regurgitation (IMR), associated with a markedly worse prognosis after myocardial infarction (MI) and coronary revascularization, is present in 10% to 20% of patients with coronary artery disease [1]. It is, therefore, essential that chronic IMR be taken into account in the treatment of patients with ischemic heart disease [2].

Although a number of techniques for IMR have been developed, none has resulted in clearly improved outcomes [1]. The most common surgical procedure currently performed for IMR is mitral annuloplasty, which involves the insertion of an artificial or pericardial ring. The initial results of mitral annuloplasty seemed encouraging, with low perioperative mortality rates, but subsequent studies revealed that recurrent MR developed in as many as 30% of patients during follow-up [3–5].

This high MR recurrence rate associated with mitral annuloplasty has led a number of investigators to examine alternative or additional surgical therapies. The phenomenon of "tethering," in which the mitral valve leaflet is pulled toward the left ventricle apex, begets MR; therefore, additional surgical procedures such as papillary muscle approximation (PMA) [6], cutting the secondary chordae of the

© 2007 by The Society of Thoracic Surgeons Published by Elsevier Inc were evaluated. After a mean follow-up of 22.2 ± 4.6 months for the nonfailure group and 18.6 ± 5.6 months for the failure group, 23 patients (24.4%) exhibited annuloplasty failure. Some variables had an effect in our univariate analysis, but only interpapillary muscle distance had a relationship with recurrent MR in the multivariate analysis. Mean preoperative interpapillary muscle distance was 15.0 \pm 4.0 and 26.5 \pm 2.9 in the nonfailure group and failure group, respectively (p < 0.0001).

Conclusions. Interpapillary muscle distance, as a reliable index of dysfunctional subvalvular apparatus in patients with IMR, can predict late postrepair MR and indicate the need for a procedure complementary to annuloplasty.

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anterior leaflet of the mitral valve [7], anterior leaflet augmentation [8], and relocation of the posterior papillary muscle [9] have been evolved to reduce or eradicate tethering and, consequently, to control regurgitation.

What remains to be clearly defined, however, is which cases of IMR should undergo one of these complementary procedures. Mitral annuloplasty is believed to be safe and effective in approximately 70% to 80% of patients, but how can we single out the remaining unlucky ones before surgery? To find an answer to this question, we sought to evaluate the predicting factors for IMR recurrence after ring annuloplasty.

Material and Methods

Patient Population

Between May 2002 and March 2004, 1617 patients were referred to Day General Hospital for elective first-time coronary artery bypass grafting (CABG). After quantitative echocardiographic measurements, 121 patients with chronic 3+ and 4+ IMR on a scale of 1 to 4, as judged by a consensus of 2 observers, underwent coronary angiography, followed by CABG and mitral annuloplasty. All the patients had had a MI at least 6 weeks previously.

The patients were evaluated with intraoperative postcardiopulmonary bypass pump (CPB) transesophageal

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echocardiography (post-CPB TEE); 114 of these patients, whose acceptable postoperative results (0+ or 1+ MR) were later confirmed by predischarge transthoracic echocardiography (TTE), were enrolled in this study. The rest of the patients, who did not show acceptable results, underwent additional procedures, including even mitral valve replacement, if necessary. Excluded were candidates for other surgical procedures and patients with structural causes for MR, including ruptured chordae, ruptured papillary muscle, abnormal leaflet thickening, and annular calcification, as well as patients who had had a MI less than 6 weeks previously, ventricular aneurysms or other valvular or congenital heart diseases. This research protocol was approved by the Institutional Review Board of Day General Hospital.

Study Design

In this prospective study, all the patients underwent a baseline TTE before surgery. The results were reconfirmed by intraoperative pre-CPB TEE, performed after the induction of surgical anesthesia and before the surgical incision. Preoperative New York Heart Association (NYHA) functional class and variables that could predict late MR, such as ejection fraction (EF), severity of MR, coaptation depth, concavity area, end-systolic volume, end-diastolic volume, sphericity index, posterior papillary muscle–to–intervalvular fibrosa distance, and interpapillary muscle distance (iPMD), were registered.

Our general policy was to intervene in cases with chronic moderate-to-severe or severe IMR (3+, 4+). After CABG with mitral annuloplasty, an intraoperative post-CPB TEE evaluation revealed acceptable results in all the cases: there was no MR or trace MR and the coaptation line was more than 6 mm. A predischarge reevaluation later on confirmed the successful result of repair in all the patients. The patients were, thereafter, rigorously followed up for approximately 2 years to check whether they showed failure of mitral annuloplasty with significant late MR. Significant MR was defined MR of 2+ or more after surgery. The variables were determined every 6 months postoperatively by another clinical evaluation in conjunction with TTE.

Echocardiography

In this prospective study, all the echocardiograms were obtained by 2 cardiologists. The mitral annulus was measured in the 4-chamber and 2-chamber views at end-systole, and the mean value was taken into account. The estimation of the MR grade on TTE was based on the vena contracta of the regurgitant jet [10]. Vena contracta, measured by Doppler color flow imaging, is the narrowest portion of the regurgitant jet (vena contracta width <3 mm, 1+; 3 to 5mm, 2+; 5 to 8 mm, 3+; >8mm, 4+). The highest grade of MR observed preoperatively was used to classify the patients. The 2 observers reached a consensus.

The characteristics of the tethering pattern of the mitral valve were assessed by means of the following indices (all the measurements were performed at end-systole):

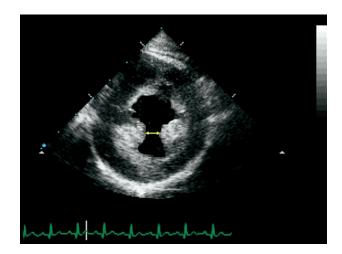


Fig 1. Interpapillary muscle distance is measured as the empty distance between the two papillary muscles (arrow) at end systole on transthoracic echocardiography.

- 1. Interpapillary muscle distance: This was measured through the parasternal short-axis view on TTE (Fig 1) and transgastric view on TEE. As shown in Figure 1, the iPMD is the empty distance between the 2 papillary muscles.
- 2. Coaptation depth: This was defined as the distance between the annulus and the coaptation point of the leaflets.
- 3. Concavity area: This was defined as the concavity area of the anterior leaflet.
- 4. Posterior papillary muscle–fibrosa: This was defined as the distance between the head of the posterior papillary muscle and the fixed intervalvular fibrosa.
- Left ventricle (LV) sphericity: This was estimated as the LV short axis-to-long axis dimension ratio at end-systole in the apical 4-chamber view.
- 6. End-systolic and end-diastolic dimensions: These were measured in the M-mode parasternal long axis.
- LV volumes and ejection fraction (EF). These were measured by a modified biplane Simpson's method.

Operative Procedure

All patients underwent full revascularization and prosthetic mitral annuloplasty. The operation was performed through a median sternotomy, aortic and bicaval cannulation, moderate hypothermic CPB, and retrograde coldblood cardioplegia. After coronary anastomosis, the mitral valve was routinely exposed through a vertical transseptal incision. The valve was inspected, and the pathophysiology was confirmed. In all the patients, although the mitral leaflets, chordae, and PMs were normal, one or both PMs were malpositioned.

The size of the mitral annuloplasty ring (Carpentier Edwards Physio Ring, Edwards Lifesciences, Irving, CA) was decided by a standard measurement of the intertrigonal distance and anterior leaflet height, thereupon downsizing by two ring sizes was done. The rings were subsequently anchored using multiple, deep U-shaped stitches of Ethibond 2-0 (Ethicon, Inc, Somerville, NJ). All the rings were size 28 or less (mean size, 26).

The post-CPB surgical results were evaluated by TEE. Because previous studies stress that intraoperative TEE downgrades MR [11], we did intraoperative TEE after provocative testing so that we could increase both preload and afterload, clarify the physiological severity of the MR, and facilitate intraoperative decision-making.

Medication

All the patients were receiving β -blockers and aspirin. Other medications were administered if the need arose.

Follow-Up

All the patients were followed up at our outpatient clinic every 6 months by TTE performed by the same cardiologists. Follow-up was 100% complete.

Statistical Analysis

Data are presented as mean \pm standard deviation, percentage, and total number, as appropriate. The association between the quantitative data was found with a two-tailed unpaired *t* test. The χ^2 test or Fisher exact test was applied to compare the categoric variables. The Cox regression analysis was used to evaluate the independent risk factors for significant late MR. All the independent variables were included in the model before the backward method, and a value of p < 0.05 was used to select variables for the model. The statistical analyses were performed using SPSS 13.0 software (SPSS Inc, Chicago, IL). A value of p < 0.05 was considered statistically significant.

Results

There were 5 postoperative in-hospital deaths. During follow-up, 14 patients died: 12 of cardiac causes (heart failure in 7, sudden death in 3, acute ischemia in 2) and 2 of noncardiac causes (accident in 1, leukemia in 1). Analysis was done on 95 patients.

The mean age of the patients was 54.6 \pm 11.3 years and 74 (77.9%) were men. MR was at grade 3 in 29 patients (30.5%) and at grade 4 in 66 (69.5%). The subjects had a mean iPMD of 17.3 \pm 6.0 mm, annular size of 38.3 \pm 3.1 mm, coaptation depth of 8.8 \pm 1.8 mm, concavity area of 38.1 \pm 11.1 mm², EF of 0.380 \pm 0.062, and LV end-systolic volume of 93.0 \pm 23.7 mL. All the patients were in NYHA functional class 3 or 4.

After a mean follow-up of 22.2 \pm 4.6 months for the nonfailure group (range, 6 to 30 months) and 18.6 \pm 5.6 months for the failure group (range, 6 to 24 months), 23 patients (24.4%) showed annuloplasty failure with MR of 2+ or more.

Table 1 summarizes the univariate analysis of the characteristics and preoperative echocardiographic data in the failure and nonfailure groups. In the univariate analysis, failure was related to iPMD, coaptation depth, concavity area, end-diastolic diameter, and sphericity index.

After all the variables had been entered into the model in a backward approach in the Cox model, only preop-

Table 1.	Characteristics	of the	Study	Patients

Variables	Nonfailure $(n = 76)$	Failure (n = 19)	p Value
$(\text{mean} \pm \text{SD or \%})$	(n = 76)	(n = 19)	p value
Age	55.0 ± 11.5	52.8 ± 10.8	0.455
Sex (M/F)	59/17	15/4	1.000
Mitral regurgitation, pre-op	3.70 ± 0.46	3.68 ± 0.48	0.912
Coronary vessel disease (n)	2.35 ± 0.65	2.43 ± 0.66	0.578
Grafts (n)	3.92 ± 0.82	4.00 ± 0.60	0.653
Area of infarction (%)			
Anterior	22.2	26.1	0.702
Inferior	62.5	69.6	0.538
Lateral	23.6	21.7	0.853
Ring size	27.6 ± 1.4	27.7 ± 1.4	0.704
iPMD pre-op (mm)	15.0 ± 4.0	26.5 ± 2.9	< 0.0001
iPMD after follow-up (mm)	16.4 ± 3.8	30.1 ± 2.6	<0.0001
Annular size pre-op (mm)	38.3 ± 3.2	38.5 ± 3.0	0.733
Coaptation depth (mm)	8.58 ± 1.79	9.84 ± 1.68	0.007
Concavity area (mm ²)	$\textbf{33.8} \pm \textbf{7.2}$	55.6 ± 5.6	< 0.0001
EF, pre-op	0.378 ± 0.063	0.387 ± 0.060	0.566
EF, post-op	0.450 ± 0.058	0.474 ± 0.053	0.130
EF, after follow-up	0.442 ± 0.080	0.463 ± 0.040	0.083
LVESV pre-op (mL)	92.2 ± 22.9	$\textbf{96.1} \pm \textbf{27.2}$	0.531
LVESV, after follow-up (mL)	84.3 ± 17.7	84.7 ± 17.1	0.940
NHYA, pre-op	3.41 ± 0.50	3.26 ± 0.45	0.231
NHYA, post-op	1.38 ± 0.57	$\textbf{2.37} \pm \textbf{0.76}$	< 0.0001
LVEDV, pre-op (mL)	162.5 ± 28.9	164.2 ± 30.6	0.810
LVEDV, after follow-up (mL)	146.0 ± 27.8	151.8 ± 24.6	0.368
Sphericity index	53.8 ± 3.7	55.5 ± 3.7	0.050

EF = ejection fraction; iPMD = interpapillary muscle distance; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; NYHA = New York Heart Association.

erative iPMD remained an independent risk factor for significant MR ($\beta = 0.275$, p < 0.0001).

Table 1 demonstrates no difference between the two groups in terms of the number of vessel diseases (2.35 \pm 0.65 in group I, 2.43 \pm 0.66 in group II, p < 0.578), the number of grafts (3.92 \pm 0.82 in group I, 4.00 \pm 0.60 in group II, p < 0.653) for each patient, and the mean size of the rings (27.6 \pm 1.4 in group I, 2.7.7 \pm 1.4 in group II, p < 0.704).

All the patients had a history of MI. In both groups, inferior MI was more frequent than anterior infarction, without significant differences between the two groups (Table 1).

As demonstrated in Table 1, preoperative and postoperative end-diastolic and end-systolic volumes and sphericity indices were not different between the two groups.

Additional procedures were done in 7 patients (mean age, 60.9 ± 9.3 years) who did not show acceptable results after repai, which led to mitral valve replacement in 5. Everyone's iPMD was more than 20, with a mean iPMD of 27.7 \pm 3.6 (range, 22 to 32). They had a mean annular size of 41.1 \pm 3.2, coaptation depth of 10.9 \pm 1.9, concavity

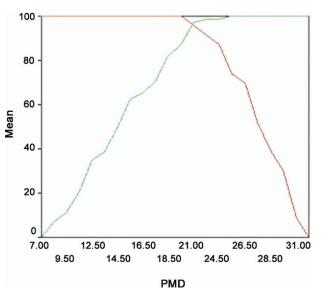


Fig 2. Receiver operating characteristic curve analysis for the optimal cutoff value for the interpapillary muscle distance (PMD). The green line represents sensitivity, and the red line represents specificity.

area of 48.0 \pm 5.1, LV end-diastolic volume of 109.9 \pm 32.1, and NYHA of 3.71 \pm 0.49, which were more than those in the nonfailure group. However, they had MR before surgery and their EFs were the same as the other group.

Figure 2 shows a receiver operating characteristic (ROC) curve analysis of iPMD, in which the optimal cutoff value for iPMD is 20. This cutoff value yielded a sensitivity of 95.7% and a specificity of 97.2%. The area under the ROC curve is 0.994 ± 0.005 .

Two patients (2.8 %) in the nonfailure group and 22 (95.7%) in the failure group had preoperative iPMD of more than 20 mm (p < 0.0001).

Comment

Indubitably, further research is required to help improve the prognosis of patients with IMR. As mentioned earlier, mitral annuloplasty is the surgical treatment of choice for patients with IMR. In the current study, 24.2% of the patients, who had successful mitral annuloplasty, showed MR recurrence (2+ or more) within 22.35 months of follow-up, an incidence almost similar to that described by other investigators [3-5]. Because annuloplasty has a considerable rate of failure and mitral annuloplasty addresses only one of the components of mitral dysfunction, there has been increasing interest in using other procedures in conjunction with ring annuloplasty to address the subvalvular apparatus. Nevertheless, a precise and reliable index for predicting the efficacy of mitral annuloplasty by determining the deformities of the subvalvular apparatus is urgently required because it still has not been clearly defined when the complementary procedures should be applied.

We know, however, that the components of the mitral apparatus belong to a single functional unit; thus, normal mitral valve function requires the coordinated operation of all the components, including the annulus, leaflets, chordae tendinea, and PMs [1]. LV distortion and remodeling after MI displaces PMs from the mitral annulus [12–14]; this displacement puts excessive tension on the chordae and results both in the tethering of the apical mitral leaflets and in restricting their coaptation during systole [13, 15–18]. As a consequence, the further the PMs are displaced, the less the mitral leaflets coapt. The measurement of the iPMD, therefore, finds application as a quantitative index of the tethering phenomenon in evaluating the remodeling process.

We followed up patients after ring annuloplasty in an attempt to evaluate predicting factors of IMR recurrence. Surprisingly, 2.8% of the patients in our nonfailure group and 95.7% of the patients in the failure group had preoperative iPMD of more than 20 mm. This finding strongly supports the hypothesis that increased iPMD can determine patients with a higher likelihood of MR recurrence.

Agricola and coworkers [19] ingeniously used mitral deformation indices and PM displacement to evaluate chronic IMR and discovered that all of these variables had a significant tendency to change in patients with IMR [19].

Our data tally with those reported by Calafiore and colleagues [20, 21], who introduced an index—the mitral valve coaptation depth—for predicting the return of functional MR after annuloplasty. Having performed mitral valve repair in a group of patients with an mitral valve coaptation depth of 11 mm or more, Calafiore and colleagues reported that postoperative NYHA functional class had remained similar to the preoperative one and that the residual functional MR degree had been higher than that in another group of patients (1.2 \pm 0.8 versus 2.5 \pm 0.7, *p* < 0.001) [7]. Mitral valve coaptation depth is, undoubtedly, a reliable index of MR recurrence (*p* < 0.01); however, we are inclined to believe that iPMD is a more accurate index (*p* < 0.001).

Braun and colleagues [22], in an excellent study, found end-diastolic volume of great significance in predicting the possibility of IMR recurrence after annuloplasty remodeling. In our study, as much as a univariate analysis showed the effects of certain variables such as enddiastolic volume and coaptation depth, a multivariate analysis was indicative of a relationship only between recurrent MR and iPMD.

Kuwahara and colleagues [23] evaluated the effect of tethering variables in late MR after annuloplasty and found that mitral annuloplasty was not sufficient when the tethering of the leaflets was more than the anterior leaflet surface. They suggested that in this situation, we need interventions addressing ventricular tethering or interventions addressing PM tethering to reduce the risk of late MR.

Leaflet tethering, caused by ventricular remodeling, is compounded by LV contractile dysfunction, which decreases the closing force on the leaflets [17]. According to Laplace's law (pressure is proportional to wall stress divided by radius of curvature), once IMR is initiated, enddiastolic LV volume and wall stress increase in tandem with preload [18, 24, 25]. The increase in wall stress causes further LV dysfunction [26], which in turn gives rise to further PM displacement and leaflet tethering. Chronic IMR therefore begets MR in a self-perpetuating manner [1]. Recurrent MR after an initially successful mitral annuloplasty may be related to continuing PM displacement, which augments the tethering on the leaflets deranging once again the ratio between the mitral orifice and covering surface of the mitral leaflets [3, 27].

The above-mentioned studies and our new finding that ventricular remodeling triggers a gradual increase in iPMD strongly support the notion that the main mechanism of IMR in most cases is tethering begotten by PM displacement. The gradual displacement of PMs perpetuates tethering and restricts the movement of the anterior leaflet, reducing coaptation and increasing regurgitation. Preoperative iPMD could, therefore, be a clue to the amount of initial tethering induced by PM displacement; if it is more than 20 mm, not only are the abnormalities in the subvalvular apparatus and the resultant tethering far too advanced to be treated by ring annuloplasty alone but it also triggers the recurrence of MR after mitral annuloplasty. Here, an additional procedure that can directly address the subvalvular apparatus is required to prevent or at least delay the recurrence of MR. Conversely, if tethering is not strong enough (low iPMD) to restrict the motion of the anterior leaflet, posterior ring annuloplasty alone can successfully impede the recurrence of IMR.

In conclusion, our prospective study shows that iPMD is a crucial index for determining whether MR might recur (if iPMD is high) after posterior annuloplasty. This prediction is potentially helpful in deciding whether to perform annulolasty alone if iPMD is 20 mm or less or resort to a complementary procedure if iPMD exceeds 20 mm).

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