Placental compliance during fetal extracorporeal circulation

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**Assad, R. S., F. Y. Lee, and F. L. Hanley.** Placental compliance during fetal extracorporeal circulation. *J Appl Physiol* 90: 1882–1886, 2001.—The fetus requires large amounts of volume when weaning from cardiac bypass. This suggests that placental vasculature can act as a large capacitor in the fetal circulation. To assess placental compliance of fetal lambs, seven isolated in situ lamb placentas were placed on extracorporeal circulation. Umbilical artery blood flow was varied from 0 to 350 ml·min⁻¹·kg fetal wt⁻¹. Because the extracorporeal circuit is a closed system, volume changes in the placenta induced by umbilical artery pressure changes were measured from reciprocal volume changes in the reservoir. There was a wide range of change in absolute volume of blood within the fetal placental compartment (216.4 ± 29.3 ml). Placental compliance was linear over the entire range of pressure changes exerted on the placental vasculature (r² = 0.83, P = 0.0001). This indicates that the placenta is a unique and sensitive capacitor in the fetal circulation. This information is important clinically because it establishes that aggressive resuscitation of the fetus using volume may be necessary when weaning the fetus from cardiac bypass.

**The ongoing research on fetal cardiovascular physiology, a growing understanding of the fetal natural history of congenital heart defects, and newly developed fetal diagnostic abilities, as well as the establishment of clinical fetal intervention for noncardiac structural lesions, have provided important insights into the concept of intrauterine correction of fetal cardiac lesions. Intrauterine surgical repair of certain forms of congenital heart disease during the early phase of cardiac development may represent a better chance of survival by preventing or ameliorating a cascade of complex anatomic and physiological derangements. Open fetal cardiac surgery may well require extracorporeal circulatory support. Previous studies in our laboratory indicate that the fetus requires large amounts of volume when weaning from cardiac bypass. This suggests that the placental vasculature can act as a large capacitor in the fetal circulation.**

The present study was designed to assess placental compliance of fetal lambs in more detail, by using an isolated placental bypass preparation. The fetus is excluded completely from the umbilical circulation. An extracorporeal circuit (ECC) substitutes for the fetus, simulating fetal cardiac output, oxygen use, and carbon dioxide production. This preparation allowed a precise evaluation of the relationship between umbilical artery perfusion pressure and placental volume changes under controlled conditions.

**MATERIALS AND METHODS**

**Animal preparation.** Seven pregnant ewes with gestational ages ranging from 125 to 145 days were studied. Each animal was fasted for 24–48 h before surgery. Anesthesia was induced with intramuscular ketamine (20 mg/kg) and maintained with inhalation of 2% halothane and 50% nitrous oxide.

The ewe was placed in the supine position. Two catheters were placed: one in the right femoral artery for continuous measurements of maternal arterial blood pressure and gas analysis; another in the jugular vein to collect blood to prime the ECC and to infuse saline solution.

The abdomen of the ewe was opened through a midline incision. Through a 10-cm incision in the uterine wall and fetal membranes, one of the fetal hindlimbs was delivered to place fetal femoral arterial and venous lines for continuous measurements of fetal arterial blood pressure and drug infusion, respectively.

Nitroprusside was used in two different parts of the experiment. First, before umbilical vessel cannulation, it was titrated to decrease the fetal blood pressure to 60% of baseline. The purpose of this infusion was to blunt the vasoconstrictor associated with umbilical vessel manipulation. Second, it was used at the start of the experimental protocol, as shown below.

The abdominal end of the umbilical cord was then exposed to perform a fetal right paraumbilical laparotomy. Thus the umbilical arteries inside the abdominal cavity and the ductus venosus were exposed and cannulated toward the placenta. This caused fetal death; however, the fetus was allowed to remain in the uterus, to avoid uterine contractions and changes in placental blood flow (12).

All animals received humane care in compliance with *Principles of Laboratory Animal Care* formulated by the National Society for Medical Research and the *Guide for the
The ECC (Fig. 1), destined to replace the circulatory system of the fetus, was designed according to previous studies examining the extracorporeal circulation of the isolated in situ lamb placenta (1, 2).

A gas-heat exchanger unit (Cobe membrane oxygenator, infant model, Cobe Laboratories, Lakewood, CO) was placed in the ECC to adjust temperature, PO2, and PCO2. An external gas mixture of 5% CO2 and 95% N2 was circulated through the gas exchanger at rates appropriate to remove oxygen and add carbon dioxide from the blood coming from the placenta. In this way, the umbilical artery blood gases were kept in the physiological range. Actually, the oxygenator of the ECC served as a “deoxygenator.”

The ECC was primed with 700 ml of maternal venous whole blood after the ewe was heparinized (4 mg/kg). An additional dose of heparin (150 mg) was added to the priming solution in the ECC. Because the pregnant ewe has a normal hematocrit of ~25%, the maternal blood prime induced moderate hemodilution, which is standard for extracorporeal circulation.

The umbilical circulation was immediately restored at a rate of 200 ml·min⁻¹·kg fetal body wt⁻¹, which represents the umbilical artery physiological blood flow. Nitroprusside was used again; this time in the arterial line of the ECC, via a side port, with a dose adjusted to maintain the umbilical artery pressure within the normal range (between 40 and 60 mmHg), at a given flow of 200 ml·min⁻¹·kg fetal wt⁻¹. When the appropriate nitroprusside dose was reached to achieve this, the infusion rate was left constant and was independent of varying placental flow rates. The purpose of this infusion was to create normal placental hemodynamics during baseline conditions.

The arterial flow rate was measured with an electromagnetic blood flowmeter (MVF-3100, Nihon Kohden, Tokyo, Japan). Placental arterial pressure was measured using a 22-gauge catheter, which was inserted through the lumen of one of the arterial umbilical cannulas with the tip positioned 1 cm away from the cannula. The blood returning to the umbilical veins was drained by gravity into a reservoir.

Protocol. Placental extracorporeal circulation was performed under temperature of 37°C and nonpulsatile conditions. Temperature measurements were taken from a port on the umbilical venous cannula.

A period of time was allowed after complete instrumentation of each preparation before data were obtained to ensure stability of the preparation. After that, the pressure at this point was the starting zero pressure, and the resulting reservoir volume was the starting zero volume. Steady-state placental flow rates were then varied from 0 to 350 ml·min⁻¹·kg fetal wt⁻¹, and umbilical artery pressure was measured. Umbilical vein pressure remained constant throughout the protocol (close to 0 mmHg, because of the siphon drainage of the ECC) to evaluate the true effect of inflow pressure over the changes of volume intrinsic to the placenta, with no interference of outflow pressure.

The order in which flow values were chosen was specifically varied with alternating high and low values to avoid any bias from a stepwise-increasing or stepwise-decreasing order. Each pressure measurement and volume changes were taken only after a minimum 5-min period after flow adjustment.

The isolated placental preparation is a closed vascular system; therefore, changes in blood volume of the fetal pla...

**Fig. 1.** Isolated placental preparation. Fetus is excluded completely from umbilical circulation. The pump and gas exchanger substitute for the fetus, simulating fetal cardiac output, oxygen use, and carbon dioxide production. NTP, nitroprusside.
central vascular compartment ($DBV_p$) can be measured easily by calculating reciprocal volume changes in the reservoir of the ECC ($DBV_r$), induced by umbilical artery pressure changes:

$$DBV_p = -DBV_r$$

Therefore, change of blood volume in the reservoir was measured for each respective pressure change measured in the umbilical artery.

**Statistical analysis.** All values were given in terms of means ± SE. Data were analyzed by linear regression. Confidence limits of regression were determined at the level of 95%. The calculation was performed through the Statistical Analysis System (21). Statistical significance was established at the 5% level.

**RESULTS**

In Table 1 are listed values for umbilical artery pressure (before and after nitroprusside infusion), as well as fetal and ECC priming values for arterial blood gases and hematocrit. These data obtained before the placenta was isolated are in the physiological range for fetal lambs (10). Continuous recording for maternal heart rate and blood pressure showed that these parameters remained within the physiological range throughout the procedures.

Figure 2 shows the incremental changes in vascular volume that occurred within the fetal placental vascular compartment when changes in umbilical artery perfusion pressure were induced (data are listed in Table 2). Volumes measured while going from a low to a high umbilical artery pressure were the same as those while returning from a similar high to a similar low pressure. Placental compliance demonstrated a linear relationship over a wide range of pressure changes exerted on placental vasculature. It can be seen that, when umbilical artery pressure was raised from 0 to 30 mmHg, the fetal placental vascular blood volume showed the same increase seen over the range between 30 and 60 mmHg. When umbilical artery pressure had a mean rise of 30 mmHg, the fetal placental vascular compartment increased by $\pm 120.20 \pm 14.32$ ml of blood.

A wide range of absolute volume of blood within the fetal placental vascular compartment ($216.4 \pm 29.3$ ml) was also demonstrated. The volume of blood contained in this vascular bed was directly proportional to the umbilical artery perfusion pressure, with a high correlation in all experiments (Table 3).

**DISCUSSION**

The present study was focused on the placenta as an isolated preparation to determine its vascular compliance more closely during conditions before, during, and after fetal cardiac bypass, when large intravascular volume shifts take place.

Characterization of various aspects of placental vascular hemodynamics using the isolated placental preparation has added new insights into the behavior of the placental vasculature during extracorporeal circulation. These insights have been and will continue to be extremely useful in the design of the ideal method of fetal extracorporeal circulatory support (13). Whether the placenta is included or not in the bypass circuit, the fetus will ultimately rely on the placenta after weaning from ECC (7).

**Critique of the preparation.** The isolated placental preparation was developed to study in detail the effects of nonpulsatile extracorporeal perfusion on placental compliance, thereby simulating the hemodynamics present in the placenta during fetal cardiac bypass. The advantages of the isolated preparation are that the pressure and flow parameters can be precisely controlled and measured and that fetal influences on the placental vascular compartment can be studied in detail.
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dPlacental volume changes in the fetal vascular compartment resulted from changes in umbilical artery perfusion pressure

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<th>ΔUA Flow</th>
<th>ΔUA Pressure</th>
<th>ΔPlacental Volume</th>
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<tbody>
<tr>
<td>1</td>
<td>-71.4</td>
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<td>2</td>
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</table>

ΔUA flow, umbilical artery blood flow change (ml·min⁻¹·kg⁻¹); ΔUA pressure, umbilical artery perfusion pressure change (mmHg); Δplacental volume, placental volume change (ml).

placental circulation are removed, allowing observation of changes intrinsic to the placenta itself. These advantages, however, must be considered in the context that the isolated organ preparation does not reflect the intact whole animal physiology.

The use of nitroprusside introduces a nonphysiological element into this model. Initially, nitroprusside was administered to the fetus before the umbilical vessels were manipulated to make the cannulation possible. Otherwise, it would have resulted in marked umbilical vasospasm, prohibiting use of the preparation.

During the extracorporeal circulation of the placent, nitroprusside was used for a different purpose: to achieve initial conditions in which the placental vascular resistance was at relatively normal levels. Under resting conditions, the placental vasculature has been demonstrated to be nearly maximally dilated (15), with resistance values ranging from 0.14 ± 0.01 to 0.30 ± 0.02 mmHg·ml⁻¹·min⁻¹·kg⁻¹ (16).

In this study, nitroprusside was titrated until placental vascular resistance approached normal levels (0.26 ± 0.03 mmHg·ml⁻¹·min⁻¹·kg⁻¹) at normal flow rates (200.7 ± 8.49 ml·min⁻¹·kg⁻¹), simulating the normal placental vascular tone observed in chronic unstressed preparations. Because the placental vasculature during resting conditions is known to be in a state of maximal vasodilatation, the resistance values achieved in our preparations using nitroprusside would suggest that our preparations were close to maximal vasodilatation. Achievement of maximal vasodilatation, however, is not critical to these experiments. The major purpose of the nitroprusside was to achieve normal baseline hemodynamic conditions.

Implications. Gow (11) defines vascular compliance as blood volume change per unit of pressure change. During clinical cardiopulmonary bypass, the standard practice is to control flow rate and allow pressure to vary independently. In the present study, therefore, placental flow was controlled, whereas pressure was measured as an independent variable. Placental blood volume change was then calculated after flow change and, consequently, pressure change. As a result, the data are presented primarily as pressure-volume relationships. These relationships provide useful information concerning clinical application during fetal cardiac bypass. Our data indicate that the placenta represents a large capacitor in the fetal circulation. This information is clinically important because it establishes that aggressive volume resuscitation of the fetus may be necessary when weaning from bypass.

The placenta receives about one-half of the fetal cardiac output (17) and contains a large volume of blood, with reports varying from 10 to 65% of total blood volume of fetal lambs (6). Corroborating these data, our work suggests that the placental vasculature can act as a unique and sensitive capacitor in the fetal circulation. There was a significant increase in umbilical vascular volume when umbilical artery pressure was raised above the surrounding pressure, while outflow pressure was held constant.

Table 3. Correlation coefficients of umbilical artery pressure change times fetal placental blood volume change relationship of each experiment

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Because the smooth muscle vascular tone was removed by infusion of nitroprusside, changes in the fetal placental vascular volume induced by umbilical artery pressure changes may reflect a passive placental vascular compliance. This could be consistent with the perfusion of channels that are closed at a lower inflow pressure. However, with the techniques used in this study, recruitment could not be separated from distention of the fetal placental vascular bed. Maseri and colleagues (14) suggested an experimental method in the pulmonary circulation in which these two possible responses to an increase in inflow pressure could be distinguished. If both the intravascular and extravascular spaces were measured, then, with recruitment of previously unperfused channels, both spaces would increase. On the other hand, if only the distention were taking place, only the intravascular space should increase. Studies of Bissonette et al. (3–5) have demonstrated that, when umbilical artery pressure is raised from 25 to 35 mmHg, both intravascular and extravascular spaces increase, suggesting recruitment of previously unperfused capillary beds. When umbilical artery pressure is raised further, only the intravascular space increased, whereas extravascular space remained constant. This indicates distention of the vascular bed with no additional recruitment.

In this work, as the umbilical artery pressure falls, distention of the placental vessel walls may diminish, or de-recruitment may occur, causing a decrease of the fetal placental vascular volume. This explanation would only be observed if the placental vasculature were already maximally, or close to maximally, dilated, such that little or no direct effect of an active vasodilator effect on the placental vasculature itself was possible. The possibility of acute vessel constriction unrelated to nitroprusside is also highly unlikely. Active vessel constriction would act in the opposite manner of autoregulation, with increased instead of decreased vessel tone occurring in response to lowered pressure. This mechanism is unlikely for two reasons. First, there is no physiological precedent for such an “anti-autoregulatory” mechanism, and, second, we have taken measures (nitroprusside) to blunt the smooth muscle response. Our present protocol eliminates smooth muscle tone under baseline conditions of flows of 200 ml·min⁻¹·kg⁻¹, although some vascular tone may be present under other conditions.

This argument, in combination with the findings of the present study, suggests that the placental vasculature truly is close to maximal vasodilatation under resting conditions. The present study documents for the first time the proportional increase in fetal placental vascular volume that occurs with increasing perfusion pressure during conditions of fetal cardiac bypass.

Largely as a result of advances in the understanding of both the fetal response to anesthesia and pathophysiology of fetal extracorporeal circulation (8, 9, 18–20), in the near future the possibility of fetal intervention might be offered to cardiologists and parents of the most severely affected fetuses. However, some gaps remain; proof of efficacy and superiority of fetal cardiac surgery over conventional postnatal therapies must be shown before widespread application of these techniques to human beings.

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REFERENCES


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