

IMPORTANCE OF RIGHT VENTRICULAR END-SYSTOLIC REGIONAL WALL STRESS IN IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION: A NEW METHOD FOR ESTIMATION OF RIGHT VENTRICULAR WALL STRESS

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Abstract

RV dysfunction in idiopathic (primary) pulmonary hypertension (IPAH) is often characterized by chamber dilation, ventricular hypertrophy, and impaired systolic function. In this study we characterize right ventricular (RV) chamber size, end-diastolic thickness, myocardial mass, and ejection fraction in patients with right ventricular heart failure from IPAH, $n = 16$ and compare these characteristics to a control population of cardiac transplant patients (TX, $n = 4$) and a group of normal subjects (N, $n = 5$). Subjects underwent both gated cardiac magnetic resonance imaging (MRI) of the right ventricle and right heart catheterization (RHC). Using parameters from both the MRI and RHC, an estimate of RV end-systolic relative wall stress (RWS) was calculated. RV RWS was 34.7 ± 8.4 and 17.3 ± 3.8 Kdynes/cm² in the cardiac transplant and control subjects respectively and was significantly elevated 104.1 Kdynes/cm² in IPAH patients (IPAH vs N and TX; $p = 0.004$ and 0.008). RV ejection fraction RVEF was lower in IPAH patients $0.36 \pm .10$ than in N and TX $0.57 \pm .04$ and $0.55 \pm .08$ respectively, ($p = 0.0006$ N and 0.0007 TX). An inverse linear correlation was demonstrated between RWS and RVEF ($y = 215-332x$; $R = .80$, $p \leq .0001$). Right ventricular RWS is significantly elevated in IPAH and may provide a useful quantitative monitoring tool in patients with IPAH to assess the benefit of different therapeutic interventions and provide prognostic information.

Key words: Idiopathic (primary) pulmonary hypertension; Right ventricular heart failure

INTRODUCTION

Primary or idiopathic arterial pulmonary hypertension (IPAH) is characterized by elevation of the pulmonary arterial pressure and progressive RV failure. The RV volume increase in IPAH can enlarge to 2-3 times the size of the normal LV and is accompanied by progressive impairment of systolic function. Massive RV enlargement in response to pressure overload is associated with variable degrees of RV hypertrophy. Technical limitations associated with the evaluation of RV func-

tion have made it difficult to relate morphologic changes of the RV to clinical parameters of right heart failure in IPAH. Hemodynamic markers of adverse long-term outcome such as elevated right atrial mean pressure, reduced cardiac output, and reduced RV ejection fraction are all measures of the severity of RV failure; however the ability of any one specific marker to predict long-term prognosis in IPAH is limited. Identification of the morphologic adaptations of the RV in combination with the hemodynamic factors that accompany progressive pressure overload may help elucidate critical factors which contribute to RV dysfunction.

Previous investigations of the LV suggest that increased chamber size results from elevated stress on the ventricular myocardium which compromises contractile function [1]. A relationship between end-systolic pressure and end-systolic volume is proposed as useful in evaluating LV contractility. This force-length relationship (pressure as force and volume as length) or wall stress originally described by Sagawa using pressure-volume loops allowed comparison of LV afterload and contractility among subjects with different sized ventricles and wall thicknesses [2].

Wood was the first to suggest that there is an important relationship between cardiac size and the extent of myocardial hypertrophy [3]. Several investigators [1, 3-9] have suggested that the myocardial hypertrophy that develops in patients with chronic heart disease due to either pressure or volume overload may actually be a useful adaptive process "designed" to normalize myocardial stress. Through adaptive hypertrophy, it was suggested that cardiac muscle exposed to either increased pressure or volume was better equipped to compensate for the additional mechanical demands [8]. Mechanical work of the loaded ventricle is defined as the tension developed during contraction. LaPlace described that the tension on the wall of a sphere is related to the internal pressure (P) divided by 2 x the thickness (h) times the radius of the sphere. Sandler and Dodge had applied this concept to the human LV to derive circumferential wall stress, a marker of homogenous ventricular contraction [1].

Disease processes such as chronic systemic hypertension, valvular regurgitation, aortic stenosis, and dilated cardiomyopathy have all been associated with increased LV wall stress. The LV in these diseases has differing relative amounts of chamber dilation, elevated chamber pressures, and hypertrophy. Investigators studied the relationship between increased pressure, chamber dimension, and wall thickness in an attempt to stratify subjects with dysfunctional ventricles since classic measurement of systolic function, such as LV ejection fraction, were significantly affected by preload and afterload. Ventricular wall stress in the LV has previously been reported to be a more load independent marker of strain on the ventricular chamber and the myocardial cell. The application of LV end-systolic wall stress measurements has also been shown to define important prognostic patient subgroups at increase risk of cardiac decompensation or death in both ischemic cardiomyopathy and valvular aortic stenosis. However, investigation of the right ventricular end-systolic wall stress has been limited by the complex geometry of the RV and difficulty with the accurate determination of the RV wall thickness throughout the cardiac cycle. Magnetic resonance imaging (MRI) has recently provided improved non-invasive resolution of changes in the RV morphology.

The objective of the present study was to evaluate the RV chamber characteristics, hemodynamic parameters, functional parameters which are integrally associated with RV regional end-systolic wall stress as estimated by the modified Janz method [10]. To characterize RV regional end-systolic wall stress we evaluated subjects with IPAH as the prototype of isolated RV (without LV) dysfunction and compared this to data from heart transplant patients with preserved RV function and normal subjects.

METHODS

GENERAL RECRUITMENT

Sixteen patients with IPAH, 4 cardiac transplant (TX) patients and 5 normal subject (N) had both right heart catheterization and gated magnetic resonance imaging (MRI) to assess RV chamber dilatation, wall thickness, ventricular mass, and ejection fraction measurements. All patients signed an informed consent form approved by the Colorado Multiple Institutional Review Board (COMIRB). Patients were screened for potential exclusions for MRI including such factors as pacemakers, internal defibrillators, cerebral vascular surgery, or non-fixed ferrous material. The IPAH patients were screened prior to institution of epoprostenol therapy under baseline conditions. The TX patients had been transplanted within two years and did not have any major episodes of cardiac rejection or significant valvular heart disease.

RIGHT HEART CATHETERIZATION

Subjects were NPO except for small amounts of water for 12 hours prior to the procedure. RHC was performed using a modified Seldinger technique from either the right neck or right groin for central venous

access. Right atrial (mean, a/v), right ventricular (systolic, end-diastolic), pulmonary arterial (systolic, diastolic and mean), and pulmonary capillary wedge pressures were measured at rest. Both estimated Fick and thermodilution cardiac outputs were obtained.

MAGNETIC RESONANCE IMAGING

Magnetic resonance images were acquired using either a 1.5 Tesla General Electric Signa Advantage system employing ECG-gated multislice, multiphase spin echo cardiac imaging technique or a 1.5 Tesla Siemens Magnetom Vision system employing an ECG-gated single-breathhold cine gradient echo imaging technique. Initial axial and coronal localizing images were performed to define the major long axis of the left ventricle using standard T2 turbo spin-echo techniques. After acquisition of localizing images, axial images were obtained from the pulmonary artery to liver. From the appropriate spin-echo image the mid cardiac long axis slice was acquired, and the short axis slices were defined perpendicular to the RV long axis. Short axis multiphase (minimum of 15 phases), single slice single breath-hold cine (gradient refocused) images were acquired on the GE Signa MRI system GE Medicals using a body coil with a TE of 20 msec, 2 signal averages, a 256 x 128 matrix size, and a slice thickness of 8 mm with a inter-slice skip of 2 mm. Image data were stored on an optical disk for subsequent analyses. In a similar protocol, images on the Siemens system were acquired using a torso array coil. After standard localizing imaging and after acquisition of a single mid-cardiac image, a long axis turbo spin-echo image was performed to determine the long axis of the heart. Single slice short-axis breath-hold cine images were acquired from the cardiac apex to behind both atrioventricular valves. Each short-axis slice was 8 - 10mm and slices were obtained in a contiguous fashion from the cardiac apex to the base. These gated cardiac images were acquired with TE of 4.8 msec/frame and into 256 x 144 matrices. These gated cardiac images were acquired using echo sharing so that 15 phases were obtained per slice.

IMAGE ANALYSIS

The short axis oblique multi-slice, multi-phase spin echo images were analyzed using the standard cardiac analysis package (Argus, Siemens Medical). The phase image with the largest volume and least volume were assigned end-diastolic and end-systolic images respectively and were used for determination of RV volumes, thickness, mass, and function. For each slice, the total myocardial area and ventricular blood pool were determined by manually tracing both the epicardium and the endocardium. Using Simpson's rule, serial slice summed technique, left ventricular volumes, mass and ejection fractions were calculated using standard methodology. Myocardial mass measurements were calculated by taking the slice thickness and multiplying this by the difference between the total myocardial surface area and the blood pool volume for each slice and then summing these over the entire length of the left ventricle. This myocardial volume was multiplied

by the specific gravity of cardiac muscle (1.05 g/cm³). Left ventricular end-diastolic and end-systolic thickness' were obtained at the mid-ventricular level of the papillary muscles attachments. Similar to calculations of left ventricular volumes and function, right ventricular volumes and ejection fractions were calculated. The mass of the RV free wall was calculated according to the method of Katz [11] using the RV free wall excluding the interventricular septum again using the difference between total myocardium and the myocardial blood pool of the right ventricle. This difference was summed for each slice from the apex to the tricuspid valve and then multiplied by the myocardial specific gravity. RV end-diastolic and end-systolic thickness' were determined at the level of the papillary muscle in the RV free wall at end-diastole. The mean of 3 measurements of RV thickness was obtained. RV wall stress calculations used the RV free wall thickness at the 45 degree radian determined at end-systole. All measurements were performed by one of two experienced observers, independent of clinical information.

RV END-SYSTOLIC REGIONAL WALL STRESS ESTIMATION

Ventricular wall stress has been simply calculated as the tension at end-systole, using the Law of LaPlace as shown in Figure 1A. However, due to the geometric constraints of the right ventricle, a new model was devised to calculate RV free wall circumferential wall stress. The regional wall stress equation as described by Janz [10] was modified for a cross-sectional half ellipse [12] and used to calculate RV end-systolic wall stress as shown in the equation below (Fig- 1A).

Application of this method as demonstrated in Figure 1B was performed on the mid RV free wall to estimate the RV circumferential regional end-systolic wall stress (RVWS). This method uses the key components of the LaPlace relationship to determine overall right ventricular tension at end systole or regional RV circumferential end-systolic wall stress. The key components include RV peak systolic pressure (P), right ventricular end systolic wall thickness (h), and right ven-

tricular diameter or radius (R). We assumed that the RV is a half-spherical shape at the mid-ventricular level within the region of the papillary muscles. From spin-echo MRI oblique images we define the maximal major and minor axes from which a radius length at a 45 degree angle and the corresponding RV wall thickness at end systole, as shown in Figure 1B, are measured to calculate the regional wall stress of the RV free wall. The right ventricular systolic pressure is obtained from right heart catheterization performed within 24 hours of the magnetic resonance imaging study since these values have been shown to change less than 6% within several days to 6 months in IPAH.

STATISTICAL ANALYSIS

The specific MRI parameters in this study are expressed as the mean values \pm the standard deviation. Analyses were performed using an unpaired t-test with between group significance determined if the p-value was <.05. Linear regression was used to assess the correlation of RVWS to other hemodynamic parameters (ANOVA statistic).

RESULTS

DIFFERENCES AMONG SUBJECT GROUPS

Table 1 shows the baseline hemodynamic characteristic of the three groups. Note that the pressure measurements, cardiac outputs, and pulmonary vascular resistances (PVR) were significantly different between normal subjects and the IPAH patients. IPAH patients demonstrated markedly increased pulmonary arterial systolic pressures, RV filling pressures and PVR as expected for symptomatic IPAH. Interestingly, there was a significant difference in cardiac output between N and TX patient and not IPAH and TX suggesting mildly reduced contractility in the TX patient even within one year of transplantation.

Morphologic differences between the three groups with published normal values shown at the top of the graph are reported in Table 2. The right ventricular

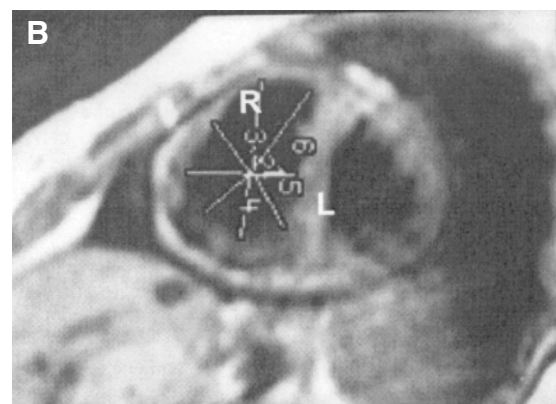
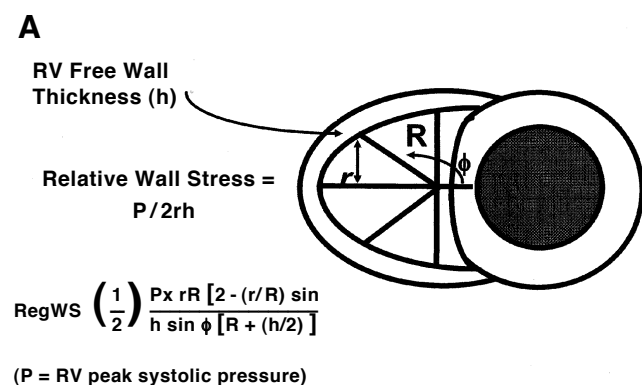


Fig. 1. Shown in figure 1A is a diagram of the calculation of RV end-systolic wall stress, RVWS as a modification of the Janz technique [10]. Note the major components are systolic pressure, radius of the ventricle and RV end-systolic thickness. Panel 1B shows an IPAH patient with dilated and thickened RV. Noted the "D" shaped RV and flattened septum. The basic radii measurements are shown.

Table 1. Group Demographics.

Group	N	TX	IPAH
SEX (M:F)	3:2	2:2	4:12
RA mean (mmHg)	2.2 ± 2.1	5.3 ± 4.1	8.1 ± 5.0*
PA systolic (mmHg)	22.0 ± 8.8	22.7 ± 4.6	95.8 ± 27.* †
PA mean (mmHg)	11.4 ± 6.2	15.3 ± 4.9	62.1 ± 18.9* †
Cardiac Output (L/min)	5.2 ± 0.5	4.2 ± 0.7	3.6 ± 1.0* ††
PVR	120 ± 32	141 ± 52	1363 ± 889* †

Table 1 shows the baseline hemodynamic characteristics for each of the 3 groups N, TX and IPAH (RA, right atrial; PA, pulmonary artery pressure; and PVR, pulmonary vascular resistance). Mean values ± standard deviation and p values, (* p = < .05, N vs. IPAH; † p = < .05, TX vs IPAH, †† p < .05 N vs TX) are shown. IPAH patients demonstrated increased PA pressure, RA mean pressures, PVR, and reduced cardiac output when compared to normal and TX subjects.

Table 2. Parameters by Subject Group.

Etiology	RVEDV (ml)	RVEF (%)	RVthck (cm)	RVmass (g)
<i>Normal values</i>	111 ± 22 ^a	60 ± 10 ^{b,c}	.44 ± .90 ^d	42 ± 7 ^e
N (n = 5)	79 ± 19	55 ± 7	.46 ± .09	56 ± 21
TX (n = 4)	68 ± 26	57 ± 04	.44 ± .16	47 ± 31
IPAH (n = 16)	139 ± 46*	35 ± 10*	.83 ± .28*	110 ± 50* †

Mean values ± SD are shown. N, normal subjects; TX, orthotopic cardiac transplant patients; IPAH, primary pulmonary hypertension; RVEDV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; RVthck, right ventricular end-diastolic thickness; RVmass, right ventricular mass. (* p = < .01, N vs. IPAH; † p = < .05, TX vs IPAH.) Reference ^a, Pattynama MT et. al., Radiology 1992 [15]; Reference ^b, Sechtem U et. al., Radiology 1987 [31]; Reference ^c Boxt LM et. al. J Am Coll Cardiol 1992 [18]; Referenced, Saito et. al., Am Rev Respir Dis 1992 [14]; Reference e, Katz et. al., J Am Coll Cardiol 1993 [13].

volume, ejection fraction, myocardial mass, and chamber thickness measurements are categorized by disease type. RV end-diastolic volume was significantly different between the normal patients and those with IPAH (p = 0.012) and between TX and IPAH patients (p = 0.01) but not between normal subjects and Tx patients (p = NS). RV ejection fraction was lower in IPAH than N and TX patients (p = 0.0007 and .0005 respectively). However, there was no difference between N and TX groups.

As a measure of the degree of RV ventricular hypertrophy, the differences between and N and TX compared to IPAH patients RV end-diastolic thickness was measured. The right ventricular end-diastolic thickness by the published normal values is 0.44 ± .09 cm and in our N population average 0.46 ± 0.9cm and in the TX subject was 0.44 ± .09 cm. Whereas, the IPAH patients demonstrated a right ventricular thickness of 0.83 ± .28 cm and in the IDC patients the RV thickness is 0.40 ± .06 cm. As expected there is significant concentric hypertrophy of the right ventricle in IPAH patients. The RV end-diastolic thickness was significantly greater between both IPAH patients and the normals and TX subjects, but again not between N and TX patients p = 0.001, 0.02, and p = NS respectively. Further evidence of global RV hypertrophy was

determined by RV mass, calculated for each group. There is a significantly greater RV mass in IPAH than in N patients (p = .003). There is also a statistically greater RV mass in the IPAH patients compared to TX subjects (p = 0.03). These values are shown are shown in Table 2. These data suggest that IPAH is associated with remodeling of the RV through thickening and hypertrophy.

COMPARISONS OF HEMODYNAMIC MEASURES VS. RVWS

Shown in Table 3 is linear regression analysis of the 25 patients using a continuous variable analysis. No correlation was identified in end-diastolic volume and cardiac output shown in Figure 2. Using all subjects, there was a correlation between RVWS and pulmonary arterial systolic pressure, but analysis of TX and IPAH patients alone or combined showed no correlation with the PA systolic and RVWS. This suggests that pressure may not be the only factor that accounts for the differences in IPAH RVWS compared to normal controls. Interestingly, there was a highly significant inverse correlation between RVWS and a measure of RV contractility, RVEF. Therefore the relationships of pressure, RV thickness and degree of dilation of the RV as ma-

Table 3. Linear Regression Analysis.

Comparison	R value	P value
RVWS vs. CO	.26	.25
RVWS vs. ED volume	.36	.08
RVWS vs. RVEF	-.80	<.0001
RVWS vs. mPA	.60	.001

Shown in Table 3. are the linear regression analyses (ANOVA regression analysis) with R values and p values. RVWS, right ventricular wall stress; CO, cardiac output; ED, end-diastolic volume; RVEF, RV ejection fraction; and mPA, mean pulmonary arterial pressure regression comparison are shown. Both CO and ED volume are not correlated with RVWS; however, mPA is positively correlated and importantly RVEF a measure of contractility, is negatively correlated with RVWS.

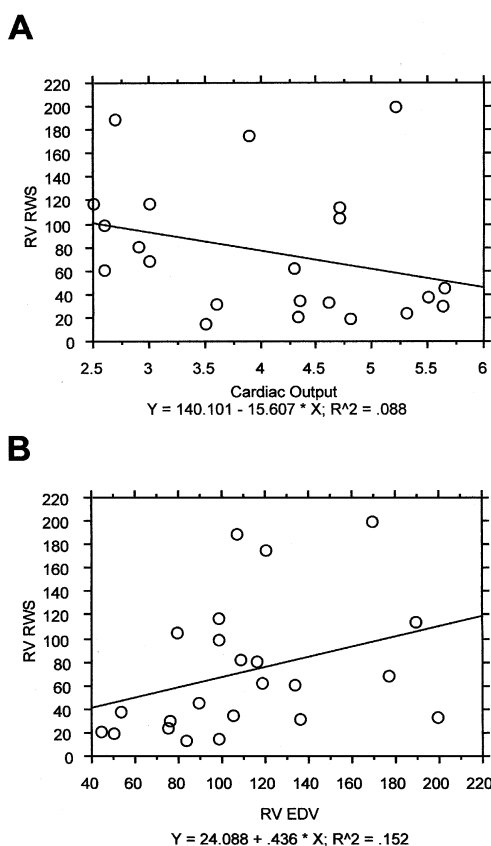


Fig. 2. Figure 2 shows the lack of correlation between RVWS (RV wall stress) and cardiac output in panel A and RV end-diastolic volume (RV EDV) in panel B.

major components of RVWS probably determine the severity of reduced cardiac function in IPAH.

DISCUSSION

This study characterizes the differences in right ventricular size, degree and type of hypertrophy, and sys-

tolic function and regional right ventricular end-systolic wall stress in IPAH, TX and normal subjects. Based on gated cardiac MRI studies, we propose that the degree of RV hypertrophy in response to different types of stress such as volume or pressure [13] helps determine the wall stress on the RV. Furthermore the degree of RV wall stress appears to be independent of RV systolic function as measured by RV ejection fraction. In patients with IPAH there was a spectrum of RV chamber volumes from relatively preserved to increased size, with variable degrees of RV wall thickness. When present significant hypertrophy (>1.0 cm) appeared to lower the relative wall stress values toward the normal range.

Prior investigations concerning the RV have focused attention on the relationship between increased pulmonary arterial pressure and the increase of RV wall thickness [14], RV mass [11, 15], function [16-18], and changes in RV area [19]. However, these individual or sometimes combined characteristics did not take into account the combined effects of these variables on RV performance. Globits and colleagues previously reported [16] the potential differences as assessed by MRI of right and left ventricular volumes [18], in patients prior to lung transplantation [16]. The majority of these patients had pulmonary fibrosis as the primary underlying diagnosis and they demonstrated a modest increase of RV end-diastolic volume index when compared to control subjects. Additionally, in this study there was only mild depression of RV ejection fraction despite inclusion of patients with significant pulmonary hypertension. In the group of severe pulmonary hypertensive patients there was moderate to severe RV dysfunction. In our study, patients with IPAH had a spectrum of RV enlargement as measured by volume which may not necessarily be related to the amount of RV hypertrophy. Of interest, a subgroup of IPAH patients demonstrated marked hypertrophy with an RV wall thickness of > 1.0 cm which was associated with preserved or near normal RV systolic function. Chronic RV pressure overload may have modulated the degree of concentric RV hypertrophy in these patients and reduced the regional wall end-systolic stress on the RV, thereby preserving RV systolic function. The RV can be characterized into phenotypic classes of eccentric or concentric hypertrophy based on the morphologic parameters and clinical states of compensation and failure as described in our prior investigations [13].

At the cellular level, Grossman[8] proposed a scenario by which patterns of concentric or eccentric hypertrophy affected ventricular wall stress associated with pressure or volume overload which lead to series and/or parallel addition of sarcomeres. Precise cell sizing in isolated myocytes has provided clear and consistent evidence [20-22] in support of Grossman's original theory. In animal models it has been demonstrated that concentric hypertrophy due to systemic [23] or pulmonary [24] hypertension is due to an increase in myocyte cross-sectional area only. In contrast, chamber dilation with hypertrophy (eccentric hypertrophy) of the left ventricle due to physiologic growth, hyperthyroidism or A-V fistula is associated with an equal increase in cell length and diameter [25]. It is reason-

able to suggest that the RV is characterized by changes similar to those of the LV; however a review of data in support of these concepts reveals limited data.

An important question is whether the morphologic changes that occurs in IPAH are permanent or reversible and is the RV capable of functional recovery. Following single lung transplantation (SLT) [26] Moulton et al showed that there was a reduction of the end-diastolic RV thickness from 8mm to 6mm within 6 months of transplantation. This was associated with a 10 fold reduction of a measure of RV wall stress using a 2-dimensional finite element analysis technique obtained from single-slice cardiac short axis MR images. The diastolic elastic modulus was also significantly reduced following SLT. Importantly, at the same time the RV velocity of contraction increased as a marker of improved RV systolic function. In our study we demonstrated an apparent relationship between normal RV ejection fraction, RV compensation (without overt RV failure), and relatively normal RVWS despite comparable pulmonary artery pressures when compared to those patients with decompensated RV failure. The exact mechanisms that account for differences between individual patients and their reverse RV remodeling are not clear. However, alteration of pressure overload, improved oxygenation or improved RV coronary blood flow resulting from SLT, likely reduce regional wall stress and improve RV systolic function.

Right ventricular glucose metabolism was investigated by Oikawa in the setting of epoprostenol therapy for advanced IPAH [27]. These investigators used 18F- 2-deoxyglucose (FDG) and ECG gated positron emission tomography (PET) to study regional glucose metabolism. In 10 patients with IPAH a 30% reduction in pulmonary vascular resistance was noted and in 5 of the 10 patients, FDG uptake was significantly reduced without any change in RV thickness after 3 months of epoprostenol therapy. Reduction in glucose metabolism was correlated with a significant reduction in estimated RV wall stress [27, 28]. The RV wall stress difference between baseline and 3-month follow-up after epoprostenol infusion therapy are comparable to the differences in our study between normal subjects and those with untreated IPAH patients. Importantly, the conclusions from this study also suggest that RV glucose metabolism/ substrate utilization is increased prior to treatment in IPAH and that epoprostenol therapy results in a decrease in pulmonary vascular resistance and RV wall stress as well as a decrease in RV myocardial FDG uptake. Whether, epoprostenol therapy lowers myocardial work leading to a normalization of glucose utilization is unknown. Clearly, there is a need to quantitatively assess how drugs used to treat IPAH affect RV function.

LIMITATIONS

Our study is a small cross-sectional study that defines a new method to estimate RV end-systolic wall stress. Presently there is no recognized gold standard for RV wall stress determinations; however our relatively simple method provides a quantitative technique or index that may integrate the effects of pressure, wall thickness, and diameter of the RV. Indeed, RV wall stress

appears to be inversely related to RV systolic function at similar peak RV or pulmonary arterial pressures when referenced to RVEF.

CONCLUSIONS

RV end-systolic wall stress using this method [10] is significantly increased in IPAH compared to other cardiac disease processes and when compared to normal controls. This method may provide a quantitative assessment of RV function for longitudinal drug studies aimed at improving symptoms and survival in IPAH. In particular, a significant reduction in RV wall stress after therapy may signal improved RV myocardial blood flow, oxygenation and metabolism; in contrast, failure of a drug or treatment to reduce RV wall stress may predict a poor outcome.

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