## *Editorial*

# Heart Development and Function Before Birth

Physicians have a tendency to characterize the immature heart as merely a miniature adult heart, with size being the primary distinguishing characteristic between young and old. However, this notion is misguided. In fact, the immature heart is an organ with anatomical and physiological differences from that of the mature heart. Many of the studies that have established our knowledge of heart development in the large mammal and influenced our therapeutic decisions for heart treatment in babies, have been performed in immature sheep. We will review several features of heart maturation that have clinical application with examples from sheep.

**Anatomic Features**

Over most of history, it has been believed that the right and left ventricles behave similarly during fetal life. This old idea was derived from Harvey and has been embraced by Pohlman(l), Dawes(2) and St. John-Sutton(3). The reason that scientists have taken this view is that the shapes of the fetal ventricles appear more similar in the fetus than in the adult. This led Dawes to agree with his predecessors that, because two ventricles are filled at the same pressures, beat against similar arterial pressures, and appear to be similar, they should also function similarly. This view became dogma. However, experimental data beginning in the late 1970s showed that the right and left ventricles of fetal heart have differences with important physiological consequence.

When the outputs of the fetal ventricles are simultaneously measured, the volume of blood ejected from the right ventricle (stroke volume) is significantly larger than from the left, with the right ventricle ejecting 55-70% of the combined ventricular output[+](4,5). It is now known that this is because anatomic measurements indicate that the right ventricle is the larger chamber(6). Thus, if the ventricles fill at the same pressure (preload) and eject the same fraction of chamber volume (ejection fraction), the larger right chamber will have the larger stroke volume. These findings are also true for the human fetus(7).

The different stroke volumes of the ventricles suggest other differences in function(8,9). Because of the open ductus arteriosus, the two ventricles of the fetus are subjected to similar increases in pressure if the pulmonary arterial pressure and aortic pressure are increased simultaneously (increased after load). As pressures to both ventricles are increased simultaneously, the right ventricular stroke volume decreases much more rapidly than does left *(Fig. 1)*. Thus, the right ventricle is more pressure sensitive than is the left(10). There could be several reasons for this. Right ventricular myocardium could be inherently less capable than the left (though there is no evidence to believe that this is true) or the right ventricle could be at a mechanical disadvantage compared to the left.

The latter is true. A simplificed version of the law of Laplace states that the stress

[+] Cardiac output is measured as biventricular output in the fetus because of arterial shunting.

in the wall of a sphere ($S_w$) is determined by the relationship between the transmural pressure ($P_t$, inside minus outside) and its radius of curvature (r) to wall thickness (h) ratio. Precisely,

$$S_w = P_t/2xr/h$$

It is clear from this equation that as the radius goes up, as for example when the ventricle dilates, wall stress will go up also, if its thickness doesn't change. As wall stress goes up, it becomes more difficult for the ventricle to eject and stroke volume decreases. In the fetus, the radius of the right ventricle is much larger than for the left ventricle and their walls are of equal thickness(6). Therefore, comparison of the radius to wall thickness ratio of the fetal right ventricle (r/h=4.5) with the left (r/h=2.6) indeed shows that the right ventricle is at a serous mechancial disadvantage. This explains the rapid loss of right sided stroke volume as arterial pressure and afterload are increased.

These mechanical findings explain heart function in the fetus and newborn. Any cause for increased arterial pressure in the fetus will affect both ventricles simultaneously with a preferential depression of right ventricular stroke volume as pressure goes up. Such increases in pressure might be those accompanying acute hypoxemia(10) or due to increased placental vascular resistance that accompanies intrauterine growth restriction(ll,12). Based on the architecture of the fetal circulation and on flow studies, it is clear that flow through the right ventricle carrying desaturated blood is directed primarily to the placenta for oxygehation while left heart saturated blood is directed mostly to heart and brain(13). Thus, a depression of right heart output during a hypertensive episode in the fetus affects the balance of flow and reoxygenation.

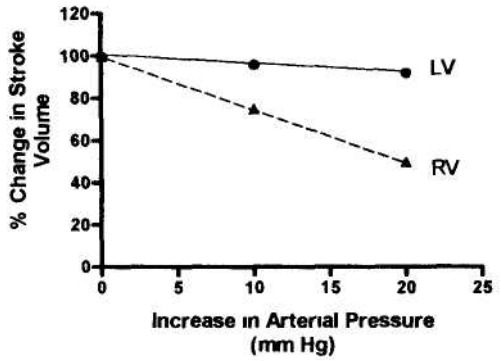


*Fig 1 Graph showing the per cent changes in stroke volume with increasing systemic and pulmonary arterial pressure simultaneously in the non-anesthetized fetal sheep Note that RV stroke volume decreases much more rapidly than does left*

**Development of the Cardiac Myocyte**

The cellular development of the heart also helps to predict its function. Myocytes are immature throughout gestation but they increasingly take on adult features with time before birth. Most work on myocyte maturation has been performed in postnatal small mammals (rat and rabbit) because the maturation of the organellar system's occurs after birth(14,15). The immature myocyte has unique features. Unlike the adult heart cell, the calcium ions that activate the contractile proteins comes from extracellular sources each beat. Calcium enters the immature myocyte during depolarization through voltage regulated calcium channels in the outer membrane (sarcolemma), causing contraction. Those same calcium ions are then extruded from the myocyte during diastole via a sodium-calcium exchanger protein in the sarcolemma. This arrangement differs from the situation in the mature myocyte in which activator calcium is released from and sequestered into an internal storage com-

partment (sarcoplasmic reticulum) over each all cycle. Thus, the immature heart depends on external calcium to activate contraction with each beat whereas the mature heart recycles its own internal calcium stores.

Large mammals tend to have young that are more mature than rodent young and thus it follows that cardiomyoctyes tend to be more mature at birth in humans and sheep than they are in rats or rabbits. However, even in sheep, the sarcoplasmic reticulum that stores internal calcium is not completely mature at birth. This explains why even the large mammal heart is more sensitive to calcium channel antagonist drugs (dihydropyridines) than is the adult heart. In the immature heart, any blockade of calcium influx will reduce the amount of activator calcium that is required to stimulate contraction. As calcium antagonist concentrations increase, contractility of the immature heart decreases (Thornburg KL *et al,* unpublished). In the adult heart, very small amounts of calcium enter the cell during depolarization just for the purpose of stimulating the massive release of activator calcium from internal stores. Contraction of the adult heart is relatively insensitive to the levels of calcium channel blockers that are effective in controlling hypertension, unlike the newborn heart where these drugs can cause serious cardiac depression.

The immature state of the calcium transporters in the newborn heart also makes it more vulnerable to relaxation abnormalities (diastolic dysfunction). Because relaxation requires that a significant fraction of the cytosolic dalcium must be extruded to the outside of the cell by the sodium-calcium exchange protein at the end of contraction, the immature heart is sensitive to rapid rates when there is too little time to extrude calcium ion before the next beat. Immature hearts tend to show dysfunction at rates above 250/min. These relaxation defects can be relieved dramatically by the administration of isoproterenol.

One feature of the rat cardiomyocyte at birth is that it contains one nucleus(16). After a few days binucleate cells appear and by 2 weeks the majority are binucleate. This signifies the stage "terminal differentation". The cell can no longer divide once they have two nuclei. These findings indicate that the heart grows by cell division (hyperplasia) until after birth when the cells lose this ability. From that time onward, all growth of the heart must be via cell enlargement and architectural rearrangement. In this regard, the sheep heart matures much like the rat heart but the "terminal differentiation" processes take place at mid gestation. At day 100 (out of 150 gestation days) sheep have 50% binucleated myocytes. At birth virtually all of the myocytes have two nuclei. Thus the number of myocytes that the heart will have for life is set by the time of birth.

***Pressure Loading in utero***

In response to increasing afterload, the fetal right ventricle changes its shape over several days so that it resembles the left ventricle(7). If the right ventricle is subjected to a mean pressure load increase of 10 mmHg for 10 days by inflating an occluder around the main pulmonary artery, its free wall thickness will increase and its radius to wall thickness ratio will decrease from ~ 4.6 to 3.2. This predicts that the loaded right ventricle will have a lower wall stress and will eject more easily in the face of increasing arterial pressure *(Fig. 2).* Compared to the normal right ventricle, the loaded right ventricle is able to eject nearly as well as the left ventricle. This change comes with a price. The right ventricular wall thickens at the expense of

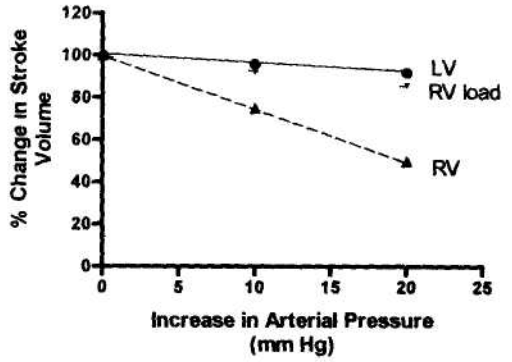


*Fig 2 Graph shows the same relationships between stroke volume and increasing pressures under control conditions and also shows decrease in slope of the RV relationship after changing radius to wall thickness ratio that accompanies 10 days of mild pressure loading*

chamber volume. Thus, while ejection fractionds maintained or improved, stroke volume is less than it would have been had the ventricle been able to grow normally. The lesson here is that the ventricle can be "conditioned" to strengthen contraction, but a conditioned ventricle may have a smaller chamber and be less able to keep up a normal stroke volume for body weight in spite of robust chamber wall.

In summary, we predict that an *acute* pressure load will cause a rapid decrease in stroke volume of the immature right ventricle as pressure increases. An acute mean pressure increase of up to 30 mmHg may prevent ejection altogether. However, after chronic loading, the ventricle may adapt, thicken its wall and give up chamber volume in order to maintain ejection fraction. This heart will be resistant to pressure induced stroke volume reduction. Another feature of the loaded sheep heart is that the programming for binucleation is altered. Loaded hearts have a larger percentage of cells that are binucleate and all cells are on average larger than normal. Therefore, the heart has grown by hypertrophy and hyperplasia.

This may have applicability in cases where placental vascular resistance goes up gradually in disease. The right heart might thicken its wall in response to increased resistance. By the time an abnormal pulsatility index has been confirmed, it is likely that the heart has already undergone growth changes. The heart born to such an individual may behave differently than normal.

**Further Direction**

Studies in animals give us insight as to the way in which the heart grows. It allows us to provide therapy in the newborn with a little more certainty about the effects of drugs and the hemodynamic environment. However, there are a number of questions that haunt us.

- If an intrauterine pressure load increases the number of myocytes that are binucleate, does that imply that fewer stem cells are available for future growth and that the heart will be at a disadvantage for life(18).
- If the wall thickens during fetal life because of placental defects will the heart wall become normal if the newborn is normotensive?
- At what point does the immature heart become mature enough that it behaves like an adult heart with regard to calcium blockers, etc?

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**REFERENCES**

1. Pohlman A.G. The course of the blood through the heart of the fetal mammal, with a note on the reptilian and amphibian circulations. Anat Rec 1909; 3: 75-109.
2. Dawes GS. The fetal circulation: *In:* Fetal and Neonatal Physiology. Chicago, Year Book Medical Publishers Inc., 1968; pp 91-105.
3. St. John Sutton MG, Gewitz MH, Shah B, Cohen A, Reichek N, Gabbe S, Huff DS. Quantitative assessment of growth and function in the cardiac chambers in the normal human fetal heart: A prospective longitudinal echocardiographic study. Circulation 1984; 69: 935-941.
4. Heymann MA, Creasy RK, Rudolph AM, Quantitation of blood flow patterns in the fetal, lamb *in utero. In:* Fetal and Neonatal Physiology: Sir Joseph Barcraft Centenary Symposium. Cambridge, Cambridge University Press, 1973; pp 129-135.
5. Anderson DF, Bissonnette JM, Faber JJ, Thornburg KL. Central shunt flows and pressures in the mature fetal lamb. Am J Physiol 1981; 241: H60-H66.
6. Pinson CW, Morton MJ, Thornburg KL. An anatomic basis for fetal right ventricu lar dominance and arterial pressure sensi tivity. J Dev Physiol 1987; 9: 253-269.
7. Rasanen J, Wood DC, Weiner S, Ludomirski A, Huhta DC. Role of the pulmonary circulation in the distribution of human fetal cardiac output during the second half of pregnancy. Circulation 1996; 94:1068-1073.
8. Thornbug KL, Morton MJ. Filling and arterial pressures as determinants of RV stroke volume in the sheep fetus. Am J Physiol 1983; 244: H656-H663.
9. Thornburg KL, Morton MJ. Filling and arterial pressures as determinants of left ventricular stroke volume in the fetal lambs. Am J Physiol 1986; 251: H961-H968.
10. Reller MD, Morton MJ, Reid DL, Thornburg KL. Fetal lamb ventricles re spond differently to filling and arterial pressures and to *in utero* ventilation. Pediatr Res 1987; 22: 621-626.
11. Fleischer A, Schulman H, Farmakides G, Bracero L, Blattner P, Randolph G. Umbilical artery velocity waveforms and intrauterine growth retardation. Am J Obstet Gynecol 1985; 151: 502-505.
12. Laurin J, Lingman G, Marsal K, Persson P. Fetal blood flow in pregnancies complicated by intrauterine growth retardation. Obstet Gynecol 1987; 69: 895-902.
13. Reuss ML, Rudolph AM. Distribution and recirculation of umbilical and systemic venous blood flow in fetal lambs during hypoxia. J Develop Physiol 1980; 2: 71-84.
14. Nakanishi T, Seguchi M, Takao A. Development of the myocardial contractile system. Experient 1988; 44: 936-944.
15. Klitzner TS. Maturational changes in excitation-contraction coupling in mammalian myocardium. J Amer Coll Cardiol 1991; 17: 218-225.
16. Clubb Jr FJ, Bishop SP. Formation of binucleated myocardial cells in the neonatal rat: An index for growth hypertrophy. Lab Invest 1984; 50: 571-577.
17. Pinson CW, Morton MJ, Thornburg KL. Mild pressure loading alters right ventricular function in fetal sheep. Circ Res 1991; 68: 947-957.
18. Barker DJP, Bull AR, Osmond CO, Simmonds SJ. Fetal and placental size and risk of hypertension in adult life. Brit Med J 1990; 301: 259-262.