Detection and quantitation of constriction of the fetal ductus arteriosus by Doppler echocardiography

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ABSTRACT Pulmonary hypertension may occur in the fetus in the presence of constriction of the ductus arteriosus. The feasibility of detection and quantitation of fetal ductal constriction by Doppler echocardiography was assessed in an animal preparation in which ductal constriction was created in the fetal lamb with a variable ligature causing varying degrees of fetal pulmonary hypertension (fetal pulmonary arterial systolic pressure 57 to 97 mm Hg and ductal gradient 9 to 42 mm Hg). Comparison of blinded, continuous-wave peak Doppler velocity (V) measurements of the ductal gradient with the modified Bernoulli assumption (gradient = 4V²) compared well with direct catheter measurements of instantaneous peak systolic gradient (r = .99, catheter = 0.95 × Doppler + 0.6), peak-to-peak gradient (r = .97), and mid-diastolic gradient (r = .85). Ductal constriction was characterized by an increase in the peak systolic and diastolic velocities. The normal human fetal ductus arteriosus blood flow velocity pattern was assessed by pulsed Doppler techniques in 25 normal human fetuses after 20 weeks gestation. The peak systolic flow velocity in the ductus arteriosus measured by image-directed pulsed Doppler echocardiography ranged from 50 to 141 cm/sec (mean 80 cm/sec) and increased with gestational age (r = .50). Diastolic velocity in the ductus arteriosus was consistently directed toward the descending aorta and ranged from 6 to 30 cm/sec. The ductal systolic velocities were the highest blood flow velocities in the fetal cardiovascular system. Application of these techniques to fetuses whose mothers were receiving indomethacin for treatment of premature labor at 30 to 31 weeks gestation confirmed this method to be sensitive for detection of fetal ductal constriction, which developed in three fetuses. Doppler echocardiography can be used to assess the flow velocity in the fetal ductus in humans and to detect constriction and a pressure gradient across it. Quantitation of fetal ductal gradient is possible and may be useful for assessment of the severity of fetal ductal constriction in such patients.


THERE IS EVIDENCE from animal experiments in the fetal lamb that constriction of the ductus arteriosus by a prostaglandin inhibitor can cause pulmonary hypertension and pulmonary arteriolar changes. The administration of a prostaglandin inhibitor in late gestation has been associated with persistent neonatal pul-

monary hypertension and there is evidence that other forms of perinatal asphyxia may be related to chronic prenatal ductal constriction and pulmonary vascular changes. A method for the detection and quantitation of fetal ductal constriction would be useful in the prenatal management of such fetuses.

It has been shown that the human fetal ductus can be imaged after 20 weeks gestation. However, a widely applicable method for ductal assessment should yield information concerning the hemodynamic significance of ductal changes. We attempted to combine observations in animals and man to answer two questions: (1) Can the pattern of blood flow velocity in the fetal ductus as determined by Doppler techniques be used for the detection of fetal ductal constriction? (2) Can
the severity of fetal ductal constriction be estimated noninvasively?

Methods

Fetal lamb experiments. Pregnant ewes ranging in gestation from 120 to 130 days (term = 148 days) were anesthetized with 2 ml (20 mg) of 1% epidural tetracaine hydrochloride and 120 mg of intravenous pentobarbital and placed supine on an operating table. The abdominal wall was opened and a hindlimb of the fetus was extracted through a small hysterotomy. A polyethylene catheter (inside diameter 0.03 inches) was inserted into a distal leg artery and advanced so that the catheter tip was located in the distal abdominal aorta or the proximal femoral artery. The hindlimb was replaced in the uterus and a uterine incision was made over the region of the fetal left chest. A left fetal thoracotomy was performed through the third intercostal space and 0.5 cm of similar polyethylene catheter was placed into the main pulmonary artery just distal to the pulmonary valve through a purse-string suture. The ductus arteriosus was dissected and a blunt right-angle hemostat was used to place umbilical tape around the ductus. Arterial blood pressures were measured with Statham P23Db transducers with zero referenced to the mid-chest. Mild (5 to 10 mm Hg) peak systolic ductal pressure gradients resulted from the dissection but lasted no more than 5 min. Electrocardiographic leads were placed on the ewe and fetal lamb for monitoring.

Four fetal lambs were successfully instrumented for instantaneous pressure measurements across the fetal ductus arteriosus and intermittent ductal constriction with a ligature. Short-term experiments consisted of a series of 1 to 3 min acute ductal constrictions of varying severity (total of 11) created with a ligature with simultaneous pressure and Doppler echocardiographic recordings. Thirty-three simultaneous instantaneous pressure and Doppler velocity measurements of ductal gradient were made to test the predictive capability of Doppler velocities for high and low values. In one experiment the hysterotomy was closed, the constricting ligature was exteriorized, and additional simultaneous measurements of arterial pressures and ductus arteriosus velocities were made.

Echocardiographic imaging (7.5 MHz) and pulsed Doppler (5 MHz) examinations of the fetal lamb were performed with Advanced Technology Laboratories equipment (600 MK). Imaging of the fetal anatomy was possible before and after hysterotomy through a fetal thoracotomy in all animals. Before the experiments, imaging of the position of the ductal ligature (figure 1) and patterns of normal pulsed Doppler sampling were obtained in the ascending aorta, pulmonary arteries, ductus arteriosus, descending aorta, and at the atrioventricular valves. Before and throughout ductal constrictions continuous-wave
Doppler examination of the ductus arteriosus was performed with a 2.5 MHz transducer and Carolina Medical Sonacolor equipment by placing the transducer directly on the fetal right ventricular outflow tract and maximizing the velocity with audio cues. Analog output of phasic changes in continuous-wave Doppler voltage output were recorded simultaneously with pressure tracings at 100 mm/sec paper speed for later analysis of the timing of the instantaneous peak velocity (figure 2, A). Videotape recordings were obtained with commercially available 1/2 inch VHS recorders for pulsed and continuous-wave Doppler data. Doppler velocity data were measured with a digitized computer system (Digisonics Inc.) and manually entered into a computer data base for analysis.

**Normal human fetal ductal velocities.** Pulsed Doppler techniques were used during clinically indicated fetal echocardiographic studies in 25 fetuses (age 20 to 39 weeks gestation, mean 27) proven after birth to be normal who were examined because of congenital heart disease in a sibling. The normal velocity of blood flow in the fetal ductus arteriosus was compared with other blood flow velocities in the human fetal cardiovascular system. Advanced Technology Laboratories 600 MK or Ultramark 8 systems were used with a 5 MHz mechanical transducer with 5 MHz image-directed pulsed Doppler capability. Pulsed Doppler examination of the ductus was performed after adequate imaging of the ductus arteriosus in a sagittal plane and the sample volume was positioned in the descending aortic end of the ductus arteriosus until the maximum velocity was attained. Sampling in the great arteries and semilunar valves was performed in a similar manner to maximize the peak systolic velocity parallel to the direction of flow. When possible, the comparison of ductal and pulmonary valve peak velocity was made by a withdrawal of the site of sampling over five to 10 cardiac cycles (figure 3). Sample volume size was 1.5 or 2.0 mm, while the intensity of Doppler ultrasonic energy was maintained at or below 100 mW/cm² spatial peak time average. Care was taken to avoid Doppler insonation outside of the fetal thorax and the examination time was limited to 15 min. Measurements obtained during fetal breathing or movement were excluded. Identification of the aortic arch was performed in each case to avoid its being mistaken for the "ductal arch."

**Doppler monitoring of fetus exposed to indomethacin.** Doppler techniques were used for assessment of ductal velocities before and during administration of indomethacin for treatment of premature labor in women between 28 and 31 weeks gestation. Two-dimensionally directed pulsed and continuous-wave Doppler examinations of the human fetal ductus were performed before and 24 hr after beginning therapy with indomethacin with the use of General Electric equipment (Pass II) and techniques similar to those used in the examination of normal patients described above. This equipment had the added facility of being continuous wave, Doppler directed, and focused at a specific location in the fetal circulation by 5 and 3.5

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**FIGURE 2.** Fetal lamb ductal constriction. A, Simultaneous aortic (Ao) and main pulmonary arterial (MPA) pressure recordings during and after release (Off) of constriction. The small black arrows on the pressure waveforms before and after constriction indicate the timing of maximum (instantaneous) fetal ductal gradient. Note that the aortic pressure is unchanged during constriction. B, Results of continuous-wave Doppler monitoring of ductal velocity accomplished by placing the transducer on the fetal right ventricular outflow tract proximal to the constriction. A typical appearance of increased systolic and diastolic velocity (top) was present with significant constriction [maximum ductal velocity of 2.4 m/sec to 240 cm/sec corresponding to a gradient of $4 \times (2.4)^2 = 23$ mm Hg], and a normal peak velocity of 1.0 m/sec was present after (Post) constriction (bottom). Although the velocities were away from the transducer they were displayed as moving upward on this equipment.
Results

Experimental fetal ductal constriction. Mechanical constriction of the ductus arteriosus in the fetal lamb experiments showed a wide range of pulmonary artery–to-descending aorta pressure gradients (up to 42 mm Hg peak and 26 mm Hg mean). The systolic, diastolic, and mean pulmonary arterial pressures increased significantly (p < .05), while the descending aortic pressures were unchanged during constrictions. Pulmonary arterial pressures ranged from a peak of 57 to 97 mm Hg. Ductal gradients predicted by continuous-wave Doppler echocardiography compared well with instantaneous and peak-to-peak systolic pressure gradients during fetal ductal constrictions (r = 1.0, .97; figure 4). This excellent correlation was due to the placement of the transducer directly on the right ventricular outflow tract, which allowed the maximal velocity wave-

FIGURE 3. Results of pulsed Doppler sampling in the normal human fetal ductus arteriosus (top), the main pulmonary artery (MPA) (middle), and at the pulmonary valve (PV) (bottom). Note the diastolic velocity directed toward the descending aorta (open black arrow) in the ductus arteriosus.

MHz imaging. The size of the pulsed-Doppler sample volume was maintained at 1 mm and ultrasound intensities were again minimized for the examination, which ranged from 15 to 25 min.

Data analysis. Pressure gradients across the ductus arteriosus were estimated with the modified Bernoulli equation for calculating the peak instantaneous systolic pressure gradient across a discrete obstruction. In this case the gradient, in millimeters of mercury, was estimated by squaring the ductal velocity and multiplying by four. This gave an estimate of the maximum instantaneous pressure gradient and was compared with instantaneous maximum and peak-to-peak ductal gradients in the fetal lamb experiments by use of linear regression. The diastolic peak velocity was obtained in mid-diastole. Peak ductal velocity data from normal human fetuses were nonlongitudinal and was plotted by fetal gestational age and tested by linear regression analysis. Interobserver error was assessed by the average and maximum difference in blinded measurements by two independent observers (J. C. H., D. S. S.) for all the variables in the animal and human experiments. Baseline and ductal constriction aortic and pulmonary arterial pressures (n = 11) were compared by paired t test.

FIGURE 4. Comparison of Doppler-derived ductal gradients and direct pressure measurements by catheter during ductal constriction by ligature in the fetal lamb. There was good correlation between maximal instantaneous systolic gradients (top), diastolic gradients (middle), and the peak-to-peak gradients (bottom).
form to be optimized. A typical pattern of constriction of fetal ductus arteriosus was encountered, with an increase in the systolic and diastolic velocities similar to that observed with coarctation of the aorta (figure 2, B). Severe constriction, corresponding to a 50% increase in mean pulmonary arterial pressure, resulted in a nearly continuous pattern of blood flow velocity toward the descending aorta. Even very mild constriction resulting in a peak pressure gradient of only 10 to 15 mm Hg produced a markedly different waveform in the ductus arteriosus velocity pattern. This abnormality was mirrored in the proximal ductus and main pulmonary artery at a lower maximum velocity, allowing recognition of the presence of downstream ductal constriction. Instantaneous continuous-wave Doppler ductal gradients also correlated with instantaneous simultaneous pressure measurements (figure 4).

Complete occlusion of the ductus arteriosus occurred during mechanical ductal constriction in five instances and in each there was an abrupt cessation of continuous-wave Doppler-measured velocities without any sudden alteration in pressure gradient. Doppler techniques were extremely sensitive in detecting the onset of reopening in the ductus arteriosus, which was prompt and followed by a rapid return to baseline of ductal gradient after loosening of the ductal ligature. The extraterine measurements made after closure of the hysterotomy agreed with the results obtained by measurement of the ductal velocity directly on the heart.

Normal human fetal ductal velocity. The systolic flow velocity in the human fetal ductus was the highest detectable velocity in the normal fetal cardiovascular system, exceeding velocities of the semilunar valves, great arteries, and the umbilical/placental cord circulation. The maximum systolic velocity ranged from 50 to 140 cm/sec, with a mean of 80 cm/sec (figure 5), while the pulmonary and aortic valve maximum velocities ranged from 37 to 113 and 34 to 116 cm/sec, respectively. Comparison of the ductal and pulmonary valve velocities showed a difference ranging from 6 to 54 cm/sec (n = 18), with a slight increase in later gestational age (r = .36, figure 5). Diastolic velocity in the ductus arteriosus was directed from the pulmonary artery toward the descending aorta in all fetuses at all gestational ages, reflecting a high resistance ratio between the pulmonary and lower body/placental circuits. Normal ductal velocity in diastole ranged from 6 to 30 cm/sec.

Human fetal ductal constriction. In three patients receiving indomethacin there was Doppler-detected evidence of fetal ductal constriction. The first patient in premature labor had a fetus with a resting systolic velocity of 100 cm/sec and a diastolic velocity of 20 cm/sec. These values increased to 220 and 50 cm/sec, respectively, after 24 hr (figure 6, A). The peak velocity of 2.2 m/sec corresponded to an instantaneous pressure gradient in the human fetus of 19.4 mm Hg according to the Bernoulli relationship. The second fetus with ductal constriction had elevation of the fetal ductal systolic and diastolic velocities similar to that in the first and also developed tricuspid insufficiency (figure 6, B). The third had mild constriction with systolic and diastolic velocities greater than pretreatment values. Within 12 hr of withdrawal of indomethacin, all abnormalities in ductal velocity had disappeared.

The interobserver errors were a maximum of 10% for both Doppler-determined and pressure data and independent calculations of correlation coefficients showed a maximum difference of .05.

Discussion

The human fetal ductus arteriosus has a systolic blood flow velocity that is higher than that in any other part of the cardiovascular system. With increasing gestational age the ductal velocity becomes increasingly

![Systolic Ductal Velocity vs Gestational Age](image1)

higher than the upstream pulmonary valve and main pulmonary arterial velocities. This suggests very mild relative obstruction to right ventricular ejection by the ductus arteriosus in the human by mild constriction of the ductus, which should be a very low-resistance pathway for blood leaving the fetal main pulmonary artery. Although of little importance with regard to normal human fetal hemodynamics, such a state of mild constriction of the fetal ductus arteriosus is consistent with the concept that the unique muscular character of the ductus and the prostaglandin environment necessary for active dilation of the ductus may make it more susceptible to alteration in later gestation. A similar diastolic runoff pattern is observed in the normal human fetal aortic arch with a lower systolic velocity, suggesting that the aortic isthmus is an area of mild obstruction as well, albeit with less diastolic flow, as suggested by Rudolph.

Animal preparations of fetal pulmonary hypertension created by administration of prostaglandin inhibitors to the ewe confirm the capability of the ductus arteriosus to undergo constriction, even early in gestation. Our preliminary data obtained in humans with Doppler techniques confirm this idea. The fact that indomethacin causes significant constriction of the ductus arteriosus in the very immature infant supports this concept. It is known that persistent pulmonary hypertension may coexist with several disease states known to be associated with asphyxia, including meconium aspiration and postmaturity. Further study in human fetuses exposed to factors known to be associated with perinatal asphyxia and persistent pulmonary hypertension by techniques such as those described here will test the hypothesis that prenatal ductal constriction is the final common pathway for the development of this difficulty in the perinatal period.

The most important result of this study was the demonstration of a sensitive technique for the assessment of the pattern of blood flow velocity in the fetal ductus undergoing constriction. Development of tricuspid insufficiency in one human fetus supported the concept that ductal constriction can affect right ventricular hemodynamics. In the fetal lamb preparation even a 5 mm Hg mean increase in pulmonary arterial pressure resulted in a detectable change in the ductal velocity waveform. This method should be extremely sensitive for detection of altered ductal pressure gradient and superior to ultrasonic imaging alone for detecting changes in ductal caliber. Further work is necessary to define the limitations of such a method in the presence of hemodynamic abnormalities and/or ventricular dysfunction. The use of Doppler techniques for the detec-
tion of the development of atrioventricular valve insufficiency could add specificity regarding the severity of fetal pulmonary hypertension.

Based on these preliminary data fetal ductal constriction causes fetal pulmonary hypertension in the human and further work is necessary in the form of longitudinal studies of fetuses at risk for this complication (a group of patients that has yet to be defined). We suggest that any fetus with evidence of chronic fetal distress or exposure to prostaglandin inhibitors undergo Doppler evaluation of the ductus arteriosus as described here. Although there are now no clinically acceptable methods for altering the fetal prostaglandin environment to attempt treatment of acquired fetal ductus constriction, the management of the pregnancy may be altered or the dose of prostaglandin inhibitor could be reduced. This may allow the identification of fetuses with ductal constriction in utero who could go on to develop persistent pulmonary hypertension in the neonatal period.

Closure of the ductus arteriosus in utero is an ominous event and has never been diagnosed before delivery in the human. In this study we observed the quality of Doppler findings during ductal occlusion in an experimental situation. High-resolution imaging in combination with image-directed pulsed and continuous-wave Doppler echocardiography could be used to differentiate a widely patent ductus from one that is completely occluded. The distinctive finding of diastolic runoff from the pulmonary trunk to the descending aorta with any degree of ductal constriction effectively excluded complete closure. Failure to identify normal ductal diastolic runoff from the pulmonary artery to the descending aorta in a fetus in association with right ventricular failure and tricuspid valve insufficiency may mean there is complete ductal occlusion.

Limitations. Transverse scans of the fetus may cause overlap of the aortic arch and the “ductal arch,” and it is important to visualize directly the aortic arch with its brachiocephalic branches in order not to mistake the blood flow velocity pattern in the transverse arch for that in the ductus arteriosus. Further work is necessary to identify the effects of altered fetal cardiovascular states such as labor and growth retardation on fetal ductal velocity throughout gestation. In our experience with fetal Doppler echocardiography in over 200 patients, an adequate evaluation of the fetal ductal velocity pattern was possible in 80% of cases.

We thank the Carolina Medical Company Inc. for the use of the continuous-wave Doppler equipment for the experimental studies. We acknowledge Michelle Dunn for her invaluable help in manuscript preparation and Grace Yoon for technical assistance.

References
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Circulation. 1987;75:406-412
doi: 10.1161/01.CIR.75.2.406

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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