Doppler tissue imaging in assessment of pulmonary hypertension-induced right ventricle dysfunction

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Submitted 19 May 2005; accepted in final form 17 July 2005

Boissiere, Julien, Mathieu Gautier, Marie-Christine Machet, Gilles Hanton, Pierre Bonnet, and Veronique Eder. Doppler tissue imaging in assessment of pulmonary hypertension-induced right ventricle dysfunction. Am J Physiol Heart Circ Physiol 289: H2450–H2455, 2005.—We aimed to assess the accuracy of Doppler tissue imaging (DTI) in detecting right ventricle (RV) dysfunction and electromechanical coupling alteration following pulmonary hypertension (PHT) in rat. PHT was induced by chronic hypoxia exposure (hypoxic PHT) or monocrotaline treatment (monocrotaline PHT). In both PHT models, we observed transpapillary RV pressure increase and remodeling, including hypertrophy and dilatation. Conventional echocardiography provided evidence for pulmonary outflow impairment with mid-systolic notch and acceleration time decrease in PHT groups (21.7 ± 1.6 and 13.2 ± 2.9 ms in hypoxic and monocrotaline PHT groups vs. 28.1 ± 1.0 ms in control). RV shortening fraction was decreased in the monocrotaline PHT group compared with the hypoxic PHT and control groups. Combining conventional Doppler and DTI was more helpful to detect RV diastolic dysfunction in the monocrotaline PHT group (E/Ea ratio = 17.0 ± 1.4) compared with the hypoxic PHT and control groups (11.5 ± 0.7 and 10.2 ± 0.4, respectively). Tei index measured using DTI highlighted global RV dysfunction in the monocrotaline PHT group (1.36 ± 0.24 vs. 0.92 ± 0.05 and 0.86 ± 0.05 in the hypoxic PHT and control groups, respectively). Q-Sm time measured from the onset of Q wave to the onset of DTI Sm wave was increased in both PHT groups. PHT-induced electromechanical coupling alteration was confirmed by in vitro activation-contraction delay measurements on isolated RV papillary muscle, and both Q-Sm time and activation-contraction delay were correlated with PHT severity. We demonstrated that Q-Sm time measured in DTI was an easily and convenient index to detect early RV electromechanical coupling alteration in both moderate and severe PHT.

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The Tei index, which combines both systolic and diastolic parameters, was suggested to determine global myocardial performance (27). It has been used in the assessment of RV dysfunction, especially in PHT (26). In conventional pulsed Doppler, the Tei index derives from both isovolumic contraction and relaxation times (IVCT and IVRT) as well as ejection time of RV outflow and therefore needs to record both tricuspid and pulmonary flow in two different windows. Doppler tissue imaging (DTI) is an ultrasound technique that provides assessment of contracting myocardium by measuring endocardial velocities (8). Interestingly, the Tei index can be measured using DTI, which allows simultaneous recording of systolic and diastolic functions (11). Typically, DTI recording is composed of a systolic (S) wave, an early diastolic (Ea) wave, and an atrial (Aa) wave. When DTI is performed on the tricuspid annulus, it allows the evaluation of the RV systolic and diastolic functions (6, 19, 31) as well as the Tei index (11). The Tei index is generally increased with PHT, indicating RV dysfunction (27). However, the mechanisms underlying this RV dysfunction remain poorly understood, because RV pressure overload (15) or electrical conduction abnormalities could contribute to a Tei index increase during PHT.

RV hypertrophy and the corresponding myocardial remodeling induce ultrastructural changes such as lateral expansion of cardiac muscle cells or an increase in myocyte numbers across the ventricular wall, as well as intermyocyte distance enlargement (23). Recently, it was shown that RV hypertrophy is associated with both disorganization of gap junction distribution and alteration of anisotropic conduction properties (28, 29). Consequently, hypertrophic remodeling might induce electromechanical coupling alteration during PHT-induced RV dysfunction (29).

In conventional pulsed Doppler, the pulmonary preejection period is used to estimate RV IVCT and is well correlated to pulmonary pressure overload (9, 12, 18, 20). On the other hand, DTI, which allows measurement of endocardial velocities, provides more accurate measurements of myocardial motion. The delay from the onset of Q wave (ECG) to the onset of DTI Sm wave (Q-Sm time) could be likened to the time for...
RV activation as previously used in left ventricle (LV) asynchrony prognosis (24).

The aim of our study was to investigate whether echocardiographic modifications occurring in animal models with different RV dysfunction severity are linked to electromechanical coupling alteration. We thus postulated that Q-Sm time measurement should provide a more accurate evaluation of RV activation-contraction delay. Therefore, we compared the electromechanical coupling delay noninvasively measured using DTI with in vitro electrophysiological and mechanical measurements in isolated papillary muscle.

MATERIALS AND METHODS

All study protocols were approved by the Comité Régionale d’Ethique pour l’Expérimentation Animale, Région Centre-Limousin, and carried out in accordance with the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health (NIH Publication No. 85-23, revised 1996) and European Directives (86/609/CEE).

Animals and pathological models. Three groups of adult male Wistar rats (10 wk old) were studied. A first group (n = 12) was exposed to hypoxia (hypoxic PHT group). The rats were housed for 3 wk in a hypobaric chamber, where atmospheric pressure was kept at 380 mmHg (estimated oxygen pressure 75 mmHg) as previously described (4). The hypobaric chamber was opened twice a week for ~10 min to change cage, food, and water. The second group of rats (n = 6) received a single injection of monocrotaline (60 mg/kg ip) (monocrotaline PHT group). Twelve rats were initially included and developed a severe PHT during the next 3 wk. During PHT development, six rats died before experimentations. Finally, only six rats were studied. The third group (n = 12) received only the vehicle (control). All the rats were fed ad libitum with free access to tap water in a room with a 12:12-h light-dark cycle and were maintained at ~21°C.

Echocardiographic measurements. Rats were anesthetized by injection of ketamine and xylazine (100 mg/kg and 7.5 mg/kg ip, respectively). Echocardiographic measurements were performed using an Acuson Sequoia ultrasonographic system with a 15-MHz transducer (Mountain View, CA). Doppler tracings were recorded at a sweep speed of 200 mm/s. In all experiments, ECG was recorded simultaneously. Pulmonary arterial pressure increase was estimated by assessment of the parietal wall diastolic RV thickness (TM mode in modified left parasternal view), by the presence of mild-systolic notch, and by the pulmonary acceleration time measurement (pulsed-Doppler mode in transverse short-axis view). RV systolic function assessment was performed by measuring RV systolic and diastolic surfaces (2-dimensional mode in apical 4-chamber view). RV shortening fraction (%) was then estimated as [(end-diastolic surface – end-systolic surface) × 100]/end-diastolic surface. Pulmonary outflow peak velocity (pulsed-Doppler mode in transverse short-axis view) and velocity time integral were also recorded. Finally, to specifically explore the right myocardium, we recorded DTI (in apical 4-chamber view) on the lateral part of the tricuspid annulus (see Fig. 1 for typical example of measurements). Sm wave peak velocity was recorded and considered as a systolic function index (19). RV diastolic function was estimated using conventional pulsed Doppler (in apical 4-chamber view). The tricuspid Ea/Aa peak velocity ratio and E-wave deceleration time were measured. Using DTI, Ea and Aa diastolic wave peak velocities and RV IVCT and IVRT (expressed in both absolute and %ECG R-R interval) were measured on the tricuspid annulus. Tricuspid Ea/Aa and E/Ea peak velocity ratios were calculated. The RV Tei index was then calculated as (IVCT + IVRT)/Sm wave duration. Finally, time for RV activation (Q-Sm time) was estimated by measuring delay from the onset of Q wave (ECG) to the onset of the tricuspid annulus Sm wave (DTI). Q-Sm time was normalized to an averaged heart rate of 250 beats/min (Q-Sm/250 time).

All measurements represent the means of three cardiac cycles. In a separate paired series of Wistar rats (n = 6), we compared the mean of each parameter between the two observers by using the method of Bland and Altman (3). No statistical differences were observed between the two observers.

Hemodynamic measurements. Systolic RV and LV pressures were measured using transpapillary intraventricular catheterization after thoracotomy, and the systolic RV/LV pressure ratio was determined. Briefly, animals were placed in the dorsal decubitus position, intubated, and ventilated with normoxic air at a 10 ml/kg volume inflow and 48 cycles/min. A surgical incision of ~20 mm was performed along the left sternal margin, exposing the fourth and fifth ribs. After exposure of the pectoralis and transversus muscles, a thoracotomy (<10 mm) was performed through the fourth intercostal space. Resting intraventricular pressure was then measured through a 20-cm polyethylene catheter filled with heparinized physiological salt solution and attached to a hypodermic needle.

Tricuspid papillary muscle electromechanical delay measurements. After hemodynamic measurements were obtained, the heart was excised and immediately placed in a cardioplegic solution. The RV papillary muscle was dissociated for electromechanical delay experimentations. Isolated papillary muscle was placed in cold 4°C physiological saline solution (PSS; containing in mmol/l: 138.6 NaCl, 5.4 KCl, 1.8 CaCl2, 1.2 MgCl2, 0.33 NaH2PO4, 10 HEPES, and 11 glucose, pH adjusted to 7.4 with NaOH), and two stainless steel hooks were fixed in the two end parts of papillary muscle. The papillary muscle was placed in a 4-ml bath filled with 37°C PSS (bubbled with 95% O2-5% CO2). One end of the muscle was anchored to a rigid support, and the other end was connected to an isometric force transducer (UF1 control; Pyoden) for contraction recording. The papillary muscle was stretched against a preload of 2 g developed over 5 min. When optimum preload was achieved, papillary muscle was equilibrated for a further 30 min. The papillary muscle was electrically stimulated via two punctuated electrodes. Measurements of membrane potential were made with a glass microelectrode (resistance of 50–80 MΩ and filled with 3 mol/l KCl solution) connected to a microelectrode amplifier (UF180; Biologic). The setup was mounted on anti-vibration system (Micro-g; TMC), and manipulations...
were carried out using a micromanipulator (MMO-203; Narishige). Different stimulation frequency ranges (100, 200, and 300 beats/min) were applied for 5 min; each stimulation series was separated by a 10-min resting period. The delay from the onset of action potential (AP) to contraction was measured (AP-contraction delay) for each stimulation frequency. Corresponding linear relations were built using linear regression, and values were normalized for a stimulation frequency. Hemodynamic data acquisition system (National Instrument) was used for signal recording, and Origin 6.0 software (Microcal Software, Northampton, MA) was used for data analysis.

Histological data. After animal death, the heart was excised and placed in cold PSS. Free RV wall and LV including septum (LV+S) were weighed separately. The ratio RV/(LV+S) was calculated as a good index of RV hypertrophy (21). Tissues were then fixed in cold 4% paraformaldehyde, dehydrated in graded ethanol, and embedded in Epon. Thin sections 0.7 μm thick were cut (Ultracut E; Reichert) and contrasted with toluidine blue added with sodium borate (pH 8.9).

Statistical analysis. All results are expressed as means ± SE. The overall comparison between the monocrotaline PHT, hypoxic PHT, and control groups was done using the Mann-Whitney rank sum test for small populations (Minitab software). A P value < 0.05 was set as the criterion for significance in all comparisons.

Table 1. Indirect estimation of PHT severity

<table>
<thead>
<tr>
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<th>Control (n = 12)</th>
<th>Hypoxic PHT (n = 12)</th>
<th>Monocrotaline PHT (n = 6)</th>
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<tbody>
<tr>
<td></td>
<td>Echographic data</td>
<td></td>
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<tr>
<td>Diastolic RV thickness, mm</td>
<td>0.41±0.27</td>
<td>0.67±0.42*</td>
<td>1.10±0.06†</td>
</tr>
<tr>
<td>Pulmonary acceleration time, ms</td>
<td>28.1±1.0</td>
<td>21.7±1.6*</td>
<td>13.2±2.9†</td>
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<tr>
<td>Hemodynamic data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic RV pressure, mmHg</td>
<td>11±3</td>
<td>27±7*</td>
<td>38±6†</td>
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<tr>
<td>Systolic RV/LV pressure ratio</td>
<td>0.22±0.03</td>
<td>0.54±0.02*</td>
<td>0.80±0.01†</td>
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<tr>
<td>Ventricle weights</td>
<td></td>
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<tr>
<td>RV/(LV+S) ratio</td>
<td>0.30±0.01</td>
<td>0.49±0.01*</td>
<td>0.60±0.03†</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = no. of rats/group. RV, right ventricle; LV, left ventricle; S, septum. *P < 0.05, comparison between pulmonary hypertension (PHT) groups and control. †P < 0.05, comparison between hypoxic PHT and monocrotaline PHT groups.

RESULTS

PHT assessment. Echocardiography, hemodynamic measurements, and the ratio RV/(LV+S) were used as an index of PHT severity (Table 1). In both PHT groups, diastolic RV thickness was significantly increased compared with the control. Furthermore, this increase was greater in the monocrotaline PHT than in the hypoxic PHT group. Pulmonary acceleration time was decreased in both PHT groups compared with the control and was significantly lower in the monocrotaline PHT than in the hypoxic PHT group. Hemodynamic data showed that both systolic RV pressure and RV/LV pressure ratio were significantly increased in both PHT groups compared with the control. This increase was more pronounced in the monocrotaline PHT than in the hypoxic PHT group. RV/LV+S ratio was significantly increased in both PHT groups compared with the control. Therefore, this increase was more pronounced in the monocrotaline PHT than in the hypoxic PHT group.

RV systolic and diastolic function assessment by echocardiography. Two-dimensional mode echocardiography showed an increase in diastolic and systolic RV surfaces in the two PHT-groups compared with the control (Table 2). These increases were more pronounced in the monocrotaline PHT

Table 2. Assessment of systolic and diastolic RV function and Tei index

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 12)</th>
<th>Hypoxic PHT (n = 12)</th>
<th>Monocrotaline PHT (n = 6)</th>
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<tr>
<td></td>
<td>2-D mode</td>
<td></td>
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<tr>
<td>Diastolic RV surface, cm²</td>
<td>0.28±0.01</td>
<td>0.35±0.02*</td>
<td>0.39±0.04†</td>
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<tr>
<td>Systolic RV surface, cm²</td>
<td>0.17±0.02</td>
<td>0.24±0.01*</td>
<td>0.32±0.06†</td>
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<tr>
<td>RV shortening fraction, %</td>
<td>36±8</td>
<td>56±5</td>
<td>15±6*†</td>
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<tr>
<td>Doppler pulmonary flow</td>
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<tr>
<td>Velocity time integral, m</td>
<td>0.04±0.01</td>
<td>0.05±0.01</td>
<td>0.04±0.01</td>
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<tr>
<td>Peak velocity, m/s</td>
<td>−0.80±0.03</td>
<td>−0.82±0.02</td>
<td>−0.80±0.05</td>
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<tr>
<td>E/A wave peak velocities ratio</td>
<td>1.35±0.50</td>
<td>1.21±0.54</td>
<td>1.29±0.45</td>
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<td>E wave deceleration time, ms</td>
<td>39.3±10.3</td>
<td>44.6±6.3</td>
<td>37.3±2.5</td>
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<tr>
<td>DTI tricuspid annulus</td>
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<tr>
<td>Sm wave peak velocity, m/s</td>
<td>0.06±0.01</td>
<td>0.06±0.02</td>
<td>0.06±0.01</td>
</tr>
<tr>
<td>Ea/Aa wave peak velocities ratio</td>
<td>0.86±0.09</td>
<td>0.93±0.24</td>
<td>0.68±0.16</td>
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<tr>
<td>E/Ea wave peak velocities ratio</td>
<td>10.2±0.4</td>
<td>11.5±0.7</td>
<td>17.0±1.4*†</td>
</tr>
<tr>
<td>IVRT/R-R interval, %</td>
<td>15.0±0.6</td>
<td>14.8±0.7</td>
<td>20.0±1.0*†</td>
</tr>
<tr>
<td>RV Tei index</td>
<td>0.86±0.05</td>
<td>0.92±0.05</td>
<td>1.36±0.24*†</td>
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</table>

Values are means ± SE; n = no. of rats/group. IVRT, isovolumic relaxation time; 2D, two-dimensional; DTI, Doppler tissue imaging. *P < 0.05, comparison between PHT groups and control. †P < 0.05, comparison between hypoxic PHT and monocrotaline PHT groups.
(+34% compared with control) than in the hypoxic PHT group (+23% compared with control). RV shortening fraction was only decreased in the monocrotaline PHT group. Regarding pulmonary flow measured in pulsed-Doppler mode, velocity time integral and peak velocity were unchanged in the three groups of rats. Nevertheless, we observed a midsystolic notch in the two PHT groups without any tricuspid regurgitation. DTI data indicated no change in $S_m$ wave peak velocity in the three groups.

In conventional pulsed-Doppler mode, no differences were observed among the three groups regarding RV diastolic function. DTI measurements indicated no changes in both Ea and Aa wave peak velocities or in the Ea/Aa wave peak velocity ratio in all groups. Nevertheless, the E/Ea wave peak velocity ratio was significantly increased in the monocrotaline PHT group. Furthermore, IVRT measurements indicated that both absolute and relative times were significantly increased in the monocrotaline PHT group, whereas no differences were observed in IVCT (data not shown). Finally, the Tei index was increased in PHT groups; however, this increase was significant only in the monocrotaline PHT group.

**Electromechanical coupling.** RV electromechanical coupling was estimated directly by using electrophysiological and mechanical measurements in isolated papillary muscle and indirectly by DTI recording (Table 3). A typical example of simultaneous AP and contraction recordings in isolated RV papillary muscle is presented in Fig. 2. AP-contraction/250 delay was significantly increased in both PHT groups compared with the control. In the monocrotaline PHT group, the AP-contraction/250 delay was higher than in the hypoxic PHT group. DTI measurements indicated that Q-Sm/250 time was significantly higher in both PHT groups compared with the control.

Linear relation between RV pressures and AP-contraction delays was observed (Fig. 3A). Moreover, significant correlation was observed between Q-Sm times and RV pressures, indicating that DTI could accurately detect electromechanical coupling dysfunction (Fig. 3B).

**Histology.** Histological analysis (Fig. 4) showed an increase in the intermyocyte distance in the RV wall with edema development in both PHT groups compared with the control. In addition, the presence of red blood cell extravasations (which indicated subendocardial necrosis areas) was observed in the severe PHT group, i.e., in the monocrotaline PHT group.

<table>
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<th>Table 3. Assessment of RV electromechanical coupling</th>
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<tr>
<td><strong>Echocardiographic data</strong></td>
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<tr>
<td>Q-Sm/250 delay, ms</td>
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<tr>
<td><strong>Microelectrode data</strong></td>
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<tr>
<td>AP-contraction/250 delay, ms</td>
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Values are means ± SE; $n =$ no. of rats/group. Delays are normalized to a cardiac frequency of 250 beats/min. * $P < 0.05$, comparison between PHT groups and control.

**DISCUSSION**

Sustained PHT is a common complication of chronic hypoxic lung diseases that is associated with increased morbidity and reduced survival. In the present study, we evaluated the accuracy of DTI in detecting RV dysfunction and electromechanical coupling alteration in two different models of PHT severity. We observed that chronic hypoxia leads to moderate PHT, whereas monocrotaline treatment leads to severe PHT. This study confirmed the benefit of echocardiography in evaluating PHT severity in rats as previously described (14). At first, our results demonstrated that RV systolic function alterations induced by RV hypertrophy could be assessed using conventional pulsed Doppler. However, DTI was more accurate in assessing both RV diastolic and global dysfunctions. Finally, DTI constituted an easy and convenient method for earlier prognosis of PHT-induced RV electromechanical coupling alteration.

PHT severity can be evaluated according to RV pressure overload and hypertrophy levels. In the present study, we used two different animal models of PHT. These two PHT models showed RV remodeling (dilation and hypertrophy) that was validated by echocardiography and hemodynamic measurements as well as the weight of ventricles. Echocardiographic data revealed a reduced pulmonary acceleration time as well as increased RV thickness and surface in both PHT groups. Both systolic RV pressure and the RV/LV pressure ratio were increased after PHT development. Finally, the RV/(LV+S) ratio was also significantly increased in both PHT groups. All these parameters were more altered in the monocrotaline PHT group than in the hypoxic PHT group (Tables 1 and 2), indicating a severe PHT in rats treated with monocrotaline (5, 30, 32) compared with a moderate PHT following chronic hypoxia exposure (16), as previously observed in some invasive studies (2, 16, 17).

Using both conventional echocardiography and DTI, we assessed RV dysfunction in moderate and severe PHT. In conventional echocardiography, systolic dysfunction occurred only in severe PHT, evidenced by shortening fraction reduction. However, DTI was of little benefit because no modification of $S_m$ wave peak velocity was observed. In this regard,
decreased Sm wave was only described in severe RV dysfunction such as RV infarction (1, 35).

In contrast, conventional echocardiography as well as DTI did not highlight RV diastolic abnormalities in both PHT groups. However, the combination of conventional pulsed Doppler and DTI was helpful in studying the RV filling pressure increase in severe-PHT rats. Indeed, the E/Ea ratio, an indicator of filling pressure increase in hypertrophic cardiomyopathies (8), was significantly increased in the monocrotaline PHT group.

In PHT, both systolic and diastolic dysfunction occur; consequently, we used the Tei index, which combines diastolic and systolic parameters, to assess global RV function (26, 27, 33). The Tei index is a powerful tool with significant prognosis for RV dysfunction in primary PHT (27, 34). It is difficult to visualize both tricuspid inflow and pulmonary outflow spectra on the same Doppler window. Furthermore, a variation in cardiac frequency between different cardiac cycles could distort IVRT and IVCT assessment. With the use of DTI, measurements of IVRT and Tei index on the lateral part of the tricuspid annulus appeared more convenient (11). Our results showed a significant increase of IVRT in the severe-PHT group. Consecutively, with this IVRT enlargement, Tei index was also significantly increased in the severe-PHT group. DTI then appears more accurate for investigating RV dysfunction in the case of severe PHT.

It has been demonstrated that RV hypertrophy induces electromechanical coupling alterations that could lead to arrhythmias (7, 28). However, electromechanical coupling assessment by conventional echocardiography remains difficult (20). Recently, the alteration of activation-contraction sequence in LV asynchronism was assessed by determining the delay from the onset of QRS (ECG) to the onset of DTI Sm wave (Q-Sm time) (24). After chronic hypoxia exposure and monocrotaline treatment, Q-Sm time was significantly increased compared with control.

To ensure that Q-Sm enlargement in PHT groups reflects RV electromechanical coupling alteration, we measured electromechanical delay in isolated RV papillary muscle. The AP-contraction delay was significantly increased in both PHT groups, indicating that Q-Sm time alteration reflected electromechanical coupling alteration. This is further supported by significant linear relations between AP-contraction and Q-Sm times to RV pressures (Fig. 3). We concluded, therefore, that DTI could accurately and noninvasively detect electromechanical coupling dysfunction in rats. DTI provide early information on RV electromechanical coupling alteration linked to PHT.

Finally, in our study, RV histology findings showed edema infiltrations in both PHT groups as well as red blood cell extravasations in the severe-PHT group, as previously shown (13, 23, 25). These structural myocardial alterations can explain the electromechanical coupling alterations observed in RV. However, we did not observe ECG abnormalities in PHT groups. Consequently, relations between overload pressure and
the occurrence of ventricular arrhythmia observed in RV cardiomyopathies need further investigation.

These data confirmed that RV remodeling could have an impact on electrical conduction. For the first time, we have shown clearly that DTI and particularly Q-Sm time measurement is a useful method to evaluate alteration in RV electromechanical coupling induced by PHT.

We have demonstrated in this study that combined conventional pulsed Doppler and DTI are able to detect RV dysfunction in case of severe PHT. Moreover, Q-Sm time measured in DTI constitutes an easy and convenient index for earlier prognosis of RV electromechanical coupling alterations in PHT.

ACKNOWLEDGMENTS

We thank M. Manuel Rebocho for technical assistance.

GRANTS

This work was supported by a grant from l’Agence de l’Environnement et de la Maîtrise de l’Energie and Pfizer Global Research and Development, Amboise, France.

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