Simultaneous pulmonary trunk and pulmonary arterial wave intensity analysis in fetal lambs: evidence for cyclical, midsystolic pulmonary vasoconstriction

Joseph J. Smolich,1,2 Jonathan P. Mynard,1,2 and Daniel J. Penny1,2,3

1Australia and New Zealand Children’s Heart Research Centre, Murdoch Children’s Research Institute; and 2Department of Paediatrics, University of Melbourne and 3Department of Cardiology, Royal Children’s Hospital, Melbourne, Australia

Submitted 14 October 2007; accepted in final form 18 February 2008

Smolich JJ, Mynard JP, Penny DJ. Simultaneous pulmonary trunk and pulmonary arterial wave intensity analysis in fetal lambs: evidence for cyclical, midsystolic pulmonary vasoconstriction. Am J Physiol Regul Integr Comp Physiol 294: R1554–R1562, 2008. The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Address for reprint requests and other correspondence: J. J. Smolich, Dept. of Cardiology, Royal Children’s Hospital, Flemington Road, Parkville, Victoria, Australia, 3052 (e-mail: joe.smolich@mcri.edu.au).

In the fetus, right ventricular (RV) output constitutes 56–67% of the combined ventricular output, while proximal pulmonary blood pressures are equal to or greater than in the aorta (1, 16, 35, 38, 40–42). Despite the high pulmonary pressures, only ~10% of RV blood entering the pulmonary trunk (PT) passes to the fetal lungs, with the remainder crossing the ductus arteriosus into the descending aorta (12, 35, 36, 42). The physiological basis of this low blood flow to the fetal lungs is incompletely understood. To determine the potential role of pulmonary vascular interaction in this phenomenon, simultaneous wave intensity analysis (WIA) was performed in the pulmonary trunk (PT) and left pulmonary artery (LPA) of 10 anesthetized late-gestation fetal sheep instrumented with PT and LPA micromanometer catheters to measure pressure (P) and transit-time flow probes to obtain blood velocity (U). Studies were performed at rest and during brief complete occlusion of the ductus arteriosus to augment pulmonary vasoconstriction (n = 4) or main pulmonary artery to abolish wave transmission from the lungs (n = 3). Wave intensity (dW) was calculated as the product of the P and U rates of change. Forward and backward components of dW were determined after calculation of wave speed. PT and LPA WIA displayed an early systolic forward compression wave (FCWfs) increasing P and U, and a late systolic forward expansion wave decreasing P and U. However, a marked midsystolic fall in LPA U to near-zero was related to an extremely prominent midsystolic backward compression wave (BCWbs) that arose ~5 cm distal to the LPA, was threefold larger than the PT BCWbs (P < 0.001), of similar size to FCWfs at rest (P > 0.6), larger than FCWis following ductal occlusion (P < 0.05) and abolished after main pulmonary artery occlusion. These findings suggest that the absence of pulmonary arterial midsystolic forward flow which accompanies a low fetal lung blood flow is due to a BCWbs generated in part by cyclical vasocstriction within the pulmonary microcirculation.

Fetal pulmonary vascular interaction; fetal pulmonary blood flow; fetal pulmonary blood pressure

where forward flow occurs only in early systole (27, 36, 37), suggests that detailed evaluation of hemodynamic interactions between these anatomically proximate sites may provide new insights into the mechanism(s) underpinning a low fetal lung blood flow.

One powerful means of obtaining quantitative and temporal information about specific components contributing to cardiovascular interactions is the relatively new method of wave intensity analysis (WIA), an approach based on the premise that circulatory function is accompanied by the propagation of infinitesimal wavefronts defined by their pressure (P) and velocity (U) effects (4, 31). In the time domain, the product of changes in P and U (“wave intensity”) represents the instantaneous energy carried by the wavefronts (23, 46). Using WIA, we can classify these waves into “forward-running” waves arising from the heart, “backward-running” waves propagating from the vasculature, “compression” waves increasing pressure, and “expansion” waves decreasing pressure (4). Calculation of wave speed enables separation of P and U into forward and backward components and of net wave intensity into the four wave types which may simultaneously exist in an overall profile, namely, “forward compression waves” increasing pressure and velocity, “forward expansion waves” decreasing pressure and velocity, “backward compression waves” increasing pressure but decreasing velocity, and “backward expansion waves” decreasing pressure but increasing velocity (4, 23).

To date, only one study has applied WIA in the fetus, with evaluation primarily of the RV-PT interaction (13). As in the adult (17, 18), the fetal PT WIA was characterized by an initial systolic forward compression wave (FCWfs) associated with impulsive RV ejection of blood, and a late-systolic forward expansion wave (FEWes) occurring just prior to pulmonary valve closure (13). However, in contrast to its absence from the adult under normal conditions (17, 18), the fetal PT also displayed a very prominent midsystolic backward compression wave (BCWbs) temporally associated with a midsystolic plateau in the flow profile (13). On the basis of its abolition by ligation of the main pulmonary artery and the calculated distance to the wave origin, it was concluded that this BCWbs arose from the pulmonary vasculature as a reflection of FCWfs (13). These findings are of particular relevance because they suggest that the abrupt midsystolic cessation of flow observed in fetal major pulmonary arteries (27, 36, 37) is related to the presence of a BCWbs, even larger than in the PT. If this is the case, however, it is unlikely that vascular reflection alone could underpin such a pulmonary arterial BCWbs, as the relative
magnitude of the PT BCW_{ms} is already double or more than that of typical reflected BCW_{ms} seen in the fetal (13) or adult ascending aorta (23, 32), or the adult PT in hypoxia (18). An alternative possibility, suggested by the increased vasoreactivity (12) and potent myogenic responses (3, 44) known to occur within the immature pulmonary vasculature, is that vasoconstriction per se also contributes to the genesis of a pulmonary arterial BCW_{ms}.

This study, in which simultaneous PT and left pulmonary artery (LPA) WIA was undertaken in anesthetized fetal lambs, therefore had two main aims. The first was to characterize PT-LPA interaction by comparison of wave intensity profiles at these sites, including their contribution to changes in local blood pressure and flow/velocity. The second was to determine therefore had two main aims. The first was to characterize the potential role of pulmonary vasoconstriction in generation of a pulmonary arterial BCW_{ms}. Studies were performed under resting conditions in all fetuses and in a subgroup of animals during brief occlusion of either the ductus arteriosus to increase pulmonary vasoconstriction via a pressure-induced rise in vessel stretch (44) or the main pulmonary artery to abolish wave transmission from the pulmonary vasculature.

**METHODS**

Experiments were approved by the institutional Animal Ethics Committee and conformed to guidelines of the National Health and Medical Research Council of Australia.

**Surgical preparation.** Ten Border-Leicester cross ewes were anesthetized at a gestation of 137 (2) days [mean (SD), term of 147 days] with intramuscular ketamine 5 mg/kg and xylazine 0.1 mg/kg, followed by 4% isoflurane delivered by mask. Animals were placed in a supine position, and the trachea was intubated. Anesthesia was then maintained with isoflurane (2–3%), nitrous oxide (30%), and oxygen-enriched air (~70%) delivered via volume-controlled ventilator (900C Servo, Siemens-Elema, Solna, Sweden), supplemented by an intravenous infusion of ketamine (1–1.5 mg·kg\(^{-1}\)·h\(^{-1}\)) and midazolam (0.1–0.15 mg·kg\(^{-1}\)·h\(^{-1}\)). Oxygen saturation was monitored continuously with a cutaneous pulse-oximetry sensor (Oximas Dura-Y, Tyco Healthcare, Pleasanton, CA) applied to the ear. The right common carotid artery was cannulated through a neck incision for monitoring of blood pressure (90308 Multiparameter Monitor, Spacelabs, Medical, Redmond, WA) and for blood gas sampling. On the basis of frequent arterial blood gas analysis (ABL 620, Radiometer, Copenhagen, Denmark), ventilation of the ewe was adjusted to maintain arterial O\(_2\) tension at 100–120 mmHg and arterial CO\(_2\) tension at 35–40 mmHg.

The pregnant horn of the uterus was exposed through a midline laparotomy, and the fetal head, left forelimb, and upper thorax were exteriorized through a hysterotomy. A multilumen cannula was inserted via the fetal left external jugular vein into the right atrium for recording of blood pressure (90308 Multiparameter Monitor, Spacelabs, Medical, Redmond, WA) and for blood gas sampling. On the basis of frequent arterial blood gas analysis (ABL 620, Radiometer, Copenhagen, Denmark), ventilation of the ewe was adjusted to maintain arterial O\(_2\) tension at 100–120 mmHg and arterial CO\(_2\) tension at 35–40 mmHg.

The pregnant horn of the uterus was exposed through a midline laparotomy, and the fetal head, left forelimb, and upper thorax were exteriorized through a hysterotomy. A multilumen cannula was inserted via the fetal left external jugular vein into the right atrium for monitoring of blood pressure (90308 Multiparameter Monitor, Spacelabs, Medical, Redmond, WA) and for blood gas sampling. On the basis of frequent arterial blood gas analysis (ABL 620, Radiometer, Copenhagen, Denmark), ventilation of the ewe was adjusted to maintain arterial O\(_2\) tension at 100–120 mmHg and arterial CO\(_2\) tension at 35–40 mmHg.
As per convention (4), wave direction was referenced to the direction of blood flow, such that waves arising from the right ventricle were defined as forward-running and those propagating from the vasculature as backward-running. Using established methodology (8, 17, 18, 32), the intensity of forward-running waves (dI_{w+}) was calculated as (dP/dt + pc\cdot dU/dt)^2/(4pc) and that of backward-running waves (dI_{w-}) as -(dP/dt - pc\cdot dU/dt)^2/(4pc). Waves causing a pressure increase were classified as compression waves and those producing a pressure decrease as expansion waves, with this characteristic defined by the sign of the pressure difference across the respective forward-running wavefront, given by \((dP/dt)_+ = 1/2\int (dP/dt + pc\cdot dU/dt)\) and the backward-running wavefront, given by \((dP/dt)_- = 1/2\int (dP/dt - pc\cdot dU/dt)\). Thus, a forward-running wave was a compression wave if \((dP/dt)_+ > 0\) and an expansion wave if \((dP/dt)_+ < 0\). Similarly, a backward-running wave was classified as a compression wave if \((dP/dt)_- > 0\) and an expansion wave if \((dP/dt)_- < 0\) (17, 18, 32).

The time interval between wave intensity peaks was obtained from separated WIA profiles and an overall distance to the origin of backward-running waves estimated from the product of wave speed and one-half the time interval between the peaks of the backward and preceding forward compression wave (18, 32). Note that this distance is an approximation, since only a single wave speed (obtained from the PT or LPA) was used in calculations, whereas available information suggests that wave speed varies within different pulmonary arterial segments and within each beat (2).

The cumulative intensity of forward-running (I_{w+}) and backward-running waves (I_{w-}), which is directly related to wave energy, was calculated by integrating the respective dI_w over the wave duration (8, 32). In addition, because forward-running compression, forward-running expansion, and backward-running compression wave profiles had major and minor components, total I_w for these waves was also calculated. The contribution of waves to P and U was obtained by measuring changes in the forward or backward components of P and U between wave onset and offset.

Statistical analysis. Statistical analyses were performed using Statistical Package for the Social Sciences ver. 12.0.1 (SPSS, Chicago, IL). Differences in PT and LPA WIA and the effects of vascular occlusion on wave profiles were evaluated using repeated-measures ANOVA. Results are expressed as means (SD), and significance was taken at the \(p < 0.05\) level.

RESULTS

Resting fetal blood gases and hemodynamics. Ascending aortic pH was 7.282 (0.030), Hb 12.8 (1.3) g/dl, Hb O_2 saturation 71 (7) %, P O_2 24.7 (2.4) mmHg, P CO_2 52.3 (3.6) mmHg, base excess -2.9 (1.8) mmol/l, mean ascending aortic pressure 59 (7) mmHg, mean PT pressure 60 (6) mmHg, and heart rate 142 (19) beats/min.

Resting pressure, velocity and wave intensity profiles. Systolic blood pressure profiles in the PT and LPA were similar, except that a shoulder in the midportion of the ascending limb was more pronounced in the former (Fig. 1A). As in previous reports, PT (13, 38) and LPA (27, 36, 37) flow profiles displayed an early systolic peak and a late-systolic negative flow, but a midsystolic flow attenuation, occurring in conjunction with rising pressure, was more marked in the LPA (Fig. 1B). Peak positive, mean, and peak negative flows were all greater in the PT. However, peak positive U was similar in the PT and LPA, suggesting that the difference in peak positive flow was largely attributable to differing vessel diameters, while peak negative U was greater in the LPA and mean U was approximately threefold greater in the PT (Fig. 1C, Table 1).

PT WIA displayed an early systolic FCW (FCW\textsubscript{ms}), a large midsystolic BCW (BCW\textsubscript{ms}), and a late-systolic FEW (FEW\textsubscript{ls}). In addition, a small and constant BEW was temporally associated with the shoulder of the ascending limb of the PT pressure pulse, while several smaller midsystolic FCWs (FCW\textsubscript{ms}) evident both before and after the peak of BCW\textsubscript{ms} were associated with further increases in pressure and rebound increases in velocity (Fig. 2, left). WIA in the LPA also demonstrated.

<table>
<thead>
<tr>
<th>Table 1. Baseline fetal pulmonary trunk and left pulmonary artery blood flows and velocities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood flow, ml/min</td>
</tr>
<tr>
<td>Peak positive</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>Peak negative</td>
</tr>
<tr>
<td>Blood velocity, m/s</td>
</tr>
<tr>
<td>Peak positive</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>Peak negative</td>
</tr>
</tbody>
</table>

Data are expressed as means (SD); \(n = 10\). PT, pulmonary trunk; LPA, left pulmonary artery.
Resting wave intensity analysis. Data are presented in Tables 2 and 3. Wave speed in the PT was ~30% higher than in the LPA (P = 0.03).

Peak FCW_{ls} dI_{W+} in the PT occurred 6 (3) ms earlier (P < 0.001) and was ~30% greater (P = 0.03) than in the LPA. FCW_{ls} comprised ~90% of total FCW_{Iw+} and was associated with a similar increase in U at both sites, but ~25% higher rise in P in the PT (P < 0.001).

Peak FEW_{ls} dI_{W+} in the PT occurred 6 (3) ms earlier (P < 0.001) and was ~50% greater (P = 0.03) than the LPA. FEW_{ls} comprised ~85% of total FEW_{Iw+} and produced a similar reduction in U at both sites but was associated with a ~35% greater fall in P in the PT (P < 0.001). In contrast to the forward-running waves, BCW_{ms} peak dI_{W-} in the LPA occurred 4 (4) ms earlier (P = 0.02) and was 3-fold larger (P < 0.001) than in the PT. Furthermore, whereas the magnitude of BCW_{ms} I_{W-} was 24 (19) % of FCW_{ls} I_{W+} in the PT, it comprised 95 (33) % of FCW_{ls} I_{W+} in the LPA (P < 0.001), with no significant difference between the amplitudes of LPA BCW_{ms} I_{W+} and FCW_{ls} I_{W+} (P > 0.6). Compared with the PT, the LPA BCW_{ms} produced a ~50% greater rise in P (P < 0.001) and double the fall in U (P < 0.001). Using the interval between BCW_{ms} peak dI_{W-} and peak FCW_{ls} dI_{W+} in the PT [51 (8) ms] and LPA [41 (12) ms], the calculated origin of BCW_{ms} from the measurement site in the PT [8.9 (2.3) cm] was almost double that from the LPA [5.3 (1.7) cm, P = 0.001].

In the PT, peak BEW dI_{W-} occurred 11 (2) ms after peak FCW_{ls} dI_{W+}, constituted 3% of the magnitude of peak FCW_{ls} dI_{W+}, and had a calculated origin 2.9 (1.9) cm distal to the measurement site.

Effect of transient vascular occlusion. Ductal occlusion produced similar morphological alterations of wave intensity profiles in the PT (Fig. 3) and LPA (Fig. 4), with the main

| Table 2. Fetal pulmonary trunk and left pulmonary artery wave intensity analysis |
|---|---|---|
| | PT | LPA | P |
| Wave speed, m/s | 3.6 (0.9) | 2.7 (0.7) | 0.03 |
| Peak dI_{W}, Wm^{-2}s^{-2} x 10^6 | | | |
| FCW_{ls} | 2.43 (0.83) | 1.85 (0.54) | 0.03 |
| FEW_{ls} | 1.68 (1.11) | 1.12 (0.67) | 0.03 |
| BCW_{ms} | -0.52 (0.43) | -1.56 (0.44) | <0.001 |
| BEW | -0.09 (0.10) | | |
| I_{W}, Wm^{-2}s^{-1} x 10^4 | | | |
| FCW_{ls} | 3.22 (1.01) | 2.62 (0.62) | 0.1 |
| FCW_{total} | 3.58 (1.13) | 2.94 (0.73) | 0.1 |
| FEW_{ls} | 1.88 (1.28) | 1.29 (0.86) | 0.03 |
| FEW_{total} | 2.22 (1.31) | 1.63 (0.75) | 0.04 |
| BCW_{ms} | -0.85 (0.73) | -2.48 (0.80) | <0.001 |
| BCW_{total} | -0.98 (0.83) | -2.57 (0.86) | <0.001 |
| BEW | -0.09 (0.12) | | |
| Peak dI_{W} ratios | | | |
| BCW_{ms}/FCW_{ls} | 0.22 (0.17) | 0.89 (0.39) | <0.001 |
| BEW/FCW_{ls} | 0.03 (0.03) | | |
| I_{W} ratios | | | |
| BCW_{ms}/FEW_{ls} | 0.24 (0.19) | 0.95 (0.33) | <0.001 |
| BEW/FEW_{ls} | 0.02 (0.02) | | |

Data are expressed as means (SD); *n* = 10. BCW_{ms} and BCW_{total}, mid-systolic and total backward compression wave; BEW, backward expansion wave; FCW_{ls} and FCW_{total}, initial systolic and total forward compression wave; FEW_{ls} and FEW_{total}, late-systolic and total forward expansion wave; dI_{W}, wave intensity; I_{W}, cumulative wave intensity.
Fig. 3. Net blood pressure (A) and blood velocity (B), shown in thick line with forward and backward components shown in thin lines, as well as net wave intensity (C) and separated forward and backward wave intensities (D) in the fetal pulmonary trunk before (left) and after occlusion of the ductus arteriosus (right). Abbreviations in D are the same as in Table 2.

Fig. 4. Net blood pressure (A) and blood velocity (B), shown in thick line with forward and backward components shown in thin lines, as well as net wave intensity (C) and separated forward and backward wave intensities (D) in the fetal left pulmonary artery before (left) and after occlusion of the ductus arteriosus (right). Abbreviations in D are the same as in Table 2.
changes comprising a decrease in the magnitude of FCW is and an increase in the amplitude of FCW ms and BCW ms. The magnitude of peak BCW ms, dW−/H increased after ductal occlusion in both the PT [from 0.38 (0.18) to 1.28 (0.29) W m−2 s−2 × 106, P < 0.01] and LPA [from 1.95 (0.56) to 3.23 (0.79) W m−2 s−2 × 106, P < 0.05]. Importantly, the amplitude of BCW ms I W− was uniformly greater than FCW is I W+ following ductal occlusion, with the BCW ms/FCW is ratio increasing from 0.25 (0.19) to 1.25 (0.34) in the PT (P = 0.01) and from 0.92 (0.16) to 1.86 (0.58) in the LPA (P < 0.05).

In the PT, occlusion of the main pulmonary artery was accompanied by disappearance of not only BCW ms but also of most of the FCW ms occurring after this BCW ms, with loss of BEW (Fig. 5). As little or no pulsatile P and U was present, no significant LPA wave intensity profiles were detected after occlusion of the main pulmonary artery (Supplemental data for this article are available online at the American Journal of Physiology—Regulatory, Integrative and Comparative Physiology Web site.).

DISCUSSION

Using the novel approach of simultaneous WIA in the fetal PT and LPA, this study has provided new insights into the hemodynamic interaction between these sites, and, in particular, the basis of their markedly different blood flow profiles and the associated low level of blood flow to the fetal lungs.

The most striking finding in our study was an extremely prominent pulmonary arterial midsystolic backward-running compression wave (BCW ms), similar in amplitude to the preceding early-systolic forward compression wave (FCW is) under baseline conditions. As evident by its temporal features (Fig. 2), amplitude (Table 2), and effect on U (Table 3), this very large BCW ms was responsible for the characteristic abrupt decline in flow to near-zero occurring after a brief initial systolic period of forward flow in major fetal pulmonary arteries (27, 36, 37). This BCW ms also made a major contribution to the local systolic pressure profile, producing a rise that was equivalent in magnitude to that of FCW is (Table 3).

In accord with a previous report (13), a prominent BCW ms was also present within the fetal PT WIA (Fig. 2) and was responsible for the midsystolic plateau in the PT blood flow/velocity profile. However, the magnitude of this BCW ms was only ~30% that of the LPA BCW ms (Table 2), with associated smaller quantitative effects on P and U (Table 3).

Taken together, several results indicate that the LPA BCW ms arose from within the lungs and gave rise to the PT BCW ms. Thus, the peak of the pulmonary arterial BCW ms preceded the PT BCW ms peak, while its amplitude exceeded that of the PT BCW ms, even when both were enhanced after occlusion of the ductus arteriosus. In accord with the finding obtained from a single fetus (13), occlusion of the main pulmonary artery also abolished the PT BCW ms. Finally, the distance of 8.9 cm from the PT to the origin of BCW ms, which is similar to a value of 9.4 cm reported previously (13), was appropriately larger than the distance of 5.3 cm calculated from the LPA.

It is widely considered that the mechanism underlying a BCW ms is a reflection of the preceding FCW is from “closed-end” reflection sites (18, 20, 22, 23, 25, 31). In accord with this view and using PT WIA alone, it was concluded that the large fetal PT BCW ms was a reflection of FCW is from the pulmonary vasculature (13). However, the combined use of PT and LPA WIA in the present study indicated that vascular reflection was not the sole mechanism underlying the fetal LPA BCW ms, and by implication, the PT BCW ms. Specifically, as the magnitude
of the LPA BCWms and its preceding FCW is were similar at rest (Table 2), reflection could only have produced this BCWms if such reflection was near complete, a phenomenon unknown in physiological systems. Even after complete occlusion of the thoracic aorta, for example, the magnitude of BCWms still only increases to 25–40% of FCW is (23, 34). Moreover, the sizes of the LPA and PT BCWms were markedly increased after occlusion of the ductus arteriosus, with both then exceeding the magnitude of FCW is (Figs. 3 and 4). As vascular reflection can return but not itself produce energy, this clearly indicated that a significant mechanism other than reflection was involved in generation of both the fetal LPA and PT BCWms.

As the fetal pulmonary arterial BCWms was equal to or greater than FCW is, a plausible mechanism for this BCWms was that it was in part generated by an impulsive compression wave arising from the pulmonary vasculature during each cardiac cycle. The most likely source of this impulsive compression wave was, in turn, a cyclical midsystolic vasoconstriction region (Fig. 2) were most likely related to additional RV impulsive contractions occurring after FCW is, perhaps reflecting incoordination in the RV systolic contraction pattern secondary to the known structural immaturity of the fetal myocardium (43). However, the observations that FCWms peaks occurring after BCWms became more prominent after ductal occlusion, which also augmented BCWms (Figs. 3 and 4) but were diminished by occlusion of the main pulmonary artery (Fig. 5) raises the possibility that these FCWms were related to proximal reflection of this BCWms and/or transmission of BCWms from the opposite pulmonary artery.

Recent data indicate that FEWls is the vascular manifestation of a ventricular rarefaction (“suction”) wave (45), and as is apparent from Fig. 2, this wave causes flow reversal at the end of systole in the fetal PT and major pulmonary arteries. The larger magnitude and earlier occurrence of FEWls in the PT compared with LPA are consistent with an RV origin for this wave. The explanation for peak negative velocity in the LPA exceeding that in the PT (Table 1), despite FEWls causing a similar decrease in velocity at both sites (Table 3), is that velocity was lower in the LPA just before onset of FEWls due to the much larger BCWms.

Although smaller than observed in the adult (17, 18), a BEW was present in all fetal PT WIA (Fig. 2). In contrast, a BEW was an inconsistent feature in the pulmonary arterial WIA, possibly because it was masked by the very large pulmonary arterial BCWms, which often commenced where a BEW was apparent in the PT WIA. As BEW produced a transient reduction in blood pressure, this wave was responsible for the prominent shoulder in the ascending limb of the PT pressure waveform (Figs. 1 and 2). The disappearance of the PT BEW during occlusion of the main pulmonary artery (Fig. 5) suggests that, as in the adult (17, 18), this wave may have arisen from the presence of an open-end reflection site related to an increase in cross-sectional area at downstream branching points.

Three methodological issues require comment. First, separation of net wave intensity into forward and backward components was an essential part of wave intensity analysis in our study, due to the extensive temporal overlapping of forward- and backward-running waves evident in both the fetal PT and LPA (Figs. 2–4). Second, wave speed in the fetal PT (3.6 m/s)}
was higher than the reported value of 2.6 m/s (13), presumably related to differences in anesthetic regimen and surgical approach. At first glance, a fall in wave speed between the PT and LPA (Table 2) may seem surprising, as other data suggest that wave speed increases from the central to peripheral vasculature (2, 24). However, because wave speed is inversely related to the square root of vessel distensibility (29), our finding could be explained if, as in the adult (15), distensibility increased between the PT and LPA. Finally, one potential limitation of our study was that it was performed under general anesthesia and open-chest conditions, an approach necessary because of the extent of surgical instrumentation required. However, blood gas data were comparable to those of unanesthetized fetuses, while the average level of mean arterial blood pressure in our study (59–60 mmHg) was at the upper end of the normal range reported in chronically instrumented late-gestation fetuses (14, 19, 33). It is thus unlikely that the qualitative features of our findings were affected by our experimental approach.

**Perspectives and Significance**

Our observation that the characteristically low lung blood flow of the fetus is accompanied by a very prominent and uniquely large pulmonary arterial BCWms that markedly attenuates midystolic blood flow/velocity and substantially elevates local blood pressure has major potential implications for both pulmonary physiology and pathophysiology in the perinatal period. As the striking midystolic decline in fetal pulmonary arterial blood flow to near-zero is not observed postnatally (27, 37), it is tempting to speculate that a marked diminution in the magnitude of the fetal pulmonary arterial BCWms accompanies the fall in pulmonary blood pressures and dramatic rise in pulmonary blood flow associated with lung ventilation and birth (5, 12, 36). On the other hand, continued presence of a large pulmonary arterial BCWms might be one factor contributing to the increased pulmonary blood pressures and reduced lung perfusion accompanying conditions such as persistent pulmonary hypertension of the newborn (12).

**ACKNOWLEDGMENTS**

We thank Magdy Sourial, Dr. Kate Simpson, and Andrew Hattam for their assistance with experimental studies.

**GRANTS**

This work was supported by the Australia and New Zealand Children’s Heart Research Centre.

**REFERENCES**


