ORIGINAL ARTICLE

Patients with Pulmonary Hypertension Exhibit Right Ventricular Dyssynchrony, a Tissue Doppler Study

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Background  Tissue Doppler imaging (TDI) has provided an objective way to quantify global and regional left ventricular (LV) and right ventricular (RV) function with improved accuracy and greater reproducibility than conventional echocardiography.

Objective  This study was conducted to assess the effect of pulmonary hypertension on the right ventricular function.

Methods  A total of 30 patients with PHT (GP1, mean PASP 56±12mmHg, mean age 43.7±11 years) and 30 healthy age and gender matched volunteers (GP2, mean PASP 20±12 6mmHg, mean age 45.6±10 years) underwent standard Doppler echocardiography and TDI. Systolic (Sm), early- and late-diastolic (Em and Am) peak velocities of the basal left and right ventricular segments were evaluated in the apical 4 chamber view. RV dyssynchrony was assessed by the myocardial systolic activation delay. This was defined as the difference in time to peak TDI systolic velocities between the RV basal lateral wall and basal septal and the difference in time to peak TDI systolic velocities between the RV basal lateral wall and LV basal lateral wall. Also, RA area, RV end-diastolic (RVEDA) and end-systolic areas (RVESA) were measured to calculate RV fractional area (RAFAC) change from the same apical 4-chamber view.

Results  GP1 had increased RA area (25.3±5 vs 11±1cm², \(P<0.05\)), RVEDA (22.±3 vs 16±2cm², \(P<0.05\)), RVESA (14.3±3 vs 10±2cm², \(P<0.05\)) and reduced RVFAC (24.8±6% vs 50±6%, \(P<0.05\)) compared to GP. With TDI; GP1s showed lower myocardial peak velocities and a significant activation delay compared with controls \(P<0.05\), positive correlation between RV activation delay and functional class and also with PASP.

Conclusions  In PHT RV myocardial systolic activation delay and right ventricular dyssynchrony assessed by TDI could offer a unique approach to predict RV dysfunction.

Keywords  Pulmonary hypertension, Tissue Doppler study, RV dyssynchrony.

INTRODUCTION

Pulmonary hypertension defines a group of diseases characterized by a progressive increase in pulmonary vascular resistance. In a normal heart the RV usually ejects against a low impedance circulation compared to the left ventricle (1).

With chronic increase in afterload, the RV dilates and develops muscular hypertrophy. The change in RV size, due to pressure or volume overload may affect the cardiac output.

In pulmonary hypertension, RV myocardial oxygen demand is increased and right coronary artery (RCA) perfusion pressure decreased. Since RV perfusion occurs during both diastole and systole, the systolic component is reduced as a result of the raised chamber pressures (2).

RV function is a major determinant of symptoms and exercise capacity in heart failure. The outcome in patients with depressed RV function, right atrial dilatation and vena cava dilatation is poor (3).

Two-dimensional (2D) echocardiography is today a well-established cardiac investigation worldwide. However, as the RV is positioned close to the sternum and also being complex in its geometrical shape, assessment by 2D echocardiography may be limited (4).
Volume and ejection fraction calculations using Simpson's formula are based on mathematical assumptions of RV geometry, therefore subject to inaccuracies and not useful in clinical practice. RV end-diastolic and end-systolic areas and the calculated fractional area change including the trabeculated apical part reflect global and regional wall motion and can be measured both manually and with automatic edge detection (4).

Pulsed Doppler recordings of pulmonary valve flow acceleration time (PAat), pre-ejection period (PEP) and ejection time (PAet) at the RV outflow tract and the RV isovolumic relaxation time (IVRI) from trans-tricuspid flow may also be used to estimate pulmonary artery pressure and resistance (5). Peak TR gradient is today the most commonly used method to assess pulmonary artery systolic pressure in clinical practice.

The Tei or myocardial performance index (MPI) is used to assess overall RV function. It is calculated as the ratio between total RV isovolumic time (contraction and relaxation) divided by pulmonary ejection time. The RV MPI has been found to correlate with pulmonary pressures and can be used to identify early RV dysfunction in different diseases. The main limitation of the MPI is with increased right atrial pressure when the MPI falls due to shortened isovolumic relaxation time. Finally, relative pulmonary pre-ejection time to aortic pre-ejection time reflects the degree of ventricular dysfunction (6).

In contrast to traditional pulsed Doppler echocardiography which detects high velocity with low amplitudes, Doppler tissue imaging (DTI) detects low velocity with high amplitudes. Tissue velocities can be displayed with spectral pulsed or colour-encoded Doppler visualized with 2D, M-mode or Doppler signals (7).

DTI is proposed to be less preload dependent compared to the traditional pulsed Doppler technique. 60 Typical recordings display 5 main velocity components and 3 time intervals that can be measured (8).

One-dimensional strain echocardiography is a dimensionless measurement which represents the fractional or percentage change in myocardial fibre shortening. As this myocardial deformation or strain is caused by fibre shortening, it can be used as a measure of ‘true’ segmental systolic performance (9).

Strain and strain rate have shown significant RV abnormalities in patients with amyloidosis, pulmonary hypertension, pulmonary stenosis, atrial septum defects and arrhythmogenic RV dysplasia. Strain measurements of the RV are best performed from the apical four-chamber view, assessing the RV free wall from the base to the apical level (10).

The latest of image acquisitions is based on detecting speckles from the myocardium with 2D echocardiography analysing motion in different directions, longitudinal, radial and circumferential (11).

This is mainly used for studying the left and right ventricular function but also in the thin-walled right ventricle (12). More studies are needed to evaluate the use of this technique in RV function in great detail.

This study was conducted to assess the effect of pulmonary hypertension on the right ventricular function measured by TDI.

METHODS

The study included thirty patients with pulmonary hypertension of different etiologies referred for echocardiography and thirty age and gender matched healthy volunteers (control group).

Patients Excluded From the Study

Patients with pulmonary artery stenosis or RV outflow tract obstruction, left ventricular cardiomyopathy, patients suffering from AF were excluded from the analysis.

Echocardiographic Examination

Transthoracic echocardiographic studies were performed with the patient in the left lateral position using Vivid 7 system. Standard two-dimensional echocardiographic evaluation of RA and RV end-diastolic and end-systolic areas were measured from the apical 4-chamber view to calculate RV fractional area change. Pulmonary artery systolic pressures (PASP) were estimated by the maximum velocity of the tricuspid regurgitant jet using the modified Bernoulli equation and then adding to this value an estimated right atrial pressure.

Tissue Doppler study: RV basal lateral wall, basal septal and LV basal lateral wall regions viewed in apical 4-chamber were obtained using TDI. A 3.5-mm pulsed wave Doppler sample volume was placed in each of the three segments. The Nyquist limits were set at 2.5cm/s using the lowest filter settings and the minimum optimum gain as recommended by the manufacturer. From each basal segment systolic myocardial velocity (Sm), early diastolic myocardial velocity (Em), late diastolic myocardial velocity (Am) and time to peak systolic velocities were measured using pulsed Doppler echocardiography combined with TDI. RV myocardial systolic activation delay was defined as the difference in time to peak TDI systolic velocities between RV basal lateral wall and basal septum. We also measured the difference in time to peak velocity between the RV basal lateral wall and LV basal lateral segment to...
evaluate right ventricular dyssynchrony (interventricular dyssynchrony).

Patients with pulmonary hypertension were then divided into groups according to WHO functional class (13):

Class I: Patients with PHT but without resulting limitation of physical activity.

Class II: Patients with PHT resulting in slight limitation of physical activity. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain or near syncope.

Class III: Patients with PHT resulting in marked limitation of physical activity, but with no discomfort at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain or near syncope.

Class IV: Patients with PHT unable to carry out any physical activity without symptoms. These patients manifest signs of right-heart failure, dyspnoea and/or fatigue which may even be present at rest.

Statistical Analysis
The mean and standard deviation (SD) or median (minimum, maximum) was calculated for all numerical data, which was determined by a single observer. Linear regression analysis was used to describe the correlation between RV myocardial systolic activation delay and RV fractional area change. A two-sided P value <0.05 was considered statistically significant.

RESULTS
The study included thirty patients with pulmonary hypertension referred for echocardiography and thirty age and gender matched healthy volunteers (control group). Both groups were comparable in age and gender. The mean of age in PHT was 45.6±10 years and was that of the controls was 43.7±11 years, P >0.05. The difference in gender distribution was insignificant.

The different etiologies of PHT in the patient group are listed in (Table 1).

Table 1: Distribution of the etiology of pulmonary hypertension:

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valvular heart disease</td>
<td>12</td>
<td>40</td>
</tr>
<tr>
<td>COPD</td>
<td>12</td>
<td>40</td>
</tr>
<tr>
<td>Primary pulmonary hypertension</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>3</td>
<td>10</td>
</tr>
</tbody>
</table>

Analysis of the Echocardiography Criteria
The echocardiographic parameters of the PHT group and the control group shows that right atrial area (11±1 vs. 25.3±5), RV end-diastolic (16±2 vs. 22±3) and RV end-systolic areas (10±2 vs. 14.3±3) were higher than the control group. RV fractional area change was found to be decreased in patients with PAH when compared with controls (24.8±6% vs. 50±6%, p <0.05) as demonstrated in (Table 2 and Figure 1, 2).

Analysis of Tissue Doppler Image (TDI)
When TDI velocities of the basal segments (septal and lateral walls of the RV) in the two groups were compared, there were lower Sm, Em and Am peak velocities in patients with PHT and the difference was statically significant (P <0.05) (Table 3 and Figure 3).

Table 2: Analysis of Echo Doppler parameters:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal (N= 30)</th>
<th>PHT (N= 30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA area (cm²)</td>
<td>11±1</td>
<td>25.3±5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>RVESA (cm²)</td>
<td>10±2</td>
<td>14.3±3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>RVEDA (cm²)</td>
<td>16±2</td>
<td>22±3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>RV FA%</td>
<td>50±6</td>
<td>24.8±6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PASP</td>
<td>20±6</td>
<td>56±12</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Figure 1: Higher right atrial area in pulmonary hypertension. (a) normal case, (b) case of pulmonary hypertension
Patients with Pulmonary Hypertension Exhibit Right Ventricular

Figure 2: Lower right ventricular fractional area change in pulmonary hypertension, (a) normal case and (b) case of pulmonary hypertension.

Table 3: Basal myocardial TDI velocity:

<table>
<thead>
<tr>
<th></th>
<th>Normal (N=30)</th>
<th>PHT</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV basal lateral wall (m/sec)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sm</td>
<td>0.13±0.03</td>
<td>0.10±0.05</td>
<td>P &lt;0.05</td>
</tr>
<tr>
<td>Em</td>
<td>0.14±0.04</td>
<td>0.09±0.06</td>
<td>P &lt;0.05</td>
</tr>
<tr>
<td>Am</td>
<td>0.12±0.04</td>
<td>0.07±0.04</td>
<td>P &lt;0.05</td>
</tr>
<tr>
<td>RV basal septal wall (m/sec)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sm</td>
<td>0.09±0.03</td>
<td>0.06±0.03</td>
<td>P &lt;0.05</td>
</tr>
<tr>
<td>Em</td>
<td>0.10±0.02</td>
<td>0.07±0.03</td>
<td>P &lt;0.05</td>
</tr>
<tr>
<td>Am</td>
<td>0.09±0.02</td>
<td>0.06±0.02</td>
<td>P &lt;0.05</td>
</tr>
</tbody>
</table>

Analysis of time to peak velocity and myocardial systolic activation delay:

When the basal septal segment in the two groups was compared the difference in the time to peak velocity value was statistically insignificant. However, in the RV lateral wall, the difference in the time to peak velocity between the two groups was statistically significant and showed that the RV myocardial systolic activation delay in pulmonary hypertension group was longer than in the control group P <0.05. There was also delayed time to peak velocity of the basal lateral segment of the RV compared to that of the LV. This was statistically significant P <0.05 (Table 4 and Figure 4).

Table 4: The time to peak velocity and myocardial systolic activation delay:

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>PHT</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to peak (ms)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal septal</td>
<td>140</td>
<td>156</td>
<td>P NS</td>
</tr>
<tr>
<td>Basal lateral (RV)</td>
<td>155</td>
<td>195</td>
<td>P &lt;0.05</td>
</tr>
<tr>
<td>RV myocardial systolic activation delay (ms)</td>
<td>10</td>
<td>50</td>
<td>P &lt;0.05</td>
</tr>
<tr>
<td>LV–RV myocardial systolic activation delay (ms)</td>
<td>12</td>
<td>45</td>
<td>P &lt;0.05</td>
</tr>
</tbody>
</table>
Patients with Pulmonary Hypertension Exhibit Right Ventricular Dysfunction

**Correlation between RV systolic activation delay and functional class:**

The correlation between the RV systolic activation delay and the functional class of the patients was positive and statically significant (P <0.05) as the mean of time delay increased proportionally with the functional class. Thus the systolic activation delay was 12±2 msec in functional class I, 25±2 msec in functional class II, 36±4 in functional class III and 50±3 in functional class IV (Figure 4a).

**Correlation between RV systolic activation delay and PASP:**

There was a positive, statistically significant correlation between the degree of PASP and RV systolic activation delay (P <0.05). The mean of time delay was 15±3 msec in mild pulmonary hypertension, 25±2 msec in moderate pulmonary hypertension and 50±2 in severe pulmonary hypertension (Figure 4b).

**DISCUSSION**

TDI has provided an objective means to quantify global and regional left ventricular (LV) and RV function with improved accuracy and greater reproducibility than conventional echocardiography (14). It has proved to be invaluable in the identification of LV dyssynchrony in patients with left-sided cardiac failure (15). In contrast to LV dysfunction, the progression of a failing right ventricle is not well characterized (16).

The present study demonstrates the usefulness of TDI in analyzing patterns of myocardial systolic activation of the right ventricle in patients with PAH. The following are the main findings of our study:

1. **Lower myocardial systolic and diastolic peak velocities in PHT:**

   According to myocardial indexes of all the analyzed regions, the present study confirms that RV global and regional dysfunction in patients with pulmonary hypertension was significantly impaired with respect to controls. Previous reports demonstrated that both systolic and early diastolic regional velocities are directly dependent on myocardial structure, characterized by the presence of interstitial fibrosis (17). Therefore, the impairment of myocardial indexes in our patients with PHT can be easily explained as a consequence of a direct involvement of RV walls by a myopathic process, which is characterized by extensive areas of interstitial and perivascular fibrosis, particularly involving the RV subendocardium.

2. **RV myocardial systolic activation delay:**

   RV myocardial systolic activation delay represented as the time difference from interventricular septum to RV lateral wall activation occurs in patients with chronic pulmonary hypertension.

   Right ventricular dyssynchrony represented as the delay between time to peak myocardial systolic velocity of the LV lateral wall and the RV lateral wall in patients with chronic pulmonary hypertension. Delayed RV myocardial systolic activation this can be explained by the conduction slowing and action potential prolongation of the right ventricle in PHT (18).

   There was also a positive correlation between the systolic activation delay and severity of functional class as well as with the severity of pulmonary hypertension.

**CONCLUSION**

The results of this study can be quite useful in the evaluation of chronic pulmonary hypertension patients, given the well-known limitations of standard echocardiography in the assessment of RV function due to the complex structure and asymmetrical shape of this cardiac chamber (19). RV myocardial systolic activation delay and right ventricular dyssynchrony measured by TDI can be considered as an index to predict RV dysfunction. It correlated with the severity of functional class and severity of pulmonary hypertension.
Study Limitations

The first limitation of this present study is the angle dependence of TDI and the possible presence of artifacts. The presence of a heterogeneous population of patients was not divided into groups with regards to the etiology of their pulmonary hypertension in this study. The effect of drugs could not be assessed due to the small number of patients.

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REFERENCE