



Clinical Research

Assessment of Right Ventricular-Pulmonary Arterial Coupling in Chronic Pulmonary Regurgitation

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See editorial by Sathananthan and Grewal, pages 816–818 of this issue.

ABSTRACT

Background: We hypothesized that noninvasively measured right ventricular (RV) to pulmonary arterial (RV-PA) coupling would be abnormal in chronic pulmonary regurgitation (PR) even in the setting of normal RV ejection fraction, and that RV-PA coupling indices would have a better correlation with peak oxygen consumption (VO_2) compared with RV systolic indices alone.

Methods: This was a retrospective study of 129 adults (repaired tetralogy of Fallot [TOF] $n = 84$ and valvular pulmonic stenosis [VPS] with previous intervention $n = 45$) with \geq moderate native PR and RV ejection fraction $> 50\%$. The 84 TOF patients were propensity matched with 84 patients with normal echocardiogram (control); age 28 ± 7 years and male sex $n = 39$ (46%). RV-PA coupling was measured according to fractional area change (FAC)/RV systolic pressure (RVSP) and tricuspid annular plane systolic excursion (TAPSE)/RVSP.

Results: RV systolic function indices were similar between TOF and control groups (FAC $43 \pm 6\%$ vs $41 \pm 5\%$ [$P = 0.164$] and TAPSE 22 ± 5 mm vs 24 ± 6 mm [$P = 0.263$]). However, RV-PA coupling was lower

RÉSUMÉ

Contexte : Notre hypothèse de travail était que le couplage entre le ventricule droit (VD) et l'artère pulmonaire (AP) (VD-AP) mesuré par une méthode non invasive serait anormal chez les patients atteints de régurgitation pulmonaire (RP), même dans les cas où la fraction d'éjection du VD est normale, et que les indices de couplage VD-AP seraient davantage corrélés à la consommation d'oxygène maximal (VO_2) qu'avec les indices VD systoliques seuls.

Méthodologie : Il s'agissait d'une étude rétrospective portant sur 129 adultes (tétralogie de Fallot [TF] réparée : $n = 84$; et sténose valvulaire pulmonaire [SVP] avec intervention antérieure : $n = 45$) avec \geq RP naturelle modérée et fraction d'éjection du VD $> 50\%$. Les 84 patients atteints de TF ont été appariés en fonction du score de propension avec 84 patients présentant un échocardiogramme normal (témoins); âge 28 ± 7 ans et sexe masculin, $n = 39$ (46 %). Le couplage VD-AP a été mesuré par les rapports VFS/PSVD (variation fractionnaire de la surface /pression systolique du VD) et ESPAT/PSVD (excursion systolique du plan de l'anneau tricuspide/PSVD).

Pulmonary regurgitation (PR) is a common complication after right ventricular (RV) outflow tract intervention.^{1,2} The patients with tetralogy of Fallot (TOF) and valvular pulmonic stenosis (VPS) with previous RV outflow tract interventions usually develop significant PR.^{1,2} Chronic RV volume overload due to PR results in RV systolic dysfunction and cardiovascular complications such as arrhythmia, heart failure, and death.^{3,4} The longitudinal assessment of RV systolic function is therefore important in the management of these patients.

Transthoracic echocardiogram is the primary imaging modality for the assessment of RV systolic function in patients with congenital and acquired heart diseases.⁵⁻⁷ The practice guidelines endorse fractional area change (FAC), tricuspid annular plane systolic excursion (TAPSE), and RV systolic tissue Doppler velocity as noninvasive indices of RV systolic function.⁵ These echocardiographic indices are load-sensitive, and therefore do not accurately reflect RV contractile function in the setting of abnormal loading conditions. Severe PR results in abnormal RV loading conditions because of increase in preload and afterload.⁸

RV to pulmonary arterial (RV-PA) coupling, a load-independent measure of RV performance is normally measured invasively during right heart cardiac catheterization.⁹ Noninvasive estimation of RV-PA coupling using a ratio of RV systolic function indices (FAC or TAPSE) and RV afterload (pulmonary artery [PA] systolic pressure) have been validated as prognostic indices in patients with heart failure due to acquired heart disease but not in patients with congenital heart

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in the TOF group (FAC/RVSP 1.10 ± 0.29 vs 1.48 ± 0.22 [$P < 0.001$]; TAPSE/RVSP 0.51 ± 0.15 vs 0.78 ± 0.11 [$P < 0.001$]) because of higher RV afterload (RVSP 42 ± 3 mm Hg vs 31 ± 3 mm Hg [$P = 0.012$]). FAC/RVSP ($r = 0.61$; $P < 0.001$) and TAPSE/RVSP ($r = 0.69$; $P < 0.001$) correlated with peak VO_2 especially in the patients with impaired exercise capacity whereas FAC and TAPSE were independent of peak VO_2 . Similar comparisons between VPS and control groups showed no difference in TAPSE and FAC between groups, but lower FAC/RVSP and TAPSE/RVSP in the VPS group.

Conclusions: There is abnormal RV-PA coupling in chronic PR, and noninvasively measured RV-PA coupling might potentially be prognostic because of its correlation with exercise capacity.

disease.¹⁰⁻¹² Because RV systolic function varied depending on loading conditions, we hypothesized that RV-PA coupling (measured noninvasively) would be abnormal in patients with chronic PR even in the setting of normal RV ejection fraction, and that RV-PA coupling indices will have a better correlation with exercise capacity compared with RV systolic indices alone.

Methods

Patient selection

The Mayo Adult Congenital Heart Disease (MACHD) database was queried for patients with native PR after RV outflow tract intervention from January 1, 2003 through December 31, 2015. The inclusion criteria were: age > 18 years, cardiac magnetic resonance imaging (CMRI)-derived RV ejection fraction $> 50\%$, at least moderate PR (defined as regurgitant fraction $> 25\%$ according to CMRI and/or qualitative assessment using Doppler echocardiography), and echocardiographic images of sufficient quality to measure FAC and TAPSE. The patients with concomitant pulmonic stenosis (defined as pulmonary valve peak velocity > 2 m/s) and the patients with previous pulmonary valve replacement or RV-PA conduit placement were excluded. We divided the patients into a TOF group and a VPS group.

For the purpose of comparison, we selected a control group comprised of patients without structural heart disease on the basis of a normal transthoracic echocardiogram performed within the study period. To minimize differences in the baseline characteristics of the TOF group and the control (no structural heart disease) group, we performed propensity matching using the following baseline characteristics: age, sex, body mass index, and body surface area. The final cohort consisted of 84 patients in each of the groups. The Mayo Clinic institutional review board approved this study and waived informed consent for patients who provided research authorization.

Data collection

The following electronic health records were reviewed in detail: transthoracic echocardiograms, CMRI reports, cardiopulmonary

Résultats : Les indices de la fonction systolique du VD des groupes TF et témoin étaient similaires (VFS, $43 \pm 6\%$ vs $41 \pm 5\%$ [$p = 0,164$] et ESPAT, 22 ± 5 mm vs 24 ± 6 mm [$p = 0,263$]). Toutefois, le couplage VD-AP était plus faible dans le groupe TF (VFS/PSVD, $1,10 \pm 0,29$ vs $1,48 \pm 0,22$ [$p < 0,001$]; ESPAT/PSVD, $0,51 \pm 0,15$ vs $0,78 \pm 0,11$ [$p < 0,001$]) en raison d'une postcharge du VD plus importante (PSVD, 42 ± 3 mm Hg vs 31 ± 3 mm Hg [$p = 0,012$]). Les rapports VFS/PSVD ($r = 0,61$; $p < 0,001$) et ESPAT/PSVD ($r = 0,69$; $p < 0,001$) étaient corrélés à la consommation de VO_2 maximal, en particulier chez les patients ayant une capacité d'exercice réduite, tandis que la VFS et l'ESPAT étaient indépendantes du VO_2 maximal. Des comparaisons similaires entre les groupes SVP et témoin n'ont mis en évidence aucune différence entre les groupes en ce qui concerne l'ESPAT et la VFS, mais les rapports VFS/PSVD et ESPAT/PSVD étaient moins élevés dans le groupe SVP.

Conclusions : Le couplage VD-AP est anormal chez les patients atteints de RP chronique, et sa mesure par une méthode non invasive pourrait avoir une utilité pronostique car il est corrélé à la capacité d'exercice.

exercise test, clinic notes, and surgical records. The clinical data obtained within 12 months from the time of CMRI were analyzed as the baseline characteristics of the cohort. For the purpose of this study, the different types of RV outflow tract interventions were grouped into 3 categories: balloon pulmonary valvuloplasty, transannular patch repair, and nontransannular patch repair (surgical valvotomy, valvectomy, or commissurotomy).

The digital echocardiographic images of all patients were reviewed and offline measurements performed (R.P.); these measurements were verified in a randomly selected sample (50% of the cohort) by one of the investigators (A.C.E.). The severity of tricuspid regurgitation, PR, RV enlargement, and RV systolic dysfunction were graded as none/trivial, mild, mild-moderate, moderate, moderate-severe, and severe on the basis of standard assessment using comprehensive echocardiogram.⁶ The protocol for volumetric assessment using CMRI at this institution has been previously described.¹³ RV stroke volume and ejection fraction were calculated from end-diastolic and end-systolic volumes. PR fraction was calculated as: (RV stroke volume – left ventricular stroke volume)/RV stroke volume. All volumetric data were indexed to body surface area. Plasma volume at the time of echocardiography was estimated by: $(1 - \text{hematocrit}) (a + [b \times \text{weight in kilograms}])$, where $a = 1530$ in men and 864 in women, and $b = 41$ in men and 47.9 in women.¹⁴

End points

The primary end point was to compare RV systolic function indices (measured using FAC and TAPSE), PA vascular function indices (measured according to PA elastance index and PA acceleration time), and RV-PA coupling indices (measured according to FAC/RV systolic pressure [RVSP] ratio and TAPSE/RVSP ratio) between the TOF group and the control group. The secondary end point was to determine the association between RV systolic function and RV-PA coupling indices and exercise capacity (measured according to percent predicted peak oxygen consumption [VO_2]). As an exploratory end point, we performed the same analyses between the VPS group and the control group. Only peak VO_2

derived from symptom-limited treadmill tests with maximum effort defined as respiratory exchange ratio > 1.1 were used for the analysis of the secondary end point. Impaired exercise capacity was defined as peak $\text{VO}_2 < 50\%$ predicted for age and sex.¹⁵

The indices of RV systolic function, PA vascular function, and RV-PA coupling used in the current study were chosen on the basis of previous studies that validated these variables as prognostic indices in patients with heart failure.¹⁰⁻¹² FAC/RVSP ratio and TAPSE/RVSP have been reported as noninvasive indices of RV-PA coupling and provide a measure of *in vivo* RV length-forced relationship.¹⁰⁻¹² PA elastance index, a lumped measure of the total “stiffness” of the arterial system, was assessed according to end-systolic PA pressure (PA systolic blood pressure $\times 0.9$)/RV stroke volume index.^{12,16} RV stroke volume assessment using Doppler echocardiography was on the basis of the hydraulic orifice formula (flow rate = cross-sectional area \times flow velocity) and calculated as $0.785 \times (\text{RV outflow tract diameter})^2 \times \text{RV outflow tract time velocity integral}$.⁶

Statistical analysis

Propensity matching was used for the selection of the TOF and control groups on the basis of age, sex, body mass index, and body surface area. Subjects within 1 SD of the probability estimate were selected for matching. The interobserver variability between the indices (FAC, TAPSE, and RVSP; measured by R.P. and A.C.E.) were assessed using intraclass correlation coefficient. Data were reported as mean \pm SD, median (interquartile range), or count (percentages). Between group differences were calculated using χ^2 test, Fisher exact test, 2-sided unpaired *t* test, or Mann-Whitney test, as appropriate. Linear regression analyses were used to assess the relationships between RV function variables and peak VO_2 . All statistical analyses were performed with JMP software (version 13.0; SAS Institute Inc, Cary, NC); $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics of TOF and control groups

We enrolled 84 patients in the TOF group and 84 patients in the control (no structural heart disease) group. The mean age was 28 ± 7 years and 39 (46%) were men. Table 1 shows the baseline characteristics of the cohorts. Compared with the control group, the TOF patients were more likely to have atrial arrhythmia, and more likely to be receiving aspirin and β and/or calcium channel blockers. Of the 84 TOF patients, 16 (19%) had previous palliative shunt procedures, the age of initial RV outflow tract intervention was 4 ± 2 years, and the types of RV outflow tract interventions were transannular patch repair in 57 (68%) and nontransannular patch repair in 27 (32%). None of the patients in the TOF group had residual branch PA stenosis on the basis of CMRI data.

Hemodynamic data of TOF and control groups

Table 2 shows the echocardiographic and CMRI data of the cohorts. By design the TOF group had more RV enlargement because of volume overload compared with the control group. RV systolic function indices were similar between the TOF and

the control groups, respectively (FAC $43 \pm 6\%$ vs $41 \pm 5\%$ [$P = 0.164$] and TAPSE 22 ± 5 mm vs 24 ± 6 mm [$P = 0.263$]; Fig. 1). Although RV systolic function indices were similar between the 2 groups, RV-PA coupling was lower in the TOF group (FAC/RVSP ratio 1.10 ± 0.29 vs 1.48 ± 0.22 [$P < 0.001$] and TAPSE/RVSP ratio 0.51 ± 0.15 vs 0.78 ± 0.11 [$P < 0.001$]) because of a higher RV afterload (RVSP 42 ± 3 mm Hg vs 31 ± 3 mm Hg [$P = 0.012$]). In concordance with the higher RV afterload in the TOF group, this group also had worse pulmonary vascular function measured according to PA elastance index (0.81 ± 0.14 mm Hg/mL/m² vs 0.68 ± 0.12 mm Hg/mL/m² [$P = 0.012$]) and PA acceleration time ($119 \pm$ ms vs 134 ± 26 ms [$P = 0.023$]; Fig. 1). The interclass correlation coefficients for FAC, TAPSE, and RVSP were 0.78, 0.91, and 0.86, respectively.

Exercise capacity of TOF group

The median percent predicted peak VO_2 was 73% (interquartile range 46-89%) in the TOF group. There was a weak correlation between RV-PA coupling indices and exercise capacity in this group (Fig. 2A). However a subgroup analysis of the patients with impaired exercise capacity defined as peak $\text{VO}_2 < 50\%$ of predicted ($n = 19$), showed a modest correlation between FAC/RVSP ($r = 0.61$; $P < 0.001$) and TAPSE/RVSP ($r = 0.69$; $P < 0.001$; Fig. 2B). There was no relationship between RV systolic function indices (FAC and TAPSE) and exercise capacity (data not shown).

VPS group

We enrolled 45 patients in the VPS group on the basis of predefined inclusion criteria. Of these 45 patients, the age of initial RV outflow tract intervention was 6 ± 3 years, and the types of RV outflow tract interventions were transannular patch repair $n = 2$ (4%) and nontransannular patch repair $n = 34$ (76%), and balloon pulmonary valvuloplasty $n = 9$ (20%). There was no significant difference in the baseline clinical characteristics between the VPS group and the control group (Supplemental Table S1). Supplemental Table S2 shows a comparison of echocardiographic and CMRI data between the VPS group and the control group.

RV systolic function indices were similar between the VPS and the control groups, respectively (FAC $42 \pm 4\%$ vs $41 \pm 5\%$ [$P = 0.267$] and TAPSE 23 ± 3 mm vs 24 ± 6 mm [$P = 0.341$]; Fig. 3). Although RV systolic function indices were similar between the 2 groups, RV-PA coupling was lower in the VPS group (FAC/RVSP ratio 1.07 ± 0.18 vs 1.48 ± 0.22 [$P < 0.001$] and TAPSE/RVSP ratio 0.59 ± 0.11 vs 0.78 ± 0.11 [$P = 0.004$]) because of a higher RV afterload (RVSP 39 ± 2 mm Hg vs 31 ± 3 mmHg [$P = 0.028$]). Similarly the VPS group also had worse pulmonary vascular function (PA elastance index 0.76 ± 0.10 mm Hg/mL/m² vs 0.68 ± 0.12 mm Hg/mL/m² [$P = 0.033$]) and PA acceleration time (123 ± 21 ms vs 134 ± 26 ms [$P = 0.046$]; Fig. 3).

In contrast to the relationship between RV-PA coupling indices and exercise capacity observed in the TOF group, there was no correlation between peak VO_2 and RV-PA coupling indices in the VPS group (data not shown). Only 7 VPS patients had peak $\text{VO}_2 < 50\%$ of predicted, and as a result a subgroup analysis for the relationship between RV-PA

Table 1. Baseline characteristics

Characteristic	TOF (n = 84)	Control (n = 84)	P
Age, years	28 ± 7	28 ± 7	0.999
Male sex, n (%)	39 (46)	39 (46)	0.999
Body surface area, m ²	27 (24-32)	27 (25-30)	0.243
Body mass index, kg/m ²	1.9 (1.6-2.2)	1.9 (1.7-2.1)	0.317
Comorbidities, n (%)			
Atrial flutter /fibrillation	16 (19)	0	0.001
Hypertension	17 (20)	13 (15)	0.551
Hyperlipidemia	15 (18)	16 (19)	0.462
Current or previous smoker	8 (10)	9 (11)	0.587
Diabetes mellitus	7 (8)	8 (10)	0.263
Sleep apnea	11 (13)	12 (14)	0.216
Previous stroke	2 (2)	0	0.754
Laboratory tests			
Hemoglobin, g/dL	14.1 ± 1.8	13.6 ± 1.4	0.613
Creatinine, mg/dL	1.1 ± 0.4	1.0 ± 0.3	0.583
NT-proBNP, pg/mL	163 ± 51 (n = 59)	89 ± 33 (n = 6)	0.062
Estimated plasma volume, mL	2955 ± 501	2436 ± 465	0.097
Medications			
Diuretics	5 (6%)	2 (2%)	0.174
β and/or calcium channel blockers	15 (18%)	6 (7%)	0.031
RAAS antagonist	13 (16%)	9 (11%)	0.351
Warfarin	2 (2%)	0	0.614
Direct oral anticoagulants	2 (2%)	0	0.614
Aspirin	31 (37%)	2 (2%)	< 0.001

NT-proBNP, N-terminal pro B-type natriuretic peptide; RAAS, renin angiotensin aldosterone system; TOF, tetralogy of Fallot.

coupling indices and exercise capacity was not performed in this group.

Discussion

Chronic PR results in progressive RV dilation and systolic dysfunction.^{3,4} Most of the echocardiographic indices of RV systolic function are load-sensitive, and do not reflect RV

performance in the setting of chronic volume overload due to PR.^{5,6} In this study, we showed that patients with chronic PR have abnormal RV-PA coupling even in the setting of normal RV ejection fraction.

RV systolic function in abnormal loading conditions

We compared echocardiographic indices of 84 TOF patients with normal CMRI-derived RV ejection fraction with

Table 2. Hemodynamic data

	TOF (n = 84)	Control (n = 84)	P
Echocardiography			
≥ Moderate RV enlargement*	76 (91%)	0	< 0.001
≥ Moderate tricuspid regurgitation*	10 (12%)	0	< 0.001
Severe pulmonary regurgitation*	74 (88%)	0	< 0.001
Tricuspid regurgitation velocity, m/s	3.2 ± 0.4	2.5 ± 0.2	0.014
RVSP, mm Hg	42 ± 3	31 ± 3	0.012
Pulmonary valve peak velocity, m/s	1.3 ± 0.2	0.9 ± 0.2	0.063
TAPSE, cm	22 ± 5	24 ± 6	0.263
FAC, %	43 ± 6	41 ± 5	0.164
RV S', cm/s	13 ± 2	14 ± 4	0.094
Medial E/e'	8 ± 2	8 ± 2	0.423
Lateral E/e'	6 ± 1	7 ± 2	0.187
LV ejection fraction, %	56 ± 4	58 ± 6	0.295
LV cardiac index, L/min/m ²	3.1 ± 0.2	3.3 ± 0.4	0.428
Heart rate, bpm	67 ± 6	69 ± 7	0.729
CMRI			
RVEDV index, mL/m ²	128 ± 18	—	—
RVESV index, mL/m ²	61 ± 7	—	—
RV stroke volume index, mL/m ²	66 ± 9	—	—
PR volume index, mL/m ²	21 ± 6	—	—
PR fraction, %	32 ± 4	—	—
RV ejection fraction, %	55 ± 3	—	—
LV ejection fraction, %	58 ± 5	—	—
LV stroke volume index, mL/m ²	44 ± 5	—	—

bpm, beats per minute; CMRI, cardiac magnetic resonance imaging; FAC, fractional area change; LV, left ventricle; PR, pulmonary regurgitation; RV, right ventricle; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion; TOF, tetralogy of Fallot.

* Qualitative assessment.

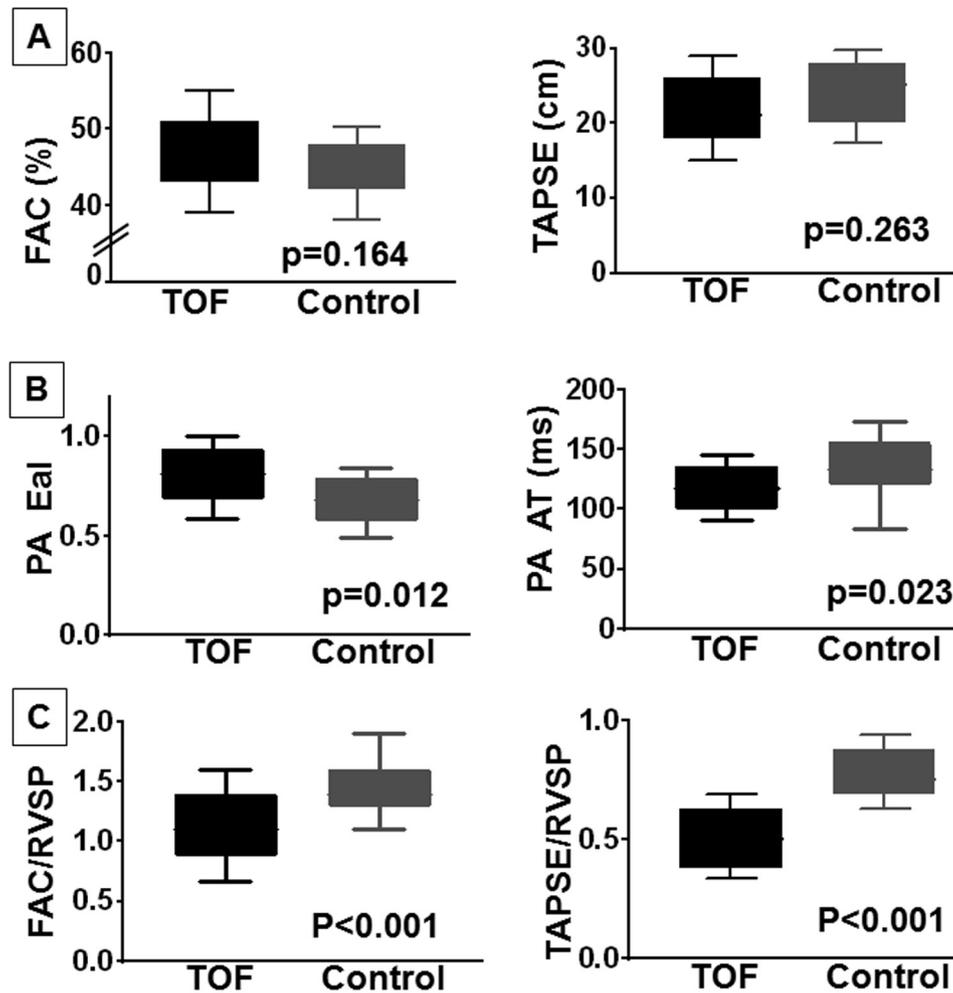


Figure 1. Box and whisker plot showing a comparison of echocardiographic indices between patients with tetralogy of Fallot (TOF) and controls. Variables are displayed as mean and 95% confidence interval. (A) Comparison of right ventricular function indices measured according to fractional area change (FAC) and tricuspid annular plane systolic excursion (TAPSE). (B) Comparison of pulmonary artery vascular function indices measured according to pulmonary artery elastance index (PA Eal) and pulmonary artery acceleration time (PA AT). (C) Comparison of right ventricular-pulmonary arterial coupling indices measured according to FAC/right ventricular systolic pressure (RVSP) ratio and TAPSE/RVSP ratio.

that of a propensity matched cohort of 84 patients without structural heart disease. Our study showed that although RV systolic function indices (TAPSE and FAC) were similar between the 2 groups, RV-PA coupling was lower in the TOF group because of a higher RV afterload.

Chronic PR results in an increase in RV preload because of the greater RV end-diastolic volume required to maintain physiologic cardiac output and adequate left ventricular filling.⁸ There is also an increase in RV afterload in chronic PR although the mechanism is not well understood. It is postulated that chronic volume overload of the proximal PA results initially in an increase in PA compliance but there is a subsequent loss of PA elasticity over time leading to increased stiffness and RV pulsatile afterload.^{8,17} Additionally patients with TOF might have genetic histologic abnormalities of the PA or acquire structural abnormalities of the PA due to distortion from a previous palliative shunt, all resulting in abnormal PA elastic properties.^{17,18} All of these factors might contribute to higher RV afterload, which becomes more

apparent when the proximal PA is subjected to the stress of volume loading in the setting of chronic PR.¹⁹ In this study, the TOF and VPS patients had higher PA elastance compared with normal controls. Arterial elastance represents a lumped measure of the total “stiffness” of the arterial system and represents the pulsatile afterload of the ventricle^{16,19}; the presence of increased PA elastance in this study supports the postulate of increased afterload in chronic PR.

RV-PA coupling in abnormal loading conditions

RV-PA coupling, a load-independent measure of RV performance, is normally measured invasively during right heart cardiac catheterization.⁹ In a study of 24 patients (mean age, 17 years) with repaired TOF and PR who underwent invasive hemodynamic assessment at rest and with dobutamine stress, Latus and colleagues showed that these patients had impaired RV-PA coupling at rest and with dobutamine stress regardless of the RV ejection fraction.¹⁹ Although the RV end-systolic

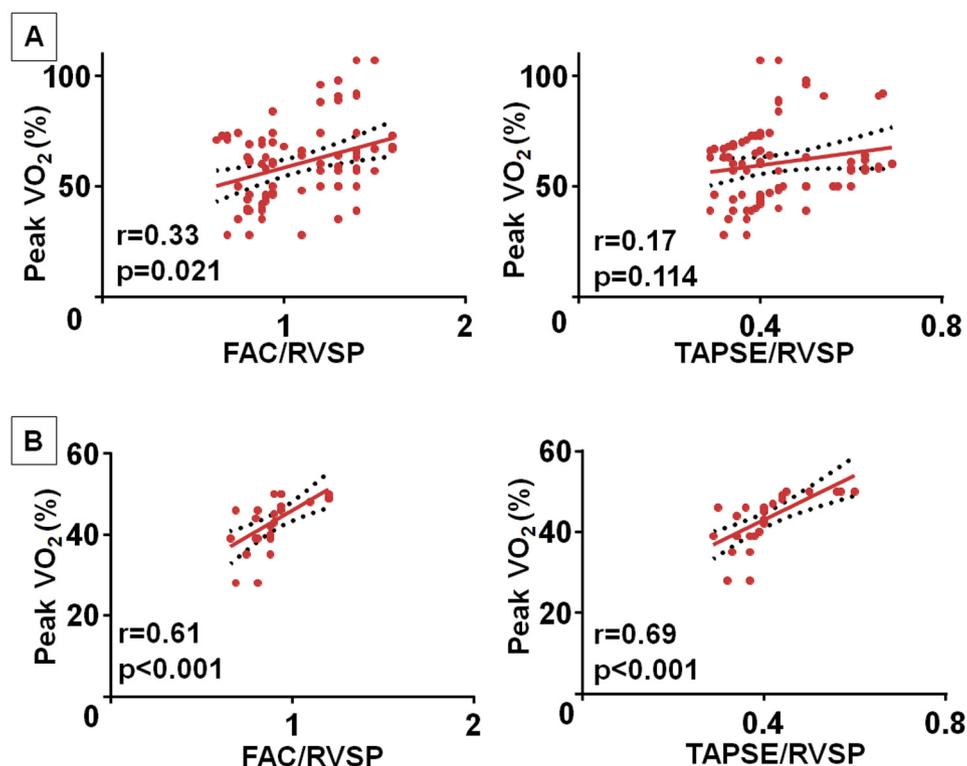


Figure 2. Linear correlation of percent predicted peak oxygen consumption (peak VO₂) and right ventricular-pulmonary arterial coupling indices in all tetralogy of Fallot (TOF) patients (A), and in the subset of TOF patients with peak VO₂ < 50% (B). FAC, fractional area change; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion.

elastance increased with dobutamine stress, there was a disproportionate increase in PA elastance resulting in a decrease in RV-PA coupling in TOF patients.¹⁹ This highlights the important role of abnormal PA elastic properties and its potential interaction with RV performance in TOF patients with PR.

Noninvasive assessment of RV-PA coupling using a ratio of RV systolic function and RV afterload has been studied in patients with heart failure due to acquired heart disease.⁹⁻¹² In a study of 293 heart failure patients, Guazzi and colleagues showed that TAPSE/RVSP ratio improved prognostic resolution compared with TAPSE or RVSP alone.¹¹ In that study, the patients with TAPSE/RVSP ratio < 0.36 had a 10-fold increase in mortality compared with a risk model using TAPSE < 16, which only predicted a fivefold increase in mortality after multivariable adjustments.¹¹ The authors postulated that the relationship between TAPSE (longitudinal RV fibre shortening) and RVSP (force generated by the RV) provides an index of *in vivo* RV length-force relationship.¹¹ The TAPSE/RVSP ratio, which is load independent represents a better measure of RV performance in abnormal loading condition. Noninvasively measured RV-PA coupling using either TAPSE/RVSP or FAC/RVSP ratio have also been shown to be of superior prognostic value compared with RV systolic function (FAC or TAPSE) in other studies of patients with heart failure due to acquired cardiovascular diseases.^{9,10,12}

In the current study we also showed a correlation between RV-PA coupling indices (TAPSE/RVSP and FAC/RVSP) and

peak VO₂ especially in the subset of patients with impaired exercise capacity (Fig. 2). There was no relationship between RV systolic function alone (FAC or TAPSE) and exercise capacity. These findings are concordant with other studies that evaluated the prognostic role of noninvasive RV-PA coupling in the heart failure population.⁹⁻¹² Our study shows that despite the significant differences in population demographic characteristics and pathophysiology of disease between the older patients with heart failure due to acquired cardiovascular diseases and the younger patients with congenital heart disease, noninvasively measured RV-PA coupling indices provide a better assessment of RV performance in the setting of abnormal loading conditions. Furthermore the abnormal RV-PA coupling in the setting of normal RV ejection fraction observed in the TOF and VPS groups suggests that the efficiency of RV performance is determined, to a large extent, by loading conditions rather than the specific disease process.

Clinical implications and future directions

In the current study we showed that abnormal RV-PA coupling can occur even in the setting of normal RV systolic function in chronic PR, and the potential for a prognostic role of noninvasively measured RV-PA coupling because of its correlation with exercise capacity. The importance of exercise capacity measured according to peak VO₂ in predicting the occurrence of cardiovascular mortality is well established in the acquired and congenital heart disease populations.²⁰⁻²²

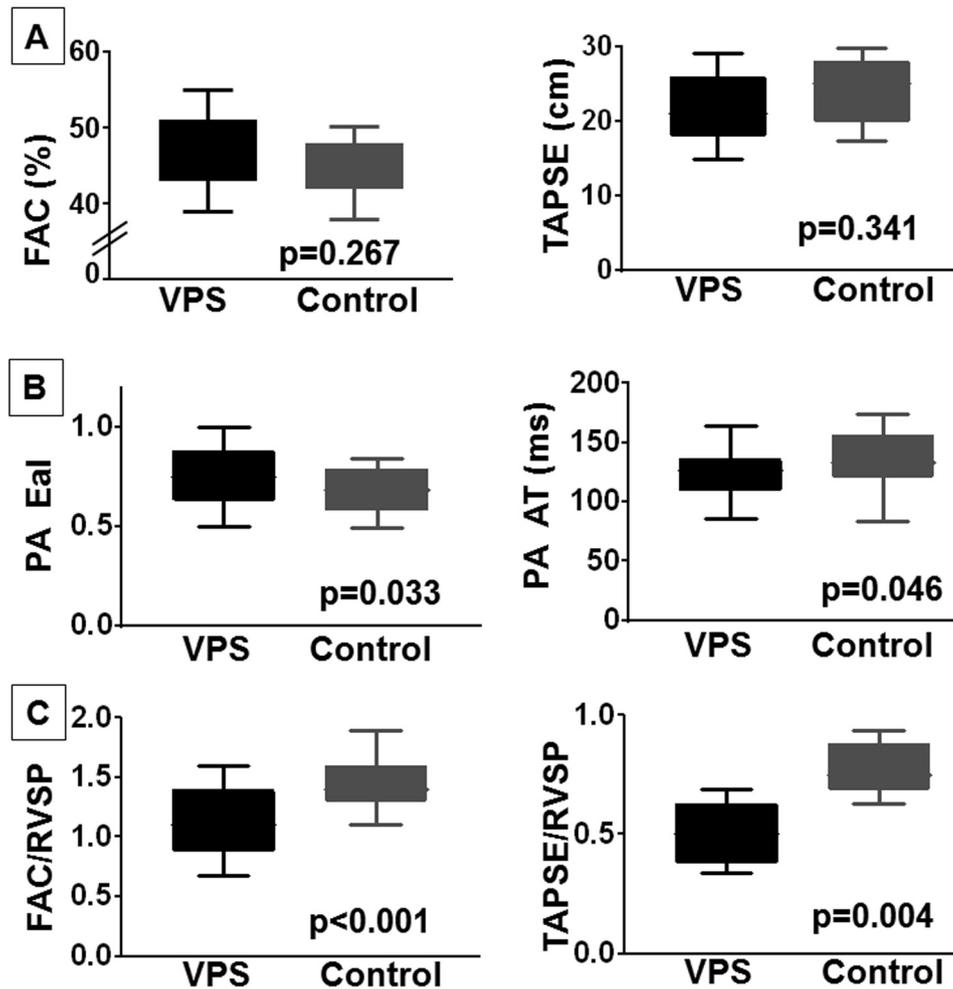


Figure 3. Box and whisker plot showing a comparison of echocardiographic indices between patients with valvular pulmonic stenosis (VPS) and controls. Variables are displayed as mean and 95% confidence interval. **(A)** Comparison of right ventricular function indices measured according to fractional area change (FAC) and tricuspid annular plane systolic excursion (TAPSE). **(B)** Comparison of pulmonary vascular function indices measured according to pulmonary artery elastance index (PA Eal) and pulmonary artery acceleration time (PA AT). **(C)** Comparison of right ventricular-pulmonary arterial coupling indices measured according to FAC/right ventricular systolic pressure (RVSP) and TAPSE/right ventricular systolic pressure (RVSP) ratio.

Ventricular wall stress is directly related to ventricular chamber dimension (preload) and ventricular systolic pressure (afterload) but inversely related to wall thickness.²³ CMRI-derived volumes and ejection fraction is currently the reference method for risk stratification and determining the timing of pulmonary valve replacement for chronic PR.²⁴⁻²⁷ Although the prognostic value of CMRI is well studied in this population, it is important to highlight that CMRI-derived indices only incorporates RV end-diastolic volume (preload) and ejection fraction (load-dependent measure of systolic function) but does not take into account the effect of abnormal RV afterload, which is present in this population.²⁸ The current study shows that noninvasively measured RV-PA coupling (which accounts for RV afterload) might be complementary to CMRI volumetric assessment in patients with chronic PR.

Although the current study is just a small-sample retrospective study that significantly limits the inference that can be

drawn from the results, it provides preliminary data for more robust future studies. Such studies will include: (1) simultaneous invasive and noninvasive assessment of RV-PA coupling in chronic PR; (2) assessment of the relationship between noninvasive RV-PA coupling and clinical markers of disease severity using a large cohort of patient in patients with chronic PR and different severities of RV systolic dysfunction; (3) simultaneous invasive and noninvasive assessment of RV-PA coupling at rest and with exercise in patients with unexplained exertional dyspnea; and (4) comparison of noninvasive RV-PA coupling before and after pulmonary valve replacement to determine if RV performance improves after the normalization of loading conditions.

Limitations

This was a small-sample retrospective study of patients with chronic pulmonary valve replacement and normal RV

ejection fraction, and does not provide information about RV-PA coupling in the setting of RV systolic dysfunction (reduced ejection fraction). There was no simultaneously acquired invasive hemodynamic data, which is necessary for correlation and validation of the noninvasively measured RV-PA coupling indices reported in the current study. The noninvasive RV-PA coupling indices described in this study is dependent on the accurate assessment of FAC, TAPSE, and RVSP, which can be challenging in patients with congenital heart disease, hence limiting the reproducibility of these indices.

Conclusions

The study shows abnormal RV-PA coupling in chronic PR even in the setting of normal RV ejection fraction, and that noninvasively measurement of RV-PA coupling (a load-independent measure RV performance) correlated with exercise capacity. Although noninvasive RV-PA coupling is used for risk stratification in the acquired heart disease population, this is first study, to our knowledge, to show its potential prognostic role in adults with congenital heart disease. Despite the limitations of the current study, it provides preliminary data for further studies to explore the application of this noninvasive load-independent measure of RV performance in the routine management of chronic PR.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

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