

Long-Term Pulmonary Regurgitation Following Balloon Valvuloplasty for Pulmonary Stenosis

Risk Factors and Relationship to Exercise Capacity and Ventricular Volume and Function

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Objectives	This study sought to examine the prevalence and predictors of pulmonary regurgitation (PR) following balloon dilation (BD) for pulmonary stenosis (PS) and to investigate its impact on ventricular volume and function, and exercise tolerance.
Background	Balloon pulmonary valvuloplasty relieves PS but can cause late PR. The sequelae of isolated PR are not well understood.
Methods	Patients were at least 7 years of age and 5 years removed from BD, and had no other form of congenital heart disease or significant residual PS. Cardiac magnetic resonance imaging and exercise testing were performed prospectively to quantify PR fraction, ventricular volumes and function, and exercise capacity.
Results	Forty-one patients underwent testing a median of 13.1 years after BD. The median PR fraction was 10%; 14 patients (34%) had PR fraction >15%; 7 (17%) had PR >30%. PR fraction was associated with age at dilation (In-transformed, $R = -0.47$, $p = 0.002$) and balloon:annulus ratio ($R = 0.57$, $p < 0.001$). The mean right ventricular (RV) end-diastolic volume z-score was 1.8 ± 1.9 ; RV dilation (z-score ≥ 2) was present in 14/35 patients (40%). PR fraction correlated closely with indexed RV end-diastolic volume ($R = 0.79$, $p < 0.001$) and modestly with RV ejection fraction ($R = 0.50$, $p < 0.001$). Overall, peak oxygen consumption (Vo_2) (% predicted) was below average ($92 \pm 17\%$, $p = 0.006$). Patients with PR fraction >15% had significantly lower peak Vo_2 than those with less PR ($85 \pm 17\%$ vs. $96 \pm 16\%$, $p = 0.03$).
Conclusions	Mild PR and RV dilation are common in the long term following BD. A PR fraction >15% is associated with lower peak Vo_2 , suggesting that isolated PR and consequent RV dilation are related to impaired exercise cardiopulmonary function. (J Am Coll Cardiol 2010;55:1041-7) © 2010 by the American College of Cardiology Foundation

Little is known about the pathophysiology of chronic isolated pulmonary regurgitation (PR). Congenital pulmonary valve incompetence is extremely rare, with most published reports consisting of individual cases (1-3). In the largest published series, Shimazaki et al. (4) described long-term outcomes of 72 patients with this condition. Symptoms of heart failure were uncommon at 20 years (6%), but the likelihood of developing them increased dramatically over time, and premature death

occurred in 3 symptomatic patients. A growing number of children and adults are subjected to long-term PR, including those with repaired conotruncal lesions as well as patients with valvar pulmonary stenosis (PS) following balloon dilation (BD). In the context of this expanding population, the need to understand the impact of chronic PR has become increasingly important.

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In this study, we evaluated patients previously treated for uncomplicated valvar PS with percutaneous BD in an effort to gain insight into the late physiologic effects of chronic, isolated PR. Percutaneous balloon pulmonary valvuloplasty was introduced in 1982 (5) and subsequently became the first-line therapy for valvar PS at most centers. In the years since, a

Abbreviations and Acronyms

BAR	= balloon: annulus ratio
BD	= balloon dilation
CMR	= cardiac magnetic resonance
EF	= ejection fraction
LV	= left ventricle/ventricular
PR	= pulmonary regurgitation
PS	= pulmonary stenosis
RV	= right ventricle/ventricular
TR	= tricuspid regurgitation
V_E/V_{CO_2}	= ratio of minute ventilation:carbon dioxide production
V_{O_2}	= oxygen consumption

number of reports have detailed medium- and long-term outcomes of this therapy. With rare exceptions (6), however, the primary focus of these reports has been freedom from recurrence of valvar stenosis (7–11). In the present study, we used cardiac magnetic resonance (CMR) imaging and exercise testing to investigate the prevalence and physiologic impact of long-term PR after balloon pulmonary valvuloplasty for congenital valvar PS. Our primary goal was to determine whether chronic PR is associated with compromised exercise cardiopulmonary function in the absence of confounding factors (such as surgical ventriculotomy, long-standing pre-procedural cyanosis, or exposure to cardiopulmonary bypass).

A secondary goal was to assess the

relationships between demographic and procedural factors at valvuloplasty and late PR, and between PR and ventricular size and function.

Methods

Patients. Subjects with valvar PS having undergone BD of the pulmonary valve were identified from the database of the cardiovascular program at Children's Hospital Boston. Inclusion criteria were: history of valvar PS treated with percutaneous balloon valvuloplasty; managed at our institution; age ≥ 7 years at the time of enrollment; and at least a 5-year interval between the pulmonary valve dilation procedure and enrollment. Patients were excluded if they had significant residual PS (≥ 30 mm Hg gradient on last available echo or CMR evaluation); other congenital heart disease, including significant atrial septal defect; or any history of cardiac surgery. Eligible patients were contacted by mail with an informational packet describing the study, followed by a series of up to 3 telephone calls. Enrolled patients were prospectively studied with CMR imaging and exercise testing. This study was performed according to a protocol approved by the Committee for Clinical Investigation at Children's Hospital Boston. All study subjects provided written informed consent.

Catheterization and balloon valvuloplasty. Balloon pulmonary valvuloplasty was performed as previously described, with a target balloon:annulus diameter ratio (BAR) of 1.2 to 1.4 (12). Catheterization reports from the pulmonary valve dilation procedure were reviewed. Recorded data included: age at catheterization, initial right ventricular (RV) pressure, the ratio of RV to systemic arterial or ventricular pressure, the diameter of the largest balloon used for valve dilation at

maximal inflation, and the pulmonary valve annulus diameter measured during systole (5). The BAR was calculated as the ratio of these 2 diameters. For patients with data missing from the catheterization report, measurements were performed by direct review of the angiograms by 1 of the authors (D.B.M.). In the event of multiple catheterizations with valve dilation, the largest BAR and the age at the first catheterization procedure were used for analysis. The pulmonary valve annulus diameter z-score was calculated relative to body surface area from published normative data obtained at our institution (13).

CMR imaging. CMR was performed using a 1.5-Tesla scanner (Achieva, Philips Medical Systems, Best, the Netherlands) and radiofrequency coils selected according to body size. All examinations were performed without sedation. Biventricular dimensions and function were assessed as previously described (14). Briefly, electrocardiogram-gated breath-held steady-state free precession imaging was performed in the ventricular short-axis plane with 12 to 14 equidistant slices completely covering both ventricles. Flow measurements were performed in the proximal main pulmonary artery with a retrospectively gated velocity-encoded cine MR pulse sequence during free breathing. CMR data were analyzed using commercially available software packages (QMASS version 6.2.3 and QFLOW version 4.1.7, Medis, Leiden, the Netherlands). Left ventricular (LV) and RV end-diastolic (maximal) and end-systolic (minimal) volumes, mass at end diastole, stroke volume, and ejection fraction (EF) were measured as previously described (15). For all patients, ventricular volumes were indexed to body surface area. RV and LV end-diastolic volume z-scores were calculated for males and females in whom published normative data are available (body surface area >1.25 m² and 1.0 m², respectively) (15). An RV end-diastolic volume z-score ≥ 2 signified at least mild dilation. PR volume was measured as the amount of retrograde flow in the main pulmonary artery per cardiac cycle, and was indexed to body surface area to yield a PR volume index (milliliters/square meter/beat); the PR fraction was calculated as the retrograde flow divided by the antegrade flow in the main pulmonary artery, expressed as a percentage (16). Tricuspid regurgitation (TR) fraction, expressed as a percentage, was quantified as: $(100 \times \text{TR volume})/\text{TR inflow}$, where TR volume = (RV stroke volume – LV stroke volume) – PR volume; and TR inflow = RV stroke volume – PR volume.

Exercise testing. Exercise testing was performed with a progressive symptom-limited protocol using a cycle (17) or treadmill (18) ergometer. Electrocardiographic monitoring and breath-by-breath expiratory gas analysis were performed using a CardiO2 exercise testing system (Medical Graphics Corp., Minneapolis, Minnesota). Cuff blood pressure measurements and 12-lead electrocardiograms were obtained at 2- to 3-min intervals during exercise, at peak exercise, and at 1, 3, and 5 min after exercise. Oxygen saturation was also monitored by pulse oximetry throughout the study. Immediately prior to each exercise test, spiromet-

ric measurements of forced vital capacity and volume of air exhaled in the first second of forced expiration were obtained. The exercise testing system was calibrated according to manufacturer specifications prior to each test.

Peak exercise parameters were expressed as the percentage of the predicted value for age, sex, and size. Normal data were taken from the following sources: age ≤ 17 years, Cooper and Weiler-Ravell (19); age > 18 years, Jones (20). Outcome parameters included the percentage of predicted values for peak oxygen consumption (VO_2), peak work rate, peak heart rate, and O_2 pulse (a measure of forward stroke volume) (20); the slope of the minute ventilation:carbon dioxide production ratio (V_E/V_{CO_2} , an index of the efficiency of gas exchange during exercise [17]); and spirometric measurements. For peak VO_2 , peak work rate, O_2 pulse, and heart rate, a subnormal value was defined as $< 85\%$ of the predicted value, in accordance with the 2003 American Thoracic Society/American College of Chest Physicians Statement on Cardiopulmonary Exercise Testing; normal V_E/V_{CO_2} was < 29 (21,22).

Data analysis. The primary hypothesis was that higher PR fraction would be associated with lower percent predicted peak VO_2 . The analysis was organized according to 3 outcome categories: PR fraction, ventricular volumes and function, and exercise function. The first outcome was PR fraction, which was considered a procedural outcome and was treated both as a continuous variable and dichotomized around 15% on the basis of receiver-operator curve analysis for percent predicted peak VO_2 . Demographic and procedural factors analyzed for association with PR fraction included age at the time of valvuloplasty (ln-transformed and dichotomized around 1 year), pre-intervention RV pressure and RV:systemic pressure ratio, and BAR (continuous and dichotomized around 1.4, the upper limit of the usual target BAR range). For the second category of outcomes, associations between PR and ventricular volumes and function were assessed. For the third category of outcomes, relationships between the primary outcome (percent predicted peak VO_2) and CMR (PR fraction and volume, RV and LV volumes and function) and demographic (age at intervention and follow-up, body mass index, gender) factors were assessed. Procedural variables were not included in the analysis of exercise function based on the rationale that any potential association between the procedure and exercise function should be reflected in cardiac physiology. Linear regression was used to assess the relationship between continuous variables, independent-samples t test to compare normally distributed continuous variables between groups, Wilcoxon rank sum test to compare continuous variables with a skewed distribution, and Fisher exact test to compare categorical variables. Exercise functional parameters were also compared with average (mean percent predicted value = 100%) using 1-sample t test. z -Scores were compared with normal (value = 0) using a 1-sample t test. SPSS (version 16, SPSS Inc., Chicago, Illinois) was used for statistical analysis.

Results

Demographic and catheterization data. Recruitment letters were sent to the last available address for 183 potentially eligible patients identified in the cardiology database. Of these, 81 were contacted by telephone (conversation or voice mail message); 41 enrolled in the study. The median age at BD in these 41 patients was 2.9 months (1 day to 27 years), and 28 (68%) were under 1 year; 18 patients (44%) were male. In 37 patients, balloon pulmonary valvuloplasty was performed at Children's Hospital Boston; in the other 4 patients, the procedure was performed elsewhere, and care was subsequently transferred to our institution. Balloon valvuloplasty was performed between 1986 and 1990 in 9 patients (22%), 1991 and 1999 in 27 (66%), and in 2000 or later in 5 (12%). At the time of intervention, the median pulmonary annulus diameter z -score was -1.0 (-3.4 to 1.7), and the median BAR was 1.3 (1.0 to 2.0). BAR was inversely related to pulmonary valve z -score ($n = 34$, $R = 0.67$, $p < 0.001$). Additional data are summarized in Table 1.

Four patients underwent repeat BD, 3 within 1 year of the initial procedure and 1 who underwent the first procedure during infancy and the second 4 years later.

Follow-up. The median age at testing was 14.4 years (7.7 to 47.2 years), and the median time interval from balloon valvuloplasty was 13.1 years (6.2 to 22.9 years). In 37 patients, CMR and exercise testing were performed on the same day; the longest duration between the 2 tests in any patient was 3 months. One patient did not consent to exercise testing. Three patients had TR fraction $\geq 20\%$.

PR. The median PR fraction was 10% (1% to 45%), and the median PR volume index was $5.3 \text{ ml/m}^2/\text{beat}$ (0.5 to $30.2 \text{ ml/m}^2/\text{beat}$). There was a very close correlation between PR volume index and PR fraction ($R = 0.98$, $p < 0.001$). Fourteen patients (34%) had a PR fraction $> 15\%$; 7 (10%) had a PR fraction $> 30\%$; and 2 (4.9%) had a PR fraction $> 40\%$.

Among demographic and procedural factors, larger BAR ($R = 0.36$, $p < 0.001$) and younger age (ln-transformed) at intervention ($R = -0.47$, $p = 0.002$) were associated with higher PR fraction (Fig. 1). PR fraction was not related to duration between valvuloplasty and subsequent testing ($p = 0.91$), year of intervention ($p = 0.96$), or the degree of RV hypertension prior to valve dilation ($p = 0.10$).

The mean BAR was higher in the 14 patients with a PR fraction $> 15\%$ than in those with a PR fraction $\leq 15\%$ (1.42 ± 0.23 vs. 1.21 ± 0.17 , $p < 0.008$). BAR ≥ 1.4 was associated with a significantly higher risk of PR fraction $> 15\%$ (odds ratio: 4.5 [1.4 to 14.5], $p = 0.01$); the median PR fraction among patients with a BAR ≥ 1.4 was 26%. A PR fraction $> 15\%$ was significantly more common in patients who underwent valvuloplasty at < 1 year of age (12 of 26 patients) than those who were ≥ 1 year of age (2 of 15; odds ratio: 1.7 [1.1 to 2.5], $p = 0.03$).

Ventricular volume and function. The mean RV end-diastolic volume z -score ($n = 35$) was 1.8 ± 1.9 ($p < 0.001$

Table 1 Catheterization, CMR, and Exercise Data

	Value		p Value
	Mean	Median	
Catheterization (n = 41)			
Age at balloon dilation (yrs)	2.3 ± 5.5	0.2 (0 to 26.7)	
Pulmonary annulus (mm)	10.6 ± 4.6	9.1 (4.0 to 21.7)	
Pulmonary annulus z-score	−0.8 ± 1.2	−1.0 (−3.4 to 1.7)	
Balloon size (mm)	13.3 ± 5.4	12 (6.0 to 30.0)	
Balloon to annulus ratio	1.3 ± 0.2	1.3 (1.0 to 2.0)	
RV:systemic pressure ratio (%)	111.2 ± 40.6	110.2 (44.2 to 206.9)	
CMR imaging (n = 41)			
PR percent	14 ± 13	10 (1 to 45)	
PR volume (indexed, ml/m ²)	8.5 ± 8.6	5.3 (0.5 to 30.2)	
RV end-diastolic volume (indexed, ml/m ²)	103 ± 28	100 (63 to 205)	
RV end-diastolic volume z-score (n = 35)	1.8 ± 1.9	1.5 (−0.2 to 8.4)	
RV stroke volume (indexed, ml/m ²)	61.5 ± 14.3	56.7 (40.8 to 104.3)	
RV EF%	60 ± 7	61 (46 to 77)	
LV end-diastolic volume (indexed, ml/m ²)	80.8 ± 12.6	77.9 (52.5 to 108.5)	
LV end-diastolic volume z-score (n = 35)	0.1 ± 1.0	−0.1 (−2.3 to 2.3)	
LV stroke volume (indexed, ml/m ²)	50.9 ± 8.5	49.2 (33.6 to 70.0)	
LV EF%	64 ± 6	63 (55 to 78)	
Exercise (n = 40)			
Peak Vo ₂ (% predicted)	92 ± 17	90 (61 to 126)	0.006
Peak work rate (% predicted)	95 ± 22	93 (60 to 149)	0.14
O ₂ pulse (% predicted)	97 ± 17	96 (60 to 128)	0.66
Peak HR (% predicted)	96 ± 7	97 (76 to 113)	<0.001
FVC (% predicted)	101 ± 13	99 (68 to 125)	0.54
FEV1 (% predicted)	100 ± 15	100 (64 to 132)	0.85

p values for the exercise data refer to percentage predicted values compared with an average value of 100% (1-sample t test).

CMR = cardiac magnetic resonance; EF = ejection fraction; FEV1 = forced expiratory volume (1 s); FVC = forced vital capacity; HR = heart rate; LV = left ventricular; RV = right ventricular; VO₂ = oxygen consumption.

compared with z-score = 0). The median value was 1.5 (range −0.2 to 8.4). z-scores were unavailable in 6 patients due to small body surface area. In 14 patients (40%), RV dilation was present (z-score ≥2); Figure 2. In 1 (3%), it was severe (z-score ≥6); the BAR for this patient was 1.45. Median values for RV and LV EF were 61% (46 to 77%) and 63% (55% to 78%), respectively. Other CMR data are summarized in Table 1.

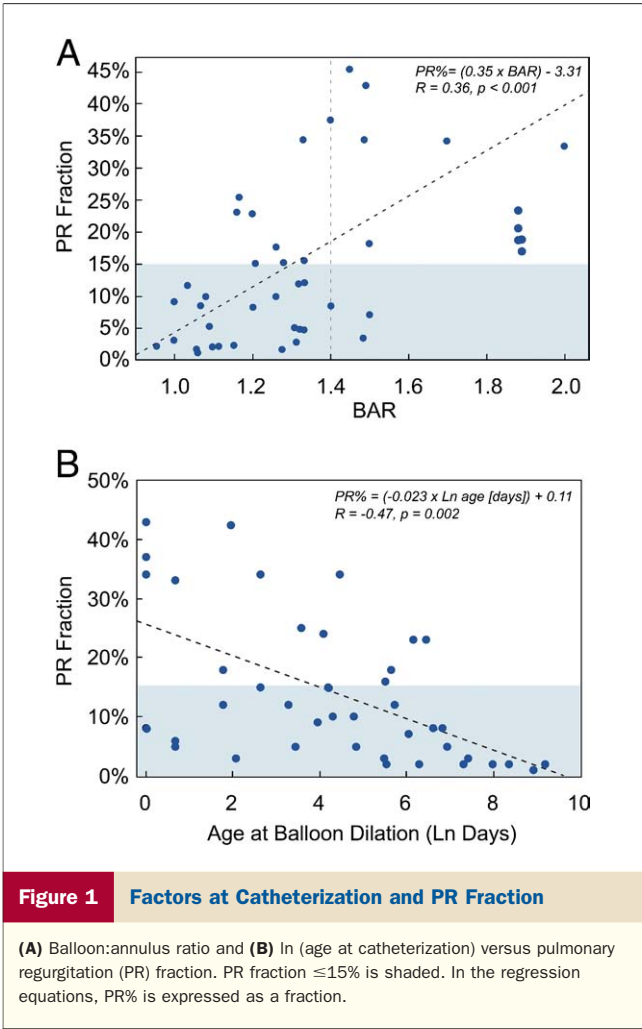
By linear regression, PR fraction correlated well with indexed RV end-diastolic volume ($R = 0.79$, $p < 0.001$) (Fig. 3). It correlated inversely, and less well, with RV EF ($R = -0.50$, $p = 0.001$) (Fig. 3). The RV EF was modestly and inversely related to the pre-intervention RV to systemic pressure ratio ($R = -0.43$, $p = 0.006$). The PR fraction was not significantly associated with LV factors such as EF, indexed end-diastolic volume, or indexed stroke volume.

Exercise function. On exercise testing with metabolic analysis using cycle ergometry (n = 34) or treadmill (n = 6), study subjects had peak VO₂ and heart rate (% predicted) that were modestly, but significantly, lower than average (Table 1). Of the 13 patients with subnormal peak VO₂, 9 (69%) had a subnormal O₂ pulse, suggesting an insufficient stroke volume response to exercise; only 1 patient had a subnormal heart rate. Mean V_E/V_{CO2} slope was 27 ± 4 .

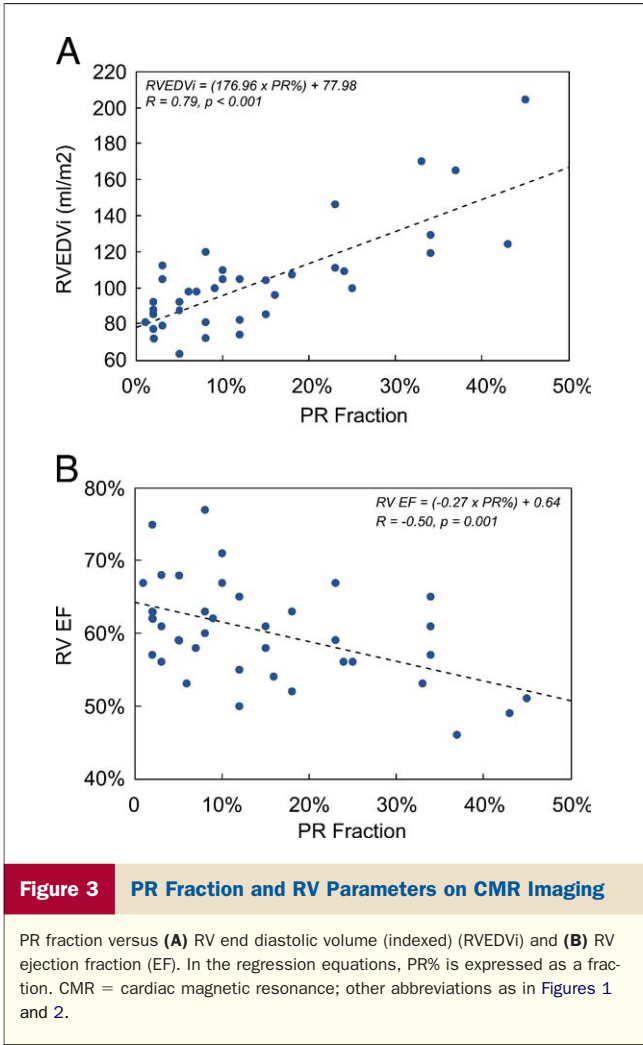
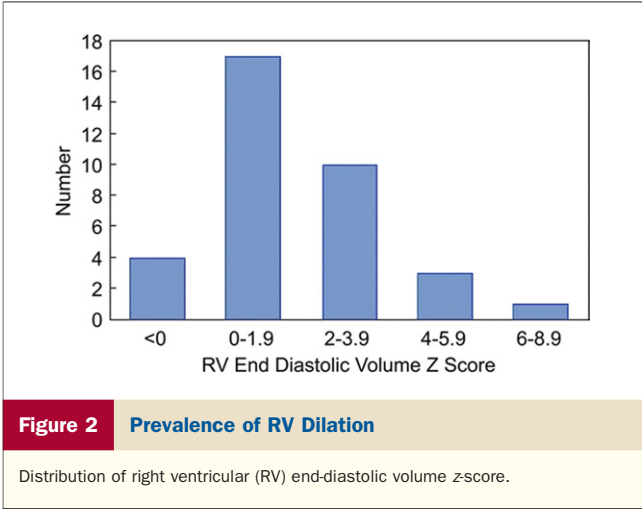
None of the demographic or continuous CMR variables correlated with the percentage of predicted peak VO₂ or peak work. Body mass index correlated modestly with the V_E/V_{CO2} slope ($R = -0.41$, $p = 0.009$), but not with other exercise outcomes. When PR fraction was dichotomized, peak VO₂ was found to be significantly higher in patients with a PR fraction ≤15% than in those in whom it was >15% ($96 \pm 16\%$ vs. $85 \pm 17\%$, $p = 0.03$) (Fig. 4). There was a trend towards a higher percentage of predicted peak work in patients with a PR fraction ≤15% as well ($99 \pm 20\%$ vs. $86 \pm 24\%$, $p = 0.06$) (Fig. 4).

Discussion

In this study, we prospectively evaluated 41 patients who had undergone balloon valvuloplasty for valvar PS a median of 13 years earlier, with minimal residual outflow tract obstruction, using CMR imaging and exercise testing. This allowed us both to characterize the prevalence of PR and its risk factors and to assess the long-term impact of PR on cardiac and exercise function. In this cohort, the degree of PR and RV dilation ranged markedly, but severe PR and RV dilation were very uncommon. Larger BAR and younger age at intervention were associated with higher PR fraction, which in turn was strongly associated with RV



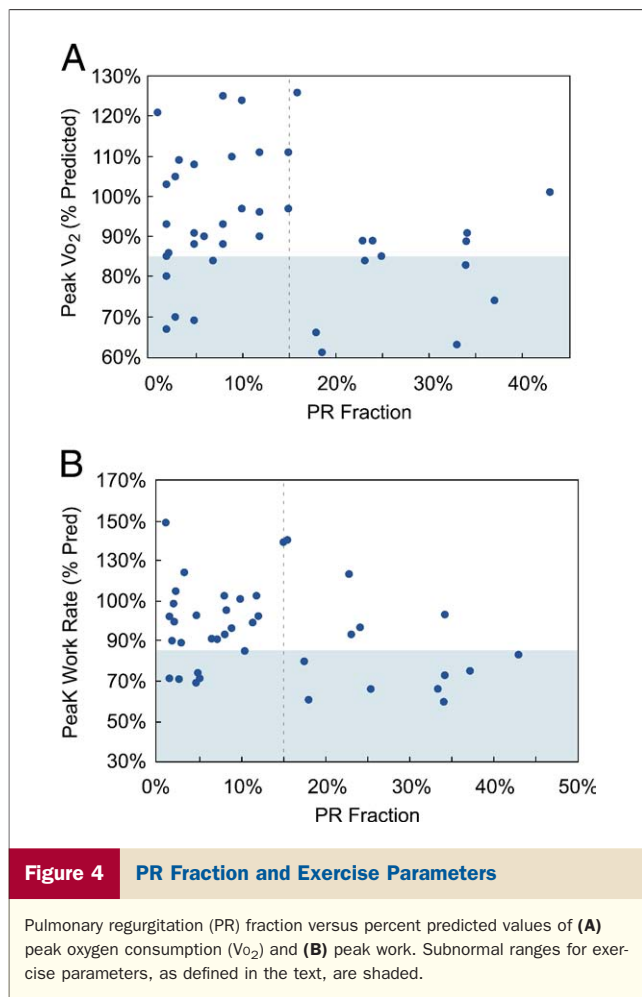
dilation and modestly with decreased RV function. Overall, exercise cardiopulmonary function in this group was modestly below average, perhaps as a consequence of impaired ability to augment stroke volume. Patients with a PR fraction $>15\%$ had significantly lower peak VO_2 than those with less PR. No significant association was found between



these variables using linear regression analysis, although this may have been due at least in part to the limited number of enrolled patients.

Some degree of RV dilation in this group was common, but was usually mild. The correlation between PR and indexed RV end-diastolic volume was fairly close, suggesting that RV compliance does not vary widely over the range of RV volumes seen in this group. In general, RV EF was normal, although there was a modest inverse relationship with PR fraction; this suggests that isolated PR and consequent RV dilation may adversely impact RV function. LV volume and function were also normal, and there was no evidence of an inverse relationship between PR fraction or RV volume/function and LV stroke volume or EF. This provides evidence that, with modest degrees of PR and RV dilation, there is unlikely to be significant ventricular interaction. As a group, no relationship was seen between time from valvuloplasty and PR fraction. Changes in this value over time for a particular individual, however, were not specifically addressed.

These findings add to a growing body of literature on the effects of chronic PR (23-25). They are unique, however, in



that the impact of PR in this patient population was studied in isolation, absent the many confounders present in other populations of patients with PR, such as those with repaired tetralogy of Fallot (26–30). Exercise data from our patients differ from those reported for patients with repaired tetralogy of Fallot in at least 2 respects. First, in contrast to the mildly reduced peak Vo_2 observed in our patients, peak Vo_2 is often substantially diminished in patients with post-operative tetralogy of Fallot (31). Second, whereas subjects in our series on average had normal values of V_E/V_{CO_2} slope, patients with tetralogy of Fallot frequently have elevations of this value (32). In tetralogy patients, these abnormalities are probably the result of ventilation/perfusion mismatch secondary to pulmonary artery stenoses, which may further exacerbate PR and RV volume load during exercise. Such stenoses would be unexpected in the patients in this series, and a more normal V_E/V_{CO_2} slope was generally preserved.

In addition to offering insight into the pathophysiology of chronic isolated PR, this study provides important long-term data on the outcomes of balloon pulmonary valvuloplasty, which has become the standard of care for treatment of congenital valvar PS. The exclusion of patients with associated anomalies or significant residual PS limits our

ability to generalize these findings to the broader population of patients who undergo BD for PS. Previous studies, however, have shown that residual or recurrent PS is relatively uncommon, and that valvar PS is usually an isolated lesion (33,34). The study design also allowed the possibility of recruitment bias, although there is no obvious means by which this would dramatically alter our findings. Thus, although these factors must be taken into account and could in principle distort assessment of prevalence, we anticipate that our findings are generally representative.

The target BAR for patients undergoing balloon pulmonary valvuloplasty, 1.2 to 1.4, was based on experimental studies in which a BAR of 1.5 or higher was associated with a greater risk of damage to the RV outflow tract (35), later substantiated in early human studies (12). In the current study, the finding that significant PR was uncommon in patients dilated with a BAR <1.4 provides support for the appropriateness of 1.2 to 1.4 as a target BAR range. In this cohort, patients with a smaller pulmonary valve z-score were more likely to undergo dilation with a larger BAR, and several patients were treated with a BAR >1.4. In patients with recalcitrant obstruction, the tradeoff between using a larger balloon in an effort to relieve PS compared with the increased risk of complications and PR is important to consider and deserves further study.

Study limitations. The power of our study and strength of its conclusions regarding the relationship between exercise outcomes and PR fraction would have benefited from a larger sample size or a higher burden of PR among enrolled patients. Although an analysis of the effect of pre-intervention pressure load on long-term outcomes was included in this study, the impact of the duration of the load was not specifically assessed, and bears further evaluation. Our findings may be confounded by the coexistence of TR, another cause of RV volume loading, with PR. However, the impact of TR was probably minimal in this cohort, given its low prevalence. The low percentage of eligible patients who enrolled may introduce bias and, as discussed above, complicates accurate estimation of the overall prevalence of PR and RV dilation. However, this factor is unlikely to have an important effect on the study's primary aims.

Conclusions

Percutaneous pulmonary valvuloplasty yields a substantial long-term prevalence of PR and mild RV dilation. In this series, 34% of patients had a PR fraction >15% and 40% had an RV end-diastolic volume z-score ≥ 2 . Severe PR or RV dilation, however, was very uncommon. Of the 41 patients, only 2 had PR fraction >40% and 1 had RV end-diastolic z-score ≥ 6 . The BAR in each of these cases was >1.4. PR was associated closely with RV dilation and modestly with RV function. No significant relationship was found in linear regression analysis between PR fraction and exercise capacity. The cohort with PR fraction

>15%, however, had significantly lower peak VO_2 than the group with PR fraction $\leq 15\%$. This finding provides evidence that significant PR, in the absence of confounding cardiac comorbidities, is associated with reduced exercise tolerance.

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Key Words: pulmonary regurgitation ■ exercise function ■ balloon valvuloplasty ■ pulmonary stenosis ■ right ventricular dilation.