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Fetal echocardiography

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Department of Obstetrics and Gynecology
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To my parents

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Introduction

This paper will attempt a synthesis of three current bodies of investigation. First, in obstetrics, attention is currently focused on the development and application of techniques for assessing fetal well-being. Some investigators have attempted to determine fetal status studying indices of cardiovascular function. Hon's studies of fetal heart rate patterns have produced a valuable technique for the diagnosis and management of fetal distress.[2a] Second, there has been, for some time, a group of investigators, among whom Dawes stands out, interested in the development of cardiovascular function in the fetal lamb.[1] Recently this field has been advanced with the development of techniques for studying in utero unanesthetized fetal lambs by Rudolph's group.[3] Third, there is currently a booming development of the field of echocardiography. In the past eight years, a new group of indices of cardiovascular function that can be measured by this technique of echocardiography have been developed by individuals such as Feigenbaum, Popp, Paraskos and Friedman.[77,75,87,86] The thesis of this paper is that by applying echocardiography to the human fetus it will be possible to extend the investigation of fetal cardiovascular function to include man and in so doing, a new technique for monitoring fetal well-being will be produced.

Fetal Cardiovascular Physiology and Response to Stress

It would seem logical to begin with a brief review of the available data on the physiology of the fetal cardiovascular system and its response to stress in order to provide a basis for the discussion of new techniques of assessing fetal cardiovascular status. On summing up his account of the fetal circulation in 1968 Dawes said, "This account of fetal circulation has been built on the evidence accumulated by a small number of investigators mainly using sheep and mainly toward the end of gestation."[1, p.103] The statement appears to still hold today. The fetal lamb has been concentrated upon because it is relatively large at birth and because the uterus of the sheep does not contract and expel the placenta immediately following caesarean section.

The relatively small brain weight and advanced muscular development of the fetal lamb could make one expect to find gross differences between the distribution of its circulation and that of the human fetus. However, in preliminary investigation Rudolph has found[3, p.1] that the course and distribution of the circulation in previable human fetuses is quite similar to that of the fetal lamb. One might also expect to find differences in the development of control mechanisms in the different species studied due to their different relative maturation at birth. In this spectrum of maturity the rat and the rabbit fall at the

immature end and the guinea pig at the mature end. The lamb and infant fall somewhere in between with the lamb relatively mature and the infant less so. Finally, it should be remembered that the basic necessity of having to develop a cardiovascular system that will sustain completely independent existence at birth unites all the species studied.

Course and Distribution

The basic course of the mammalian fetal circulation is fairly well established.[1, p.91] The blood is oxygenated in the placenta and returns to the fetus via the umbilical vein which joins the portal vein in the portal venous sinus. A portion of the blood in the portal venous sinus traverses the ductus venosus (D.V.) to join the inferior vena cava (I.V.C.). The remainder of the blood flows through the substance of the liver to join the IVC. The blood returning to the heart by the IVC is split into two streams by the crista dividens, the lower end of the septum secundum which overhangs the upper end of the IVC. One stream crosses the foramen ovale to the left atrium. The other enters the right atrium and mixes with the venous return from the superior vena cava and the coronary sinus. The blood from the right atrium then traverses the tricuspid valve to the right ventricle and is ejected through the main pulmonary artery to the lungs and the ductus arteriosus (D.A.). In the left atrium the blood crossing the foramen ovale from the IVC mixes with the pulmonary venous return. The blood from the left atrium is ejected from the left ventricle through the ascending aorta (A.A.) to the coronaries, forelimbs, head, neck and brain. A portion of this blood also crosses the isthmus to join the flow from the DA and makes up the flow down the descending aorta. The descending aorta then supplies the lower body, gut and umbilical artery

thus completing the circuit of the major fetal vessels.

Most studies of the distribution of the fetal circulation begin with an evaluation of the cardiac output. As Mahon has noted "since the inception of reasonably precise studies of the fetal circulation by Hugget in 1927 there has been difficulty in obtaining accurate measurement of cardiac output in the fetus."[22, p.191] In 1946, Bancroft, using a crude cardiometric method that did not evaluate the individual ventricular output, first estimated combined ventricular output in the fetal sheep as 240 ml/Kg/min. The more sophisticated measurement of fetal cardiac output that has been made since that time will now be reviewed. In considering these studies one should keep in mind that since the fetal ventricles pump essentially in parallel, the fetal cardiac output is generally spoken of as combined ventricular output (C.V.O.), the output of both ventricles, whereas, in the adult, because the ventricles pump in series, the cardiac output is taken to be the output of a single ventricle.

In 1954, Dawes et al., derived the relative distribution of cardiac output in six lambs within ten days of term.[21] By choosing four points in the fetal circulation where streams of blood with different oxygen (O_2) contents meet (right atrium, upper end of the IVC, left atrium, and the junction of the ductus arteriosus and descending aorta); measuring the O_2 content of the contributory and resulting streams; and thereby calculating the relative contributions

of the mixing streams, they were able, with simultaneous sampling of O_2 content in eight different vessels, to calculate the blood flow in all the principle vessels as a fraction of the cardiac output. They found the left ventricular output at 55% of CVO to be significantly greater than right ventricular output at 48% of CVO. Then using the calculation of placental flow as a fraction of CVO and a separate series of direct measurements of umbilical flow they estimated CVO as 230 ml/Kg/min. In addition to the assumption involved in their calculations, the authors felt that alteration of the physiologic state of the fetus secondary to barbiturate anesthesia, removal from the uterus and surgical procedures such as thoracotomy and ligation of the femoral arteries and veins, were the major possibilities for error in their results.

Assali, Morrow and Beck,[23] in 1965 investigated cardiac output in the fetal lamb using electromagnetic flowmeters around the ascending aorta, main pulmonary artery and ductus arteriosus. They found "effective cardiac output," which is the sum of flow through the ascending aorta and the ductus arteriosus, not including pulmonary or coronary flow, to be 198 ml/Kg/min. The flow in the pulmonary artery at 138 was significantly higher than that in the ascending aorta at 97. The pressures in the RA, RV, and pulmonary artery were higher than those of the LA, LV, AA, respectively. The results indicated a predominance of the right side of the fetal heart both in terms of work and output. The authors

found RV greater than LV output even when an estimate of coronary flow from adult values was added. However, Dawes had observed that fetal coronary flow may be quite high in the fetal lamb and this estimate was questioned.[22] Alteration in physiologic state secondary to spinal anesthesia, wide thoracotomy, and the probable nerve damage from the extensive dissection necessary for the placement of the flowmeters were sources of error in their results.

The next year Mahon, Goodwin and Paul[22] reported on studies of cardiac output done by indicator dilution techniques in fetal lambs within 10 days of term. The authors felt that the fact that this study could be done by catheterization whereas the previous studies had required thoracotomy and the speed with which it was done (mean time from delivery to first study was 3.71 minutes, while the same time in the Dawes study was 70.6 minutes), gave them a preparation which better approached a normal physiologic state. They obtained an output of 179.7 ml/Kg/min. for the RV and 181.7 ml/Kg/min. for the LV without a significant difference between the two. They also found a volume of 2.78 for the RV and 2.87 for the LV. Finally they found that cardiac output and stroke volume decreased steadily with the passage of time and this decrease appeared to involve both ventricles equally. Their study has been criticized because of the average heart rate of 252 reported. The normal rate for a fetal lamb is 180-200.[1]

In 1967, Heyman and Rudolph published results showing, as had been suspected, that exteriorization of the fetal lamb

did indeed produce changes in the fetal circulation. Using the steady state diffusion antipyrine method applied to fetuses catheterized in utero, they found significant decrease in placental flow and a significant increase in placental vascular resistance after delivery. The placental flow decreased by an average of 332.5 ml/min. (range 26-61%), and the vascular resistance increased by 26 mg Hg/L/min. These changes took place without a significant change in umbilical arterial pH, pO_2 or pCO_2. In the umbilical venous blood the pO_2 was significantly higher. The fact that these changes in the distribution of the circulation could take place without significant changes in the arterial blood gases (ABG's) was crucial, as all previous investigators had used stability of the fetal ABG's as an indication of a "normal" circulatory state in the fetus. Heyman and Rudolph felt the decreased placental flow could be secondary to decreased CVO, as well as to the increase in vascular resistance. They attributed the increased vascular resistance to partial placental separation and possible umbilical arterial constriction. The increased venous pO_2 was felt to be secondary to greater oxygen uptake per unit of flow because of the low flow rate.

Dawes' statement that "the difficulty in determining to what extent the condition of the experimental procedure modified the results from that which would have been obtained in the unanesthetized lamb in utero is obvious,"[2, p.581] could be applied to all of the previous studies. Finally in 1970 Rudolph and Heyman reported the results of studies on

just such in utero unanesthetized lambs. These studies were done by assessing the distribution of radioactive microspheres injected through chronically maintained catheters in the fetal lamb and comparing it to the independent simultaneous measurement of placental flow by the steady state diffusion antipyrine method. They obtained a CVO of 548 ml/Kg/min. in late gestation fetuses. (They also found in assessing fetuses of different ages that CVO increased proportional to increasing fetal weight so that cardiac output/Kg was similar for all groups.) A later study by the same investigators[5] with an improved technique found the previous results to underestimate consistently by 8-10% due to neglect of the pulmonary and coronary venous flow. The later study also found 57% of the CVO to be from the RV and 23% from the LV. These investigators felt that the three previous studies had underestimated CVO because of the anesthesia exteriorization and surgery involved. They attributed the proportionately lower RV output in previous studies to an actual decrease in RV output secondary to an increased resistance in the circuit to which the RV pumps, the placenta and lower body, attendant to exteriorization.

One fact that can be derived from all of these studies is that cardiac output in the fetal lamb is higher than that of the adult sheep (CVO 115-123 ml/Kg/min.).[1] Using the figures of Rudolph and Heyman[3,9,56] we can see that the cardiac output of the newborn lamb, 180-200 ml/Kg/min. individual ventricular output equals 360-400 ml/Kg/min. CVO,

in about 25% less than the CVO of the fetal lamb, 500 ml/Kg/min. Assali et al., showed directly in their studies that effective cardiac output decreased upon ventilation and cord severing in their fetal lambs. The reason for the relatively high cardiac output in the fetus will become apparent as the distribution and oxygenation of this output is very briefly considered.

The distribution of the fetal circulation as a percent of CVO and the O_2 saturation of the blood at various points in the fetal circulation is indicated in Figure 1. As the course of the circulation has already been reviewed, only a few major points will be touched on here.[3,21,9,56] Forty percent of the CVO returns from the placenta with 80% saturation. Twenty to eighty percent of the portal venous flow crosses the ductus venosus. The upper end of the IVC returns 69% of the CVO with an O_2 saturation of 67%. One-third of this flow (27% of CVO) crosses the foramen ovale and joins with 7% of the CVO returning from the pulmonary veins, with O_2 saturation of 42%, to give a left ventricular output of 34% of CVO with an O_2 saturation of 52%. The other two-thirds of the IVC flow (42% CVO) mixes with 21% of the CVO at 25% O_2 saturation from the superior vena cava, and 7% of the CVO from the coronary sinus to give a RV output of 66% CVO with an O_2 saturation of 62%. Fifty-nine percent of the CVO crosses the ductus arteriosus to join with 10% of the CVO crossing the aortic isthmus to give a descending

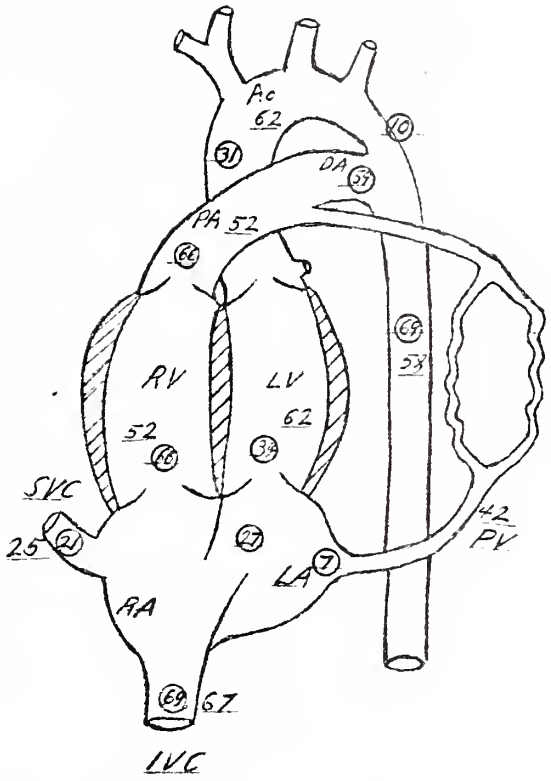

Figure 1 Distribution of the fetal circulation as a percent of CVO (in circles) and percent oxygen saturation. SVC = superior vena cava, IVC = inferior vena cava, RA = right atrium, LA = left atrium, RV = right ventricle, LV = left ventricle, A_o = aorta, PA = pulmonary artery, DA = ductus arteriosus, PV = pulmonary veins. Adapted from: Rudolph, A M, Congenital Diseases of the Heart, Chicago: Yearbook Medical Publishers, Inc., co. 1974.

aortic flow of 69% of CVO with 58% saturation.

It is evident from the above description that the abdominal organs, lower body and placenta get blood of a lower O_2 saturation (58%) than the head, neck, brain, forelimb and coronaries (62%). This difference in O_2 supply was first postulated by Sabatier in 1778 and has since been confirmed in many studies. It occurs because highly saturated blood from the IVC crosses the foramen ovale to the LA and thence the LV while poorly saturated blood from the superior vena cava is directed only to the RV.[1,21,3] This happens because the foramen ovale opens off of the upper end of the IVC, not the RA, and because the flow in the IVC is much higher (3x) than that of the superior vena cava.[21] It has been found, however, that under certain conditions, i.e. asphyxia or hypoxia with decreased heart rate or decreased heart rate secondary to vagal stimulation, large quantities of superior vena caval blood will cross the foramen ovale. Thus under various physiologic conditions, particularly those that might alter venous return to the heart, this preferential streaming of highly saturated blood to the brain and heart may be interrupted. Finally, it should be noted that this preferential streaming is of questionable physiologic significance as fetuses with premature closure of the foramen ovale, aortic atresia, or pulmonic atresia where it would not be expected and transposition of the great arteries, where it would be reversed, certainly survive until birth.

The study of Rudolph and Heyman in 1970 also assessed the changes which took place in the distribution of the fetal circulation from 60 to 150 days gestation. They found the CVO increased proportionately to the increase in fetal weight, so that CVO/Kg was similar for all groups. They also found a significant increase in flow per unit weight to the brain and lungs with increasing age. Other experimentors had found indications that the umbilical flow decreased toward term.[30] Rudolph and Heyman found no decrease in proportion to fetal weight. However, the umbilical flow did decrease from 50 to 40% of the CVO during the period studied. The authors could not determine whether a decrease in peripheral resistance in the fetal body or an increase in placental resistance was the cause of this change.

It should be obvious, now, that the fetal circulation is characterized by high blood flow. This is indicated by the high cardiac outputs noted above and by the short transit times found by Mahon et al.[22] Because fetal 0_2 consumption per unit weight is not greatly different than that of the adult while the oxygen saturation (0_2 sat.) of its blood is, the increased flow has been viewed as a mechanism to compensate for the low 0_2 sat. Assali et al. have shown that "this high cardiac output is closely related to the presence of the fetal cardiovascular shunts, particularly the ductus arteriosus and placenta. A decrease in the magnitude of flow through these shunts invariably reduces the magnitude of the cardiac output."[23, p.124] The fetal circulation is also responsive to

varying physiologic situations. The fact that the fetal ventricles pump in parallel makes the intra- and extra-cardiac distribution of flows particularly sensitive to changes in local vascular resistance.[20] We have already seen the types of changes in flow across the foramen ovale that different physiologic states can produce and various investigators have commented on the variations in distribution of the circulation found in different lambs.[3,21] In conclusion, the variation in the values for cardiac output reported by different investigators may well be best explained as actual variations in output induced by the different physiologic states they obtained. In the next section the mechanisms by which the fetal cardiovascular system makes these responses to different physiologic states will be examined.

Control Mechanisms and Response to Stress

This section will begin with a brief discussion of the intrinsic physiologic properties of the fetal heart, as many of the control mechanisms, in part, take effect by influencing these properties. In isolated right ventricular (R.V.) moderator bands from sheep Friedman found that the extent of force development in isometric preparations, and both the extent and velocity of shortening in isotonic preparations was less in near term fetal hearts than in adult hearts.[8] However, as tension approached zero in the isotonic preparations, the velocity of shortening curves appeared to intersect, i.e. V max's or intrinsic velocities of shortening appeared to be equal. He also found that passive tension at any given length was increased in the fetal bands. Expanding upon this, Romero et al. found in intact hearts that both ventricles of the near term fetus were less compliant than those of the adult sheep. The adult's RV compliance was greater than its left ventricular (LV) compliance while the fetal ventricles had similar compliance. Also the fetal RV compliance was decreased more quickly by LV filling than was that of the adult. In the newborn, left ventricular pressure-volume and tension-radius relationships approached those of the adult and this appeared to be associated with LV wall thickening.

The differences in ultrastructure in fetal and adult hearts probably explain these variances. Sheep fetal hearts contain fewer sarcomere per unit mass because there is more

loose areolar tissue between the myocardial cells and because the cells themselves contain a larger proportion of non-contractile elements, i.e. nuclei, mitochondria and surface membranes.[3,8] Friedman attributed the decreased contractile indices in the fetus to this smaller proportion of contractile mass.[8] If the data are normalized for this difference it would appear that each fetal sarcomere is capable of force generation similar to that of the adult sarcomere. This similarity was already indicated by the equal intrinsic velocities of shortening. Romero et al. had noted in previous experiments that compliance increased with increasing development of cardiac muscle. Therefore, after excluding an increase in collager concentration as the cause, they attributed the decreased compliance of the fetal heart to the increased proportion of noncontractile mass.[24]

Rudolph[3,5a] has conducted a number of studies on the basic parameters affecting cardiac output in the fetus. Rudolph[3,5a] and Downing[32] have both found that increasing afterload decreases stroke volume (S.V.) in the fetus and neonatal lamb. This effect begins immediately upon increasing afterload,[3,5a] lasts as long as this increase is maintained,[3,5a] and appears at levels of afterload that would not affect an adult sheep. Thus one would expect fetal cardiac output (C.O.) to decrease with increasing peripheral resistance. This effect appears to be due to the fact, noticed by Friedman, that the extent of shortening of fetal myocardium is decreased relative to adult values at any given

level of isotonic afterload. Rudolph also found that fetal SV increased only minimally with decreasing heart rate (H.R.) and that SV drops off steeply at high rates.[5a] Therefore, CO is very dependent on H.R. in the fetus. Finally, he has found that cardiac output (C.O.) increased only minimally with an increase in end diastolic pressure (E.D.P.) produced by infusion of saline into the superior vena cava.[3] This may be due to the decreased compliance and to the flattening of the length-active tension curve shown by Friedman.[8] Rudolph concluded that, while the adult can increase C.O. by increasing S.V. or by increasing rate, "the fetus can increase cardiac output only to a limited degree and this is mainly by increasing rate."[3, p.14]

There is some data concerning the factors which affect the inotropic and chronotropic state of the fetal lamb heart. The autonomic factors will be considered first. In adult animals and man increasing the number of impulses traversing the sympathetic nerves to the heart increases the contractility of the heart and this is apparently due to the release of norepinephrine from the nerve endings.[29] In the fetal lamb beta stimulation with isoproterenal causes an increase in H.R. as 0.4 gestation.[3] Isolated myocardial strips from near term lambs show increases in contractility to isoproterenal similar to those of adult sheep[5a] and fetuses receiving isoproterenol infusion have higher S.V. and C.O. at any given rate than those not receiving influsions.[5a] Finally, norepinephrine is three times more potent in the fetus than in the adult in augmenting

contractility.[8] Turning to the parasympathetic effects one finds that acetylcholine decreases fetal H.R. as early as 80 to 85 days.[3,5a] Isolated atrial[8] and ventricular[5a] muscle from late gestation lambs shows a decrease in contractility in response to acetylcholine. Finally, S.V. and C.O. at any given rate are consistently decreased during vagal stimulation.[5a]

Talner and Downing have investigated the metabolic factors which influence cardiac performance in the newborn lamb.[25,26,27,28] One might expect these factors to effect the fetal heart similarly. They found that metabolic acidosis produced by infusions of lactic acid or hydrochloric acid did not decrease left ventricular stroke volume or mean rate of ejection for a given rate and end diastolic pressure.[27] They attributed this maintenance of contractility to the capacity of cardiac muscle to buffer the changes in external pH and allow only a minimal change in internal pH. Next they showed that hypoxia reduce left ventricular performance slightly. Then, when acidosis was superimposed on hypoxia there was a great decrease in left ventricular stroke volume for a given rate and end diastolic pressure.[28] Talner and Downing felt this synergy was due to a compounding of the hypoxia by a decrease in the oxygen carrying capacity of the acidotic blood (Bohr shift) and/or a compounding of the intracellular pH drop by anaerobic metabolism. On the other hand, Friedman has found a decrease in the isotonic velocity of shortening with metabolic acidosis in his isolated fetal

myocardial strips. However the decrease was more pronounced when the acidosis was produced by increasing carbon dioxide concentration.[8] This finding might be explained by the high permiability of CO_2 allowing it to more effectively lower the intracellular pH.

What is known about the interaction of these two classes of influences on the myocardium? In the adult literature acidosis has been reported to depress responsiveness to catecholamine stimulation.[27] Talner et al. and Downing et al. have shown in separate studies that lactic acidosis does not decrease myocardial responsivity to norepinephrine or sympathetic nerve stimulation in newborn lambs.[27,25] Downing et al., however, found that hypercapnic acidosis did indeed decrease or abolish the normal increase in contractility produced by sympathetic nerve stimulation.[25] Friedman found a similar decrease in the contractile response of strips of fetal myocardium to norepinephrine during acidosis produced by increasing pCO_2 in the bathing solution. It should be noted that this decreased response to adrenergic stimulation was in neither case dependent on hypoxia. It appears, then, that "respiratory" acidosis does indeed interfere with sympathetic influences on the myocardium and this may be due to the lowering of intracellular pH by the highly permiable carbon dioxide.

The autonomic nervous system is one of the principle regulators of the fetal circulation in the lamb. The sympathetic division will be considered first. The evidence for

the development of receptor sites and end organ responsiveness in the heart has already been mentioned. There is similar evidence concerning the fetal vasculature. Alpha stimulation with methoxamine produces vasoconstriction of the kidneys and peripheral circulation with a resultant increase in blood pressure at 0.5 gestation.[5a,3] Alpha stimulation with norepi produces pulmonary vasodilation at 75 to 90 days.[5a] Turning to the development of sympathetic innervation one notes that the hyperresponsivity of fetal myocardium to norepinephrine might be due to a lack of sympathetic nerves within the muscle to inactivate norepinephrine by taking it up. Accordingly, Friedman found norepinephrine, tyrosine hydroxylase and monoamine oxydase, substances usually confined to the sympathetic nerves, to be decreased in the fetal heart.[8] The existence of adult levels of tyrosine hydroxylase in the adrenal gland and of catechol 0 methyl transferase in the heart indicated that the decreased levels of the other enzymes were not due to a generalized immaturity of synthesis of enzymes involved in norepinephrine metabolism. Finally he used a histochemical stain for sympathetic nerves which would fail only if the uptake and binding of catechols was immature and found a decreased sympathetic supply to the atria and ventricles. These results indicate the decreased extent of sympathetic supply to lambs within several weeks of term.[3] The newborn lamb was found to have better developed, but not completely adult, sympathetic innervation.[8] It has been shown by Downing et al. that stimulation of the inferior cardiac

sympathetic nerves[25] and sympathetic reflexes due to cephalic hypotension[26] are both sufficient to increase cardiac contractility in the newborn lamb. It should be pointed out that there is wide species variation in the development of sympathetic innervation to the heart. In the rabbit it does not appear until 10-14 days after birth,[14,3] while the guinea pig is basically mature in this respect at birth.[3]

If, then, the fetal lamb has responsive end organs with receptor sites and developing sympathetic innervation what resting functions does this system serve and to what stimulie does it respond. Concerning the first point an injection of hexamethonium, a ganglionic blocker, will cause a decrease in heart rate and blood pressure as early as 100 days gestation. Breaking this down, alpha blockade with phenoxybenzamine after 100 days will cause a decrease in blood pressure similar to that of the newborn. Beta blockade with propranolol will show a major decrease in heart rate after 120 days and a decrease in contractility near term.[34] Concerning the second point it is known that in men the sympathetic nervous system is important in maintaining circulatory adequacy when an imbalance develops between the cardiac output and the perfusion requirements of the peripheral tissues.[29] In the near term fetal lamb mild to moderate hypoxia produces an immediate increase in heart rate and blood pressure. This response can be reproduced by infusing norepinephrine and is presumably due to a sympathetic reflex.[14] Both of these increases appear by 100 days gestation.[12] In newborn

lambs cephalic hypotension produces an increase in heart rate and systemic vascular resistance, with blood pressure held constant. It produces a decrease in left ventricular and diastolic pressure and an increase in dp/dt max. when aortic pressure, heart rate, and cardiac output are held constant.[26] anglionic blockade virtually eliminated these responses and parasympathetic blockade only affected the heart rate response. Therefore these are primarily sympathetic responses of neural origin. The fetal lamb, then, has some background sympathetic activity involved in heart rate and blood pressure management. It also responds to stress with reflex sympathetic augmentation of blood pressure, heart rate and probably contractility. The latter two would tend to increase cardiac output. Again, the development of this response has species variation. It does not appear until eleven days after birth in the rabbit.[14]

The final component of the sympathetic nervous system to be treated will be the adrenal gland. Hypoxia appears to be the specific stimulus for secretion from the adrenal medulla, hypercapnea and acidosis being without effect.[10] There is a direct effect of hypoxia leading to secretion of norepinephrine which appears at 80-90 days, peaks at 118-130 days and declines to very low levels near term.[11] By 140 days the neural supply to the adrenal gland has developed and becomes the main pathway for adrenal secretion. It produces a greater secretion and responds at a higher PO_2 than the direct effect. It produces noradrenaline release at a PO_2 of 12-16

mm Hg, epinephrine being added at a PO_2 of 8 mm Hg. This upper level of PO_2 is very near that reported as normal for term fetuses in some laboratories. It should be noted once again that there is species variation. The calf maintains its direct response until 24 hours after birth and doesn't develop the neural response until 2-3 weeks after birth. Considering the supersensitivity of the fetal myocardium to norepinephrine one might expect that adrenal release of catechals would be more critical to maintenance of contractility in the fetus than in the adult. In fact, Downing et al. found evidence that the adrenal gland was acting to increase cardiac contractility during hypercapnic acidosis in the newborn lamb and that it was in fact more effective at increasing contractility than stimulation of the sympathetic nervous supply of the heart was under these conditions.

Parasympathetic

The parasympathetic division of the autonomic nervous system is also involved in circulatory regulation and appears to develop this function somewhat earlier than the sympathetic division. The existence of receptor sites and end organ responsiveness of the fetal heart has already been described. Vasodilation of the pulmonary vasculature at 75 days gestation indicates development of receptor sites there.[5a] Using a histochemical stain for acetylcholenesterase, Friedman found the density of cholenergic fibers to the SA node, AV node, atria, and ventricles of the lamb, several weeks from term,

to be equal to that of the adult.[8] Stimulation of the vagi causes a decrease in the heart rate as early as 90 days gestation. At term the decrease is nearly equivalent to that observed in the adult.[1,12] If there are functioning nerves and receptor sites and responsive end organs, what function does this system serve? Parasympathetic blockade with atropine produced increases in heart rate in fetuses at 85 days, the effect reaching a maximum at 120 days.[5a] At 119 days gestation, clamping of the umbilical cord causes an immediate decrease in heart rate which is abolished by cutting the vagi.[13] Again there is species variability. The immature rabbit does not show a decrease in heart rate to severe asphyxia until several days after birth.[14] However, in man, a decrease in fetal heart rate, secondary to head compression has been blocked by administration of atropine to the term fetus in utero.[1] Thus it appears that the parasympathetic nervous system becomes functional relatively early in gestation and plays a role in regulating heart rate and possibly contractility at rest and in response to severe asphyxia and head compression.

The final subject to be covered in assessing the autonomic nervous system are the varoreceptor and chemoreceptor reflexes which act through this system. Concerning the baroreceptor, impulses consistent with heart rate have been recorded from the carotid sinus nerve in late gestation. Dawes found that as early as 90 days gestation the acute bradycardia following administration of norepinephrine could be blocked by

cutting the vagi.[33] Rudolph found the decrease in heart rate produced by inflating a balloon in the aorta of a fetal lamb was abolished by cutting the carotid sinus nerves and stripping the aorta.[59] Concerning the other half of the varoreceptor reflex, near term occlusion of the carotid artery causes an increase in blood pressure.[1] However, the response isn't convincingly tied to the varoreceptors as cephalic hypotension after sectioning of the carotid sinus nerves still lead to an increase in sympathetic discharge.[26] The functioning of the chemoreceptors of the aortic and carotid bodies in the fetal lamb is less well established. In the adult carotid chemoreceptors are primarily concerned with respiration and aortic chemoreceptors with circulation.[1] Accordingly, Dawes has found that increased blood pressure and tachycardia produced by fetal hypoxia is abolished by section of the aortic nerves or cervical vagi.[59] In unpublished data he found similar results with cyanide stimulation of the aortic bodies.[1] Rudolph,[99] on the other hand, in preliminary investigation found cyanide stimulation of the aortic and carotid bodies consistently produced bradycardia and hypotension. Thus the baroreflex appears to be functional in the fetal lamb and the chemoreceptors may be functional in mediating the fetal response to hypoxia.

"The most important stress to which the fetus is subjected is hypoxia and asphyxia, a combination of hypoxia and acidenua.[23] Now that the various components regulating fetal

circulation have been examined, let us see how the near term lamb fetus responds to this stress. In a series of experiments on unanesthetized fetal lambs in utero, Rudolph found an increase in blood pressure, a decrease in heart rate and a decrease in cardiac output.[3,215,59] In another series of experiments on an exteriorized fetus, Born, et al., found an increase in blood pressure, heart rate and apparently cardiac output.[19] They however found that as asphyxia was intensified an intermediate stage was passed through in which blood pressure continued to increase while heart rate decreased. Finally in severe anoxia, heart rate, blood pressure and apparently cardiac output were decreased. Organ, et al.,[34] also found that mild fetal hypoxemia produced an initial increase in fetal heart rate while severe hypoxia produced an initial decrease in fetal heart rate. In both investigations there appears to have been a sympathetic discharge tending to increase blood pressure by increasing peripheral resistance, to increase heart rate and probably to increase contractility, the latter two then tending to increase cardiac output. On the other hand the vagal nerve was acting to decrease heart rate and possibly to decrease contractility. These effects along with the increased afterload tended to decrease cardiac output. The difference between the experiments being the point at which the vagal reflex overcomes the sympathetic stimulation.

To understand how the fetal response to hypoxia is adaptive, one must examine more closely the increased blood

pressure. This must be due to an increase in overall peripheral resistance as it was a consistent increase while cardiac output at least sometimes decreases. Campbell et al., found the increased blood pressure due to partial asphyxia produced by partial occlusion of the umbilical cord was associated with increased pulmonary, renal and femoral resistance.[19] The femoral increase being a neural reflex[19] and the pulmonary increase being secondary to the direct effect of decreased pH.[1,27,19] There was however a decrease in coronary and cerebral vascular resistance. Turning to the umbilical circulation we find it is basically without nervous reflexex[12] and relatively insensitive to ABG's and pH.[12,19] Thus the umbilical flow is rather passively dependent on the blood pressure.[1,19] Accordingly, Rudolph has found in hypoxic unanesthetized lambs in utero that the proportion of cardiac output to the myocardium, brain and adrenal glands is increased while the proportion to the limbs, kidneys and lungs is decreased and that to the placenta is maintained. The fetus adapts, then, by redistributing flow to the essential heart, placenta and brain at the expense of the rest of the fetal body, rather than by increasing cardiac output. In addition, Born et al. have found that fetal O_2 consumption falls when umbilical O_2 saturation falls drastically presumably synergizing with the redistribution of flow to promote fetal survival.[12]

One particular cause of asphyxia, occlusion of the um-

bilical cord, deserves separate attention. The hypoxia and acidosis associated with occlusion of the umbilical cord produce basically the same changes in the fetal lamb circulation as described above. However in this case the low resistance vascular shunt of the placenta is removed abruptly, drastically, increasing peripheral resistance and thus blood pressure.[23] As would be expected there is an immediate reflex decrease in heart rate.[1] Thus one would expect a consistent and immediate decrease in cardiac output in such cases as opposed to the situation in simple hypoxia where the heart rate and possibly cardiac output may be variable in the early stages. In species in which the baroreflex or parasympathetic system was poorly developed the heart rate decrease would await the direct effects of prolonged asphyxia and there might be an initial increase in heart rate secondary to sympathetic discharge.[14] Even in these situations cardiac output would probably be expected to decrease secondary to the drastically increased afterload.

What, then, are the clinical situations which lead to hypoxia of the fetus? Comline et al. have reported that in normal lamb fetuses pO_2 increases and pCO_2 increases as term is approached in fetal lambs.[10] Dawes et al. have reported that umbilical flow per unit weight decreases toward term.[30] Rudolph in more recent studies on unanesthetized lambs in utero has not found these changes and has attributed both of the previous findings to exteriorization and the resultant

interference with placental and uterine flows.[9,20] However, Rudolph did find placental flow as a percentage of C.V.O. to decrease, and he showed pO_2 to increase not decrease on exteriorization of the fetus. In the human literature Walker and Turnbull have reported a decreasing O_2 content and O_2 saturation toward term associated with an increasing hemoglobin and red cell count. They attributed the latter to a decreasing oxygen supply.[16] However, it has been pointed out that these changes in arterial blood gases may be due to acute hypexia during labor.[1] Also, Born et al. have shown that oxygen carrying capacity of the fetal blood can be acutely increased in response to hypoxia, possibly through splenic contraction.[12] Fine and Haavards have found that erythropoetin, a substance which necessitates several hours of hypoxia to effect a change in its levels, is significantly higher in full term infants than in prematures. Finally in accord with the theory of decreasing oxygen supply toward term Walker and Turnbull also found a substantial decrease in oxygen content and an increase in hemoglobin in pregnancies extending beyond 41 weeks.[16] However, other investigators have not found this in uncomplicated prolonged pregnancies and have attributed these findings to inclusion of dysmature infants.[18]

Though it is not clear whether normal fetuses become increasingly hypoxic as pregnancy nears term there are pathologic situations in which there is more substantial evidence

of prolonged intrauterine hypoxia. The study of Finne and Haavard using erythropoetin levels in cord blood is perhaps the best, as these levels would not be expected to change with labor.[8] Of his groupings babies of preeclamptic mothers had the highest frequency of elevated erythropoetin levels. Erythroblastotic infants with hemoglobin less than 13 grams showed significantly increased levels. Some of the dysmature infants had significantly increased levels too. Finally, in one case of fetal death in a diabetic mother the amniotic fluid contained very high levels, and such levels correlate well with cord blood levels. Berglund and Zetterstrom found the oxygen content of umbilical venous blood to be less than controls and the number of nucleated red blood cells to be abnormally high in infants of diabetic mothers.[17] They felt the later change had to be secondary to increased erythropoiesis, a process not expected to be influenced by labor. In a study of dysmaturity Sjostedt et al. found that as dysmaturity became increasingly severe the oxygen saturation of cord blood decreased and hemoglobin increased.[18] They also found much other clinical and laboratory data indicating placental insufficiency. Kyank and Eggert found significantly decreased pH in mothers with toxemia of late pregnancy and there have been other reports of decreased pO_2, increased pCO_2 and increased reticulocyte counts in such infants.[15] The increased erythropoetin levels in erythroblastosis were thought to be due to decreased oxygen delivery to the tissues because of the decreased oxygen carrying capacity

of the blood. Concerning the other data, all of the authors attributed their findings to prolonged intrauterine hypoxia secondary to reduced uteroplacental blood flows. Conditions such as obliterative lesions in the uterine vessels, placental infarctions, and abruptio placental have been proposed to explain such decreases in uteroplacental flows.[9,17,20]

The situation during which the occurrence of fetal hypoxia is best established is that of labor. During normal human labor there is a progressive fall in scalp blood pH, pO_2 and oxygen content and a progressive rise in pCO_2.[1] This fall in oxygen content during labor is probably the result of decreased maternal placental flow during contractions.[1] If this decreased uteroplacental flow during contractions is unduly accentuated the fetus may become hypoxic and its viability may be threatened.[2] There is a characteristic heart rate pattern produced in such situations.[2] Finally, the umbilical cord may be intermittently occluded during contractions and this too produces a characteristic heart rate pattern.

Noninvasive Correlates of Pump Function and Contractility

Systolic time intervals (STI), established measures of cardiac function, and ventricular volumes, ejection fraction (E.F.), posterior wall velocity (PWV), and mean velocity of circumferential fiber shortening (VCF), a group of new measures of function now being popularized by the development of echocardiography, will be investigated. Next the results of this

investigation will be collated with the data on fetal circulatory physiology reviewed above in an attempt to predict the values of these parameters of cardiac function in the resting and stressed fetus. Then a proposal for a method of measuring these parameters in the fetus will be made. Finally, the importance of making such measurements will be assessed.

STI

Marey noted changes in arterial and venous wave forms in cardiac disease, using his sphygmograph, as far back as 1860.[58] Later Garrod measured the length of ventricular systole from tracings of the brachial pulse.[59] In 1921 Wiggers divided ventricular systole into isometric contraction preceding aoritic valve opening and isotonic systole following opening.[60,61] Katz and Feil developed what is essentially the modern technique by simultaneously recording an E.K.G., phonocardiogram, and a central arterial pulse.[62,63] The current technique in man involves simultaneous high speed recording of E.K.G. phonocardiogram, and carotid or brachial arterial pulse (Figure 2).[64,53,52] From these recordings one may obtain:

total electromechanical systole = Q to A_2

left ventricular ejection time (LVET) = carotid upstroke to incisura.

preejection period (PEP) = total electromechanical systole —— LVET

isovolumic contraction time (ICT) = (S_1 to A_2) —— LVET

electromechanical delay (EMD) = Q to onset of ventricular contraction

onset of ventricular contraction to S_1 (C to S_1).

The situation is not as complex as it appears because only three intervalsare generally dealt with: PEP the period from electrical depolarization to opening of the aortic valve, ICT the period from closing of the mitral valve to opening of the

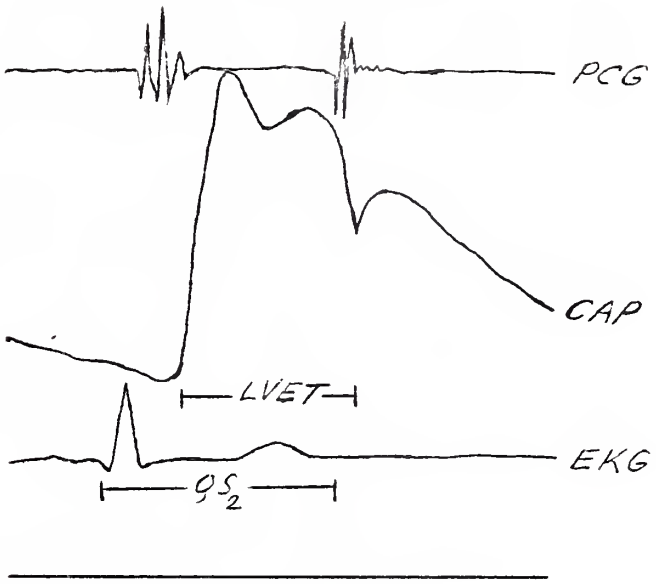

Figure 2 Conventional determination of STI. PCG = phonocardiogram, CAP = carotid arterial pulse, and EKG = electrocardiogram. Adapted from Weissler AM, Harris WS, Schoenfeld CD: Systolic time intervals in heart failure in man. Circulation 37: 149, 1968.

aortic valve, and LVET the period from opening to closing of the aortic valve. Also must authors subsume EMD and C to S_1 into the period Q to S_1.

Two factors regarding interchangeability of data should be mentioned. First it might be expected that externally measured values for PEP and LVET might be somewhat inaccurate due to factors such as difference in transmission speeds of upstroke and incisura or difficulty in accurately identifying beginning of A_2 or one of these pulse waves. However, internal measures of PEP and LVET by catheterization and external measures have generally been found to be in close agreement. Thus, the specific method used to obtain these parameters in various experiments will not be routinely identified in this paper. Secondly, PEP equals Q to S_1 plus ICT. It has been shown that PEP is well correlated with ICT throughout a variety of physiologic situations in man.[48] This seems to occur because most perturbations of the circulation effect ICT and not Q to S_1[48,41] or effect them both in the same direction.[66] Therefore reported changes in ICT will be discussed in conjunction with changes in PEP.

It will be shown that PEP and LVET are parameters which relate to overall pump function and to contractility. As such they are influenced by a number of intra and extramyocardial factors. Chief among the factors are preload, afterload, heart rate, and contractility. Their relationship to STI will now be examined.

PEP

Increasing preload has generally been found to decrease PEP.[35,37,38,42] Talley et al.[35] in catheterized dogs found that, with aortic pressure, heart rate, and contractile indices held constant, increasing left ventricular end diastolic pressure (LVEDP) decreased PEP markedly. Wallace et al.,[37] using stroke volume (SV) as a correlate of preload by holding aortic pressure and heart rate constant, found as SV increased, ICT decreased in his denervated dog heart preparation. Shah et al.,[42] also using stroke index as a correlate of preload and holding heart rate (HR) steady, found an inverse relationship between PEP and stroke index in men in whom stroke index was varied by application of tourniquets and infusion of low molecular weight dextran. Finally in men in whom end diastolic volume (EDV) varied secondary to atrial fibrillation a beat to beat analysis by Athansios et al.[38] showed PEP to vary inversely with EDV (= 0.92).

There is also general agreement that PEP is directly proportional to afterload.[35,37,50,45,38,44] In their days Talley et al.[35] found a small but significant increase in PEP upon increasing aortic pressure with LVEDP, HR, and contractile indices held constant. Both Wallace et al.[37] and Rolett and Vallis[50] found ICT to increase with increasing aortic pressure in their dogs. Flessas et al.[38] in his study of men with atrial fibrillation found PEP to be directly correlated with aortic pressure (F = 0.76). Harris et al.[48]

gave pressor drugs to men and found PEP to increase with increasing aortic pressure. Harris et al.[46] in a similar study found that the increase in PEP secondary to vasoconstricting drugs was blocked by atropine and was not present at all in patients with autonomic insufficiency, i.e. without vagal efferents to the heart. Therefore, they proposed that this increase in PEP was due to a vagal reflex. However, it is notable that the dogs of Wallace and Rolett had been sympathectomized and those of Talley et al. had received atropine or hexamethonium. A more simple minded explanation might be that the increase in afterload increases the difference in pressure between the pre and afterload which the ventricle has to generate during the PEP.[45]

It is less clear what effect heart rate has upon PEP. Talley et al. found PEP uneffected by HR in their dogs.[35] However, Wallace et al. found ICT to be inversely related to HR in their dogs.[37] In man Harris found changes in HR produced by atropine or atrial pacing were without effect on PEP. Weissler et al. found PEP to be inversely related to natural variations in HR.[66] In normal newborns aged one to three days Levy et al. found PEP to be inversely related to HR. Golde and Burstin found the same in children from one month to thirteen years.[52] They also found this relationship to be due to an inverse relationship between HR and onset of ventricular contraction to S_1 (C to S_1) while EMD and ICT were independent of rate. Harris et al. also found ICT to be independent of HR in newborns and children to age thirteen.[53]

Also in accord with Golde and Burstin, Goodlin et al. found Q to S_1 (which = EMD +) (to S_1) to be inversely proportional to HR in newborns.[55] Walsh and Gyulai found this inverse relationship to exist on the first day of life but to disappear by the end of the first week.[56] In the only good study of human fetuses Murata and Martin found PEP to be independent of HR.[118] Thus, it appears there might be an inverse relationship to rate at least in the newborn. However, even in those studies that found such a relationship the regression equations relating PEP to HR had only a small negative slope[51,52,66] indicating a small decrease in PEP with increasing HR. Finally, it might be hypothesized that the decrease in PEP with increasing HR was really due to the increase in contractility that occurs with increasing HR,[102] as Talley et al. the only ones to hold indices of contractility constant found no relationship.[35]

There is good agreement that other things being equal increasing contractility decreases PEP.[35,37,51,48,41,43,66] One way to investigate this relationship is to pharmalogically alter contractility and see how PEP changes. Wallace et al. found that with aortic pressure, SV, and HR held constant administration of norepinephrine or cardiac glycosides decreased ICT in their dog hearts.[37] Talley et al. found a highly significant correlation between time to max dp/dt (a contractile index) and PEP over a wide range of ionotropic stimulie.[35] In man Harris et al. found isoproterenol, epinephrine, low dose norepinephrine, cardiac glycosides, and psychogenic

stress all decreased PEP.[45] Ahmed et al.[48] and Leightas et al.[41,43] with aortic pressure, HR, and LVEDP held constant found isoproterenol decreased PEP while increasing contractile indices. In newborns with and without congestive heart failure cardiac glycosides have been shown to significantly decrease PEP.[51] Another method of investigating the effect of contractility on PEP has been to compare normals with persons whose myocardial disease decreases their contractility. Weissler et al. found patients in congestive heart failure (CHF) secondary to atherosclerotic heart disease, hypertensive cardiovascular disease, and primary myocardial disease had prolonged PEP.[66] Ahmed et al. found a strong correlation between PEP and indices of contractility in patients with CHF due to left ventricular disease.[48] Thus it appears that PEP rather accurately reflects contractility under a variety of conditions. However, as we would expect from the discussion of preload, afterload, and HR this is only true when such factors do not interfere. In the study of Talley et al. variations in aortic pressure had a small but significant effect on the relationship between PEP and contractility while LVEDP had an even larger effect.[35] In one of the studies of Leighton's group the correlation between PEP and contractility was strengthened by eliminating those with valvular regurgitation,[43] while in the study of Ahmed et al. there was no correlation between PEP and contractility for patients with valvular disease, shunts, or corpulmonale.[48] Thus it appears that PEP reflects contrac-

tility only when extramyocardial factors, such as preload, afterload, and heart rate, are not determining cardiac performance.

LVET

Left ventricular ejection time increases with increasing stroke volume.[36,37,38,46,47,54] Stroke volume depends upon preload, afterload, and contractility. However under proper conditions increased preload produces increased SV and the data on LVET and preload are in terms of SV. Braunwald et al. with an isolated dog heart preparation[36] and Wallace et al. in the denervated dog heart[37] found that increasing SV increased LVET with HR and aortic pressure held constant. However, Braunwald et al. found this to be a small effect. In resting man Weissler et al. found LVET to have a strong correlation with SV.[46] However in resting man HR and SV may have tended to vary inversely thus confounding the results. Jones and Foster on the other hand varied stroke index by exercise in man and found a significant but weak correlation between stroke index and LVET.[47] In this study the increased contractility attendant to exercise may have masked the effect of SV. Flessas et al. came up with the best experimental design by measuring beat to beat changes in SV due to atrial fibrillation.[38] They found a strong correlation (= 0.94) between SV and LVET. There are also indications in the work of Guylai and Walsh that this direct relation of LVET to SV holds in newborns.[54]

The relationship of LVET to afterload is in much dispute. In the dogs of Talley et al.[35] and Wallace et al.[37] as aortic pressure increased LVET decreased. Braunwald et al. found no effect of aortic pressure on LVET in his dog heart

preparations until the pressure reached 175-200 mm. Hg at which point the LVET prolonged.[36] In man James and Foster found exercise induced increases in aortic pressure produced decreases in LVET, while Shaver et al. found that methoxamine induced increases in aortic pressure produced lengthening of LVET.[67] Looking at more chronically increased afterload Weissler and coworkers found hypertensive patients to have a nonsignificant decrease in LVET relative to SV, but patients with aortic stenosis had prolonged LVET relative to SV.[46] It appears, then, that no conclusion can be drawn from the data about the relationship of LVET to afterload.

There is, however, an interesting fact that emerges from these studies. In the study of Wallace's group increasing aortic pressure decreased LVET while SV, HR, and LVEDP remained constant.[37] This ejecting of a constant volume of blood against an increased afterload at a faster rate implies an increase in contractility. Indeed, Talley et al. found that increasing aortic pressure significantly increased max dp/dt without changing LVEDP in dogs given hexamethonium.[35] The denervation of the heart in the study of Wallace and coworkers and the administration of hexamethonium by Talley's group would seem to rule out nueral reflexes as a basis for this change in performance. The lack of change in LVEDP in either case would rule out participation of the Frank-Starling mechanism. Sarnoff et al.

also found that increasing aortic pressure increase myocardial performance without increasing LVEDP.[68] They suggested that the increase in the level of tension generation per unit time required of the myocardium somehow lead to an increase in contractility. They called this process homeometric autoregulation. However, it should be noted other workers have found that in their dogs increasing afterload increased end diastolic volume and decreased dp/dt/P.

Left ventricular ejection time is inversely related to heart rate.[36,37,46,43,51,52,53,118] In the dogs of Wallace's group and the dog heart preparations of Braunwald's group HR and LVET were inversely related when SV and aortic pressure were held constant.[36,37] In adult man changes in HR occurring naturally at rest and secondary to isoproterenol or exercise have been shown to be inversely correlated with HR.[46,43,47] Golde and Burstin have found this inverse relationship to hold in children one month to thirteen years old.[52] Levy et al. have found it to hold in newborns and have published a linear regression equation of LVET on HR. Harris et al. have found this linear relationship to hold for neonates and children at rates less than 150. At rates greater than 150 the correlation was poor and the slope of the regression equation less negative. In the only study of human fetuses outside of labor Murata and Martin found LVET to be inversely related to rates from 180 to 115, but with rates less than 115 there was no further prolongation.[118] This finding is consistent with the fact that unlike adults,

fetuses do not increase SV much with decreasing HR.

The relationship between contractility and left ventricular ejection time is not clear. These studies, like those on PEP and contractility have been performed by giving ionotropic drugs and checking changes in LVET or by comparing LVET in individuals expected to have depressed contractility with LVET in normals. The administration of sympathomimetic amines and cardiac glycosides to dog heart preparations has been shown to decrease LVET when SV, aortic pressure and HR are held constant.[36,37] In man, Leighton et al. found no significant change of LVET with isoproterenol infusion when HR was controlled by atrial pacing.[43] In adults and newborns cardiac glycosides have been shown to decrease LVET, but this change may be only transient.[51] When the dog heart preparations of Braunwald's group were on the descending limb of the Frank-Starling curve, i.e. in CHF, LVET increased even with decreasing SV.[36] In man Flessas et al. found LVET to be inversely proportional to the velocity of circumferential fiber shortening (an index of contractility).[38] However Ahmed et al. found no correlation between LVET and contractile indices and found no significant changes in LVET from normal in groups with left ventricular disease and decreased contractile indices.[48] In two studies by Weissler and coworkers LVET was found to be decreased in patients with myocardial failure but this decrease was found to be due to decreases in SV.[46,66] Thus, it appears that in dogs, where SV can be controlled, LVET is inversely proportional to contractility but in intact

men, where SV varies, the relationship becomes blurred. In these cases SV tends to vary directly with contractile state and although decreases in contractility may tend to increase LVET the attendant decrease in SV shortens it.

Because this paper is basically concerned with the fetal circulatory system it would seem wise to investigate the effect of maturity on preejection period and left ventricular ejection time. Golde and Burstin found both PEP and LVET were directly proportional to age independent of HR variations. They also found that the increasing PEP with age was due to a direct relationship of EMD and ICT to age independent of rate. Harris et al. also noted that the values for ICT in newborns and children were less than those reported for adults.[53] There are also indications in the work of Walsh and Guylai that LVET increases during the first week of life independent of changes in rate.[56] On the other hand Harris et al. found LVET corrected for HR to be longer in premature neonates than in mature neonates and children, but this difference appeared to be due to anemia and the attendant increase in SV.[53] There is one study in human fetuses showing PEP to be directly proportional to gestational age.[118] It has been suggested that because of the law of LaPlace if the tension generated by the child's myocardium rose at the same rate as that generated by the adult myocardium the pressure would rise more rapidly in the child's smaller ventricle thus shortening the ICT.[53]

Recently the ratio of PEP to LVET has been used as an

indicator of ventricular performance.[69] This seems logical in the case of adults with left ventricular disease for, as has been shown, PEP tends to lengthen and LVET tend to shorten in such cases thus the ratio would magnify their difference from normals. Ahmed et al. have found the ratio to have a good negative correlation with indices of contractility and pump function in normals, patients with left ventricular disease, and patients stimulated with isoproterenol or exercise.[48] Bush and Lewis also found decreases in PEP/LVET correlated with increases in dp/dt/P.[40] In newborns with and without CHF Digoxin significantly decreases PEP/LVET.[51] This ratio tends to be independent of rate in adults,[69] children,[52] and newborns.[51] Golde and Burstin found the ratio to be inversely proportional to age in children,[52] while Levy et al. found PEP/LVET to be only slightly longer in their newborns than the values published for normal adults.[51] It must be mentioned that, as with PEP, Ahmed et al. found PEP/LVET was not correlated with measures of pump function in patients where extramyocardial factors markedly influenced performance, i.e. in patients with valvular disease, shunts, or corpulmonale.[48]

Another recent development in the measurement of STI by echocardiography (ultrasonacardiography, UCG). Vredevoe et al.,[70] first reported the measuring of STI by simultaneous recording of an EKG and a UCG of the aortic valve. With their method PEP = Q wave - aortic valve opening, while LVET = aortic valve opening - closing. These UCG's were recorded

from an oscillograph onto polaroid film at a sweep speed of 25-50 mm/sec. The values were in close agreement with values obtained from the same patient by traditional methods. Later Stefadouros and Whitman,[71] in adults, and Hirschfield et al.,[72] in children used the same procedure but recorded on a strip chart with sweep speeds of 75-125 mm/sec. allowing measurement accuracy of 5 milliseconds. They both obtained excellent correlations with simultaneous standard measures. Hirschfield et al.[72] added another dimension, they obtained right ventricular PEP (RPEP) and right ventricular ejection time (RVET) by recording an EKG and a UCG of the pulmonary valve. They validated this method with simultaneous recordings from cardiac catheterization. They also noted that in normals RPEP was shorter than LPEP, and RVET was longer than LVET. These relationships were reversed in children with transposition of the great arteries and were attributed to the lower pressure in the pulmonic as opposed to the systemic circulation.

What prediction, then, might one make from this knowledge of fetal circulatory physiology and STI's in the mature fetus?

There would be a few differences from adults at rest. Both PEP and LVET would be expected to be shorter as they are directly related to age. The PEP would be inversely proportional to heart rate. The LVET, though initially shorter for a given rate would drop off less sharply with an increase in rate. Fetal heart rate is already in the 150 range, and above this range it has been shown LVET drops off less sharply

with an increase in rate. This may be because fetal SV does not drop sharply until heart rate exceeds 200.[3]

How would the fetal STI's respond to the stress of hypoxia? As has been shown in the mature fetal sheep, in initially or mild hypoxia, there is a predominant adrenergic discharge from the sympathetics to the heart and from the adrenal glands. Comline, et al.,[10,11] showed that the adrenal glands excrete norepinephrine at first. Harris et al.,[45] showed that moderate levels of norepinephrine decreased PEP. LVET might be expected to also shorten because of this increase in contractility and to the rapidly decreasing fetal SV that attends a rising blood pressure. The initial rise in heart rate would also be expected to decrease these intervals. As hypoxia became more severe or prolonged, the direct effect would couple with the increase in parasympathetic discharge to decrease contractility. This factor, along with the steadily increasing blood pressure and the more decreasing heart rate would tend to prolong PEP. The decreasing contractility, the increasing blood pressure and the inability of the fetal heart to increase SV to lowered rates would all tend to further shorten LVET. This shortening would be most pronounced if LVET were corrected for rate. Finally, the eventual acidosis would further decrease contractility and thus accentuate PEP prolongation and LVET shortening. The only difference to be expected from this scenario in a fetus stressed by cord occlusion would be the

lack of an initial shortening of PEP and perhaps a greater initial shortening of LVET due to the immediate and marked rise in blood pressure.

There are two reports on changes in fetal STI's and they seem to agree with the scenario presented above. Organ et al.,[34] measured STI's in exteriorized, catheterized mature fetal lambs. They found PEP was inversely related to FHR and reflected changes in maximum dp/dt produced with isoproteranol or propranalol. They produced fetal hypoxia by respirating the ewe with 100% O_2 for only 1-1/2 minutes and found PEP to decrease proportionately to fetal PO_2. They also noted the decrease in PEP began with PO_2 in the range of 12-16 mm Hg. which was the level Comline et al.,[10,11] found to begin the adrenal release of norepinephrine. They also found umbilical cord occlusion for 30 seconds increased PEP. Finally there is a report of prolonged PEP in the third trimester of human pregnancies being associated with FHR signs of utero-placental insufficiency during labor.[73] These pregnancies were complicated by diabetes mellitus, hypertension, erythro blastasis fetalis, intrauterine growth retardation or prolonged pregnancy, the very conditions suspected to be associated with intrauterine hypoxia. Presumably the hypoxia they were subjected to was more prolonged and/or more severe than that faced by the fetal lambs in Organ's group. One possible alternative explanation is that the studies which showed initially predominant adrenergic effects, i.e. increased heart rate, were done in exteriorized lambs while those done with in utero lambs

showed a predominant vagal effect from the first. Thus the exteriorized lambs would have an initial shortening of PEP while the in utero fetuses might never go through this stage.

There are also some reports of the measurement of fetal STI during labor. Goodlin and coworkers have reported that S_1 to S_2 (= ICT + LVET) is fixed during labor, i.e. does not vary with rate.[65,115,116] They did find Q to S_2 to vary with rate and atrributed this to variation in Q to S_1 (= EMD + C to S_1).[115,116] Murata, et al., while finding LVET to vary with rate, did report PEP to be 10 milliseconds longer in labor than during the six weeks before.[118,111,73] Goodlin also reported prolongation of $Q\text{-}S_2$, $Q\text{-}S_1$ and $S_1\text{-}S_2$ in three stressed intrapartum fetuses. This is consistent with the prolongation of PEP in severely hypoxic fetuses. However, it may or may not be consistent with the predicted shortening of LVET in such fetuses. Finally, the small increment of PEP during normal labor found by Murata, et al., is consistent with the finding that even normal fetuses became somewhat hypoxic during labor.[1]

Echocardiographic Indices

There are a group of indices of cardiac performance which can be measured from the m mode recording of an echocardiogram (ultrasonocardiogram UCG). These indices are generally ones that were originally developed from cineangiography and they are validated by comparison with cineangiographic results. Their current popularity is due to the popularization of the noninvasive technique of echocardiography.

The most extensively investigated of these techniques is the measurement of end diastolic, end systolic and stroke volume of the left ventricle (LV). Teigenbaum et al.,[77] first used UCG to estimate LV stroke volume in 1967. He made a recording of the motion of the mitral ring area from the apex of the heart, i.e. along the LV major axis, and of the epicardium of the anterior and posterior heart walls from about the fourth intercostal space, along the minor axis. He reasoned that stroke volume should be proportional to the amplitude of mitral ring excursion and diastolic diameter of the heart and found a good correlation with simultaneous measurements by the direct Frick method ($r = 0.973$). It should be noted that this diastolic diameter of the heart included part of the RV. Later in 1969, Popp, et al.,[75] recorded good UCG's of the interventricular system at a level just below the mitral valve with the transducer at about the fourth intercostal space. This allowed him to record a left ventricular interval diameter (LVID) from the side of the interventricular system (IVS) to the LV endo-

cardium. He found the mean LVID was significantly increased in patients with marked aortic regurgitation or mitral regurgitation. Later the same year Feigenbaum et al.,[93] found the cube of LVID in diastole (LVIDd) correlated excellently within nonsimultaneous angiographic determination of left ventricular end diastolic volume. Finally in 1970, Popp and Harrison using a prolated ellipse as a model of the left ventricle and the LVID as an approximation of the minor axis derived the equation: end diastolic volume (EDV) = K (LVIDd);[3] end systolic volume (ESV) = K ($LVIDd^3$ - $LVIDs^3$). He found the stroke volume so calculated correlated well with nonsimultaneous Frick measurements of SV (r = .966) and that addition of the amplitude of excursion of the mitral ring area did not improve the correlation.

Since that time there have been a rash of papers correlating estimates of ventricular volumes by Popp's method with cineangiographic measurements of these volumes.[76,79,80,81,82,91,92,98] A number of these papers using cubic functions of LVID have found excellent correlations for LVIDd and EDV, the correlations for LVIDs and ESV being somewhat less strong.[80,82,86] Fortnin et al.,[79] found a high correlations between LVIDd and EDV, LVIDs and ESV, and LVIDd - LVIDs and SV but found that cubing the internal diameter decreased the correlation by overestimating volumes in larger hearts. Meyers et al.,[76] found an excellent correlation between LVIDd and EDV in infants and children but found the regression equation describing this relationship was different from those of adults.

They also proposed a different equation for estimating stroke volume from LVID in infants and children. The study of Feigenbaum et al.[82] indicates the reproductability of this technique as they obtained good correlations even when the UCGs were done by eight different individuals with different levels of training from different institutions. The study of Myerowitz in dogs indicates its precision in a variety of physiologic states as they obtained high correlations between UCG SV and flowmeter SV during a variety of procedures expected to increase or decrease SV.[92] Finally the strength of the above correlations is particularly appreciated when it is realized that the UCG and angiographic measurements were non-simultaneous.

In the original paper by Popp and Harrison a number of assumptions were made which should be mentioned. They assumed that the LV cavity was a prolate ellipse (ellipsoid of revolution about the major axis). Thus the minor diameters were assumed to be equal and the LVID was taken as a measure of the anterior-posterior minor axis. They also assumed this shape held in diastole and systole. In other words the major axis must be a constant multiple of the minor axis. Finally their work assumes that these conditions hold in all groups.[96] These assumptions led to the following equation:

$$
\begin{aligned}
V &= (\pi/6)\, LD^2 \\
&= (\pi/6)\, KD\ D^2 \\
&= (\pi/6)\, KD^3 \qquad \text{using } K = 2 \\
&= \pi(2/6)\, D^3 \\
&= D^3
\end{aligned}
$$

Where V = volume of the L.V.

L = major axis

D = minor axis

K = the constant relating D to L.

Is the LVID a true minor axis? Several authors have found high correlation between UCG LVID and the angiographic minor axis in adults [79,80,81] and children.[76] However, in children the angiographic minor axis was higher than LVID during systole, secondary to dye filling the interstices of the endocardium and the cineangiographic camera angle not being perpendicular to the septum. Thus some authors have concluded that the LVID is a true minor axis.[79,95] However, a weak correlation between LVID and the major axis has been shown[93,80] and other authors have held that the LVID is an oblique axis reflecting both minor and major axes.[80,89,82,93] It has been suggested that the reason for these divergent opinions is that different axes are being measured in different people depending on the individual's unique anatomy.[90] This problem of standardizing the measurement was recognized from the beginning[78] but it was felt that there was only a small area in the LV body in which the IUS and posterior wall endocardium could be recorded.[78,82] Later, Feigenbaum et al.,[89] suggested that parts of both mitral valve leaflets, or chordal, be included to further restrict the area recorded. Then Popp, et al.,[83] noticed that an acceptable recording could still be recorded from several interspaces, as it was impossible to tell

where one was crossing the septum even if the position on the posterior wall was defined, and this induced variability into the measurement. Accordingly, they proposed a method for determining a standard interspace in each patient. The problem of error in spatial orientation may be more serious in newborns.[86] The study of Pumbo et al.,[81] finding that different observers, making their own measurements on the same subject, had only a small difference in their results, indicates that whether or not different axes are being measured in different subjects, at least the measurement in an individual patient is reproducible.

Even if one can in fact measure the minor axis with UCG, what of the other assumptions? First there are reports of the anterioriposterior and lateral minor axes not being equal in children[25] and adults[86] though this difference has not appeared to be great. Then there are many reports of variation in the ratio of major to minor axis in different patients. Meyer et al.,[76] found that there were different ventricular configurations in children with different types of congenital heart disease. In the failing (or volume overloaded) heart the ventricle became more spherical.[78,81,94,89] This change decreases the major and minor axis ratio and leads to overestimation of LV volume by the UCG method.[95,81,79,96] Because this sphericity occurs with increased LVIDd, it has been proposed that different constants for the ratio of major to minor axis be used for larger LVIDd's. Similarly it has been proposed that different constants for the ratio be used for different

types of congenital heart disease.[76] Finally the shape of the LV may change from diastole to systole. Lewis and Sandler[85] found that during systole the minor axis changed by 27.5% while the major axis changed by 13%. Meyer et al.,[76] found the major axis changed by only 6.9% in children and proposed a different formula for SV from that for adults. Several authors have found that in ventricles with abnormally contracting segments secondary to ASCUD that the diastolic volume predicted by UCG may be accurate but the systolic volume will be inaccurate because of the irregular shape of the ventricle.[89,95,98]

Having knocked all of the theoretic underpinnings out from under the calculation of ventricular volume from echocardiography, let us take heart in the strong empiric correlations that have been found with angiography and proceed to find what physiologic changes in LV pump function can be detected by these echocardiographic measures.* Myerowitz et al.,[92] found in dogs that propranalol and aortic constriction increase LVIDd. On the other hand increased heart rate with pacing or increased heart rate with pacing and isoproteranol both decrease LVIDd. Bargraff and Parker[106] found that decreasing blood pressure with amul nitrate or nitroglycerine lead to a significant decrease in UCG determined EDV and ESV in normal subjects. They found a significant decrease in UCG determined

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*Lest one should think he can get off this easily, it must be pointed out that the regression formula for prediction of L.V. volume differ considerably from author to author and will allow the calculation of markedly different volume from a given echocardiographic LVID.[90]

S.V. after nitroglycerine. Redwood et al.,[105] also found a significant decrease in LVIDd and LVIDs with nitroglycerine. They found the upward tilt and phenylephrine, increase blood pressure and significantly increase LVIDd. In patients with atrial fibrillation, LVIDd was correlated with R-R interval, i.e. greater preload. Thus it appears that with all its limitations, echocardiographically determined ventricular volumes can detect alterations in L.V. pump function.

There are a number of indices of cardiac function which can be determined by applying different methods of measurement and calculation to the same UCG's used to determine ventricular volumes. Ejection fractions (EF) can be calculated from the same LVID described above. Some authors have taken the volumes calculated as a cube function of LVID and used the equation (EDV-ESV) $\div$ EDV = EF.[87,91,80] Others have determined a direct relationship between EF and the relative change of LVID and used the formula (LVIDd - LVIDs) $\div$ LVIDd = K(EF).[96,90,79] Myer et al.,[96] noting that the relative change of minor and major axes with systole is different in children than adults have proposed a more complex formula for the relationship of E.F. to change in LVID in children. Another adapted cineangiographic index, the mean velocity of circumferential fiber shortening (VCF), can be calculated from the LVID and the LVET as:

$$VCF = (\pi\, LVIDd - \pi\, LVID_S) \div (LVIDd)(LVET)$$

$$= (LVIDd - LVID_S) \div LVIDd \times LVET$$

It is a measurement of the rate of shortening of the L.V. minor

circumference and is expressed as circumference/second.[101] In adults LVET has been obtained as the interval from the peak of the QRS complex to the smallest $LVID_s$ minus 50 milliseconds for PEP.[88] Salin, et al.,[86] have noted from multiple crystal cross sectioned studies that the mitral valve hangs further into the L.V. in newborns than in older children or adults. Accordingly they measure the LVID is the plane of maximal excursion of the anterior leaflet of the mitral valve. Then they used the mitral valve to time end diastole and end systole. They make no correction for the ICT and isovalomic relaxation periods thus included in LVET. The final indice to be mentioned will be the first echocardiographic technique developed to assess L.V. function.[89] Posterior wall velocity (PWV) is a measure of the rate of anterior motion of the L.V. wall which echocardiography is particularly suited to measure because of its sampling rate of 1000/sec.[89] It can be calculated as mean PWV = total excursion of the L.V. posterior wall/LVET or maximum PWV = slope of a tangent to the steepest area of anterior motion.[88] The recording is probably best made at the level used to record LVID.

The results of echocardiography and cineangiographic determination of these indices in the same patients have been compared for each of these techniques. Ejection fraction is probably the best studied indice. Some authors have found strong a correlation between UCG and angiographic determinations of EF using the EDV - ESV/EDV formula for echo EF.[88,91,81] Others have used the simpler LVIDd - $LVID_s$/LVIDd formula and

obtained comparable results.[79,80] Pumbo et al.,[81] and Fortnin, et al.,[79] have found the use of a cube function of LVID to determine volume, to provide a slightly better correlation when both formulas were applied to the same data. Echocardiographic determinations of VCF have been shown to correlate perhaps even more strongly (r up to 0.97) with angiographic results in adults and newborns.[88,86] Cooper et al.,[88] compared mean and maximum PWV with angiographic determinations of EF and UCF and found only weak correlations (r = 0.40 - 0.51).

There are a number of theoretical advantages of these indices over echocardiographic volume determinations. Since it is not necessary to use a cube function of LVID to determine these indices, any error in the measurement need not be also cubed.[86,90] Then both EF and VCF are standardized for LVIDd and this has two benefits. First it becomes possible to make quantitative comparisons of LV function between groups with different sized ventricles.[101] Second, if the LVID is somewhat oblique to the true minor axis, i.e. it is equal to a constant times the true minor axis, the constant relating the two will drop out in the calculation.[90,86] Accordingly, Sohn et al.,[86] have found in newborns that values for VCF obtained from slightly different areas of the mid portion of the same ventricle are essentially identical. This is in contrast to their finding regarding volume calculations in newborns noted above. These latter two considerations would presumably apply to PWV as they also do not necessitate the calculation of volumes or the measurement of a particular internal dimension.

What do these indices reveal about cardiac function? Chronic volume overload (increased preload) in both children and adults has been found to increase EDV and ESV proportionately so that SV remains a constant percent of EDV, i.e. EF remains normal.[104,84] Adults and children with chronically increased afterload may also maintain normal EF.[104,100] In these cases, apparently the heart volumes remain basically normal.[104] Decreased EF which is caused by a disproportionate increase in ESV is considered evidence of decreased myocardial performance.[104] This occurs in patients with cardiomyopathy and coronary otherosclerosis and in general is associated with and increase in EDV.[104,84] Accordingly, UCG determined EF, has been shown to distinguish between patients with congestive heart failure and those with mitral stenasis or compensated volume overload. There is evidence however that EF may not reflect a contractile state in patients with a decreased preload secondary to mitral regurgitation which likely tends to increase EF.[101] In a recent editorial Ross and Peterson concluded that angiographic VCF "provides at present the most reliable measure of vasal contractility in the individual patient."[102,p.437] There is evidence in chronically volume overloaded dogs and in men with chronically altered pre and afterload, that VCF reflects contractile state rather than the pump functions which are sensitive to these alterations.[101,102] With acute alterations in pre and afterloads, the relationship between VCF and the contractile state is less consistent.[102,105] VCF is highly correlated with age and R-R intervals in infants and children.[99]

It also seems to be effected by decreased afterload secondary to severe mitral regurgitation,[87] though perhaps not as drastically as EF is effected.[88] UCG measured VCF in infants and children has been shown to be significantly decreased from normals in patients with myocardial disease but not significantly decreased from normals in patients with pressure overload.[99] Cooper et al.,[88] also found UCG VCF differentiated very accurately between normals and patients with decreased myocardial performance while UCG EF did not differentiate quite as accurately. Sahn, et al., in regards to newborns[86] and Paraskos, in regards to adults,[87] have concluded that UCG determined VCF will be especially valuable for the serial determination of LV performance. PWV's have been reported to be sensitive to changes in LV performance secondary to exercise, vasoactive drugs, myocardial infarction and cardiac transplants.[88,87] They have proved to be of some value in following individual patients,[89] but their ability to distinguish consistently between normal and abnormal myocardial performance has been questioned.[88] It may be concluded then that these indices tend to reflect contractility (to a lesser or greater extent) under stable conditions. The relationship possibly being obscured by acute changes in pre and afterload.

If parameters of pump function and contractility, discussed in this section, could be determined in fetuses, what changes might they be expected to undergo during hypoxic stress? As we have seen the increase in blood pressure would immediately decrease SV. This decreased SV appears to continue with

chronically increased blood pressure.[3] If the ventricle behaved as that of a child, the EDV might be expected to increase transiently and return to normal through homeometric autoregulation.[104] This initial increase would be expected to be most marked if umbilical cord occlusion had occurred. The fetal ventricle, however, is not like that of a child in its compliance, Starling curve, and ability to maintain SV in the face of chronic preoverload. Thus this change in EDV is conjectural. However, as the ventricles begin to fail secondary to the metabolic insult of prolonged or increased hypoxia or acidosis, the EDV would be expected to increase. The indices of contractility; EF, VCF and PWV, might be expected to increase initially secondary to the predominant adrenergic response to mild or transient hypoxia. Then as hypoxia continued or became more severe the decreased contractility secondary to predominant vagal discharge, hypoxia, and acidosis would be expected to decrease these indices. The acute increase in afterload might, however, prevent these indices from increasing with the initial increase of contractility.

Measurement Indices of Cardiac Function in the Human Fetus

Now that some of the noninvasively obtained indices of cardiac function have been reviewed, the possibility of measuring these parameters in the fetus will be investigated.

Perhaps the first measurement of fetal cardiac activity, aside from auscultation, was the recording of a fetal EKG (FEKG) in 1906.[74] This was followed two years later by the recording of a fetal phonocardiogram (FPCG).[4] It wasn't, however, until 1941 that the two cardiograms were recorded simultaneously.[122] Since that time there have been a number of studies recording the two simultaneously and examining, Q-S, Q-S_2, and S_1-S_2.[74,115,55] The FEKG is currently measured from leads on the maternal abdomen, or after the rupture of membranes during labor, from a lead attached to the fetal scalp. The abdominal leads generally produce only an R wave so that the intervals studied are altered slightly. The fetal EKG is not recordable until the seventeenth to eighteenth week of gestation.[139] More recently the Dappler technique has been developed to detect fetal heart beats. It is reliable after twelve weeks and has become the accepted technique of monitoring fetal heart rate.[120]

The use of the Dappler technique, the recording of the change in frequency of a continuous wave ultrasonic beam reflecting off a moving structure, has also been used to identify valve motion. In 1961, Yoshida et al.,[113] first reported the temporal localization of the opening and closing of the semilunar and atrioventricular valves. They recorded a rather

high frequency band of the Dappler output between 500-1000 Hz and noted a number of discrete signals. These were shown to be secondary to valve opening and closing by their temporal location relative to simultaneous EKG and PCG. In the dog, this was shown by applying the transducer to the surface of the exposed heart and finding the appropriately timed high frequency signals to occur over the valves. In 1971, Murata et al., applied this technique to the human fetus. Simultaneously using a Dappler with 800 Hz high pass filter FEKG and PCG they were able to record Q-A_o (or PEP), A_5 A_c (or LVET), and A_c-A_o (or ICT). These were apparently done during labor. Results are shown in Table I. Organ et al.,[117] did a similar study during labor using a band pass filtered Dappler and scalp FEKG. He obtained aortic opening in 77% of the subjects, and aortic opening with mitral valve closing in 36% of the subjects (Table I). Other valve motions were less frequently recorded. The timing of aortic opening was stable from beat to beat and over large periods of time so that PEP calculated from it was felt to be reliable. Murata and Martin[118] also did a study during labor employing a scalp lead, FEKG and a band pass filtered dappler. They were able to measure Q wave to aortic opening (Q-A_o), mitral closure to aortic opening (M_c-A_o), and aortic opening to closing (A_o-A_c) [see table 1]. Later Murata, Skenone, and Martin[73] measured PEP in the last half of the third trimester of uncomplicated pregnancies using an abdominal FEKG and band pass filtered dappler. These results were approximately ten milliseconds shorter than the

intrapartum values. Hon, et al.,[120] and Goodlin, et al.,[116] have reported developing recorders which will continuously display the R to aortic opening interval during labor. However, the accuracy of individual measurements and the percentage of cases in which they may be obtained is open to question.[116,120] It should also be noted that measurements from abdominal FEKGs and from these machines are most easily done from the R wave and therefore are not strictly comparable to STI measured from the Q wave.[116] Finally it should be noted that Goodlin's group[115 + 55] has attempted to measure STI's during labor by employing a blood volume pulse (BVP) obtained with a photoelectric scalp probe and using this pulse as an analog of the carotid pulse (Table 1). They have, however, reported that the BVP is quite variable in its timing and is not often obtainable during stress because of vasoconstriction.[116]

There are a number of problems with the filtered dappler method of determining aortic valve opening and closing Yashida et al.,[113] in their original article noted that the semilunar valve is so small a target that it requires a limited site of the transducer and a limited direction of the ultrasonic beam. This would obviously be a larger problem in the fetus when cardiac orientation is unknown and the fetus may be moving. Murata and Martin[118] also found that high amplitude signals for a particular valve could be recorded only for a very narrow sector. Organ et al.,[117] noted that the valve being recorded would often change more than once over the course of a minute. Goodlin et al., found aortic opening difficult to follow during

labor and felt that the variability in timing of the dappler signal, even without obvious material or transducer motion made the dappler technique "unsuitable for determining STI's."[55, p.299] The only way to identify which valve is being recorded with a dappler in the fetus is by its timing. It seems to be circular reasoning to identify a valve by the timing of the dappler signal it creates and then judge this timing as normal or abnormal. This problem appears when Goodlin, et al., propose an electronic blocking period to eliminate dappler signals from mitral closure and this period spills over into aortic opening.[116] Fig. 4,p.72. Even if it is possible to distinguish semilunar from atrioventricular valve motion, it is impossible to distinguish aortic opening from pulmonary valve motion.[117] This may be important as some authors have found right and left ventricular pre and afterload to be different in the fetus.[23] Then there is a variable time delay in dappler recording of valve motion depending on the angle at which the beam strikes the valve. Murata and Martin[118] found this time delay to vary as much as three milliseconds in a model but felt there would be less variation within the sector producing good dappler signals. The in vivo situation is unknown. Finally the continuous wave of the dappler technique gives the fetus greater energy exposure than that produced by pulsed ultrasound technique though this may be of little importance.[117,109]

In recent years pulsed ultrasound with distance (A mode) and distance-time (m mode) representations, has been used to

TABLE 1

Authors	PEP(sec.)	LVET(sec.)	ICT(sec.)
Intrapartum			
Murata et al.[111]	0.071(S.D.0.0079)	0.177(S.D.0.0124)	0.028(S.D.0.0026)
Organ et al.[117]	0.073(S.D.0.010)		
Goodlin and Lowe[115]	0.064(41-60)	0.220(208-250)	
Goodlin et al.[116]	0.043-0.070		
Murata et al.[118]	0.0700(±0.00238)	varied with rate	0.0294 (±0.00561)
Antepartum			
Murata et al.[73]	0.0623		

record fetal heart motions.[108-112, 121] As such, the technique is essentially the same as that used in adult echocardiography. In 1967, Krachowil and Eisenhut[108] first reported the use of this technique. Using a vaginal transducer they detected fetal heart beats on the A mode as early as seven weeks menstrual age and found it reliable after ten weeks. The next year Bang and Holm rediscovered the technique.[109] They added the use of an m mode recording and using an abdominal transducer they found no error in determining presence or absence of a heart beat in a group of pregnancies between ten and thirty-nine weeks with and without fetal demise. Robinson[110] added the use of a preliminary B scan to locate the fetal thorax. This shortened the time needed for an examination and he found the technique to be without error after the forty-eighth day from the last menstrual period. In 1971, Murata et al.,[111] recorded an m mode fetal UCG with a simultaneous scalp lead FEKG. By comparing these tracings with fetal high pass dappler recording of valve timing, and newborn UCG's, they were able to argue that the structures recorded were the septum and atrioventricular valves though the valves were certainly different in appearance than those of the newborn UCG. Finally in 1972, Winsberg[112] made recordings of the septum and LV endocardium of fetuses in the last trimester. From these he determined LVID. Then using $SV = (LVIDd)^3 - (LVID_s)^3$ he calculated LV output as 109 ml/Kg/min. Assuming LV output equals 55% of CVO and this equals umbilical flow, he found this to agree well with the measurement of umbilical

flow in the human fetus by Assali et al.,[122] at 10-23 weeks as 110 ml/Kg/min. and by Stemberaat term as 75 ml/Kg/min. He also measured the diastolic thickening of the LV wall to be 6 mm.

Besides recording fetal heart rate, what parameter of fetal cardiac function will this new technique allow one to measure? As just discussed, fetal cardiac volumes, EDV, ESV, SV and cardiac output, can be calculated when accepable tracings are made. These same tracings should allow calculation of EF and PWV. If a fairly clear mitral valve or a simultaneous FEKG could be obtained for timing purposes VCF could be calculated. Finally if one could obtain a clear picture of the aortic or pulmonic valve with a simultaneous FEKG, STI's could be calculated.

Why would one wish to measure such parameters in the fetus? As we have seen there are a number of maternal conditions and complications of labor which can produce fetal hypoxia. In monkeys it has been shown that extended periods of partial asphyxia can produce brain damage similar to that found in some human fetuses.[2a] Accordingly, some authors have suggested that the primary cause of many cases of mental retardation and spastic dipelegia formerly attributed to birth injury may be a period of severe anoxia preceding the onset of labor.[16] Some authors noting that the fetal mortality rates in various of these maternal diseases rise as pregnancy lengthens, have proposed early delivery of pregnancies in which the fetus is undergoing pronounced hypoxia.[17,18] But one needs to know when and in which individual cases this stress is occurring.

As Kelley has said, "There is a pressing need to be able to ascertain when a fetus is slowly deteriorating in utero due to maternal disease. Termination of pregnancies in situations such as erythroblastosis, diabetes and toxemia would be much easier if these were an objective index of fetal distress."[74, p.1148] As has been shown, many of the parameters which fetal UCG's may allow one to measure, are altered by fetal hypoxia. Perhaps one or a combination of them, could be the needed index. These UCG derived parameters might also tell us about the effect on the fetal heart, of reserpine and ganglion blocking agents used in the treatment of the hypertensive or toxemic mother. Finally, as Dawes has noted "much of our knowledge of fetal physiology is based on observations made under abnormal conditions. These echocardiographic techniques might allow us to investigate fetal cardiovascular physiology in an essentially undisturbed state."[1,p.115]

Of course, other parameters of fetal cardiac function have already been investigated in regard to fetal distress. The patterns of fetal heart rate (FHR) deceleration during uterine contraction in labor have been found to be of ominous and benign types. The pattern of late deceleration believed to be caused by fetal hypoxia has been associated with fetal acidosis, damage, and death, as well as newborn depression and respiratory distress syndrome.[2] When recognition of these FHR patterns was used for the diagnosis and management of fetal distress in high risk pregnancies, there was a decreased incidence of intrapartum fetal mortality.

Baseline fetal heart rate variability reflects the integrity of the nervous mechanism controlling the fetal heart.[29] As such, it indicates the ability of the fetus to cope with any stress it is undergoing.[115] Loss of this variability has been associated with severe fetal distress, intrauterine growth retardation and newborns with acidosis and low Apgar scores.[2b] Some authors have found it helpful antepartally, in assessing placental insufficiency while awaiting urine estrial determinations.[2b] One non-cardiac parameter now used to assess intrapartum fetal condition, fetal scalp blood gases has obvious correlations with fetal oxygenation and cardiovascular status.

If then one can follow FHR variability antepartum and add FHR deceleration patterns and scalp blood gases during labor, what need have we of other parameters of cardiovascular function? These are indications that some of the UCG measured parameters may be superior indicators of fetal stress. Hon has noted that intrapartum conditions expected to produce fetal hypoxia do not necessarily produce an immediate decrease in FHR.[2a] Organ et al., found hypoxia in the exteriorized fetal lamb produced a consistent decrease in PEP which was proportionate to the severity of hypoxia. FHR, on the other hand responded quite variably, decreasing initially in 55% and increasing initially in 45% though initial decrease tended to be associated with more severe hypoxia. STI's may be measured by dappler but the UCG might offer some advantages. It would not only differentiate between the atrioventricular and semi-

lunar valves but would differentiate between aortic and pulmonary valves. It could eliminate the variable time delay with variation in beam angle and it would involve a lower energy exposure to the fetus. Mahon et al.[22] found that as their fetal preparation deteriorated, CVO and SV decreased while FHR remained stable. They concluded "rate alone is an imprecise measure of fetal deterioration."[22, p.197] In a more chronic experiment Rudolph also found that CVO decreased as a result of increasing pulmonary artery constriction without changes in heart rate.[59] Finally, in the fetal lamb, hemorrhage and exteriorization with attendant decrease in placental flow have both been associated with an increase in umbilical venous and therefore fetal arterial PO_2.[20,7] This brought Heyman and Rudolph to conclude that "the monitoring of fetal blood gases and the status of acid base balance may be misleading."[20,p.7]

It appears then many of the indices of cardiac function determined by UCG in adults, children, and newborns could be quite valuable parameters to assess in the fetus. The door has been opened by the advent of fetal echocardiography. What is now needed is a refinement of this technique to a level allowing measurement of these indices. The qualitative and quantitative refinement of the technique of fetal echocardiography was, then, the goal of the research to be presented now.

Materials and Methods

Fetal echocardiograms were attempted in 45 pregnant women referred for a variety of reasons to the Obstetrics and Gynecology ultrasound lab for a variety of reasons for uterine B scans. Only pregnancies greater than 20 weeks gestation were studied. The women were studied supine or occasionally lying on one side. After the abdomen was prepped mineral oil or Aquasonic transmission gel a scan of the abdomen with the Picker EDC system using grey scale was made. Occasionally the scan was done with the ADR real time ultrasound machine instead. From this scan the position of the fetus in relation to the abdominal wall and placenta, and the location of the fetal heart were determined.

Next, after cleaning small areas on the abdomen alcohol and lightly abraiding the skin 2 pregelled silver/ silverchloride FEKG electrode pads were placed in a vertical line at the center of the abdomen or over the placenta. A third suction cup electrode which would later be converted to a pad was placed between the other two. The suction cup electrode could be moved about the abdomen if no FEKG could be obtained in the original position. These electrodes feed into a prototypic chorometric model 415 abdominal FEKG processor.

An attempt was then made to record a fetal echocardiogram. As the position and orientation of the fetal thorax was now known when possible the transducer was placed and

angled so that the ultrasonic beam was perpendicular to the thorax along the left sternal border. Thus an approximation of the transducer position and angulation used in adults and children was made. When possible the ultrasonic beam was also passed in through a placenta free sector. In this position the fetal thorax was searched until a mobile A mode peak usually corresponding to the ring of one of the atrioventricular valves was located. This signal was centered on the A mode screen and the scale maximally expanded. When the left ventricular posterior wall pericardium and endocardium and the septum could be identified recordings were taken in the plane of maximal excursion of the anterior leaflet of the mitral valve which included both leaflets or just caudal and lateral to this where fragments of both leaflets of the mitral valve could be identified. Then a mitral-aortic sweep was performed and an attempt to record the aortic valve made (Fig. 3).

Two ultrasound machines were used. One was a Unirad 100 series diagnostic echoscope system in which results were displayed on a storage screen and conventionally photographed or were played across a nonstorage screen and recorded with time lapse photography. The other was a Picker echoview 10 main frame with a Honeywell 1856 strip chart recorder and a Picker 611 storage M mode slave scope. The EKG amplifier of the Picker mainframe was modified to accept the output of the Chorometrics FEKG processor so that the FEKG could be simultaneously printed on the strip chart. At the end of the study

a Jerry rigged variable time delay was added to the Honeywell strip chart recorded so that the recording could be delayed to begin at the anterior wall of the heart and then the time/cm control used to expand the area beyond maximally.

Measurements and Calculations

STI

The preejection period was not obtainable in this experiment. The left ventricular ejection time was measured from the echocardiographically determined aortic opening to aortic closing according to the method of Hirschfeld et al. (Fig. 4).[72] Measurements for each individual were made over 4 to 6 cycles and averaged. The results are listed in Table 2.

Echocardiographic Indices

According to the method of Sahn et al. the left ventricular internal diameter at end diastole (LVIDd) was taken at the point of closure of the mitral valve and the left ventricular internal diameter at end systole (LVIDs) was taken at the point of opening of the mitral valve (Fig. 5).[86] If no clear valve was present the LVIDd was measured as the largest diameter between the septum and left ventricular wall and the LVIDs was measured at their closest approach according to the method of Paraskos et al.[87] The ejection time was taken as the period from LVIDd to LVIDs. Four to six consecutive beats were measured for each individual and the raw numbers

for diameters and ejection times were converted to centimeters and milliseconds with the use of the timing and distance markers on the recordings.

From these measurements it was possible to calculate end diastolic volume (EDV), end systolic volume (ESV), stroke volume (SV), ejection fraction (EF), relative change of LVID with systole (% delta S), and mean velocity of circumferential fiber shortening (VCF). The calculations of ventricular volumes were made from a number of different formulae. According to the equations of Popp and Harrison described above:

$V = LVID^3$ where V = left ventricular volume

therefor $EDV = LVIDd^3$

$ESV = LVIDs^3$

$SV = EDV-ESV$

and $EF = SV/EDV$

The regression formulae derived by Pumbo et al.[81] and Fortnin et al.[79] in adults and Meyer et al.[76] in children for these volumes were also used. According to Fortnin et al.[79] delta S was calculated as:

$$\%\text{delta S} = (LVIDd-LVIDs)/LVIDd$$

Finally, VCF was calculated as:

VCF = (LVIDd-LVIDs)/(LVIDd)(ejection time) according to Sahn et al.[86]

Fetal left ventricular output (LVO) and left ventricular output per kilogram (LVO/Kg) were also computed. Left ventricular output was calculated as SV times HR, rate being determined from a beat to beat interval within the group of

beats measured. Left ventricular output per kilogram was calculated by dividing LVO by an estimate of fetal weight made from gestational age (Table 4).[112,123]

The same tracings were used to obtain mean and maximum posterior wall velocities (mean and max. PWV). According to Cooper et al. mean PWV was calculated by dividing total excursion of the posterior wall from end diastole to end systole by ejection time.[86] Maximum PWV was taken as the slope in cm/sec of a tangent to the steepest part of anterior movement of the left ventricular posterior wall (Fig. 6).[86]

The results of all of the measurements of echocardiographic indices are listed in Table 3.

Using a Hewlett Packard 98304 computer, means and standard deviations (SD) were calculated for the STI and for each of the echocardiographic indices. Left ventricular ejection time was regressed on rate and a correlation coefficient calculated. Each of the echocardiographic indices was regressed on rate, gestational age, and estimated fetal weight and correlation coefficients calculated. In addition, a number of echocardiographic indices were regressed on one another. Results of these computations are listed in Tables 2, 5, and 6.

Figure 3 Fetal echocardiogram: aortic-mitral sweep.

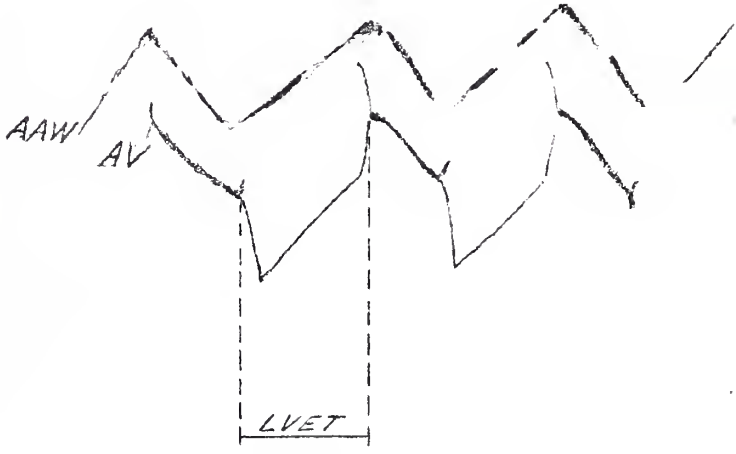
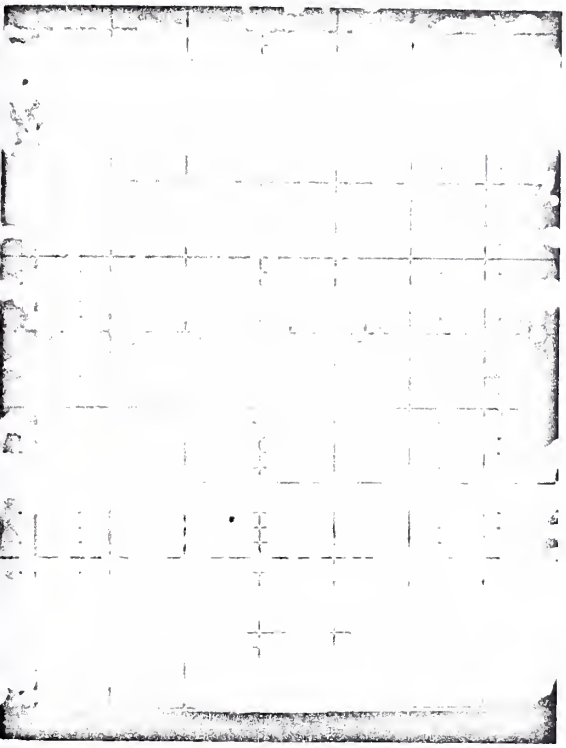


Figure 4 Fetal echocardiogram: echocardiographic determination of LVET. AAW = anterior aortic wall and AV = aotic valve.



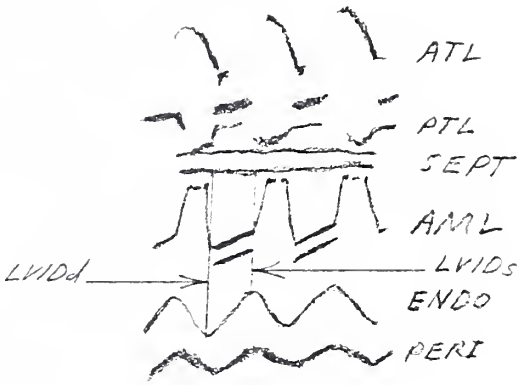


Figure 5 Fetal echocardiogram: measurement of LVIDd and LVIDs from a tracing with a mitral valve. ATL = anterior tricuspid leaflet, PTL = posterior tricuspid leaflet, SEPT = septum, AML = anterior mitral leaflet, ENDO = endocardium, and PERI = pericardium.

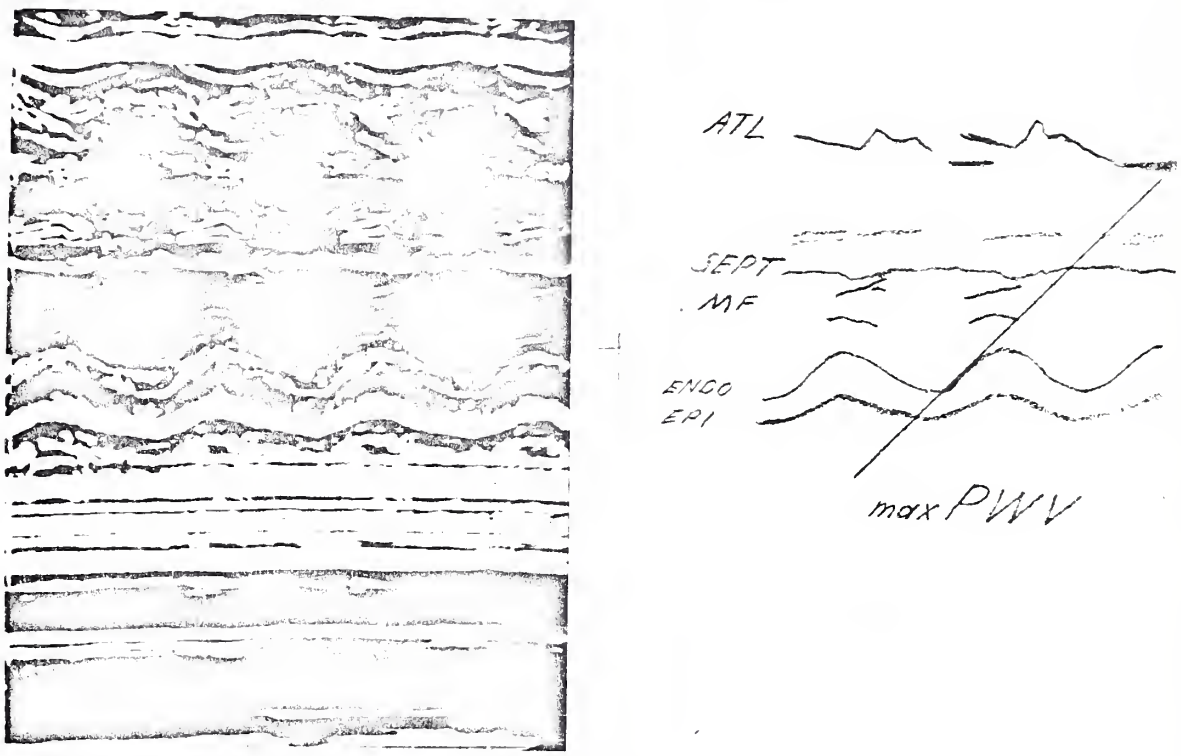


Figure 6 Fetal echocardiogram: echocardiographically determined max PWV. ATL = anterior tricuspid leaflet, SEPT = septum, MF = mitral fragments, END = endocardium, and PERI = pericardium.

Results

Table 2 lists the results of the fetal LVET measurements. The mean LVET was 192.1 with SD 11.23. The echocardiographically determined LVET of one newborn is also listed for comparison. This value is within one SD of the fetal mean. The fact that the fetal LVET's were recorded at sweep speeds of 50 mm/sec rather than the standard 100 mm/sec makes them less valuable for distinguishing between groups than they could be. The strong positive correlation between LVET and rate is surprising as a negative correlation would be expected. With such a small number of samples the reliability of this result is extremely questionable.

Table 3 displays the individual and mean values for the battery of echocardiographic indices measured. Only the ventricular volumes calculated from the simple cube functions of Popp and Harrison are listed because all of the formulae derived from regression equations of studies of the larger ventricles of children and adults produced negative results. B.B.B. was the child born to S.B. His echocardiographic indices at one day of life are also presented for comparison. He falls more than four S.D. above the fetal mean for LVIDd, EDV, SV, and LVO, while he is within one standard deviation for EF. It was not possible to calculate VCF from the recording of S.B. The LVO/Kg. of the fetus of patient A.R. is far above the range of the other fetuses. It appears, then, to be in error. Two possible sources for this error are dating

as it was done from last menstrual period in this case, and the calculated SV as this case has the highest EF. The mean LVO/Kg. and its S.D. are perhaps falsely elevated by this case. Mean LVO/Kg. in the other four cases is 86.9 ml./Kg./min. with a much narrower S.D. of 14.62. The heart rate, gestational age determined from biparietal diameter or last menstrual period, and an estimate of fetal based on gestational age for the subjects of Table 3 are presented in Table 4.

Table 5 is a correlation matrix of the echocardiographic indices on HR, gestational age, and fetal weight. Not surprisingly LVIDd, EDV, SV and LVO all had strong positive correlations with gestational age. Also logically the volumes EDV, SV, and LVO were even more strongly correlated with estimated fetal weight. The correlation between EDV and fetal weight being an excellent $r = 0.8167$ respectively. Quite surprisingly the indices EF, 90 delta S, VCF and max PWV were all strongly negatively correlated with gestation age. The negative correlation between these indices and fetal weight being mildly weaker. The LVO/Kg. had a strong negative correlation with gestational age and fetal weight, $r = -0.7698$ and $r = -0.7163$ respectively. This was partially due to the very high value for LVO/Kg. in the youngest fetus A.R. However the correlation of LVO/Kg. on age is still $r = -0.6830$ if the value for A.R. is excluded.

Table 6 lists the correlation between rate and age, and a number of interesting correlations between various echo-

cardiographic parameters. As expected HR was negatively correlated with gestational age. Left ventricular output and was correlated $r = 0.9905$ with SV and only $r = 0.2331$ with rate indicating that the fetal LVO varied more due to changes in SV than to changes in rate. However, LVO/Kg. (i.e. corrected for changes in fetal and therefore ventricular size) is strongly correlated with rate ($r = 0.8656$) and is not correlated SV ($r = 0.0302$).

TABLE 2

STI

	Patient	LVET (m sec)	Rate (B.P.M.)
Newborn			
	B.G.H.	198.0	151
Fetal			
	K.A.	184.5	115
	C.P.	186.8	138
	A.W.	205.0	158
	Mean and	192.1	
	Standard Deviation	11.23	
	Correlation of LVET on rate		0.8955

TABLE 3

Echocardiographic Indices

Patients	LVIDd (cm)	LVIDs (cm)	EDV (cc)	SV (cc)	EF
Newborn					
B.B.B. (S.B.)	1.80	1.19	5.79	4.096	0.706
Fetal					
A.N.	1.36	0.84	2.50	1.91	0.763
J.H.	1.36	0.97	2.50	1.61	0.647
K.T.	1.02	0.53	1.10	0.93	0.801
A.R.	1.18	0.57	1.64	1.46	0.890
S.B.	1.27	0.97	2.05	1.12	0.596
Fetal mean	1.24	0.77	1.96	1.41	0.729
S.D.	0.139	0.213	0.598	0.389	0.135

Patients	% delta S	VCF (circ/sec)	max PWV (cm/sec)	LVO (cc/min)	LVO/Kg (cc/min/Kg)
Newborn					
B.B.B. (S.B.)	0.337		3.037	565.2	243.6
Fetal					
A.N.	0.379	2.316	4.263	263.4	94.92
J.H.	0.294	1.372	1.984	219.4	65.01
K.T.	0.485	2.034	2.870	124.5	92.22
A.R.	0.517	3.327	6.715	215.2	286.9
S.B.	0.233		2.492	159.6	95.25
Fetal mean	0.382	2.262	3.665	205.6	134.8
S.D.	0.121	0.813	1.904	58.31	102.3

TABLE 4

Further Parameters on Echocardiogram Patients

Patient	H.R.	Gestational age	Estimated weight
newborn	(B.P.M.)	(wks)	(Kg.)
B.B.B. (S.B.)	138	38	2.320
fetal			
A.N.	138	38.5	2.775
J.H.	136	41.0	3.375
K.T.	134	30.5	1.350
A.R.	148	26.0	0.750
S.B.	142	32.5	1.675

TABLE 5

Correlations Matrix

	Heart Rate	Gestational Age	Estimated Weight
LVIDd	0.5124	0.7466	0.7269
EDV	-0.0333	0.8000	0.8144
SV	0.0982	0.5741	0.6013
EF	0.2513	-0.5160	-0.4772
% delta S	0.1937	-0.6277	-0.5986
VCF	0.8800	-0.8074	-0.7956
maximum pwv	0.8167	-0.6585	-0.5775
LVO	0.2331	0.4676	0.5087
LVO/Kg.	0.8656	-0.7698	-0.7163

TABLE 6

Other Correlations

LVO/Kg.	and S.V.	.0302
LVO	and S.V.	0.9905
Rate	and age	-0.6206

	VCF	EF	% delta S
Maximum PWV	0.9854	0.7749	0.6955

Discussion

A number of problems relating to the echocardiographic machine, transducers and methods of recording the results were encountered during this study. Of the two machines, the Unirad appeared to have a couple of advantages. It seemed possible to more consistently record low amplitude or closely spaced echoes with this machine, and the m mode storage scope displayed more detail and held the image better. The slave scope on the Picker machine tended to blend closely spaced echoes, not record low amplitude echoes, and not retain the image at all when sweep speed or scale were increased to the level necessary for good visualization. Because of the depth, small size and mobility of the fetal heart, it would seem that a long focus, high frequency and perhaps larger diameter transducer would be best for this study. A 5 mega hertz (mHz) transducer generally did not penetrate adequately. The 2.25 mHz transducers available did not always seem to provide the resolution necessary and their medium focus was occasionally too short. There are now on hand a number of long focus, larger diameter transducers with frequency of up to 3.5 mHz. The most significant of these problems was the difficulty in the recording of the echocardiogram. Photographing the Unirad m mode storage scope lost some resolution at sweep speeds of 25 mm/sec. and was clearly unacceptable at 100 mm/sec, the speed necessary for STI. Time lapse photography from this scope

in a nonstorage mode improved the resolution and allowed high sweep speeds. However, this method was technically cumbersome, deprived one of the M mode display, and could only record approximately one beat at a time at high sweep speeds, thus preventing measurements from multiple consecutive beats. The Honeywell strip chart of the Picker machine was superior in terms of resolution, usable sweep speeds, and technical ease of operation. For the duration of the experiment it was not possible to delay the beginning of the recording. Thus, the strip chart always began its recording at the abdominal surface. Because a scale of one to one produced a recording extending to about 10 cm depth and the fetal heart generally lay between 7 and 13 cm depth, attempts to expand to even a one to one scale often dropped the fetal heart out of the area recorded. A variable delay has now been Jerry-rigged onto the strip chart.

There are a number of methodologic difficulties which have been noted by other authors and are theoretically remediable. First it was often possible to locate value motion on the A mode when none could be recorded on the M mode. Bang has also noted similar problems.[107] The Picker representatives have recently attempted to adjust their machine to record lower amplitude echoes on the M mode. It became standard procedure to determine the fetal orientation and cardiac location by real time on conventional B scan of the abdomen. This saved time in locating the heart. It also aided in the interpretation of the UCG's obtained, which could be quite

bizarre depending on the orientation of the heart relative to the ultrasound beam.

The time available for the exam proved to be a significant problem. Most of the women examined had just been through a 30-45 minute diagnostic B scan and were becoming tired of lying prone. Also, the fetus seemed to become more active as the period of lying prone increased (or perhaps secondary to some element of the B scan itself). It was because of the time necessary to obtain a fetal EKG, and the low success rate, about 33%, that this procedure was dropped.

There were a number of irremedial problems related to fetal and maternal characteristics. The orientation of many fetuses was such that it was impossible to record a satisfactory UCG. It seemed impossible to get more than sinusoidal motion of what appears to be semilunar valve rings in fetuses less than 25 weeks. Werisberg has also noted both of these problems.[112] Some fetuses were so active it was impossible to keep the ultrasonic beam on the heart long enough to get oriented; set gain, T.G.C., position, and scale controls; and record the result. Finally anterior placentas markedly decrease the penetration which could be achieved even at highest gain settings.

All of these difficulties then reduced the percentage of acceptable studies and only 5 from which echocardiographic indices could be determined and 3 from which STI could be determined were obtained out of 45 studies.

These are a few theoretic problems concerning the

measurement of echocardiographic indices in the fetus. The problem of measuring a standardized LVID from patient to patient is accentuated in the fetus. It is obviously impossible to obtain the standardized interspace suggested by Popp et al.,[89] and the extent to which the LVID measured can be standardized solely by relationships to internal cardiac anatomy is questionable. The depth of the fetal heart also presents a problem as the inherent random error if any measurement made by ultrasound increases with distance from the transducer. Close approximation of chordal and endocardial echoes in the small fetal heart make differentiation between the two more difficult.[112] The small size of the fetal ventricle also makes errors due to these problems relatively more significant than in the larger adult heart. This problem led Sahn to believe that volume determination in the small newborn heart were probably unreliable.[86] The internal cardiac landmarks will, however, allow one to measure the same LVID in the same patient, from day to day.[90] Thus it should be reliable in following the course of a single patient, even if it doesn't allow comparison to a norm, and in obstetrics what is needed is a parameter which can be monitored from day to day to indicate deteriorating fetal status. Finally, UCF, EF and % delta S are corrected for the LVID and thus should partially eliminate the between individual variation due to differences in the diameter measured.

How do the quantitative results of this experiment compare to those in the literature? As can be seen in Table 7,

TABLE 7

Comparison of the Results of this Study with those of Winsberg[112]

	Winsberg	This Study
LVIDd (cm)	1.31	1.24
LVIDs (cm)	.72	0.77
SV (c.c)	1.85	1.41
$\dot{V}O$ (ml/min)	260	205.6
$\dot{V}O$/Kg (ml/min/Kg)	109	134.8

the mean values for LVIDd, $LVID_s$, SV, LVO and LVO/Kg. are very similar to the values obtained by the only comparable study, that done by Winsberg. As the fetuses were of similar age range (this study: 26-41 weeks, Winsberg's study: 31-40 weeks) this similarity is to be expected and indicates the reproductability of the technique. There are two studies of umbilical flow in the human fetus from which estimates of LVO/Kg might be made. Assali, et al., used a limited caesarean section to expose the cord in pregnancies of 10-28 weeks gestation and obtained an umbilical flow of 110 ml/Kg/min with an electronic flow meter.[124] Stenbera et al. in infants within two minutes of normal delivery found an umbilical flow of 75 ml/Kg/min with a thermodilution technique. If one uses Dawes' data in similarly "exteriorized" lamb fetuses umbilical flow at 57% of CVO approximately equals left ventricular output at 55% of CVO. The left ventricular output/Kg of 134-8 ml/Kg/min in this study is markedly higher than that of Stenbera et al. However, if one rejects the previously mentioned high value for LVO/Kg in subject A.R., the new mean of 89.6 ml/Kg/min falls squarely between the results of these authors. Finally using Rudolph's estimate of LVO as 34% of CVO in the in utero lamb, even the lower estimation of LVO gives a CVO of 270 ml/Kg/min.[3] As expected, this is considerably higher than the cardiac output of the newborn at 164 ml/Kg/min.[112]

There are also some interesting correlations within the data of this experiment. The estimated fetal weights at the end of the period measured were in the ratio of 4.5 to 1.

Therefore, the LVID would be expected to be in the ratio $\sqrt[3]{4.5}$ to $\sqrt[3]{1}$ = 1.6 to 1. The strong correlation between LVID and EDV and estimated fetal weight, r = .7669 and = .8144, indicate that the technique was sensitive enough to detect this growth and that it was in fact measuring a similar LVID from fetus to fetus. The strong negative correlation between the indices of contractility (EF, % delta S, VCF and max PWV) and gestational age is surprising. It is consistent with increasing hypoxia with age and with development of parasympathetic basal discharge proceeding while sympathetic basal discharge has yet to develop. Both of these possibilities have already been raised by the lamb literature. Perhaps the simplest explanation is that this negative correlation is really secondary to the decrease in fetal heart rate with age. The decrease in LVO/Kg with age is inconsistent with the work in fetal lambs. It does agree with the difference between the results of Stenbera et al., and those of Assali et al. However, this difference is likely to be due to differences in technique rather than differences in age. Finally, the extremely strong correlation between max PWV and VCF (r = 0.9854) indicates that maximum PWV may be a valuable indicator of myocardial performance in the fetus.

There are a number of qualitative results to be discussed. Aortic to mitral sweeps and aortic valves of sufficient clarity to allow measurement of LVET were obtained on occasion (Fig. 3), neither of which have been reported previously. It was also possible, particularly with the strip

chart, to obtain mitral and tricuspid valves with two peaks indicating the valve tips had been recorded. Murata et al. were unsuccessful in attempting this[111] and no examples appear in the literature.

This study has, then, had a few very modest successes. A number of indices of cardiovascular function LVET, VCF and max PWV have been measured in the fetus for the first time by echocardiography. The age at which successful studies have been performed, 26 weeks versus 31 weeks, and the proportion of successful studies, 7 out of 45 versus 13 out of 150, have been slightly improved from the previous study.[112] Perhaps most importantly, the qualitative results of fetal echocardiography have been improved somewhat.

What immediate improvements might be made in this technique? The addition of a variable delay to the Honeywell strip chart on the Picker echoview 10 should help. The addition of the system now used in the Unirad 100 series machines which automatically adjusts the area recorded on the strip chart to conform to that seen on the A mode screen would be even better. A storage M mode slave scope that does not lose the image at great expansion or high sweep speed should be acquired. Use of one long focus, large diameter and high frequency transducers may also help. Perhaps, most importantly, the selection of patients solely for fetal echocardiography and the use of a real time scanner to locate the fetal heart should provide considerably more time for the exam and allow the reintroduction of the FEKG. As the fetal ventricles are

similar in shape and pump in parallel,[1] it may be possible and valuable to make the same measurements in the right ventricle that have been made in the left ventricle. There is precedent for this in the original work of Popp et al.[75] Finally, the success rate might be improved if one attempted to make tracings from which max PWV could be measured even when a clear septum and mitral valve could not be obtained.

Looking toward the more distant future, there is a group of machines for producing cross sectional images of the heart which might profitably be applied to the fetus. These machines produce a cross sectional view of the ventricle which in theory should be more accurate at determining ventricular volume and EF than the current single LVID.[90] Also in the fetus, a section through the entire heart might be used to calculate combined ventricular SV and CVO which is more important than individual ventricular output in the fetus. In using an ADR "real time" machine, employing the multiple crystal cross-sectional technique developed by Bom in the lab, we have noted it to be much easier to locate the heart, determine its orientation and follow it during fetal activity, than it is with the traditional echocardiograph. In adults there is a problem with losing the cardiac apex due to chest wall curvature[90] which would be eliminated in the fetus. The sector scanner developed by Walter Henry is another of the cross-sectional techniques which might be adapted to the fetus. In adults, the sector scanned by the machine, does not include the whole ventricle, but with the small and relatively distant

heart of the fetus, the sector would probably include the whole heart. There are three problems to be solved with such techniques in the fetus, defining the endocardium; developing a suitable method of recording; and standardizing the cross-section obtained.

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