Noninvasive Assessment of Murine Pulmonary Arterial Pressure
Validation and Application to Models of Pulmonary Hypertension

Hélène B. Thibault, MD, PhD; Baptiste Kurtz, MD; Michael J. Raher, BS; Rahamthulla S. Shaik, MS; Aaron Waxman, MD, PhD; Geneviève Derumeaux, MD, PhD; Elkan F. Halpern, PhD; Kenneth D. Bloch, MD; Marielle Scherrer-Crosbie, MD, PhD

Background—Genetically modified mice offer the unique opportunity to gain insight into the pathophysiology of pulmonary arterial hypertension. In mice, right heart catheterization is the only available technique to measure right ventricular systolic pressure (RVSP). However, it is a terminal procedure and does not allow for serial measurements. Our objective was to validate a noninvasive technique to assess RVSP in mice.

Methods and Results—Right ventricle catheterization and echocardiography (30-MHz transducer) were simultaneously performed in mice with pulmonary hypertension induced acutely by infusion of a thromboxane analogue, U-46619, or chronically by lung-specific overexpression of interleukin-6. Pulmonary acceleration time (PAT) and ejection time (ET) were measured in the parasternal short-axis view by pulsed-wave Doppler of pulmonary artery flow. Infusion of U-46619 acutely increased RVSP, shortened PAT, and decreased PAT/ET. The pulmonary flow pattern changed from symmetrical at baseline to asymmetrical at higher RVSPs. In wild-type and interleukin-6–overexpressing mice, the PAT correlated linearly with RVSP ($r^2 = 0.67$, $P = 0.0001$), as did PAT/ET ($r^2 = 0.76$, $P = 0.0001$). Sensitivity and specificity for detecting high RVSP ($>32$ mm Hg) were 100% (7/7) and 86% (6/7), respectively, for both indices (cutoff values: PAT, <21 ms; PAT/ET, <39%). Intraobserver and interobserver variability of PAT and PAT/ET were <6%.

Conclusions—Right ventricular systolic pressure can be estimated noninvasively in mice. Echocardiography is able to detect acute and chronic increases in RVSP with high sensitivity and specificity as well as to assess the effects of treatment on RVSP. This noninvasive technique may permit the characterization of the evolution of pulmonary arterial hypertension in genetically modified mice. (Circ Cardiovasc Imaging. 2010;3:157-163.)

Key Words: echocardiography | right ventricular systolic pressure | mice

Pulmonary arterial hypertension (PAH) is characterized by pulmonary vascular remodeling and is associated with elevated right ventricular systolic pressure (RVSP) and pulmonary vascular resistance (PVR) that may result in progressive right ventricular (RV) failure, low cardiac output, and premature death.1,2 Despite the development of new therapeutic strategies such as endothelin receptor antagonists, phosphodiesterase type-5 inhibitors, and prostanoids,3 the prognosis of patients with PAH remains poor.2 Advances in understanding the pathophysiological mechanisms that contribute to PAH are critical to the discovery of new therapeutic targets. Small rodent models, in particular genetically modified mice, offer the unique opportunity to study the signaling pathways involved in PAH and to evaluate the effectiveness of therapeutic interventions.
Although right heart catheterization is required to confirm the diagnosis of PAH, echocardiography is a pivotal screening test in humans for PAH and the only noninvasive technique to follow the course of the disease. Pulmonary artery systolic pressure is usually estimated from the tricuspid regurgitation peak flow velocity. Tricuspid regurgitation is often visualized in the apical or subcostal views. In contrast, the estimation of pulmonary artery pressure in mice using echocardiography remains technically challenging. Apical and subcostal views are not reliably obtained, preventing proper flow alignment and accurate measurement of tricuspid regurgitation by Doppler in these views. Furthermore, tricuspid regurgitation appears to be uncommon in rodents except at very high pulmonary pressures.

Nevertheless, echocardiography may be a reliable tool to noninvasively assess RVSP in mice. Importantly, PVR may also be measured because mouse cardiac output can be quantified using echocardiography. The pulmonary acceleration time (PAT, time from the onset of pulmonary flow to peak velocity by pulsed-wave Doppler recording) and the ratio of PAT to ejection time (ET, time interval between the onset and end of the systolic flow velocity) have been proposed as alternative estimates to measure RVSP, when tricuspid regurgitation is insufficient to reliably measure its peak velocity. In response to an increase in pulmonary artery systolic pressure, the pulmonary valve tends to close prematurely, and peak flow velocity is reached earlier in systole. Therefore, PAT decreases as pulmonary pressure increases. Pulmonary acceleration time correlates inversely and linearly with mean pulmonary artery pressure in humans and with RVSP in rats.

Pulmonary acceleration time may represent a useful index of pulmonary artery pressure in mice. A parasternal short-axis view of the heart at the level of the aortic valve can easily be obtained in mice, allowing for correct alignment with the pulmonary artery flow. This view provides precise pulsed-wave Doppler recording and measurement of RV systolic time intervals such as PAT and ET. Furthermore, the increased spatial resolution of recently developed high-frequency echocardiographic probes permits better visualization of the pulmonary valve and more precise sampling of the flow.

The objective of the present study was to investigate whether RVSP and thus pulmonary arterial systolic pressure could be estimated noninvasively in mice. Echocardiographic parameters of RVSP were compared with RVSP measured using a pressure catheter. Two models of pulmonary hypertension were studied: an acute model induced by infusion of the thromboxane agonist, U-46619, and a chronic model induced by lung-specific overexpression of a transgene encoding interleukin-6 (IL-6).

Methods

Hemodynamic Measurements
Mice were anesthetized with intraperitoneal ketamine (120 mg/kg) and fentanyl (200 µg/kg), intubated, and mechanically ventilated (115 breaths per minute, FiO2=1). A PE-10 polyethylene catheter was placed in the left carotid artery for continuous heart rate (HR) and systemic arterial pressure monitoring. Another polyethylene line was placed in the left jugular vein for infusion of U-46619. A micro manometer pressure catheter (Model FTS-1211B-0018, SciSense Instruments, London, Ontario, Canada) was placed in the right jugular vein and advanced into the right ventricle. The systemic arterial pressure, HR, and RVSP were recorded and analyzed using a data acquisition system (Chart, AD Instruments, Colorado Springs, Colo). RVSP and echocardiographic parameters were simultaneously acquired.

Echocardiography
Transthoracic closed-chest echocardiography was performed using a mechanical transducer centered on 30 MHz (Vevo 770, Visualsonics, Toronto, Ontario, Canada). Two-dimensional images of the pulmonary infundibulum were obtained from the parasternal short-axis view at the level of the aortic valve (Figure 1, upper panel) and pulsed-wave Doppler recording of the pulmonary blood flow was obtained (Figure 1, lower panel). The pulsed-wave Doppler sample was positioned at the tip of the pulmonary valve leaflets and aligned to maximize laminar flow. Sample volume was 0.027 mm³. Doppler tracings were recorded at a sweep speed of 400 mm/s. Measurements were performed offline (Vevo 770 workstation) by 2 different readers (H.T. and B.K. for the acute study, B.K. for the chronic study) blinded to the condition or genotype of the mice. The following variables were measured: systolic time-velocity integral of pulmonary flow (TVI, the area under the flow curve), PAT, and RV ET. All measurements were averaged on 5 cardiac cycles.

Experimental Protocols

Acute Model of Pulmonary Hypertension
Seven C57BL6 wild-type (WT) male mice (3 months old) were studied. RVSP and echocardiographic parameters were simultaneously acquired at baseline. U-46619 was then infused at a rate of
1.5 μmol/kg/min for 5 minutes. RVSP and an echocardiogram were obtained. The infusion was discontinued for 15 minutes, and after the RVSP returned to baseline, U-46619 was infused (3 μmol/kg/min for 5 minutes) for a second set of measurements.

To test whether echocardiography could detect the effect of a treatment lowering pulmonary artery pressure, RVSP and echocardiographic parameters were simultaneously acquired in 4 C57BL6 WT mice at baseline and after infusion of U-46619 (1.5 μmol/kg/min for 5 minutes). The infusion was continued for the entire experiment. After the RVSP had increased by 30%, 80 ppm of inhaled nitric oxide (NO) was added to the air breathed by the mouse. A set of echocardiographic and hemodynamic measurements was recorded 5 minutes after the start of inhaled NO.

**Chronic Model of Pulmonary Hypertension**

CC10–IL-6 transgenic mice (IL-6 Tg) were bred on a C57BL6 (Tg) background. In these mice, the Clara cell 10-kDa promoter (CC10) was used to constitutively drive lung-specific expression of IL-6. Nine mice with lung-specific overexpression of IL-6 (IL-6 Tg) and 5 C57BL6 WT mice were studied in a blinded manner. In 10 mice, echocardiography was first obtained using isoflurane (2% for induction followed by 0.5 to 0.7% for anesthesia). A second infusion of increasing doses of U-46619 progressively shifted the peak of the Doppler flow pattern toward early systole. The quality of the images allowed measurements of RV systolic time intervals in all cases. At baseline, the pulmonary systolic flow pattern was symmetric. In the second set of acute PAH model experiments, U-46619 increased RVSP by 43% (from 23 ± 1 to 33 ± 1 mm Hg) and systolic blood pressure by 71% compared with baseline. Inhaled NO did not affect blood pressure but decreased RVSP by 24% (to 25 ± 2 mm Hg).

**Results**

**Acute Model of Pulmonary Hypertension**

**Hemodynamic Effects of U-46619 Infusion and NO Inhalation**

In the first set of experiments, infusion of 1.5 and 3.0 μmol/kg/min U-46619 into C57BL6 mice markedly increased systolic blood pressure and RVSP (Table 1). U-46619 increased RVSP in a dose-dependent manner. U-46619 did not affect the HR.

**Figure 2.** Representative example of the pulsed-wave Doppler of pulmonary flow recorded in the same mouse at baseline (A), after infusion of 1.5 μmol/kg/min of U-46619 for 5 minutes (B), and after infusion of 3 μmol/kg/min of U-46619 for 5 minutes (C). RVSP measured simultaneously is displayed next to each pulsed-wave Doppler tracing.

**Table 1.** Hemodynamic and Pulmonary Pulsed-Wave Doppler Measurements Obtained at Baseline and During U-46619 Infusion in 7 Mice

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1.5 μmol/kg/min</th>
<th>3 μmol/kg/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodynamics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, bpm</td>
<td>392±1</td>
<td>415±25</td>
<td>410±18</td>
</tr>
<tr>
<td>SAP, mm Hg</td>
<td>79±5</td>
<td>141±15*</td>
<td>140±10*</td>
</tr>
<tr>
<td>RVSP, mm Hg</td>
<td>27±1</td>
<td>34±2*</td>
<td>46±3†</td>
</tr>
<tr>
<td>Pulmonary TVI, cm</td>
<td>1.6±0.1</td>
<td>1.1±0.2*</td>
<td>0.8±0.1†</td>
</tr>
<tr>
<td>PAT, ms</td>
<td>30±1</td>
<td>20±1*</td>
<td>14±1†</td>
</tr>
<tr>
<td>ET, ms</td>
<td>64±2</td>
<td>58±3*</td>
<td>50±3†</td>
</tr>
<tr>
<td>PAT/ET, %</td>
<td>46±2</td>
<td>35±2*</td>
<td>28±2†</td>
</tr>
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</table>

*P<0.01 versus baseline; †P<0.01 versus U-46619 (1.5 μmol/kg/min).
In the present study, C57BL6 WT mice had an RVSP of 28 mm Hg. Elevated RVSP was defined as RVSP above the mean ± 2 SD of the normal values (27 ± 5)\(^{19}\), yielding a threshold value for elevated RVSP of 32 mm Hg. The hemodynamic and echocardiographic characteristics of the mice with normal or elevated RVSP are shown in Table 2. All mice with an elevated RVSP were IL-6 Tg\(^+\) mice. There were no differences in HR, systolic arterial pressure, or pulmonary TVI between groups. Pulmonary acceleration time was shorter and PAT/ET was lower in the mice with elevated RVSP than in mice with RVSP within normal values (Table 2).

A cutoff value of 21 ms (value corresponding to an RVSP of 32 mm Hg) was chosen for the PAT. Using this cutoff, echocardiographic analysis had a sensitivity of 100% (7/7) and a specificity of 86% (6/7) in the detection of RVSP higher than 32 mm Hg. Similarly, using a cutoff value of 39% for the PAT/ET ratio, the sensitivity in the prediction of high RVSP was 100% (7/7) and specificity was 86% (6/7).

Table 2. Hemodynamic and Pulmonary Pulsed-Wave Doppler Flow Measurements Obtained in WT and IL-6 Tg\(^+\) Mice

<table>
<thead>
<tr>
<th>Hemodynamics</th>
<th>RVSP =&lt; 32 mm Hg (n=7)</th>
<th>RVSP &gt;32 mm Hg (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, bpm</td>
<td>462±20</td>
<td>433±21</td>
</tr>
<tr>
<td>Systolic arterial pressure, mm Hg</td>
<td>95±6</td>
<td>91±3</td>
</tr>
<tr>
<td>RVSP, mm Hg</td>
<td>28±1</td>
<td>42±2*</td>
</tr>
<tr>
<td>Pulmonary pulsed-wave Doppler</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary TVI, cm</td>
<td>2.3±0.2</td>
<td>2.2±0.2</td>
</tr>
<tr>
<td>PAT, ms</td>
<td>23±1</td>
<td>16±1*</td>
</tr>
<tr>
<td>ET, ms</td>
<td>53±1</td>
<td>56±2</td>
</tr>
<tr>
<td>PAT/ET, %</td>
<td>43±1</td>
<td>28±1*</td>
</tr>
</tbody>
</table>

\*P<0.01 versus normotensive mice.

PAT and PAT/ET Detect Mice With Elevated RVSP

In the present study, C57BL6 WT mice had an RVSP of 27±2.5 mm Hg. Elevated RVSP was defined as RVSP above the mean ±2 SD of the normal values (27±5), yielding a threshold value for elevated RVSP of 32 mm Hg. The hemodynamic and echocardiographic characteristics of the mice with normal or elevated RVSP are shown in Table 2. All mice with an elevated RVSP were IL-6 Tg\(^+\) mice. There were no differences in HR, systolic arterial pressure, or pulmonary TVI between groups. Pulmonary acceleration time was shorter and PAT/ET was lower in the mice with elevated RVSP than in mice with RVSP within normal values (Table 2).

A cutoff value of 21 ms (value corresponding to an RVSP of 32 mm Hg) was chosen for the PAT. Using this cutoff, echocardiographic analysis had a sensitivity of 100% (7/7) and a specificity of 86% (6/7) in the detection of RVSP higher than 32 mm Hg. Similarly, using a cutoff value of 39% for the PAT/ET ratio, the sensitivity in the prediction of high RVSP was 100% (7/7) and specificity was 86% (6/7).

RVSP Can Be Measured With Echocardiography Using Light Anesthesia

Pulmonary acceleration time measured during light (isoflurane) anesthesia correlated with PAT measured during deep anesthesia (ketamine and fentanyl used for RV catheterization) in IL-6 Tg\(^+\) and WT mice (\(r^2=0.85, P<0.0001\)) (Figure 4A). Similarly, PAT/ET measured during light anesthesia correlated closely with the PAT/ET obtained during deep anesthesia (\(r^2=0.87, P<0.0001\)) (Figure 4B). All mice that were defined as having high RVSP using PAT or PAT/ET during deep anesthesia had also high RVSP during isoflurane anesthesia (7/7).
shortened PAT.13 Of note, the PAT/ET ratio in mice was accelerated rapidly to a peak in early systole, resulting in a velocity pattern. In mice with high RVSP, the flow velocity conditions. Normotensive mice displayed a "dome-like" flow pattern similar to those reported in humans12 in both high and normal RVSP. Invasive and noninvasive measurements of RVSP both invasively and noninvasively in mice with established chronic pulmonary hypertension (lung-specific IL-6–overexpressing transgenic mice).4 The chronic mice models of PAH may also be more relevant to the human PAH condition than the acute and major increases in pulmonary pressure obtained with pharmacological interventions. The IL-6 Tg mice have pulmonary TVI similar to WT mice, demonstrating that mice of both genotypes have similar cardiac output. The correlation of invasively determined RVSP and echocardiographic parameters is close in IL-6 Tg and WT mice, suggesting that mice of both genotypes have similar cardiac output. The correlation of invasively determined RVSP and echocardiographic parameters is close in IL-6 Tg and WT mice, suggesting that mice of both genotypes have similar cardiac output. The correlation of invasively determined RVSP and echocardiographic parameters is close in IL-6 Tg and WT mice, suggesting that mice of both genotypes have similar cardiac output. The correlation of invasively determined RVSP and echocardiographic parameters is close in IL-6 Tg and WT mice, suggesting that mice of both genotypes have similar cardiac output. The correlation of invasively determined RVSP and echocardiographic parameters is close in IL-6 Tg and WT mice, suggesting that mice of both genotypes have similar cardiac output.

In both acute and chronic models of PAH, RVSP measured invasively and pulmonary flow velocity were recorded simultaneously, enabling the comparison of the echocardiographic parameters with the pressure measurement “gold standard.” Echocardiography allowed the noninvasive detection of acute changes in pulmonary artery pressure induced by pharmacological interventions within the same mouse. Both PAT and PAT/ET shortened with increasing doses of U-46619 and increasing RVSP. One characteristic of U-46619 is that it may decrease cardiac output.22 The decrease in cardiac output was reflected in our acute model of PAH by the decrease in TVI. Pulmonary flow equal to the product of pulmonary flow TVI and pulmonary artery area. Because pulmonary area does not change when pulmonary arterial pressure is acutely increased,22 the decrease in TVI suggests the occurrence of a decrease in pulmonary flow and therefore of stroke volume. Such a decrease in stroke volume may by itself decrease PAT.13 To eliminate the potential effects of a decrease in stroke volume in our model, we measured RVSP both invasively and noninvasively in mice with established chronic pulmonary hypertension (lung-specific IL-6–overexpressing transgenic mice).4 The chronic mice models of PAH may also be more relevant to the human PAH condition than the acute and major increases in pulmonary pressure obtained with pharmacological interventions. The IL-6 Tg mice have pulmonary TVI similar to WT mice, suggesting that mice of both genotypes have similar cardiac output. The correlation of invasively determined RVSP and echocardiographic parameters is close in IL-6 Tg and WT mice, demonstrating that a change in cardiac output is not responsible for the decreased PAT and PAT/ET observed in mice with high RVSPs.

In the chronic PAH model, RVSP correlated closely with PAT and PAT/ET. The strength of the correlation obtained in mice between PAT or PAT/ET with RVSP is close to that described in humans. In humans, PAT correlates with HR,23 necessitating a normalization of PAT by ET. In the present study, the range of HR was between 330 and 520 bpm. No correlation of PAT with HR was noted in that range. The ratio of PAT/ET, however, may be useful to compare mice with different cardiac outputs, because both PAT21 and ET24 decrease with a decrease in cardiac output.

### Table 3. Intraobserver and Interobserver Variability of Pulsed-Wave Doppler Measurements

<table>
<thead>
<tr>
<th></th>
<th>Mean Error±SD</th>
<th>Mean Error±SD, %</th>
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</thead>
<tbody>
<tr>
<td>Intraobserver</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAT, ms</td>
<td>0.4±1.2</td>
<td>1.3±3.9</td>
</tr>
<tr>
<td>ET, ms</td>
<td>0.1±1.1</td>
<td>0.3±1.8</td>
</tr>
<tr>
<td>PAT/ET</td>
<td>0.01±0.02</td>
<td>1.0±3.3</td>
</tr>
<tr>
<td>Pulmonary TVI, cm</td>
<td>0.00±0.02</td>
<td>-0.3±1.5</td>
</tr>
<tr>
<td>Interobserver</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAT, ms</td>
<td>2.0±1.8</td>
<td>6.7±6.0</td>
</tr>
<tr>
<td>ET, ms</td>
<td>1.2±1.3</td>
<td>1.8±2.0</td>
</tr>
<tr>
<td>PAT/ET</td>
<td>0.02±0.03</td>
<td>4.9±5.6</td>
</tr>
<tr>
<td>Pulmonary TVI, cm</td>
<td>0.01±0.06</td>
<td>0.5±4.1</td>
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**Discussion**

This study demonstrates that noninvasive assessment of pulmonary artery systolic pressure is feasible in mice. Both the PAT and the ratio of PAT to the ejection time measured using high-frequency echocardiography correlated closely with invasively measured RVSP. Pulmonary acceleration time and PAT/ET were able to detect acute and chronic increases in RVSP with high sensitivity and specificity as well as to assess the effects of treatment on RVSP.

The pulmonary flow velocity patterns in mice were similar to those reported in humans12 in both high and normal RVSP conditions. Normotensive mice displayed a "dome-like" flow velocity pattern. In mice with high RVSP, the flow velocity accelerated rapidly to a peak in early systole, resulting in a shortened PAT.13 Of note, the PAT/ET ratio in mice was close to that seen in normal humans as well as in patients with PAH. In humans without PAH, the ratio is 46±3% (43±1% in control mice). In patients with a mean pulmonary artery pressure >40 mm Hg, the PAT/ET ratio is 26±2%; this value is close to the ratio found in mice with high RVSP (28±2% when the RVSP is 46±3 mm Hg).11,20,21
Although the assessment of pulmonary arterial systolic pressure is widely used to monitor PAH, echocardiography may also provide additional information by noninvasively estimating PVR. A novel noninvasive echocardiographic index that correlates closely with invasively measured PVR has been recently described in humans.25 This index is obtained by measuring RVSP using the maximum velocity of tricuspid regurgitation and dividing the RVSP by the cardiac output estimated by the pulmonary TVI. In mice, pulmonary TVI also correlates closely with invasively measured cardiac output,9 potentially allowing the use of the echocardiographic PVR index in mice.

Anesthesia in mice can change the hemodynamic state and cardiac function.26 It is therefore important to use light anesthesia rather than deep anesthesia for cardiac evaluation. Echocardiographic assessment of RVSP obtained under deep anesthesia was reproduced in more physiological conditions using light anesthesia. Specifically, both PAT and PAT/ET measured using light anesthesia correlated closely with the same parameters measured using deep anesthesia, suggesting that echocardiographic parameters may be used to assess pulmonary artery systolic pressure under light anesthesia.

Both intraobserver and interobserver variabilities were below 6% for both the PAT and the PAT/ET. These variabilities compare favorably to the variabilities observed using invasive RVSP measurements in humans.27 In conclusion, RVSP can be estimated noninvasively in mice. Transthoracic echocardiography can monitor acute and chronic changes in RVSP. This noninvasive technique may permit the characterization of the evolution of PAH in genetically modified mice.

Acknowledgments
We thank Paul B. Yu, MD, for sharing his experience on genetically modified mice with us.

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Disclosures
None.

References


CLINICAL PERSPECTIVE

Despite the development of new therapeutic strategies such as endothelin-receptor antagonists, phosphodiesterase type-5 inhibitors, and prostanoid, the prognosis of patients with pulmonary arterial hypertension (PAH) remains poor. Advances in understanding the pathophysiological mechanisms that contribute to PAH are critical to the discovery of new therapeutic targets. In this setting, small rodent models, in particular genetically modified mice, offer the unique opportunity to study the signaling pathways involved in PAH and to evaluate the effectiveness of therapeutic interventions. Indeed, the ability to study pulmonary artery pressure or right ventricular systolic pressure (RVSP) in mice underexpressing or overexpressing a gene will help to elucidate the functional role of this particular gene in the regulation of pulmonary pressure. In mice, right heart catheterization is the only available method to measure RVSP and is a terminal procedure. The absence of a noninvasive technique that would allow serial assessment of RVSP in mice has significantly undermined progress in the field of PAH, preventing the rapid evaluation and development of mouse PAH models. In the present study, pulmonary artery flow measurements obtained using transthoracic echocardiography detect acute and chronic increases in RVSP with high sensitivity and specificity and identify the effect of treatment on RVSP. Transthoracic echocardiography may allow the characterization of the evolution of PAH and the evaluation of therapeutic interventions noninvasively in mice.
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