0031-3998/93/3406-0834$03.00/0
PEDIATRIC RESEARCH
Vol. 34, No. 6, 1993
Printed in U.S.A.


# Inhibition of Fetal Breathing: A Pilot Study

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**ABSTRACT. Fetal breathing occurs sporadically and is inhibited during periods of hypoxemia, when blood, returning from the placenta, is mainly taking the shortcut through the ductus venosus. The hypothesis tested is that this inhibition might be caused by an expansion of the ductus venosus. Such expansion is pronounced during fetal life but ceases to occur after birth. Regular breathing of newborn lambs was recorded, and it was noted how the breathing was affected when blood, with the aid of a roller pump, was infused from the umbilical arteries into the umbilical veins. Nine lambs were examined, and for a maximal period of 2 min blood was infused into the umbilical veins at a rate of 50–150 mL/min. During 12 infusions, breathing temporarily came to a complete stop; in 30 cases, respiration was only partially inhibited; and in five cases, it was not affected. It is concluded that a very clear breathing inhibition may be obtained with an infusion of blood into the umbilical vein. It is speculated that expansion of the ductus venosus may trigger the inhibition and that the reason the effect varies may have to do with the fact that blood entering the body through the umbilical veins may predominantly take one of two routes: the ductus venosus or the hepatic vessels. (*Pediatr Res* 34: 834–836, 1993)**

Real-time ultrasonic scanners have made it possible to observe the breathing motions of human fetuses for long periods of time. The breathing is noted to be intermittent and during the last 10 wk of human pregnancy occurs only during about one third of a 24-h observation period (1). Because intrauterine breathing requires as much as 15–30% of the total oxygen supply (2) and will do nothing to augment it, it would be beneficial if it were to be interrupted during periods of inadequate oxygen delivery from the placenta.

Periods of fetal hypoxia cause a release of catecholamines and a redistribution of cardiac output, so that vital organs such as heart, brain, and placenta receive a greater proportion of ejected blood and blood returning from the placenta takes the shortcut through the ductus venosus (3–5). A total obstruction of fetal breathing has been observed during fetal hypoxia (6) and thus coincides with the redistribution of blood flow.

After birth, the situation changes abruptly in that breathing becomes absolutely necessary for gas exchange, and it would be beneficial for the newborn if hypoxia stimulated respiration. Evolution has seemingly resulted in the most functional response to hypoxia: hypoxia inhibits breathing in the fetus but acts as a stimulus in the neonate. Possibly, this difference in response is due to a mechanism causing an inhibition of breathing that is strongly expressed by the fetus but not by the newborn.

It is hypothesized that during fetal life breathing is inhibited as long as there is a flow of blood through the ductus venosus. By causing an active expansion of the ductus, the blood might stimulate baroreceptors in the wall of the vessel. When, after birth, blood is no longer flowing through the umbilical vessels and consequently the ductus venosus is not expanded, the inhibition would cease to exist.

This study was initiated to test the hypothesis that breathing, when it has become regular after birth, can be inhibited if blood is once again made to flow through the ductus venosus.

Received for rapid publication August 2, 1993; accepted August 18, 1993.
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Supported by NIH Grant HL 40896 and the Women and Children's Health Research Foundation, Children's Hospital.

## MATERIALS AND METHODS

*Animal preparations.* With approval from the Laboratory Animal Care Committee, State University of New York at Buffalo, halothane anesthesia was used when nine fetal lambs from eight ewes were delivered by cesarean section at term. Immediately after birth, catheters were introduced into each of the four umbilical vessels in the direction of the lamb, and heparin (1000 IU) was injected on the venous side. The catheters were advanced so that the tips of those in the arteries were expected to have proceeded far, at least to the common iliac arteries, perhaps to the aorta, whereas the tips of the venous catheters were ensured to be only just inside the umbilicus. Blood infused through the venous catheters could then flow as it does in fetal life: either through the ductus venosus, through the portal veins, or through both of those routes.

As soon as the umbilical catheters had been inserted, a tracheal tube was introduced, through which the lamb would breathe spontaneously. The breathing activity was recorded by introducing a PE 50 catheter into the tracheal tube. The changes in pressure caused by the flow of air through the tracheal tube were transmitted via the air-filled catheter to a sensitive pressure transducer (Validyne, Northridge, CA). In this way, the rate of breathing was clearly recorded, but the amplitude of the tracing was of limited significance because it would be influenced by the location of the tip of the PE 50 catheter. If it happened to be near the center rather than at the periphery of the tracheal tube, the amplitude would be greater. However, for each individual lamb, the catheter's position in the tracheal tube would not be altered, which means that a change in amplitude indicated a change in flow rate and thus an altered respiratory effort.

Arterial and venous blood pressures were recorded by introducing catheters deep into femoral vessels and connecting them with pressure transducers.

Via a wide and completely blood-filled tube, each of the catheters introduced into an umbilical artery was joined with a vein catheter. The two wide connecting tubes were fitted into a roller pump, which, when turned off, compressed and thereby occluded the connections between arteries and veins. With this setup, the roller pump, which was allowed to run for no more than 2 min at a time, would transfer arterial blood directly from the aorta to the umbilical veins at a rate of 50–150 mL/min.

With the arrangement just described, it would not be known whether the effect on respiration was caused by increased pressure or by high oxygen tension. For this reason, the flow was arranged differently for four experiments. The roller pump was made to compress four wide tubes instead of two. Two would transfer blood from the arteries to a container, and from another container, heparinized venous blood taken from the ewe was transferred to the umbilical veins. The container with maternal blood held 400 mL. The pump was turned on for no more than 2 min at a maximal rate of 150 mL/min. At the end of an infusion, the containers were exchanged so that the one with arterial blood was used as source for the catheters in the umbilical veins. With this setup, the infusion into the umbilical veins was twice with venous and twice with arterial blood.

*Evaluation of recordings.* When the recorded breathing was regular, the respiratory rate was determined, as was the pressure amplitude. It was noted how those values, assessed over a 5-s period, would be maximally reduced when blood was infused into the umbilical veins.

## RESULTS

Breathing of the nine lambs was monitored continuously as blood was being repeatedly infused into the umbilical veins. A total of 47 experiments could be evaluated. When blood gas analysis indicated asphyxia, further experiments were abolished.

It was never observed that breathing was stimulated when blood was withdrawn from the arterial side and simultaneously infused into the venous side. Instead, this procedure completely inhibited breathing in 12 instances (Fig. 1), in 30 cases it caused a partial suppression (Figs. 2 and 3), and in five there was no noticeable effect.

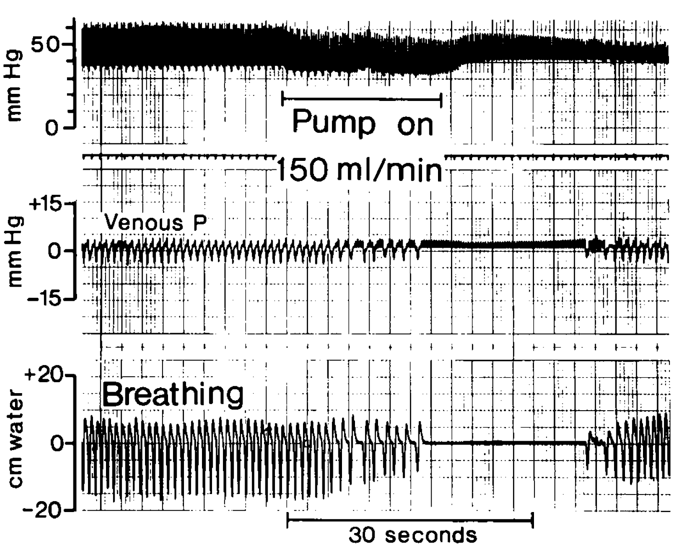


Fig. 1. When blood was withdrawn from the umbilical arteries and simultaneously infused into the umbilical veins at a rate of 150 mL/min, breathing came to a complete stop in this case. When in this lamb venous blood was infused instead of arterial blood, the effect was identical. When the blood exchange came to an end, breathing eventually returned. Note how arterial pressure was lowered when the pump was turned on. Probably this was caused by a "shunt" opening up, reducing peripheral resistance.

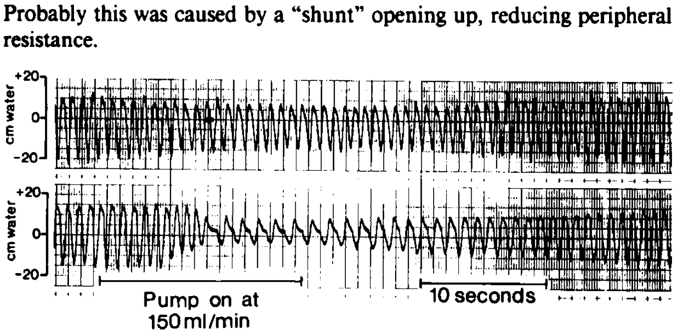


Fig. 2. Tracings showing that in one lamb the effect on breathing could vary although infusions were only minutes apart.

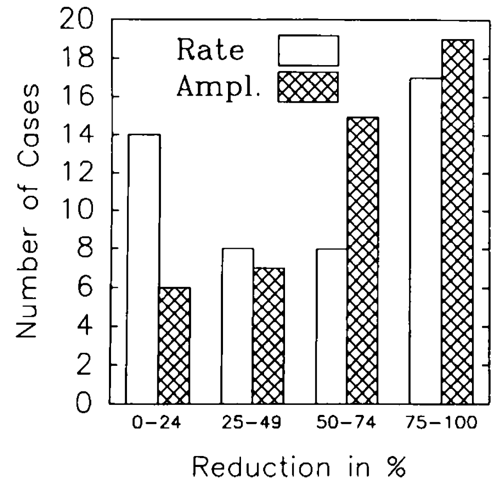


Fig. 3. Infusion of blood into the umbilical veins could cause a complete suppression of breathing. This was noted in 12 cases. The results were quite erratic, and this figure shows that the reduction in rate and amplitude was very variable. In five cases, neither rate nor amplitude was affected.

It made no difference whether the blood was oxygenated or not, because in the animal alternatively receiving arterial and venous blood, breathing was completely inhibited by both (Fig. 1).

The effect on breathing in identical experiments differed between animals, but even in the same animal the response could deviate. Figure 2 shows the results of two consecutive experiments that were carried out in one of the lambs. The upper tracing demonstrates that, during the first time the pump was turned on, the effect was minimal, but when the experiment was repeated shortly afterward, breathing was clearly inhibited.

## DISCUSSION

It was obvious that breathing could be inhibited by an infusion of blood into the umbilical vein. Most likely, the inhibition was initiated by stimulation of baroreceptors rather than chemoreceptors, inasmuch as it made no difference whether the blood was oxygenated or deoxygenated.

Soon after birth, the ductus is no longer functionally open (7) and it will not be expanded by a flow of blood from the placenta. It has been assumed that the rich nervous supply surrounding the ductus venosus is required for an activation of a sphincter function (8). Might it be, however, that some of the nerve tissue has another function: an inhibition of fetal breathing?

It is unclear why the response, inhibition of breathing, varied so much. One explanation might be that blood from the umbilical vein may take the shortcut through the ductus venosus, or a sphincter in the ductus, close to the umbilical vein, may contract and thereby direct blood to the hepatic sinusoids (9, 10). The sphincter may thus have the ability to hinder blood from expanding the ductus venosus, and this might prevent breathing from being inhibited. Another reason for an increase in hepatic blood flow might be that liver vessels relax and open up, as they might do when the fetal blood contains more glucose. Perhaps this is the reason ultrasound examinations have shown that after the mother's intake of sugar, fetal breathing is stimulated (11).

The hypothesis that expansion of the ductus venosus causes breathing to be inhibited could in the future be tested by visualizing the vessels with angiography. Contrast medium rather than blood would then be injected into the umbilical veins. One might then be able to observe that when breathing was severely suppressed the contrast medium had taken the shortcut through the ductus and thus caused it to become expanded. When the injection had minimal effect on breathing, one might see that the sphincter in the ductus was restricting flow and forcing the contrast medium to expand hepatic vessels.

If indeed the ductus venosus has receptors that are activated by the vessel's expansion, then there might be a chance that these receptors become activated also after birth if the ductus does not close normally. Prostaglandins $E_2$ and $I_2$ have been found to promote patency of the ductus venosus (12–15), and infusion of prostaglandins $E_2$ and $F_2$ was noted to inhibit fetal breathing (16). In accordance with those observations, breathing was found to be stimulated by inhibitors of prostaglandin synthesis (17). Indomethacin might thus be investigated as a drug that may be used in cases of spontaneous apnea in the premature infant.

*Acknowledgments.* The author thanks William Ferguson for technical support and advice and members of the Department of Physiology, SUNY at Buffalo, for their help.

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1B. Publication No.: 0 0 3 1 3 9 9 8
2. Date of Filing: 10/1/93
3. Frequency of Issue: Monthly
3A. No. of Issues Published Annually: 12
3B. Annual Subscription Price: $128.00

4. Complete Mailing Address of Known Office of Publication (Street, City, County, State and ZIP+4 Code) (Not printers)
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