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The Role of the Thyroid Gland
in Postnatal Cardiovascular Adjustments

by

Jeffrey Alan Breall

DISSERTATION

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The Role of the Thyroid Gland in Postnatal Cardiovascular Adjustments

Jeffrey Alan Breall

This Work is Submitted as the Thesis Requirement for the Ph.D. Degree in Physiology at the University of California, San Francisco

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Dedication

This thesis is dedicated to my father, Dr. William S. Breall, who has served as an inspiration for me to pursue a career in science and medicine for the past 27 plus years; without his support and encouragement in times of need, this work would surely never have been completed.

Abstract

To assess the effects of the neonatal surge in thyroid hormone concentrations on postnatal cardiovascular adjustments, we measured cardiac output and oxygen consumption in three groups of lambs during the first six hours after birth. For each lamb, catheters were placed into the ascending aorta, descending aorta, distal inferior vena cava, left atrial appendage, and main pulmonary artery at about 129 days gestation (term equals 145 days). Group I consisted of five control animals; Group II consisted of five animals thyroidectomized as fetuses at a gestational age of about 129 days; and Group III consisted of four animals which were thyroidectomized at term during delivery by Caesarean section, prior to clamping the umbilical cord. The animals in Group I exhibited an immediate postnatal rise in triiodothyronine (T_3) concentration similar to those previously described, reaching a peak value of about 5 ng/ml. Although the postnatal surge in T_3 concentration was arrested in the animals of both Groups II and III, the fetuses in Group II had no detectable T_3 levels immediately before clamping the umbilical cord, whereas the animals in Group III had T_3 concentrations within the previously reported range for term fetuses (about 80 ng/dl). As compared to the neonatal lambs in Group I, the lambs in Group II showed a 40 to 50 per cent reduction in left ventricular output (297 vs. 190 ml/kg/min), systemic blood flow (286 vs. 155 ml/kg/min), and oxygen consumption (20.2 vs. 9.8 ml/kg/min), over the entire six hour period. The lambs in Group II also had significantly lower mean arterial blood pressures (72 vs. 56 torr), and heart rates (192 vs. 131 beats/min). The reduction in cardiac

output for the animals in Group II could be accounted for by a reduction in blood flow to the carcass. Blood flow per 100 grams of tissue was not significantly different among the three groups for the rest of the individual organs. There was no significant difference for left ventricular output, systemic blood flow, oxygen consumption, mean arterial blood pressure, heart rate, or organ blood flows between the animals in Group I and Group III. These studies suggest that the increase in thyroid hormone concentrations which occurs after birth is not as important for postnatal cardiovascular adjustment as are the levels of thyroid hormones during the last two to three weeks of gestation. We believe that the absence of thyroid hormones late in gestation has its effects on postnatal cardiovascular adjustments by inhibiting the normal development of beta-adrenergic receptors.

IV. List of Important Abbreviations

AM - amniotic cavity

CA - fetal ascending aorta

CO - cardiac output

CVO - combined ventricular output

FA - fetal descending aorta

IVC - fetal distal inferior vena cava

LA - left atrial appendage

MA - maternal descending aorta

MV - maternal distal inferior vena cava

PA - main pulmonary artery

PCO_2 - partial pressure of carbon dioxide

pH - negative log of the hydrogen ion concentration

PO_2 - partial pressure of oxygen

rT_3 - 3,3',5' triiodothyronine

T_3 - 3,3',5 triiodothyronine

TRH - thyrotropin releasing hormone

TSH - thyrotropin

VO_2 - oxygen consumption

V. Introduction

Birth marks a period of extreme physiological change in mammals. The cardiovascular changes that occur in the immediate newborn period have been described in detail. These changes are concerned with the adaptation from fetal to extrauterine life and include the removal of the umbilical-placental circulation, the establishment of an adequate pulmonary blood flow, the closure of the ductus arteriosus, and the closure of the foramen ovale. Also, there is a change in the amount of blood that is delivered to the organism by the heart. In the fetus the right ventricle ejects about 330 ml/kg/min, while the left ventricle ejects about 170 ml/kg/min. After birth, both ventricles eject about 300ml/kg/min, corresponding to little or no change in right ventricular output, but a 75 to 100 per cent increase in left ventricular output. The reasons for the dramatic increase in left ventricular output postnatally are not certain, although it has been suggested that these changes may be secondary to metabolic demands, or due to other factors which may be influencing myocardial function. From a metabolic standpoint, total body oxygen consumption in the fetus is about 8 ml/kg/min. This value increases about 90 per cent to 15 ml/kg/min in the newborn--a per cent increase similar to that which occurs in left ventricular output of the neonate. There are many humoral changes which also occur at birth, and we thought that perhaps one of them might be responsible for changing both hemodynamics and metabolism together. Because of the heightened circulatory and metabolic states that are associated with hyperthyroidism in adult animals, we considered the thyroid gland as a likely candidate for mediating these changes. Thus,

the working hypothesis for this study was that the hemodynamic and metabolic changes which occur after birth are due to the endogenous postnatal release of thyroid hormones.

The intricate association between the thyroid and the heart really begins early during ontogeny from the anatomical viewpoint. Apparently, it is the primitive heart structure, to which the thyroid is attached, that initially guides the descent of the thyroid from the lingual area into its normal position along the upper end of the trachea. Occasionally, these two organs remain in contact, and then the thyroid may reside in the mediastinum near the heart. There are two reasons for suspecting that the thyroid gland is at least in part responsible for the hemodynamic and metabolic changes which occur postnatally. Firstly, immediately after birth there is a large rise in the level of thyrotropin, followed shortly thereafter by about a ten fold increase in the levels of both triiodothyronine and thyroxine. During the first few hours of extrauterine life the neonate is thereby transformed into a state of chemical hyperthyroidism. Secondly, there are the documented effects that excess thyroid hormones have on both metabolic rate and hemodynamics in various adult species. These effects are dose dependent, but it is not uncommon to see oxygen consumption and cardiac output double in hyperthyroidism. Excess triiodothyronine or thyroxine is also known to increase heart rate, pulse pressure, and left ventricular stroke work to various degrees, again depending upon the amount and duration of excess hormone present. In contrast to this, spontaneous or experimentally-induced hypothyroidism usually causes the above mentioned hemodynamic and metabolic variables to have values lower than normal.

Because of the relationship that appears to be present between the thyroid and the circulatory states in the adult, and because of the profound changes that occur in these two systems at the time of birth, we were interested in determining the extent to which the increase in thyroid hormones at birth is responsible for the changes which occur in circulatory dynamics and oxygen consumption in neonatal sheep.

VI. Background

A) The Lamb as an Experimental Preparation

Since the mid-1960s, the study of fetal physiology has been conducted using the chronic fetal sheep preparation which was first described by Meschia.[1] The long-term maintenance of indwelling catheters as well as other instrumentation, in the fetal sheep preparation, has allowed the measurement of various physiological variables at different gestational ages. Furthermore, these measurements could be made chronically, after the fetus had recovered from any surgically-induced strain. It is now possible to study hemodynamics and endocrinology in the fetus under normal conditions as well as in response to any of a number of stresses.[2]

The technique of chronic catheterization has made the study of circulatory and endocrine physiology possible in newborn and young lambs as well. In these animals the technique requires the surgical procedure of an arterial and/or venous cutdown at various anatomic locations. Although these are done aseptically, they are relatively simple and noninvasive in comparison with setting up a chronic fetal preparation. As long as no thoracotomy is performed on the young animal, the time required to recover to baseline is significantly less than after the more extensive fetal surgery.[17]

When studying the sheep fetus one may pay relatively little attention to the ambient conditions as long as the ewe is kept relatively calm and the study conditions are relatively constant from one day to the next. This may be done because of the constancy of the amniotic environment that surrounds the fetus itself. One must be much more careful when

studying the newborn, however. Slight changes in ambient temperature, for example, may have profound effects on plasma thyroid hormone levels as well as on hemodynamics.[3-6]

If one compares the results of studies of sheep fetuses at various gestational ages with those of young lambs at various ages, one may obtain a developmental continuum of any given physiological variable. In this continuum, if one wants to study events that occur within minutes to hours after birth, there are several problems. First, it is difficult to know exactly when the birth of the animal occurred, unless someone is constantly watching for spontaneous vaginal delivery when the fetus is close to term. (We have found that knowing the breeding date, we can only estimate the date of delivery within three to five days.) Second, waiting until after birth to prepare the neonate for a given experimental protocol (assuming this is done immediately after delivery) would preclude one from making some crucial measurements in the immediate newborn period. We have circumvented these difficulties by doing the following two things: 1) the animal was prepared for postnatal studies by placing various catheters in the fetus late in gestation; and 2) at term, "birth" was initiated by delivering the animal by Caesarean section. This is the method of choice for doing hemodynamic studies in the immediate newborn period as the animal already has patent catheters in place, and the investigator can control the time of birth by delivering the animal when it is judged to be full term. We were able to estimate term by using ewes that had a known breeding date and by measuring the total protein concentration in the fetal plasma. Bland and his coworkers have shown that the plasma protein concentration rises

rapidly at term in the cord blood of human infants.[7] We found that we could use an absolute plasma protein concentration value of 4.5 mg/dl to indicate the fetus was full term. Indeed, this plasma protein value corresponded to a gestational age of 140 to 145 days.

Finally, one should mention the fact that when comparing physiological variables in the fetus to those in the neonate, one would like ideally to study the same animal during unstressed fetal life as well as following delivery. Such sequential data do not exist, but information from different groups of fetal and newborn animals of the same species (primarily sheep) does exist.

B) Circulatory Changes in the Neonatal Lamb

The fetal circulation is unlike that of the adult as the heart does not pump in a series fashion, but rather some blood from both ventricles is simultaneously ejected to the lower fetal body. Therefore, the term that is used to describe the amount of blood circulating per minute in the fetus is Combined Ventricular Output (CVO), rather than Cardiac Output (CO) which is used to describe the postnatal circulating volume per unit time.[8] The CVO in the sheep fetus is about 500 ml per kg fetal body weight per minute. Of this volume, roughly two-thirds or 330 ml/kg/min is ejected by the right ventricle and one-third or 170 ml/kg/min is ejected by the left ventricle.[9-11] Left ventricular blood, which is more highly oxygenated, is distributed preferentially to the upper body and heart, whereas right ventricular blood goes to the lower body, lungs, and placenta.[12-14]

Immediately after birth, the umbilical-placental circulation is removed and the oxygenating function of the placenta is replaced by the lungs with the establishment of an adequate pulmonary circulation and ventilation (respiration). Concomitantly, there is a physiologic closing of both the foramen ovale and the ductus arteriosus. The blood is now serially pumped from the right side of the heart, to the lungs, back to the left side of the heart and then to the rest of the organs of the body, then to return to the right side of the heart.[8] The total output of the heart increases with each ventricle ejecting about 300 ml/kg/min (making the total output of the heart about 600 ml/kg/min).[15-18] Compared to the fetus, the newborn right ventricle ejects about the same volume whereas the left ventricle increases its

output by approximately 100 percent.

The reason for the increase in cardiac output after birth is not completely understood, but it may be due in part to the increased metabolic needs of the animal.[16] After birth the mammalian neonate experiences a greater demand on body temperature regulation, as it is no longer in the temperature-controlled environment of the amniotic cavity. There is a parallel increase in total body oxygen consumption and left ventricular output. On a percentage basis, these two increases are almost identical. Furthermore, Sidi, et. al., have shown that dropping the ambient temperature by as little as seven degrees Celsius will cause a 14 per cent increase in heart rate and an 18 per cent increase in cardiac output.[6] Another possible explanation for the increase in cardiac output after birth is a change in left ventricular compliance. Romero, et. al., have shown that the newborn left ventricle in vitro has a compliance in between that of the fetus and the adult. Studies by Heymann and Rudolph as well as by Gilbert have shown that increasing preload to the late gestation fetal ventricle will increase output only by about 15 per cent.[19,21] Similarly, Klopfenstein and Rudolph have shown that volume loading in one-week-old lambs increased left ventricular output by only 35 per cent. So, although there probably is some increase in both compliance and the slope of the Frank-Starling curve in the newborn left ventricle,[22] these factors alone probably do not account for the 100% increase in left ventricular output after birth. It is also possible that the newborn myocardium has a greater adrenergic responsiveness. We know, for instance, that many species exhibit a progressive increase in sympathetic innervation to the myo-

cardium throughout gestation and that this process may not be complete until some time after birth.[23-26] Plasma catecholamine concentrations are known to rise immediately after birth, particularly norepinephrine concentrations.[27] The extent to which this rise in circulating catecholamines affects left ventricular output in the neonate has not been fully delineated. It appears, however, that resting beta-adrenergic activity is not a major factor, because Klopfenstein and Rudolph have shown that propranolol decreased heart rate and aortic flow in one-week-old lambs by only 12 and 15 per cent respectively.[15] Finally, there are increases in both alpha and beta-adrenergic receptors throughout gestation, and in some species these increases continue until well after birth. These increases occur in the myocardium as well as other organs, and seem to be regulated by a number of humoral agents, including the thyroid hormones.[28-30] Experimentally induced hyper- and hypothyroidism have been shown to increase and decrease respectively the number of beta adrenergic receptors .

C) Changes in Oxygen Consumption of the Neonate

As mentioned previously, the oxygen consumption (VO_2) of the neonatal lamb is, like cardiac output, very high relative to that of the near term fetus. Values for total body oxygen consumption of the sheep fetus vary from 5 to 9 ml/min per kg body weight, with a near-term fetus having a value of about 8 ml/min/kg.[31,32] Measurements of fetal VO_2 are calculated by the Fick method, where umbilical blood flow and arteriovenous oxygen content difference across the fetal side of the placenta are measured. Umbilical blood flow has been measured using different techniques, possibly accounting for at least some of the variation in reported values. After birth, oxygen consumption has been reported to be between 15 and 21 ml/min per kg body weight.[6,16,17] This two-fold and greater increase in VO_2 is no doubt due to the increased metabolic demands of the extrauterine environment. Postnatally, VO_2 can also be calculated by the Fick method. Recently, however, it has become possible to measure VO_2 directly in newborn lambs and human infants by means of a continuous flow-through device.[33] Sidi, et. al., also showed that a decrease in ambient temperature of only seven degrees Celsius will cause a 40 per cent increase in oxygen consumption in normoxemic lambs, in addition to the previously mentioned effects on heart rate and cardiac output. Thus, different environmental temperatures in the different studies might explain part of the variability in reported postnatal values for oxygen consumption.[6]

(D) Perinatal Thyroid Function

In the human fetus development of the thyroid gland occurs throughout gestation and thyroid function appears to be mature at about four weeks after birth, whereas in sheep, thyroid function seems to be mature by two weeks postnatally.[34] In both species, the hypothalamic-pituitary-thyroid axis does not begin to function until mid-gestation.[35-37] An important corollary to this is the fact that the fetal thyroid system is completely independent of maternal thyroid status throughout gestation. None of the thyroid hormones cross the placenta, and there is no significant passage of either thyrotropin releasing hormone (TRH) or thyrotropin (TSH) across the placenta.[38-46] TSH responsiveness to exogenous TRH is present early in the third trimester in both primate and sheep fetuses; in sheep the response of TSH to a given dose of TRH is markedly less in the neonate relative to the response to the same dose of TRH given to the fetus in the third trimester. The normal feedback inhibitory mechanism of triiodothyronine (T_3) on TSH is quite insensitive during the end of gestation.[47,48]

The levels of the thyroid hormones vary throughout fetal development. Total serum thyroxine (T_4) concentration in the fetus is quite low at mid-gestation and progressively rises until term, when fetal total T_4 concentration is about equal to maternal total T_4 concentration.[35,38] This rise in T_4 concentration is partially mediated by a rise in TSH concentration at mid-gestation; however, T_4 concentration continues to rise during the third trimester despite constant TSH levels.[37,49] In the young fetus (mid-gestational) not only is total serum T_4 concentration very low, but the binding protein, thyroxine-

binding globulin (TBG) concentration is also quite low (20 ng/ml). TBG concentration increases throughout gestation, and in sheep, TBG is the only binding protein for thyroid hormones (other than albumin), unlike the human fetus which has albumin and thyroxine-binding prealbumin as well. T_4 secretion rises more rapidly relative to the level of TBG so that free T_4 concentration increases and at term actually exceeds that of maternal free T_4 concentration.[35,36,50]

Total fetal serum T_3 concentration is very low, and may not be detectable throughout most of gestation, and studies show that the T_3 that is present is directly released from the thyroid gland.[37,51] Any peripheral conversion of T_4 via monodeiodination goes to form reverse triiodothyronine (rT_3), which is present in extremely high concentrations in the fetus (4 ng/ml).[51] In fetal sheep, serum T_3 levels gradually increase during the week immediately preceding parturition, rising from 20 to 100 ng/dl.[52,53] This increase in prenatal T_3 correlates well with the prenatal increase in serum cortisol concentrations. In fact, there is evidence to suggest that the increase in prenatal T_3 is mediated by cortisol, which probably causes more T_4 conversion to T_3 instead of rT_3. This would explain why rT_3 concentrations decline during the last week of gestation in the sheep fetus.[52,54-57,68]

With birth, and the exposure of the neonate to the extrauterine environment, there is a dramatic change in the pituitary-thyroid axis. Pituitary TSH is released, and serum concentrations increase six- to eight-fold, reaching a peak within 30 minutes.[37,58] This TSH surge is partially caused by the cooling of the animal, and it results in a surge

in the iodothyronines as well.[3,4,58] Serum T_4 and free T_4 concentrations progressively increase, peaking at 24 hours of age.[3,4,58-61] Serum T_3 concentrations rise immediately, and within several hours after birth, total and free T_3 levels increase three to six fold. This initial peak at two to four hours is followed by a second, more gradual increase in T_3 concentration between 24 and 36 hours.[59-61] The initial rise in T_3 concentration may be due to an increased peripheral conversion from T_4. In support of this theory, there is an increase in the rate of hepatic T_4 to T_3 conversion, in vitro, during this period.[55] The second surge is due to a greater secretion of T_3 directly from the thyroid gland in response to TSH.[60] In sheep, it has been found that the early T_3 surge can be dissociated from the TSH surge by a delay in cutting the umbilical cord or by giving alpha-methyl-paratyrosine, a specific inhibitor of catecholamine synthesis.[37,62]

In studies on fetal and neonatal thyroid hormone concentrations, it has been shown that there is a tremendous increase in thyroid activity immediately after birth in newborn pigs, calves, lambs, and humans. This is true regardless of whether the animal was delivered spontaneously or by Caesarean section.[58] In the human and the sheep, if the neonate is slightly premature but otherwise healthy, the thyroidal changes are qualitatively the same but the absolute values of the increases in all pituitary-thyroid axis hormone concentrations may be less.[63-68]

(E) The Circulatory Effects of Thyroid Hormones

The relationship between altered thyroid gland function and the cardiovascular system was first described almost 200 years ago by the English physician, Caleb Hillier Parry. Parry's description of exophthalmic goiter marked the first time cardiovascular symptoms were actually attributed to the altered thyroid state; now they are considered to be one of its hallmarks.[69]

Hemodynamic findings in hyperthyroidism, whether spontaneous or induced, almost always include increases in cardiac output, stroke volume, heart rate, and pulse pressure; and decreased peripheral vascular resistance and circulation time.[70-74] The magnitudes of these findings vary quantitatively as they are both time and dose dependent. These changes generally correlate closely with changes in oxygen utilization, suggesting that metabolic needs are important determinants of the hyperdynamic circulatory state. In hyperthyroidism, however, augmentation of cardiac output, when compared to oxygen utilization, is far in excess of that observed during exercise or other hypermetabolic states.[70,75,76] This suggests that direct (or indirect via another humoral agent) cardiostimulatory effects of thyroid hormones also contribute to the increased cardiac output. In the adult, hyperthyroidism also alters the distribution of blood flow . Cerebral and hepatic blood flow are normal, and renal blood flow is normal or slightly increased.[77-79] Coronary, skeletal muscle, and skin blood flows are all markedly increased; increases in excess of 100 per cent are not uncommon.[80,81]

In contrast, in hypothyroid adult animals, cardiac output, stroke

volume, and heart rate are generally reduced.[73,82,83] Peripheral vascular resistance is either normal or slightly increased. Circulation time is prolonged. Cerebral blood flow and oxygen consumption are reduced in hypothyroidism, and renal blood flow and glomerular filtration rate are slightly reduced.[84-86] Blood flow to the skin may be reduced up to 75%.[87] Coronary blood flow is decreased in proportion to the decrease in myocardial oxygen consumption.[88]

Myocardial effects of excess thyroid hormones include increased contractile function,[89-96] coronary blood flow, and myocardial oxygen consumption. These changes cannot be wholly accounted for by the increase in total body oxygen consumption. As mentioned previously, the evidence to date supports a cardiostimulatory effect of thyroid hormones on the heart. The exact mechanism of action by which this effect is mediated still remains uncertain, and the proposals fall into two categories - 1) direct; and 2) indirect.

The evidence for a direct effect of thyroid hormone on the heart is not convincing at the present time. It has been proposed that thyroid hormones may interact with a membrane receptor, causing an immediate rise in adenylate cyclase. This is supported by the fact that hyperthyroid animals are found to have an increase in adenylate cyclase activity.[97-99] Furthermore, whereas l-thyroxine has peripheral as well as myocardial effects, d-thyroxine was found to have strictly myocardial effects, suggesting a unique myocardial receptor.[100] However, several investigators have questioned how rapidly the heart responds to excess thyroid hormones. They have also questioned the accumulation of myocardial adenylate cyclase.[97,101] It has also been proposed that

thyroid hormones may have a direct effect on the sarcoplasmic reticulum. In vitro studies with myocardium obtained from hyperthyroid dogs showed sarcoplasmic reticulum that was able to accumulate and exchange calcium at an increased rate. This may represent an enhancement of the excitation-contraction-relaxation cycle of cardiac muscle in vivo.[102,103] Finally, a number of studies have suggested that thyroid hormones alter myocardial contractile proteins, including myosin ATPase. Increased activity of this enzyme has been found in the hearts of hyperthyroid guinea pigs and rabbits, and is thought to increase the rate of turn-over of actin-myosin cross bridges.[104,106] Also, the increase in this protein could partially account for the increased heart weight that is seen in hyperthyroidism.[105]

The proposed way in which thyroid hormones may indirectly affect the myocardium is via the sympathetic nervous-adrenal medullary system.[109] A definite adrenergic contribution to the clinical manifestations of hyperthyroidism was first suggested by the finding that total or near total sympathetic block produced by the subarachnoid injection of procaine could successfully relieve or prevent thyrotoxic storm.[108] Since this time, many experimental studies have shown that sympatholytic agents or adrenergic blockers prevent or reverse the effects of hyperthyroidism.[110-113] The exact nature of the sympathoadrenal-thyroid hormone interaction in the heart is still uncertain, but possible interactions include the following: 1) adrenergic receptors might be sensitized by thyroid hormone to the activating effects of catecholamines, resulting in a potentiated response;[109,114,115] 2) tissue levels of free catecholamines might be increased;[97,121,122] or

3) thyroid hormones may increase the number of adrenergic receptors on the organ. The most recent experimental evidence strongly suggests that the heart is not hypersensitive to the effects of catecholamines during hyperthyroidism[89,116-120], although this was originally thought to occur.[109,114,115] The problems with the earlier studies were that they lacked statistical analysis, and no dose response curve was obtained upon administering exogenous catecholamines to the hyperthyroid animals. The possibility that hyperthyroidism causes the adrenal medulla to increase its secretion of catecholamines has been the subject of conflicting reports.[97] There is no evidence that hyperthyroidism alters plasma or urinary catecholamines or their metabolites.[123,124] This does not exclude the possibility that there is an increase in the rate of sympathetic nervous transmission or an increase in sympathetic nerve transmitter release to the myocardium.[125] These possibilities have not been explored thoroughly. Most recently, several studies have indicated that the thyroid-sympathetic interaction might be at the receptor level. Changes in thyroid status are not only associated with hypertrophic growth of the ventricular myocardium, but also there is a high correlation between thyroid status and beta-adrenergic receptor number.[126] Pharmacologic doses of thyroid hormones have been shown to increase the number of myocardial beta-adrenergic receptors in vivo.[30,126] This also occurs in myocardium exposed to the hormones in vitro.[127] Hypothyroidism has been shown to cause a decreased number of alpha and beta adrenergic receptors in adult rat myocardium. Furthermore, this decrease is much more pronounced in developing rat pups

made hypothyroid.[128]

Whether its effects are direct or indirect, it is clear that the thyroid hormones have profound cardiovascular influences.

VII. Materials and Methods

(A) Animals

Pregnant ewes with a known breeding date were obtained from local suppliers. They were housed in special sheep facilities furnished by the University of California, San Francisco, and handled according to the guidelines set forth by the Animal Care Director at the University of California and the Occupational Safety and Health Administration. They were fed a standard laboratory diet of alfalfa meal with molasses (LA Hearne Warehouse Co., Greenfield, CA), and were allowed free access to water. Twenty-four hours prior to surgery, the ewes were fasted and allowed access to water only.

Three groups of animals were used in these experiments. Group I consisted of 5 control animals and the initial in utero surgery for chronic fetal catheterization was performed at a gestational age of 129 $\pm$ 2 days (mean $\pm$ SD). Group II consisted of 5 animals operated on at a gestational age of 129 $\pm$ 3 days. Surgery for this group consisted of chronic catheterization as well as total thyroidectomy. Group III consisted of 4 animals whose gestational age at surgery was 128 $\pm$ 3 days. The animals in Group III were prepared in the same way as were those in Group I; however, they were thyroidectomized 10 to 14 days later, at the time of delivery by Caesarian section.

(B) Animal Preparation

On the day of the surgical procedure, the ewe was blindfolded and its lower lumbar area was shaved and washed with alcohol and povidone-iodine solution (Betadine). Anesthesia of the lower abdomen and hindlimbs of the ewe was then achieved by low spinal injection of 3 ml of 1% tetracaine hydrochloride (Pontocaine HCl, Breon Laboratories, New York, NY). The ewe was placed supine on the operating table. Polyvinyl catheters (2.3 mm outside diameter, 1.3 mm internal diameter) were passed into the left pedal artery and vein and advanced to the maternal descending aorta (MA) and distal inferior vena cava (MV). These catheters were passed subcutaneously through a trocar to exit through the skin on the left maternal flank. The arterial catheter was filled with 1000 u of heparin (Liquaemin Sodium, Organon, Inc., W. Orange, NJ) and sealed with a copper plug . One million units of penicillin G (potassium G penicillin, E. R. Squibb and Sons) and 400 mg kanamycin sulphate (Kantrim, 200mg/ml, Bristol Laboratories, Syracuse,NY) were administered to the ewe through the MV catheter. The venous catheter was connected to a continuous infusion of 10% dextrose in 0.9% sodium chloride solution which was given throughout the procedure. Intravenous ketamine HCl (Vetalar, Parke-Davis, Morris Plains, NJ) was administered as a 100 mg bolus intermittently, as needed for sedation of the ewe.

The maternal abdomen was shaved and washed with alcohol and povidone-iodine solution. Using strictly aseptic techniques, the abdomen was opened through a midline incision which extended from the umbilicus to the mammary tissue, and the uterus was exposed. A fetal hindlimb was located and a 3 cm incision was made in the uterine horn over the limb.

The hindlimb was exteriorized, and using 0.25% lidocaine hydrochloride (Elkins-Sinn, Inc., Cherry Hill, NJ) for local anesthesia, polyvinyl catheters (1.2 mm outside diameter, 0.8 mm inside diameter) were passed into a pedal artery and vein and advanced to the fetal descending aorta (FA) and distal inferior vena cava (IVC). The limb was replaced and a polyvinyl catheter with multiple side holes (2.3 mm outside diameter, 1.3 mm internal diameter) was placed in the amniotic cavity (AM). The uterine incision was closed.

The position of the left side of the fetal chest was identified by palpating the spine and ribs, and the uterus was exteriorized further to expose this area. Extreme care was taken to avoid compression of the uterine vessels at the caudal margin of the abdominal incision. A 6 cm incision was made in the uterine horn just below the left forelimb. The remainder of the uterus was covered with a towel dampened by normal saline. The removal of the limb from the uterus was facilitated by prior intravenous administration of 5 mg of succinylcholine chloride (Anectine, Burroughs Wellcome Co., Research Triangle Park, NC) to paralyze the fetus. The limb was exteriorized and the left chest area around the fourth intercostal space was anesthetized with 0.25% lidocaine hydrochloride. A thoracotomy was performed in this fourth intercostal space. The lung was retracted using a small cotton sponge. The internal thoracic artery was located and a polyvinyl catheter (1.2 mm outside diameter, 0.8 mm inside diameter) was inserted into it and advanced to the fetal ascending aorta (CA). An incision was made in the pericardium in order to expose the main pulmonary artery (PA) and left atrial appendage (LA).

The fetal left atrial appendage is quite delicate and it tends to bleed quite easily. To avoid unnecessary atrial manipulation, a new cannula was developed to aid in the catheterization of the left atrium. A tapered 20 gauge teflon cannula (20G2 I.V. Cath, Becton-Dickinson, Rutherford, NJ) is cut 1.5 cm from the tip after removing the 23 gauge inner needle. The cut must be made with a sharp blade so as not to kink the teflon. A short piece of polyvinyl catheter material (1.2 mm outside diameter, 0.8 mm inside diameter) is then placed on the 23 gauge inner needle. The length of the polyvinyl material should be about 0.75 cm shorter than the needle itself. The 1.5 cm tapered tip is then advanced 0.75 cm into the lumen of the polyvinyl catheter, using the needle as a guide. Care must be taken so as not to puncture the wall of either the polyvinyl or the teflon with the point of the needle. A slightly larger (2.3 mm outside diameter, 1.3 mm inside diameter) polyvinyl ring is stretched to fit over the polyvinyl catheter and is positioned at its edge, where the teflon piece enters its lumen. The ring is then bonded to the polyvinyl catheters using cyclohexanone, a polyvinyl solvent (see Fig. 1). A purse-string suture consisting of three stitches was placed in the wall of both the main pulmonary artery and left atrial appendage. The suture was 4-0 silk on an atraumatic needle (Taper C-1, Ethicon Inc., Summerville, NJ).

The special teflon-modified catheter was then inserted 0.75 cm through each purse-string suture, and tied in place. The CA, PA, and LA catheters were exteriorized through the fourth intercostal space, and the fetal chest was closed. These catheters were cut 10 cm from their exit point from the fetal chest, filled with heparin and sealed with copper

plugs. With the aid of polyvinyl rings and suture material, these catheters were anchored to the skin over the left chest of the fetus, and the distal catheter ends were allowed to float freely in the amniotic cavity. The limb was replaced in the uterus.

For the animals in Group II, the fetus was repositioned so as to exteriorize its head through the same uterine incision. The head and snout were covered with a towel dampened by normal saline to keep the fetus from breathing. The neck was palpated and the hyoid cartilage was located. 0.25% lidocaine hydrochloride was injected in the skin in the midline of the neck, and a 3 cm midline incision was made over the trachea. The thyroid gland was carefully dissected away from the trachea and adjacent tissues and then removed completely. Great care was taken to remove all thyroid tissue, including the isthmus as well as both lobes. The skin of the neck was sutured and the fetal head was replaced, taking care not to tear the uterus in the process. The second uterine incision was then closed. In both groups of non-thyroidectomized animals (Groups I and III), the fetal head was not exteriorized, and the uterine incision was closed after replacing the left forelimb into the uterus.

Calcium homeostasis was assumed to remain normal in the thyroidectomized fetuses, because in sheep, an outer pair of parathyroid glands is located near the submaxillary artery, rather than within the tissue of the thyroid gland itself.[138]

Amniotic fluid that was lost during the procedure was replaced with warm 0.9% sodium chloride solution. Also antibiotics were given into the amniotic sac in the same amounts given to the ewe. The FA, IVC, and AM catheters were passed across the maternal abdominal wall and tunneled

subcutaneously through a trocar, exiting from the skin on the left flank of the ewe. The catheters were protected by a cloth pouch sewn to the skin. The MV catheter, after being filled with heparin and sealed with a copper plug, was also placed in the pouch, as was the MA catheter. The maternal abdominal incision was sutured.

The ewe was returned to its pen immediately following the surgical procedure and positioned for easiest access to both food and water. Its blindfold was removed.

(C) Postoperative Care and General Study Procedures

Twenty-four hours following the surgical procedure, the ewe was placed in a study cage. The heparin was removed and discarded from each catheter. Two million units of penicillin G and 800 mg of kanamycin sulphate were administered to the ewe, half intravenously and half into the amniotic cavity. Three ml of blood were withdrawn from the FA catheter and the fetal plasma was separated from the cells. A hematocrit tube was filled with plasma and the remainder was frozen for later analysis of thyroid hormone content. The plasma from the hematocrit tube was dropped onto a refractometer (Temperature Compensated Goldberg Refractometer, American Scientific Products, McGaw Park, IL) for analysis of total plasma proteins. An additional 1 ml of blood was withdrawn from the FA catheter as well as from the MA catheter to determine both fetal and maternal blood hemoglobin, percent oxygen saturation, pH, PO_2, and PCO_2. The blood gases and pH were determined on a Corning model 173 blood gas analyzer (Corning Co., Medford, MA). The blood hemoglobin concentration and hemoglobin oxygen saturation were determined in duplicate on a Radiometer model OSM2 hemoximeter (London Co., Oakland, CA) on the basis of quantitative spectrophotometric analysis of total and oxyhemoglobin concentration. The ewe was returned to its pen and this procedure was subsequently repeated on every other day.

Between five and seven days postoperatively the fetuses in Group II also received a 10 mcg bolus dose of triiodothyronine (3, 3', 5-triiodo-L-thyronine, sodium salt, Sigma Chemical Co., St. Louis, MO) intravenously, with a second 10 mcg bolus dose given two days later.

This was done in an attempt to counteract any side effects of hypothyroidism in the fetus.[129,130]

The athyriotic fetus remained in utero for approximately two weeks postoperatively. A fetus was considered to be at term when either it reached a gestational age of 145 days (term equals 145 to 150 days), or when the total fetal plasma proteins reached a value of 4.5 mg/dl. In preliminary studies, we found that when fetuses were delivered with lower plasma protein concentrations, they tended to have respiratory difficulty, probably related to immaturity of lung development.

(D) Specific Protocol

When the fetus was considered to be at term, the ewe was blindfolded and low spinal anesthesia was again administered with 3 ml of 1% tetracaine hydrochloride. The ewe was placed supine on the operating table. In order to avoid the adhesions, a right ventromedial incision was made, 4 cm parallel to the old incision and the uterus was exposed. The fetal parts were identified and a 6-8 cm incision was made in the uterine horn over the mouth of the fetus. The entire fetus was exteriorized, taking care not to twist or compress the umbilical cord. The fetus was towel dried. If, at this point, the fetus was not breathing vigorously, it was intubated, and excess tracheal fluid was removed with light suction. All the fetal catheters were checked for patency and 3 ml of blood were withdrawn from the FA catheter. This blood was immediately centrifuged and the plasma was subsequently frozen. All of the catheters were then flushed with 0.9% sodium chloride solution. The umbilical cord was tied with umbilical tape and then cut.

The newborn lamb was immediately taken to a predesignated study area, and placed on a study table in the lateral decubitus position. Descending aortic, ascending aortic, and pulmonary arterial pressures were measured by Statham P23Db pressure transducers (Statham Instruments, Oxnard, CA) and recorded on a Beckman direct-writing recorder (Beckman Instruments, Palo Alto, CA). Atmospheric pressure was used as the zero reference point, recorded at the mid-chest level of the lamb. If respiratory insufficiency was present, as determined by blood gas analyses, the endotracheal tube was connected to a ventilator.

The lamb was also connected to a precalibrated oximeter and recorder

for the measurement of total body oxygen consumption according to the method of Lister, et. al.[132] Briefly, this method consists of placing a hood around the head of the lamb while a constant volume of room air is withdrawn through the hood by means of an accurate air suction pump. The air, including the expired gas from the animal, is withdrawn through a mixing chamber. The oxygen concentration of the mixture of room air and expired gas is constantly measured with an oxygen analyzer (Servomex, Type OA 150, Crowborough, Sussex, England) and recorded on a strip chart recorder (Hewlett Packard model 680). Oxygen consumption can then be calculated by multiplying the flow rate of air through the system by the difference in oxygen concentration between room air and the mixed expired gas. If the lamb was connected to a ventilator, the same procedure was used; however the constant volume of room air was withdrawn from around the expired gas valve of the ventilator instead of from around the snout of the animal.

15 um diameter radionuclide-labeled microspheres were injected into the left atrium one hour after delivery. Heymann, et. al.[131], have shown that such microspheres injected into the left atrium will be adequately mixed in the left side of the heart and distributed according to the blood flow to all the organs of the body. Reference samples were withdrawn from the ascending aorta (CA catheter) and the descending aorta (FA catheter), during and after the injection of microspheres, into preweighed syringes for 1.5 minutes at a constant rate of approximately 7 ml/min. Immediately afterwards a 3 ml sample of blood was withdrawn from the descending aorta to measure plasma T_3 concentrations. Following local anesthesia with 0.25% lidocaine hydrochloride, a 2 cm incision was

made on the right side of the neck of the lamb and a catheter (Swan-Ganz #4F) was passed into the right jugular vein and advanced to the right ventricle. Right ventricular pressure was also monitored. One ml of blood was simultaneously withdrawn from both the right ventricle and the descending aorta to determine systemic blood flow by the Fick method. A 3 ml sample of blood was again withdrawn from the descending aorta immediately afterwards to determine the plasma T_3 concentration. A pulmonary arterial sample, which is usually considered to be the best representation of mixed venous blood, could not be used in the Fick determination, because usually a left-to-right shunt across the ductus arteriosus caused the oxygen content to be slightly higher in the pulmonary artery than in the right ventricle. For this reason, the right ventricular sample was the best representation of mixed venous blood in these studies. Any blood removed from the lamb for study purposes was replaced within five minutes with maternal blood.

Left ventricular output and blood flow distribution were measured on six occasions at hourly intervals, beginning at the first hour after delivery, by the radionuclide-labeled microsphere technique. This method allows for a limited number of measurements because a) we have the capability to discriminate between only 9 gamma labels at the present time in our laboratory, and b) there is a critical number of microspheres which, once attained, will adversely affect the circulation. However, it has been shown that repeated measurements can be made without interfering with myocardial hemodynamics, when a total of 2 million microspheres per kilogram body weight are injected into the left atrium of an adult dog.[132] Since we are injecting less than 3 hundred thousand micro-

spheres per kilogram body weight into the left atrium of these lambs, it is assumed that cardiovascular dynamics are also unaffected by this procedure. Systemic blood flow was determined by the Fick method at hourly intervals on six occasions, with the first measurement taking place at 1.5 hours after delivery. Values for left ventricular output were determined independently of those for systemic blood flow, as some of the blood ejected from the left ventricle in the immediate newborn period may shunt across the ductus arteriosus to the lungs, instead of contributing to the systemic circulation. At the end of the studies the lambs were killed with an intravenous injection of sodium pentobarbital. The lambs were dissected as previously described.[9] Their individual organs were incinerated in an oven and counted for radioactivity in a 1000-channel (Ino-tech, Inc. Fort Atkinson, WI) pulse height analyzer. Blood flow to the various organs was calculated with the aid of a 370 IBM computer. Left ventricular output was measured by determining radioactive counts of the entire animal.

The preparation of the animals in Group III was slightly different from either Group I or Group II. This group was prepared initially in the same manner as was the control group - all of the previously mentioned fetal catheters were chronically implanted as described, and the thyroid glands were left intact. Upon reoperating to deliver the term fetus, the head was first delivered and the snout was covered with a dampened towel to keep the fetus from breathing. At this time the thyroid gland was carefully removed under local anesthesia as previously described. 2 ml of fetal blood were withdrawn immediately before and after the removal of the thyroid glands for the analysis of triiodo-

thyronine. After suturing the skin of the neck, the remainder of the fetal body was delivered, and the study proceeded as usual.

Total plasma T_3 concentrations were measured at a later time by radioimmunoassay (T_3 RIA Kit, Corning Medical). The lower limit of the assay was 0.25 ng/ml. All individual samples were run in duplicate, and there was an intra-assay variation of 18 percent. The interassay variation was 12 per cent. T_3 rather than T_4 concentrations were measured for two reasons. First, T_3 has a much shorter biological half-life than does T_4 (24 hours versus 8 days). Secondly, T_3 has the highest biological activity of all of the thyroid hormones - five times that of T_4.

Left ventricular output, systemic blood flow, mean arterial blood pressure, heart rate, and blood flow distribution to various organs were analyzed and compared among Groups I through III on an hourly basis during the first 6 hours of neonatal life. A repeated measures two-way analysis of variance was used, weighted for the fact that there were five animals in Groups I and II, but only four in Group III. The Newman-Keuls multiple comparisons test was employed to look at statistical significance between the various groups. A difference was considered to be statistically significant at $P \leq .05$. Mean values over the first 6 hours of life were obtained for pH, PO_2, PCO_2, and total body weight, and these values were compared among Groups I through III using a simple one-way analysis of variance and the Newman-Keuls multiple comparisons test. Fetal values for pH, PO_2, and PCO_2 were obtained 24 hours prior to delivery, and compared among the three groups by the same statistical methods.

VIII. Results

The blood gas values from the descending aorta of all the fetuses 24 hours before delivery are as shown in Table 1. There were no significant differences in PO_2, PCO_2, or pH between the three groups.

There was no significant difference in total body weights between the three groups on the day of delivery (Table 1).

The mean blood gas values for each group over the six hour study period are also given (Table 1). Although some animals were connected to a respirator while others were not, there was no significant difference in PO_2, PCO_2, or pH.

Total plasma T_3 concentrations were measured immediately before clamping the umbilical cord (hour 0) and for the first six hours after delivery (Fig. 2). Immediately before clamping the cord, Group I and Group III had T_3 concentrations which were almost identical, whereas there was no detectable T_3 in Group II animals. All three groups were significantly different from one another between hour 1 and hour 6 ($P < .001$). After delivery, the animals in Group I exhibited a marked increase in T_3 concentrations over the next six hours, whereas the animals in Group III exhibited T_3 concentrations that were essentially unchanged from their prenatal values at hour 0. The animals in Group II continued to have undetectable T_3 concentrations during the six hours after delivery.

The values for left ventricular output during the time the study was conducted are shown in Figure 3. Group II had left ventricular outputs that were significantly lower than those of either Group I or Group III ($P < .005$). The values for Group I were not significantly different from

those of Group III. There was no significant change in the values with time for any of the three groups over the six hour period after delivery.

The values for systemic blood flow are shown in Figure 4. The value for each individual animal represented the mean of two determinations - one by the Fick method and one by the radionuclide-labeled microsphere technique. It has previously been shown by Kuipers, et. al., that the correlation coefficient between these two methods is greater than 0.89.[18] Group II animals had systemic blood flows which were significantly lower than those for both Group I and Group III ($P < .005$). Group I and Group III were not significantly different. There was no significant change with time for any group over the six hour period.

The difference between left ventricular output and systemic blood flow can be used to estimate the magnitude of the shunt through the ductus arteriosus. (It will only give an estimate since systemic blood flow as determined by the microsphere technique did not include flow to the bronchial circulation, because total counts in the lungs included a component which arose from ductus arteriosus shunting.) These shunts ranged from 0 to 25 per cent of left ventricular output for each group and there was no difference in size of the shunt between the groups.

The values for total body oxygen consumption for the three groups during the study are given in Figure 5. The values for oxygen consumption in Group II were significantly lower than those for Groups I and III ($P < .001$), and there was no significant difference between the values for the latter two groups. There was no time effect over the six hours.

The values for mean arterial pressure and heart rate are as shown in Figures 6 and 7 respectively. Both mean arterial pressure and heart rate were significantly lower in Group II than in either Groups I and III ($P < .001$ for each), and they remained significantly lower over the first six hours of postnatal life.

The blood flow to major organs in ml/100gm/min is presented in Figures 8 through 17. Although there seemed to be a trend for the flows to be lowest for the animals in Group II, there was in fact no significant difference in blood flow among the three groups for any of the organs with the following exceptions. Group II did have significantly lower flows to the lower and upper carcass (Figs. 13 and 15, $P < .05$). With respect to blood flow to the gut (Fig. 12), Group II was significantly lower than Group III ($P < .05$), but not different from Group I.

There was no difference in blood flow to the myocardium or the lungs among the three groups (Figs. 16 and 17). Blood flow to the lungs, as measured by the microsphere technique, represents bronchial flow, any blood shunted across the ductus arteriosus to the pulmonary arteries, plus any peripheral shunting of microspheres.

Any of the slight differences, either within a group over time or between groups, which were not found to be significant at the $P \leq .05$ level may have been due to the small number of animals and large standard deviations in each group.

IX. Discussion

The purpose of this investigation was to determine whether the increase in cardiac output and oxygen consumption after birth were related to the postnatal surge in thyroid hormone concentrations which occurs in the immediate newborn period.

The control animals (Group I) exhibited the surge in their T_3 concentrations with the levels increasing after delivery by about five fold as described previously.[52,59] The absolute values for T_3 concentrations in both the term fetuses (immediately before delivery) and in the neonates (after delivery) were in the same range as those previously reported.[51-53, 59-61] The values obtained for left ventricular output and oxygen consumption in this group of animals were very similar to values previously reported for twenty-four to forty-eight hour old lambs delivered spontaneously. In those studies, left ventricular output was measured by the Fick and microsphere methods.[6, 16-18]

Initially, we decided to arrest the postnatal surge in thyroid hormones by completely removing the thyroid gland in utero 10 to 14 days before delivery (Group II). This caused a 40 to 50 per cent reduction in left ventricular output, systemic blood flow, and oxygen consumption, as well as a significant reduction in heart rate and mean arterial pressure in the newborn animals. Although a replacement dose of 20ug of the sodium salt of T_3 was given back to these fetuses in an attempt to counteract any of the effects of fetal hypothyroidism, there were no detectable T_3 levels in these fetuses 24 hours prior to delivery. Also, after delivery no T_3 could be detected in their plasma. It was

not apparent whether the effects on hemodynamics and oxygen consumption were due to arresting the T_3 surge postnatally, or rather due to hypothyroidism during fetal life. In two additional fetuses higher replacement doses of T_3 were administered after removing the thyroid gland (36 and 50ug respectively). Although there was still no postnatal rise in T_3 concentrations in these two animals, they did have mean values for systemic blood flow and oxygen consumption for the six hours after delivery which were intermediate between the values obtained for Group II and Group I (systemic blood flow = 245 and 285 ml/kg/min; oxygen consumption = 14.6 and 17.5 ml/kg/min respectively). This suggested that it was indeed the prenatal thyroid hormone levels which were essential to normal hemodynamics and oxygen consumption in the neonate rather than the postnatal surge of thyroid hormone concentrations.

To confirm this hypothesis, studies were performed in another series of animals (Group III) in which the thyroid gland was removed immediately before clamping the umbilical cord. Sack, et. al., showed that the postnatal surge in thyroid hormone concentrations will not occur until the umbilical cord was clamped and cut.[62] In our Group III animals, the fetuses had T_3 concentrations which were within the normal range for term animals. After delivery, however, there was no significant rise in their T_3 concentrations. In spite of arresting the T_3 surge in these animals, cardiac output, heart rate, mean arterial blood pressure, and oxygen consumption were not significantly different from the values in the control animals (Group I).

There was no significant difference among the three groups in total body weight of the newborn animals. Also, there was no difference among

the three groups with respect to weights of individual organs. Blood flow to individual organs, measured as flow per 100 grams of tissue was not significantly different among the three groups, except for significantly reduced flow to the carcass in Group II. Thus, the significant reduction in left ventricular output and systemic blood flow in Group II can be accounted for by a reduction in flow to the carcass. Carcass in this instance is defined as bone, muscle, brown fat, and skin and subcutaneous tissue. Unfortunately, when analyzing the flow to the carcass, we did not dissect it into its components. Blood flow to the carcass could have been reduced in one or more of these parts. The blood flow to the gut in Group II, although significantly lower than in Group III, was not significantly different from Group I. The reason for this discrepancy is not apparent.

Although the fetuses in Group II did have markedly reduced cardiac outputs and oxygen consumptions, there were several variables which were notable for not having been affected by the late term fetal thyroidectomy (and fetal hypothyroidism). First, there was no effect on total body weight. Although other studies have demonstrated that fetal thyroidectomy caused a marked reduction in total body weight, these thyroidectomies were all done much earlier in gestation.[129,130] Secondly, thyroid hormones have been considered to be important in lung maturation and pulmonary surfactant development.[136,137] The neonates in Group II, however, were ventilated on room air with the same efficiency as were Groups I and III. Therefore, the thyroid hormones do not appear to to be very important for lung maturation in the lamb during the last two weeks of gestation. Thirdly, because of the demonstrated

maturational effects of glucocorticoids on pulmonary function and the ductus arteriosus[133-135], and because of the suggestion that the prenatal rise in T_3 concentration may be mediated by the prenatal rise in cortisol concentration[54,56], we thought that the mechanism of glucocorticoid action on the ductus arteriosus might be via thyroid hormones. However, there appeared to be no difference in postnatal left-to-right shunting across the ductus arteriosus among the three groups. Furthermore, in a separate series of experiments, we found no difference in postnatal ductal reactivity in premature lambs given a continuous infusion of T_3 for 80 hours prior to delivery (R. Clyman and J. Breall, unpublished observations). Thus, it appears that a deficiency of thyroid hormones during the last two weeks of gestation affects neither growth, nor the fetus' ability to produce active pulmonary surfactant, nor the postnatal reactivity of the ductus arteriosus.

The studies on these three groups of animals suggest that the postnatal surge in thyroid hormone concentrations is not important in hemodynamics and oxygen consumption during the first six hours after delivery. However, a lack of thyroid hormone secretion during the latter two to three weeks of gestation has a profound effect on postnatal adjustment, with a failure of the neonate to demonstrate the normal increase in cardiac output and oxygen consumption. The animals in Group II, upon being studied as neonates, were found to be very similar from a cardiovascular standpoint to chronically hypothyroid adult animals, having decreased left ventricular outputs, oxygen consumptions, heart rates, mean arterial pressures, and reduced blood flows to the periphery. The exact mechanism responsible for the depressed neonatal

hemodynamics and oxygen consumption with fetal hypothyroidism has not been fully delineated. However, we believe that the mechanism is most likely via a sympathoadrenal system interaction. Moreover, in view of the recent findings by Whitsett, et. al.[29], where rat pups made hypothyroid as fetuses were found to have fewer myocardial beta-adrenergic receptors, we believe that the lack of thyroid hormones during the last two to three weeks of gestation is having its effects by inhibiting the normal development of beta-adrenergic receptors.

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Legend to Tables and Figures

Table 1: Values represent means ± SD.

Figure 1: Teflon-modified catheter

Figures 2 through 7: Values represent means ± SD. Circles represent Group I animals (n = 5). Crosses represent Group II animals (n = 5). Squares represent Group III animals (n = 4).

Figures 8 through 17: Values represent means ± SD. Circles represent Group I animals (n = 5). Crosses represent Group II animals (n = 5). Squares represent Group III animals (n = 3).

* - significantly lower than Groups I and III; $P < .001$

\+ - significantly lower than Groups I and III; $P < .005$

\# - significantly lower than Groups I and III; $P < .05$

** - significantly lower than Group III only; $P < .05$

Table 1

	Group I (n=5)	Group II (n=5)	Group III(n=4)
Fetal pH	7.38 ± .04	7.37 ± .04	7.37 ± .04
Fetal PO_2 (torr)	20 ± 3	19 ± 2	19 ± 3
Fetal PCO_2 (torr)	48 ± 4	49 ± 3	49 ± 4
Weight (kg)	3.48 ± .70	3.95 ± .71	3.42 ± .77
Neonatal pH	7.38 ± .06	7.40 ± .08	7.42 ± .08
Neonatal PO_2(torr)	63 ± 7	57 ± 8	63 ± 4
Neonatal PCO_2(torr)	35 ± 4	33 ± 5	31 ± 4

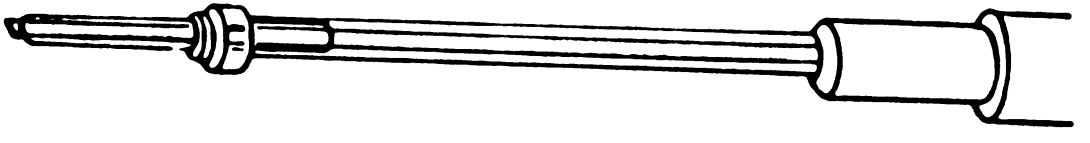

Fig. 1

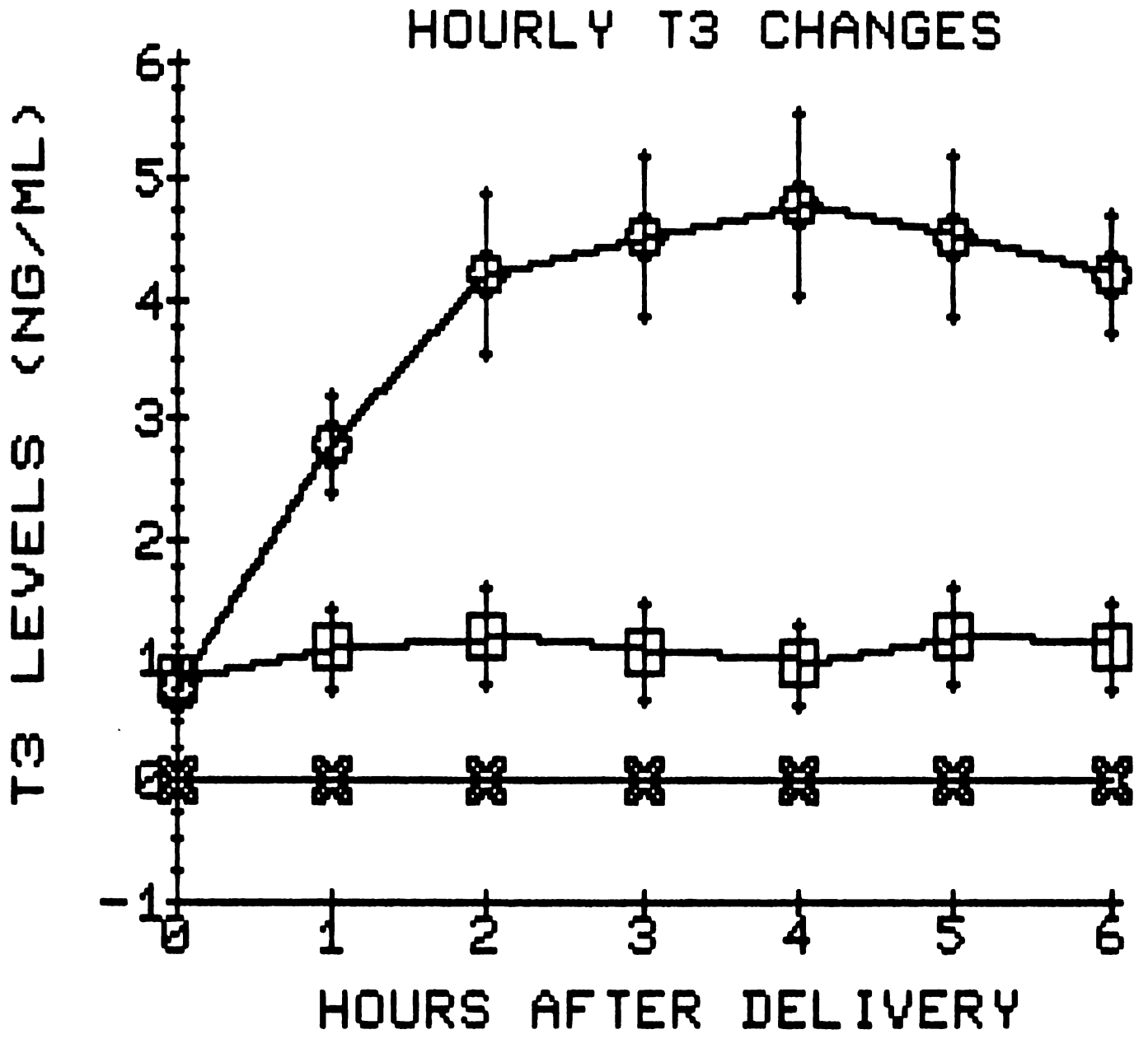
HOURLY T3 CHANGES
T3 LEVELS (NG/ML)
6
5
4
3
2
1
0
-1
0
1
2
3
4
5
6
HOURS AFTER DELIVERY

Fig. 2

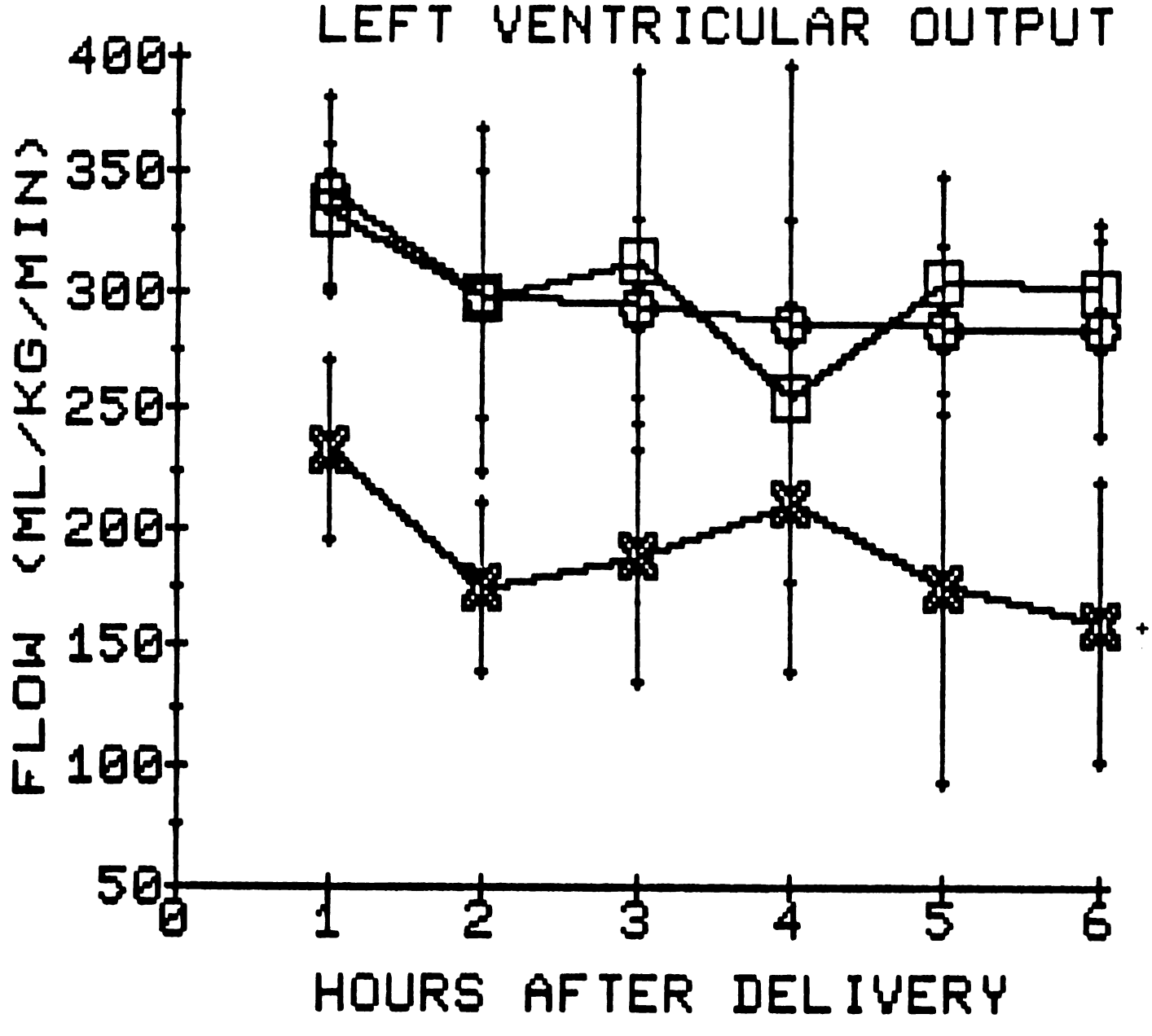
LEFT VENTRICULAR OUTPUT
FLOW (ML/KG/MIN)
400
350
300
250
200
150
100
50
0
1
2
3
4
5
6
HOURS AFTER DELIVERY

Fig. 3

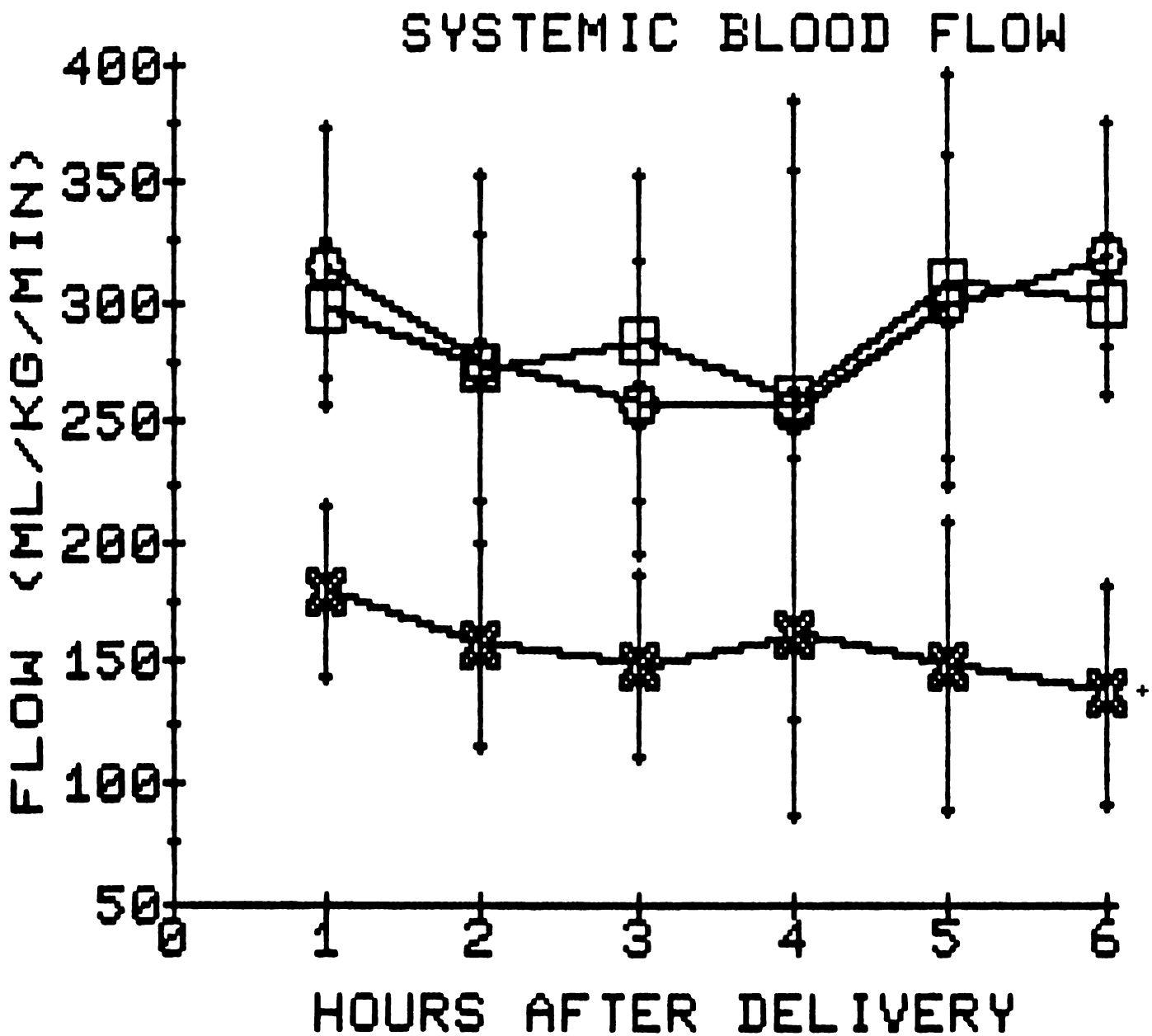
SYSTEMIC BLOOD FLOW
FLOW (ML/KG/MIN)
400
350
300
250
200
150
100
50
0
1
2
3
4
5
6
HOURS AFTER DELIVERY

Fig. 4

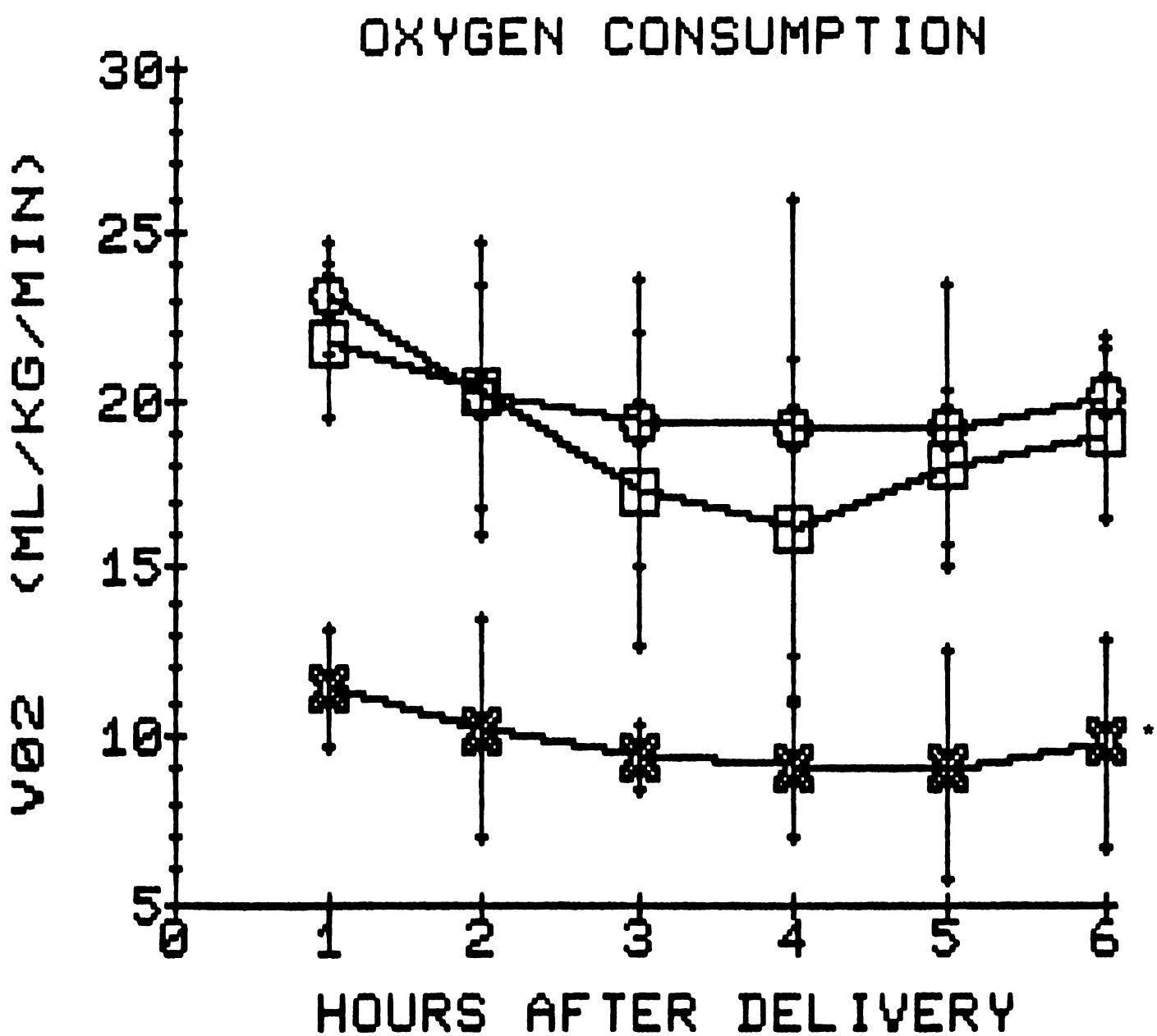
OXYGEN CONSUMPTION
VO2 (ML/KG/MIN)
30
25
20
15
10
5
0
1
2
3
4
5
6
HOURS AFTER DELIVERY

Fig. 5

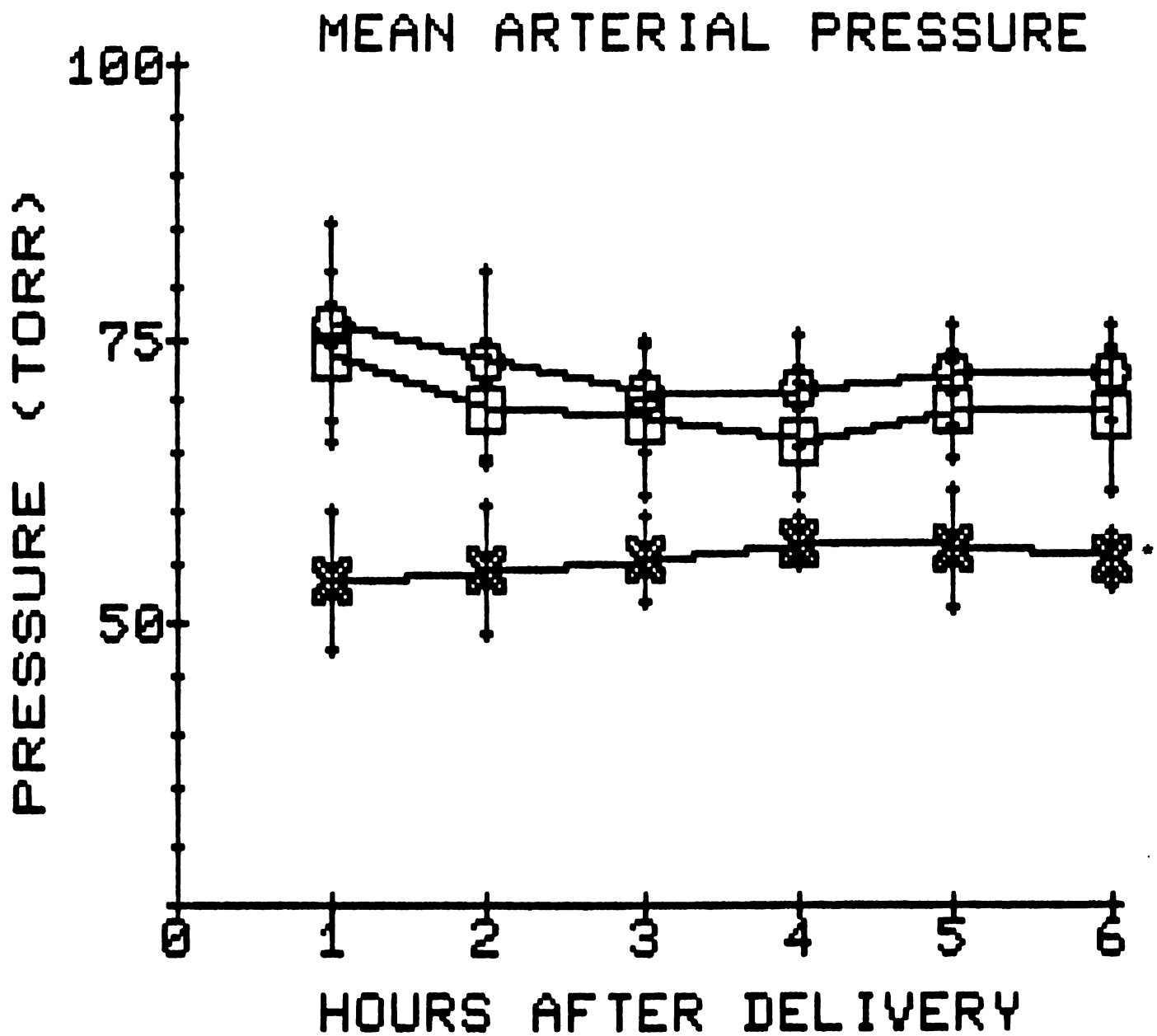
MEAN ARTERIAL PRESSURE
100
75
50
PRESSURE (TORR)
0
1
2
3
4
5
6
HOURS AFTER DELIVERY

Fig. 6

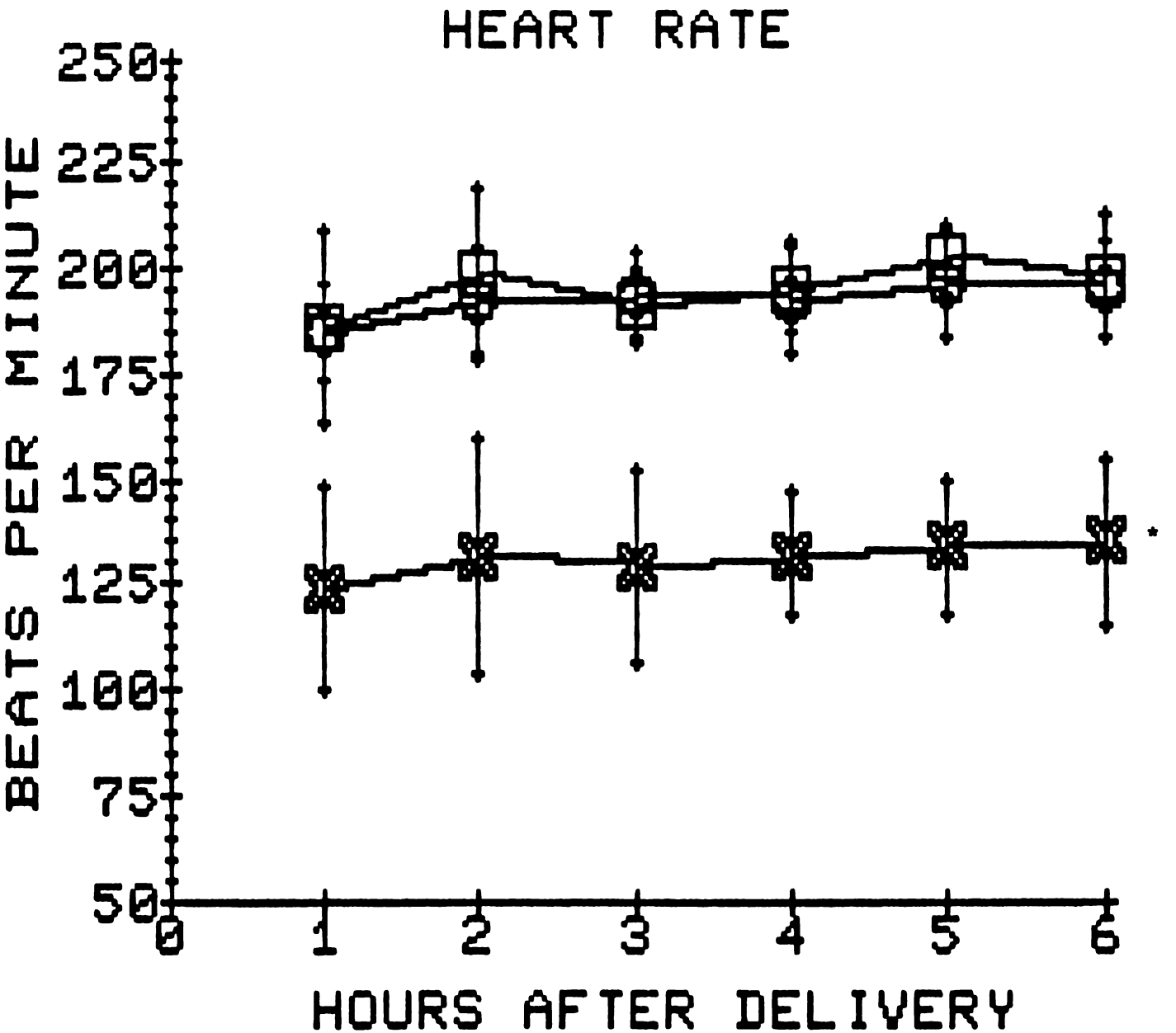
HEART RATE
BEATS PER MINUTE
250
225
200
175
150
125
100
75
50
0
1
2
3
4
5
6
HOURS AFTER DELIVERY

Fig. 7

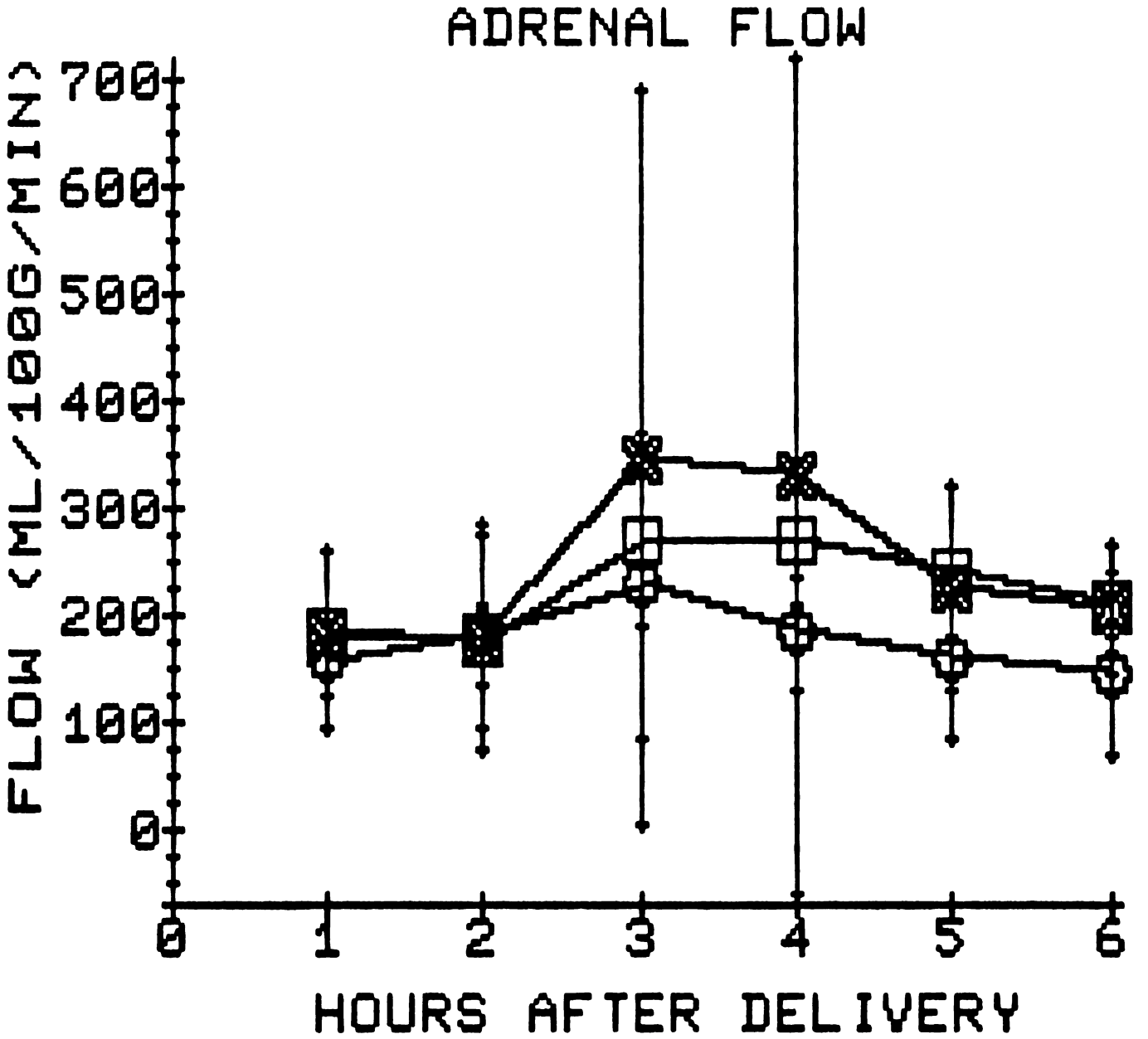
ADRENAL FLOW
FLOW (ML/100G/MIN)
700
600
500
400
300
200
100
0
0
1
2
3
4
5
6
HOURS AFTER DELIVERY

Fig. 8

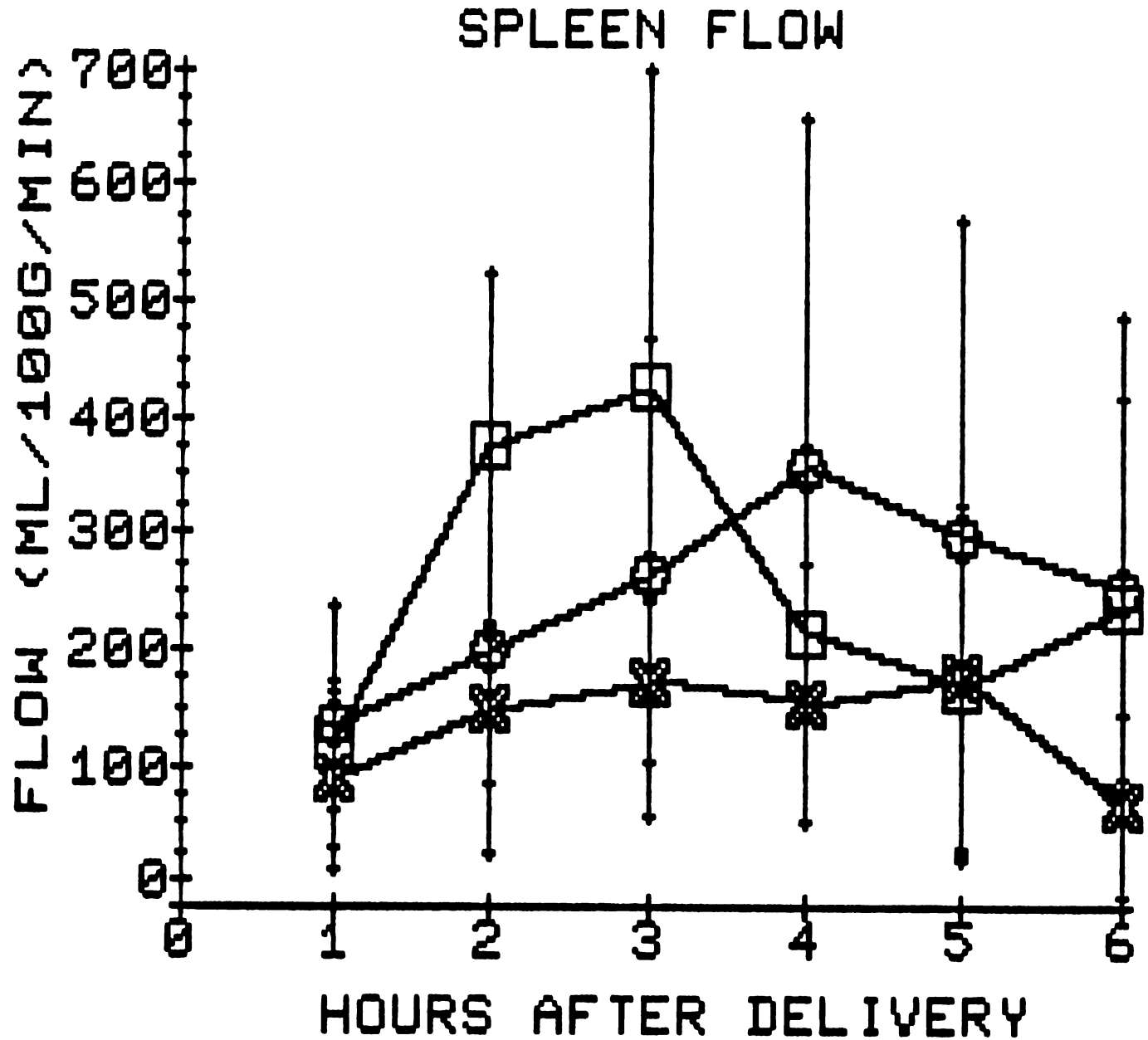
SPLEEN FLOW
FLOW (ML/100G/MIN)
700
600
500
400
300
200
100
0
0
1
2
3
4
5
6
HOURS AFTER DELIVERY

Fig. 9

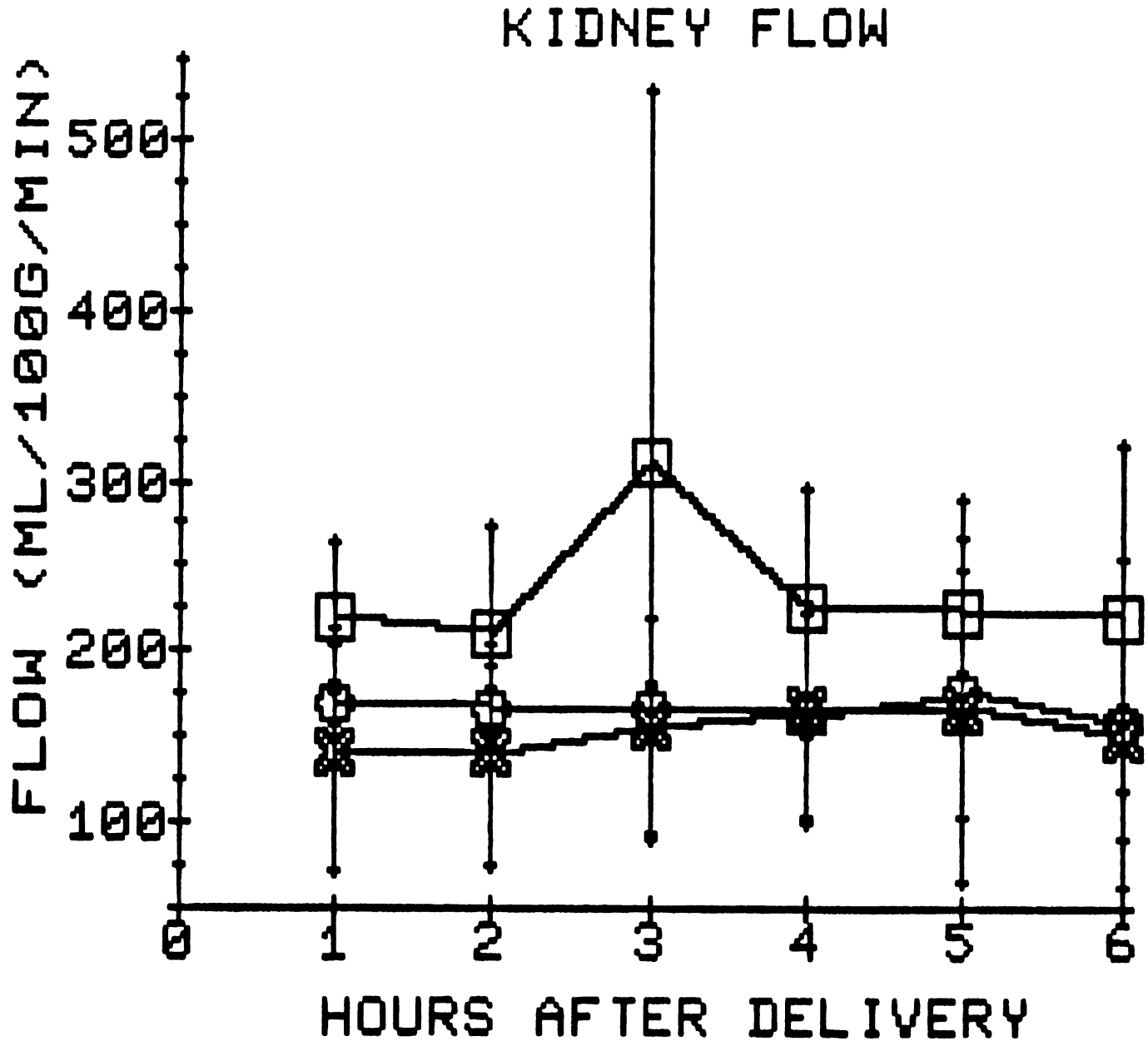
KIDNEY FLOW
FLOW (ML/100G/MIN)
500
400
300
200
100
0
1
2
3
4
5
6
HOURS AFTER DELIVERY

Fig. 10

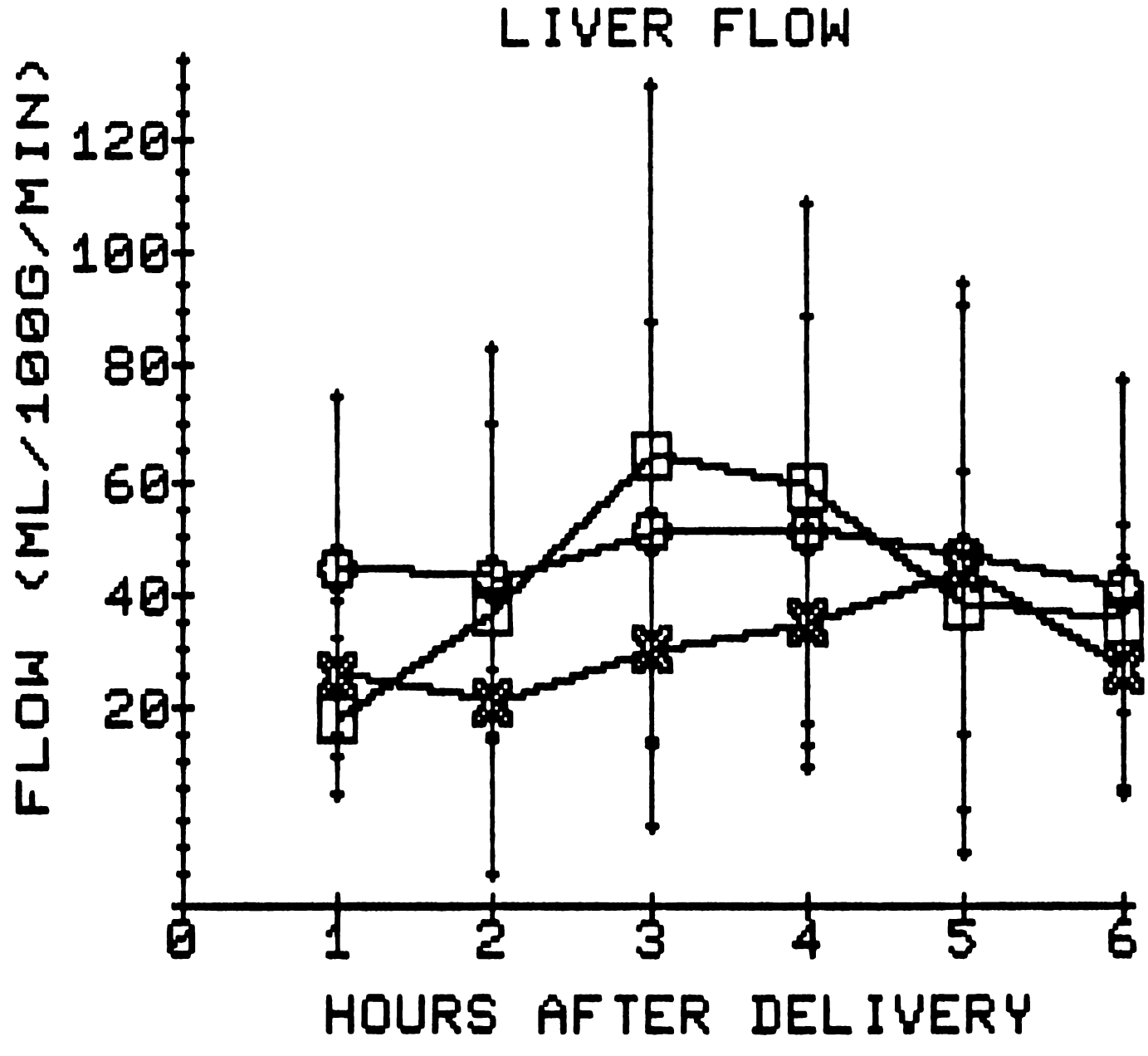
LIVER FLOW
FLOW (ML/100G/MIN)
120
100
80
60
40
20
0
1
2
3
4
5
6
HOURS AFTER DELIVERY

Fig. 11

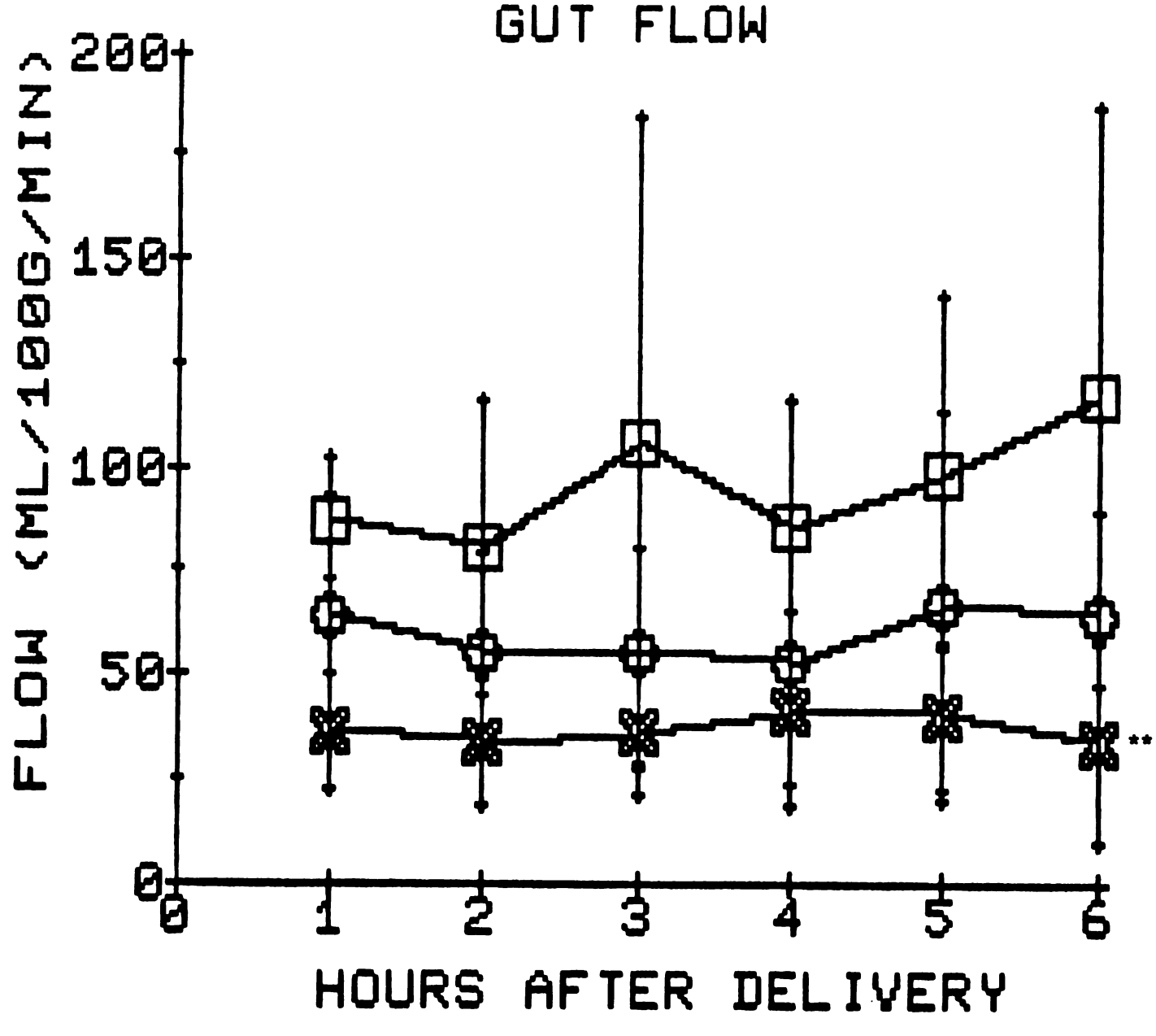
GUT FLOW
FLOW (ML/100G/MIN)
200
150
100
50
0
0
1
2
3
4
5
6
HOURS AFTER DELIVERY

Fig. 12

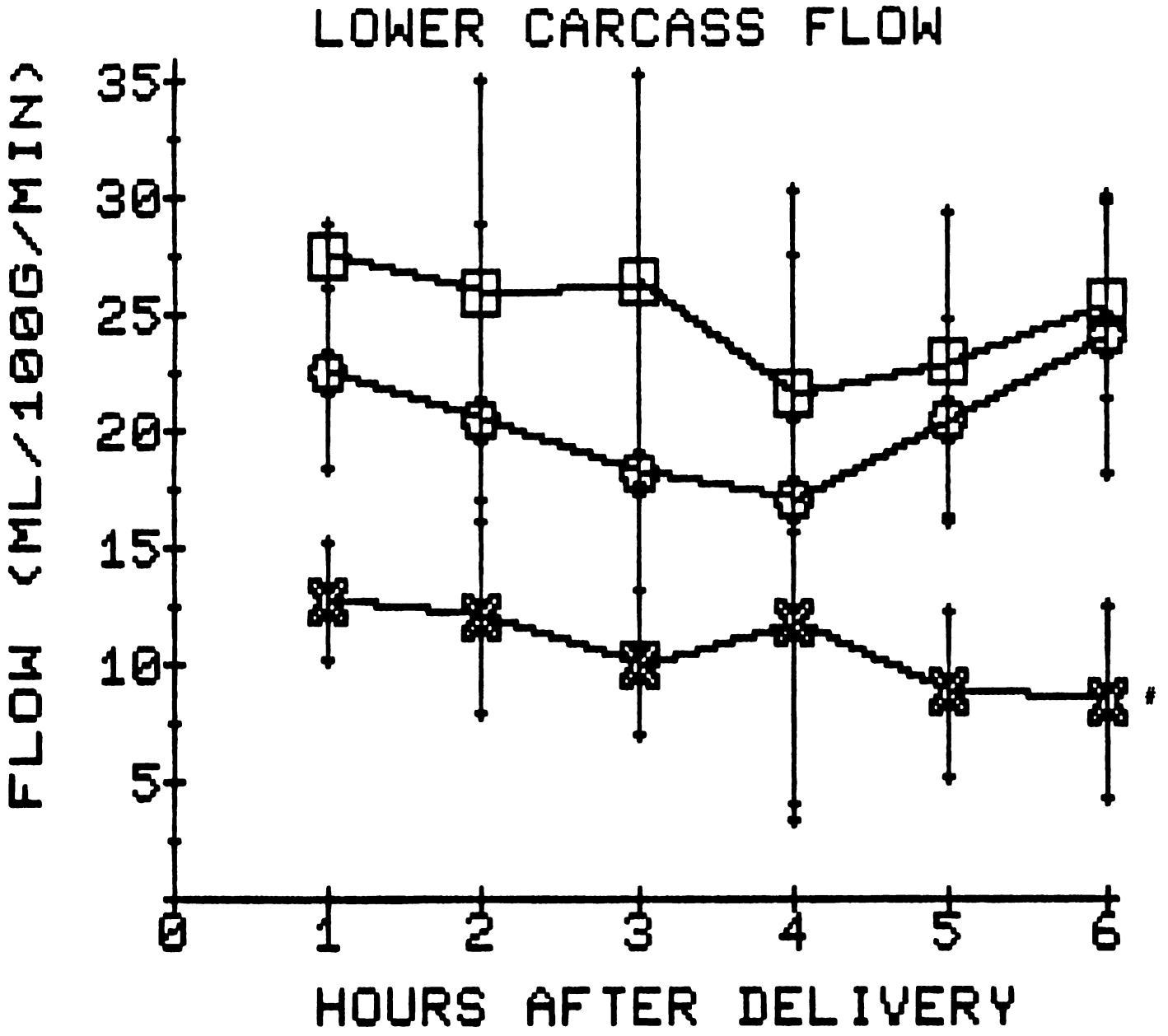
LOWER CARCASS FLOW
FLOW (ML/100G/MIN)
35
30
25
20
15
10
5
0
1
2
3
4
5
6
HOURS AFTER DELIVERY
#

Fig. 13

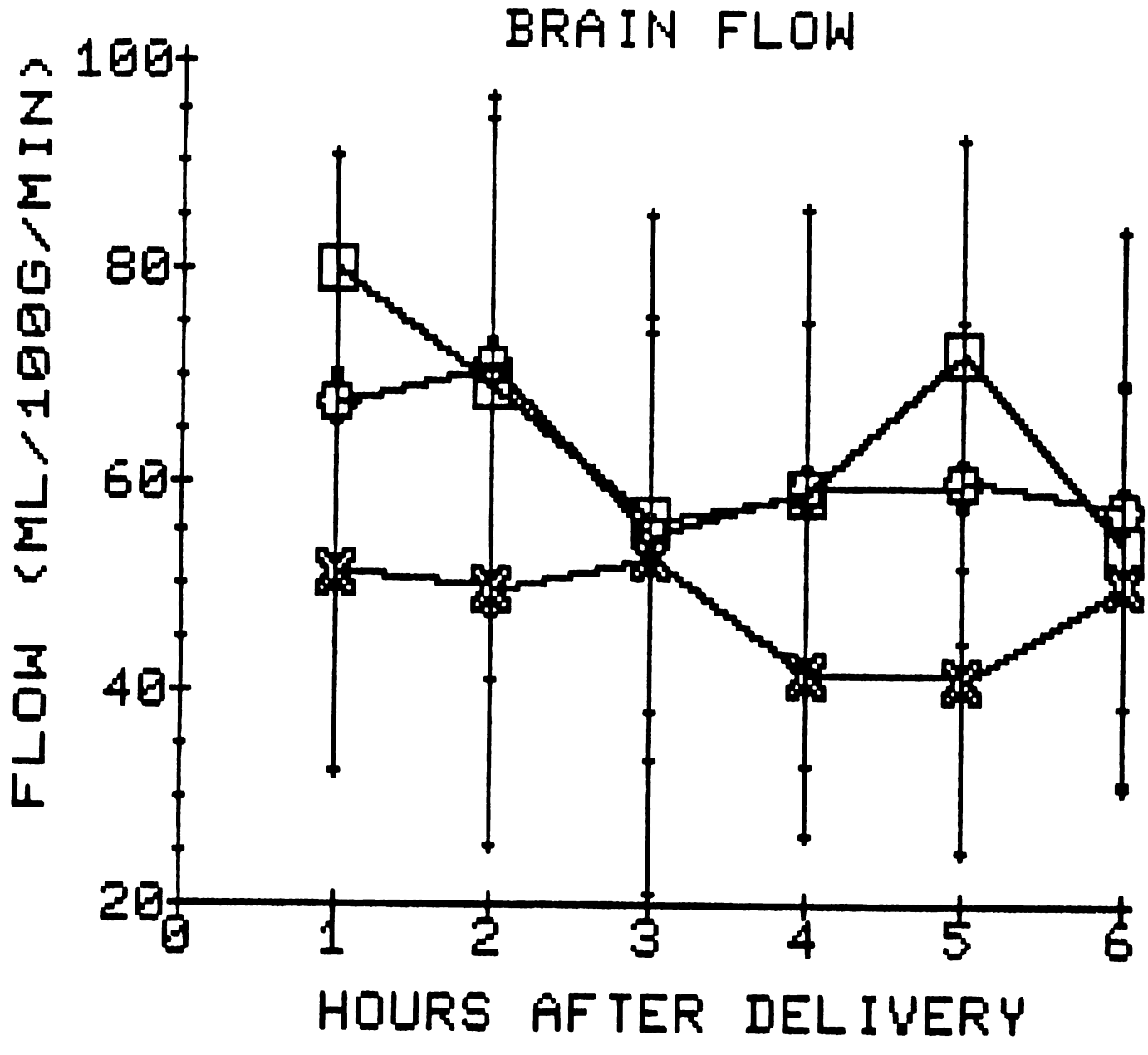
BRAIN FLOW
FLOW (ML/100G/MIN)
100
80
60
40
20
0
1
2
3
4
5
6
HOURS AFTER DELIVERY

Fig. 14

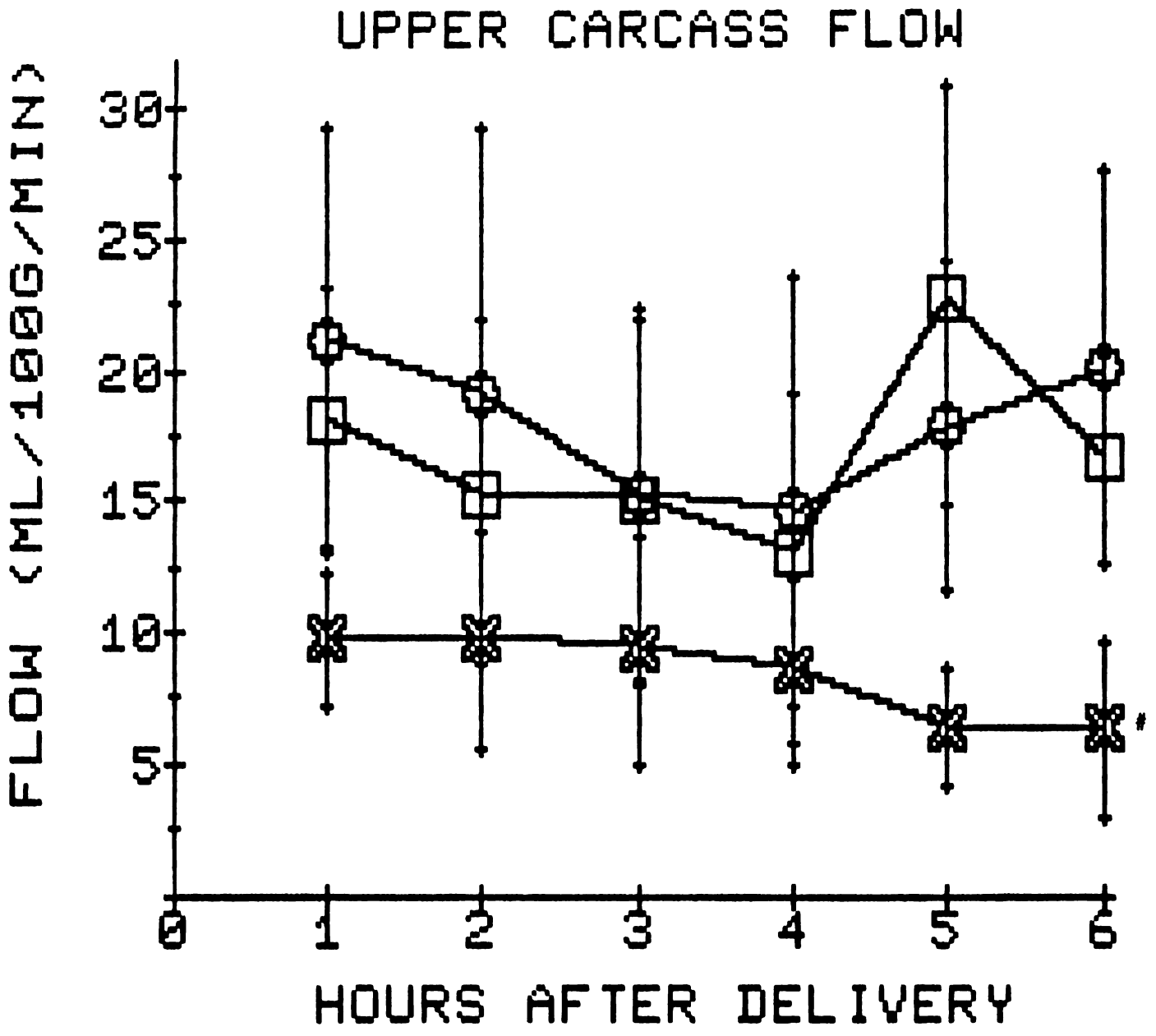
UPPER CARCASS FLOW
FLOW (ML/100G/MIN)
30
25
20
15
10
5
0
1
2
3
4
5
6
HOURS AFTER DELIVERY

Fig. 15

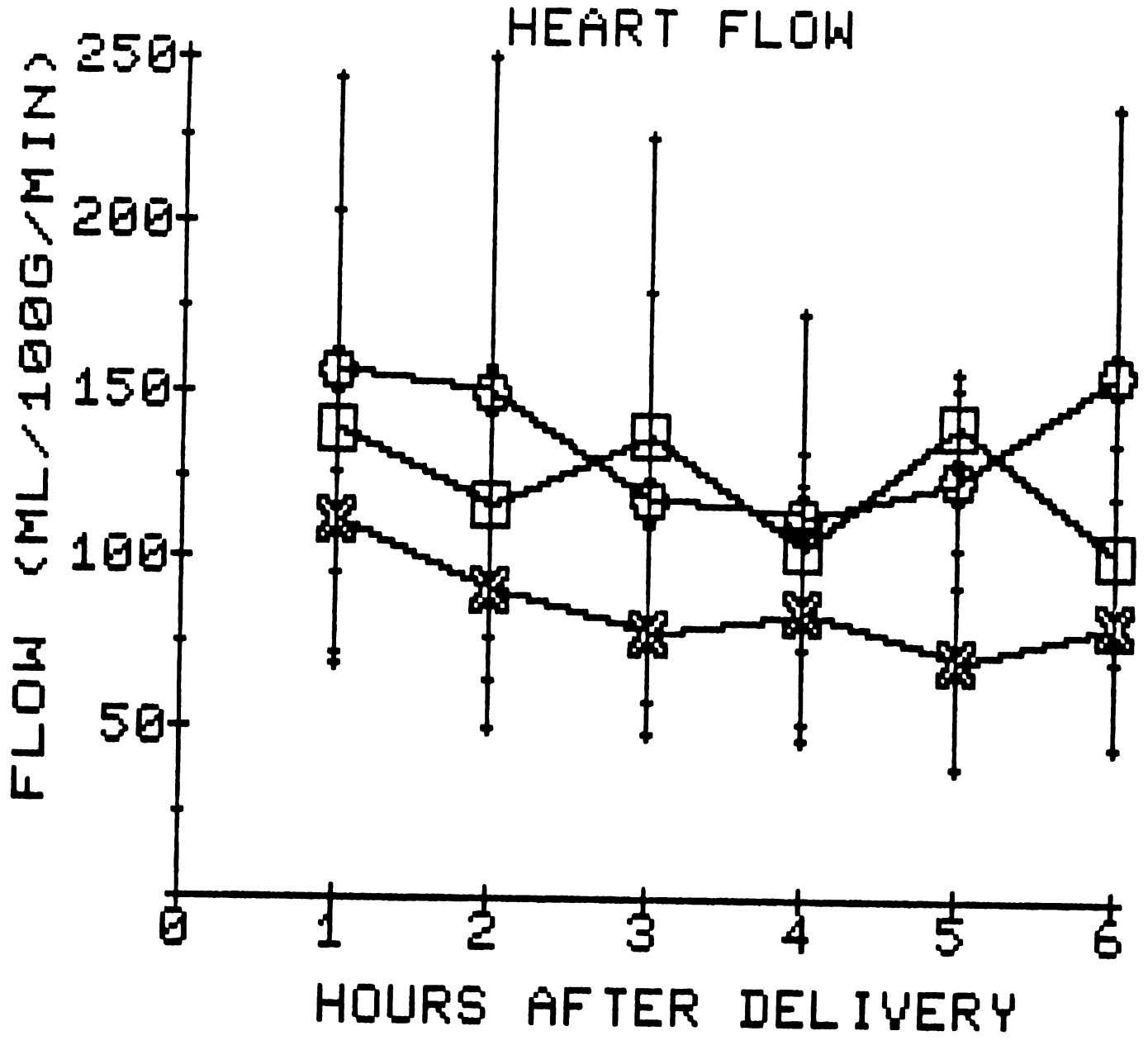
HEART FLOW
FLOW (ML/100G/MIN)
250
200
150
100
50
0
1
2
3
4
5
6
HOURS AFTER DELIVERY

Fig. 16

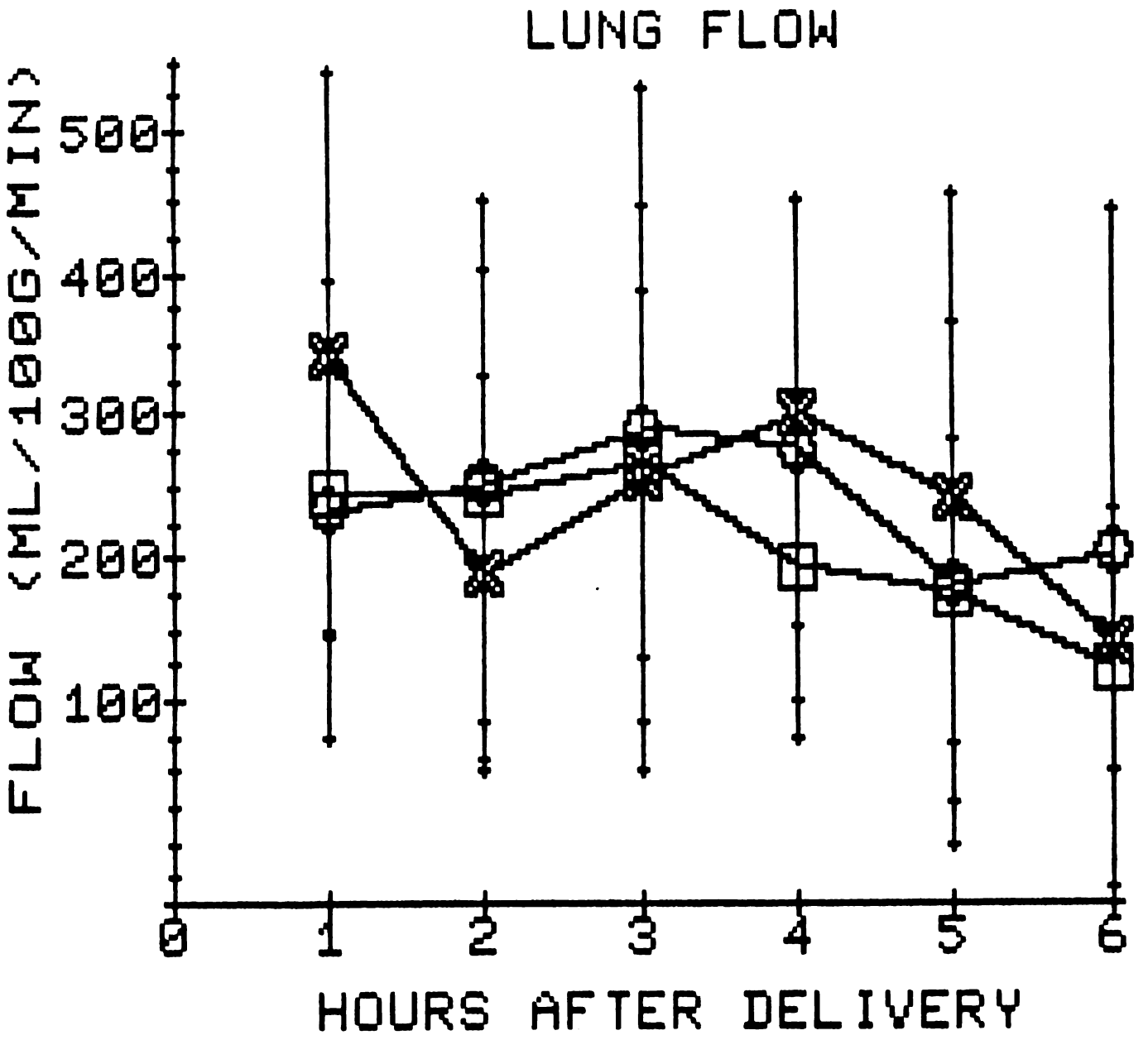
LUNG FLOW
FLOW (ML/100G/MIN)
500
400
300
200
100
0
1
2
3
4
5
6
HOURS AFTER DELIVERY

Fig. 17

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