DIRECT OBSERVATION OF THE FETAL CEREBRAL CIRCULATION DURING LIGATION OF THE MATERNAL INFERIOR VENA CAVA

by

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*Murphy, R. F. If anything can go wrong, it will. Zeitschrift für gearshift und crankshaft, 4, 1827, 12-13.

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INTRODUCTION

Variations of blood pressure with postural changes are well known. Less well known is the fact that certain pregnant women, near term, will exhibit marked arterial hypotension when supine, and that this hypotension is quickly relieved by a change of position. The symptom complex associated with this phenomenon has been termed the supine hypotensive syndrome, or variously, the inferior vena cava syndrome since the etiology appears to be a compression of the inferior vena cava by the gravid uterus.

Animals, especially pregnant females, do not of their own accord assume the supine position. The custom of delivering the pregnant woman from a supine or lithotomy position began only with the introduction of the obstetric forceps (40) and has been used essentially for the convenience of the obstetrician. Therefore, an accepted procedure practiced by the great majority of obstetricians, at least in this country, can possibly aggravate, if not produce, a potentially hazardous condition for both mother and fetus.

In discussing any change produced in maternal hemodynamics, consideration must be given to possible effects upon the fetal circulation. Of particular interest is the fetal cerebral circulation, for although the fetal central nervous system comprises only 15% of the body weight at term (78), it is the most rapidly metabolizing area of the body. The oxygen needs of the 2% total body weight that comprise the adult central nervous system are approximately 20% of the oxygen utilized by the individual at rest. Consider, then, the increased demand for oxygen by the rapidly growing, comparatively larger fetal central nervous system. Also, the fetus is entirely dependent for its

oxygen supply and other metabolic materials, as well as for the removal of waste products, upon the integrity of both its own circulatory system and that of its maternal host. Any changes affecting the normal metabolism of the fetal nervous system may result in neuronal damage. Any method of avoiding such damage thus has clinical significance.

Techniques developed for the examination of the microcirculation in living animals have been modified and adapted to the study of regional circulation in the living fetus (15). Christiansen, Bacon and Stewart (16) and Stewart (85) have demonstrated the feasability of these methods in evaluating fetal cerebral vascular responses to maternal administration of drugs and gases. The function of this study has been two-fold; to attempt to reproduce the clinical complex of supine hypotension of pregnancy in the laboratory rat, and to observe the resultant effects on the fetal cerebral circulation.

The Supine Hypotensive Syndrome

The development of hypotension in the supine pregnant female has probably been observed by many practitioners, but has been reported by relatively few. The clinical aspects have been best summarized by Howard *et al.* (40):

1. It occurs late in pregnancy.
2. It is relieved by turning to either side or by standing erect.
3. It is cured by delivery.
4. Full development requires 3 to 7 minutes.
5. It is not clinically recognizable during labor.
6. Varicose veins are more distended when the syndrome is present.

7. Deep inspiration partially relieves the blood pressure depression.

The full-blown hypotensive syndrome includes depression of systolic and diastolic pressures as well as pulse pressure, tachycardia and tachypnea. Typical patients are pale, sweat profusely, are cool and clammy and may exhibit muscular twitching. They may complain of abdominal, flank, or back pain. Syncopal episodes are not uncommon.

In 1950, Brigedon et al. (12) suggested supine hypotension was probably the result of compression of the inferior vena cava by the gravid uterus. Bull (13) and Brigedon et al. (12) further suggested that the marked lumbar lordosis frequently seen in late pregnancy may predispose to occlusion of the vena cava. McRoberts (56) in 1951 reported six clinical cases, comparing blood pressures in supine and lateral position, and suggested abdominal venous compression as the etiology of the syndrome, "causing a rise in venous pressure caudally and a fall in pressure in the right auricle". DeRegende (20) differed regarding the etiology, believing the syndrome dependent on stimulation of nervous structures behind the uterus. Howard et al. (40) reported in 1953 on two clinical cases of the syndrome including typical blood pressure patterns. They artibrarily selected a systolic pressure depression of 30 mm. or an observed systolic pressure of 80 mm. or less as minimum criteria of supine hypotension. Using these criteria, 18 of 160 term pregnant women exhibited the syndrome, a rate of 11.2 percent. They also produced marked depression of blood pressures in pregnant bitches by ligation of the inferior vena cava. Non-pregnant bitches showed no significant depression of blood pressure; faradic stimulation of the celiac ganglion or the lumbar sympathetic chain was noted to

elevate the systolic pressure. These investigators also suggested that the conspicuous absence of the hypotensive syndrome during labor is due to the firm, contracting uterus "riding" on the vertebral column without exerting pressure posteriorly on the vena cava; the flaccid uterus, on the other hand, is free to extend posteriorly and laterally from the vertebral column and can easily compress the thin-walled, low-pressure vena cava.

Holmes (38), in 1960, reporting on 500 near-term pregnant women, demonstrated a decrease in systolic arterial pressure of 30% or more in 8.2% of patients when placed supine. Grennell (31) also showed an 8% incidence of supine hypotension during conduction anesthesia in term women.

The etiology of the hypotension observed is considered due to a decrease in venous return to the heart, and consequent decrease in cardiac output. Kerr and Samuel (48), in 1964, demonstrated by retrograde vena cavograms that obstruction of the inferior vena cava is the rule in late pregnancy while supine and is not an abnormal situation. Samuel (77) demonstrated venous collaterals in the paraspinal and ascending lumbar veins during compression of the inferior vena cava by the gravid uterus. Following cesarean section, flow immediately returned to the vena cava. Kerr (47) concluded that these venous collaterals are variable and probably always less efficient than the vena cava itself, and that the supine hypotensive syndrome is probably due to poor collateral flow. The cardiac output in pregnancy is considered to be increased by about 40% over the non-pregnant state (24) and the greatest percentage of this blood flow directed to perfusion of the placenta. Therefore, any decrease in venous return from the

areas supplied by the vena cava is greatly magnified in pregnancy.

Abruptio placentae has also been reported in association with compression of the inferior vena cava. Mengert et al. (57) described two cases of premature placental separation produced experimentally at the time of cesarean section by manual occlusion of the vena cava for 5 minutes; extreme maternal hypotension was also noted following caval occlusion. Since 1953, several cases of abruptio placentae have been reported as related to the supine hypotensive syndrome (73, 75, 82, 86).

Morse (61), in 1918, isolated and ligated the ovarian, mesometrial and uterovaginal veins for periods of 2-4 hours in pregnant rabbits, and produced partial placental separation and small myometrial hemorrhages. Barcroft, Herkel and Hill (5), in 1953, noted incidentally that pressure on the uterine vein caused hemorrhage in the pregnant rabbit uterus. Howard, Goodson and Mengert (40), in 1953, noted one placental separation while attempting to reproduce the supine hypotensive syndrome. Howard and Goodson (41) produced placental separation in dogs by inferior vena caval ligation for 5-60 minutes. Nesbitt et al. (66), in 1958, produced placental separation in 35 of 44 pregnancies in dogs by ligation of the inferior vena cava for 90 minutes. They also subjected the fetuses to microscopic examination post mortum and noted petechial hemorrhages on the pleura, adrenals, kidneys, meninges and the brain substance as well. In 1963, Haynes (35) produced an abruptio-like state in the rabbit placenta by ligation of the vena cava for 5 minutes. Microscopic examination of the placentae 24 to 48 hours after this procedure revealed fibrinoid deposition and focal pseudo-aneurysmal dilatation, thrombosis, and vacuolar degeneration of decidual vessels, as well as coagulation necrosis of villous tufts and myometrial hemor-

rhage.

Methods of Studying Cerebral Circulation

The techniques applied to the study of cerebral circulation have been many and varied, each with advantages and disadvantages. It is not within the scope of this discussion to dwell at length upon these techniques, which were well-reviewed by Stewart (85), but some mention should be made of the more important methods which have contributed to present-day knowledge of cerebral blood flow.

Direct observation techniques were used by early investigators (26, 89) who opened the skull and observed changes with varying stimuli in the pial vessels on the surface of the cerebral cortex. This method provided qualitative data and gave little knowledge of cerebral blood flow, since only the superficial vessels were visible.

Qualitative estimates of cerebral blood flow were also achieved by placing a hypodermic thermocouple within the cerebral cortex or in the venous outflow of the brain (29, 79). The extent and rapidity of changes in temperature of the thermocouple are used to calculate blood flow. The temperature of the experimental animal must obviously be carefully maintained.

As blood traverses the cerebral circulation, the rate of oxygen uptake is dependent upon the metabolic activity of the brain and upon the rate of blood flow. With the metabolic rate held relatively constant, the A-V oxygen difference can be used to calculate blood flow.

The nitrous oxide technique of Kety and Schmidt (49) has been the major method of determining cerebral blood flow in man. Applying the Fick principle, cerebral flow per unit weight of brain is calculated from arterial and venous concentrations of N_2O and the partition

coefficient for nitrous oxide between brain and blood. Variations of this technique have been made using radioactive tracers.

Cerebral flow can be measured directly on the arterial side by channeling flow through a flowmeter (23). Flow in both carotids and the vertebral-basilar system have been measured simultaneously.

Modification of dye dilution techniques using P_{32} labeled erythrocytes have given results for cerebral blood flow closely correlated to the N_2O method (67). Clearance techniques using Krypton 85 have provided similar results. Data from autoradiographs of slices of cerebral tissue after exposure to radioactive inert gas in arterial flow have given values for cerebral blood flow in localized areas of the brain (83).

Physiology of Cerebral Blood Flow

The ultimate control of blood flow to the central nervous system depends on the interaction of two factors; the pressure gradient between arterial and venous supply of the brain, and the resistance offered the flow of blood by these vessels. In the adult, the average cerebral blood flow appears to lie between 700 and 900 ml/min. (49, 67). It also appears that there is a wide variation in blood flow through different areas of the brain at any given time. Several methods of regulation of the cerebral blood flow have been investigated, but their exact interrelation still remains obscure.

For many years it was felt that the cerebral blood flow responded passively to changes in arterial pressure. Munro, in 1783, proposed that since the brain was nearly incompressible due to the rigid confines of the skull, the amount of blood within these confines could not be altered, except in pathologic states (65). This concept was challenged in 1937 by Forbes *et al.* (27) and again in 1938 by Fog (25), who demon-

strated constriction in pial vessels in response to a systemic pressure rise, and dilatation with a fall in pressure. Numerous investigators (54, 62, 63, 64) have demonstrated that neither essential nor drug-induced hypertension or hypotension caused any significant difference in cerebral blood flow when compared to normal controls. Only with severe hypotension was cerebral vasodilatation insufficient to compensate for low arterial pressure (32). It is, therefore, fairly well established that there is autoregulation of cerebral blood flow, at least over a wide range of systemic pressure. The ways in which this regulation is effected are still obscure. It has been suggested that a direct effect on myogenic tone may be involved (9) as well as an effect of tissue P_{CO_2} (53).

The effects of increased central venous pressure on cerebral blood flow are thought to be negligible. Jacobson, Harper and McDowall (46) have demonstrated a slight increase in cerebral blood flow following ligation of the superior vena cava. Likewise, moderate increases in intracranial pressure seem to have little effect on cerebral blood flow, as systemic blood pressure can adequately compensate for moderate changes. Above 45 cm. H_2O increases in intracranial pressure have been shown to decrease blood flow (80).

Although the major cerebral arteries are well-supplied with both myelinated and unmyelinated nerve fibers, the role of these perivascular nerves in the control of blood flow is uncertain. Some experimenters (26, 79) have demonstrated mild vasoconstriction of cerebral arteries and slight reduction in blood flow with stimulation of the cervical sympathetics; others (22) have failed to confirm this. Forbes et al. (27) have demonstrated mild dilatation of pial vessels on stimulation

of the vagus nerve, but this was not confirmed by the studies of Schmidt (79). It would appear that stimulation of the sympathetic and parasympathetic nerves do not exert much effect on the control of cerebral blood flow.

The effects of epinephrine on the cerebral blood flow are uncertain. In man, King et al. (51) demonstrated an increase in blood flow as well as an increased cerebral oxygen consumption following injection of epinephrine into the general circulation. Dumke and Schmidt (22), however, showed a vasoconstriction following injection of epinephrine into the internal carotid artery of the monkey. King et al. (51) also demonstrated a decrease in cerebral blood flow and increase in cerebral vascular resistance following injection of norepinephrine into the systemic circulation. Although there was a simultaneous increase in systemic pressure, this was insufficient to return cerebral flow to normal.

Studies in both man and animals indicate that although the aforementioned factors may play some role in the control of cerebral blood flow, the major control is exerted by changes in cerebral vascular resistance, and that this, in turn, is affected directly by carbon dioxide and oxygen levels in the blood. Cerebral blood flow appears to be directly proportional to the arterial P_{CO_2} concentration. Kety and Schmidt (50), and Patterson (70) have shown that inhalation of 5% CO_2 causes about 50% increase in cerebral blood flow in man, and 7% CO_2 causes a 100% increase in flow. Hypoventilation sufficient to cause a 9 mm. Hg. reduction of Pa_{CO_2} caused a 35% reduction of cerebral blood flow (50). Harper and Glass (34) have found a continuous change in cerebral blood flow in dogs with changes in Pa_{CO_2}, although Patterson

et al. (70) have suggested that an increase in blood flow is not noted until a CO_2 concentration of 3.5% in inhaled air is reached. Harper and Glass (34) also noted that Pa_{CO_2} levels below 20 mm. Hg. produced no further reduction of cerebral flow. These same investigators report that at hypotensive levels (50 mm. Hg. systolic pressure) in dogs, no vasodilation was noted with increasing levels of Pa_{CO_2}.

It has been suggested that the marked sensitivity of cerebral vessels to carbon dioxide is to maintain tissue homeostasis. As cerebral metabolic activity increases, the tissue P_{CO_2} would rise; a resultant vasodilation with increase in blood flow would then return tissue P_{CO_2} levels to normal. A reduction of tissue metabolic rate would have the reverse effect. This mechanism would maintain tissue P_{CO_2} levels relatively constant. The rise in arterial pH which often accompanies increases in blood P_{CO_2} has been shown to have no affect of itself on cerebral vessels (33).

Blood levels of oxygen have been shown to have an inverse effect on cerebral blood flow. Harper (32) reports an increase in cerebral blood flow when the arterial P_{O_2} falls below 40 mm. Hg. At a Pa_{O_2} of 20 mm. Hg. the flow is increased 100%. McDowall (55) also demonstrated an increase in cerebral blood flow with hypoxia when blood Pa_{CO_2} levels were held constant. Turner et al. (87) verified these results, showing that 8% O_2 inhalation produced a 36% increase in flow rate. Inhalation of oxygen between 1 and 2 atmospheres pressure has been shown to cause a reduction in cerebral blood flow (45) and vasoconstriction.

There is a relative paucity of information concerning the effects on fetal cerebral blood flow by alterations in arterial gases and drugs.

Assali (3) subjected the maternal sheep to 8% CO_2 inhalation and found a 70% increase in fetal carotid blood flow, but made no mention of any possible cerebral vasodilation. Under conditions of mild hypoxia, investigators (3, 11) have found moderate increases in fetal carotid flow and systemic pressure. More recently, Stewart (85) has demonstrated fetal cerebral arterial dilation during maternal inhalation of 7% CO_2. Christiansen, Stewart and Bacon (16) have demonstrated constriction of the middle cerebral artery in fetal mice following topical application of norepinephrine.

Maternal-Fetal Relationships

The relation of the fetus to the maternal organism in vivipara may be described as that of parasite to host. The maternal host provides for protection, maintains a suitable environment, supplies raw materials for nourishment and growth, facilitates excretion of waste, supplies moderate amounts of hormones and immunologic factors; she derives little in return except, perhaps, satisfaction. The intermediary in this exchange in mammals is the placenta, which acts as the principle organ of fetal homeostasis during the major period of gestation.

The true placenta is unique to the mammal; other classes of animals provide varying degrees of protection and support to their larval stages. It is perhaps due to the placenta that mammals enjoy uncommon success in the propagation of offspring as compared to lower animals which, to ensure success of the species, must produce and fertilize thousands of eggs, of which relatively few survive.

Placentas vary among species of mammals both in anatomical type and in efficiency. The greatest anatomical difference appears to be

the number of tissue layers separating the maternal and fetal circulations. As the blastocyst attaches to the uterine epithelium, the trophoblastic capsule, later known as the chorion, invades the maternal tissue to varying depths. This area becomes differentiated as the placenta. When the uterine epithelium remains in contact with fetal chorionic ectoderm, the placental type is termed epitheliochorial (pig, horse, sheep). In carnivores, the chorionic epithelium erodes deep into the uterine mucosa until it is in close apposition with the endothelium of the uterine vessels, creating an endotheliochorial placenta. In the hemochorial placenta of anthropoids, rodents and bats, the uterine vessels are eroded, and maternal blood directly bathes fetal tissue. The human hemochorial placenta is villous in type, in which branching chorionic villi, containing trophoblast-covered capillaries, are bathed in a cavernous sinus of maternal blood. The rodent has a labyrinthine placenta in which maternal blood circulates through a maze of channels within the chorionic syncytium. There is evidence (2) that the rate of transfer of substances from the blood of the mother to that of the fetus increases as the number of placental layers decreases, and in this respect the placentas of the rodent and anthropoid should allow efficient transfer.

Of the many substances that pass the placental membrane, oxygen and carbon dioxide are of particular importance since interruption in their exchange may quickly endanger fetal survival. Also, the control of cerebral blood flow is intimately associated with these respiratory gases. It is generally agreed that gas exchange through the placenta occurs by passive diffusion (1). The basis for this assumption lies in the pioneer work by Huggett (44); corroborative research has been

done by Prystowsky (72).

The rate of diffusion of gases can be predicted with reasonable accuracy from Fick's diffusion equation. Modified from Metcalfe et al. (58), this can be written:

$$\dot{V} = K_p \cdot A \frac{\bar{P}_M - \bar{P}_F}{L}$$

where $\dot{V}$ = rate of gas transfer across the placental membrane

K_p = placental diffusion constant for the gas being considered

A = placental surface area

$\bar{P}_M$ = average gas tension in maternal placental blood

$\bar{P}_F$ = average gas tension in fetal placental blood

L = average transplacental diffusion distance.

Applying the above factors to placental gas transfer, it is apparent that the rate of gas exchange from maternal to fetal circulations may be increased at constant $\frac{K_p \cdot A}{L}$ by increasing $\bar{P}_M$ or decreasing $\bar{P}_F$, and vice versa.

There are several physiological mechanisms affecting transplacental oxygen exchange. Fetal blood has been shown to possess a higher oxygen affinity than maternal blood (23, 36). Also, the fetal blood has a higher concentration of hemoglobin than maternal blood (84). These factors increase the amount of bound oxygen in fetal blood, which acts to lower the oxygen tension relative to maternal blood at any given oxygen concentration.

The change in affinity of hemoglobin for oxygen with varying levels of plasma pH is known as the Bohr effect. In the placenta, Bartels (8) has described a "double" Bohr effect. As CO_2 and "fixed" acids pass into the maternal blood from the fetal circulation, the resultant lowering of pH of maternal blood causes a decreased affinity of maternal hemoglobin for oxygen. Consequently, the oxygen tension of maternal blood is increased. At the same time, the fetal blood becomes more alkaline and fetal hemoglobin has an increased affinity for oxygen, which decreases fetal blood oxygen tension.

The rate of flow of both maternal and fetal blood past the placental membrane also affects the transfer of oxygen. If fetal placental flow is reduced, with fetal oxygen consumption remaining unchanged, the oxygen tension in fetal blood entering the placenta will be lowered, and vice versa. On the maternal side, a decrease in placental flow would allow for greater oxygen extraction by the fetus per unit time, and would result in a decreased oxygen tension of maternal blood.

Estimates of transplacental oxygen pressure gradients have been made for several species. Barron et al. (6, 7) have derived values for sheep and rabbit of 40 mm. Hg. and 10 mm. Hg., respectively. The gradient of oxygen for man is estimated as 20 mm. Hg. (71).

Carbon dioxide is more soluble in plasma than oxygen and the diffusion constant across the placental membrane has been estimated as about twenty times that of oxygen (58). The direction of transfer of CO_2 in the placenta under normal conditions is from fetus to mother, although the transplacental CO_2 gradient is small (4, 91). Carbon dioxide may dissolve in maternal plasma or it may react with water

within the erythrocyte to form bicarbonate and hydrogen ions. This reaction is catalyzed by carbonic anhydrase. Intracellular bicarbonate diffuses into the plasma and is replaced by chloride ions, thus promoting further reaction of CO_2 and H_2O. The hydrogen ions are buffered primarily by hemoglobin. Some carbon dioxide combines with hemoglobin, forming carbamino hemoglobin. On the fetal side, the reverse processes take place.

As fetal blood takes up oxygen, its affinity for carbon dioxide decreases and the CO_2 tension rises; this has been termed the Haldane effect. Conversely, as maternal blood loses oxygen to the fetus, its carbon dioxide affinity increases. Thus, there appears to be a "double" Haldane effect (58), much like the "double" Bohr effect, which magnifies the CO_2 tension gradient between fetus and mother.

In recent years, interest has grown concerning the fetal responses to alterations in the maternal circulation and placental blood flow. The majority of these studies consist of evaluation of fetal heart rate and blood pressure following injection of drugs or hormones into the maternal circulation or following the production of fetal hypoxia. A multitude of methods has been used to produce hypoxia in the fetus, including administration of low levels of oxygen to the mother, occlusion of the maternal trachea, clamping of uterine vessels and occlusion of the umbilical vessels. Most investigators have found an elevation of fetal systemic arterial pressure with mild to moderate hypoxia (4, 11, 74). The effect upon the fetal heart rate has been variable (11, 74) with mild hypoxia causing a tachycardia and moderate hypoxia causing either a tachycardia or a bradycardia. Severe hypoxia (fetal blood oxygen tension ca. 12 mm. Hg.) caused a fall in fetal blood pressure and

a bradycardia.

There appears to be a redistribution of blood flow in the fetal circulation during hypoxia. Mild hypoxia has been shown to cause an increase in umbilical blood flow (11, 69) accompanying the rise in fetal systemic arterial pressure. Parker and Purves (69) have demonstrated an increase in pulmonary artery pressure and a greater proportion of right ventricular blood flow diverted to the descending aorta via the ductus arteriosus during fetal hypoxia. Blood flow to the fetal extremities is also decreased during hypoxia (59). Rudolph and Heyman (76) have demonstrated that an increased proportion of inferior vena cava blood flow is shunted through the foramen ovale into the left atrium and thus into the ascending aorta during fetal hypoxia; they also, however, found an increased superior vena caval flow through the foramen ovale. These investigators suggested that the diversion of well-oxygenated inferior vena caval blood to the left atrium is an attempt to maintain the heart and brain with adequate oxygen; they noted, however, that the diversion of less well-oxygenated blood from the superior vena cava would serve to lower the oxygen tension of blood leaving the left ventricle and reaching the brain. They inferred that the net effect would be merely to maintain cerebral blood flow. However, Geber (28) studied fetal regional blood flow under a variety of conditions, and noted a decrease in flow to the brain and an increase in carotid artery pressure during asphyxia.

In summary, the fetus apparently can adapt to hypoxia by increasing umbilical blood flow at the expense of other organs. This ability is limited, however. With severe or prolonged hypoxia, umbilical blood flow decreases (18) possibly due to increased umbilical and placental

resistance. The cause of such an increase in vascular resistance is unknown, but may be due to the action of pressor substances (18).

Dawes et al. (19) found that injections of adrenaline and noradrenaline into fetal lambs caused a larger rise in systemic arterial pressure and heart rate than did hypoxia. An increase in umbilical blood flow paralleled the rise in systemic pressure. Geber (28) demonstrated a decrease in fetal brain blood flow, an increase in carotid artery pressure, and a marked decrease in fetal heart rate following injection of vasoconstrictor agents. Interestingly, Chernoff (14) found a decrease in fetal blood pressure accompanying a decreased heart rate following injection of adrenaline into maternal rats. Comline and Silver (17) have demonstrated the release of catecholamines, particularly norepinephrine, from the adrenal medulla as part of a generalized systemic discharge during severe fetal hypoxia. Thus, it is possible that the fetal cardiac and circulatory responses to hypoxia may be related to the release of pressor substances. Dawes (18) further suggests that the increased umbilical resistance seen during severe hypoxia is due to the prolonged action of these pressor agents on these vessels.

The effects of increases in fetal blood carbon dioxide tensions have not been studied to any great extent. Assali et al. (3) have demonstrated an increase in systemic arterial pressure, increased carotid arterial blood flow, bradycardia and increased umbilical flow in the fetal lamb while the mother was inhaling 8% carbon dioxide. Panigel (68) has demonstrated vasodilatation of umbilical arteries perfused with fluid containing high tensions of carbon dioxide. Together with the increased arterial pressure noted in Assali's study, this vasodilation would serve to increase umbilical and placental blood flow. The brady-

cardia which develops, however, would tend to decrease placental flow.

The effects of maternal hypotension on the fetus have received little attention; those studies that have been done have primarily evaluated only fetal heart rate. Bieniarz et al. (10) showed maternal hypotension produced by vasodilator drugs did not cause any significant effect on fetal heart rate. Hon et al. (39), however, demonstrated fetal bradycardia of the "hypoxic type" beginning about 5 minutes after the onset of maternal hypotension. They suggested that this was due to inadequate maternal placental perfusion with resultant fall of fetal PaO_2.

In summary, there are certain basic concepts and information available in the literature which are relevant to this paper.

1) There is a well-defined clinical complex known as the supine hypotensive syndrome of pregnancy, characterized by maternal shock and thought due to the compression of the inferior vena cava by the gravid uterus. The effects on the fetus have not been well-studied.
2) Maternal hypotension has been reproduced in pregnant dogs by inferior vena caval ligation.
3) The control of cerebral blood flow in the adult involves several factors; the most important appears to be brain tissue and arterial concentrations of oxygen and carbon dioxide. Systemic arterial pressure and pressor agents have also been shown to exert a control on the cerebral blood flow.
4) The oxygen and carbon dioxide content of fetal blood is intimately associated with the integrity of the maternal circulation, particularly that of the placenta.

5) The effects of variations in the carbon dioxide and oxygen concentrations of fetal blood have been studied along several parameters.

6) Cerebral vessels of the rodent at this stage of development have been shown to possess the capacity for vasomotor responses.

MATERIALS AND METHODS

Animals

Rats of the Long-Evans and Sprague-Dawley strain were used, with maternal animals varying in age between three and six months. All rats were maintained in standard wire cages. Diet consisted of Purina Lab Chow tablets and water ad lib, as well as weekly supplements of fresh greens.

Fetal observations were done on third trimester fetuses. The rat has a 21 day gestation period, but fetuses older than 17 days gestation were considered too large and their craniums too thick for adequate transillumination. Therefore, all observations were made on fetuses between $14\frac{1}{2}$ and 17 days gestation.

Vaginal smears were examined to determine the stage of estrus in each female of breeding age. Animals found to be in pro-estrus were placed with males of the same strain for a period of up to six hours. Vaginal smears were repeated every two hours and those animals found with sperm or a mucous plug in the vagina were placed in separate cages. The midpoint of the two hour period in which evidence of mating was established was considered the beginning of gestation. The rat tends to breed during the night with some strain difference in hours. For the convenience of the investigator, all rats were housed in an inverted light-cycle room which was dark from 10:00 A.M. to 10:00 P.M. so that breeding could be accomplished during the day.

Anesthesia

Several types of anesthetics were tried, but it was finally decided that Sodium Pentobarbital would provide the most consistent and satisfactory anesthesia. Very light anesthesia was provided by a sub-

cutaneous injection of a 50 mg./kg. dosage. The site chosen for injection was the loose skin of the back of the neck. This route of administration provided slower induction of anesthesia than by the intraperitoneal route, but was felt to be safer and to provide a more sustained and lighter level of anesthesia. Occasionally, it was necessary to administer a second dose of 10 mg./kg. after 45 minutes as determined by the animal's response to manipulation. Anesthesia was considered adequate if the animal responded only to deep pain. Skin incisions were made through areas that had been injected lightly with 1% Procaine hydrochloride as the level of Pentobarbital anesthesia generally was insufficient to prevent some maternal response to incision if not otherwise implemented.

Surgical Preparation

A. Arterial Pressure Measurements

After the anterior neck was shaved, a midline incision was made from just beneath the mentum to just above the sternum. By blunt dissection, the loose connective tissue and the two large anterior lymph glands were separated in the midline. The sterno-cleido-mastoid muscle on the left was dissected free from surrounding areolar and connective tissue and was retracted laterally. The omohyoid muscle was split, exposing the common carotid artery in its sheath. The sheath was carefully dissected away from the artery and the vagus nerve was retracted laterally. Approximately one centimeter of the carotid artery was exposed in this manner. Three 3-0 silk sutures were passed under the freed artery; the uppermost suture was tied, ligating the artery to prevent back-flow from above. Traction was placed on the lowermost suture, occluding

arterial flow and a small incision made in the arterial wall near the midpoint of the exposed segment. A PE-50 polyethylene tube, connected by a 23 gauge needle to a 10 cc. syringe filled with heparinized saline, was passed into the lumen of the artery and was secured in place by the third suture. The lowermost suture was released and arterial free-flow checked by aspiration of the syringe. The neck incision was then closed by skin clips to prevent drying of tissues.

After shaving the lower abdomen, a four centimeter midline skin incision was made, exposing the linea alba through which an almost bloodless entrance into the peritoneal cavity was made. The small bowel was reflected cephalad and the abdominal aorta and inferior vena cava exposed. The surrounding fatty and connective tissues were dissected free and the vena cava immediately beneath the junction of the renal veins was separated from the aorta. A 2-0 silk suture was passed beneath the vena cava and the suture ends were brought to the abdominal surface. The linea alba was sutured together and the skin incision closed with skin clips.

B. Observations on Fetuses

The peritoneal entrance was made as described above and a silk suture was passed beneath the vena cava as described. One uterine horn was then located and a segment containing one implantation site was delivered through the incision site, which was then sutured so as to hold this segment externally. The skin incision was then closed by skin clips (Figure 1).

A 4 inch by 6 inch piece of transparent cellulose film was placed over the exteriorized uterine segment. A two cm. incision

was made through the cellulose and the uterine wall on the anti-mesometrial side, so as to avoid the placentation site and the more vascular areas of the uterus. Following such an incision, the fetus, wrapped in its yolk sac and amnion, delivered spontaneously onto the surface of the cellulose drape. The drape was then positioned over a small lucite chamber form; the surface of the drape was indented so as to form a transparent chamber of sufficient size to hold the fetus (Figure 2). The uterus and placenta remained covered by the cellulose drape, which prevented drying of these surfaces.

Next the yolk sac of the fetus was opened. Since the yolk sac circulation is confluent with the fetal circulation, it is important not to enter any large yolk sac vessel, as the fetus may exsanguinate or, at the very least, the fetal hemodynamics may be greatly altered. It was decided that the safest method of entrance through the highly vascular yolk sac would be obtained by a careful cauterization of a large artery and vein at their base followed by an eliptical incision through the most avascular area served by these vessels (Figure 3). The area of the yolk sac which was opened was over the fetal cranium. Incision of the yolk sac allowed the amnion-covered fetal cranium to be visible; the amnion next was carefully grasped with a microdissection forceps and an incision made in it with an ophthalmologic scalpel, after which the edges were easily retracted giving excellent exposure of the fetal cranium (Figure 4).

Fetal Homeostasis

At all times efforts were made to maintain the fetus in conditions as close as possible to those in utero. Mammalian Ringer's solution was used to moisten all exposed tissues. At all times exposed maternal

tissues were covered by moistened gauze sponges, except for the uterus and placenta which were under the cellulose drape and, therefore, not exposed to air. Fetal structures were placed in the transparent chamber, as described, and were immersed at all times in Ringer's solution. As an added precaution, the fetus, with the exception of the cranium, and the umbilical cord were covered with a small piece of cellulose film to further prevent evaporation and drying. The Ringer's solution was kept at a constant temperature of 38.5° C. by passing a polyethylene conduit through a constant temperature water bath. The warmed solution was then directed into the fetal chamber at a rate to constantly replenish the chamber every 20-30 seconds. The temperature in the chamber itself was checked frequently with a Tri-R electronic thermometer equipped with a micro-tip sensor. All fetal surfaces, including the umbilical cord, were thereby maintained at as near normal intrauterine temperature and hydration as possible.

Maternal temperature was checked and recorded by a rectal electronic thermometer connected to a small one-channel recorder. Every attempt was made to ensure against maternal cooling by evaporation by covering and/or irrigating all exposed surfaces. Attention was paid to closing and covering the peritoneal cavity which provides a large surface for evaporation. The opened segment of uterus and placenta were adequately moistened by peritoneal fluid.

Particular attention was paid the umbilical cord. In addition to the above mentioned measures to prevent drying, it was necessary to position the fetus in such a way as to guard against compression of the structures of the cord. The fetal chamber was designed so as to put a minimum of stress on the umbilical cord. Periodic checks were

made on the flow in the umbilical vessels and if any compression was noted this fetus and observations were discarded.

Previous investigators using the technique of fetal transillumination have used light sources which emit large quantities of infra-red radiation and, therefore, heat which by itself may affect fetal blood flow. The light used in all observations recorded in this dissertation was transmitted by a 24 inch long, 1/4 inch diameter, flexible fiber-optic cable from a cooled, self-contained light source. A Zeiss interference green filter was interposed between the light source and the fiber-optic cable and transmitted light primarily in the 4912 to 5750 Å range. With this fiber-optic system, no detectable heat was radiated from the tip of the cable. The chance of any amount of non-detectable heat affecting the fetus was further reduced by the rapid renewal of the circulating solution with its high specific heat, as well as the fact that at no time did the tip of the fiber-optic cable touch the fetus. Also, the light source was used only intermittently and for short periods of time.

Methods of Observation

A. Maternal Pressure Recordings

After surgical preparation of the maternal animals as described, the polyethylene catheter in the carotid artery was connected to a Statham P 23 AC 0-75 cm. Hg. pressure transducer by means of the #23 gauge needle hub. The transducer was connected to a Grass Model 5 Polygraph. After calibration of the polygraph and careful flushing of the catheter to be sure there was no clotting, the mean arterial pressure of the animal was recorded for a period of time sufficient to establish a baseline pressure. Following this, in both pregnant

and non-pregnant animals, the silk suture around the inferior vena cava was drawn taut to occlude the vein and pressure recordings were continued for several minutes. Changes occurring in arterial pressure were measured from the polygraph tracings and tabulated.

Following the completion of these pressure recordings, the vena caval occlusion was continued until 25 minutes total occlusion time had elapsed. The uterine horns of the pregnant animals were then removed and fixed in Bouin's solution for 36 hours. The fixed uterine segments were then subjected to razor-blade section under a dissecting microscope to determine any evidence of placental separation or hemorrhage.

B. Observations on Fetuses

The principles and techniques involved in transillumination have been developed by Knisley (52) and modified to the study of the living fetus by Christiansen (15) and Stewart (85). With the methods outlined by these investigators, a light source of sufficient intensity is provided to permit microscopic examination of transilluminated tissue in vivo. The light sources used by these investigators have had the disadvantages of cost, large and cumbersome size, inflexibility, and have transmitted considerable amounts of heat. Recent developments in the fiber-optic cable have provided a means of transmitting light from a fixed source which has almost eliminated the disadvantages of previous systems. A great advantage is gained by the extreme flexibility of the fiber-optic cable which allows easy positioning of the light source and reduces manipulation of the tissue to be examined.

For my observations, I chose a fiber-optic system with self-

contained light source manufactured by Donner Electronics. This system provides a light source of variable intensity which is self-cooled, is small in size and weight, and produces no vibration. The only disadvantages noted in this system was an insufficient intensity of light to adequately transilluminate large fetuses older than 18 days gestation.

As noted previously, a Zeiss green filter was interposed between the light source and the fiber-optic cable. This provided maximal light in the 4912-5750 Å range. As hemoglobin absorbs light maximally in the 5200-6000 Å range, this filtered light provided for a sharp contrast between vascular structures and surrounding tissue, with the vessels appearing nearly black.

After exposure of the fetus enveloped in its yolk sac from the uterus and positioning in the transparent chamber, the fiber-optic cable was positioned beneath the fetus and turned on at low intensity for gross inspection. The yolk sac and amnion were opened as described and the fiber light was used to give gross examination of the cord structures and rate and quality of the fetal heart beat. The yolk sac incision was inspected for evidence of blood loss. If these parameters were considered normal, the fiber-optic cable was positioned beneath the fetal cranium and adjusted to give maximal transillumination. The middle cerebral artery was located as it emerges posterior and superior to the fetal eye. The trifurcation of the artery was located and a suitable area of the trifurcation was selected for subsequent observation (Figure 5).

Observations were made using a trinocular Bausch and Lomb Zoom microscope with a 3.5 X objective and 12 X wide field oculars

(Figure 6). The zoom scope provides continuously variable magnification of 1-2 X so that observations were conducted under magnification of 42-84 X. The magnification chosen was that which gave greatest clarity of the structures being observed and was not varied during the observation period. The microscope was mounted on a moveable carriage attached to a weighted drill press stand. This allowed the scope to be positioned by movements horizontally and vertically, as well as radially around the drill press post. Further flexibility was provided by a specially constructed pivot joint at the attachment of the scope to the moveable carriage which allowed for positioning of the scope itself at angles between 0° and 90° to the horizontal.

All observations reported have been made by sequential 35 mm. still photographs. A Bessler Topcon 35 mm. single lens reflex camera with a focal plane light meter was used. After centering and focusing the microscope in the desired field, all light was shunted through the vertical camera-tube of the scope by means of a built-in prism. All subsequent focusing and field adjustment was done through the reflex mirror of the camera. Fine focusing was improved by substitution of the coarse ground-glass focusing screen of the camera with a clear glass screen of the same size and thickness.

The photographic film used in all observations was Kodak Tri-X which made possible relatively high speed shutter settings under relatively low light intensity. Due to the movement of the field observed, both from maternal respirations and an occasional muscle twitch by the fetus, it was necessary to use shutter speeds between 1/30th and 1/60th second. Higher shutter speeds were impossible due

to the small intensity of the light passing through the fetal cranium and the high magnification used, which provided a small field. Use of such a high speed film sacrificed the fine grain and high contrast available in slower films.

As soon as possible following exposure of the fetus and determination of normalcy of blood flow in the umbilical circulation, the microscopic apparatus was positioned over the middle cerebral artery and photographic observations were recorded at intervals determined by an electronic stopwatch. At least two initial control observations were made on each fetus at intervals between two and five minutes following the first observation. At least two photographs were taken at each timed interval throughout the observation period to decrease the chance of an observation being made during a maternal respiratory movement which would blur the recorded image.

Following the recording of the last control observation, the suture around the inferior vena cava was drawn taut, thus occluding the venous flow, in those animals used in the experimental series. In the control series the sutures were untouched. Subsequent photographic recordings of the middle cerebral artery were made at intervals between 60 and 240 seconds in each group. The total observation time on each animal varied between 15 and 30 minutes; several control animals were observed for up to one hour but these observations are not included in the reported data. Following the completion of the observation period, the observed fetal heart rate was recorded and the litter-mates exposed and examined for heart rates and condition. The placentas were also examined for gross evidence of placental separation or hemorrhage. Throughout the observation

period recognition of placental drying, umbilical compression, change in temperature of irrigating solution, or evidence of fetal bleeding or "sludging" of fetal blood flow was considered sufficient evidence for procedurally induced trauma and data from those fetuses were discarded.

All negatives were developed in a small daylight tank in Kodak D-76 developer for 10 minutes, washed, fixed, cleared in hypo-clearing agent, and rinsed in Kodak Photoflo Solution before drying. Evaluation of the negatives presented some difficulty and was finally thought best achieved by projection from a Leitz projector set at a fixed distance, and the greatly enlarged vessel images traced on paper. A fixed reference point from which to compare vessel size was felt best achieved by carefully establishing the apex of the "V" formed by a constantly present bifurcation. This point was established in all tracings and all measurements were made in reference to it. Three tracings were made of each negative and were numbered according to their experimental sequence. All negatives considered of poor quality were discarded. All tracings were made with the greatest possible accuracy and by a person other than the investigator, one who had no foreknowledge of the experimental sequence, so as to reduce the chance of bias.

The vessel diameter was determined by drawing a circle with its center at the apex of the fixed bifurcation reference point and tangent to the opposite wall (Figure 7). The radius of this circle was then measured with calipers and recorded in millimeters. This was done for each of the three tracings and the mean value was computed; this value was considered the vessel diameter for that

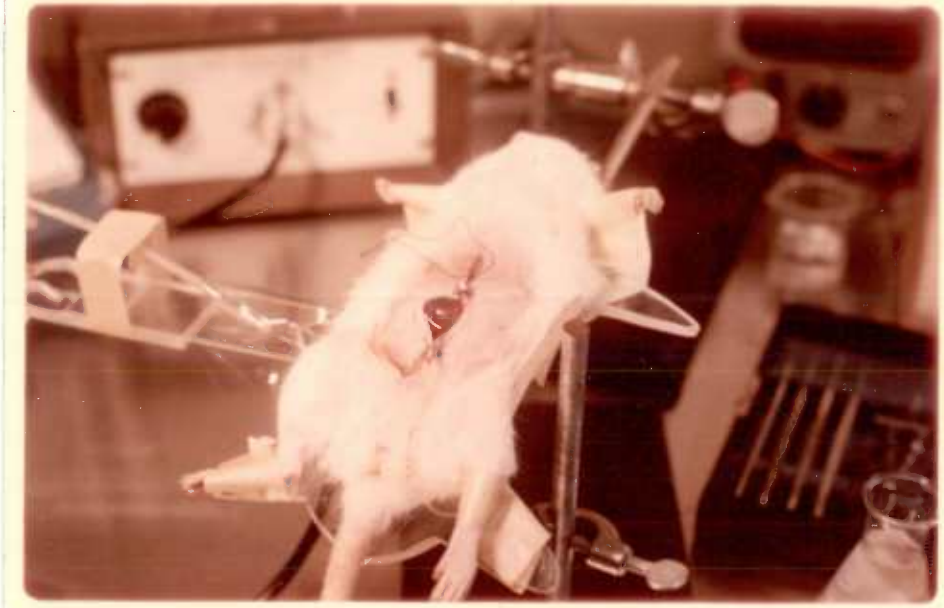
specific time period. The data thus obtained was tabulated and subjected to statistical analysis.

FIGURE 1

The anesthetized mother is supported by a contoured lucite frame. One uterine segment has been exteriorized and the abdominal and skin incisions closed. A 3-0 silk suture has been passed around the inferior vena cava. The ends of the suture can be seen exiting from the upper pole of the abdominal wound.

FIGURE 2

The lucite frame which supports the maternal animal is in the foreground in this photograph. At right angles is the lucite chamber frame over which a piece of cellulose film has been positioned so as to form a transparent chamber to hold the fetus. The portion of the chamber form closest to the animal is a discontinuous ring which allows the umbilical cord to be supported only by the cellulose film, to avoid compression. The polyethelene conduit for the warmed Ringer's solution is seen entering the photograph at the upper left hand corner. The transparent chamber is partly filled with solution, and is positioned over the fiber-optic cable.



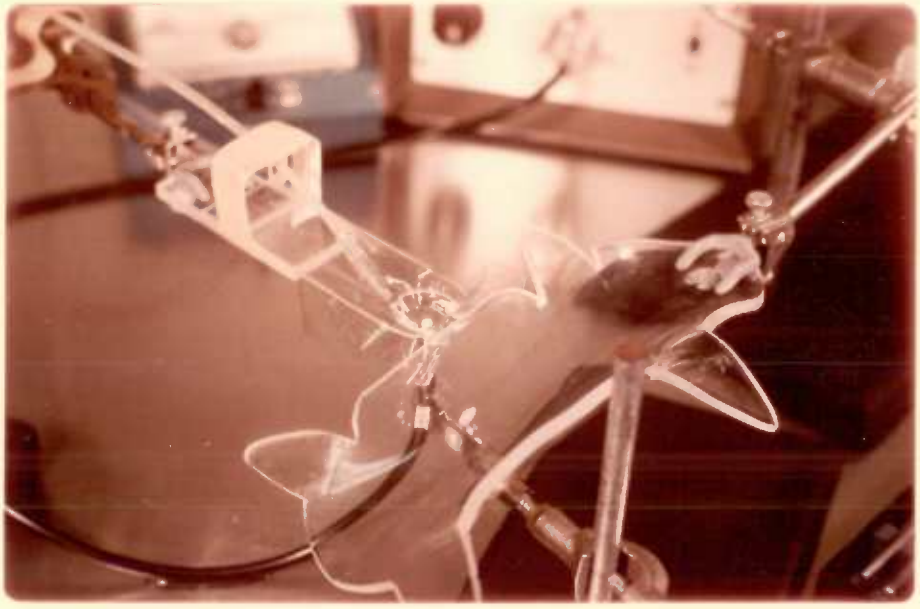


FIGURE 3

The fetus enclosed by the yolk sac and amnion is positioned in the transparent chamber. The larger yolk sac vessels and the placenta can be seen in this photograph. Careful cauterization is done at the base of the largest artery and vein serving the area of the yolk sac marked by the dotted line. An incision is then made through this line and the fetal head delivered into the chamber through the incised yolk sac.

FIGURE 4

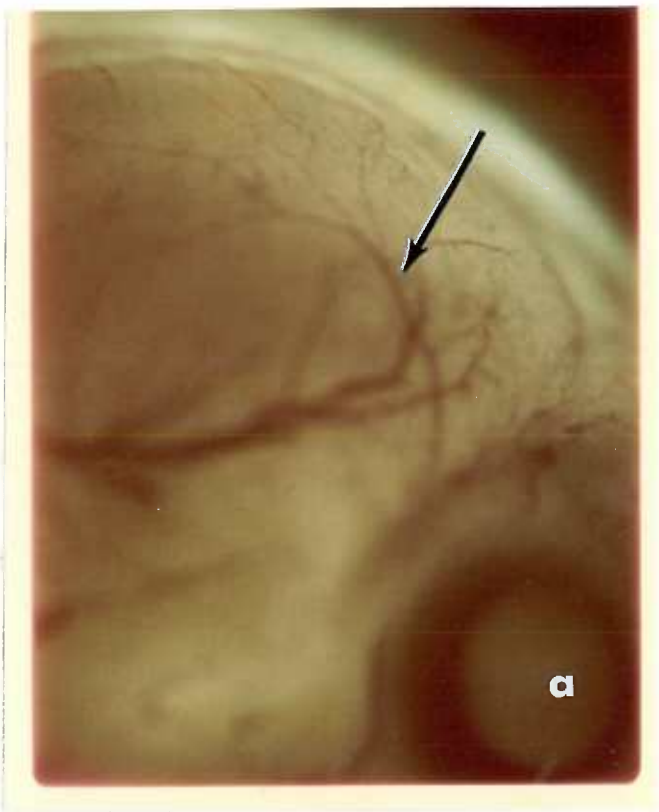
The fetal cranium has been delivered through the yolk sac incision. The fetal eye can be seen just above and to the left of the placenta. The cranium is partially transilluminated by low intensity light from the fiber-optic cable system which is positioned beneath it. The superficial vessels of the fetal cranium are well seen.

FIGURE 5_a

This photomicrograph shows the anterior portion of the fetal head. The developing fetal eye (a) is apparent. Posterior and superior to the eye is the middle cerebral artery (arrow). A large superficial vein is seen crossing the artery at right angles.

FIGURE 5_b

A better view of the middle cerebral artery is seen in this photomicrograph. The characteristic trifurcation is clearly visible. The area of the artery between the arrows was chosen for observation in each case presented in this paper.


a

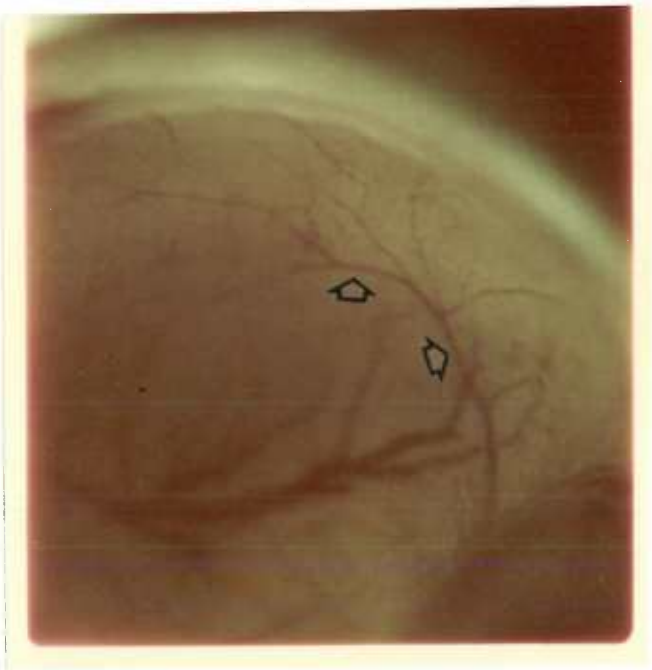


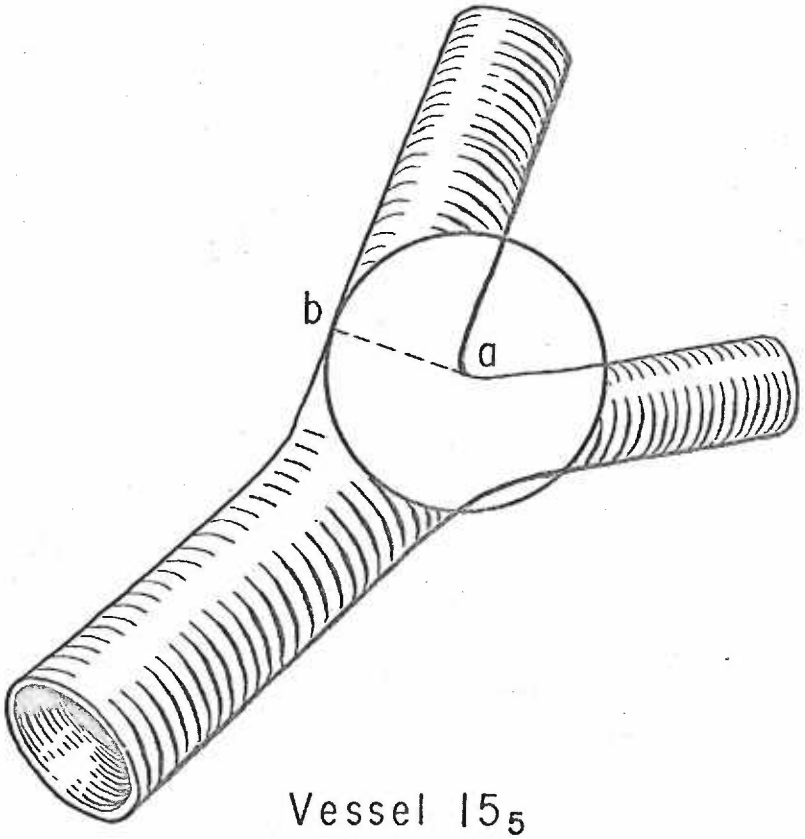
FIGURE 6

This photograph shows most of the equipment used during observations on the fetus. Observations were made with a trinocular microscope (a). Transilluminating light was provided by a self-contained light source (c) and transmitted by a fiber-optic cable (arrow). Maternal temperature was checked by a rectal probe attached to an electronic thermometer (b) and recorded by a one-channel recorder (d). Observations were timed by an electric stopwatch (e). All surgical procedures were done using microdissection tools (f). Beneath the microscope the frame for maternal support and the lucite fetal chamber form can be seen, as previously described. Not shown is the constant temperature water bath for warming the Ringer's solution.

a
b
c
d
e
f

FIGURE 7

This drawing of one of the tracings made of fetal vessel #15 demonstrates the method used to determine the vessel diameter. The bifurcation reference point (a) was established. A circle was drawn tangent to the opposite wall at point (b). The radius of this circle (ab) is the measured diameter of the vessel and is proportional to the actual vessel diameter.



Vessel 15_5

RESULTS

A. Maternal Arterial Pressure

Six pregnant and six nonpregnant rats were studied. Carotid artery pressure changes were recorded for about four minutes following vena caval ligation in each animal. The first 100 seconds of the polygraph records are reproduced in Figure 8 for all six pregnant and five nonpregnant animals. The sixth nonpregnant animal's response was recorded at a different paper speed and would not fit into the composite. Table I summarizes the pressure changes in all animals. As can be seen, a significant fall of mean carotid arterial pressure occurred in each of the pregnant animals following vena caval occlusion, with the mean reduction of pressure being about 84 mm. Hg. The mean reduction of arterial pressure was 30 mm. Hg. in the nonpregnant animals. In this latter series, animals 4 and 6 showed a large reduction of mean arterial pressure. This will be considered in the discussion.

It was noted that immediately following vena caval occlusion, tachypnea and deep inspiratory efforts developed, but were more marked in pregnant animals. The deep inspiratory efforts decreased with time and the tachypnea decreased but remained above the resting respiratory rate.

B. Examination of Placentas

The purpose of this investigation was not to produce placental pathology *per se*, and with this in mind examination of the uteri and placentas was limited to dissection microscope observations at 30 X power of tissue fixed in Bouin's solution. Six uteri from the pregnant animals used in the arterial pressure recordings were

examined. Prior to fixation of the uteri, it was noted that in each case there was marked engorgement of the uterine veins; the uterus itself was dark in color. A total of 49 placentas was found; these were sectioned with a razor blade and examined for evidence of hemorrhage or placental separation. In 2 of the 49 placentas, small areas were found which were consistent with intraplacental hemorrhage or infarction. In one placenta, there was a large marginal sinus hemorrhage which had nearly filled the cavity of that uterine segment. The other 46 placentas were considered normal. The placenta which had shown the large hemorrhage was from a rat at $17\frac{1}{2}$ days gestation.

C. Observations on Fetuses

Following ligation of the maternal inferior vena cava, there was a variation in the response of each fetus observed. Some fetuses appeared to undergo an early vasoconstriction of the middle cerebral artery, while others, although they eventually demonstrated this vasoconstriction, were delayed in any response. It appeared that most fetuses developed an early, transient tachycardia, although this was not quantitated. As the period of maternal vena caval ligation progressed, however, definite bradycardia was noted. When the heart rate fell below 30 per minute, the experiment was terminated. The litter mates were exposed and examined for their condition. The data from no experimental fetus is presented in this paper whose litter mates did not demonstrate similar heart rates and condition.

At the termination of each experiment, the fetus was also examined to determine the state of the peripheral arteries. The arterial

tree of both the fore and hindlimbs were seen to be constricted in all animals in the experimental groups.

It should be noted that one fetal exposure was terminated when a large marginal sinus placental hemorrhage was noted. This was a 17 day gestation fetus and was the only placental hemorrhage noted during the course of fetal observations. The observations on the cerebral arteries of this fetus were discarded.

The mean diameter of the middle cerebral artery was calculated for each time period from the photographic tracings as described. This value is proportional to the actual vessel diameter. The volume of blood flow through any vessel is directly proportional to the cross-sectional area of the vessel, so in each case the calculated vessel diameter was squared. This value then provided a more adequate estimation of blood flow.

Due both to the distribution of timed observations and to provide ease for statistical analysis, each fetal artery was evaluated for mean vessel size over the control period and the mean vessel size for subsequent intervals of five minutes each. The calculated vessel size obtained for the control period was designated as baseline size and assigned the value of 100 percent; each subsequent measurement was then expressed as percent of the baseline value.

The control group contains nine fetuses with mean vessel sizes calculated for the control or baseline period and for five subsequent intervals of five minutes each. The experimental group is divided into two sub-groups: E_1 and E_2. Group E_1 contains nine fetuses with mean vessel sizes calculated for the baseline period

and for five subsequent intervals of five minutes each. Group E_2 contains five fetuses with vessel sizes calculated for the baseline period and for two subsequent intervals of five minutes each. The experimental group was subdivided according to variations in the fetal responses, as will be explained.

Table II presents an analysis of the data obtained on the control fetuses which did not undergo maternal vena caval occlusion. Total observation time was 25 minutes following the control observation. Time 00 is the baseline observation period; since the mean vessel size was used for each five minute observation period, subsequent times are expressed as the midpoint of each interval. An F test was done to determine whether there was a significant variance of mean vessel sizes between or within the control group itself. Any such variation may be attributable to the procedure itself and would invalidate any comparison between the control and experimental data. As can be seen, however, there was no significant difference in the variances ($p = 0.01$).

The responses of the experimental fetuses fell into two distinct categories: those fetuses which demonstrated early vasoconstriction of the cerebral arteries and early bradycardia, and those fetuses which demonstrated a later vasoconstriction and bradycardia. There were nine fetuses in this latter group, group E_1, and data from this group is summarized in Table III_a. As can be seen, these fetuses were observed for a total of 25 minutes following maternal inferior vena caval ligation. The observations were terminated when it became obvious that fetal death was imminent. Experimental group E_2 contains five fetuses which progressed rapidly to a state of

cerebral vasoconstriction and imminent death. These fetuses were observed for a total time of 10 minutes after maternal vena caval ligation; data from these fetuses is presented in Table III_b.

In Table IV the mean vessel size over the total observation time is compared between the control fetuses and the experimental group E_1 fetuses. Comparison using the student t test demonstrates that there is a significant difference in vessel size between the experimental and control fetuses ($p = 0.01$). It is obvious that the direction of change is towards vasoconstriction in the experimental group. In like manner, Table V compares the mean vessel size between the control fetuses and experimental group E_2 fetuses. Since a time period of 10 minutes after vena caval ligation was used for the group E_2 fetuses, the mean vessel size for the control group was also calculated for this time period. The student t test demonstrates a significant difference in vessel sizes ($p = 0.01$) between these two groups.

An F test was done to compare the variances within each experimental group to the variance within the control group. Table VI summarizes these F tests. As can be seen, there is no significant difference between the variances which might account for an error in accepting the results of the t tests.

Figure 9 presents in graph form the mean vessel cross-sectional areas in percent for each group of fetuses at the midpoint of each time interval, with standard deviations calculated.

FIGURE 8

A composite of the maternal carotid artery pressure recordings is presented for the first 100 seconds following ligation of the inferior vena cava. Time in seconds is on the abscissa. Time 0 is the point of ligation.

Mean blood pressure in mm. Hg. is on the ordinate. As can be seen, the calibration varied between (100 mm. = 2.0 cm.) and (100 mm. = 2.5 cm.); the appropriate value is marked for each tracing.

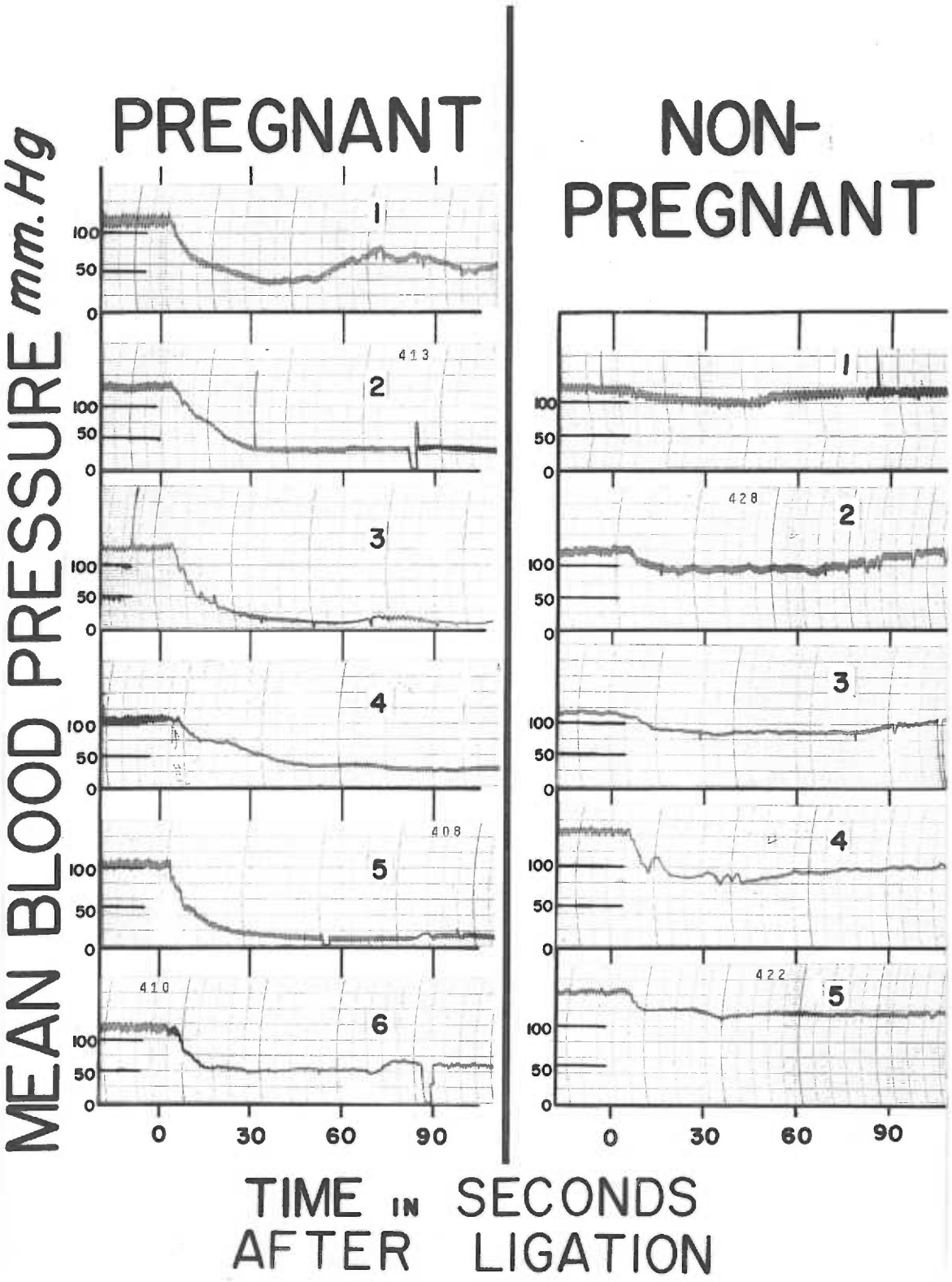

PREGNANT
NON-
PREGNANT
MEAN BLOOD PRESSURE mm.Hg
100
50
0
1
2
413
3
4
5
408
6
410
428
422
0
30
60
90
TIME IN SECONDS
AFTER LIGATION

TABLE I

This table summarizes the reduction of mean carotid arterial pressure for pregnant and non-pregnant animals following ligation of the inferior vena cava.

PREGNANT				NON-PREGNANT			
#	baseline pressure	vena cava ligated	total change	#	baseline pressure	vena cava ligated	total change
1	116 mm.	55 mm.	-61 mm.	1	125 mm.	110 mm.	-15 mm.
2	130 mm.	30 mm.	-100 mm	2	120 mm.	95 mm.	-25 mm.
3	125 mm.	15 mm.	-110 mm	3	118 mm.	84 mm.	-34 mm.
4	105 mm.	28 mm.	-77 mm.	4	144 mm.	90 mm.	-54 mm.
5	105 mm.	15 mm.	-90 mm.	5	140 mm.	116 mm.	-24 mm.
6	120 mm.	55 mm.	-65 mm.	6	112 mm.	60 mm.	-52 mm.

Mean pressure decrease for pregnant animals 83.83 mm.

Mean pressure decrease for non-pregnant animals 30.16mm.

TABLE II

This table summarizes the mean vessel sizes obtained over 5 minute intervals for each control fetus. Time 00 is the baseline or control observation period; subsequent times are expressed as the midpoint of each interval. An F test was done to compare the variances between groups and within groups.

Mean Vessel Cross Sectional Area in % of Baseline Size

	fetus number	20	21_2	25	18	37	38	39	26	33
Time in Minutes	00	100	100	100	100	100	100	100	100	100
	2.5	104	100	80	105.5	103	95	97	111.5	106.5
	7.5	95	120	101.5	140	105.5	90	101	94	92
	12.5	95	114	127	118	104	100	90	80	101
	17.5	97	120	129	100	108	106	92	85.1	101
	22.5	95	106	115	90	102	103	103	98	91
	ΣX	586	660	652.5	653.5	623.5	594	583	568.6	591.5
	$\bar{X}$	97.66	110	108.75	108.91	103.91	99	97.16	94.76	98.58

$$H_o = m_a = m_b = \cdots = m_i$$

$$H_e = m_a \neq m_b \neq \cdots \neq m_i$$

Significance level :

F at 8/45 D.F. at($p = 0.01$) = 2.92

Calculated F = 1.84

$\therefore$ accept H_o

TABLE III_a

This table summarizes the mean vessel sizes obtained over 5 minute intervals for each fetus in experimental group E_1. Time 00 is baseline or control observation period; subsequent times are expressed as the midpoint of each interval.

Mean Vessel Cross Sectional Area in % of Baseline Size

	fetus number	13	15	24	42	16	31	21_1	22	30
Time in Minutes	00	100	100	100	100	100	100	100	100	100
	2.5	116	68.5	107	81	59	99	102.5	109	82
	7.5	98	65	116	43	48.5	68.5	77	74	85
	12.5	61	31.5	75	43	44	76	55	47.5	80
	17.5	51	26	80	46	48	55	60	50	70
	22.5	39	27	47	48	31	55	40	50	56
	ΣX	468	318	525	361	330.5	453.5	434.5	430.5	473
	$\bar{X}$	78	53	87.5	60.17	55.08	75.58	72.42	71.75	78.83

TABLE III_b

This table summarizes the mean vessel sizes obtained over 5 minute intervals for each fetus in experimental group E_2. Time 00 is baseline or control observation period; subsequent times are expressed as the midpoint of each interval.

Mean Vessel Cross Sectional Area in % of Baseline Size

	fetus number	27	29	32	40	41				
Time in Minutes	00	100	100	100	100	100				
	2.5	93	77	76.5	61.5	59				
	7.5	56.5	54	60	31	37				
	ΣX	249.5	231	236.5	192.5	196				
	$\bar{X}$	83.16	79	78.83	64.16	65.33				

TABLE IV

In this table the mean vessel sizes over the total observation time are compared between the control fetuses and the experimental group E_1 fetuses. A t test was done to establish significance.

fetus number	CONTROL Mean Vessel Size for Observation Period in % baseline area	fetus number	EXPERIMENTAL E_1 Mean Vessel Size for Observation Period in % baseline area
20	96.66	13	78
21_2	110	15	53
25	108.75	24	87
18	108.92	42	60.17
37	103.91	16	55.08
38	99	31	75.58
39	97.16	21_1	72.42
26	94.76	22	71.75
33	98.58	30	78.83
$\bar{X}_T$ = 102.08		$\bar{X}_T$ = 70.26	

$$H_o = m_c = m_{e_1}$$

$$H_e = m_c > m_{e_1}$$

Significance level :

t at 16 D.F. at (p=0.01) = 2.921

Calculated t at 16 D.F. = 14.02

$\therefore$ reject H_o , accept H_e

TABLE V

In this table the mean vessel sizes over the total observation time for the group E_2 fetuses are compared to the mean vessel sizes of the control fetuses for the same length of time. A t test was done to establish significance.

fetus number	CONTROL Mean Vessel Size for Observation period in % baseline area	fetus number	EXPERIMENTAL E_2 Mean Vessel Size for Observation Period in % baseline area
20	99.66	27	83.16
21_2	106.66	29	77
25	115.16	32	78.83
18	93.83	40	64.16
37	99.50	41	65.33
38	103.16		$\bar{X}_T = 73.60$
39	95		
26	99.33		
33	101.83		
$\bar{\bar{X}}_T = 101.57$			

$$H_o = m_c = m_{e2}$$

$$H_e = m_c > m_{e_2}$$

Significance level :

t at 12 D.F. at (p=0.01) = 3.055

Calculated t at 12 D.F. = 6.9933

$\therefore$ reject H_o , accept H_e

TABLE VI

This table summarizes the results of F tests done to compare the variance of mean vessel sizes obtained within the control group of fetuses to the variance of mean vessel sizes obtained within each experimental group of fetuses.

Control and E_1

$F = \frac{s_1^2}{s_2^2}$; where s_1^2 = the larger of the two sample variances

s_2^2 = the smaller of the two sample variances

$H_o = m_c = m_{e_1}$

$He = m_c \neq m_{e_1}$

Table F at 8/8 D.F. at (p= 0.01) ..... = 6.03

Calculated $F = \frac{30.7123}{10.6562}$ ..... = 2.882

$\therefore$ accept H_o

Control and E_2

$F = \frac{s_1^2}{s_2^2}$

$H_o = m_c = m_{e_2}$

$H_e = m_c \neq m_{e_2}$

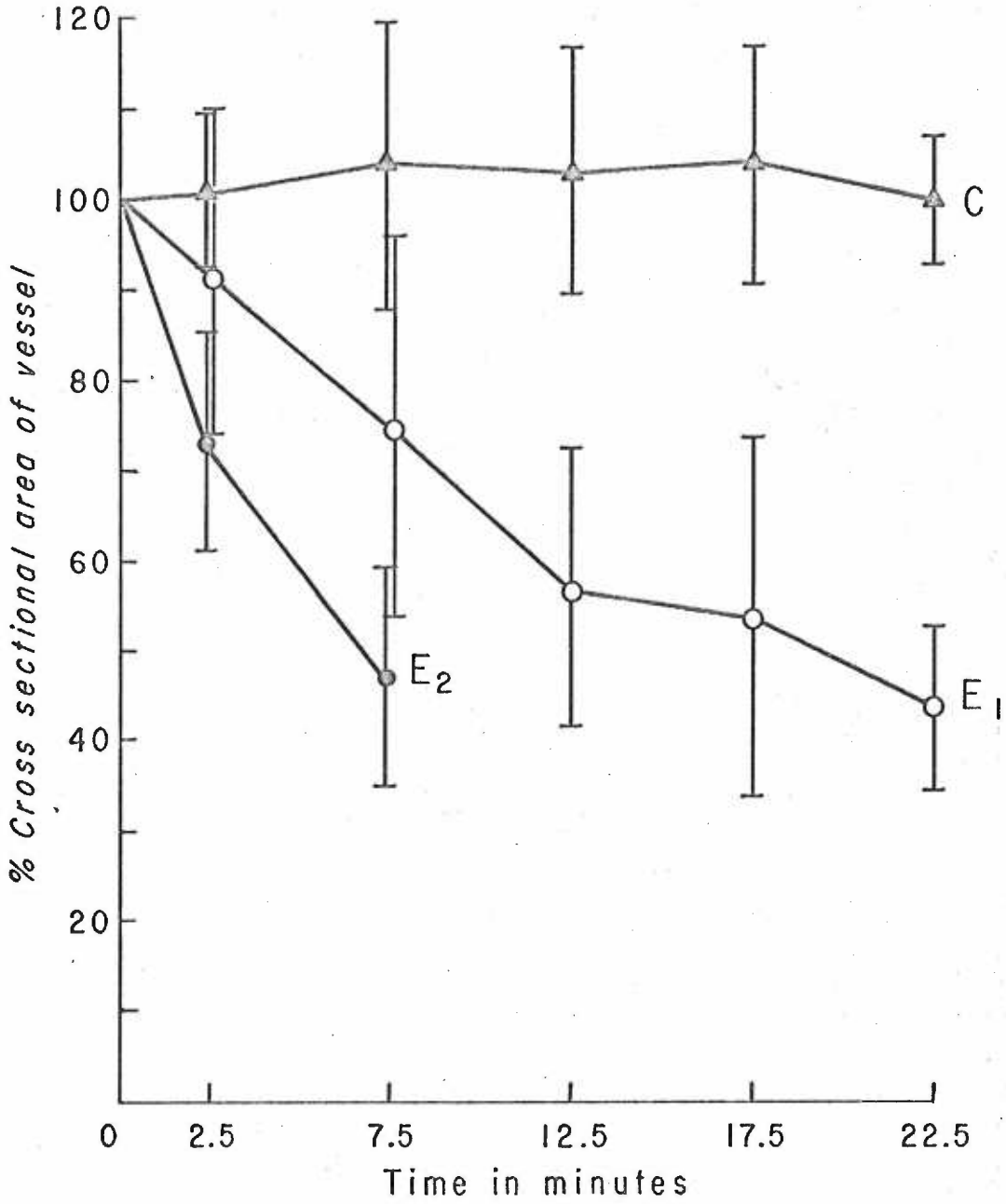
Table F at 4/8 D.F. at (p= 0.01) ..... = 7.01

Calculated $F = \frac{57.5534}{30.6196}$ ..... = 1.8739

$\therefore$ accept H_o

FIGURE 9

The mean vessel cross-sectional areas in percent of baseline size are presented in graph form for all groups. Time is expressed as the midpoint of each five minute interval. Standard deviations are indicated.


120
100
80
60
40
20
% Cross sectional area of vessel
C
E2
E1
0
2.5
7.5
12.5
17.5
22.5
Time in minutes

DISCUSSION

A. Maternal Arterial Pressure Response

The hypotension demonstrated by the maternal rats following inferior vena caval ligation is striking and parallels closely the responses recorded by Howard *et al.* (40) in pregnant bitches. The mean value for arterial pressure depression in their study was 55 mm. Hg. More interesting in this present study is the arterial pressure depression observed in the nonpregnant rats following vena caval occlusion, since Howard *et al.* reported little or no depression of arterial pressure following vena caval ligation in nonpregnant dogs. Especially interesting are the responses shown by nonpregnant rats 4 and 6, which showed a fall in pressure of 54 and 52 mm. Hg., respectively. These results reinforce the concept that each animal reacts in its own individual way to the same stimulus. It may be speculated that the venous collaterals of the inferior vena cava vary within animals of the same species, as well as between species. Both the rat and the dog do not naturally assume the supine position and it may be argued that they would not have well-developed venous collaterals to those areas drained by the inferior vena cava. It is possible, however, that the venous collaterals of the dog are able to more efficiently meet the demands imposed by inferior vena caval ligation than are the venous collaterals of the rat, at least in the nonpregnant state. During late pregnancy, however, in both the rat and the dog, a significant arterial hypotension develops following inferior vena caval ligation. This would suggest that the increased venous return from the pregnant uterus is of sufficient amount so that collateral channels cannot meet the demand placed on

them following vena caval occlusion, with resultant decrease in stroke volume and cardiac output. There is some collateral return of vena caval blood following occlusion of the vena cava below the level of the renal veins, at least via the ovarian veins which are not occluded in this procedure, but this is apparently insufficient to maintain adequate venous return.

The development of tachypnea and deep inspiratory efforts seen following vena caval ligation would appear to be an attempt to increase return flow to the heart by creating a thoracic vacuum. An adequate compensation was, however, never achieved. Thus, there was venous pooling in the uterine veins and, presumably, in the lower extremities, as well as a decreased cardiac output and decreased systemic arterial pressure. The net effect would be to greatly reduce the perfusion of the placenta due both to increased venous pressure and to decreased arterial pressure and stroke volume.

B. Placental Evaluation

Other investigators (41, 61, 66) have demonstrated significant numbers of placental separations or hemorrhages in animals following inferior vena caval ligation or total ligation of the venous drainage of the uterus. In the rat placentas reported in this paper, however, only four placentas demonstrated evidence of hemorrhage or separation. There are several possibilities which may explain this discrepancy. Most studies as described have subjected the maternal animal to inferior vena caval ligation for periods of time approaching or exceeding one hour. All rats whose placentas were examined in this study had undergone vena caval ligation for 25 minutes

maximum time.

The choice of the laboratory animal used may well influence the outcome of an experiment. Most previous investigators have used the rabbit, in which mere manipulation of the uterus may produce spontaneous placental damage or even abortion. Those investigators who have used dogs have observed both marginal placental separations, retroplacental hematomas, and intraplacental hematomas. The dog placenta is an annular structure; when the uterus is opened there is a retraction of the cut surfaces which of itself may produce placental separation and hemorrhage. The dog placenta also has a large marginal "green-zone" or marginal hematoma which is now considered a "hemophagous" zone and is a normal occurrence in later pregnancy. The rat placenta, on the other hand, is an extremely tenacious organ, especially at this stage of fetal development. It is firmly anchored by the central artery; the marginal sinus is also well-anchored. As the placenta ages, however, the area of marginal attachment becomes relatively smaller. It is important to note that the two rats which developed a marginal sinus placental separation in this study were 17 days in gestation. No separations were seen in younger animals. Other investigators, with the exception of Haynes (35), did not specify the ages of gestation of their animals, other than that they were late in gestation. If, indeed, the animals were close to term, a placental separation would be more easily produced.

The placental observations in this study were, admittedly, rather superficial, with examination only under 30 X magnification. It is entirely possible that had more detailed observation been done

lesions similar to those described by Haynes (35) would have been seen. The fact that so few frank hemorrhages were seen is valid, however.

C. Fetal Responses

The evaluation of the fetal responses to maternal inferior vena caval ligation presents more difficulty. With markedly decreased placental perfusion by the maternal blood, the exchange of respiratory gases will be greatly decreased due to several factors. In the introductory chapter, it was noted that a decreased maternal blood flow to the placenta would have the effect of lowering the relative oxygen tension gradient between maternal and fetal blood over a given unit of time. Applying this to Fick's diffusion equation, the rate of transfer of oxygen from maternal to fetal blood would decrease, and if near stagnation of maternal blood occurred, the rate of transfer would approach zero. At the same time, carbon dioxide transfer from fetal to maternal blood would decrease as maternal blood became more saturated with CO_2.

With near stagnation of maternal placental flow, the effect on fetal oxygen uptake would be greater than that seen with simple maternal hypoxemia, for, as the fetal blood became more saturated with carbon dioxide, the so-called "double Bohr" effect would be lost. As the fetal blood became more acid, due to increased CO_2 saturation as well as to decreased transfer of fixed acids to the maternal blood, the oxygen affinity of fetal hemoglobin would be decreased. As the oxygen saturation of the fetal blood decreased, the affinity for carbon dioxide would increase, and a sort of vicious circle would be set up. The net effect would be to greatly

decrease the oxygen and carbon dioxide transfer across the placental membrane, with resultant decrease in fetal PaO_2 and increase in fetal $PaCO_2$.

It has been well demonstrated (34, 50, 70) that an increase in $PaCO_2$ causes cerebral vasodilatation and increased cerebral blood flow in the adult. A decrease in PaO_2 has the same effect (32, 55, 87). Stewart (85) has demonstrated that increased $PaCO_2$ causes fetal cerebral vasodilatation. It has been postulated that the control of cerebral blood flow resides primarily with the arterial resistance within the brain itself, and that this in turn is most responsive to variations in the tissue and arterial concentrations of the respiratory gases. With these concepts in mind, it would be logical that a dilation of the fetal cerebral arteries would have been observed following maternal vena caval ligation. This was not the case, however, and other explanations must be sought.

As was mentioned in the introduction, the adult cerebral arterial tree can react to an increase in systemic arterial pressure by vasoconstriction, thus maintaining cerebral blood flow at near normal levels. It has been demonstrated (4, 11, 74) that mild to moderate hypoxia produces a systemic hypertension in the fetal lamb. There is the possibility that the early vasoconstriction seen in the cerebral arteries of the fetal rats was a compensation for systemic hypertension. The mechanism of such a response in the adult cerebral arteries is most likely a response to increased "washout" of CO_2 from the cerebral tissues by an increased cerebral blood flow. However, in the rat fetus during maternal vena caval ligation, $PaCO_2$ would be increased and vasodilation would be the expected result, even with

increased cerebral blood flow.

The redistribution of fetal blood flow during hypoxia provides an explanation for the vasoconstriction seen in the fetal cerebral arteries. As more blood is diverted to the umbilical and placental circulation, proportionately less of the cardiac output is directed to the brain. There are two possibilities which would explain a cerebral vasoconstriction. First, the cerebral arterial tree could respond passively to a decrease in blood flow by constricting in order to maintain perfusion pressure, or, second, an increase in cerebral vascular resistance produced by a vasoconstriction of the arterial tree could precede and be, in part, responsible for the diversion of blood flow to the descending aorta and thus to the placenta. The latter possibility seems more tenable. The etiologic factors involved in such an increase in vascular resistance are open to speculation, but may involve neurologic mediation or the liberation of pressor agents. The end result, however, would be to increase placental flow in an attempt to increase the arterial oxygen concentration.

Eventually, however, as hypoxia is sustained, the fetal heart fails and cardiac output is decreased. This would further decrease the amount of blood reaching the fetal brain and would possibly induce further vasoconstriction. The vasomotor tone of an artery tends to constrict the vessel while pressure within the vessel tends to dilate it. According to the law of La Place, the force tending to stretch the muscle fibers of the vascular wall is proportional to the diameter of the vessel and the vascular pressure. As pressure decreases, the vessel diameter also decreases. The force tending to keep the vessel

wall stretched then decreases much more rapidly than could be accounted for merely by a decrease in pressure, with resultant rapid vasoconstriction.

An attractive theory to explain the etiology of the vasoconstriction seen in the cerebral arteries has been made possible by the work of Comline and Silver (17), who demonstrated the release of significant amounts of catechol amines, particularly norepinephrine, from the fetal lamb adrenal during hypoxia. Other workers (33) have demonstrated an elevation of fetal systemic pressure and an increase in umbilical flow following injection of pressor agents. In the adult, norepinephrine has been shown to cause an increase in cerebral vascular resistance and a decrease in cerebral blood flow (51). Christiansen et al. (16) have demonstrated that the fetal cerebral vascular tree will respond to vasopressor drugs by constricting. Geber (28) has demonstrated increased carotid artery pressure and decreased cerebral blood flow following injection of pressor agents. If the fetal rat adrenal responds to hypoxia with the release of pressor agents, particularly norepinephrine, the resultant vasoconstriction seen in the cerebral arteries may be attributed to the direct action of these agents.

Epinephrine-like agents capable of causing increases in fetal blood pressure were found in the fetal adrenal as early as 1899 (60). It was demonstrated that in many species the fetal adrenal at midterm contained significant amounts of pressor agents. It is now well-established that the major percentage of these catecholamines is norepinephrine (81). Extracts of the fetal mouse adrenal have been shown to demonstrate pressor activity as early as 14 days

(30). However, Hökfelt (37) was unable to demonstrate catecholamine activity in fetal rat adrenals before 17 days gestation. Other chromaffin tissue exists, however, which seems particularly active during fetal life. The organ of Zuckerkandl has been shown to have a higher concentration of norepinephrine during fetal life than does the adrenal (88). The glomus cells and the carotid body have also been shown to contain significant amounts of norepinephrine. Thus, it remains possible that under hypoxic conditions pressor agents are released from the chromaffin cells of the fetal rat. This is speculative at this time, but remains an attractive possibility.

Little has been said of cerebral blood flow, as it was not possible by the technique employed to quantitate flow rate. It is true that the rate of flow through any vessel is proportional to the cross-sectional area, but other factors, such as the stroke volume and heart rate, are also determinants of flow rate. Geber (28) has demonstrated a decreased cerebral flow during hypoxia. It seems logical that the vasoconstriction seen in the middle cerebral arteries of the fetal rat heralds a decrease in blood flow. Admittedly, a vasoconstriction coupled with increased systemic arterial pressure and tachycardia would act to maintain cerebral blood flow at near normal levels. As the cardiac output and rate declined, however, persisting cerebral vasoconstriction would surely indicate a decreased cerebral blood flow.

There is the possibility that a transient vasodilatation in the cerebral arteries occurred during the early moments of vena caval occlusion, but, if so, the methods of observation were not

sufficient to establish this. Perhaps if photographic records had been made at closer intervals during the first few minutes of observation, a vasodilatation would have been seen, but this is speculation only.

Comparing the cerebral vascular responses of those fetuses in experimental groups E_1 and E_2 to the control fetuses, an obvious difference is seen. There was a significant and early vasoconstriction seen in experimental group E_2, while in group E_1, the mean vessel size was not significantly reduced after $2\frac{1}{2}$ minutes. It is only after $7\frac{1}{2}$ minutes that a marked vasoconstriction was seen. The concept of an oxygen reserve for the placenta may be invoked at this point. The oxygen reserve is that length of time which indicates the upper limit over which stored oxygen can continue its transfer when replacement is interrupted. The oxygen reserve for the human placenta is estimated as between 2 and 3 minutes (1) following cessation of placental flow. The oxygen reserve has not been calculated for the rat fetus, but may well be within this range. This may explain the time-lag seen for vasoconstriction in experimental group E_1.

Group E_2 fetuses demonstrate a more rapid vasoconstriction and an earlier bradycardia. It is possible that the oxygen reserve of these fetuses was reduced prior to maternal vena caval ligation, possibly due to the effects of anesthesia or to the surgical procedure. Observations made by Geber (28) provide an alternative explanation. Geber noted that fetuses from the same litter exhibited variations in vascular responses during both control and experimental conditions. He interpreted this to mean that each fetus has its own

physiologic as well as anatomic orientation and susceptibility within the uterus. He also considered the possibility that the physiologic status of that area of the uterus shared by the fetal and maternal tissues changes from moment to moment and that this factor may be the variable that determines the ultimate response of the fetus. With these ideas in mind it seems possible that litter mates of fetuses in experimental group E_1 would have demonstrated responses similar to those observed in group E_2 animals, and vice versa.

Comparing the end-point vascular size for both experimental groups, it is noted that they are remarkably similar. This may represent a point of maximum possible vasoconstriction. Other workers have noted that there appears to be a point at which cerebral blood flow cannot be further reduced by vasoconstriction alone (34).

Speculation as to cause and effect aside, it is obvious that ligation of the maternal inferior vena cava has profound effects upon the fetal cerebral arteries and upon the general condition of the fetus. As vena caval occlusion is prolonged and cerebral vasoconstriction and decreased cardiac output both occur, the cerebral blood flow is undoubtedly reduced. The PaO_2 of cerebral blood may well reach extremely low levels. The net effect would be to create an almost anoxic condition for the fetal brain. Although the adult brain can withstand anoxia for approximately three to four minutes only, the fetal brain can apparently withstand longer periods of anoxia. Several mechanisms aid the fetus in surviving during extreme hypoxia. As oxygen saturation and umbilical blood flow decrease, the

rate of fetal oxygen consumption decreases (18). When threatened by asphyxia, the fetus can apparently derive energy by anaerobic glycolysis (42, 43). During anaerobic glycolysis, significant amounts of lactate are produced which must be disposed of by the placenta or the maternal circulation. During inferior vena caval ligation, however, the blood supply to the placenta is markedly decreased and the removal of lactate from the fetal circulation would be decreased. Fetal lactic acidemia would then occur. The effects of prolonged hypoxia, anaerobic metabolism and acidemia on the developing fetal cerebral cortex may be profound. Wood et al. (90) have shown a direct correlation between fetal acidemia and a low Apgar score in newborns. In their series, several newborns with low blood pH were stillborn or died soon after delivery.

Downing et al. (21) have demonstrated that myocardial depression of newborn lambs is significantly increased by the presence of both hypoxemia and acidemia, and is greater than that expected from the additive effects of either. This may explain the failure of the fetal rat heart under prolonged periods of hypoxia with decreased placental exchange. Under these conditions, the fetal blood should show acidemia as well as hypoxemia.

Studies should be attempted to further define the parameters of fetal responses to maternal inferior vena caval ligation. With larger animals it should be possible to quantitate fetal cerebral blood flow as well as carotid artery pressure during maternal vena caval ligation. With a larger fetus, blood gases could be measured in umbilical vein and artery, from the maternal side of the placenta, and possibly from the carotid artery itself. If, indeed, there is

a significant release of catecholamines from the fetal adrenals or other chromaffin bodies, this could be quantitated and perhaps correlated with the cardiovascular status of the fetus.

It would be informative to allow inferior vena caval ligation to occur for various lengths of time and to allow the fetus to then reach term. An evaluation of the neurological status of such animals after birth and subsequent development would provide information as to the effects upon the cerebral cortex. Dr. David Gunberg[1] has clamped the uterine arteries of pregnant rats for up to 25 minutes with fetal survival. Unfortunately, an evaluation of the neurologic status of the offspring was not statistically significant due to a small sample size.

A critical analysis of the methods used in this procedure is appropriate, as there is always the possibility that any changes in fetal response are procedurally induced.

The anesthetic used in all cases was Sodium Pentobarbital; the dosage used was the same in each animal. Sodium Pentobarbital is known to cause respiratory depression in large dosage, and also is known to cross the placenta. The level of anesthesia in all animals was extremely light, however, and no maternal animal was used who demonstrated respiratory depression. The subcutaneous site of injection of the anesthetic also provided for a slow, sustained absorption of anesthetic. A depression of maternal respiration would have increased the $PaCO_2$ of the maternal blood and might have had an effect upon the fetal cerebral arteries; specifically, vasodilatation

[1]Dr. David L. Gunberg. Personal Communication. April 17, 1968.

should have been seen. As can be seen in the control fetuses, however, no significant vasodilatation occurred with time. Several fetuses in the control group demonstrated both a moderate vasoconstriction and vasodilation from moment to moment. This is probably in keeping with Geber's observations, as previously mentioned.

It should also be mentioned at this point that no tracheostomy was done on the maternal animals, primarily to avoid a further surgical procedure and prolonged time prior to fetal observations. Maternal animals were carefully watched for signs of obstruction of the airway and respiratory distress, as mentioned, and no animal was used who demonstrated any obstruction.

It seemed possible that the fetal responses seen in the experimental animals could possibly be consistent with a slow exsanguination of the fetus due to a surgical error. As was mentioned in discussing the methods of fetal observation, every effort was taken to prevent and to detect any fetal bleeding. Also, each fetus observed was compared with its litter mates at the termination of the experiment. In each case reported in this paper, the litter mates of the experimental fetuses were in obvious cardiovascular distress or dead; an examination of the cerebral arteries showed a state of constriction. Also, it seems unlikely that the same surgical procedure would result in exsanguination of the experimental series while the control series showed no such evidence.

It is admitted that this procedure does not provide perfect homeostasis for the fetus. The very act of removing the fetus from the uterus may produce alterations in the cardiovascular physiology. It is, of course, impossible to maintain the fetus at its normal intra-

uterine pressure with equipment presently available. However, every other possible attempt was made to maintain the fetus at intrauterine conditions. Whether or not intrauterine conditions were perfectly maintained, it is apparent that the cardiovascular responses of the experimental animals were significantly different than the control animals.

It is always tempting, and always dangerous, to apply information gained from animal experimentation to humans. It has been well-demonstrated that there are differing responses to the same stimulus both between species and within the same species. Nonetheless, significant clinical information has often been gained from prior animal studies.

It has been estimated that the incidence of the supine hypotensive syndrome of pregnancy is about 8% to 12% in near-term women. The chance of complications occurring in even this fairly large percentage of cases is further reduced by the fact that any pregnant woman who experiences the symptoms of supine hypotension will not voluntarily remain supine. There are always the unexpected cases, possibly following trauma, in which a pregnant woman may be comatose and may be placed in a supine position for considerable lengths of time. The occurrence of shock-like symptoms in such a case may be attributed to possible injuries by the attending personnel and corrective therapy begun without considering the possibility of supine hypotension.

During the course of labor, there is little chance for the development of supine hypotension, as was discussed. Should labor cease, as not uncommonly occurs with certain forms of anesthesia,

supine hypotension may occur, particularly if the woman is in the lithotomy position. In such cases, most obstetricians and anesthesiologists would recognize the symptoms and place the patient in a lateral recumbent position. Recognition of any symptom complex depends, however, on knowledge of the etiology and significance of a change in the condition of a patient. As Howard et al. (40) pointed out, several unnecessary surgical procedures have been done by failing to recognize supine hypotension.

The effects of a prolonged maternal hypotension and inferior vena caval occlusion on the human fetus may well be similar to those seen in the rat fetus. From one to two percent of children born in the United States suffer from significant mental retardation. A significant percentage of these cases are attributed to perinatal brain damage, particularly to the effects of anoxia. If, indeed, a prolonged duration of maternal supine hypotension is a possible factor in decreasing oxygenation of the fetal brain, this is a syndrome of pregnancy which should be diagnosed as early as possible and actively guarded against.

SUMMARY AND CONCLUSIONS

An attempt was made to reproduce the clinical symptom complex known as the supine hypotensive syndrome of pregnancy in the laboratory rat. Significant hypotension was produced in third trimester pregnant rats by ligation of the inferior vena cava below the level of the renal veins.

Direct observations of the fetal cerebral hemodynamics were made using a modification of the transillumination technique used to study the adult microcirculation in vivo. Rat fetuses of 14½ to 17 days gestation were surgically exposed and maintained at as near intrauterine conditions as possible. Microscopic examination of vasomotor changes in the middle cerebral artery was photographically recorded over timed periods for an experimental group of fetuses during ligation of the maternal inferior vena cava, and for a control group of fetuses for the same length of time but with no maternal manipulation. The extent of variations in the cross-sectional area of the middle cerebral arteries for each group was compared statistically. It was found that a significant vasoconstriction occurred in the experimental group following maternal vena caval ligation.

The control of the adult cerebral vascular tree is thought to reside primarily with arterial levels of oxygen and carbon dioxide. Ligation of the maternal inferior vena cava should greatly reduce the transfer of respiratory gases across the placental membrane, resulting in a high fetal Pa_{CO_2} and low Pa_{O_2} and one would expect to see vasodilation in the cerebral arterial tree. The results of this study indicate that the fetal responses to such a catastrophic event is vasoconstriction in the cerebral arterial tree, and probably in other

organ systems as well, perhaps in an attempt to increase umbilical and placental blood flow. The etiologic factors in such a response are open to speculation, and await further confirmation and study in larger animals which are amenable to pressure-flow apparatus and blood-gas studies.

A critical analysis of this technique is presented. There are numerous possible applications of these techniques to future study of fetal responses to maternal stimulation, as well as to fetal development.

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