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Right atrial size and function in patients with pulmonary hypertension associated with disorders of respiratory system or hypoxemia

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Abstract *Background and aim:* Pulmonary hypertension (PH) determines various adaptive changes in right ventricular (RV) geometry which may progressively lead to hypertrophy, mechanical dysfunction and dilatation with pump failure. Right atrium (RA) is theoretically involved in this physiopathological process, but its role has never been investigated. We hypothesized that RA increases volume and function to assist RV during the chronic pressure overload exposition due to PH.
Methods: We prospectively enrolled 66 consecutive patients referred to our echo-lab with a diagnosis of PH [defined as pulmonary artery systolic pressure (PASP) >30 mmHg] associated with disorders of the respiratory system and/or hypoxemia and normal RV systolic function. Ejection force was taken up as index of RA systolic function and calculated according to the Manning's formula. Thirty-three healthy subjects for whom PH was definitely excluded by echoDoppler evaluation were used as controls.
Results: PASP was 42 ± 10 and 20 ± 8 mmHg in PH patients and controls, respectively; $p = 0.00001$). In comparison with controls, PH patients exhibited higher RA volume (37 ± 13 vs 32 ± 13 ml, $p = 0.04$) and RA ejection force (6.7 ± 3.0 vs 3.5 ± 1.8 Kdynes, $p = 0.00001$). Both variables were positively related to PASP ($r = 0.23$ and 0.48, $p = 0.02$ and 0.00001, respectively).

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Conclusions: In patients with chronic PH, RA size and systolic function significantly increase and parallel signs of activation of the Frank-Starling mechanism in both right chambers. The magnitude of these phenomena is positively related to PASP levels.

Introduction

Chronic pulmonary hypertension (PH) determines various adaptive changes in right ventricular (RV) geometry which can progressively result in hypertrophy, mechanical dysfunction and dilatation with pump failure. Right atrium is theoretically involved in this pathophysiological process, but its role has never been investigated. What the sonographers classically describe in patients with chronic PH is the final echocardiographic feature of a marked enlarged right atrium which usually parallels RV dilatation and systolic dysfunction, and leads to chronic atrial fibrillation. However, it is not known when changes in right atrial (RA) size arise during the natural history of chronic PH and whether these changes come up together with increase in RA performance. In patients with systemic arterial hypertension and normal left ventricular (LV) systolic function, as well as in other models of LV overload,[1,2] an early increase in left atrial size and function has been shown to be a mechanism counterbalancing impairment of LV filling and the progression of LV diastolic dysfunction.[3,4] Similarly, we hypothesize that right atrium initiates to increase volume and systolic function prior to the development of RV dilatation and systolic dysfunction for assisting the right ventricle during the chronic pressure overload exposition due to PH. Accordingly, the purpose of this study was to assess RA size and systolic function in patients with PH and normal RV systolic function, and define the relations of RA function to clinical, echocardiographic and hemodynamic parameters in this group of patients.

Methods

Candidates for this study were subjects >18 years of age in stable sinus rhythm who were addressed from their General Practitioners to our laboratory to perform a standard transthoracic echocardiography. The echocardiograms were required as part of the normal clinical evaluation for clarifying the etiology of various symptoms such as breathless or asthenia or reduction in functional capacity to exclude cardiovascular and pulmonary diseases. We selected patients with PH associated with disorders of the respiratory system and/or hypoxemia but normal RV systolic function (as defined below). Diagnosis of pulmonary disease and/or hypoxemia was confirmed on the basis of anamnesis, clinical examination, plain chest radiography and lung function testing. Exclusion criteria were: a possible diagnosis of PH resulting from thrombotic and/or embolic disease, the presence of RV and/or LV systolic dysfunction, more than mild LV diastolic dysfunction,[5] RV and LV wall motion abnormalities and or dilatation, more than mild valvular regurgitation (defined as maximal regurgitant area $<2.5\ cm^2$ measured by echo-Color-Doppler technique) or any grade of valvular stenosis, documented episodes of sustained atrial arrhythmias occurred within one month before echocardiogram. Patients taking medications to prevent recurrences of atrial arrhythmias were also not eligible. New York Heart Association classification was used for the functional assessment of the study patients.

Echocardiography

Standard transthoracic echocardiographic studies were performed in a dimly light room with all patients in partial left decubitus position with a Megas Esaote Biomedica machine (Florence, Italy) equipped using a 2.5—3.5 MHz annular-array transducer and a second harmonic application. They were recorded on Super-VHS Panasonic videotape for subsequent analysis. LV chamber dimensions, septum and posterior wall thickness were measured according to the American Society of Echocardiography,[6] using M-mode tracings. The Penn Convention was used only to calculate LV mass from 2D-guided M-mode echocardiograms.[7] LV mass was therefore normalized for height to the 2.7 power[8] and LV hypertrophy was defined as LV mass $>51\ g/m^{2.7}$.[8] Maximal RA volume and LV end-systolic and diastolic volumes were calculated by 2D-mode apical 2 and 4-chamber views using the area — length method.[9,10] RA ejection force was taken up as index of RA systolic function representing the estimation of the force exerted

by the contracting right atrium to accelerate the blood into the right ventricle. It was calculated according to the formula previously used for left atrium by Manning et al.,[11] with calculation of the tricuspid valve area from the tricuspid diameter, assuming a circular geometry. The formula we used was:

$$\text{RA ejection force} = 0.5 \times \rho \times \text{tricuspid orifice area} \times (\text{peak A velocity})^2$$

whereas ρ was the density of blood (1.06 g/cm^3) and A was the wave velocity passing through the tricuspid orifice during the accelerative phase of RA systole (peak late diastolic flow velocity of transtricuspid flow).

To optimally relate measurements of RV diastolic trans-tricuspid flow velocity to volume flow, trans-tricuspid flow velocities were recorded by use of pulsed-wave Doppler scanning from the apical 4-chamber view, positioning the sample volume between the tricuspid leaflets at the middle of the tricuspid annulus, the diameter of which varies modestly during diastole, as opposed to the leaflet tips, where the orifice shows substantial variation through the cardiac cycle: peak early diastolic flow velocity (E), peak late diastolic flow velocity (A) and their ratio (E/A), E deceleration time and E deceleration rate were obtained at the end of inspiration during a short period of apnea from average of 5 consecutive cycles and measured using the leading-edge convention.[12] We also estimated the RA end-diastolic stress multiplying RA ejection force $\times$ RA volume. Such index is actually a measure of wall strain which, however, can be assumed approximately as a measure of wall stress considering the thinness of atrial walls, the inter-individual variability of which is trivial and has no influence on the calculation of these hemodynamic variables.

Pulmonary artery systolic pressure (e-PASP) was non-invasively estimated with echo-Doppler techniques from systolic RV-RA gradient (peak instantaneous systolic pressure drop from right ventricle to right atrium) and RA pressure. RV-RA gradient was estimated by the peak velocity of the tricuspid regurgitant flow signal using the simplified Bernoulli equation (continuous-wave Doppler at the apical 4-chamber view), while RA pressure was obtained calculating the means of the inferior vena cava collapsibility index measured in the subcostal view (2D and M-Mode techniques).[13] RV systolic function was assessed measuring both percent fractional area change (FAC) using 2D-mode technique[14] and tricuspid annular plane systolic excursion (TAPSE) using M-mode technique[15]: RV end-diastolic and end-systolic area were measured from the 4 chamber apical view and FAC was estimated as end-diastolic $-$ end-systolic area/end-diastolic area $\times$ 100. TAPSE was measured positioning the M-mode cursor at the junction of the tricuspid valve plane with the RV free wall and was defined as the distance in the displacement of the tricuspid valve plane from end-diastole to end-systole. RV end-diastolic diameters (measured both at the inflow tract from apical 4-chamber view using 2D-mode technique and at the outflow tract from parasternal view using M-mode technique) were used as index of RV size.

Control group

Among individuals who referred to our laboratory for ''asthenia'', ''palpitations'' or ''harmless cardiac murmur'' with no echocardiographic evidence of cardiac or valvular disease and with a physiologic mild tricuspid regurgitation and normal e-PASP, thirty-three subjects matched for age and gender were selected and used as controls. Echocardiographic parameters resulting from these patients were used to identify the cut-off of abnormality for the study population which had been *a priori* defined as values exceeding the mean $\pm$ 2 standard deviations of the normal distribution of control population.

Echo measurements were obtained by videotape analysis without the knowledge of categorization as PH patients or controls. Reproducibility of M-Mode, 2D-Mode and pulsed-wave Doppler echocardiographic measurements from our laboratories has been previously reported.[1,4,16,17]

The protocol of the present study was approved by the local institutional review board and written informed consent was obtained from all recruited patients.

Definitions and statistical analysis

In most of previous studies, PH was roughly and rigorously defined as values of e-PASP exceeding 30 mmHg. Considering the observations of McQuillan et al.[18] who showed a close independent association between age and e-PAPS among normal individuals with an average increase in e-PASP of $\cong$1 mmHg per decade attributed to an higher vascular resistance and lower LV compliance with aging, in our study PAH was taken to be present if e-PASP was $>$32 mmHg at echocardiographic evaluation. On the basis of parameters resulting from the control group, RV systolic dysfunction

was diagnosed when TAPSE was <16 mm and/or FAC was <35%, RV dilatation was identified in case RV end-diastolic diameter was greater than 46 mm (inflow tract) or 24 mm (outflow tract), LV systolic dysfunction was defined as LV ejection fraction <50%. These cut-off points were used for an accurate patient's selection into this study. K-means clustering analysis was performed to split the study population into subgroups by maximizing between-cluster variation in baseline e-PASP. Two distinct clusters were identified (<42 mmHg and ≥42 mmHg) and compared using Euclidean distance metric. These clusters represented two subgroups of patients defined as ''mild'' and ''moderate-severe PH'', who were studied in a separate analysis. ''*Supernormal RA ejection force*'' was identified when values of RA ejection force were greater than the mean value + 2 standard deviation of the mean of controls.

Data are reported as mean value ± 1 standard deviation. Unpaired Student's test and χ^2 statistics were used for descriptive statistics. Between-group comparisons of continuous and normally distributed variables were performed by the analysis of variance (ANOVA). Least squares simple regression analyses were used to investigate the relation of RA ejection force and maximal RA volume to the clinical and echocardiographic parameters considered in this study, and to identify factors associated with high RA ejection force and size. Therefore, the independent relation of the factors significantly related to RA ejection force and maximal RA volume at the univariate analysis was investigated through multiple regression analyses. A two-tailed value of $p < 0.05$ was considered as statistically significant.

Results

Recruitment period lasted from October 2004 to March 2005. During this period, 66 subjects with PH met the enrolment criteria defined in the study protocol. Their mean age was 75 ± 9 years, the cause of PH was chronic obstructive pulmonary disease in 52 patients (79%), interstitial lung disease in 7 (10%), alveolar hypoventilation disorders in 4 (6%), chronic inflammatory conditions in 3 (5%). The main clinical and echocardiographic characteristics of these subjects were compared with those of 33 patients selected as controls. Individuals with PH exhibited lower functional class, greater RV free wall thickness, higher RA size, ejection force and end-diastolic stress. In particular, RA ejection force, was about 2-fold higher in PH patients than controls and such difference was due to an increase in both tricuspid orifice area and A wave flow velocity. Even trans-tricuspid peak E/A ratio was significantly different between the 2 groups being higher in controls (Table 1).

Right atrial systolic function

The relations of RA ejection force to the clinical and echocardiographic parameters resulting from the univariate regression analyses are reported in the Table 2 (top list). Fig. 1 shows the close relationship existing between the RA ejection force and RA end-diastolic stress. To verify whether relation of RV systolic function with RA ejection force was independent of confounders, we performed a multiple regression analysis including both patients and controls. Such analysis was initially performed excluding parameters of RV diastolic function; it revealed that RV systolic function (valuated with TAPSE) was positively associated with RA ejection force and this association was independent of e-PASP (Table 3, top list). These positive relationships were lost when parameters of RV diastolic function were tested (Table 4, top list).

Supernormal RA performance was identified as values of RA ejection force exceeding 6.7 Kdynes (the mean value + 2 standard deviation of the mean of controls). This condition was detected in 44 of 66 patients with PH (67%) and in 3 of 33 controls (9%, $p = 0.00001$) (Fig. 2). Considering the whole study population, patients with supernormal RA ejection force differed from those with normal RA ejection force for having a worse NYHA functional class (2.7 ± 0.8 vs 1.9 ± 0.7, $p = 0.0001$), higher LV mass (59 ± 18 vs 48 ± 15 g/m$^{2.7}$, $p = 0.02$), higher e-PASP (48 ± 10 vs 38 ± 12 mmHg, $p = 0.0001$), higher RA pressure (5.2 ± 2.0 vs 4.4 ± 1.7, $p = 0.04$) and RA end-diastolic stress (345 ± 159 vs 145 ± 80 Kdynes/cm^2, $p = 0.0000001$). All these variables, but RA pressure, remained significantly higher in patients belonging to the supernormal RA ejection force group also when only patients with PH were considered (data not shown). Parameters of RV systolic function, RV dimensions and age were similar between the 2 groups.

RA size

Table 2 (bottom list) reports the clinical and echocardiographic parameters significantly related to maximal RA volume resulting from the univariate regression analyses. Fig. 3 shows the relation existing between the maximal RA volume and the indexes of RV size. Multiple regression analysis

Table 1 Comparison between the main clinical and echocardiographic characteristics of patients with pulmonary hypertension and controls measured at baseline evaluation

Variables	PAH 66	Controls 33	*p*
Age (years)	75 ± 9	76 ± 8	ns
Men (%)	28	36	ns
NYHA functional class	2.5 ± 0.8	1.5 ± 0.5	0.00001
Systolic arterial blood pressure (mmHg)	136 ± 15	135 ± 16	ns
Diastolic arterial blood pressure (mmHg)	81 ± 5	81 ± 5	ns
Diabetes mellitus (%)	8	4	ns
Systemic arterial hypertension (%)	48	67	ns
Left ventricular ejection fraction (%)	61 ± 7	62 ± 6	ns
Left ventricular mass (gr/h$^{2.7}$)	52 ± 11	52 ± 18	ns
LV hypertrophy (%)	39	36	ns
Relative wall thickness	0.40 ± 0.06	0.40 ± 0.06	ns
Pulmonary artery systolic pressure (mmHg)	42 ± 10	20 ± 8	0.00001
Right atrial pressure (mmHg)	5.5 ± 2	4.1 ± 2	0.005
RV end-diastolic diameter (inflow tract) (2D-mode) (mm)	38 ± 7	36 ± 5	ns
RV end-diastolic diameter (outflow tract) (M-mode) (mm)	19 ± 5	18 ± 3	ns
RV free wall thickness (mm)	10 ± 3	8 ± 1	0.0001
RV fractional area change (%)	53 ± 10	55 ± 10	ns
TAPSE (tricuspid annular plane systolic escursion) (mm)	27 ± 5	26 ± 4	ns
Peak E wave transtricuspid flow (cm/s)	40 ± 9	37 ± 9	ns
Peak A wave transtricuspid flow (cm/s)	45 ± 10	38 ± 10	0.001
Peak E/A wave ratio	0.88 ± 0.24	1.01 ± 0.28	0.01
Deceleration time E wave transtricuspid flow (msec)	235 ± 68	226 ± 73	ns
Deceleration rate E wave transtricuspid flow (cm/s^2)	1.8 ± 0.8	1.9 ± 0.9	ns
Tricuspid orifice area (cm^2)	6.2 ± 1.4	4.6 ± 1.3	0.00001
Right atrial maximal volume (ml)	37 ± 13	32 ± 13	0.04
Right atrial ejection force (Kdynes)	6.7 ± 2.7	3.5 ± 1.6	0.00001
Right atrial end-diastolic stress (Kdynes/cm^2)	252 ± 147	107 ± 58	0.00001

NYHA: New York Heart Association; RV = right ventricular.

revealed that RA size was positively and independently related to greater RV dimension and increased RV systolic function, while no association was found with RA pressure or e-PASP (Table 3, bottom list). The relationship between maximal RA volume and RV end-diastolic diameter was maintained in spite of the effects of parameters of RV diastolic function (Table 4, bottom list).

Mild and moderate-severe PH

Among 66 patients with PH, 20 (30%) had a mild increase and 46 (70%) had a moderate-severe increase in e-PASP (mean 35 ± 4 and 51 ± 8 mmHg, respectively). These two subgroups of patients differed for many variables which are listed in the Table 5. In comparison with controls, patients with mild PH had similar RA ejection force (3.5 ± 1.6 vs 4.1 ± 2.0 Kdynes) and maximal RA volume (32 ± 13 vs 34 ± 14 ml), while these two variables were significantly higher in patients with moderate-severe PH (7.0 ± 3 Kdynes and 38 ± 14 ml, respectively; $p < 0.01$ both vs mild PH group and controls). RA ejection force was independently related in both groups only to parameters of RV diastolic function. Similarly, RA size closely correlated to parameters of diastolic function together with TAPSE in patients with mild PH, and RV dimensions in moderate-severe PH (Table 6).

Discussion

When a cardiac chamber is exposed to chronic pressure and/or volume overload and its diastolic properties begin to change, the Frank-Starling mechanism starts working to counterbalance the increase in pressure resulting in a progressive augmentation in chamber size and performance. This behaviour, which might be limited by the degree of diastolic dysfunction,[3,4,19,20] has been clearly documented in various pathophysiological conditions in both the left ventricle and left atrium, and characterized in patients with aortic valve disease and systemic arterial hypertension.[1,4,21]

Table 2 List of the clinical and echocardiographic parameters significatively related to the right atrial ejection force and maximal right atrial volume

	r	SEE	*p*
Right atrial ejection force			
Peak E/A wave ratio transtricuspid flow	−0.62	2.1	0.00001
Right atrial end-diastolic stress (Kdyne/cm^2)	0.84	1.56	0.0001
Pulmonary artery systolic pressure (mmHg)	0.49	2.5	0.0001
NYHA functional class	0.47	2.6	0.0001
TAPSE (tricuspid annular plane systolic escursion) (mm)	0.31	2.8	0.002
Right atrial pressure (mmHg)	0.26	2.8	0.01
Left ventricular mass (gr/h$^{2.7}$)	0.21	2.8	0.04
Maximal right atrial volume			
Right atrial end-diastolic stress (Kdyne/cm^2)	0.60	10.4	0.0001
RV end-diastolic diameter (inflow tract) (2D-mode)	0.41	11.9	0.0001
RV end-diastolic diameter (outflow tract) (M-mode)	0.38	12.1	0.0001
TAPSE (tricuspid annular plane systolic escursion) (mm)	0.36	11.8	0.0003
Deceleration time E wave transtricuspid flow (msec)	0.36	11.0	0.001
Right atrial pressure (mmHg)	0.32	12.2	0.001
Pulmonary artery systolic pressure (mmHg)	0.23	12.7	0.02
Left ventricular mass (gr/h$^{2.7}$)	0.23	12.9	0.03

NYHA: New York Heart Association; RV: right ventricular.

In this study, we sought to assess RA size and systolic performance and define the relations of RA function to clinical, echocardiographic and hemodynamic parameters in patients with PH. The RA size is routinely measured with validated echocardiographic methods in patients with PAH and its enlargement is one of independent predictors of adverse outcome in the setting of primary PH.[22] In contrast, RA ejection force has never been studied before despite it provides a relatively simple measure of RA systolic function and a useful index for assessing RA contribution to RV diastolic performance. For its quantification, we applied the Manning's formula based on Newtonian mechanics validated for calculating left atrial ejection force utilizing two-dimensional and Doppler techniques.[11] Describing this method, the authors underlined that the use of a circular approximation for the measurement of the mitral orifice (the shape of which is actually not circular), was a bias which was maintained constant through the study. Conversely, the assumption of a circular

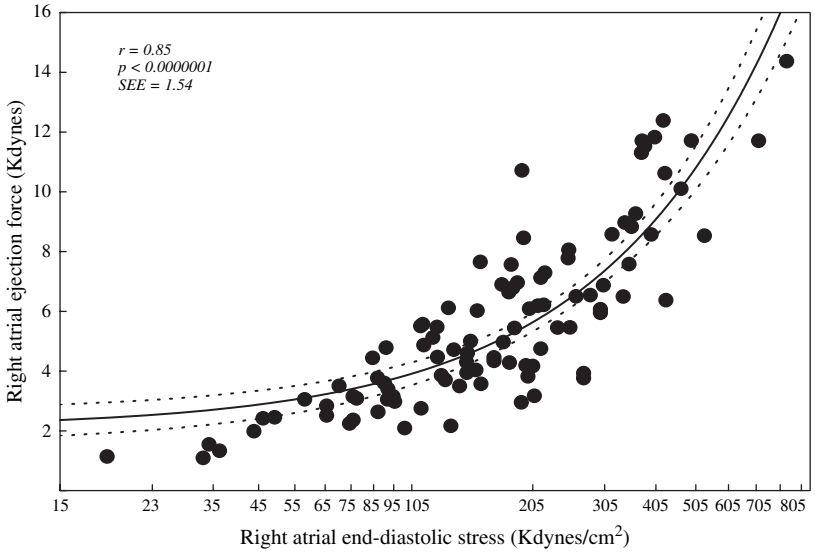

Figure 1 Relation between right atrial ejection force (linear scale) and right atrial end-diastolic stress (logarithmic scale) in the whole study population. Scatter plot of linear correlation and 95% confidence limits are shown.

Table 3 Multiple regression analysis testing the independent relation of the variables associated with right atrial ejection force and maximal right atrial volume which emerged to the univariate analysis (excluding parameters of RV diastolic function)

Right atrial ejection force	Multiple $R = 0.55$	$R^2 = 0.30$	Intercept $= -2.7$
	SEE $= 2.4$	$F = 19.5$	$p = 0.0001$
Variables		Coeff. β	*p*
Pulmonary artery systolic pressure (mmHg)		0.45	0.0001
TAPSE (tricuspid annular plane systolic escursion) (mm)		0.29	0.001
Maximal right atrial volume	Multiple $R = 0.66$	$R^2 = 0.44$	Intercept $= -35.5$
	SEE $= 9.9$	$F = 11.3$	$p = 0.0001$
Variables		Coeff. β	*p*
RV end-diastolic diameter (outflow tract) (M-mode)		0.34	0.0001
RV end-diastolic diameter (inflow tract) (2D-mode)		0.29	0.001
TAPSE (tricuspid annular plane systolic escursion) (mm)		0.22	0.01

RV = right ventricular.

orifice applies much better to the tricuspid valve so that the measurement of tricuspid orifice area and consequently RA ejection force should theoretically be more accurate than the mitral orifice area and left atrial ejection force measured using the initial Manning's assumption.

In the present study, realized in a clinical setting, we found out that the Frank-Starling mechanism operates also in the right atrium of patients suffering from chronic PH. For this investigation, a homogeneous group of elderly patients with chronic pulmonary disorders (obstructive pulmonary disease was highly prevalent) was accurately studied with clinical and echocardiographic evaluations. Compared to controls, they had a significant increase in RA size, RA end-diastolic stress and RA systolic function, all changes that increased with increasing severity of PH. It is also of note that these changes have been shown in patients with normal RV dimension and RV systolic function, so that they could be considered an early warning sign concerning the negative interaction between hemodynamic and right-sided structural changes in chronic PH. Our analysis indicated that an increase in RA performance was systematic in PH patients and a supernormal RA ejection force was found in a large part of them. This phenomenon had an expected significant positive relationship with RV systolic function and this link was independent of e-PASP, indicating that a higher RA effort is required for those patients having a right ventricle solicited to compensate the increased end-systolic stress caused by PH throughout recruitment of Starling forces, allowing preservation of RV function. Since the RA myocardium is particularly thin and inclined to respond with dilatation rather than hypertrophy to overload, this higher effort inexorably leads to higher RA diastolic strain and stress with increase in RA preload.

Table 4 Multiple regression analysis applied on the whole study population testing the independent relation of the variables associated with right atrial ejection force and maximal right atrial volume which emerged to the univariate analysis (including parameters of RV diastolic function)

Right atrial ejection force	Multiple $R = 0.91$	$R^2 = 0.82$	Intercept $= 5.8$
	SEE $= 1.2$	$F = 106.5$	$p = 0.00001$
Variables		Coeff. β	*p*
RA end-diastolic stress (Kdyne/cm^2)		0.68	0.00001
Peak E/A wave ratio transtricuspid flow		−0.45	0.00001
Deceleration rate E wave transtricuspid flow (msec)		0.20	0.0009
Maximal right atrial volume	Multiple $R = 0.84$	$R^2 = 0.70$	Intercept $= -27.9$
	SEE $= 7.2$	$F = 36.8$	$p = 0.00001$
Variables		Coeff. β	*p*
RA end-diastolic stress (Kdyne/cm^2)		0.67	0.00001
RV end-diastolic diameter (outflow tract) (M-mode)		0.35	0.00001
Peak E/A wave ratio transtricuspid flow		−0.31	0.0001
RV end-diastolic diameter (inflow tract) (2D-mode)		0.27	0.0004

RV = right ventricular.

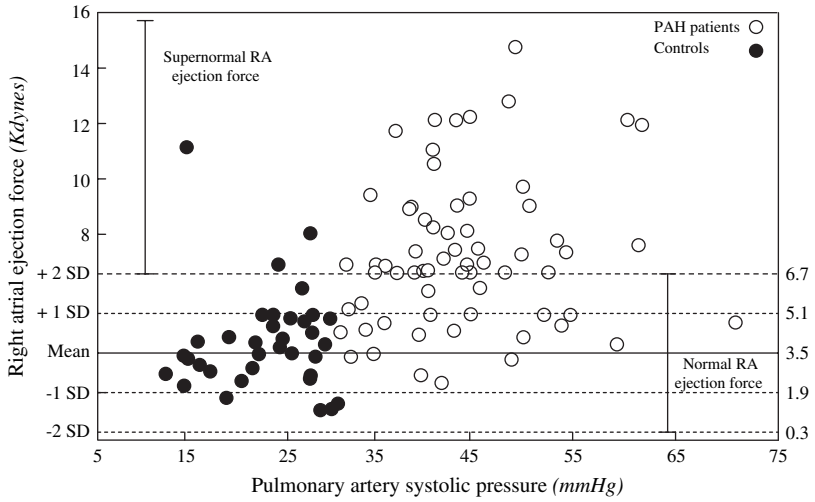

Figure 2 Bland-Altman plot showing the deviation of values of right atrial ejection force measured in the patients with pulmonary hypertension (white circles) from the mean value measured in the controls (black circles). The horizontal lines indicate the mean value of right atrial ejection force measured in controls (central line) and 1 and 2 standard deviations of this mean (upper and lower dashed lines). Three of 33 controls (9%) and 44 of 66 patients with pulmonary hypertension (67%) had supernormal right atrial ejection force defined as value exceeding 6.7 Kdynes.

RA size was indeed significantly augmented in PH patients and closely associated with RV dimension together with parameters of RV function. Thus, the augmentation in RA size and function may be interpreted as the two faces of a same coin representing two early compensatory mechanisms which develop together with an initial increase in RV systolic function, the first one activated proportionally to the degree of RV volume overload, the second one according to the degree of RV pressure overload both caused by PH. The *primum movens* of this pathophysiological process, however, remains the changes in RV geometry, and particularly, in RV diastolic properties as a consequence of PH. The rise in systolic RV and RA performance may be interpreted as purely epi-phenomena which constantly follow RV remodelling, RV impaired relaxation (expressed by lower peak E/A wave ratio of trans-tricuspid flow) and herald increase in RA stress and dilatation. Thus, the scenario emerging from these findings is consistent with a general activation of the Starling forces in

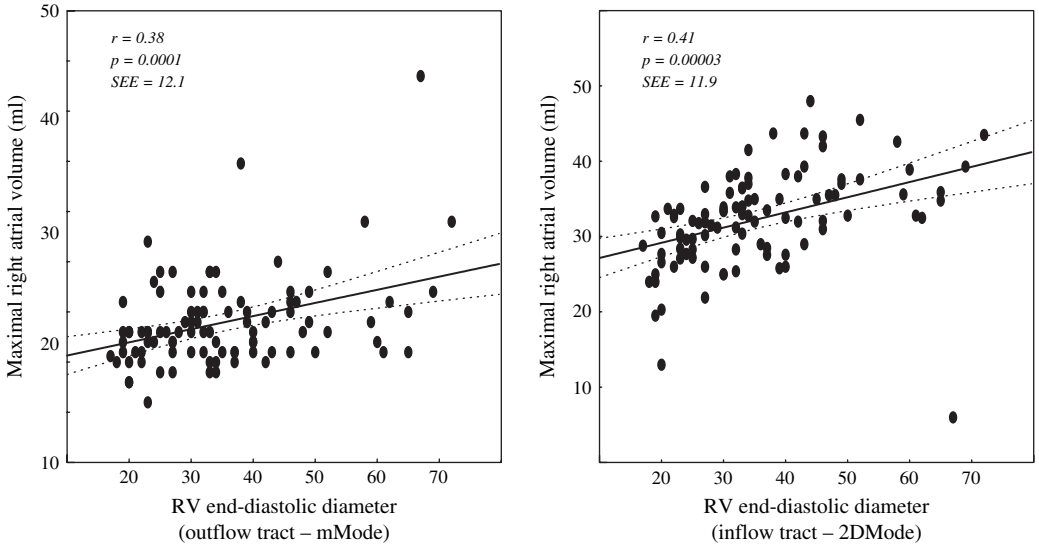

Figure 3 Relation between maximal right atrial volume (ml) and right ventricular diastolic diameters measured at the inflow tract from apical 4-chamber view using 2D-mode technique (left panel) and at the outflow tract from parasternal view using M-mode technique (right panel). Scatter plot of linear correlation and 95% confidence limits are shown.

Table 5 Comparison between patients with mild ad moderate-severe pulmonary hypertension

Variables	Mild PAH 20	Moderate-severe PAH 46	*p*
NYHA functional class	1.8 ± 0.7	2.7 ± 0.8	0.00001
Pulmonary artery systolic pressure (mmHg)	35 ± 4	51 ± 8	0.00001
RV end-diastolic diameter (inflow tract) (2D-mode) (mm)	35 ± 7	39 ± 5	0.04
Peak A wave transtricuspid flow (cm/s)	38 ± 8	46 ± 10	0.004
Peak E/A wave ratio	1.04 ± 0.2	0.84 ± 0.2	0.004
Right atrial ejection force (Kdynes)	4.1 ± 2	7.0 ± 3	0.0001

List of variables which were statistically different between the 2 groups.

the right heart, to face with the increased RV end-systolic stress and stiffness caused by PH, in a context of patients without substantial RV dilatation or RV systolic dysfunction. Right atrium increases its ejection force thanks to the increased preload and, in turn, increases late RV filling pressure, which can recruit Starling forces to sustain RV systolic function.

Study limitations

Our investigation presents some limitations. We do not have invasive hemodynamic data to measure directly RV filling pressure and end-diastolic pressure. However an increased force during RA contraction is very likely to produce an increased RV filling pressure. Although RV diastolic properties were not defined in our study, a possible abnormal RV compliance might produce changes in resistance to trans-tricuspid flow affecting peak A wave velocity and consequently the estimation of RA ejection force. Thus, increased RV stiffness might reduce the sensitivity of our data and obscure some additional information, without substantially modifying the hemodynamic model emerging from these findings.

Table 6 Multiple regression analysis testing the independent relation of the variables associated with right atrial ejection force and maximal right atrial volume in the subgroups of patients with mild and in those with moderate-severe pulmonary artery hypertension

Right atrial ejection force		
Mild PAH	Coeff. β	*p*
RA end-diastolic stress (Kdyne/cm2)	0.69	0.00001
Peak E/A ratio transtricuspid flow	−0.50	0.0001
Deceleration rate E wave transtricuspid flow (cm/sec^2)	−0.28	0.03
Multiple $R = 0.95$ $R^2 = 0.90$ Intercept = 5.4 SEE = 0.8 $F = 37.5$ $p = 0.00002$		
Moderate-severe PAH	Coeff. β	*p*
RA end-diastolic stress (Kdyne/cm^2)	0.66	0.00001
Peak E/A ratio transtricuspid flow	−0.36	0.0001
Multiple $R = 0.86$ $R^2 = 0.75$ Intercept = 6.7 SEE = 1.3 $F = 53.6$ $p = 0.00001$		
Maximal right atrial volume		
Mild PAH	Coeff. β	*p*
RA end-diastolic stress (Kdyne/cm^2)	0.88	0.00001
Peak E/A wave ratio transtricuspid flow	−0.58	0.00002
Deceleration rate E wave transtricuspid flow (msec)	−0.43	0.001
TAPSE (mm)	0.30	0.005
Multiple $R = 0.97$ $R^2 = 0.94$ Intercept = − 18.6 SEE = 3.7 $F = 39.8$ $p = 0.00001$		
Moderate-severe PAH	Coeff. β	*p*
RA end-diastolic stress (Kdyne/cm^2)	0.74	0.00001
Peak E/A wave ratio transtricuspid flow	−0.43	0.00001
RV end-diastolic diameter (outflow tract) (m-mode)	0.35	0.0009
Multiple $R = 0.76$ $R^2 = 0.51$ Intercept = −24.6 SEE = 9.1 $F = 14.1$ $p = 0.00001$		

RV = right ventricular.

Conclusions

This study provides new information about the adaptive mechanisms which operate in the right cardiac chambers in patients with chronic PH. RA size and systolic function and wall stress significantly increase in this condition and parallel signs of activation of the Frank-Starling mechanism in both right chambers. Further investigations are needed to verify whether measurements of RA ejection force improves the prognostic prediction obtained by measuring RA dimension in patients with chronic PH, normal RV dimension and preserved systolic function.

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