Enhanced central and conduit pulmonary arterial reservoir function offsets reduced ductal systolic outflow during constriction of the fetal ductus arteriosus

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Smolich JJ, Penny DJ, Mynard JP. Enhanced central and conduit pulmonary arterial reservoir function offsets reduced ductal systolic outflow during constriction of the fetal ductus arteriosus. Am J Physiol Regul Integr Comp Physiol 302: R175–R183, 2012. First published October 12, 2011; doi:10.1152/ajpregu.00459.2011.—Constriction of the fetal ductus arteriosus (DA) has disparate effects on mean and phasic hemodynamics, as mean DA blood flow is preserved until constriction is severe, but DA systolic and diastolic blood velocities change with only mild constriction. To determine the basis of this disparity and its physiological significance, seven anesthetized late-gestation fetal sheep were instrumented with pulmonary trunk (PT), DA, and left pulmonary artery (PA) micromanometer catheters and transit-time flow probes. Blood flow profile and wave intensity analyses were performed at baseline and during mild, moderate, and severe DA constriction (defined as pulmonary-aortic mean pressure differences of 4, 8, and 14 mmHg, respectively), produced with an adjustable snare. With DA constriction, mean DA flow was initially maintained but decreased with severe constriction (P < 0.05) in conjunction with a reduction (P < 0.05) in PT flow (i.e., right ventricular output). By contrast, DA systolic flow fell progressively during DA constriction (P < 0.001), due to decreased transmission of both early and midsystolic proximal flow-enhancing forward-running compression waves into the DA. However, DA constriction was also accompanied by greater systolic storage of blood in the PT and main PA (P < 0.025), and increased retrograde diastolic flow from compliant major branch PA (P < 0.001). Transductal discharge of these central and conduit PA blood reservoirs in diastole offset systolic DA flow reductions. These data suggest that, during DA constriction in the fetus, enhanced central and conduit PA reservoir function constitutes an important compensatory mechanism that contributes to preservation of mean DA flow via a systolic-to-diastolic redistribution of phasic DA flow.

wave intensity analysis; pulmonary hemodynamics; pulmonary blood flow, right ventricular output, pulsatility index

Present, widely accepted concepts about pulmonary trunk (PT), ductus arteriosus (DA), and pulmonary arterial (PA) flow interactions in the fetus have principally been founded on the distribution pattern of mean blood flows. Thus, on the basis of techniques such as radiolabeled microspheres or Doppler echocardiography, which indicate that only 10%–40% of right ventricular (RV) output ejected into the PT passes into the fetal lungs (4, 23, 33, 34, 47, 49), it has long been considered that this output mainly bypasses the high-resistance pulmonary vasculature and instead preferentially flows across the widely patent DA to the lower-resistance placental and lower fetal body circulations (11, 36).

Recent work from our laboratory using a combination of 1) direct comparison of phasic blood flow profiles; 2) wave intensity (WI) analysis, a time domain approach for characterizing the forward- and backward-running energy waves that accompany phasic changes in pressure and flow/velocity waveforms; and 3) computer modeling has suggested, however, that flow dynamics in the fetal PT-DA-PA region are not fully characterized by assessment of mean blood flows alone (44). Thus, despite mean PA flow comprising < 20% of RV output in the baseline fetal state, the impulsive component of PT flow related to an initial systolic forward-running compression wave (FCW ms) was preferentially transmitted into the major PA rather than the DA, as characteristic impedance was higher in the DA (44). Indeed, predominant DA flow only emerged in midsystole when a large flow-reducing PA backward-running compression wave (BCW ms) was transmitted into the DA as a midsystolic forward-running compression wave (FCW ms) that increased DA flow. Furthermore, substantial DA forward flow occurred in diastole due to transductal discharge of blood stored during systole in a compliant PT-PA reservoir, supplemented at the time of pulmonary valve closure by a transient retrograde PA flow peak arising from a PA late-systolic forward-running expansion wave (FEW ls) generated by the RV (44).

The findings that the initial phasic distribution of RV output is preferentially directed into the PA and that PT-PA reservoir function substantially influences DA blood flow patterns have potentially important implications for dynamic mechanisms underlying a number of pathophysiological conditions affecting the fetal pulmonary-ductal region. Of prime interest is DA constriction, which can occur spontaneously (50) or more commonly after exposure of the fetus to prostaglandin inhibitors such as indomethacin (7–9, 19, 25) or acetylsalicylic acid (12), and which has been implicated in the pathogenesis of persistent pulmonary hypertension of the newborn (6). DA constriction in the fetus increases PT and PA pressures (12, 19) and the aortopulmonary mean blood pressure difference (5, 8, 9, 12, 13, 19). Somewhat surprisingly, mean DA flow appears to be preserved until the occurrence of marked elevations in this pressure difference (5, 9), even though increases in Doppler-echocardiographic DA diastolic velocity relative to peak systolic velocity occur with only mild degrees of DA constriction (14). The basis for this disparity and its physiological significance is unresolved, although one clear possibility is that alterations in phasic DA flow patterns serve to dampen reductions in mean DA flow. However, little is known about the
precise nature of these alterations and their evolution during DA constriction or their relationship to any accompanying changes in either PT-DA-PA phasic flow interactions or PT-PA reservoir function.

This study, which was performed in anesthetized late-gestation fetal lambs during steady-state, incremental DA constriction produced with an adjustable snare, had three main aims. The first was to directly compare changes in PT, DA, and PA blood flow profiles induced by DA constriction in systole and diastole. The second was to examine associated alterations in PT-DA-PA systolic interactions via evaluation of WI interrelationships and their associated flow effects. The third was to quantify changes in PT-PA reservoir function and determine their contribution to changes in DA flow patterns.

Table 1. Fetal aortic blood gas variables during stepwise ductal constriction

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.30 ± 0.04</td>
<td>7.29 ± 0.03</td>
<td>7.29 ± 0.04</td>
<td>7.28 ± 0.04b</td>
</tr>
<tr>
<td>Hemoglobin, g/dl</td>
<td>12.1 ± 1.1b</td>
<td>12.4 ± 1.2</td>
<td>12.2 ± 1.3</td>
<td>12.4 ± 1.2</td>
</tr>
<tr>
<td>Hemoglobin O2 saturation, %</td>
<td>69.4 ± 4.5</td>
<td>69.8 ± 4.7</td>
<td>67.6 ± 3.6</td>
<td>64.6 ± 5.3b</td>
</tr>
<tr>
<td>PO2, mmHg</td>
<td>23.9 ± 2.6</td>
<td>24.3 ± 2.8</td>
<td>23.3 ± 1.9</td>
<td>22.6 ± 1.4b</td>
</tr>
<tr>
<td>PCO2, mmHg</td>
<td>48.8 ± 4.0</td>
<td>50.0 ± 3.0</td>
<td>49.8 ± 3.0</td>
<td>49.4 ± 2.6</td>
</tr>
<tr>
<td>Base excess, mmol/l</td>
<td>−3.1 ± 1.6</td>
<td>−2.8 ± 1.8</td>
<td>−3.0 ± 2.0</td>
<td>−2.9 ± 2.2</td>
</tr>
</tbody>
</table>

Data are means ± SD; n = 7. DA, ductus arteriosus. *P < 0.05 and †P < 0.01 compared with other states.
mean pressure differences of two further tightenings of the DA snare, which produced PT-AoT dynamic measurements and AoT blood sampling were repeated after taken for blood gas analysis just before the 5-min recording. Hemo-
blocks of data were recorded 1 and 5 min later, with an AoT sample
once steady-state hemodynamics had been attained, 15- to 20-s
mmHg) was noted. The DA snare was then tightened to increase this
Physiological data. AoT and PT fluid-filled catheter blood pressures were measured with transducers referenced to atmospheric pressure at the level of the left atrium and calibrated against a water manometer before each study. Signals from fluid-filled and microma-
nerometers of DA and left PA micromanometer waveforms were then matched to the corre-
the PT-AoT pressure difference (A)
mean pressure differences of ~8 mmHg (moderate DA constriction) and ~14 mmHg (severe DA constriction). At the end of the study, animals were killed with an overdose of pentobarbital sodium (100 mg/kg), and the left and right lungs were weighed.

PT, DA, and PA blood flow measurements comprised 1) mean flow, 2) systolic flow, and 3) diastolic flow. As the diastolic offset of both DA and PA flows changed during DA constriction, the timing of the PT flow profile was used to define systolic and diastolic flow components at all sites, with systolic flow measured from the start of the PT systolic upstroke to the point where this flow returned to zero, and diastolic flow constituting the remainder of flow during the cardiac cycle. Note that 1) diastolic flow included the transient negative flow peak occurring around the time of pulmonary valve closure, which was previously measured as a separate protodiastolic component (44); and 2) raw systolic and diastolic flow values were multiplied by the quotient of flow duration and cardiac cycle length, so that their sum was equal to mean flow. To permit a direct comparison with PT and DA flows, reported PA flows refer to the calculated combined left and right PA flow values. To assess relative changes in the degree of excursion of the DA flow signal during DA constriction, a pulsatility index was calculated as the maximum-to-minimum flow difference divided by mean flow (10).

Blood flow stored in the central PT and main PA reservoir was defined as that portion of PT flow that did not cross the DA or enter left and right PA during systole and was calculated as the difference between mean PT flow and the sum of the DA and PA systolic flows. Note that mean, rather than systolic PT flow was used in this calculation as inclusion of the diastolic PT flow component provided a measure of any net reservoir PT flow arising from between the pulmonary valve and PT flow probe, which might be expected to increase with the PT dilatation that accompanies DA constriction (24). The net reservoir flow arising from left and right conduit PA and discharging across the DA was assumed to be equivalent to the absolute value of PA diastolic flow. The sum of the central and constituting the remainder of flow during the cardiac cycle. Note that 1) diastolic flow included the transient negative flow peak occurring around the time of pulmonary valve closure, which was previously measured as a separate protodiastolic component (44); and 2) raw systolic and diastolic flow values were multiplied by the quotient of flow duration and cardiac cycle length, so that their sum was equal to mean flow. To permit a direct comparison with PT and DA flows, reported PA flows refer to the calculated combined left and right PA flow values. To assess relative changes in the degree of excursion of the DA flow signal during DA constriction, a pulsatility index was calculated as the maximum-to-minimum flow difference divided by mean flow (10).

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WI analysis. WI analysis was performed as previously described (29, 42–46). Briefly, after conversion of blood flow to velocity (U) using cross-sectional area derived from caliper measurement of vessel diameters, the rates of change of PT, DA, and left PA blood pressure (dP/dt) and velocity (dU/dt), and the product of these differentials (i.e., time-corrected net WI), were calculated. Net WI was then separated into forward and backward components after calculation of wave speed with the PU loop method (18). As per convention, forward-running waves propagated away from the ventricle and back-
Fig. 2. Changes in fetal pulmonary (PT) and aortic trunk (AoT) pressures, and the PT-AoT pressure difference (A), the PT, ductus arteriosus (DA) and pulmonary arterial (PA) flow profiles (B), and the difference between PT inflow and the sum of the DA and PA outflows (C) at baseline and during mild, moderate, and severe ductal constriction. Note that C, which approximates cyclical changes in the central PT and main PA blood reservoir, is positive in systole and negative in diastole.
Table 2. Effect of stepwise ductal constriction on blood pressures

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
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<tbody>
<tr>
<td><strong>AoT blood pressure, mmHg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>66.4 ± 3.8†</td>
<td>64.2 ± 4.2b</td>
<td>61.4 ± 2.9</td>
<td>60.5 ± 3.9</td>
</tr>
<tr>
<td>Mean</td>
<td>58.5 ± 2.6†</td>
<td>57.1 ± 3.8b</td>
<td>54.8 ± 2.3</td>
<td>53.8 ± 3.5</td>
</tr>
<tr>
<td>Diastolic</td>
<td>49.9 ± 2.6†</td>
<td>49.2 ± 3.7b</td>
<td>47.6 ± 2.4</td>
<td>47.0 ± 2.9</td>
</tr>
<tr>
<td><strong>PT blood pressure, mmHg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>74.3 ± 2.5</td>
<td>79.4 ± 5.2d</td>
<td>84.9 ± 5.0#</td>
<td>94.6 ± 8.5#</td>
</tr>
<tr>
<td>Mean</td>
<td>60.2 ± 1.8</td>
<td>61.1 ± 3.6</td>
<td>62.6 ± 1.8#</td>
<td>67.4 ± 3.3#</td>
</tr>
<tr>
<td>Diastolic</td>
<td>49.9 ± 2.5</td>
<td>49.2 ± 3.8</td>
<td>48.9 ± 3.3</td>
<td>51.1 ± 3.6#</td>
</tr>
<tr>
<td><strong>PT-AoT difference, mmHg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>7.9 ± 3.1</td>
<td>15.2 ± 4.3f</td>
<td>23.6 ± 6.9#</td>
<td>34.1 ± 9.9#</td>
</tr>
<tr>
<td>Mean</td>
<td>1.7 ± 1.0</td>
<td>4.0 ± 1.1†</td>
<td>7.9 ± 2.3#</td>
<td>13.5 ± 3.3#</td>
</tr>
<tr>
<td>Diastolic</td>
<td>0.0 ± 1.2</td>
<td>0.0 ± 0.8</td>
<td>1.3 ± 1.7#</td>
<td>4.1 ± 2.5#</td>
</tr>
</tbody>
</table>

Data are means ± SD; n = 7. AoT, aortic trunk; PT, pulmonary trunk. *P < 0.025, †P < 0.005, and ‡P < 0.001 compared with subsequent states; §P < 0.05, ¶P < 0.005, and ™P < 0.001 compared with preceding states.

RESULTS

Blood gases and hemodynamics. Blood gas variables did not change during DA constriction, apart from a small increase in hemoglobin and, with severe constriction, minor reductions in pH, hemoglobin O2 saturation, and PO2 (Table 1).

Systolic PT blood pressure rose stepwise with DA constriction, mean PT pressure with moderate and severe constriction, but PT diastolic pressure only with severe constriction. Moreover, as DA constriction was also associated with a progressive reduction in AoT pressures, increases in PT-AoT differences were greatest for systolic, intermediate for mean, and least for diastolic pressure (Fig. 2A, Table 2).

During DA constriction, mean PA flow was unchanged, while mean PT and DA flows were initially maintained, but fell by 12% and 18%, respectively, with severe constriction (Table 3). As a result, the proportion of mean PT flow distributed into the PA tended to increase between baseline (14 ± 15%) and severe constriction (20 ± 12%, P = 0.06). By contrast, changes in PA and DA phasic flows between baseline and severe DA constriction were more striking (Fig. 2B, Table 3). Thus, while PA systolic flow increased by 35%, this was largely offset by near doubling of a negative PA diastolic flow. On the other hand,

Table 3. Effect of stepwise ductal constriction on mean and phasic blood flows

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
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<tbody>
<tr>
<td><strong>Mean flow, ml/min</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT</td>
<td>801 ± 106</td>
<td>772 ± 97</td>
<td>757 ± 134</td>
<td>701 ± 85†</td>
</tr>
<tr>
<td>DA</td>
<td>675 ± 105</td>
<td>642 ± 123</td>
<td>620 ± 164</td>
<td>564 ± 127†</td>
</tr>
<tr>
<td>PA</td>
<td>126 ± 117</td>
<td>130 ± 108</td>
<td>137 ± 117</td>
<td>137 ± 88</td>
</tr>
<tr>
<td><strong>Systolic flow, ml/min</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT</td>
<td>803 ± 96</td>
<td>762 ± 124</td>
<td>738 ± 157</td>
<td>679 ± 89°</td>
</tr>
<tr>
<td>DA</td>
<td>528 ± 123</td>
<td>441 ± 103†</td>
<td>372 ± 113#</td>
<td>300 ± 74°</td>
</tr>
<tr>
<td>PA</td>
<td>198 ± 60°</td>
<td>225 ± 55°</td>
<td>256 ± 47</td>
<td>268 ± 36</td>
</tr>
<tr>
<td><strong>Diastolic flow, ml/min</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT</td>
<td>−2 ± 33</td>
<td>9 ± 39</td>
<td>19 ± 28</td>
<td>22 ± 30b</td>
</tr>
<tr>
<td>DA</td>
<td>147 ± 82†</td>
<td>201 ± 90°</td>
<td>248 ± 117</td>
<td>264 ± 96</td>
</tr>
<tr>
<td>PA</td>
<td>−72 ± 69°</td>
<td>−95 ± 71°b</td>
<td>−118 ± 78</td>
<td>−132 ± 61</td>
</tr>
</tbody>
</table>

Data are means ± SD; n = 7. *P < 0.025, †P < 0.005, and ‡P < 0.001 compared with subsequent states; §P < 0.05, ¶P < 0.025, ‡P < 0.01, and ™P < 0.001 compared with preceding states; bP < 0.05 compared with baseline.
DA systolic flow fell by 43%, but DA diastolic flow rose by 80%, so that the proportion of DA flow occurring in diastole increased progressively from 22% to 46% (Fig. 3A). In conjunction with this systolic-to-diastolic redistribution of phasic DA flow, the DA pulsatility index fell from 3.0 to 1.2 between baseline and severe DA constriction (Fig. 3B).

The instantaneous difference between PT flow and the sum of the DA and PA flows, which approximates to the cyclical storage and discharge of the central PT and main PA reservoir, was positive in systole and negative in diastole (Fig. 2C). The contributions of the central (75 ml/min) and conduit PA reservoir (72 ml/min) to DA diastolic flow were similar at baseline, and both increased ~80% after severe DA constriction (central to 133 ml/min, PA to 132 ml/min). However, while DA diastolic flow rose with both mild and moderate DA constriction, it did not increase further with severe constriction (Fig. 4).

Wave intensity analysis. Between baseline and severe DA constriction, FCW\textsubscript{s} CI was unchanged in the PT, but increased by 32% in the PA and decreased by 69% in the DA, so that the PA-to-PT FCW\textsubscript{s} CI ratio rose 26%, while the DA-to-PT FCW\textsubscript{s} CI ratio fell 71%. On the other hand, as FCW\textsubscript{ms} CI increased 4.4-fold in the PT and 10-fold in the PA, but was unaltered in the DA, the PA-to-PT FCW\textsubscript{ms} CI ratio rose 147%, while the DA-to-PT FCW\textsubscript{ms} CI ratio fell 81%. During DA constriction, BCW\textsubscript{ms} CI increased at all sites, with commensurate rises in the BCW\textsubscript{ms}-to-FCW\textsubscript{s} CI ratios. These changes were associated with a 54% rise in the PT-to-PA BCW\textsubscript{ms} CI ratio but a 45% fall in the DA FCW\textsubscript{ms}-to-PA BCW\textsubscript{ms} CI ratio. Furthermore, FEW\textsubscript{ms} CI rose in the PT and PA, but fell by 42% in the DA (Table 4). The pattern of changes in ΔQ related to waves was similar to that of CI except that, whereas DA FCW\textsubscript{ms} CI was unchanged, DA FCW\textsubscript{ms} ΔQ fell by 43% (Table 5).

DISCUSSION

This study has confirmed the finding that, during DA constriction, mean DA blood flow is preserved until constriction is severe (5, 9). Furthermore, in accord with the report that changes in systolic and diastolic blood velocity profiles on Doppler echocardiography are an early feature of DA constriction (14), alterations in DA phasic flow patterns were evident with mild DA constriction and became more marked with greater degrees of DA constriction. These altered phasic DA flow patterns, which consisted of a reduction in DA systolic flow but an increase in DA diastolic flow, contributed to a preservation of mean DA flow via a systolic-to-diastolic flow redistribution, and were underpinned by changes in both systolic PT-DA-PA interactions and PT-PA reservoir function.

Use of WI analysis in our study indicated that reductions in DA systolic flow during DA constriction had both early and midsystolic components. The early systolic fall in DA blood flow was temporally related to a marked drop in transmission of the PT FCW\textsubscript{s} into the DA, with both DA FCW\textsubscript{s} CI and ΔQ, and their corresponding DA-to-PT ratios, decreasing progressively with each increment in DA constriction (Tables 4 and 5). Correspondingly, the midsystolic fall in DA blood flow was due to a substantial decrease in the DA FCW\textsubscript{ms} ΔQ (Table 5), even though the magnitude of DA FCW\textsubscript{ms} CI was unchanged (Table 4). Importantly, however, DA FCW\textsubscript{ms} CI was reduced relative to its source waves. Thus, on present evidence, the DA FCW\textsubscript{ms} appears to have a dual origin, with one portion arising directly from antegrade transmission of the PA BCW\textsubscript{ms} into the DA as a FCW\textsubscript{ms} and another portion originating indirectly via retrograde transmission of the PA BCW\textsubscript{ms} into the PT as a BCW\textsubscript{ms}, followed by reflection of this wave at the RV-PT.
interface as a FCWms (44). The marked falls in DA FCWms-to-PA BCWms CI and ΔQ ratios during DA constriction suggested a reduction in the direct contribution, while the decrement in the DA FCWms-to-PT FCWms CI and ΔQ ratios was commensurate with a decrease in the indirect component (Tables 4 and 5).

In accord with clinical (21, 22) and experimental observations (38), DA flow was positive in diastole under baseline conditions. As such, positive flow is related to transductal transmission of the PT FEWls into the PA and DA, as the magnitude of PA FEWls ΔQ rose, but that of DA FEWls ΔQ fell (Table 5). Given that the flow effect of the PA FEWls mainly acts to augment DA flow, thereby counteracting the flow-reducing action of the DA FEWls (44), both of these changes served to promote forward DA flow.

One important and direct consequence of enhanced central and conduit PA reservoir function during DA constriction was a progressive shift of DA flow from systole to diastole, with almost half of DA flow occurring in diastole during severe constriction. This shift offset reductions in DA systolic flow, and thus preserved mean DA flow while PT flow (i.e., RV output) was maintained during mild and moderate DA constriction. However, although still present, this mechanism was no longer able to maintain mean DA flow once RV output fell with severe DA constriction. This combination of decreased DA systolic flow and increased diastolic flow during DA constriction additionally underpinned the fall in the DA pulsatility index, a phenomenon that has also been observed in clinical Doppler-echocardiography studies (32, 51).

Even though PA diastolic flow became progressively more negative during DA constriction, mean PA flow was unaltered, due to a parallel increase in PA systolic flow. WI analysis indicated that this increase was supported by both early and midystolic changes. As evident in the rise of PA FCWls CI and ΔQ, and the associated PA-to-PT ratios (Tables 4 and 5), the early systolic increase in PA flow was due to increased transmission of the PT FEWls into the PA. The midystolic rise in PA flow during DA constriction primarily emanated from a larger PA FCWms that was produced by two main factors. The
first was an augmentation of PT FCWms, the main source wave for PA FCWms. As the PT FCWms appears to principally arise as a reflection of the PT BCWms at the RV-PT interface (44), its greater size was therefore, in part, related to an increase in PT BCWms during DA constriction. The latter, in turn, resulted from a combination of a larger PA FCWms generating a larger PA BCWms (43) and, as indicated by rises in the PT-to-PA BCWms CI and ΔQ ratios (Tables 4 and 5), a greater transmission of this BCWms into the PT. The second factor contributing to a rise in the magnitude of PA FCWms and its corresponding greater ΔQ effects was that transmission of PT FCWms into the PA also increased during DA constriction, as the PA-to-PT FCWms CI and ΔQ ratios rose (Tables 4 and 5).

Three methodological issues require comment. First, to permit hemodynamic and WI analyses within the DA, a discrete constriction was applied with a snare on the distal part of this vessel, just beyond the DA micromanometer and flow probe. This approach therefore differed from the more widespread DA constriction produced by either a balloon cuff (1, 27, 48) or pharmacological inhibition of prostaglandin synthesis (7–9, 12, 19). However, as the pattern of change in DA systolic and diastolic velocities is similar, whether DA constriction is produced by a snare (14) or inhibition of prostaglandin synthesis (32, 51), flow changes are also likely to be comparable.

Second, while mean PA blood flow did not change significantly during DA constriction in the present study, previous studies of DA constriction in chronically instrumented fetal lambs, where absolute fetal PA flow was measured with a flow probe, have reported an increased PA flow (1, 27, 48). However, studies in chronically instrumented fetal lambs have frequently assumed that PA flow is zero at end diastole (1, 2, 17, 48), with adjustment of mean PA flow by a correction factor equal to the difference between the internal zero calibration of the flowmeter and the measured end-diastolic flow (15, 16). Our data suggest that this method is not reliable in the fetus, due to the presence of a negative PA flow offset in diastole, a phenomenon that is also frequently observed in chronically instrumented fetal lambs (3, 30, 35, 38). An assumption of zero PA flow at end diastole would therefore overestimate baseline mean PA flow by the magnitude of any negative PA flow offset. More importantly, this overestimation would become more pronounced with any increase in the negative PA flow offset resulting from DA constriction. Indeed, if a zero-offset, end-diastolic flow correction was to be applied to our data, then the combined left and right PA mean blood flow would increase progressively from 146 ± 63 ml/min at baseline to 160 ± 30 ml/min with mild, 189 ± 53 ml/min with moderate, and 205 ± 45 ml/min with severe DA constriction (P < 0.005).

Finally, due to the extent of the instrumentation required for physiological measurements, it was necessary to perform experiments under general anesthesia and with the fetus partially exteriorized and acutely instrumented. However, as noted previously (42–46), baseline blood gas and pressure data, and the morphology of PA and DA blood flow profiles in our experimental preparation were comparable to those of unanesthetized, chronically instrumented late-gestation fetal lambs (3, 4, 20, 27, 30, 31, 35–38, 40, 41, 47, 49). Furthermore, specific aspects of blood pressure and blood gas changes observed during DA constriction in the present study have also been reported in chronically instrumented fetuses, including a pre-
dominant increase in PT systolic blood pressure (8), a decrease in aortic blood pressure (1), and a slight deterioration in aortic blood gas status (7). Additionally, in the context of the type of PT-DA-PA flow interactions examined in the present study, any potential adverse effects of general anesthesia and acute surgical preparation on hemodynamic or WI profiles were outweighed by the ability to perform a zero calibration of all flow probes immediately before the experimental protocol, a step that is not feasible in chronically instrumented fetuses. Nonetheless, we cannot exclude the possibility that dissection around major vessels and subsequent placement of flow probes around the PT, DA, and left PA, as well as insertion of associated micromanometers, may have altered blood pressure and flow profiles, and wave transmission characteristics, although the magnitude of any such effect is likely to be quite minor.

Perspectives and Significance

The fetal DA is a very reactive vascular segment with its tone (and thus caliber) influenced by numerous factors, including blood oxygen tension, circulating humoral substances, paracrine signaling, and neural activity (39). The results of this study have suggested a physiological mechanism, namely enhanced central and conduit PA reservoir function leading to a redistribution of phasic DA flow from systole to diastole, whereby mean DA flow can be preserved during a reduction in luminal dimensions produced by mechanical DA constriction. These findings imply that alterations in the balance between DA systolic and diastolic flow components in the fetus may subserve a homeostatic function by enabling maintenance of mean DA flow during variations in DA caliber.

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GRANTS

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