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Gas Exchange and Artificial Lung

Vasoconstrictive eicosanoid responses to extracorporeal circulation with or without an oxygenator in fetal lambs

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ABSTRACT: Introduction. *This study measured levels of vasoconstrictive eicosanoids during ovine fetal cardiac bypass and compared the measurements between two groups: (1) a group in which the placenta functioned as the only source of oxygen supply during the bypass (the placenta group), and (2) a group in which an artificial oxygenator, instead of the placenta, was included in the bypass circuit (the oxygenator group).*

Materials and Methods. *A total of 16 fetal lambs were randomly assigned into either the oxygenator group or the placenta group. Following anesthesia, the fetal cardiac bypass procedure was performed. The placenta group used a centrifugal pump as the pumping device without an oxygenator during the bypass. The bypass circuit in the oxygenator group consisted of a roller pump and a membrane oxygenator. The fetal cardiac bypass procedure was performed for 30 minutes at normothermia in both groups. For the measurements of thromboxane B_2(TXB_2) and prostaglandin E_2 (PGE_2), blood sampels were taken before the bypass, at 5 minutes, 15 minutes, and 30 minutes after the start of cardiac bypass, and at 15 minutes after weaning from the bypass. TXB_2 and PGE_2 levels were determined by radioimmunoassay with PGE_2(^{125}I) and TXB_2(^{125}I) assay systems. Hemodynamic observations and arterial blood gas analyses were done every 10 minutes.*

Results. *The mean arterial pressure and heart rate ranged from 69.8 to 82.6 mmHg and 169 to 182/min during the bypass in the oxygenator group, and from 14.4 to 44.7 mmHg and 64.3 to 75/min in the placenta group. Arterial blood gas analysis showed severe hypercapnia and hypoxemia with acidosis during and after the bypass in the placenta group. Bypass flow rates were maintained at 140.3-164.0 ml/kg/min in the oxygenator group, while flow rates were suboptimal (74.3-97.0 ml/kg/min) in the placenta group. There were no statistically significant differences in PGE_2 concentrations before, during, or after bypass, although the placenta group displayed a tendency to higher measurements during bypass, compared to the oxygenator group. The placenta group also showed higher TXB_2 measurements than the oxygenator group during the bypass ($p=0.0457$).*

Conclusions. *We have demonstrated increase measurements of PGE_2 and TXB_2 in the placenta group when compared with the oxygenator group in an ovine fetal cardiac bypass model, although the PGE_2 difference failed to reach statistical significance. (Int J Artif Organs 2000; 23: 436-40)*

KEY WORDS: Fetal cardiac bypass, Eicosanoid, Prostaglandin, Thromboxane

INTRODUCTION

Recently, intrauterine surgical intervention has been proposed as a possible and more helpful option for certain congenital cardiac anomalies (1-4). However, current experimental work indicates that the morbidity and mortality related to fetal cardiac bypass may outweight the benefits to be gained by the intrauterine cardiac repair (5-7). Progressive fetal hypercarbia caused by elevated placental resistance following weaning from bypass, along with fetal stress response, are the major limitations in successful clinical application of fetal intervention for cardiac anomalies (5). Some studies suggest that an increase in placental vascular resistance and a decrease in placental blood flow are the result of the production of placental vasoconstructive eicosanoids, such as thromboxane and prostaglandin E_2, in the placenta during bypass (8, 9). To date, however, there has been only indirect supporting evidence; indomethacin and high-dose steroids prevent the rise in placental vascular resistance during and after bypass (8, 9).

On the other hand, fetal cardiac bypass utilizing an artificial oxygenator instead of the placenta as a source of oxygenation has been proposed as a possible alternative for the prevention of the unwanted placental vasoconstrictive response as it may provide less stimulation of the placental vasculature during bypass (5, 10).

Therefore, we planned to directly measure levels of vasoconstrictive eicosanoids during and after the fetal cardiac bypass procedure in an ovine experimental model and to compare the measurements between two groups: (1) a group in which the placenta functioned as the only source of oxygen supply during fetal bypass, and (2) a group in which an artificial oxygenator, instead of the placenta, was included in the extracorporeal circulation.

MATERIAL AND METHODS

Anesthetic management

A total of 16 fetuses from pregnant ewes of the Corridale breed were studied. Gestational age ranged from 120 to 140 days and weight of the fetuses from 1.9 to 5.2 kg. Anesthesia was induced with ketamine 60 mg/kg intramuscularly and the pregnant ewe was intubated with an 8 mm intratracheal tube via a tracheostomy. The lungs of the animals were ventilated artificially with 100% oxygen. Ringer's lactate solution was used as maintenance fluid, being infused through the cephalic or recurrent tarsal vein. The anesthesia was maintained with intravenous ketamine at 5 mg/kg/h, with intermittent administration of vecuronium (0.2 mg/kg).

Surgical procedure

The fetus was exposed through a midline maternal laparotomy and a vertical hysterotomy. Intravenous fluid was administred sufficiently to keep the ewe's hematocrit value around 25%. Intramuscular injections of ketamine, 50 mg/kg and succinylcholine 5 mg/kg were given to the fetal lamb. A fetal neck incision exposed the carotid artery, which was cannulated toward the heart for arterial blood pressure monitoring and blood sampling. The fetal heart was exposed through a median sternotomy, and cannulation of the main pulmonary artery was done with a 12 G cannula for arterial inflow. The right atrial appendage was cannulated with a 14 or 18 Fr venous cannula for venous uptake.

Fetal cardiac bypass

We divided the animals into two groups: 1) one in which the placenta functioned as the only source of oxygen supply during fetal bypass (the placenta group), and 2) one in which an artificial oxygenator, instead of the placenta, was included in the extacorporal circulation (the oxygenator group). The placenta group used a centrifugal pump (Biopump, Medtronic, Bio-medicus, Eden Prairie, Minn, USA), without inclusion of oxygenator, as the pumping device during cardiac bypass. The bypass circuit in the oxygenator group consisted of a roller pum (American Optical Corporation, Greenwich, CT, USA) and a membrane oxygenator (micro-safe, Polystan, Denmark).

Experimental studies

Animals were randomly assigned to one of the two groups: the placenta group (n=8) or oxygenator group (n=8). Fetal cardiac bypass was performed for 30 minutes at normothermia in both. To measure thromboxane B_2 and prostaglandin E_2, blood samples were taken before the fetal cardiac bypass procedure, at 5 minutes, 15 minutes, and 30 minutes after the start of cardiac bypass, and 15 minutes after weaning. Thromboxane B_2 and prostaglandin E_2 levels were determined by radioimmunoassay with prostaglandiin $E_2(^{125}I)$ and thromboxane $B_2(^{125}I)$ assay

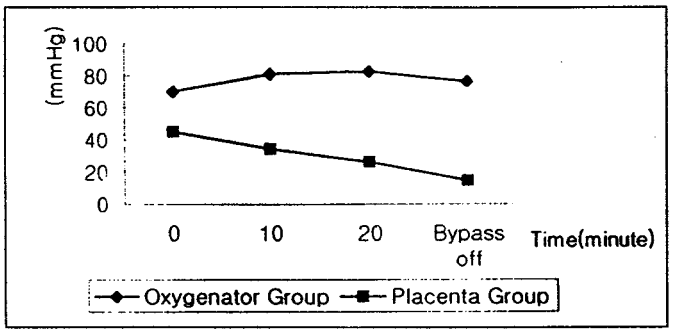

Fig. 1 - *Changes in fetal mean arterial pressure during fetal cardiac bypass.*

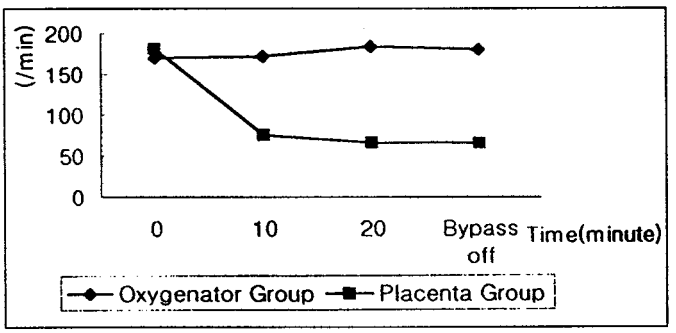

Fig. 2 - *Changes in fetal heart rate during fetal cardiac bypass.*

system (RPA530, Amersham, UK). Hemodynamic observations (mean arterial pressure, right atrial pressure, and heart rate) and arterial blood gas analyses of the fetuses were made every 10 minutes during bypass. At the conclusion of the experiment, the ewe and fetuses were sacrificed with phenobarbital and potassium chloride if the heart beat had not spontaneously stopped.

Statistical analysis

Differences between the placenta group and the oxygenator group were tested using repeated measured ANOVA. Time related differences within the group were tested by paired t-test. A value of $p<0.05$ was considered statistically significant.

RESULTS

Two animals in the placenta group died prematurely during the procedure. In the oxygenator group (n=8), mean arterial pressure and heart rate ranged from 69.8 to 82.6 mmHg and 169 to 182/min during bypas (Figs. 1, 2), and in the placenta group (n=6), from 14.4 to 44.7 mmHg and 64.3 to 75/min. The fetal bypass and post-bypass values for PH, PaO_2, $PaCO_2$ and HCO_3 are shown in

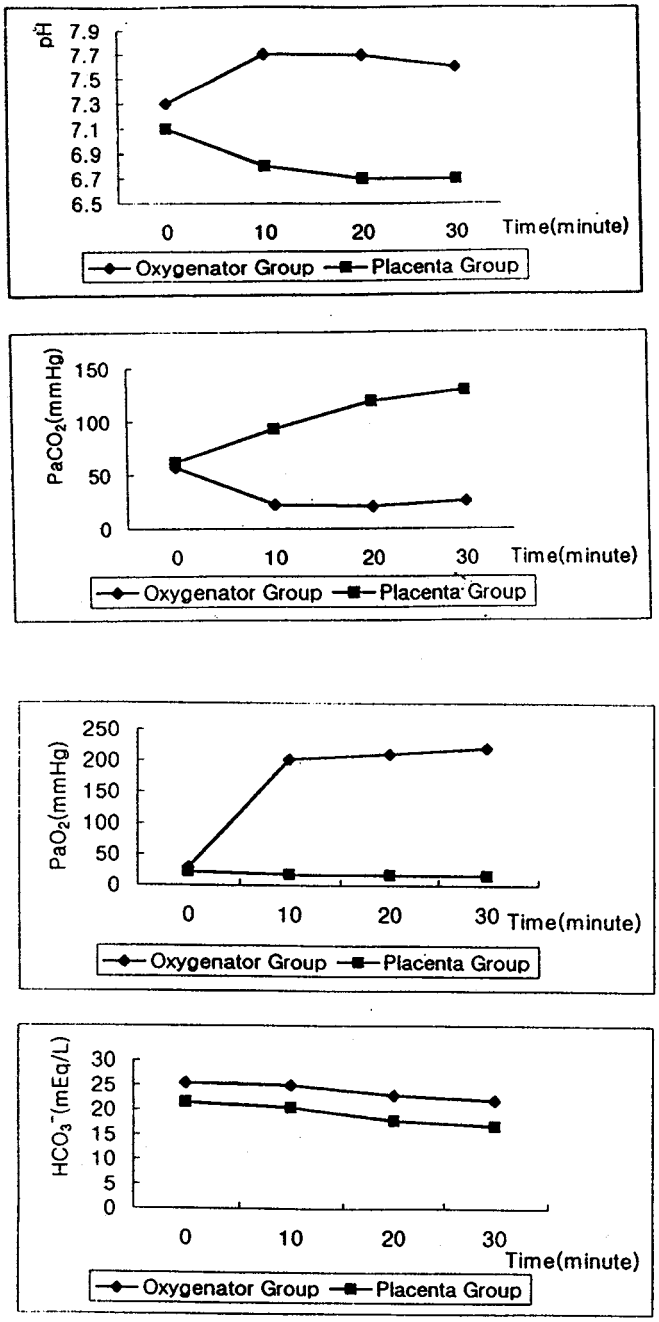

Fig. 3 - *Findings of arterial blood gas analysis during fetal cardiac bypass.*

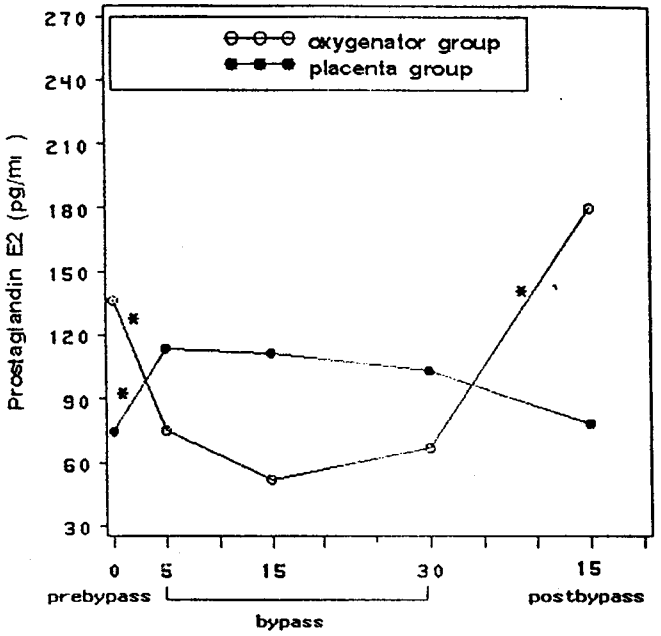

Fig. 4 - *Prostaglandin E_2 concentrations during fetal cardiac bypass either with an oxygenator (oxygenator group) or without (placenta group).*

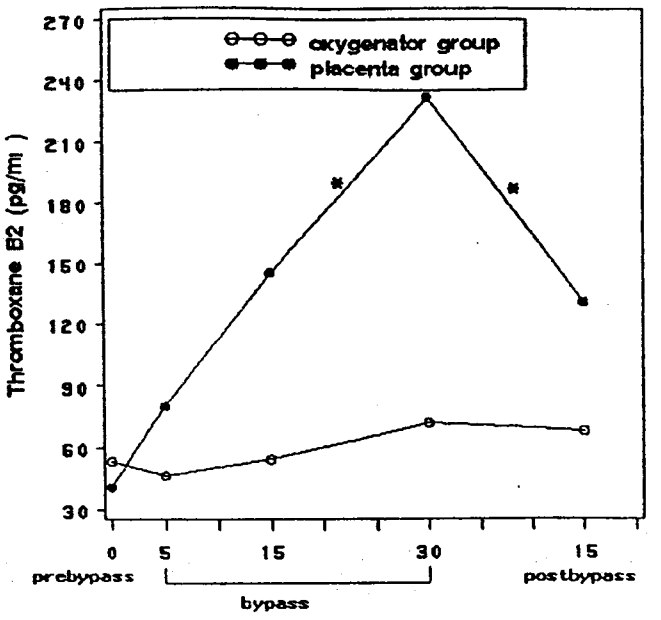

Fig. 5 - *Thromboxane B_2 concentrations during fetal cardiac bypass either with an oxygenator (oxygenator group) or without (placenta group).*

Figure 3. Arterial blood gas analyses in the placenta group showed severe hypercapnia and hypoxemia with acidosis during bypass. Bypass flow rates were maintained at 140.3-164.0 ml/kg/min in the oxygenator group, while flow rates were suboptimal (74.3-97.0 ml/kg/min) in the placenta group.

There were no statistically significant differences in prostaglandin E_2 concentrations between the two groups before, during, or after bypass, although the placenta group showed a tendency toward greater increased measurements during bypass (Fig. 4). Additionally, the placenta group showed higher thromboxane B_2 measurements than the oxygenator group during bypass ($p=0.0457$) (Fig. 5).

DISCUSSION

Decreased placental blood flow with hypercarbia following fetal cardiac bypass has been reported to be a main cause of acute fetal death. In experimental results using indomethacin and corticosteroids, vasoconstrictive eicosanoids, such as prostaglandin E_2 and thromboxane, have been implicated as important mediators of the placental vasoconstrictive response following fetal bypass (10). Because they are derived from a polyunsaturated eicosanoic (C20) fatty acid, thromboxanes and prostaglandins, along with epoxygenases, leukotrienes, and lipoxins, are collectively known as eicosanoids (11). The demonstration of a marked reduction in the unwanted placental response to fetal cardiac bypass with the use of indomethacine or corticosteroids (blocking agents of the arachidonic acid cascade), however, only provides indirect evidence of the involvement of eicosanoid products in the cardiac bypass-related response of the fetus (8, 9). In this regard, we attempted to demonstrate the fetal cardiac bypass-related changes of ecosanoid products through direct measurement of prostaglandin E_2 and thromboxane B_2 in an ovine fetal cardiac bypass model. Thromboxane B_2 is the stable metabolite of thromboxane A_2 and can be measured using radioimmunoassay.

We compared measurements of the two possible circuits for fetal extracorporeal circulatory support as suggested by Dr. Hanley (5); a gravity venous drainage circuit with a roller pump and an oxygenator (oxygenator group), and an active venous drainage circuit with a centrifugal pump and no oxygenator (placenta group).

The results of our experiment demonstrated increased

levels of prostaglandin E_2 and thromboxane B_2 during fetal cardiac bypass in the placenta group, when compared to the oxygenator group, although the prostaglandin E_2 difference did not reach statistical significance. Because fetal cardiac bypass with an artificial oxygenator and umbilical-placental occlusion theoretically stimulates placental vasculature less than bypass with the use of the placenta as an oxygenation source, the present results were as predicted before the experiment began. However, in this experiment, unlike previous studies, we were unable to obtain sufficient bypass flow in the placenta group. At this point, we do not know exactly whether this was due to early release of vasoconstrictive eicosanoids or from some other unknown problem in our experimental circuit. However, the rapid downward course of the animals in the placenta group during the bypass procedure, suggests that this is more likely to be due to an increase in eicosanoic products.

Before the start of the bypass procedure, the control data of the oxygenator group showed increased levels of both prostaglandin E_2 and throboxane B_2 when compared to those of the placenta group. A possible explanation is that the more manipulative procedure required to set the circuit for the oxygenator group caused a greater release of both prostaglandin E_2 and thromboxane B_2.

In conclusion, we demonstrated increase levels of PGE_2 and TXB_2 in the placenta group when compared to the oxygenator group in an ovine fetal cardiac bypass model, although the PGE_2 difference was not statistically significant.

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