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ORIGINAL ARTICLE

Myocardial metabolism and diastolic function after aortic valve replacement for aortic stenosis: influence of patient–prosthesis mismatch

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Abstract

OBJECTIVE: This study evaluated the impact of patient–prosthesis mismatch on myocardial function and high-energy phosphate metabolism after aortic valve replacement for pure aortic stenosis. Patients with and without patient–prosthesis mismatch were compared using magnetic resonance techniques.

METHODS: Thirty patients who had undergone aortic valve replacement with Medtronic Mosaic bioprosthesis were evaluated. Fifteen patients with patient–prosthesis mismatch were compared to 15 matched patients without patient–prosthesis mismatch. These two homogeneous groups were studied for myocardial metabolism and left ventricle function preoperatively and at 12 months postoperatively with magnetic resonance imaging and ^{31}P spectroscopy.

RESULTS: All patients experienced improvement in myocardial metabolism and left ventricle function. Left ventricle mass regression was impaired in both groups. Impaired diastolic filling was associated with increased left ventricle wall mass in both groups (patient–prosthesis mismatch: $R^2 = -0.71$, $p = 0.002$; no patient–prosthesis mismatch: $R^2 = -0.88$, $p < 0.001$). Myocardial phosphocreatine/adenosine triphosphate ratio revealed a modest correlation with left ventricle function as evaluated by early acceleration peak (patient–prosthesis mismatch: $R^2 = 0.37$, $p = 0.03$; no patient–prosthesis mismatch: $R^2 = 0.17$, $p = 0.02$) and early deceleration peak (patient–prosthesis mismatch: $R^2 = 0.30$, $p = 0.01$; no patient–prosthesis mismatch: $R^2 = 0.39$, $p = 0.008$). No significant correlation between the phosphocreatine/adenosine triphosphate ratio and left ventricle mass was found (patient–prosthesis mismatch: $R^2 = 0.39$, $p = 0.6$; no patient–prosthesis mismatch: $R^2 = 0.40$, $p = 0.08$).

CONCLUSION: Aortic valve replacement leads to early improvement of left ventricle function and myocardial metabolism in all patients regardless of the occurrence of patient–prosthesis mismatch.

Keywords: Aortic valve replacement • Mismatch • Metabolism • Magnetic resonance imaging • Magnetic resonance spectroscopy

INTRODUCTION

Aortic stenosis is associated with left ventricle (LV) hypertrophy that involves diastolic and systolic disturbances, collagen network abnormalities, impaired coronary perfusion, and alterations in myocardial high-energy phosphate metabolism [1–4]. Aortic valve replacement (AVR) leads to hemodynamic and metabolic improvement and to favorable changes in myocardial perfusion contributing to prolongation of survival [3,5–7]. A number of factors may influence long-term clinical results after successful AVR. Among these, the impact of patient–prosthesis mismatch (PPM) on surgical results is still an intriguing matter of debate [8–12]. Many variables, largely unknown, might influence clinical results in patients with PPM; the energetic state of the myocardium and the relationship with LV function following AVR have not been studied in details so far in these patients.

This study investigated the high-energy phosphate metabolism and its relationship with LV geometry and LV diastolic dysfunction in patients with PPM versus a comparative model of patients without PPM.

MATERIALS AND METHODS

Definition of PPM

PPM occurs when the size of an artificial valve is inadequate for the patient body size. As previously reported, PPM can be predicted by calculating the projected effective orifice area derived from the published normal values for the model and size of prosthesis indexed to body surface area [13]. PPM was previously defined as not clinically significant (i.e., mild or no PPM) if effective orifice area was >0.85 cm m^{-2}, as moderate if the area was >0.65 cm m^{-2} and 0.85 cm m^{-2} or less, and severe if it was 0.65 cm^2 m^{-2} or less. For the purpose of this study, we defined PPM as an indexed effective orifice area of 0.75 cm^2 m^{-2} or less. The selection of this value was based on results of previous

Table 1: Preoperative and surgical variables

Variable	PPM ($n = 15$)	No PPM ($n = 15$)	p
Preoperative variables			
Age (years)	69.5 ± 4.1	67.4 ± 5.8	0.5
Male sex	15	15	
BSA (m^2)	1.95 ± 0.16	1.78 ± 0.17	0.008
BMI	29.4 ± 2.8	27.9 ± 2.1	0.1
NYHA Class III	4 (26.6%)	3 (20.0%)	1
EOAi ($cm^2\ m^{-2}$/BSA)	0.69 ± 0.05	0.79 ± 0.04	<0.001
Surgical variables			
Pump time (min)	82 ± 11	76 ± 18	0.3
Cross clamp time (min)	68 ± 28	61 ± 30	0.5
Valve size			
21 mm	14 (93.3%)	5 (33.3%)	<0.001
23 mm	1 (6.7%)	10 (66.7%)	<0.001

Values are expressed as mean ± standard deviation or number (%). The p value determined by analysis of variance or χ^2 test. BSA: body surface area; BMI: body mass index; EOAi: indexed effective orifice area.

studies [10,12–14]. In addition, we did a preliminary analysis that confirmed that this cutoff value provides the best compromise between sensitivity and specificity in the aim of this study end point.

Study population

Between January 2007 and January 2009, all patients undergoing AVR for pure aortic stenosis with an aortic annulus of 19–23 mm, determined after adequate (transthoracic and/or transesophageal) echocardiographic examination, were evaluated for inclusion in the study. Indications for surgery were mean gradient higher than 50 mmHg and/or an aortic valve area less than 1.0 cm^2. To obtain a population as homogeneous as possible and to avoid any confounding interference on results, exclusion criteria were: age <60 years, female sex, contraindications to valve replacement with bioprosthesis, associated aortic diseases, simultaneous mitral or tricuspid replacement or repair, previous myocardial infarction, evidence of coronary lesions, poor cardiac function as indicated by ejection fraction <40%, chronic atrial fibrillation, diabetes mellitus, and fasting low-density lipoprotein (LDL)-cholesterol level higher than 160 mg dl^{-1}. On the basis of projected effective orifice area indexed for body surface area of <0.75 $cm^2\ m^{-2}$, 15 patients with PPM were identified. They were compared to 15 patients without PPM matched for main demographic, clinical, and surgical variables (Table 1). All patients had implanted a Medtronic Mosaic® porcine valve.

Surgical technique did not change throughout the study period [13]. Nineteen patients (63.3%) received a 21-mm prosthesis and 11 patients (36.7%) received a 23-mm prosthesis.

Preoperatively, all patients were evaluated with magnetic resonance (MR) imaging and ^{31}P MR spectroscopy. Both these analyses were again performed at 12 months after surgery. All drug treatment affecting the myocardial metabolism and the LV function was withdrawn 72 h before echocardiographic or MR evaluations.

The study protocol was approved by the hospital ethics committee and patients' informed consent was obtained.

Echocardiographic acquisition

All patients had echocardiographic evaluation before surgery and were followed up 12 months after the operation and according to the recommendations of the American Society of Echography [15]. The peak and mean prosthetic gradients were calculated from continuous-wave Doppler measurements using the modified Bernoulli equation.

MR data acquisition and processing

MR imaging was performed on a 1.5-T scanner (Philips Medical System, The Netherlands) using an electrocardiogram-triggered cine gradient echo for short- and long-axis two-dimensional sequence [4]. Slice thickness was 8 mm, interslice gap 2 mm, by means of a breath-hold technique in end-expiratory position. Images encompassed the entire LV. Phase-contrast flow-velocity measurements across the mitral valve orifice were obtained by using a gradient-echo sequence with retrospective electrocardiographic gating. Velocity maps were acquired across the mitral orifice by using a flip angle of 30° and an echo time of 10–12 ms. The image section had a thickness of 8 mm and a field view of 350 mm and consisted of two measurements of a 128 × 128 acquisition matrix that was interpolated to a display matrix of 256 × 256 pixels. Depending on the heart rate, between 30 and 50 time frames were distributed during the cardiac cycle, resulting in a temporal resolution of 25–35 ms. Total acquisition time was about 5 min. The maximum phase shift of 180° was set to occur at a velocity of 100 cm s^{-1}. The LV short-axis acquisitions were used to assess dimensions, wall mass, and systolic function. For the analysis, the images were displayed on a computer monitor in a movie-loop mode. The endocardial and epicardial borders of the end-diastolic and end-systolic images from each short-axis section were manually traced with a cursor. Whenever the epicardial borders were outlined, the epicardial fat was excluded; whenever the endocardial borders were drawn, the papillary muscle was regarded as being part of the ventricular cavity.

During the entire MR examination, blood pressure and heart rate were recorded every 2 min. Image analyses were performed by two blinded observers. The surface areas of the endocardial tracings in end diastole and end systole were summed up and multiplied by section thickness and section factor to produce the LV end-diastolic chamber volume and LV end-systolic chamber volume which were normalized for body surface area. Stroke volume was the difference between LV end-diastolic chamber volume and LV end-systolic chamber volume. Cardiac output was stroke volume multiplied by the average heart rate. LV ejection fraction was stroke volume divided by the LV end-diastolic chamber volume. LV wall volume was obtained by the difference between summed diastolic epicardial and endocardial borders multiplied by section thickness. LV wall volume was multiplied by factor for specific density of cardiac muscle (1.05 g cm^{-3}) to yield LV mass, which was normalized to body surface area. LV hypertrophy was defined as an indexed LV mass more than 130 g m^{-2} in men [16]. Volumetric flow across the mitral valve was calculated by manually tracing the borders of the mitral valve in all time frames of the velocity map series. Flow curves were analyzed following indication of the start of early filling, peak early filling, peak atrial contribution to filling, and the end of filling.

Table 2: Left ventricle geometry, function and metabolism before and after AVR

	PPM			No PPM			p^*
	Before AVR	After AVR	p	Before AVR	After AVR	p	
MPG	85 ± 14	21 ± 9	<0.001	87 ± 12	19 ± 5	<0.001	0.3
ILVM	183 ± 58	148 ± 12	0.02	181 ± 52	142 ± 20	0.01	0.2
LVEF	51 ± 8	53 ± 7	0.5	51 ± 9	54 ± 11	0.4	0.7
CO	4.3 ± 0.5	4.5 ± 0.6	0.3	4.3 ± 0.4	4.4 ± 0.7	0.6	0.7
EAP (ml s^{-3})	5.8 ± 0.9	6.5 ± 0.6	0.01	6 ± 0.9	6.7 ± 0.8	0.01	0.4
EDP (ml s^{-3})	−2.8 ± 0.6	−3.1 ± 0.4	0.1	−2.8 ± 0.8	−3.3 ± 0.6	0.06	0.3
ILVM/ILVEDV ratio (g ml^{-1})	1.91 ± 0.4	1.83 ± 0.3	0.05	1.92 ± 0.5	1.86 ± 0.6	0.05	0.8
ILVEDV (ml m^{-2})	94 ± 28	79 ± 17	0.03	95 ± 25	77 ± 19	0.03	0.7
PCr/ATP	1.12 ± 0.1	1.42 ± 0.5	0.03	1.13 ± 0.2	1.48 ± 0.5	0.01	0.7

ATP: adenosine triphosphate; AVR: aortic valve replacement; CO: cardiac output; EAP: early acceleration peak; EDP: early deceleration peak; ILVEDV: indexed left ventricular end-diastolic volume; ILVM: indexed left ventricular mass; LVEF: left ventricular ejection fraction; MPG: mean trans-prosthetic gradient; p: p values within groups before and after AVR; p^*: p values between groups after AVR; PCr: phosphocreatine.

Acceleration and deceleration peak values were calculated as the maximal change in ml s^{-1} (expressed as ml s^{-2}) obtained from the velocity-encoded MR imaging acquisitions.

These parameters were not indexed due to similar cardiac output and body mass index between the groups. LV diastolic performance was evaluated according to Thomas and Weyman [17].

^{31}P MR spectroscopy was performed with a 1.5-T system (Philips Medical System, The Netherlands) equipped with multinuclei hardware for ^{31}P MR. Considering that myocardial high-energy phosphate metabolism can be measured by ^{31}P MR spectroscopy in several ways, technical details were assessed according to Lamb and Bayerbacht [4,18]. A 100-mm-diameter surface coil served as both transmitter and receiver of the radio-frequency signals. Changes in myocardial high-energy phosphate metabolism were expressed as changein the myocardial phosphocreatine/adenosine triphosphate ratio. Myocardial ^{31}P spectra were obtained from the anterior wall of the LV, with subjects in supine position. Acquisition of ^{31}P MR spectra was triggered 200 ms after the R wave of the electrocardiographic signal, with a minimum recycle time of 3 s. Acquisition time for a single spectrum was 30 min. The adenosine triphosphate level in the cardiac ^{31}P MR spectra was corrected for the adenosine triphosphate contribution from blood present in the volume of interest. Spectra were also corrected for partial saturation effects. Mean repetition time was 3.6 s, resulting in a correction factor of 1.35, which was applied to all blood-corrected cardiac phosphocreatine/adenosine triphosphate ratios.

Statistical analysis

Continuous data are presented as mean ± standard deviation and categorical data as proportion. Comparison between continuous variables was done by the Student's t-test for normally distributed features; otherwise, the Mann–Whitney U test was used for variables not normally distributed. Results were compared by analysis of the χ^2 test or the Fisher's exact test as appropriate. A p-value of <0.05 was considered to indicate a statistically significant difference. Pairwise correlations were determined by using linear regression analysis to determine associations between LV mass, LV function, and myocardial phosphocreatine–adenosine triphosphate ratio. One-way analysis of variance (ANOVA) was performed in order to determine whether the association between the variables was statistically significant. To assess the effect of PPM on variables, we developed a first model with PPM entered as a dichotomous variable (PPM: indexed effective orifice area ≤0.75 cm^2 m^{-2} vs no PPM) and then a second model with indexed effective orifice area entered as a continuous variable.

RESULTS

Myocardial function

Mean indexed orifice area was 0.71 ± 0.06 cm^2 m^{-2} in patients with PPM vs 0.79 ± 0.04 cm^2 m^{-2} in patients without PPM ($p < 0.001$). Postoperative mean prosthetic gradients were low without any statistical difference between groups ($p = 0.3$). Regression of indexed LV mass was significant in both groups, although the mean values were overall persistently high in both groups. Preoperative mean indexed LV diastolic volume was 96 ± 25 ml m^{-2}, while 12 months after surgery it improved significantly to 79 ± 17 ml m^{-2} in PPM group ($p = 0.03$) and to 77 ± 19 ml m^{-2} in no PPM group ($p = 0.03$). Mean preoperative early acceleration peak was 5.9 ± 0.9 × 10^{-2} ml s^{-2}. Twelve months after valve replacement, it increased to 6.5 ± 0.6 × 10^{-2} ml s^{-2} in PPM patients ($p = 0.01$) and to 6.7 ± 0.8 × 10^{-2} s^{-2} in patients without PPM ($p = 0.01$). Mean preoperative early deceleration peak was −2.8 ± 0.6 × 10^{-2} ml s^{-2}. Twelve months after surgery it decreased to −3.1 ± 0.4 × 10^{-2}ml s^{-2} in the PPM group ($p = 0.1$) and to −3.3 ± 0.6 × 10^{-2} ml s^{-2} in the no PPM group ($p = 0.06$) (Table 2).

Myocardial metabolism

The mean myocardial phosphocreatine/adenosine triphosphate ratio before surgery was 1.13 ± 0.1. It increased significantly to 1.42 ± 0.5 ($p = 0.03$) in the PPM group and to 1.48 ± 0.5 ($p = 0.01$) in the no PPM group (Table 2).

Relation between LV geometry, LV function, and myocardial high-energy phosphate metabolism

Correlations between LV geometric and functional parameters were determined for all patients before AVR and 12 months after surgery. For this purpose, for each group of patients the

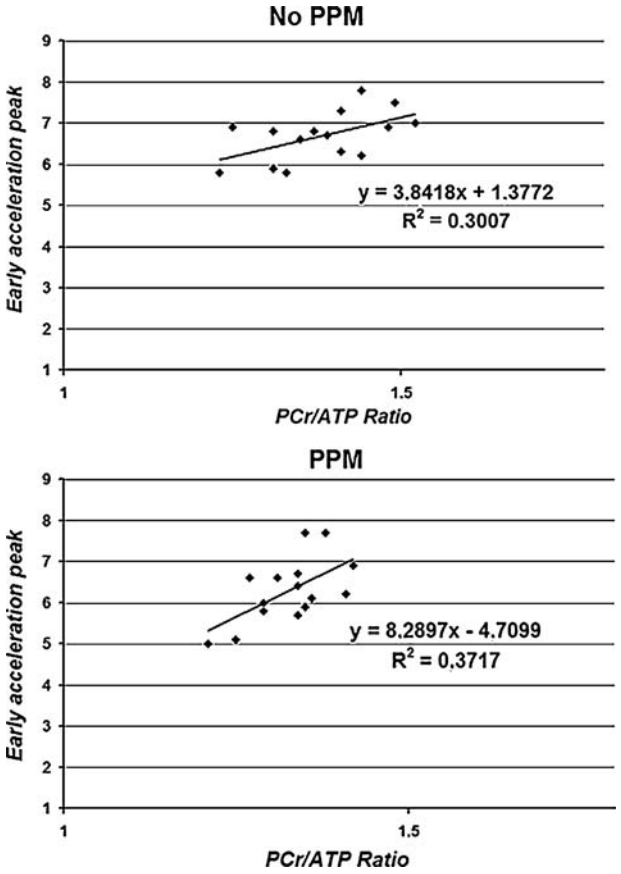

Figure 1: Diastolic function parameters (early acceleration peak) analyzed for correlation to myocardial high-energy phosphate (HEP) metabolism expressed as myocardial phosphocreatine (PCr)-to-adenosine triphosphate (ATP) ratio.

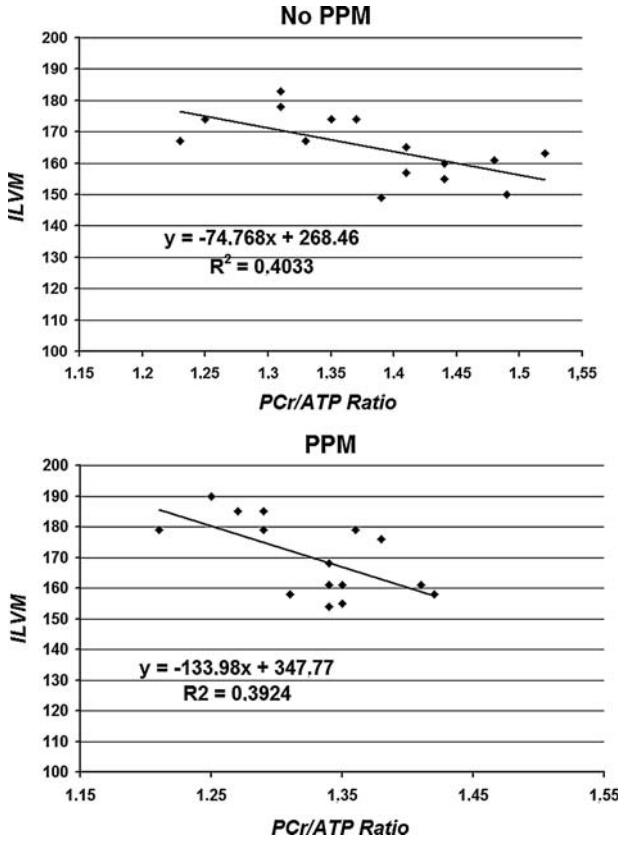

Figure 2: Indexed left ventricular mass index (ILVM) analyzed for correlation to myocardial high-energy phosphate (HEP) metabolism expressed as myocardial phosphocreatine (PCr)-to-adenosine triphosphate (ATP) ratio.

indexed LV mass was analyzed for correlation to LV systolic and LV diastolic function parameters. Impaired diastolic filling was associated with increased LV wall mass in both groups, as reflected by a significant correlation between indexed LV mass and early acceleration peak (PPM group: $R^2 = -0.71$, $y = -12.15x + 245.5$, $p = 0.002$; no PPM group: $R^2 = -0.88$, $y = -17.56x + 278.6$, $p < 0.001$) and early deceleration peak (PPM group: $R^2 = 0.68$, $y = 24.74x + 92.2$ $p < 0.001$; no PPM group: $R^2 = 0.68$, $y = 28.85x + 87.7$, $p < 0.001$).

For all 30 patients, myocardial high-energy phosphate metabolism data were analyzed for correlation to parameters describing LV geometry and function. The myocardial phosphocreatine/adenosine triphosphate ratio was modestly correlated to the early acceleration peak in both the groups (PPM group: $R^2 = 0.37$, $y = 8.28x + 4.7$, $p = 0.03$; no PPM group: $R^2 = 0.17$, $y = 3.85 + 1.3$, $p = 0.02$) (Fig. 1), and to the early deceleration peak (PPM group: $R^2 = 0.30$, $y = -2.8x + 5.8$, $p = 0.01$; no PPM group: $R^2 = 0.39$, $y = 2.88x + 6.99$, $p = 0.008$). There was no significant correlation between the phosphocreatine/adenosine triphosphate ratio and indexed LV mass (PPM group: $R^2 = 0.39$, $y = -133.9x + 347.7$, $p = 0.6$; no PPM: $R^2 = 0.40$, $y = -74.76x + 268.4$, $p = 0.08$) (Fig. 2).

DISCUSSION

Preoperative impaired myocardial high-energy phosphate metabolism in patients with aortic valve stenosis improved following valve replacement. A statistically significant correlation between myocardial high-energy phosphate metabolism and LV diastolic function was demonstrated in both groups of study. Our results failed to evidence significant differences between the groups of patients with or without PPM.

Diastolic function

Impaired diastolic function in patients with aortic valve stenosis is a risk factor for early and late mortality after surgery [19]. Patients with clinically significant aortic stenosis show impaired diastolic filling influenced by several determinants such as left atrial pressure, LV end-diastolic volume, LV systolic function, intrinsic myocardial stiffness, and the LV relaxation constant [20,21].

AVR relieves LV pressure overload and reduces wall stress both of which could affect LV hypertrophy regression. As a consequence, improvement in diastolic function after AVR has been usually attributed to the regression of LV mass. Nevertheless, these assumptions are incongruent with the evidence that patients with low gradients had similarly impaired LV hypertrophy regression during the mild-term follow-up as patients with higher gradients. Therefore, it is reasonable that the early reduction in pressure overload immediately after surgery, when hypertrophy is still present, could itself lead to improvement in diastolic function. Our results are consistent with this hypothesis. Despite the occurrence of PPM, LV mass was persistently impaired, whereas almost all patients showed a significant

remission of mean prosthetic gradients and had a recovery of LV diastolic volume.

Myocardial metabolism

The effect of AVR on myocardial high-energy phosphate metabolism has been previously evaluated by Beyerbacht who first reported that it is substantially deranged in patients with severe aortic stenosis and normal coronary artery [4]. A reduced myocardial metabolism before AVR may be an indicator of a relative myocardial ischemia due to myocardial oxygen mismatch from decreased coronary flow reserve and abnormal coronary blood flow velocity in a hypertrophic heart. The decrease in coronary flow reserve and abnormal coronary blood flow-velocity profiles have been found to correlate with an increase in LV wall stress [22,23]. Relief of LV wall stress by means of a near to normal trans-prosthetic gradient after AVR, as obtained in both groups of patients, led to a nearly complete normalization of myocardial high-energy phosphate metabolism regardless of the occurrence of PPM.

Relation between function and metabolism

Both groups of patients, in spite of PPM, had a significant improvement of postoperative myocardial phosphocreatine/adenosine triphosphate ratio, which was associated with better LV diastolic function. The exact nature of the relation between myocardial high-energy phosphate metabolism and heart diastolic function and geometry is not yet completely clear. It seems likely that relieved gradient after AVR leads to improved coronary flow, which may play a key role for optimized myocardial metabolism and for LV remodeling by a number of structural and functional changes [22,24]. In addition, it is reasonable that the relieved hemodynamic burden reduces the wall stress and restores a near-to-normal myocardial metabolism despite the complete normalization of LV mass, which is a slow process that takes years to ameliorate and may continue for decades after surgery by the regression of both muscular and nonmuscular, predominantly collagen, tissue [25]. Our results support the hypothesis that the relief of aortic obstruction due to AVR constitutes the main mechanism of restored high-energy phosphate metabolism and improved LV function. The absence of a significant correlation between myocardial phosphocreatine/adenosine triphosphate ratio and indexed LV mass, in spite of the occurrence of PPM, could confirm that LV hypertrophy by itself has no negative consequences for cardiac metabolism and it is not a prerequisite of impaired myocardial metabolism, as described in patients with hypertension and high LV mass who did not show any significant correlation between myocardial phosphocreatine/adenosine triphosphate ratio and indexed LV mass [18].

This study has several limitations that deserve mention. First, the relatively small sample size of patients enrolled due to the long examination time needed for the combined MR imaging and ^{31}P MR spectroscopy. However, although a sample of 30 patients may appear underpowered, the strict selection criteria of a highly homogeneous population of study enabled to draw statistically significant conclusions. In addition, the small sample size reflects the single-center design of study, which, on the other hand, guarantees the essential uniformity in patient selection, surgical technique, and postoperative care. Second, we were unable to monitor changes in loading conditions and left atrial filling pressures, which may all affect LV function. In an effort to reduce the impact of these variables, we enrolled patients with isolated aortic stenosis and normal systolic function, who were not taking any drug treatment affecting the filling conditions. Ultimately, systemic metabolic data affecting high-energy phosphate metabolism (e.g., plasma free fatty acid levels) have not been evaluated. However, all patients were selected as not having evidence of metabolic disorders.

In conclusion, AVR for aortic stenosis leads to improved myocardial metabolism and LV diastolic function in parallel with reduction in aortic gradient, regardless of the occurrence of PPM. The present study may provide another piece of evidence in the ongoing discussion of PPM, which still remains a matter of unresolved debate.

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