TABLE 3. Continued

Variable	Baseline	1 mo	1 y	2 y	*P* Value
TMPG (mm Hg)					
All		4.2 ± 1.5	4.3 ± 1.6	4.7 ± 2.3	NS
Mild PH group		4.7 ± 1.6	4.6 ± 1.3	4.9 ± 2.0	NS
Moderate PH group		3.7 ± 1.3	3.9 ± 1.3	4.7 ± 2.1	NS
Severe PH group		4.4 ± 1.4	4.5 ± 2.6	4.5 ± 3.4	NS

LVEDD, left ventricular end-diastolic dimension; *PH*, pulmonary hypertension; *LVESD*, left ventricular end-systolic dimension; *LVEF*, left ventricular ejection fraction; *LA*, left atrial; *PAP*, pulmonary artery pressure; *MR*, mitral regurgitation; *TR*, tricuspid regurgitation; *TMPG*, transmitral pressure gradient. **P* < .05 versus values at baseline in each group. †*P* < .05 versus severe PH group at each point.

(71%) of 17 patients with moderate PH, and 2 (25%) of 8 with severe PH (*P* = NS) at their most recent examination (Table 4). Univariate analysis identified LV systolic dysfunction (*P* = .022), a longer duration of heart failure (*P* = .01), and severe PH (systolic PAP > 60 mm Hg; *P* = .004) as important predictors of failure of reverse LV remodeling. In addition, multivariate analysis identified severe PH as a significant predictor.

Prediction of Postoperative Adverse Cardiac Events

Finally, the potential predictors of postoperative adverse cardiac events were examined using a Cox proportional hazard model (Table 5). Univariate analysis identified preoperative LV systolic dysfunction (*P* = .04), a longer duration of heart failure (*P* = .021), and severe PH (systolic PAP > 60 mm Hg; *P* = .002) as important predictors. In addition, multivariate analysis identified severe PH as a significant predictor.

DISCUSSION

The results of the present study suggest that PH in patients with advanced cardiomyopathy undergoing RMA is significantly associated with adverse short-term clinical outcome in terms of overall survival, adverse cardiac events (including cardiac death, readmission for heart failure, and fatal arrhythmia), improvements in NYHA functional class and serum BNP levels, acute hemodynamic changes, and serial echocardiographic changes in LV dimensions and function. Our findings have also demonstrated that severe PH (systolic PAP > 60 mm Hg) was an important hemodynamic predictor of adverse cardiac events, as well as failure of LV reverse remodeling after surgical treatment for functional MR and LV dysfunction.

In previous studies, clinical variables such as advanced age, preoperative hemodialysis and diabetes,[4] larger LV dimensions,[5,6] and nonischemic etiology and a longer duration of heart failure[7] were shown to be significantly associated with poor outcomes after RMA. In addition, the more sophisticated echocardiographic parameters of LV systolic and diastolic dysfunction such as LVEDD (> 65 mm) and left ventricular end-systolic dimension (> 51 mm),[8] myocardial performance index, systolic sphericity, wall motion score index,[14,15] restrictive LV filling

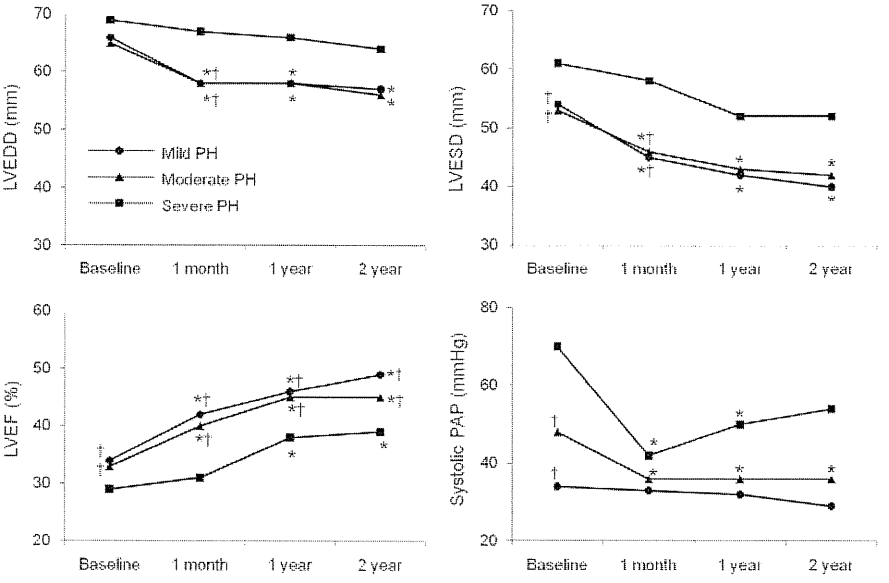

FIGURE 4. Serial echocardiographic changes after restrictive mitral annuloplasty. **P* < .05 versus value at baseline, †*P* < .05 versus value for severe PH group. *LVEDD*, Left ventricular end-diastolic dimension; *LVEF*, left ventricular ejection fraction; *LVESD*, left ventricular end-systolic dimension; *PAP*, pulmonary artery pressure; *PH*, pulmonary hypertension.

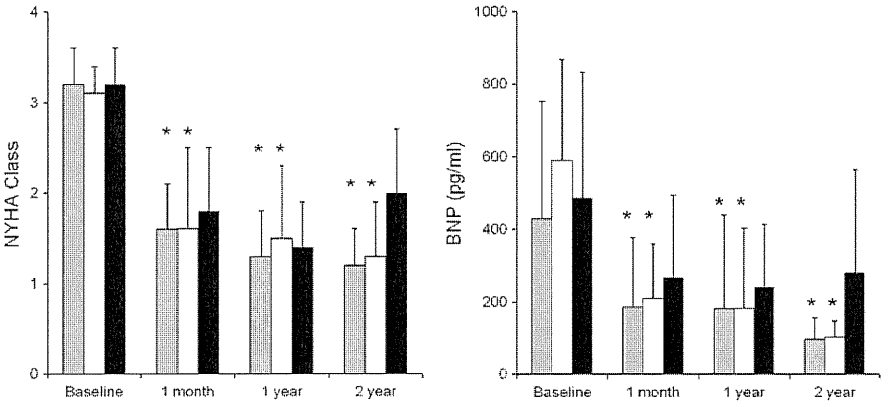

FIGURE 5. Serial changes in New York Heart Association *(NYHA)* functional class and serum brain natriuretic peptide *(BNP)* level. *$P < .05$ versus value at baseline. *Gray*, *white*, and *black* bars indicate mild, moderate, and severe groups, respectively.

pattern and mitral deceleration time (< 140 ms)[16] have been reported to be strong predictors of poor outcome or a lack of LV reverse remodeling after RMA. These parameters have also been shown to predict late MR recurrence after mitral annuloplasty. The present results have suggested that the PH level is a strong predictor of outcome after RMA and also provided additional important prognostic information that is complementary to the classic echocardiographic parameters of LV systolic and diastolic dysfunction.

The etiologies of PH in patients with cardiomyopathy are heterogeneous, and the determinants of its reversibility after an annuloplasty procedure have not been fully clarified. Classically, PH in patients with cardiomyopathy has been attributed to elevated LV filling pressures, reactive pulmonary arterial vasoconstriction, pulmonary vascular remodeling, or all three[17]; it has also been associated with functional MR.[18] The increased PAP associated with early-stage cardiomyopathy principally results from elevated LV filling pressures.[18] In addition, longstanding elevation of LV filling pressures can lead to several histologic changes in pulmonary circulation, including medial hypertrophy of arterioles, intimal fibroproliferation, and arterialization of the pulmonary veins.[17] These changes have also been associated with neurohumoral activation, in particular of endothelin-1,[19,20] a potent vasoconstrictor that is markedly increased in patients with advanced heart failure. These pathophysiologic changes are dependent on the chronicity and severity of PH and can initially be reversible, although the conditions can eventually become irreversible.[17]

The changes in pulmonary hemodynamics seen in the present severe PH group were consistent with this sequence of PH progression. The patients in the severe PH group had had a longer duration of heart failure and greater PVR values before surgery. Furthermore, the mean PVR value in this group remained considerably elevated at 1 month

TABLE 4. Predictors of failure in left ventricular reverse remodeling

	Univariate			Multivariate		
Variable	*P* Value	Odds ratio	95% CI	*P* Value	Odds ratio	95% CI
Age	NS					
Ischemic etiology	NS					
Duration of HF	.01	1.1	1.02–1.15	NS		
History of VT	NS					
LVEDD (continuous)	NS					
LVEDD (> 65 mm)	NS					
LVESD (continuous)	NS					
LVESD (> 50 mm)	NS					
LA dimension (mm)	NS					
LVEF (%)	.02	0.8	0.70–0.97	NS		
Severe PH*	.004	25.7	4.3–155	.03	10.0	1.3–75
MR grade	NS					
TR grade	NS					

CI, Confidence interval; *HF*, heart failure; *VT*, ventricular tachycardia; *LVEDD*, left ventricular end-diastolic dimension; *LVESD*, left ventricular end-systolic dimension; *LA* , left atrial; *LVEF*, left ventricular ejection fraction; *PH*, pulmonary hypertension; *MR*, mitral regurgitation; *TR*, tricuspid regurgitation. *Systolic PAP > 60 mm Hg.

TABLE 5. Predictors of adverse cardiac events

	Univariate			Multivariate		
Variable	*P* Value	Hazard ratio	95% CI	*P* Value	Hazard ratio	95% CI
Age	NS					
Ischemic etiology	NS					
Duration of HF	.02	1.05	1.01–1.10	NS		
History of VT	NS					
LVEDD (continuous)	NS					
LVEDD (> 65 mm)	NS					
LVESD (continuous)	NS					
LVESD (> 50 mm)	NS					
LA dimension (mm)	NS					
LVEF (%)	.04	0.89	0.79–0.96	NS		
Severe PH*	.002	9.1	2.3–35	.04	6.9	1.1–44
MR grade	NS					
TR grade	NS					

CI, Confidence interval; *HF*, heart failure; *VT*, ventricular tachycardia; *LVEDD*, left ventricular end-diastolic dimension; *LVESD*, left ventricular end-systolic dimension; *LA*, left atrial; *LVEF*, left ventricular ejection fraction; *PH*, pulmonary hypertension; *MR*, mitral regurgitation; *TR*, tricuspid regurgitation. *Systolic PAP > 60 mm Hg.

after surgery. The elevated PAP levels (> 40 mm Hg) persisted at all follow-up examinations, suggesting the presence of irreversible pulmonary vascular disease. In contrast, the moderate PH group showed a decline in the systolic PAP without a change in the lowered PVR at discharge. Also, the lower PAP values were maintained until the latest follow-up examination, suggesting that PH was reversible in these patients. Thus, our findings emphasize the importance of assessing PVR and the degree of pulmonary vascular remodeling. In addition, our results might support the use of surgery for patients with medically uncontrollable severe functional MR before the pulmonary vascular disease becomes irreversible.

The degree of PH is not only related to the severity of LV systolic dysfunction, but is also strongly associated with the LV diastolic dysfunction (ie, a greater level of PH has been associated with a shorter mitral deceleration time).[18] Gelsomino and colleagues[21] reported that the Doppler-derived mitral deceleration time was prognostic for LV reverse remodeling after undersized mitral annuloplasty. Our results are not necessarily inconsistent with those of previous studies, because a strong correlation between the Doppler-derived systolic PAP and mitral deceleration time has been reported.[18] Also, the prevalence of a restrictive filling pattern has been inversely related to the LVEF. PH has also been significantly associated with right ventricular function and right heart hemodynamics. In contrast, the right ventricular EF will correlate with the systolic PAP and is an independent predictor of survival in patients with moderate heart failure.[22] This association between PH and right ventricular dysfunction could explain why the level of PH provides additional prognostic information beyond the LV systolic and diastolic dysfunction variables.

It remains controversial whether patients with end-stage heart failure and functional MR can benefit from RMA.[23-25] In our study, patients with mild and moderate PH (Doppler-derived PAP < 60 mm Hg) showed functional improvement and satisfactory long-term survival. In contrast, those with severe PH (systolic PAP > 60 mm Hg) had relatively poor outcomes. Our results have shown that RMA was able to improve hemodynamics and symptoms in these patients. However, the lack of an untreated control group did not allow us to investigate the survival benefit conferred by RMA for patients with significant MR and severe LV dysfunction. Additional studies of late mortality after RMA in similar patient populations are needed.

Study Limitations

The main limitations of the present study were its retrospective nature and the small number of subjects. The inclusion of patients with ischemic and nonischemic cardiomyopathy and those who had undergone concomitant coronary artery bypass grafting, tricuspid annuloplasty, and a maze procedure for atrial fibrillation might have influenced the results. However, these concomitant procedures are usually required in a population of very sick patients who present with similar clinical and pathophysiologic status despite the etiology of LV dysfunction. To minimize the potential bias related to patient selection, our study population consisted only of patients with advanced nonischemic or ischemic cardiomyopathy owing to anterior infarction and functional MR. Patients with less LV remodeling and ischemic MR secondary to predominant inferior/posterior infarction, who have often been included in previous studies,[6-8,15,16,21,24] were excluded from our study. Therefore, our results would not be applicable to patients with previous inferior or lateral infarction.

During the late follow-up examinations, systolic PAP was determined noninvasively using Doppler echocardiography and not measured by catheterization. This noninvasive method has been fully validated and currently represents a standard approach for PH determination. In the present study, we confirmed that systolic PAP estimated using Doppler echocardiography correlated significantly with the nonsimultaneously catheter-derived systolic PAP ($r = .833$, $P < .001$). Moreover, Bland-Altman analysis showed that the 2 modalities had good agreement in the measurements of systolic PAP, although it was slightly overestimated using Doppler echocardiography (mean bias 1.5 ± 8.4 mm Hg).

The medical treatments administered could have also affected our findings. However, the preoperative medical therapies were continued without significant modifications after surgical intervention. In particular, the use and dosage of angiotensin-converting enzyme inhibitors and angiotensin-II receptor blockers were not changed; thus, their influence on LV remodeling and pulmonary vascular remodeling in our patients was considered to be negligible.

CONCLUSIONS

Noninvasive assessment of systolic PAP was found to be an excellent prognostic tool for patients who underwent RMA for functional MR secondary to advanced cardiomyopathy. Additional studies are needed to define the mechanism of PH and its postoperative reversibility in patients with cardiomyopathy to establish new treatment strategies.

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APPENDIX

The following variables were tested: age, gender, body surface area, NYHA functional class, ischemic etiology, hypertension, diabetes, hyperlipidemia, chronic obstructive pulmonary disease, chronic renal failure, peripheral vascular disease, cerebral vascular disease, atrial fibrillation, history of ventricular arrhythmia, duration of heart failure (in months), multivessel coronary artery disease, previous coronary artery bypass grafting, previous percutaneous coronary intervention, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin-II receptor blocker, diuretics, LVEDD (continuous), LVEDD (>65 mm), left ventricular end-systolic dimension (continuous), left ventricular end-systolic dimension (> 50 mm), left atrial dimension, LVEF, tenting height, coaptation length, MR grade, TR grade, systolic PAP (continuous), and severe PH (systolic PAP > 60 mm Hg).

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Does Stringent Restrictive Annuloplasty for Functional Mitral Regurgitation Cause Functional Mitral Stenosis and Pulmonary Hypertension?

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Background—It remains controversial whether restrictive mitral annuloplasty (RMA) for functional mitral regurgitation (MR) can induce functional mitral stenosis (MS) that may cause postoperative residual pulmonary hypertension (PH).

Methods and Results—One hundred eight patients with left ventricular (LV) dysfunction and severe MR underwent RMA with stringent downsizing of the mitral annulus. Systolic pulmonary artery pressure (PAP) and mitral valve performance variables were determined by Doppler echocardiography prospectively and 1 month after RMA. Fifty-eight patients underwent postoperative hemodynamic measurements. Postoperative echocardiography showed a mean pressure half-time of 92±14 ms, a transmitral mean gradient of 2.9±1.1 mm Hg, and a mitral valve effective orifice area of 2.4±0.4 cm^2, consistent with functional MS. Doppler-derived systolic PAP was 32±8 mm Hg, which correlated weakly with the transmitral mean gradient (ρ=0.23, P=0.02). Postoperative cardiac catheterization also showed significant improvements in LV volume and systolic function, pulmonary capillary wedge pressure, cardiac index, and systolic PAP; the latter was associated with LV end-diastolic pressure [standardized partial regression coefficient (SPRC)=0.51], pulmonary vascular resistance (SPRC=0.47), cardiac index (SPRC=0.37), and transmitral pressure gradient (SPRC=0.20). In a multivariate Cox proportional hazard model, postoperative PH (systolic PAP >40 mm Hg), but not mitral valve performance variables, was strongly associated with adverse cardiac events.

Conclusions—RMA for functional MR resulted in varying degrees of functional MS. However, our data were more consistent with the residual PH being caused by LV dysfunction and pulmonary vascular disease than by the functional MS. The residual PH, not functional MS, was the major predictor of post-RMA adverse cardiac events. **(*Circulation*. 2011;124[suppl 1]:S97–S106.)**

Key Words: functional mitral regurgitation ■ cardiomyopathy ■ restrictive mitral annuloplasty ■ functional mitral stenosis ■ pulmonary hypertension ■ patient-prosthesis mismatch

Restrictive mitral annuloplasty (RMA), which involves the insertion of an undersized prosthetic ring, has become the preferred surgical option for the treatment of patients with medically uncontrollable, severe functional mitral regurgitation (MR). Previous studies[1–4] have shown that stringent RMA can effectively eliminate functional MR, resulting in reverse left ventricular (LV) remodeling, and improved symptoms, and survival in the great majority of patients.

In contrast to these beneficial effects of the RMA procedure, Magne et al[5] first reported that the insertion of such an undersized ring may induce an iatrogenic "functional" mitral stenosis (MS) similar to prosthesis-patient mismatch (PPM), a condition that is frequently found after mitral valve replacement with a small prosthetic valve.[6–8] The effective orifice area (EOA) of a prosthetic valve or annuloplasty ring is often too small in relation to body size, causing a mismatch between the EOA and the transmitral flow, and yielding relatively high gradients. Several recent studies have reported a high incidence of functional MS, in which the mitral valve area is less than 1.5 cm^2[9] or the mean pressure gradient is greater than 5 mm Hg, after RMA.[10] In contrast, most prior

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echocardiographic studies did not describe problems with functional MS or ring PPM after mitral valve repair using an undersized annuloplasty ring.[3,4]

Magne et al[5] also found that this hemodynamic consequence (functional MS) may be associated with residual pulmonary hypertension (PH) after RMA. However, little data from invasive hemodynamic monitoring techniques with regard to functional MS have been reported. The purpose of this study was to evaluate the post-RMA hemodynamic data, to determine whether stringent RMA for functional MR results in functional MS, and whether this hemodynamic consequence is mainly responsible for residual PH after the operation. We also attempted to determine factors predicting residual PH and short-term outcome in patients undergoing the RMA procedure.

Methods

Patients

Between July 2003 and November 2009, 195 patients underwent RMA for functional MR using a semirigid complete ring (Carpentier-Edwards Physio ring; Edwards Lifesciences, Irvine, CA) at 3 university-affiliated hospitals. Functional MR associated with cardiomyopathy was defined as a combination of moderate-to-severe MR with (1) a history of at least 1 hospitalization for heart failure in the previous 6 months, despite maximal medical treatment, (2) global LV dysfunction (LV ejection fraction <40%) with a significantly enlarged left ventricle, and (3) type IIIb leaflet dysfunction, according to Carpentier classification. Of these patients, 87 were excluded because of concomitant surgical ventricular reconstruction (n=69), redo mitral valve surgery owing to MR recurrence (n=4), postoperative infective endocarditis (n=2), or early hospital death (n=12). The final study population consisted of 108 patients (86 men, 22 women), who had a mean body surface area (BSA) of 1.65±0.19 cm^2 (range, 1.30 to 2.26). Because the patients with a 26-mm Physio ring had a larger BSA than those with a 24-mm Physio ring, patient baseline characteristics are presented according to the size of the ring (Table 1). Before surgical referral, all the patients had been treated with optimized medical regimens by his or her attending cardiologist, including angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, β-blockers, and diuretics.

Ethical committee approval was obtained from each institution, and individual consent was waived for this retrospective analysis. Written informed consent for the procedure was obtained from each patient before surgery.

Echocardiography

Two-dimensional and Doppler transthoracic echocardiography examinations were performed before and 1 month after surgery. All echocardiographic studies were done using commercially available 3.75-MHz transducers (Toshiba, Tokyo, Japan, and Hewlett-Packard Sonos) by expert echocardiographic examiners who were blinded to the clinical status of the patients and their operative data. Echocardiographic measurements included LV end-diastolic and end-systolic dimensions, LA dimension, LV ejection fraction, and right ventricular (RV) end-diastolic dimension. Postoperative transmitral mean gradient were measured by Doppler echocardiography. The mitral valve EOA was determined by the pressure half-time method[11] and indexed for BSA. The severity of regurgitation was classified as none (0), trivial (1+), mild (2+), moderate (3+), or severe (4+) in the present study.

Doppler-Derived Pulmonary Artery Pressure

Systolic pulmonary artery pressure (PAP) was calculated by adding the systolic pressure gradient across the tricuspid valve derived from tricuspid regurgitation, to the estimated right atrial pressure value.[12,13]

Table 1. Patient Characteristics

Variables	Physio 24 mm (n=66)	Physio 26 mm (n=42)
Age, y	67±9	63±9
Males	47 (71%)	39 (93%)
Body surface area, m^2	1.61±0.19	1.70±0.17*
New York Heart Association class		
I	0 (0%)	0 (0%)
II	2 (3%)	3 (7%)
III	54 (81%)	24 (57%)
IV	10 (15%)	15 (36%)
Echocardiographic data		
LV end-diastolic dimension, mm	64±6	70±9*
LV end-systolic dimension, mm	54±7	60±11*
LV ejection fraction, %	29±8	29±8
Left atrial dimension, mm	46±7	50±9
RV end-diastolic dimension, mm	33±7	33±5
Systolic PAP, mm Hg	46±14	47±13
Mitral regurgitation, 0/1+/2+/3+/4+	0/0/0/38/28	0/0/0/17/25
Tricuspid regurgitation, 0/1+/2+/3+/4+	2/22/17/16/9	2/7/21/11/1
ECG		
Left bundle-branch block	14 (21%)	9 (21%)
QRS duration >130 ms	13 (20%)	11 (26%)
History of cardiac resynchronization therapy	2 (3%)	5 (12%)
DDD pacemaker	1 (2%)	0 (0%)
Comorbidity		
Hypertension	39 (59%)	19 (45%)
Diabetes	36 (55%)	17 (40%)
Hyperlipidemia	28 (42%)	12 (29%)
Chronic obstructive lung disease	4 (6%)	4 (10%)
Chronic renal failure	27 (41%)	16 (38%)
Peripheral vascular disease	10 (15%)	3 (7%)
Cerebral vascular accident	14 (21%)	6 (14%)
Atrial fibrillation	24 (36%)	14 (33%)
History of ventricular arrhythmia	7 (11%)	12 (29%)
Previous cardiac surgery	6 (9%)	1 (2%)
Etiology of cardiomyopathy		
Idiopathic	22 (33%)	20 (48%)
Ischemic	44 (67%)	22 (52%)
Medications		
β-Blockers	43 (65%)	24 (57%)
ACE inhibitors	17 (26%)	6 (14%)
Angiotensin II receptor blockers	25 (38%)	8 (19%)
Long-acting nitrates	11 (17%)	8 (19%)
Diuretics	48 (73%)	26 (62%)
Operative data		
Cardiopulmonary bypass time, min	181±62	189±63
Aortic cross-clamp time, min	97±44	110±45
Concomitant procedures		
Coronary artery bypass grafting	27 (41%)	19 (45%)
Tricuspid annuloplasty	47 (71%)	21 (50%)
Modified maze procedure	16 (24%)	13 (31%)
Pulmonary vein isolation	8 (12%)	1 (2%)

LV indicates left ventricular; RV, right ventricular; PAP, pulmonary artery pressure; ACE, angiotensin converting enzyme; and NS, not significant ($P>0.05$).

*$P<0.05$ versus Physio 24-mm.

Cardiac Catheterization

Right and left heart catheterization procedures were performed, using standard techniques before and 1 month (within 1 day of echocardiography) after surgery. The purposes of the cardiac catheterization and the invasive nature of the procedure were explained in detail to all patients, and only those who gave informed consent underwent catheterizations. The indications for postoperative catheterization were not selective. None had complications at the preoperative or postoperative catheterization. As a result, preoperative coronary arteriography was performed for all 108 patients, but left ventriculography and hemodynamic measurements were performed for 97 (90%) and 75 (69%), respectively. After surgery, 89 of the 108 patients (82%) underwent left ventriculography and 58 (54%) underwent hemodynamic measurements.

Before left ventriculography, standard pressure measurements were obtained to evaluate the LV systolic pressure, LV end-diastolic pressure (LVEDP), pulmonary capillary wedge pressure (PCWP); systolic, diastolic, and mean PAP; RV systolic pressure, RVEDP, and right atrial pressure. Right-sided pressures were obtained using a Swan-Ganz catheter. Cardiac output was determined with the thermodilution method. In addition, the systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) were also calculated.

Hemodynamic Assessment of Mitral Valve Performance

The gradient across the mitral valve was calculated as the pressure difference between mean PCWP and LVEDP, although it is better to determine transmitral gradients using simultaneous recordings.

Classification of the Severity of MS, Prosthesis-Patient Mismatch, and PH

MS severity was categorized classically as mild (EOA >1.5 cm^2, mean gradient <5 mm Hg), moderate (EOA 1.0 to 1.5 cm^2, mean gradient 5 to 10 mm Hg), or severe (EOA <1.0 cm^2, mean gradient >10 mm Hg).

Indeed, there is no single parameter that defines the severity of functional MS that is possibly induced by an RMA procedure. In the present study, functional MS severity was categorized according to the level of the in vivo EOA in relation to patient body size; PPM was defined as mild and not clinically significant if the indexed EOA was >1.2 cm^2/m^2, as moderate if it was >0.9 to 1.2 cm^2/m^2, and as severe if it was ≤ 0.9 cm^2/m^2.[8]

The severity of PH was also categorized as mild (systolic PAP <40 mm Hg), moderate (systolic PAP 40 to 60 mm Hg), or severe (systolic PAP >60 mm Hg).

Surgical Procedures

A median sternotomy was performed under a mild hypothermic cardiopulmonary bypass with intermittent cold blood cardioplegia. A stringent restrictive (2 to 3 sizes smaller than measured) mitral annuloplasty was performed for all patients. The ring size was selected according to the surgeon's preference (Ka.T., T. M., and Y.S.) at each hospital, considering the patient's body size. Sixty-six (61%) patients received a 24-mm Physio ring (geometric orifice area, 2.74 cm^2) and 42 (39%) a 26-mm Physio ring (geometric orifice area, 3.25 cm^2). Data regarding the geometric orifice area of the ring were supplied by the manufacturer. All relevant surgical data are summarized in Table 1.

Clinical Follow-Up

Clinical follow-up examinations were completed for all 108 patients (100%), with a mean duration of 33 ± 18 months. Every 6 months to 1 year, each patient was assessed in the department as well as by his or her primary cardiologist. A retrospective review of the medical records of these patients was performed to obtain the preoperative and postoperative data. Current information was obtained by calling the patient or the referring cardiologist. We also reviewed the postoperative adverse cardiac events defined as late cardiac-related death, myocardial infarction, thromboembolism, readmission for heart failure, and ventricular arrhythmia requiring implantation of an intracardiac defibrillator.

Statistical Analysis

Continuous variables are summarized as mean$\pm$SD and categorical variables as frequencies and proportions. All the continuous variables were checked for normality using the Shapiro-Wilk test and normal probability plot. Normally distributed variables were compared using the Student t test and nonnormally distributed variables were compared with the Mann-Whitney U test. Categorical variables were compared using the χ^2 analysis or Fisher exact test, as appropriate. Preoperative and postoperative hemodynamic variables were assessed by repeated-measures ANOVA with group, time, and group-time interaction effects. Nonnormally distributed variables tested in the repeated ANOVA were natural log-transformed to satisfy normality of the used models, as appropriate. Correlation between nonnormally distributed variables were tested with Spearman correlation coefficient (ρ).

Stepwise multiple linear regression analyses were performed to identify the determinants of Doppler-derived or catheter-measured systolic PAP. The Doppler-derived systolic PAP and catheter-measured systolic PAP were natural log-transformed to satisfy normality of the used models. Factors obtaining a probability value less than 0.1 in the univariate analysis, based on Spearman correlation coefficient were then entered appropriately into the stepwise multiple linear regression model. Regression diagnostics was used to assess the obtained models for collinearity and residual nonnormality and heteroscedasticity. The results are summarized as correlation coefficients (ρ) and standardized partial regression coefficients (SPRCs).

Univariate and multivariate analyses of the predictors for adverse cardiac time to events were performed using Cox proportional hazards models. Factors obtaining a probability value less than 0.1 in the univariate Cox proportional hazards analysis were then entered appropriately into the multivariate fashion, using stepwise variable selection. The results are summarized as hazard ratios (HRs) and 95% confidence intervals (CIs). Statistical significance was defined as a probability value <0.05. Statistical analyses were performed using JMP 7.0 (SAS Institute, Cary, NC) and SPSS software (version 17.0, SPSS Inc).

Results

Postoperative Echocardiographic Data

After surgery, none of the patients showed a significant ($>2+$) level of residual MR (Table 2). The pressure half-time was 92 ± 14 ms in all the patients (range, 67 to 129 ms versus normal value, 40 to 60 ms), which was prolonged and suggested the presence of gradients across the mitral valve. The transmitral mean gradient value was 2.9 ± 1.1 mm Hg (range, 1.1 to 6.2 mm Hg). Ninety-eight of the 108 patients (91%; 95% CI, 84% to 95%) had a transmitral mean gradient value <5 mm Hg (mild MS), whereas 10 (9%; 95% CI, 5% to 16%) had a mean gradient value ≥ 5 mm Hg (moderate MS). The mitral valve EOA value was 2.4 ± 0.4 cm^2 (range, 1.7 to 3.3 cm^2), and none of the patients had a value <1.5 cm^2. The indexed EOA value was 1.51 ± 0.32 cm^2/m^2 (range, 0.84 to 2.46 cm^2/m^2). Twenty-one (19%; 95% CI, 13% to 28%) showed moderate PPM (an indexed EOA >0.9 to ≤ 1.2 cm^2/m^2), and 2 (2%; 95% CI, 0.5 to 6.5%) had severe PPM (an indexed EOA ≤ 0.9 cm^2/m^2). The mean value for systolic PAP was 32 ± 8 mm Hg (range, 18 to 53 mm Hg). Seventeen patients (16%; 95% CI, 11% to 26%) showed moderate PH (systolic PAP, 40 to 60 mm Hg), and none had severe PH (systolic PAP >60 mm Hg) after surgery. Notably, patients with a 24-mm ring

Table 2. Postoperative Echocardiographic Measurements

Variables	All Cases (n=108)	Physio 24 mm (n=66)	Physio 26 mm (n=42)	*P* Value*
Geometric orifice area, cm^2		2.74	3.25	
Indexed GOA, cm^2/m^2	1.80±0.22	1.72±0.20	1.93±0.19	<0.001
Pressure half-time, ms	92±14	96±15	86±11	<0.001
Mitral mean gradient, mm Hg	2.9±1.1	3.1±1.1	2.6±1.1	0.01
<5 mm Hg	98 (91%)	58 (88%)	40 (95%)	NS
≥5 mm Hg	10 (9%)	8 (12%)	2 (5%)	
Mitral valve EOA, cm^2	2.4±0.4	2.3±0.4	2.6±0.3	<0.001
≥1.5 cm^2	108 (100%)	66 (100%)	42 (100%)	NS
<1.5 cm^2	0 (0%)	0 (0%)	0 (0%)	
Mitral valve EOA/GOA	0.83±0.12	0.86±0.13	0.80±0.10	0.01
Indexed EOA, cm^2/m^2	1.51±0.32	1.48±0.34	1.54±0.27	NS
>1.2 cm^2/m^2	85 (79%)	48 (73%)	37 (88%)	NS
>0.9 to 1.2 cm^2/m^2	21 (19%)	17 (26%)	4 (10%)	
≤0.9 cm^2/m^2	2 (2%)	1 (1%)	1 (2%)	
Indexed EOA/GOA, $/m^2$	0.52±0.11	0.54±0.12	0.48±0.08	0.003
Systolic PAP, mm Hg	32±8	31±9‡	32±6‡	NS
Not determined†	9 (8%)	5 (8%)	4 (10%)	NS
<40 mm Hg	82 (76%)	51 (77%)	31 (74%)	
40–60 mm Hg	17 (16%)	10 (15%)	7 (17%)	
>60 mm Hg	0 (0%)	0 (0%)	0 (0%)	
LV end-diastolic dimension, mm	61±9	59±7‡	64±10‡	NS
LV end-systolic dimension, mm	52±11	50±9‡	55±12‡	0.04
LV ejection fraction, %	33±10	34±10‡	32±10‡	NS
Left atrial dimension, mm	43±7	42±6‡	45±8‡	NS
RV end-diastolic dimension, mm	29±6	30±6‡	27±6‡	NS
Residual mitral regurgitation, 0/1+/2+/3+/4+	66/34/8/0/0	40/22/4/0/0	26/12/4/0/0	NS
Residual tricuspid regurgitation, 0/1+/2+/3+/4+	9/86/13/0/0	5/56/5/0/0	4/30/8/0/0	NS

GOA indicates geometric orifice area; EOA, effective orifice area; PAP, pulmonary artery pressure; LV, left ventricular; and RV, right ventricular.

*Physio 24-mm versus Physio 26-mm.

†Data were not available due to absence of tricuspid regurgitation.

‡$P<0.05$ versus variables at baseline in each group.

had a greater mean transmitral gradient, smaller mitral valve EOA, and longer pressure half-time compared with those with a 26-mm ring, whereas there was no difference between the groups with regard to the indexed EOA and systolic PAP. In general, the transmitral mean gradient correlated inversely with the indexed EOA value ($\rho=-0.30$ $P=0.002$), and correlated positively with the BSA ($\rho=0.27$, $P=0.006$).

Other LV dimension and function variables substantially improved in both groups.

Determinants of Postoperative Doppler-Derived Systolic PAP 1 Month After RMA

Postoperative Doppler-derived systolic PAP correlated with the Doppler-derived transmitral mean gradient ($\rho=0.23$, $P=0.02$) but did not correlate with the EOA or indexed EOA(Table 3). Postoperative systolic PAP also correlated with the catheter-derived postoperative PCWP ($\rho=0.40$, $P=0.002$), LVEDP ($\rho=0.38$, $P=0.004$), and PVR ($\rho=0.66$, $P<0.001$). Multivariate analysis showed that PVR had the most important contribution (SPRC=0.62), followed by LVEDP (SPRC=0.28), whereas the transmitral gradient had a minimal contribution (SPRC=0.24). Postoperative PCWP was not entered into the multivariate analysis because of a strong correlation between PCWP and LVEDP ($\rho=0.87$). Regression diagnostics showed no evidence of collinearity and residual nonnormality and heteroscedasticity in the obtained models.

Preoperative and Postoperative Hemodynamic Data

From baseline to 1 month after surgery, LV volumes decreased and ejection fraction improved in both patient groups (Table 4). LV systolic pressure did not change, whereas LVEDP, PCWP, systolic, and mean PAP decreased significantly. Other hemodynamic parameters such as cardiac index, PVR, and SVR also improved significantly or showed a trend toward normal in both groups. Importantly, there were no differences in postoperative LV function or hemodynamic parameters between the 2 groups, which received different sized rings.

Table 3. Determinants of Postoperative Doppler-Derived Systolic PAP 1 Month After RMA

	Univariate		Multivariate	
Variables	ρ	*P* Value	SPRC	*P* Value
Preop echocardiographic parameters (n=108)				
LVEDD, mm		NS		
LVESD, mm		NS		
LV ejection fraction, %		NS		
LA dimension, mm	0.22	0.03		
RVEDD, mm		NS		
Systolic PAP, mm Hg	0.35	<0.001		
Preop volume and function parameters (n=97)				
LVEDVI, mL/m^2		NS		
LVESVI, mL/m^2		NS		
LV ejection fraction, %		NS		
Preop hemodynamic parameters (n=75)				
LVSP, mm Hg		NS		
LVEDP, mm Hg	0.21	0.08		
PCWP, mm Hg	0.21	0.08		
Systolic PAP, mm Hg	0.21	0.08		
Cardiac index, L/min/m^2	−0.28	0.009		
PVR, dyne · s · cm^{-5}	0.63	<0.001		
SVR, dyne · s · cm^{-5}	0.26	0.02		
Postop echocardiographic parameters (n=108)				
LVEDD, mm		NS		
LVESD, mm		NS		
LV ejection fraction, %		NS		
LA dimension, mm	0.18	0.07		
RVEDD, mm		NS		
Mitral valve EOA, cm^2		NS		
Indexed EOA, cm^2/m^2		NS		
Pressure half-time, ms		NS		
Mitral mean gradient, mm Hg	0.23	0.02	0.24	0.01
Postop volume and function parameters (n=89)				
LVEDVI, mL/m^2		NS		
LVESVI, mL/m^2	0.25	0.02		
LV ejection fraction, %	−0.26	0.02		
Postop hemodynamic parameters (n=58)*				
LVSP, mm Hg		NS		
LVEDP, mm Hg	0.38	0.004	0.28	0.01
PCWP, mm Hg†	0.40	0.002		
Mitral gradient (mean PCWP-LVEDP), mm Hg		NS		
Cardiac index, L/min/m^2		NS		
PVR, dyne · s · cm^{-5}	0.66	<0.001	0.62	<0.001
SVR, dyne · s · cm^{-5}		NS		

SPRC indicates standardized partial regression coefficient; LV, left ventricular; RV, right ventricular; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; EOA, effective orifice area; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LA, left atrial; RVEDD, right ventricular end-diastolic dimension; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; LVSP, left ventricular systolic pressure; and NS, not significant ($P>0.05$).

*Postoperative catheter-measured systolic PAP was not tested in this analysis.

†Postoperative PCWP was not entered into the multivariate analysis because of a strong correlation between PCWP and LVEDP ($\rho=0.87$).

The postoperative transmitral pressure gradient value, calculated as the pressure difference between mean PCWP and LVEDP, was 3.0±1.2 mm Hg (range, 1 to 7 mm Hg). The mean value for catheter-measured postoperative systolic PAP was 33±8 mm Hg (range, 18 to 54 mm Hg). Fifteen of the 58 patients (26%; 95% CI, 16% to 38%) showed moderate PH (systolic PAP, 40 to 60 mm Hg), and none had severe PH (systolic PAP, >60 mm Hg) after surgery. Notably, patients with a 24-mm ring had greater transmitral pressure gradients compared with patients with a 26-mm ring, whereas there was no difference in systolic PAP between the groups. There were also no differences for the other hemodynamic measurements.

In general, the transmitral pressure gradient correlated positively with cardiac output ($\rho=0.77$, $P<0.001$) and heart rate ($\rho=0.27$, $P=0.05$).

Determinants of Postoperative Catheter-Measured Systolic PAP 1 Month After RMA

In univariate analyses, the postoperative catheter-measured systolic PAP correlated with the PCWP ($\rho=0.70$, $P<0.001$), LVEDP ($\rho=0.56$, $P<0.001$), transmitral pressure gradient ($\rho=0.52$, $P<0.001$), cardiac index ($\rho=0.28$, $P=0.04$), and PVR ($\rho=0.54$, $P<0.001$) (Table 5). Multivariate analysis showed that LVEDP had the most important contribution (SPRC=0.51), followed by PVR (SPRC=0.47) and the cardiac index (SPRC=0.37), whereas the transmitral pressure gradient had a minimal contribution (SPRC=0.20). Postoperative PCWP was not entered into the multivariate analysis because of a strong correlation between PCWP and LVEDP ($\rho=0.87$). Regression diagnostics showed no evidence of collinearity, and residual nonnormality and heteroscedasticity in the obtained models.

Correlation Between Invasive Hemodynamic Measurements and Noninvasive Doppler-Derived Variables

Spearman correlation analysis showed a strong correlation ($\rho=0.94$, $P<0.001$) between the catheter-measured mitral pressure gradient and Doppler-derived transmitral mean gradient values. There was also a substantial correlation

Table 4. Preoperative and Postoperative Hemodynamic Measurements

	Physio No. 24 (n=32)		Physio No. 26 (n=26)				
Variables	Preop	Postop	Preop	Postop	Group	Time	Group-Time
LV end-diastolic volume index, mL/m^2	135±35	109±35	150±47	126±49	NS	<0.001	NS
LV end-systolic volume index, mL/m^2	101±30	78±33	113±44	90±48	NS	<0.001	NS
LV ejection fraction, %	26±7	30±12	26±8	31±12	NS	0.002	NS
LV systolic pressure, mm Hg	115±21	121±14	123±21	124±24	NS	NS	NS
LVEDP, mm Hg	17±6	9±3	17±7	11±3	NS	<0.001	NS
PCWP, mm Hg	21±6	13±3	21±8	13±3	NS	<0.001	NS
Mitral gradient (=mean PCWP−LVEDP), mm Hg		3.3±1.4		2.6±1.0*			
Systolic PAP, mm Hg	46±13	34±9	46±16	34±9	NS	<0.001	NS
<40 mm Hg	10 (31%)	24 (75%)	11 (42%)	19 (73%)			
40–60 mm Hg	19 (60%)	8 (25%)	10 (38%)	7 (27%)			
>60 mm Hg	3 (9%)	0 (0%)	5 (19%)	0 (0%)			
Mean PAP, mm Hg	32±7	21±6	33±9	22±6	NS	<0.001	NS
Right atrial pressure, mm Hg	8±4	8±3	7±4	8±2	NS	NS	NS
Heart rate, beats/min	78±11	79±13	76±15	81±10	NS	NS	NS
Cardiac index, L/min/m^2	2.7±0.7	2.9±0.7	2.3±0.6	2.8±0.6	NS	<0.001	0.02
Stroke volume index, mL/m^2	36±11	38±10	31±9	35±5	NS	0.02	NS
PVR, dyne · s · cm^{-5}	235±73	150±75	250±71	156±67	NS	<0.001	NS
SVR, dyne · s · cm^{-5}	1470±460	1370±440	1620±400	1220±250	NS	<0.001	0.02

LV indicates left ventricular; RV, right ventricular; PAP, pulmonary artery pressure; EDP, end-diastolic pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; EOA, effective orifice area; and NS, not significant (P>0.05).

*P<0.05 versus Physio 24-mm.

(ρ=0.67, P<0.001) between the catheter-measured systolic PAP and Doppler-derived systolic PAP values.

Clinical Outcomes

In this series, the actuarial survival rates at 1, 2, and 3 years after surgery were 95±2%, 92±3%, and 87±4%, respectively. During the follow-up period, there were 6 late cardiac-related deaths, 29 late readmissions due to heart failure, 1 myocardial infarction, and 4 ventricular arrhythmias. Freedom from adverse cardiac events at 1, 2, and 3 years after surgery was 88±3%, 78±4%, and 68±5%, respectively. There was no difference in freedom from adverse cardiac events between patients with an indexed EOA of >1.2 cm^2/m^2 versus ≤1.2 cm^2/m^2.

Among the preoperative variables investigated, preoperative PAP >60 mm Hg (HR, 4.5; 95% CI, 2.2 to 8.9) and a history of ventricular arrhythmia (HR 2.1, 95% CI: 1.0 to 4.6) were the predictors of the postoperative adverse cardiac events (Table 6). Furthermore, among the postoperative echocardiographic variables and surgical data, a postoperative PAP >40 mm Hg (HR, 4.6; 95% CI, 2.3 to 9.3) and residual tricuspid regurgitation (HR, 2.5; 95% CI, 1.0 to 6.1) were the predictors of adverse cardiac events (Table 7).

Discussion

This study constitutes an initial report evaluating the association between iatrogenic functional MS, PPM in terms of in vivo indexed EOA, residual PH, and clinical outcome (late adverse cardiac events) after RMA in patients with advanced cardiomyopathy.

The present echocardiographic results are largely consistent with those presented in previous studies, especially in terms of the transmitral mean gradient, mitral valve area, and systolic PAP.[3,4,14–16] In contrast, Magne et al[5] reported a higher mean gradient (6±2 mm Hg), smaller mitral valve area (1.5±0.3 cm^2), and higher systolic PAP (42±13 mm Hg) values compared with other prior studies. Among the 24 patients in their study, 54% (n=13) had a mean gradient ≥5 mm Hg, 54% (n=13) had a valve area ≤1.5 cm^2, and 45% (n=11) had a systolic PAP ≥40 mm Hg. From those findings, they concluded that a large proportion (>50%) of the patients who underwent RMA had moderate functional MS and significant PH after the operation. In addition, a recent study[9] also reported a high prevalence (42%) of patients with a small valve area, ≤1.5 cm^2. However, in that study, the transmitral gradients were similar to those reported in many other studies.[3,4,14–16]

In the present study, only 9% of the patients showed a mean gradient ≥5 mm Hg, and none had a valve area ≤1.5 cm^2. The contrasting results with regard to valve area as compared to the study of Magne et al[5] can be explained by the different methods utilized for determining valve area. Magne et al[5] calculated mitral valve area using the continuity equation, whereas many other investigators, including our group, determined it using the pressure half-time method or direct planimetry.[3,4,14–16] In addition, the difference in results for the transmitral gradient may be due to subject selection bias or the patient's BSA. The mean BSA of their patients was greater than that of our patients (1.8±0.2 m^2 versus 1.65±0.19 m^2). Magne et al[5] also found a significant corre-

Table 5. Determinants of Postoperative Catheter-Measured Systolic PAP 1 Month After RMA

	Univariate		Multivariate	
Variables	ρ	*P* Value	SPRC	*P* Value
Preop echocardiographic parameters (n=108)				
LVEDD, mm		NS		
LVESD, mm		NS		
LV ejection fraction, %		NS		
LA dimension, mm	0.35	0.007	0.23	0.009
RVEDD, mm		NS		
Systolic PAP, mm Hg	0.54	<0.001		
Preop volume and function parameters (n=97)				
LVEDVI, mL/m^2		NS		
LVESVI, mL/m^2		NS		
LV ejection fraction, %		NS		
Preop hemodynamic parameters (n=75)				
LVSP, mm Hg		NS		
LVEDP, mm Hg	0.26	0.08		
PCWP, mm Hg	0.28	0.06		
Systolic PAP, mm Hg	0.33	0.02		
Cardiac index, L/min/m^2		NS		
PVR, dyne · s · cm^{-5}	0.28	0.04		
SVR, dyne · s · cm^{-5}		NS		
Postop echocardiographic parameters (n=108)*				
LVEDD, mm		NS		
LVESD, mm		NS		
LV ejection fraction, %		NS		
LA dimension, mm	0.42	0.001		
RVEDD, mm		NS		
Mitral valve EOA, cm^2		NS		
Indexed EOA, cm^2/m^2		NS		
Pressure half-time, ms		NS		
Mitral mean gradient, mm Hg	0.52	<0.001	0.20	0.006
Postop volume and function parameters (n=89)				
LVEDVI, mL/m^2		NS		
LVESVI, mL/m^2		NS		
LV ejection fraction, %		NS		
Postop hemodynamic parameters (n=58)				
LVSP, mm Hg		NS		
LVEDP, mm Hg	0.56	<0.001	0.51	<0.001
PCWP, mm Hg†	0.70	<0.001		
Mitral gradient (mean PCWP−LVEDP), mm Hg	0.44	<0.001		
Cardiac index, L/min/m^2	0.28	0.04	0.37	<0.001
PVR, dyne · s · cm^{-5}	0.54	<0.001	0.47	<0.001
SVR, dyne · s · cm^{-5}		NS		

LV indicates left ventricular; RV, right ventricular; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; EOA, effective orifice area; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LA, left atrial; RVEDD, right ventricular end-diastolic dimension; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; LVSP, left ventricular systolic pressure; and NS, not significant ($P>0.05$).

*Postoperative Doppler-derived systolic PAP was not tested in this analysis.

†Postoperative PCWP was not entered into the multivariate analysis because of a strong correlation between PCWP and LVEDP ($\rho=0.87$).

lation between the mitral peak gradient and systolic PAP ($r=0.70$) and concluded that functional MS after RMA was strongly associated with postoperative elevated PAP and reduced exercise capacity. We found a weak but significant correlation between the mean mitral gradient and systolic PAP, which may support their speculation. However, it remains unknown whether the mitral gradient is the sole factor that affects postoperative elevated PAP.

There have been few hemodynamic studies on possible functional MS after RMA. Our hemodynamic results provide additional information about the gradients across the mitral valve and possible factors relating to postoperative PH. The present study also found a small but significant transmitral pressure gradient, calculated as the pressure difference between mean PCWP and LVEDP, which ranged from 1 to 7 mm Hg. The actual value may be slightly smaller than predicted by this pressure difference.[17] Nevertheless, about 10% of our patients (6 of 58) had a pressure gradient ≥5 mm Hg, suggesting the presence of hemodynamically substantial MS. Interestingly, in the present study, we found a strong correlation between the catheter-determined pressure gradient calculated from the mean PCWP and LVEDP, and the Doppler-derived mean gradient. This close correlation allowed us to predict the actual transmitral mean gradient, based on the pressure difference at end-diastole and to analyze relevant factors related to postoperative PH.

Hemodynamic Determinants of Postoperative PAP

Our multivariate analysis using hemodynamic variables showed that the most important determinant of systolic PAP was LVEDP, followed by PVR, and then cardiac index, whereas the contribution of the transmitral pressure gradient was the lowest of the parameters investigated. These findings suggest that the main mechanism of postoperative PH may be high LVEDP, probably due to LV systolic and diastolic dysfunction, whereas another may be pulmonary vascular disease secondary to a preoperative pulmonary hypertensive state. The contribution of a transmitral pressure gradient created by the use of an undersized ring to postoperative PH seemed relatively small in our patients.

Table 6. Preoperative Parameters Associating With Adverse Cardiac Events

	Univariate		Multivariate	
Variables	*P* Value	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)
Clinical variables (n=108)				
Age, y	NS			
Ischemic etiology	NS			
Female	NS			
Duration of heart failure, mo	<0.001	1.01 (1.01–1.02)		
Hypertension	NS			
Diabetes	0.09	1.8 (0.9–3.6)		
Hyperlipidemia	NS			
Chronic renal failure	NS			
Peripheral vascular disease	NS			
Cerebral vascular accident	NS			
Atrial fibrillation	NS			
History of ventricular arrhythmia	0.03	2.3 (1.1–4.9)	0.04	2.1 (1.0–4.6)
Chronic obstructive pulmonary disease	NS			
Previous cardiac surgery	NS			
Preop echocardiographic parameters (n=108)				
LV end-diastolic dimension, mm	NS			
LV end-diastolic dimension >65 mm	NS			
LV end-systolic dimension, mm	0.02	1.05 (1.01–1.08)		
LV end-systolic dimension >50 mm	NS			
LV ejection fraction, %	0.006	0.94 (0.90–0.98)		
LV ejection fraction <25%	0.03	2.2 (1.1–4.3)		
Left atrial dimension, mm	NS			
RV end-diastolic dimension, mm	NS			
Systolic PAP, mm Hg*	0.04	1.02 (1.00–1.05)		
Systolic PAP >60 mm Hg	<0.001	4.6 (2.3–9.1)	<0.001	4.5 (2.2–8.9)
Preop volume and function parameters (n=97)				
LV end-diastolic volume index, mL/m^2	NS			
LV end-diastolic volume index >120 mL/m^2	NS			
LV end-systolic volume index, mL/m^2	NS			
LV end-systolic volume index >90 mL/m^2	NS			
LV ejection fraction, %	NS			
LV ejection fraction <25%	NS			
Preop hemodynamic parameters (n=75)				
LV systolic pressure, mm Hg	NS			
LVEDP, mm Hg	NS			
PCWP, mm Hg	NS			
Systolic PAP, mm Hg	NS			
Mean PAP, mm Hg	NS			
Cardiac index, L/min/m^2	0.07	0.6 (0.3–1.1)		
PVR, dyne · s · cm^{-5}	0.002	1.008 (1.00–1.01)		
PVR index, dyne · s · cm^{-5} · m^2	0.004	1.004 (1.001–1.007)		
SVR, dyne · s · cm^{-5}	0.08	1.001 (1.000–1.002)		
SVR index, dyne · s · cm^{-5} · m^2	NS			

CI indicates confidence interval; LV, left ventricular; RV, right ventricular; PAP, pulmonary artery pressure; EDP, end-diastolic pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; and NS, not significant ($P>0.05$).

*Systolic PAP (continuous variable) was not entered into the multivariate analysis.

Table 7. Postoperative Parameters Associating With Adverse Cardiac Events

	Univariate		Multivariate	
Variables	*P* Value	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)
Postop echocardiographic parameters (n=108)				
LV end-diastolic dimension, mm	0.03	1.04 (1.00–1.08)		
LV end-systolic dimension, mm	0.005	1.05 (1.01–1.08)		
LV ejection fraction, %	0.001	0.94 (0.91–0.98)		
Left atrial dimension, mm	NS			
RV end-diastolic dimension, mm	NS			
Systolic PAP, mm Hg*	<0.001	1.1 (1.04–1.13)		
Systolic PAP >40 mm Hg	<0.001	5.2 (2.6–10)	<0.001	4.6 (2.3–9.3)
Mitral valve EOA, cm^2	NS			
Indexed EOA, cm^2/m^2	NS			
Indexed EOA ≤1.2 cm^2/m^2	0.09	0.53 (0.26–1.09)		
Pressure half-time, ms	0.07	1.02 (0.99–1.04)		
Mitral mean gradient, mm Hg	0.03	1.36 (1.04–1.78)		
Mitral mean gradient ≥5 mm Hg	NS			
Residual mitral regurgitation†	NS			
Residual tricuspid regurgitation†	0.004	3.55 (1.5–8.4)	0.04	2.5 (1.0–6.1)
Surgical data (n=108)				
Ring size	NS			
Concomitant coronary artery bypass grafting	0.02	0.4 (0.2–0.8)		
Concomitant tricuspid annuloplasty	NS			
Concomitant maze procedure	NS			

CI indicates confidence interval; LV indicates left ventricular; RV, right ventricular; PAP, pulmonary artery pressure; EOA, effective orifice area; and NS, not significant ($P>0.05$).

*Systolic PAP was not entered into the multivariate analysis.

†Greater than or equal to mild grade.

Impact of the RMA Procedure on Hemodynamic and Clinical Results

The present patients with a 24-mm ring had a smaller mitral valve area and slightly greater transmitral mean gradient in echocardiographic findings, as well as a greater valve gradient in the hemodynamic evaluation, compared with those with a 26-mm ring. Despite these differences in mitral valve performance, there were no differences between the 2 groups in regard to postoperative LV volume and systolic function, PAPs, or the other measured hemodynamic parameters. Thus, in our patients, who had a lower BSA compared with those in previous studies, the use of a small prosthetic ring (24-mm Physio ring) did not appear to have a negative influence on the postoperative hemodynamic state over the short term.

Given that the normal mitral valve area is 4.0 to 5.0 cm^2, the 24- and 26-mm rings have obviously smaller orifice areas and are at least mildly obstructive to the antegrade mitral flow. The severity of this PPM can be categorized as mild, moderate, or severe according to the "in vivo" EOA indexed for the patient's BSA, as in previous studies.[7,8] Several studies have demonstrated that after mitral valve replacement, moderate PPM (indexed EOA ≤1.2 cm^2/m^2) is not uncommon, and that it has negative impacts on postoperative residual PH and late mortality and morbidity.[7,8,18] Other authors have suggested that moderate PPM in these patients is of less importance.[19,20]

In contrast, the prevalence and prognostic impact of PPM after RMA has not been well established. Our data showed that, following RMA, a considerable proportion (>20%) of patients had PPM, defined as an indexed EOA ≤1.2 cm^2/m^2. This mismatch occurred in 27% of the patients with a 24-mm ring and 12% with a 26-mm ring, which was not statistically different. Given that the pressure half-time method may overestimate the actual valve orifice area by about 10%, our in vivo EOA values suggest that the size 24- and 26-mm prosthetic rings may be too small, respectively, for patients with a BSA >1.75 to 1.80 m^2 or >1.90 to 2.00 m^2. However, it remains unclear whether such a mismatch after RMA has a negative impact on patient's prognosis.

In the present study, preoperative and postoperative residual PH, due to LV dysfunction and secondary pulmonary vascular disease, was more strongly associated with adverse cardiac events after RMA than was the severity of functional MS or the level of PPM. A Doppler-derived mean gradient of ≥5 mm Hg or an indexed EOA of ≤1.2 cm^2/m^2 did not predict adverse cardiac events during our short-term follow-up. We speculate that our identification of a negative prognostic role (a higher risk of adverse cardiac events) of this iatrogenic MS would have been masked in our analysis by the more important risk factors.

Study Limitations

The main limitation of this study is its retrospective design, as hemodynamic data could not be obtained from all of the patients, which may have resulted in a bias and restrict the statistical power of the findings. Also, in fully describing these data we have performed a large number of statistical tests, inflating the probability of making one or more type I errors across all the analyses presented. Therefore, our results should be interpreted cautiously until verified in an independent, prospective study. Furthermore, simultaneous LA and LV pressure tracings were not available, and therefore the actual mean transmitral pressure gradients and mitral valve EOA could not be determined using the Gorlin formula. In our echocardiographic and hemodynamic evaluations, the parameters were measured only in a resting condition; a dynamic exercise test with a bicycle ergometer, dobutamine stress test, or 6-minute walk test was not performed. However, data obtained from those stress tests would not have changed our conclusion. Finally, we only investigated patients who received a 24- or 26-mm Physio ring. Therefore, the results may not be applicable to patients who receive a different size or type of ring.

Conclusion

In the present study, the RMA procedure led to varying degrees of mitral valve obstruction in terms of higher transmitral mean pressure gradients (about 9% of patients) and a lesser EOA, as indexed for each patient's BSA (>20% of patients). This hemodynamic sequel was weakly associated with postoperative residual PH. However, postoperative elevated PAP was strongly associated with an elevated LVEDP and increased PVR. PH caused by LV dysfunction and pulmonary vascular disease was the most important predictor for outcomes in this study. The prognostic impact of iatrogenic MS after RMA would be hard to detect because of masking by more important risk factors.

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None.

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Posterior maximization and averaging for Bayesian working model choice in the continual reassessment method

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The continual reassessment method (CRM) is a method for estimating the maximum tolerated dose in a dose-finding study. Traditionally, use is made of a single working model or 'skeleton' idealizing an underlying true dose–toxicity relationship. This working model is chosen either by discussion with investigators or published data, before the beginning of the trial or simply on the basis of operating characteristics. To overcome the arbitrariness of the choice of such a single working model, Yin and Yuan (*J. Am. Statist. Assoc.* 2009; 104:954–968) propose a model averaging over a set of working models. Here, instead of averaging, we investigate some alternative Bayesian model criteria that maximize the posterior distribution. We propose three adaptive model-selecting CRMs using the Bayesian model selection criteria, in which we specify in advance a collection of candidate working models for the dose–toxicity relationship, especially initial guesses of toxicity probabilities, and adaptively select the only one working model among the candidates updated by using the original CRM for each working model, based on the posterior model probability, the posterior predictive loss or the deviance information criteria, during the course of the trial. These approaches were compared via a simulation study with the model averaging approach. Copyright © 2011 John Wiley & Sons, Ltd.

Keywords: dose-finding; phase I; posterior model probability; posterior predictive loss; deviance information criterion

1. Introduction

The purpose of a dose-finding clinical trial is to determine the maximum tolerated dose (MTD) of a new agent or combination of drugs for subsequent use in phase II and phase III trials. For cytotoxic agents, the MTD is in practice a dose with some given acceptable rate of toxicity, and is determined through a sequential allocation rule.

A number of designs to determine the MTD have been developed for phase I dose-finding trials. Nonparametric designs such as the standard '3+3' design [1], its extension '$A+B$' designs [2], grouped up-and-down designs [3, 4] are easy to understand and implement since they do not require explicit model specification for a dose–toxicity relationship. On the other hand, innovative designs have been proposed such as the continual reassessment method (CRM) [5]. These are often referred to as model-based approaches [6, 7], since a single-parameter working model (sometimes called a skeleton or an initial guess for the dose–toxicity relationship) needs to be specified prior to the trial beginning. In practice, only one working model is usually chosen.

For the CRM there are a wide number of choices of model family and the particular parameterization for any model. Shen and O'Quigley [8] provided sufficient conditions for a broad range of models to

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correctly locate the MTD for large samples. Simulations, under an extensive array of possible situations, have shown that the CRM, along with other recently developed techniques, outperforms the standard '3+3' designs [9, 10]. Model-based approaches, such as the CRM, use fewer patients overall, reach the MTD more quickly using fewer patients and treat more patients at and close to the MTD.

In various methodological developments for the CRM, its modified versions and applications, an important issue is the requirement of pre-specification of the working model to be used in the trial. As the toxicity profile is often unknown for a new drug, such pre-specification is largely arbitrary. O'Quigley and Zohar [11] have pointed out the risk in choosing a 'reasonable' class of working models. A 'reasonable' working model is one that would exhibit good robustness properties. Some working models, while respecting the constraints of Shen and O'Quigley [8], could be anticipated not to be reasonable in this sense. When the algorithm attempts to distinguish competing dose levels as candidates for the current estimate of the MTD, the more the spread out, the better the dose levels. As an example, if we consider three dose levels, two of which are very close while the third is well removed from both of them, then it is easier deciding in favor of this third dose as opposed to choosing between the other two. If we are given I, the total number of possible doses then it is usually an idea to spread them as much as we can, specifically, in the case where the doses lie in the interval (0,1), to roughly divide this interval into $I+1$ subintervals of a similar length. When using the original CRM proposed by O'Quigley *et al.* [5], the underparameterized working model is usually chosen for the dose–toxicity model, combined with the vague prior density. Overall fit is not an important objective of phase I studies [5, 12] and for this reason such a one-parameter working model is rich enough for the purpose of identification of the MTD.

Some authors have proposed methods either calibrating the working model prior to the beginning of the trial [13, 14] or while the trial is being carried out [15]. Cheung and Chappell [13] have illustrated that operating characteristics are less sensitive to some working model choices than others. These authors have developed a numerical technique to evaluate the model sensitivity in the CRM in order to choose one working model that will be used in the clinical trial. Lee and Cheung [14] have recently used indifference intervals, and the working model used in the CRM is then selected by specifying a range of acceptable toxicity probabilities in addition to the target probability of toxicity. An algorithm was proposed for obtaining the indifference interval that maximizes the average percentage of correct selection across a set of scenarios of true probabilities of toxicity and providing a systematic approach for selecting a working model before the beginning of the trial. A different methodological approach is that of Yin and Yuan [15]. They proposed a Bayesian model averaging (BMA) approach to obtain the posterior estimates for the true toxicity probabilities by weighing the estimates from each working model with the corresponding posterior model probability (PMP).

Our aim is to investigate model selection in the CRM in the spirit of Yin and Yuan [15]. The proposed methods can include all the elicited or possible working models provided by investigators. In this case, there is no need to choose only one working model prior to the beginning of the trial or to average several working models into a single one during the course of the trial. Only one working model is adaptively and sequentially selected during the course of the trial, based on the Bayesian model selection criteria. The model selection criteria used in our approach are the posterior predictive loss (PPL) [16], the deviance information criterion (DIC) [17] and the PMP [15, 18].

In Section 2 the original CRM is briefly described. In Section 3 Bayesian model selection criteria are introduced, and three adaptive model-selecting CRMs are proposed. In Section 4 we compare these approaches with the original CRM and the CRM using the Bayesian model averaging [15], through a simulation study with several scenarios.

2. Basic method

The basic structure of the CRM was described by O'Quigley *et al.* [5], where the details can be found. Here we recall the main ideas.

Let n be the number of patients included in the trial on I fixed ordered doses, $d_1, \ldots, d_I$. During the trial, a pair of two random variables (X_j, Y_j) is observed for the jth patient ($j=1, \ldots, n$), where X_j is a dose administered to the jth included patient, which takes a real value $x_j \in \{d_1, \ldots, d_I\}$, and Y_j is a binary response variable for toxicity after the patient is administered dose x_j, where it takes one for a toxic response and zero otherwise.

The probability of suffering from toxicity, for the jth patient, at dose x_j, is given by

$$R(x_j)=\Pr(Y_j=1|X_j=x_j)\approx\psi(x_j,a),\quad j=1,\ldots,n,$$

where $R(x_j)$ is the true probability of suffering from a toxicity and $\psi(x_j,a)$ only provides a working approximation to $R(x_j)$. We restrict our attention to a simple working model [12], given by $\psi(d_i,a)=\alpha_i^a$; $i=1,\ldots,I$. A single value of α_i for dose level i is usually pre-specified by investigators such that $\alpha_i<\alpha_{i+1}$ for $i=1,\ldots,I-1$, and a $(0<a<\infty)$ is a parameter to be estimated. After the first j included patients' data $\Omega_j=\{(x_l,y_l);l=1,\ldots,j\}$ $(j=1,\ldots,n)$ (pairs of dose and response) are obtained, the posterior density for parameter a is given by

$$f(a|\Omega_j)=\frac{L(\Omega_j)g(a)}{\int_0^\infty L(\Omega_j)g(a)\,\mathrm{d}a},$$

where $L(\Omega_j)$ is the likelihood, given by $L(\Omega_j)=\prod_{l=1}^{j}\{\psi(x_l,a)\}^{y_l}\{1-\psi(x_l,a)\}^{(1-y_l)}$, and $g(a)$ represents a vague prior. In O'Quigley *et al.* [5] a gamma prior is suggested and, mostly, it is enough to consider the special case of the gamma $g(a)=f(a|\Omega_0)=\exp(-a)$, that is, we assume a unit exponential distribution for the prior of a.

If a is estimated by $\tilde{a}_j=\int_0^\infty af(a|\Omega_j)\mathrm{d}a$ after the observation of the jth patient, the estimated probability of toxicity for patient j treated at dose $X_j=x_j$ is given by $\tilde{R}(x_j)=\psi(x_j,\tilde{a}_j)$. The CRM allocates the dose level with the estimated toxicity probability closest to any target θ^* (from 0 to 1), to the $(j+1)$th patient, and hence estimates the MTD as the dose level at which $(n+1)$th patient would be treated.

3. Model-selecting continual reassessment methods

To overcome the arbitrariness in pre-specification of a single working model, especially for a phase I trial in which initial guess of the toxicity probabilities is rarely accurate, as well as to avoid poor pre-specification, our proposal consists of the following procedures: (1) to use all elicited or possible working models corresponding to initial guesses of the toxicity probabilities given by investigators before the start of the trial, (2) to update each of them by the CRM simultaneously, (3) to select one working model out of them, automatically and adaptively by using some criterion, during the course of the trial, and (4) to estimate the MTD based on the selected working model and allocate the estimated MTD to each included patient.

In the following, three Bayesian model selection criteria: the PPL [16], the DIC [17] and the PMP [15, 18], are proposed and adapted to the sequential feature of dose-finding designs, and a Bayesian model averaging CRM (CRM-BMA), which has been recently proposed by Yin and Yuan [15] is described. A dose-finding algorithm of the model-adaptive CRM using either of the above three criteria are given at the end of the section.

3.1. Posterior model probability

Suppose that there exists a set of M working models corresponding to initial guesses of I toxicity probabilities for the available doses, $d_1,\ldots,d_I$, which reflects investigators' quite different opinions, before the start of the trial, on the underlying true probability of toxicity associated with each of the doses. Let us denote these as $\{(\alpha_{1,1},\ldots,\alpha_{I,1}),\ldots,(\alpha_{1,M},\ldots,\alpha_{I,M})$. Then the mth working model used in the CRM is given by

$$\psi(d_i,a_m)=\alpha_{i,m}^{a_m},$$

where a_m is the parameter for the mth working model. In the same way as the original CRM (see Section 2), after the first j included patients' data Ω_j $(j=1,\ldots,n)$ are obtained, the posterior density for the parameter a_m is given by

$$f(a_m|\Omega_j)=\frac{L_m(\Omega_j)g(a_m)}{\int_0^\infty L_m(\Omega_j)g(a_m)\mathrm{d}a_m},$$

where $L_m(\Omega_j)$ is the likelihood for the mth working model, given by $L_m(\Omega_j)=\prod_{l=1}^{j}\{\psi(x_l,a_m)\}^{y_l}\{1-\psi(x_l,a_m)\}^{(1-y_l)}$, and $g(a_m)=f(a_m|\Omega_0)=\exp(-a_m)$.

Under the mth working model a Bayesian estimator of the toxicity probability, for the jth included patient, at the ith dose d_i, is given by $\theta_{ij,m}=\psi(d_i,\tilde{a}_{j,m})$, where $\tilde{a}_{j,m}=\int_0^\infty a_m f(a_m|\Omega_j)\mathrm{d}a_m$. For the mth working model we hold $d_{i^*,m}$ such that

$$i^*=\underset{i\in(1,\ldots,I)}{\operatorname{argmin}}\ |\theta_{ij,m}-\theta^*|.$$

Here, let us consider selecting only one working model and allocating the dose level found on it to $(j+1)$ th included patient. A simple idea for selecting one working model out of a set of M working models would be to use the PMP. That is, we can select the working model with the highest PMP value. This method was briefly mentioned by Yin and Yuan [15], where the normal prior was used, and the estimation method for the toxicity probabilities was different from ours. Denoting the mth working model as M_m, the PMP for the mth working model is defined by

$$\Pr(\mathsf{M}_m|\Omega_j)=\frac{\Pr(\mathsf{M}_m)\int_0^\infty L_m(\Omega_j)f(a_m|\Omega_j)\mathrm{d}a_m}{\sum_{m=1}^{M}\Pr(\mathsf{M}_m)\int_0^\infty L_m(\Omega_j)f(a_m|\Omega_j)\mathrm{d}a_m},\tag{1}$$

where $\Pr(\mathsf{M}_m)$ is such that $\sum_{m=1}^{M}\Pr(\mathsf{M}_m)=1$ and represents the probability that the mth working model is true. $\Pr(\mathsf{M}_m)=1/M$ indicates the probability for each model and in this case the PMP results in the ratio of the marginal likelihoods. We call the CRM using this PMP criterion as the CRM-PMP.

In this connection, the BMA estimate for the toxicity probability, for the jth included patient, at dose level i, under model M_m, can be derived from the PMP, and be applied to find the dose (see [15] for the details):

$$\bar{\theta}_{ij}=\sum_{m=1}^{M}\psi(d_i,\tilde{a}_{j,m})\Pr(\mathsf{M}_m|\Omega_j).$$

Thus, we then find the dose $d_{i^*_{\mathrm{BMA}}}$ such that

$$i^*_{\mathrm{BMA}}=\underset{i\in(1,\ldots,I)}{\operatorname{argmin}}\ |\bar{\theta}_{ij}-\theta^*|.$$

The BMA approach automatically assigns a higher weight to a better-fitting model. In Section 4 we will use it for comparisons with other approaches.

3.2. *Posterior predictive loss*

With prediction in mind, we can think of the unknown as a future observation which is a replicate of the jth patient's toxicity data y_j. If we denote it by $y^{\mathrm{rep}}_{j,m}$ for the mth working model and assume y_j and $y^{\mathrm{rep}}_{j,m}$ have the same distribution, we can define a modification of the posterior predictive loss criterion that was proposed by Gelfand and Ghosh [16], as follows:

$$PPL_{j,m}=\min_{\mathscr{A}_{j,m}}\mathrm{E}_{y^{\mathrm{rep}}_{j,m}|\Omega_j,m}[\Delta(y^{\mathrm{rep}}_{j,m},\mathscr{A}_{j,m};\Omega_j,\tilde{a}_{j,m})],\tag{2}$$

where the expectation in equation (2) is with respect to the posterior predictive distribution associated with $y^{\mathrm{rep}}_{j,m}$, given by,

$$p(y^{\mathrm{rep}}_{j,m}|\Omega_j)=\int_0^\infty p(y^{\mathrm{rep}}_{j,m}|a_m)f(a_m|\Omega_j)\mathrm{d}a_m,$$

where $p(y^{\mathrm{rep}}_{j,m}|a_m)$ is assumed to be a Bernoulli distribution with probability $\alpha^{a_m}_{i,m}$ of $y^{\mathrm{rep}}_{j,m}=1$, denoted by $\mathrm{Bern}[\alpha^{a_m}_{i,m}]$ and $\mathscr{A}_{j,m}$ is an action for the jth included patient under the mth working model, trying to accommodate both y_j and what we predict for $y^{\mathrm{rep}}_{j,m}$. Here, for $y^{\mathrm{rep}}_{j,m}$ and $\mathscr{A}_{j,m}$, with a univariate loss

function $\Delta(y, \mathscr{A})$, we can define

$$\Delta(y_{j,m}^{\text{rep}}, \mathscr{A}_{j,m}; \Omega_j, \tilde{a}_{j,m}) = \Delta(y_{j,m}^{\text{rep}}, \mathscr{A}_{j,m}) + q\Delta(y_j, \mathscr{A}_{j,m}), \quad q \geqslant 0,$$

where the specified weight q indicates the relative regret for departure from y_j compared with departure from $y_{j,m}^{\text{rep}}$. In particular, the case when $q=0$ represents that the action $\mathscr{A}_{j,m}$ is a 'guess' for $y_{j,m}^{\text{rep}}$. If we take $\mathscr{A}_{j,m}$ as y_j to avoid the arbitrariness of choice of q, we no longer require minimization over $\mathscr{A}_{j,m}$ in equation (2), and further can define the loss function using the logarithm of the product of the likelihood ratio for each patient:

$$\Delta(y_{j,m}^{\text{rep}}, \mathscr{A}_{j,m}; \Omega_j, \tilde{a}_{j,m}) = \Delta(y_{j,m}^{\text{rep}}, y_j) = \log \prod_{l=1}^{j} \frac{\{\psi(x_l, \tilde{a}_{l,m})\}^{y_{l,m}^{\text{rep}}} \{1-\psi(x_l, \tilde{a}_{l,m})\}^{(1-y_{l,m}^{\text{rep}})}}{\{\psi(x_l, \tilde{a}_{l,m})\}^{y_l} \{1-\psi(x_l, \tilde{a}_{l,m})\}^{(1-y_l)}}.$$

Therefore we can redefine $\text{PPL}_{j,m}$ in equation (2) as:

$$\text{PPL}_{j,m} = \text{E}_{y_{j,m}^{\text{rep}}|\Omega_j,m} \left[\log \prod_{l=1}^{j} \frac{\{\psi(x_l, \tilde{a}_{l,m})\}^{y_{l,m}^{\text{rep}}} \{1-\psi(x_l, \tilde{a}_{l,m})\}^{(1-y_{l,m}^{\text{rep}})}}{\{\psi(x_l, \tilde{a}_{l,m})\}^{y_l} \{1-\psi(x_l, \tilde{a}_{l,m})\}^{(1-y_l)}} \right]. \tag{3}$$

The expectation over $y_{j,m}^{\text{rep}}$ can be calculated using the Monte Carlo integration. Thus, we can select the working model with the smallest value of the PPL in equation (3). We call the CRM based on the PPL criterion as the CRM-PPL.

3.3. *Deviance information criterion*

The deviance information criterion for the jth included patient under the mth working model is defined by

$$\text{DIC}_{j,m} = 2\bar{D}_{j,m} - D_{j,m}, \tag{4}$$

where $\bar{D}_{j,m}$ is the posterior mean of the log-likelihood, given by $\bar{D}_{j,m} = \text{E}_{a_m|\Omega_j}[-2\log L(\Omega_j, a_m)]$ and $D_{j,m} = -2\log L(\Omega_j, \tilde{a}_{j,m})$. So we can select the working model with the smallest value of the DIC. The CRM using the DIC is called as the CRM-DIC. The computations about the PPL and the DIC were performed using WinBUGS [19] in our example and simulation.

3.4. *The dose-finding algorithm of the model-adaptive CRM*

Given either of these above criteria, the dose-finding algorithm of the model-adaptive CRM proceeds as follows:

Step 1: Determine the starting dose. For example, for safety reasons the lowest dose level may be often chosen.

Step 2: Apply the CRM as shown in Section 2 to each of all elicited or possible working models at every observation following the inclusion of each patient or cohort of patients.

Step 3: Select one working model out of the working models that were updated by the CRM in Step. 2, through use of either of the PMP, the PPL or the DIC.

Step 4: Allocate the dose found by the selected working model in Step 3, to the next cohort of patients. Repeat Steps 2–4 until the last patient's data are observed.

We could add a stopping rule after Step 3 in the above algorithm, if necessary, in the same way as the original CRM. That is, the trial can be terminated for safety if given the first j included patients' data Ω_j, the lowest dose d_1 is too toxic:

$$\Pr(\psi(d_1, \tilde{a}_{j,m^*}) > \theta^*) > 0.9, \tag{5}$$

where m^* denotes the index of the selected working model. If the BMA approach is used, a stopping rule is given by

$$\sum_{m=1}^{M} \Pr(\psi(d_1, \tilde{a}_{j,m}) > \theta^*) \Pr(\text{M}_m|\Omega_j) > 0.9. \tag{6}$$