Effects of Heart Rate and Pulmonary Artery Pressure on Doppler Pulmonary Artery Acceleration Time in Experimental Acute Pulmonary Hypertension*

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Chronic pulmonary hypertension in humans is characterized by shortening of the pulmonary artery acceleration time as measured by Doppler echocardiography, such that the higher the pulmonary artery pressure, the shorter the pulmonary acceleration time. Increases in heart rate are also known to produce decreases in the pulmonary artery acceleration time. To explore the relationship between mean pulmonary artery pressure, heart rate, and Doppler pulmonary artery acceleration time, experimental acute pulmonary hypertension was created in nine Duroc swine, either by infusion of Sephadex beads with embolization of the pulmonary arterial circulation or by partially occluding the main pulmonary artery 8 to 10 cm distal to the pulmonic valve. Pulmonary artery Doppler flow velocity recordings and invasive pressure measurements were made at baseline and at paced atrial rates ranging from 60 to 160 beats per minute, in 20-beat increments. The results in this acute animal model reveal that increases in heart rate produced significant decreases in Doppler pulmonary artery acceleration time at mean pressures below 25 mm Hg. However, with mean pulmonary artery pressures greater than 25 mm Hg, both heart rate and increases in pulmonary artery pressure had no significant effect on acceleration time.

\[ AT = \text{acceleration time}; \ ET = \text{ejection time}; \ PFV = \text{peak flow velocity} \]

Doppler echocardiography provides a noninvasive real-time method for evaluating blood flow characteristics in patients. For example, a characteristic shortening of the pulsed Doppler pulmonary acceleration time has been observed in patients with chronic pulmonary hypertension. However, increased heart rate is also known to shorten pulmonary artery acceleration time. The relative contributions of heart rate and pulmonary pressure to pulmonary artery acceleration time abbreviation are not fully understood. To explore the relationship between heart rate, pulmonary artery pressure, and pulmonary acceleration time in a circulatory system similar to human, we created a model of experimental pulmonary hypertension in swine.

**METHODS**

Nine Duroc 50- to 90-kg swine were anesthetized with intramuscular ketamine (25 mg/kg), endotracheally intubated, and maintained anesthetized on a ventilator using 0.5 to 2.0 percent halothane. Surgical cutdowns were performed on the right and left carotid arteries and veins. A 7.5-French (Fr) Gold balloon-tipped flow-directed pulmonary artery thermocatheter was advanced under fluoroscopic guidance into the right pulmonary artery. An arterial pressure line was established in the right carotid artery and a 5-Fr pigtail catheter was placed in the left ventricle via the left carotid artery. A 6-Fr bipolar pacing wire was advanced into the right atrium under fluoroscopic guidance and placed such that its pacing threshold was less than 1.5 mA. Conventional fluid-filled catheter systems were used for pressure recording with a multichannel physiologic recorder (Honeywell Electronics for Medicine VR-6).

Echocardiography was performed using an ultrasound unit (Honeywell) equipped with 2.5- and 3.5-MHz transducers. Pulsed Doppler flow velocity recordings were performed using the two-dimensional parasternal short-axis view imaging plane for placement of a 5- to 10-mm sample volume (in axial extent) in the main pulmonary artery. The transducer was angled in order to record beats with the highest peak flow velocity; acceleration time and ejection time were measured as previously described by averaging five cardiac cycles from hard copy\(^2\) (Fig 1). High-quality pulmonary artery pulsed Doppler tracings were measured. Peak flow velocity (PFV), corresponding to the peak modal velocity, was measured as the velocity in the middle of the darkest portion of the velocity envelope at the peak of the curve. Acceleration time (AT) was measured from the time of onset of the pulmonary flow to the time of the peak of the velocity envelope (Fig 1).

The experimental protocol consisted of obtaining a baseline two-dimensional echocardiogram and pulmonary artery Doppler flow velocity recording at atrial pacing rates of 60, 80, 100, 120, 140, and 160 beats per minute. Then 100 to 300-μm Sephadex beads (Sigma Chemical) were injected into the jugular vein in 1-g aliquots as a slurry with 10 to 20 ml of physiologic saline solution.\(^4\) After each injection of beads, the pulmonary artery pressure was allowed to stabilize for two minutes, and the echocardiogram and pulmonary Doppler studies were repeated at the same spectrum of heart rates. At each heart rate, the following hemodynamic determinations were made: systemic arterial pressure, right atrial pressure, pulmonary arterial pressure, pulmonary capillary wedge pressure, left ventricular pressure, and cardiac outputs by thermodilution. Bead injections were repeated during the course of the experiment resulting in incremental rises in pulmonary arterial pressure. If systemic hypotension occurred, intravenous saline solution was given to maintain the pulmonary capillary wedge pressure in the normal range (>5 mm Hg). Data collected from moribund swine (mean systemic arterial pressure <30 mm Hg) were not included in the analysis.

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It was noted that the first injection of beads sometimes resulted in a precipitous fall in systemic blood pressure and death. In fact, two swine who died during the initial bead injection were not included in this data analysis. For this reason, a second method for producing pulmonary hypertension was developed. A midline thoracotomy was performed in two other swine; the pericardium was opened and the pulmonary artery was exposed, and a vascular clamp was placed partially across the distal main pulmonary artery just before its bifurcation. The relative extent of pulmonary artery cross-clamping was adjusted to provide a desired degree of pulmonary hypertension as measured by the pulmonary catheter, which was positioned proximal to the clamp. The distance from the pulmonic valve to the clamp on the distal main pulmonary artery was about 10 cm, providing a reasonably large vascular space to sample using the Doppler. An additional 13 pigs who had undergone atrial pacing at the same heart rates, but not given beads or pulmonary clamping, were used as controls. The data from these pigs are shown in the first column in Table 1 (mean pulmonary artery pressure = 5 to 14 mm Hg).

Statistical Analysis

The mean pulmonary acceleration times were compared at each heart rate and pulmonary pressure category by one-way and two-way analyses of variance. Statistical significance was set at an alpha level less than 0.05. This analysis assumed all measurements were independent. Furthermore, no other covariates were considered.

RESULTS

The mean pulmonary pressure for anesthetized swine in sinus rhythm was 14 ± 4 mm Hg (see Table 1). The mean pulmonary artery pressure was easily varied by either bead injection or pulmonary clamping up to 45 mm Hg. Incremental injections of beads were performed at 30-minute intervals. This interval was chosen as it took about 30 minutes for the collection of data for all heart rates from 50 to 160 beats per minute at each pulmonary artery pressure. Attempts to raise mean pulmonary artery pressure above 45 mm Hg resulted in profound (and fatal) systemic hypotension with low left ventricular filling pressures resistant to fluid challenges. Pulmonary arterial mean pressures above 40 mm Hg and atrial pacing rates above 120 beats per minute could not be simultaneously achieved because of severe hypotension.

Sinus rates faster than, and, therefore, usurping the atrial pacing rates, were seen only at pacing rates below 80 beats per minute. Because of mild acceleration of the heart rate resulting from the induced pulmonary artery hypertension, data collection at mean pulmonary artery pressures greater than 25 mm Hg was not possible at heart rates below 80 beats per minute. A comparison of the two pigs undergoing pulmonary artery clamping with the seven pigs receiving intravenous beads showed no differences in pulmonary artery acceleration time, cardiac output, or systemic arterial pressure at similar pulmonary artery pressures (p = not significant).

The results of the effects of heart rate and mean pulmonary artery pressure on pulmonary artery acceleration time are shown in Table 1. The acceleration time shortened dramatically with both increased heart rate and pulmonary hypertension. The effect of heart rate on pulmonary artery acceleration time was seen at mean pulmonary artery pressures below 25 mm Hg. Above mean pulmonary artery pressures of 35 mm Hg, increasing heart rate had no further significant effect on pulmonary artery acceleration time. At a given heart rate, increases in mean pulmonary artery pressure shortened pulmonary artery acceleration time, but this effect was less prominent at higher heart rates. Once a mean pulmonary artery pressure >25 mm Hg was achieved, no additional shortening of the pulmonary artery acceleration time was seen.

Table 1—Doppler Pulmonary Artery Acceleration Time (in ms) in Acute Experimental Pulmonary Hypertension as a Function of Heart Rate and Mean Pulmonary Artery Pressure

<table>
<thead>
<tr>
<th>Heart Rate, bpm</th>
<th>Mean (±SD) Pulmonary Artery Pressure, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-14</td>
<td>15-24</td>
</tr>
<tr>
<td>60</td>
<td>146 ± 20</td>
</tr>
<tr>
<td>80</td>
<td>125 ± 16</td>
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<tr>
<td>100</td>
<td>122 ± 20</td>
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<tr>
<td>120</td>
<td>119 ± 19</td>
</tr>
<tr>
<td>140</td>
<td>88 ± 24</td>
</tr>
<tr>
<td>160</td>
<td>83 ± 13</td>
</tr>
</tbody>
</table>

*bp = beats per minute; SD = standard deviation.
regardless of how rapid the heart rate or how high the pulmonary artery pressure.

A one-way analysis of variance comparing pulmonary artery acceleration times at mean pulmonary pressures of 10 mm Hg across heart rate categories showed mean pulmonary acceleration time values to differ significantly (p<0.001). Similar comparisons across heart rate categories at mean pulmonary pressures of 20, 30, and 40 mm Hg showed no significant differences in mean pulmonary acceleration time. Two-way analysis of variance comparing pulmonary acceleration times simultaneously across pressure and heart rate categories showed significant overall differences across these factors. The acceleration time was shorter for higher pressures and longer for lower heart rates. The regression analyses assumed linear trends across categories of heart rate. At a pressure of 10 mm Hg, there was a strong inverse association (p<0.001) between acceleration time and heart rate, which was not demonstrated at higher increments of pressure.

**Discussion**

We have developed a model of acute pulmonary hypertension in swine. Bead-induced pulmonary hypertension does not appear to be reversible. Pulmonary clamping produces reproducible elevations in mean pulmonary artery pressure, with the potential benefit of reversibility of the induced obstruction to pulmonary artery blood flow. Pulmonary artery pressure may be returned toward normal if unacceptable systemic hypotension occurs by removing the clamp. An additional characteristic of the pulmonary artery clamping technique is that the ultrasound recordings are excellent since echocardiographic and Doppler recordings are from the surface of the heart. On the other hand, bead-induced pulmonary hypertension allows more physiologic closed-chest echocardiogram and Doppler recording. This latter distinction may be of only theoretic interest in an acute mode since we found no difference between the Doppler data at given heart rates and pulmonary artery pressure for the two techniques.

In this model, pulmonary artery acceleration time shortened with increasing heart rate at normal and mildly elevated pulmonary artery pressures. However, when significant pulmonary hypertension was induced acutely, the effect of heart rate on pulmonary artery acceleration time was not apparent. At any given heart rate, pulmonary artery acceleration time shortened as pulmonary artery pressure was increased up to a mean of 25 mm Hg; further increases in...
pulmonary artery pressure had no additional effect on pulmonary artery acceleration time. In this model, decreases in pulmonary artery acceleration time appear to reflect fundamental immediate changes in right ventricular mechanics and peripheral vascular properties as the ventricle responds to a pressure load. These changes are limited in their extent, as evidenced by the limitation in acceleration time shortening.

Changes in the Doppler pulmonary artery flow velocity pattern in later systole, or in diastole, were not specifically examined in this study. Frantz and coworkers\(^5\) used an intraluminal 20-MHz Doppler crystal to study blood flow velocity in the pulmonary artery of dogs in whom acute pulmonary hypertension was induced by hypoxia. These workers reported trends toward increased diastolic negative velocities, primarily in the posterior pulmonary artery, in pulmonary hypertension, compared with control dogs.\(^5\)

It is of interest that shortening of the pulmonary artery acceleration time in the setting of pulmonary hypertension is not dependent on hypertrophy of the right ventricle. Pulmonary artery acceleration time abbreviation was observed within seconds of elevation of the pulmonary artery pressure, too quickly for subacute or chronic compensatory mechanisms to develop.

It should be noted that the present study involves acute pulmonary hypertension and does not apply directly to chronic clinical pulmonary hypertension. Previously reported animal models of chronic pulmonary hypertension have included ligation of a single pulmonary artery in pigs\(^6\) and Sephadex bead embolization of the pulmonary arterial system in the dog.\(^4\) Furthermore, because this study evaluated Doppler and hemodynamic changes in swine, the results may not be applied directly to acute pulmonary hypertension in humans. Various types of acute pulmonary hypertension in patients lack the abrupt acuity of onset produced in this model. Important variables that require further study include the time course of changes in hemodynamic variables after bead injection or pulmonary artery clamping, and the effect of an open vs a closed chest model on Doppler measurements.

We conclude that increases in a swine model of acute pulmonary hypertension in both heart rate and mean pulmonary artery pressure shorten pulmonary artery acceleration time at lower mean pulmonary artery pressures, but have little additional effect on pulmonary artery acceleration time at higher mean pulmonary artery pressures.

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REFERENCES