INFLUENCE OF MATERNAL HYPEROXIA OR HYPERCARBIA ON THE HEMODYNAMICS OF THE PLACENTA AND FETAL BRAIN

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Synopsis Pregnant rabbits were subjected to inhalation of different gases, and the changes in placental blood flow (PBF), fetal heart rate (HR), and fetal cerebral blood flow (CBF) associated with the changes in maternal blood gas levels were studied. The results are given below.

In maternal hyperoxia, maternal blood pressure (BP) was not much influenced and PBF remained unchanged or was slightly decreased when the PCO₂ level was not varied or when it was lowered. In contrast, not only maternal BP but also PBF was increased when the PCO₂ level was elevated. In the absence of a conspicuous increase in PCO₂, neither fetal HR nor CBF varied, regardless of PBF.

Both maternal BP and PBF were increased in mild to moderate maternal hypoxia (PO₂>40mmHg) and decreased in severe hypoxia (PO₂<30mmHg). The decreasing trend of fetal HR or CBF was strengthened as maternal hypoxia was intensified. An obvious decrease in either parameter was observed in severe maternal hypoxia (PO₂<30mmHg). Fetal HR and CBF were well maintained in hypoxic dams with increased PBF as compared with those with unchanged or decreased PBF. The higher the PO₂ level or the lower the pH value, the more was fetal bradycardia that was apt to occur, even in a mildly hypoxic state.

Key words: Maternal hyperoxia • Hypercarbia • Placental blood flow • Fetal cerebral blood flow

Introduction

It is one of the most important tasks imposed upon obstetricians to establish methods for the prevention and treatment of brain damage associated with fetal or neonatal distress. However, this is not possible without elucidating pathophysiology in the process of development of the lesion.

In the previous experiment¹, we studied the factors regulating cerebral hemodynamics in neonates with the following results: In physiological neonates, the cerebral blood vessels were constricted by oxygen (O₂) inhalation and dilated by carbon dioxide (CO₂) inhalation. However, in severe bradycardia induced by a high concentration of CO₂, neonatal heart function was suppressed and the increase in cerebral blood flow (CBF) was no longer seen. In neonatal hypoxia, CBF as well as cardiac function was recovered by O₂ inhalation.

On the basis of the knowledge acquired previously, the present experiment was undertaken to clarify the factors regulating the cerebral hemodynamics of fetuses by means of following up changes in fetal CBF induced via the fetoplacental system after gas inhalation by dams.

Materials and Methods

The animals used were 93 pregnant rabbits (on day 27~31 of gestation) weighing 2.3~4kg. Under intraperitoneal urethane (1~1.5g/kg) anesthesia, the animals were fixed in the supine position and subjected to airway cannulation to maintain air passage. Concurrently, a cannula was inserted into the femoral vein to perform maintenance transfusion using Klinisalz B® or Klinisalz S®. It was administered at a rate of 0.3~2ml/kg/hr, while caution was exercised not to affect blood pressure (BP).

For serial measurement of placental blood flow (PBF), fetal CBF, fetal heart rate (HR), and intrauterine pressure (AFP), median laparotomy was performed and the following procedures were carried out on the uterus.

Tissue blood flow was measured by a thermocouple method (UM meter CTE201, Unique Medical Co.). For the measurement of PBF, a wire type
element for thermocouple was inserted into the placenta under the guidance of a straight needle. For the measurement of fetal CBF, the fetal head was fixed with fingers from outside of the uterus, then the puncture point as illustrated in the previous report was detected by palpation and a wire type element for thermocouple was inserted under the guidance of a straight needle. Fetal HR was measured electrocardiographically with an electrode, which was inserted via the uterus, and it was serially recorded with a fetus-monitoring apparatus. The electrode used for fetal HR measurement was inserted into the fetus through the uterine wall. AFP was measured with an electric sphygmomanometer (LPU0.1 or TP101T, Nihon Koden), which was connected to a polyethylene tube inserted into the amniotic cavity. A polyethylene tube was also inserted into the carotid and the femoral arteries for maternal BP measurement and blood sampling. Maternal BP measurement was made serially with an electric sphygmomanometer (MPU0.5 or TP101T, Nihon Koden). The arterial blood drawn was examined with a pH-blood gas analyzer (165-2, Corning Co.).

In order to alter arbitrarily the partial pressure of inhaled gas, dams were subjected to inhalation of air mixed with O2/nitrous oxide (N2O/CO2 using an open circle or a semi-closed circle. All data except those on blood gas were serially recorded with a direct transcription type pen recorder (Nihon Koden).

Results

1) Maternal hyperoxia
Maternal arterial blood PO2 was increased to 180mmHg or more by inhalation of a high concentration of O2, and we tried to determine what effects the hyperoxic state so produced in dams might have upon maternal BP, PBF, and fetal CBF.

Fig. 1 displays the findings in a representative case of maternal hyperoxia. Maternal arterial PO2 was increased from 107mmHg to 508mmHg by O2 inhalation at a rate of 3l/min. This was accompanied by a modest increase in maternal arterial PCO2 (from 10mmHg to 31mmHg). However, maternal BP remained practically unchanged and maternal mean blood pressure (MBP) was kept almost constant. PBF showed a transient decrease due to the contraction of the uterus but no notable change during maternal hyperoxia. In addition, in a fetus with marked bradycardia (about 60 bpm), no evident recovery of fetal HR was brought about by O2 inhalation by the dam, thought the influences of uterine contractions on fetal HR and CBF were recognized.

Table 1 shows the observations in all dams whose arterial PO2 was increased to 180mmHg or more. These dams were classified into three groups according to maternal PCO2: group I with a marked increase in PCO2 (80mmHg ≥ PCO2 ≥ 60mmHg), group II with a slight to moderate increase (60mmHg > PCO2 > pretreatment level), and group III without any appreciable increase or with a decrease. Groups I, II, and III comprised 17, 36, and 30 dams respectively (83 dams in total). In these dams, the possible effects of inhalation of a high concentration of O2 upon maternal BP and PBF were investigated. Thirty-eight of them (6 dams in group I, 18 in group II, 14 in group III) were further examined for fetal HR and CBF.

The lower half of Table 1 presents the data in group III. Maternal BP remained unchanged or
slightly decreased in 70% (21/30), increased by 10% or more in 3% (1/30), and increased by less than 10% in the remaining 8 dams. The mean variance in maternal MBP was as small as $-0.3 \pm 3.6\%$ in this group. In group III, PBF was not influenced by $O_2$ inhalation in 43% (13 dams, MBP variance $-1.5 \pm 3.5\%$), decreased in 30% (9 dams, $-1.8 \pm 2.6\%$), and increased in 27% (8 dams, $+4.2 \pm 4.5\%$). Thus, the findings were rather inconsistent in the dams whose $PCO_2$ levels were not increased.

Fetal HR remained unvaried in 93% (13/14) of the dams examined. Of these dams without a variance in fetal HR, fetal CBF was also unchanged, either, in 77% (10/13).

The middle part of the same table exhibits the findings in group II. Maternal BP tended to be increased in this group as compared with group I. To be more precise, an increase of 10% or more in MBP was observed in 14% (5/36) of the dams and an increase of less than 10% in 72% (26/36). In this group which showed a weak tendency to increase in MBP ($+6.3 \pm 3.4\%$), PBF was augmented in approximately half of the dams (53% of 19/36, variance in MBP $+8.8 \pm 3.3$) and reduced in only 17% (6/36, $+1.2 \pm 2.9$).

Fetal HR remained almost unchanged in 83% (15/18) of the dams examined. Fetal CBF was also unaffected in most of them. Both fetal HR and CBF were increased in some exceptional dams (one dam without a change in PBF, two with an increase in PBF).

The upper part of Table 1 presents the observa-
tions made on group I. The increase in maternal MBP (+16.8±12.9%) was conspicuous as compared with that observed in group III and group II. Sixty-one percent (12/17) of the dams of group I showed an MBP increase of 10% or more. PBF was increased in 82% (14/17) of the dams of this group with a marked increase in MBP.

With regard to fetal HR and CBF, only six dams were examined in group I. No change in either parameter was caused in half of them and both parameters were increased in two (33%).

2) Maternal hypoxia

Maternal arterial blood PO₂ was reduced by inhalation of gas containing a low concentration of O₂, and the possible effects of the maternal hypoxia so produced on maternal and fetal hemodynamics were studied.

Fig. 2 shows a representative case. In a dam subjected to inhalation of 0.5l/min of O₂ mixed with 3l/min of N₂O, the arterial blood O₂ level was gradually lowered to 56mmHg at point (a) them to 40mmHg at point (b) from the pretreatment level (106mmHg), while PCO₂ was greatly increased to 51mmHg at point (a) then to 65mmHg at point (b) from the pretreatment level (28mmHg). At point (a), maternal MBP was increased remarkably by 25% and pulse pressure (PP) was also increased by approximately 50%. At point (b), maternal MBP and PP were increased by about 15% and 10% respectively. As stated above, both maternal MBP and PP were increased as a low concentration of O₂ was inhaled. It may be pointed out, however, that the tempo of increase of both MBP and PP was slowed down between the two points of observation. PBF continued to increase until point (a) in spite of transient decreases due to uterine contractions. After that, it became rather rare with enhancement of hypoxia that PBF surpassed the pretreatment level. In mild hypoxia (PO₂>50mmHg, PCO₂<50mmHg), a transient decrease in fetal HR (bradycardia due to uterine contractions) or fetal CBF was seen, but, baseline fetal CBF was rather increased. In severe hypoxia, however, marked bradycardia was developed and fetal CBF was decreased.

After the gas inhalation was discontinued, maternal BP, PBF, fetal HR, and fetal CBF were all recovered.

For in-depth analysis of the data, the animals were sorted into the following four groups by the arterial PO₂ level: group I (above 60mmHg), group II (60~40mmHg), group III (40~30mmHg), and group IV (below 30mmHg) (Table 2, 3).

Table 2 is useful for analysis of PBF in relation to maternal MBP and PP in each hypoxic state. Maternal MBP and PP showed an evident trend of increase in group I and group II. PBF was increased in 56% of the animals in group I (n=32) and 51% in group II (n=68). There was no animal whose PBF was decreased in either of the two groups. In group III with severer hypoxia (n=36), PBF was increased in 38% of the animals, remained unchanged in 46%, and was decreased in 16%. In the last subgroup (with a decrease in PBF) of group III, maternal MBP was reduced in four of the six animals (67%) and PP was also reduced in two (33%). It is suggested, therefore, that maternal systemic hemodynamics is impaired in severe hypoxia. In the dams whose PO₂ stayed above a 30mmHg level, PBF was maintained in spite of the
Table 2. Effects of maternal hypoxia on maternal mean blood pressure (MBP), pulse pressure (PP), and placental blood flow (PBF) in rabbits.

<table>
<thead>
<tr>
<th>PaO2</th>
<th>Alteration of PBF</th>
<th>Mean Blood Pressure</th>
<th>Pulse Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>~60 mmHg</td>
<td>↑56% (18/32)</td>
<td>MBP ↑ ≥10%</td>
</tr>
<tr>
<td>I</td>
<td>60~40 mmHg</td>
<td>↑51% (35/68)</td>
<td>MBP ↑ 10%~0%</td>
</tr>
<tr>
<td>II</td>
<td>40~30 mmHg</td>
<td>↑38% (15/39)</td>
<td>MBP ↑ 10%~0%</td>
</tr>
<tr>
<td>III</td>
<td>30 mmHg &gt;</td>
<td>↓100% (7/7)</td>
<td>MBP ↓</td>
</tr>
</tbody>
</table>

↑ Increase
↓ Decrease
- No change

Table 3. Effects of maternal hypoxia on placental blood flow (PBF), fetal heart rate (HR), and fetal cerebral blood flow (CBF) in rabbits.

<table>
<thead>
<tr>
<th>Degree of Hypoxia</th>
<th>PBF (%)</th>
<th>FHR (%)</th>
<th>CBF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal arterial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PO2 Control ~60 mmHg</td>
<td>↑56% (18/32)</td>
<td>(5) 27</td>
<td>(3) 18</td>
</tr>
<tr>
<td>I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60~40 mmHg</td>
<td>↑51% (35/68)</td>
<td>(5) 71</td>
<td>(1) 10</td>
</tr>
<tr>
<td>II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40~30 mmHg</td>
<td>↑38% (15/30)</td>
<td>(3) 33</td>
<td>(1) 17</td>
</tr>
<tr>
<td>III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 mmHg &gt;</td>
<td>↑100% (7/7)</td>
<td>(7) 100</td>
<td>(4) 100</td>
</tr>
<tr>
<td>IV</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Control PO2 120~180 mmHg
↑ : Increase
↓ : Decrease
- : No change

x2 = 10.258
P < 0.01

intensification of hypoxia, in so far as BP and PP were maintained. The increase in MBP or PP was marked and greater by more than 10% in the animals with an increase in PBF, irrespective of the degree of hypoxia or which group they belonged to. However, in severe hypoxia (PO2 <30mmHg), neither MBP nor PP was maintained and PBF was distinctly decreased.

Table 3 was prepared to study PBF in relation to fetal HR and fetal CBF in a total of 71 dams. In group I with mild hypoxia (PO2 >60mmHg) (n=18), PBF was well maintained in general and fetal HR as well as fetal CBF was stationary in 78% (14/18). Fetal HR and CBF were decreased in only 11% (2/18). In group II with intensified hypoxia (n=25), PBF was still maintained, but fetal bradycardia and a decrease in fetal CBF were observed in 52% (13/25). In group III with more intensified hypoxia (n=21), PBF was decreased in some dams and fetal bradycardia with a concurrent decrease in fetal CBF was developed in 89% (17/21). In group IV with the most intensified hypoxia (n=7), placental circulation was disrupted and fetal bradycardia and a decrease in fetal CBF were recognized in all the dams. As shown above, fetal HR and CBF were apparently on the decrease with the intensification of hypoxia.

The possible relationship between placental and fetal hemodynamics was sought with the following results: In group I, fetal hemodynamics was not exacerbated, as long as PBF was on an increased level. However, of the dams whose PBF remained unchanged, fetal bradycardia and a decrease in fetal CBF were observed in 29% (2/7). In group II,
fetal bradycardia was seen in 36% (4/11) of the dams with increased PBF and 64% (9/14) of those with unchanged PBF. In group III, the respective ratios were as high as 67% (4/6) and 82% (9/11). The incidence of fetal bradycardia was significantly higher in the subgroup with unchanged PBF (n=32) than in that with increased PBF (n=28) (p<0.01). Thus, fetal hemodynamics was better maintained in the latter subgroup.

3) Relationship between maternal blood gas levels and fetal bradycardia

In order to look into the possible relation between maternal blood gas levels and fetal bradycardia, the gas levels after the onset of fetal bradycardia were compared with those before its onset in the dams in which a reduction of more than 30 bpm in fetal HR lasted for more than two minutes.

The findings are presented in Fig. 3. The values marked ○ were the blood gas levels before the onset of bradycardia and those marked × were the levels after its onset. The left half of the figure shows the relation between PO$_2$ and PCO$_2$ and the right half that between PO$_2$ and pH. The higher the PCO$_2$ level or the smaller the pH value, the more was fetal bradycardia apt to occur, even in mild hypoxia. Concerning the 38 hypoxic dams whose PO$_2$ levels became lower than the control level, a regression line representing PO$_2$ (Y) and PCO$_2$ (X) before and after the manifestation of bradycardia was drawn, and the following equation was obtained from the regression line:

$$Y = 29.1 + 0.473X \quad (r = 0.69, \ p < 0.001)$$

In the same fashion, another equation including Y (PO$_2$) and X (pH) was formed, as follows:

$$Y = 459.2 - 58.4X \quad (r = 0.03, \ p < 0.05)$$

Comment

In our previous report$^6$, we commented as follows: PBF was decreased by a maximum of 60% at maximum at the time of uterine contraction and, subsequently, O$_2$ supply to fetuses was reduced. Furthermore, this reduction affected the functional reserve of the fetoplacental system, inducing bradycardia eventually.

Fig. 3. Critical points of onset of fetal bradycardia studied in consideration of the relationship between maternal arterial blood PO$_2$ and PCO$_2$ levels and between PO$_2$ levels and blood pH in rabbits.
Among those factors that may possibly cause fetal or neonatal distress, the changes in maternal blood gas levels were taken up as the subject of the present study and their effects on placental hemodynamics and fetuses were investigated.

1) Maternal hyperoxia

It has been suggested that hyperoxia experimentally induced by O₂ inhalation may trigger constriction of the placental blood vessels, resulting in a decrease in PBF. To our knowledge, however, no investigator has studied the effects of hyperoxemia on PBF or uterine blood flow, except Peeters et al. who measured the blood flow from fetus to placenta in sheep dams by a microsphere method. They reported as follows: The increase of fetal arterial O₂ consequent upon maternal hyperoxia did not lead to an evident change in umbilical blood flow.

Maternal hypercarbia or the increase of blood PCO₂ in dams is considered to induce vasodilation in the periphery, on the one hand, and have an influence upon catecholamine release via the chemoreceptor in the autonomic nerve system, on the other. Naturally, a change in PCO₂ is thought to have a bearing on PBF, though no evidence attesting to this has been presented.

In this investigation, the possible effects of maternal hyperoxia (PO₂≥180mmHg) on PBF were studied in consideration of the arterial PCO₂ level. PBF remained unvaried in 43% of the dams with unchanged or decreased PCO₂ levels and was decreased in 30% of them. Maternal BP remained almost unchanged in the animals concerned. It was inferred that the decrease in PBF was due to placental vasoconstriction. However, in hyperoxia accompanied by hypercarbia, PBF as well as maternal BP tended to augment with an increase of PCO₂. In this respect, it was postulated that the direct action of CO₂ upon the vascular wall to dilate the placental blood vessels might have exceeded the vasoconstriction due to the enhanced release of catecholamine associated with hypercarbia to induce an increase of PBF eventually. In addition, the increase of PBF may be ascribed in part to the increase in cardiac output consequent upon the promoted catecholamine release. In consequence, maternal arterial PCO₂ played a more important role than PO₂ in the regulation of PBF.

Clinically, maternal O₂ inhalation is often done in the expectation that it may exert a favorable effect on the fetus. Nevertheless, it remains unanswered what effects maternal hyperoxia has on fetal hemodynamics. In the present animal experiment, neither fetal HR nor fetal CBF was appreciably altered by maternal hyperoxia (PO₂>180mmHg) when the PCO₂ level was lower than 60mmHg. They tended to increase when the PCO₂ level was within the range of 60 to 80mmHg. Both of them decreased in spite of hyperoxia when the PCO₂ level was higher than 80mmHg. In our previous experiment, a decrease in CBF without any change in HR was observed in 71% of hyperoxic neonates. In this connection, it seemed that the fetal PO₂ level was not so much elevated in maternal hyperoxia. In man, umbilical venous PO₂ reportedly showed only a slight increase (from 31.6±1.6 to 38.1±3.1mmHg) even when maternal arterial PO₂ was increased to 400mmHg. Thus, the fetal PO₂ level was considered rather insusceptible to a change in maternal PO₂ level.

2) Maternal hypoxia

It was reported that umbilical blood flow was not conspicuously changed, or was decreased by hypoxia in dams. No ample information is available as regards the effects of maternal hypoxia on uterine blood flow, though Dilts et al. measured uterine blood flow in sheep dams with an electromagnetic flowmeter and demonstrated that it was decreased during 6% O₂ inhalation, and that the decrease in uterine blood flow was concurrent with a marked decrease in maternal arterial PO₂ (from 99.6 to 32±3.4mmHg) and a 10% decrease in maternal MBP.

In this study, it was attempted to relate maternal BP to PBF in pregnant rabbits in different hypoxic states. In hypoxia with a PO₂ value of not less than 40mmHg, maternal BP as well as PP tended to be increased in the relevant dams and PBF was increased in about a half of them. This tendency was more remarkable in the dams with increased PBF than in those with unchanged PBF. In hypoxia with a PO₂ value of 40mmHg or less, PBF showed a decreasing trend. When PO₂ was lowered below 30mmHg, the decrease in PBF became obvious and it was accompanied by a decrease in not only maternal BP but also PP. These findings suggest that cardiac function is impaired in severe hypoxia, and that PBF was under the strong
influence of the pressure of placental perfusion by maternal cardiac function.

Some authors have investigated HR and CBF in experimental fetal hypoxia produced by compelling dams to inhale gas containing a low level of O₂. According to their reports, fetal HR was maintained or increased\(^\text{7,10}\), or decreased\(^\text{5,9}\). The inconsistency of their data may be attributable to the discrepancies in the species of mammals used and the severity of hypoxia induced. On the other hand, fetal CBF was consistently increased in association with fetal hypoxia\(^\text{13,18}\). Besides, it was reported that fetal CBF was sensitively regulated by fetal BP: fetal CBF was prominently increased as fetal BP was heightened, and it was distinctly decreased as fetal BP was lowered\(^\text{9}\).

Information has been lacking with respect to maternal hypoxia as a factor responsible for changes in placental and fetal hemodynamics until we studied it this time. In our experiment, apparent fetal bradycardia was generally associated with a reduction in fetal CBF. It must be mentioned, however, that fetal CBF was increased transiently prior to the advent of bradycardia. In the stage before the manifestation of a lowering of fetal cardiac function due to hypoxia, CBF was probably increased through the following mechanisms: 1) As a consequence of the enhancement of catecholamine release in response to hypoxia, peripheral vascular resistance and, accordingly, fetal BP were increased, but the cerebral blood vessels, which are scarcely sensitive to catecholamine, were not constricted, hence an increase in fetal CBF. 2) The cerebral blood vessels were dilated and cerebrovascular resistance was reduced, hence an increase in fetal CBF.

When fetal hypoxia is so intensified as to impair cardiac function and induce bradycardia in fetuses, cardiac output is considered to be reduced to cause a decrease in CBF. In fact, the present observations supported the association of fetal bradycardia with a decrease in fetal CBF. Likewise, in maternal hypoxia, fetal HR and fetal CBF were relatively well maintained when PBF was increased.

It is generally accepted that fetal distress is closely associated with maternal hypoxia or acidosis. However, what degree of change in PCO₂ or pH may cause bradycardia in a hypoxic state has not been clarified. In an attempt to ascertain the critical level of PCO₂ or pH, we determined maternal arterial blood gas levels before and after the onset of fetal bradycardia in which a reduction of more than 30 bpm in fetal HR continued for at least two minutes. In dams whose PO₂ levels were lower than 30 mmHg, fetal bradycardia was induced, even when their PCO₂ levels were lowered or pH was increased. Fetal bradycardia was also induced even in dams with mild hypoxia, when PCO₂ was increased or pH was decreased. Similarly, the possibility of fetal bradycardia is high in hyperoxia with severe hypercarbia (PCO₂ > 80 mmHg) or in acidosis with a pH value below 6.8.

References

胎児循環の変動と胎盤血流量の増加との関係について検討した。I) 胎児循環動態、a）胎児ヘマトクリットの変動、胎盤血流量の増加が見られ、胎児循環動態を良好とする。b）胎児ヘマトクリットの増加が見られ、胎児循環動態を悪化させる。II) 胎盤循環動態、a）胎盤血流量の増加が見られるが、胎児循環動態を良好とする。b）胎盤血流量の増加が見られ、胎児循環動態を悪化させる。c）胎児循環動態を良好とするが、胎盤血流量の増加が見られない。