Right ventricular adaptation to pulmonary hypertension: an interspecies comparison

Pierre Wauthy, Alberto Pagnamenta, Fabio Vassalli, Robert Naeije, and Serge Brimioulle. Right ventricular adaptation to pulmonary hypertension: an interspecies comparison. Am J Physiol Heart Circ Physiol 286: H1441–H1447, 2004. First published December 18, 2003; 10.1152/ajpheart.00640.2003.—Right ventricular (RV) adaptation is an important prognostic factor in acute and chronic pulmonary hypertension. Pulmonary vascular basal tone and hypoxic reactivity are known to vary widely between species. We investigated how RV adaptation to acute pulmonary hypertension is preserved in species with low, intermediate, and high pulmonary vascular resistance and reactivity. Acute pulmonary hypertension was induced by hypoxia, distal embolism, and proximal constriction in anesthetized dogs (n = 10), goats (n = 8), and pigs (n = 8). Pulmonary vessels were assessed by flow-pressure curves and by impedance to quantify distal resistance, proximal elastance, and wave reflections. RV function was assessed by pressure-volume curves to quantify afterload, contractility, and ventricular-arterial coupling efficiency. First, hypoxia was associated with a progressive increase of resistance, elastance, and wave reflection from dogs to goats and from goats to pigs. RV contractility increased proportionally to RV afterload, and optimal coupling was preserved in all species. Second, embolism increased resistance and wave reflection but not elastance. The increase in RV contractility matched the increase in RV afterload and optimal coupling was preserved. Finally, proximal pulmonary artery constriction increased resistance, increased and accelerated wave reflection, and markedly increased elastance. RV contractility increased markedly and coupling showed a nonsignificant trend to decrease. We conclude that optimal or near-optimal ventricular-arterial coupling is maintained in acute pulmonary hypertension, whether in absence or presence of chronic species-induced pulmonary hypertension.

Sagawa and co-workers (17, 32) previously developed a concept of ventricular-arterial coupling based on left ventricular pressure-volume curves. In that approach, ventricular and arterial mechanical properties are quantified by ventricular end-systolic elastance (Ees) and arterial effective elastance (Ea). The resulting Ees-to-Ea ratio (Ees/Ea) yields a direct assessment of ventricular-arterial coupling efficiency, in isolated hearts and in intact animals or humans (2, 6). Ees/Ea values around 2 are associated with maximal efficiency, i.e., the highest ratio between hydraulic work production and myocardial oxygen consumption. Decreasing values indicate a progressive reduction in efficiency, and values below 1 indicate an increasing inability to maintain flow (2, 6). Whether the Ees/Ea ratio can be used to assess the RV adaptation to pulmonary hypertension remains incompletely documented. In theory, the concept of ventricular-arterial coupling is valid in the RV (9, 23), but its application has been restricted by methodological limitations in measuring instantaneous RV volumes (16).

We recently reported a method to assess RV contractility and RV pulmonary arterial coupling without measuring RV volumes and without modifying preload or afterload (5). To investigate the ability of the RV to adapt to acute and chronic pulmonary hypertension, we undertook in the present study 1) to compare ventricular-arterial coupling in three species with naturally low, intermediate, and high pulmonary vascular resistance and elastance, i.e., dogs, goats, and pigs, 2) to investigate how ventricular-arterial coupling is affected by hypoxic pulmonary vasoconstriction (HPV) in those species with different HPV magnitude, and 3) to assess how ventricular-arterial coupling is affected by pulmonary hypertension induced by distal pulmonary embolization and by proximal pulmonary artery constriction in dogs and in goats. Pulmonary hemodynamics were characterized by flow-pressure relationships and by pulmonary vascular impedance (4). RV contractility and ventricular-arterial coupling were assessed by single-beat analysis of pressure-volume loops (5).

METHODS

All experiments were conducted in accordance with the Guide for the Care and Use of Laboratory Animals and after approval by the Committee on the Care and Use of Animals in Research of the Brussels Free University School of Medicine. Experiments on pigs could not be performed as planned due to changes in regulations. To maintain the initial scope of the study, we included in the present study some data obtained from pigs used as controls in a previous study (36). Data from pigs therefore are available in the baseline and hypoxic states but not during pulmonary arterial constriction or pulmonary embolism.
Preparation. The study included 10 dogs (mean 24 kg), 8 goats (mean 24 kg), and 8 pigs (mean 21 kg). In dogs and pigs, anesthesia was induced with 10 mg/kg iv propofol and maintained by 10 μg/kg iv and 2–3 μg·kg⁻¹·h⁻¹ sufentanil and 100 mg/kg iv and 50 mg·kg⁻¹·h⁻¹ α-chloralose. In goats, because of a poor cardiac tolerance to chloralose during thoracotomy, 10 mg·kg⁻¹·h⁻¹ propofol was infused until the end of surgery and then replaced with α-chloralose. Details of our preparation were published (4, 5). Ventilation was initiated with a rate of 10/min, a tidal volume of 15–20 ml/kg, and a positive end-expiratory pressure of 5 cmH₂O. Tidal volume and inspired oxygen fraction were adjusted to maintain arterial P CO₂ at 35–40 mmHg and to ensure an arterial P O₂ (PaO₂) ~180 mmHg at baseline. Ringer lactate was infused to maintain a left atrial pressure (PLa) of 8–10 mmHg. A thermistor-tipped catheter (model 93A-131-7F, Edwards, Santa Ana, CA) was inserted into the pulmonary artery to measure temperature and thermodilution cardiac output. A balloon catheter (Percor catheter,Datascope,Paramus,NJ) was placed in the inferior vena cava to cause a titratable reduction of cardiac output by reducing venous return. Temperature was maintained at 36–38°C with an electric heating pad.

Thoracotomy. Thoracotomy was performed in the fourth left intercostal space, with additional sufentanil (2 μg/kg iv boluses) if needed to prevent any increase in heart rate or systemic pressure. A nonconstricting 16- or 20-mm ultrasonic flow probe (Transonic,Ithaca,NY) was introduced through a right ventricular purse string, one into the RV and the other one into the main pulmonary artery with the tip just distal to the flow probe. Lung atelectasis was reversed by several double tidal volume insufflations and a transient increase of positive end-expiratory pressure to 10 cm water. The chest was tightly closed and pleural air was evacuated. Thrombus formation along catheters was prevented by 100 U/kg iv heparin at the end of the surgical procedure. At least 30-min stabilizations were allowed before measurements.

Measurements. Fluid-filled catheter-derived pressures were zero referenced at midchest level and processed using disposable transducers (Baxter-Bentley,Uden,the Netherlands) and a Sirecust 404 monitoring system (Siemens,Erlangen,Germany). Micromanometer-derived pressures were processed using TCB-500 units (Millar), and flow was measured using a T-206 unit (Transonic) with the 100-Hz low-pass filter setting. Pressures and flow signals were recorded continuously (model 2400S,Gould,Cleveland,OH). Cardiac output was measured by thermodilution (REF-1 computer,Edwards,Irvine,CA), using the mean of three determinations.

Data analysis. All pressures and flow signals were digitized at 200 Hz and stored in a personal computer for off-line analysis. Flow-pressure relationships were obtained from five beats sampled throughout a short flow-reduction maneuver (4). Pressure and flow values were submitted to linear correlation analysis to generate individual regression lines (4). Pulmonary vascular impedance was calculated from the Fourier series expressions of pressure and flow waves (4). From impedance, spectra were derived from the 0-Hz impedance modulus or total resistance (Z₀), and the characteristic impedance (Zc) was computed as the average of moduli between 2 and 15 Hz (4). The pressure wave was separated into forward and backward components, and wave reflection was quantified as the amplitude of the reflected pressure wave (Ampl) (14, 21, 37). Figure 2 summarizes how RV-arterial coupling was analyzed from RV pressure-volume curves using a single-beat method (5). RV contractility was estimated as the slope of the end-systolic pressure-volume relationship (Eₚₛ), and the pulmonary arterial effective elastance (Eₐ) was estimated as the slope of the end-diastolic to end-systolic relationship (5). Ventricular-arterial coupling efficiency was assessed as the Eₚₛ/Eₐ ratio (5, 6).

Protocol. In each set, flow and pressure signals were collected at steady state for impedance and ventricular-arterial coupling analysis (5, 6) and during a transient preload reduction maneuver for flow-pressure curve determination (4). Data sets were first obtained at baseline and after 10-min hypoxia (inspired oxygen reduction for PaO₂ of ~40 mmHg). After return to hyperoxia and 30-min stabilization, in dogs and goats, data sets were again collected at baseline and at two levels of proximal pulmonary artery constriction. After complete release of the constriction and 30-min stabilization, in dogs and goats, data sets were finally collected at baseline and at two levels of pulmonary embolization by 0.5-mm glass beads.

Statistics. Results are expressed as means ± SE. Data were submitted to an analysis of variance with one or two factors (dogs vs. goats vs. pigs, baseline vs. intervention). Post hoc comparisons were submitted to the Sidak-Holm procedure. Effects of constriction and embolism (baseline vs. level 1 vs. level 2) were assessed by trend analysis. P values below 0.05 were accepted as indicating statistical significance.
Baseline. Flow-pressure relationships showed a progressive shift to higher pressures from dogs to goats and to pigs (Fig. 3). At similar flow, dogs showed lower $P_{PA}$ and $P_{PA-PLA}$, goats intermediate values, and pigs higher $P_{PA}$ and $P_{PA-PLA}$ (Table 1). $Z_c$ and Ampl were comparable in the three species. $E_a$ increased progressively from 0.8 mmHg/ml in dogs to 1.5 mmHg/ml in goats and to 2.4 mmHg/ml in pigs. $E_{es}$ also increased from 1.3 mmHg/ml in dogs to 2.0 mmHg/ml in goats and to 2.8 mmHg/ml in pigs. $E_a$ markedly increased from 1.2 mmHg/ml in dogs to 1.7 mmHg/ml in goats and 1.5 mmHg/ml in pigs. $E_{es}$ also markedly increased from 1.3 mmHg/ml in dogs to 2.0 mmHg/ml in goats and to 2.4 mmHg/ml in pigs. As a result, $E_{es}/E_a$ was close to 2 (1.7 to 1.8) and quite similar in the three species (Fig. 4).

**Hypoxia.** Flow-pressure relationships showed a shift to higher pressures, which increased from dogs and goats to pigs (Fig. 3). At similar flow, hypoxia increased $P_{PA}$ and $P_{PA-PLA}$ in goats more than in dogs and in pigs more than in goats (Table 1). $Z_c$ and Ampl also increased from dogs to pigs. $E_a$ markedly increased from 1.2 mmHg/ml in dogs to 1.7 mmHg/ml in goats and to 2.8 mmHg/ml in pigs. $E_{es}$ also markedly increased from 1.5 mmHg/ml in dogs to 2.4 mmHg/ml in goats and to 5.4 mmHg/ml in pigs. $E_{es}/E_a$ remained close to 2 (1.7 to 1.9) in the three species (Fig. 4).

![Fig. 3. PA flow-pressure relationships in dogs (circles), goats (triangles), and pigs (squares) at baseline (filled symbols) and in hypoxia (open symbols). Values are means ± SE (n = 10 dogs, 8 goats, and 8 pigs). Basal tone and hypoxic response are lower in dogs, intermediate in goats, and higher in pigs.](image)

![Fig. 4. RV afterload ($E_a$; A), RV contractility ($E_{es}$; B), and RV-arterial coupling efficiency ($E_{es}/E_a$ ratio; C) in dogs (D), goats (G), and pigs (P) at baseline and during hypoxia. At baseline, afterload increases from dogs to pigs, contractility increases proportionally, and coupling is optimal in all species. In hypoxia, afterload is higher but contractility is also higher, and coupling remains optimal in all species. *P < 0.05, pigs vs. goats vs. dogs (factor analysis).](image)

**Table 1. Pulmonary vascular impedance and ventricular-arterial coupling in dogs, goats, and pigs**

<table>
<thead>
<tr>
<th>Flow, l/min⁻¹·m⁻²</th>
<th>Dogs</th>
<th>Goats</th>
<th>Pigs</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>HR, beats/min</td>
<td>106 ± 9</td>
<td>112 ± 5</td>
<td>115 ± 8</td>
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</tr>
<tr>
<td>$P_{PA}$, mmHg</td>
<td>19 ± 1</td>
<td>23 ± 1</td>
<td>25 ± 1</td>
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<tr>
<td>$P_{PA}$, mmHg</td>
<td>8 ± 1</td>
<td>8 ± 1</td>
<td>6 ± 1</td>
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<tr>
<td>$P_{PA}$, mmHg</td>
<td>9 ± 1</td>
<td>10 ± 1</td>
<td>7 ± 1</td>
<td></td>
</tr>
<tr>
<td>$P_{PA-PLA}$, mmHg</td>
<td>10 ± 1</td>
<td>13 ± 1</td>
<td>18 ± 1</td>
<td>*</td>
</tr>
<tr>
<td>$Z_c$, dyn·s·cm⁻⁵</td>
<td>343 ± 35</td>
<td>515 ± 63</td>
<td>558 ± 47</td>
<td>*</td>
</tr>
<tr>
<td>$Z_c$, dyn·s·cm⁻⁵</td>
<td>115 ± 18</td>
<td>116 ± 24</td>
<td>104 ± 16</td>
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<tr>
<td>Ampl, mmHg</td>
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<td>3.2 ± 0.5</td>
<td>5.0 ± 0.5</td>
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</tr>
<tr>
<td>$E_a$, mmHg/ml</td>
<td>0.8 ± 0.1</td>
<td>1.3 ± 0.1</td>
<td>1.5 ± 0.2</td>
<td>*</td>
</tr>
<tr>
<td>$E_{es}$, mmHg/ml</td>
<td>1.3 ± 0.2</td>
<td>2.0 ± 0.4</td>
<td>2.4 ± 0.2</td>
<td>*</td>
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<tr>
<td>$E_{es}/E_a$</td>
<td>1.8 ± 0.2</td>
<td>1.7 ± 0.3</td>
<td>1.7 ± 0.2</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 10 dogs, 8 goats, and 8 pigs. HR, heart rate; $P_{PA}$, pulmonary arterial pressure; $P_{RA}$, right atrial pressure; $P_{LA}$, left atrial pressure; $Z_c$, characteristic impedance; Ampl, amplitude of reflected pressure wave; $E_a$, arterial effective elastance; $E_{es}$, end-systolic elastance. *P < 0.05, pigs vs. goats vs. dogs (factor analysis).

**Embolism and constriction in dogs.** Effects of embolism and of proximal constriction in dogs are shown in Table 2. Neither embolism nor constriction did decrease flow. Embolism markedly increased $P_{PA}$ and $P_{PA-PLA}$, increased Ampl, but did not affect $Z_c$. $E_a$ and $E_{es}$ markedly increased to 2.4 and 2.7 mmHg/ml, whereas $E_{es}/E_a$ again remained unchanged (1.7 to 1.8; Fig. 5). Proximal constriction increased $P_{PA-PLA}$ and Ampl somewhat less than embolism, but it increased $Z_c$ much more.
more. $E_a$ and $E_{es}$ markedly increased to 2.5 and 2.9 mmHg/ml, and $E_{es}/E_a$ remained unchanged (1.4 to 1.1).

**Embolism and constriction in goats.** Effects of embolism and of proximal constriction in goats are shown in Table 3. Both embolism and constriction were associated with a decrease in flow. Embolism markedly increased $P_{PA}$ and $P_{PA}-P_{LA}$, and increased Ampl but also $Z_c$. $E_a$ and $E_{es}$ markedly increased to 3.2 and 6.9 mmHg/ml, whereas $E_{es}/E_a$ again remained unchanged (1.8 to 2.2; Fig. 6). Proximal constriction increased $P_{PA}-P_{LA}$-like embolism, increased Ampl somewhat less, and increased $Z_c$ much more. $E_a$ and $E_{es}$ markedly increased to 5.0 and 4.6, and $E_{es}/E_a$ remained unchanged (1.5 to 1.1).

**DISCUSSION**

**Interspecies differences.** The pulmonary circulation is characterized by interspecies differences in resting tone and HPV. Peake et al. (28) reported that HPV is weak in dogs, intermediate in cats, and strong in pigs. At 3,500- to 4,500-m altitude, Anand et al. (1) reported $P_{PA}$ values of 17 mmHg in yaks, 19 to 24 mmHg in interbreed animals, and 47 mmHg in goats. Tucker et al. (35) reported baseline $P_{PA}$ values of 19 mmHg in dogs, 20 mmHg in sheep, and 27 mmHg in pigs. These values increased to respectively 22, 23, and 72 mmHg after sustained exposure to a simulated 4,500-m altitude. The RV-to-left ventricular weight ratio was 0.28 in dogs, 0.32 in sheep, and 0.36 in pigs and increased to 0.38, 0.39, and 0.57, respectively, after sustained hypoxia (35). Increases in weight ratio and in $P_{PA}$ were strongly correlated with initial medial thickness. The anatomic data thus suggest that RV adaptation does exist in species-induced chronic hypertension and in hypoxia-induced sustained hypertension. Whether the adaptation is sufficient to maintain or to restore an optimal coupling efficiency is unknown. We therefore measured ventricular-arterial coupling in species with and without pulmonary hypertension. We also studied the ability of these species to tolerate additional acute hypertension due to hypoxia, embolism, and proximal pulmonary artery constriction. Dogs, goats, and pigs were selected for their availability in our country, for the possibility to obtain weight-matched animals, and for their respective lower, intermediate, and higher values of $P_{PA}$ and HPV. Unfortunately, minipigs became unavailable shortly before the experiments. For the purpose of interspecies comparisons, we therefore included some data from a previous study done in pigs (36). This explains why pigs had a different mean weight and why they did not undergo embolism and pulmonary artery constriction.

**Baseline.** Interspecies comparisons showed progressive changes from dogs to goats and from goats to pigs. $P_{PA}$, pressure-flow curves, and impedance spectra showed an increase in the resistance of small distal vessels. The existence of such a “natural pulmonary hypertension” has been reported previously in calves and in pigs (21, 22, 35). The hypertension
has been related to the amount and extension of pulmonary vascular muscles in those species (19, 35). Variations in muscularity, in turn, have been related to differences in the amount of collateral ventilation (19). Despite the differences in pressure and resistance, $Z_e$ was similar in the three species. The absence of change suggests a balance between some decrease due to proximal vessels distension and some $Z_e$ increase due to proximal vessel stiffness. Chronic pulmonary hypertensive, when associated with higher pressure values, is generally associated with an increased $Z_e$ due to increased elastance and with increased wave reflection, due to arterial remodeling (11, 14, 20). Many previous studies reported RV hypertrophy in response to pulmonary hypertension. Tucker et al. (35) reported a strong correlation between medial thickness, pulmonary arterial pressure, and ventricular weight ratio in different species. In the present study, $E_a$ confirmed that RV afterload was low in dogs, intermediate in goats, and high in pigs. $E_a$ showed a corresponding progressive increase in RV contractility from dogs to pigs. $E_{es}/E_a$ values were remarkably similar in the three species, indicating the existence of RV adaptation to species-related pulmonary hypertension. These results confirm previous observations made in dogs and in pigs (5, 36) and extend these observations to goats. $E_{es}/E_a$ was not only similar but also close to 2 in the three species. This value has been associated with maximal coupling efficiency, as defined by the ratio of work production to oxygen consumption (6). Ventricular-arterial coupling is thus optimal in the three species, whether in absence or in presence of chronic species-related pulmonary hypertension.

**Hypoxia.** Previous studies showed that HPV is weak in dogs, low or intermediate in goats, and strong in pigs (1, 22, 28, 35). These results are confirmed in the present study. The variable HPV amplitude has also been related to the extent and amount of smooth muscles in pulmonary arteries (19, 35). Variations in muscularity and hypoxic response, in turn, have been related to differences in collateral ventilation (18, 19). The concept is that collateral ventilation is an efficient protection against local alveolar hypoxia. Dogs have good collateral ventilation, experience less local hypoxia, require less HPV, and show limited pulmonary vascular muscularity (19). Pigs have no collateral ventilation, experience more local hypoxia, require more HPV, and show extensive muscularity (19). In goats and pigs, the increased resistance was associated with an increase in proximal elastance and in wave reflection. These results also confirm previous findings in pigs (22). As expected, the increases in resistance, elastance, and wave reflection resulted in an increase in RV afterload. The increase in afterload was associated with a proportional increase in RV contractility in all species. Previous studies showed the ventricular adaptation to result both from hypoxia-induced adrenergic stimulation and from the Anrep effect or homeometric autoregulation (5, 27). As a result, $E_{es}/E_a$ remained unchanged and close to 2 in the three species. Ventricular-arterial coupling thus remains optimal during acute hypoxia, whether in absence or in presence of chronic species-related pulmonary hypertension.
Pulmonary embolism. Pulmonary embolism did not affect flow in dogs, due to fluid administration (right atrial pressure increased by 4 mmHg and P_{LA} did not change). Flow decreased in goats, due to lesser fluid administration (right atrial pressure increased by only 2 mmHg and P_{LA} decreased). Pulmonary embolism markedly increased the resistance of small distal vessels and the amount of wave reflection. It did not affect Z_{e} in dogs, suggesting a balance between a Z_{c} increase due to hypertension and a Z_{c} decrease due to passive proximal vessel distension (7, 21). Embolism increased Z_{c} in goats, suggesting that distension was limited by the higher elastance of proximal vessels. These results confirm previous observations made in dogs and pigs (21) and further show that goats are an intermediate species between dogs and pigs. As a result of the increased distal resistance and increased wave reflection, pulmonary embolism markedly increased RV afterload. This increase in afterload was associated with a marked increase in RV contractility, which may also result from adrenergic stimulation and/or from the Anrep effect (5). As we already observed in hypoxia, E_{es}/E_{a} remained unchanged and close to 2 in dogs and in goats. Ventricular-arterial coupling thus remains optimal in severe hypertension due to pulmonary embolism, even in the presence of chronic species-related pulmonary hypertension.

Pulmonary artery constriction. Pulmonary artery constriction markedly increased pulmonary vascular resistance in both species. In contrast to embolism, it markedly increased Z_{c} in dogs and in goats. As hypertension was similar during embolism and constriction, the increased Z_{c} clearly reflected increased elastance (decreased compliance) here due to the vessel ensnarement. Compared with embolism, reflected waves were of somewhat lower amplitude but occurred earlier. These observations of higher elastance and earlier wave reflection in proximal vs. distal obstruction are consistent with theory and confirm previous observations made in dogs (7, 12, 13, 29). As a result of increased resistance, increased elastance, and increased wave reflection, pulmonary artery constriction markedly increased RV afterload. When compared at similar pressure (35 mmHg in dogs and 33–34 or 41–42 mmHg in goats), proximal constriction increased afterload more than distal embolism. This effect mainly results from the reflected waves that already come back during systole (before closure of the pulmonary valve) and thus directly oppose blood ejection during ventricular contraction (12, 13). Again, the increase in RV afterload was associated with a corresponding increase in RV contractility, so that no change was observed in the E_{es}/E_{a} ratio. The RV adaptation to constriction-induced pulmonary hypertension has been shown to result from adrenergic stimulation and from the Anrep effect or homeometric autoregulation (5, 10). Despite the absence of statistical change, E_{es}/E_{a} showed a trend to decrease in both species. This trend to decrease and the final values close to 1 suggest that the present condition may represent the limit of optimal RV adaptation to acute pulmonary hypertension. Ventricular adaptation thus appears to remain optimal or near optimal in proximal constriction associated with increased resistance, increased elastance, and increased wave reflection, even in the presence of chronic species-related pulmonary hypertension.

Clinical application. Clinical signs of right heart failure vary greatly in the presence of similar severity of pulmonary arterial hypertension as evaluated by P_{PA} measurements and resistance calculations (34). Pulmonary vascular resistance is insufficient to evaluate RV afterload because this composite variable is flow dependent and because it does not integrate changes in arterial elastance and wave reflections (30, 34). An improved evaluation of RV afterload is possible with the help of PVZ calculations, but this approach does not describe the adequacy of RV function adaptation. As the clinical consequences of pulmonary hypertension relate to the ability of RV function to maintain adapted flow output (3, 8, 24, 25, 33), quantifying RV arterial coupling seems the most logical improved hemodynamic approach. Although we show that this approach does not necessarily require the measurement of instantaneous RV volumes (5), bedside applications will obviously require simplified and noninvasive approaches. Current progress in echodoppler technology make this possible, allowing for example for point-by-point recalculation of RV pressure curves from the envelope of tricuspid regurgitant jets (15) and synchronized measurement of instantaneous pulmonary artery flow (26).

In summary, we observed that pulmonary vascular resistance and elastance increased from dogs to goats and from goats to pigs, both at baseline and in hypoxia. Ventricular-arterial coupling analysis showed an optimal RV adaptation to chronic species-induced and to acute hypoxia-induced pulmonary hypertension. Coupling analysis also showed an optimal or near-optimal RV adaptation to more severe pulmonary hypertension due to embolism or arterial constriction, even in animals with species-induced pulmonary hypertension. Further studies are necessary to show wide applicability of the approach to chronic experimental or clinical pulmonary hypertension.

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