

## MINIREVIEW

### Prenatal Development of the Heart and the Blood Circulatory System

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#### Summary

The article concerns recent basic information on the development of the foetal heart and haemodynamics based upon a review of experimental, pathoanatomical and echocardiographic studies.

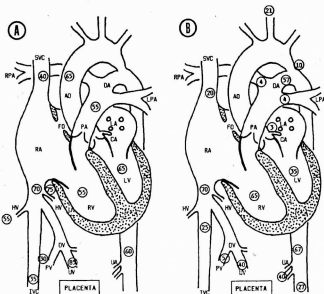
Owing to development of ultrasonic diagnostic techniques the limit which for paediatric cardiologists was once the infant's actual birth has been pushed far back into the prenatal period. The interpretation of foetal echocardiographic findings requires a knowledge of foetal haemodynamics which differs from postnatal ones in many respects.

The source of foetal nutrition and the site of gas exchange is the placenta, which receives foetal blood from the two umbilical arteries (Fig. 1).

Oxygenated blood is returned to the foetus *via* the umbilical vein. In foetal lambs, 55 % of this blood continues *via* ductus venosus to the heart while 45 % perfuses the liver, mainly its left lobe (Rudolph 1983). The blood supply of the right lobe comes mainly from the portal vein. Venous return is regulated by a change in the vascular resistance of the ductus venosus and the liver vascular bed. If the umbilical flow falls, perfusion of the liver is reduced and the relative flow in the ductus venosus increases.

The ductus venosus, the hepatic veins and the inferior vena cava unite and the blood flows into the right atrium. The higher oxygen saturation of the blood from the ductus venosus and the left hepatic vein is distributed preferentially, *via* the foramen ovale, to the left atrium, while most of the less oxygenated blood from the lower part of the inferior vena cava the right hepatic vein and the superior vena cava continues *via* the tricuspid valve to the right ventricle. This "streaming" results in different saturations in the right and left ventricle, and hence also in the aorta and the pulmonary artery (Fig. 1). Blood with a higher oxygen saturation supplies the myocardium and the brain. The systolic pressures in the ventricles and great arteries are the same (70 mm Hg), the filling pressures are low (3–5 mm Hg) and the pressure in the left atrium is lower than in the right atrium. In foetal lambs, the

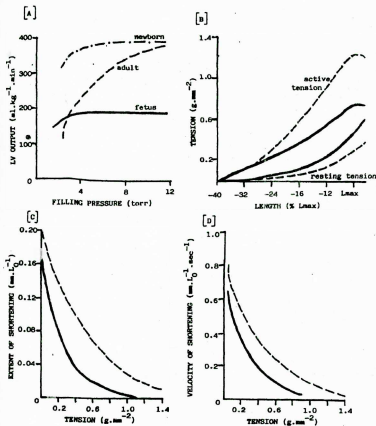
combined ventricular output is about 450-500 ml.kg<sup>-1</sup>, some 40 % of which is distributed to the placenta (Rudolph and Heymann 1967, Heymann *et al.* 1973). The right ventricle, which ejects 65 % of combined ventricular output, is clearly dominant (Fig. 1B). Because of the high pulmonary vascular resistance, most of the blood from the right ventricle flows through the ductus arteriosus to the descending aorta. Blood from the left ventricle feeds the coronary and brachiocephalic arteries, while a small part of its output continues *via* the aortic isthmus to the descending aorta. The narrow isthmus is a site of increased resistance causing functional separation of the output of the two ventricles.



**Fig.1**

Diagram of fetal circulation. A. Hemoglobin oxygen saturation (%). B. Distribution of combined cardiac output (%). AO = aorta, CA = coronary arteries, DA = ductus arteriosus, DV = ductus venosus, FO = foramen ovale, HV = hepatic vein, IVC = inferior vena cava, LA = left atrium, LPA = left pulmonary artery, LV = left ventricle, PA = pulmonary artery, PV = portal vein, RA = right atrium, RPA = right pulmonary artery, RV = right ventricle, SVC = superior vena cava, UA = umbilical artery, UV = umbilical vein. (Data from Rudolph and Heymann 1967, Heymann *et al.* 1973)

The reserves for raising cardiac output by an increase in the heart rate are small (about 10-15 %) (Rudolph and Heymann 1976). Every further increase in the heart rate significantly reduces both the stroke volume and cardiac output. A decrease in the heart rate reduces cardiac output, because the increase in the stroke volume is only minimal.



**Fig.2**  
 A. Relationship between the left ventricular (LV) output and filling pressure in fetal, neonatal and adult sheep. B. Isometric passive and active length-tension curve. C. Relationship between the extent of shortening and developed tension. D. Relationship between the velocity of shortening and developed tension. (According Rudolph 1986, Friedman 1972)

The effect of a preload on cardiac output has been studied by means of fast infusions or by haemorrhage. (Heymann and Rudolph 1973, Gilbert 1982). A decrease in the volume of circulating blood lowers cardiac output, while an increase in filling pressure above normal values raises it only minimally (Fig. 2A). The foetal heart thus works at the peak of the functional curve and has no reserves for increasing cardiac output by the Frank-Starling mechanism. In newborn lambs the functional curve is also flat, but the heart works at a significantly higher contractility

level (Rudolph 1986). When interpreting foetal findings, we must take into account the effect of the increase in the afterload which occurs when the circulatory volume is raised by infusions. Moreover, the Frank - Starling relationship is based on initial fibre length and not on enddiastolic pressure, which at low compliance of the ventricle can rise rapidly even after a small volume change.

Studies performed on isolated preparations (Fig. 2B) showed that the foetal myocardium is characterized by greater resting tension than the adult muscle (Friedman 1972). The length-tension curve has a steeper course and the differences become greater with increasing fibre length. Active tension, calculated per unit of cross-sectional area, is likewise greater in foetuses, throughout the full range of fibre length, than in adults. Ultrastructural ontogenetic differences could play a significant role in the above dissimilarities. In foetuses the muscle fibres are arranged irregularly and their ratio to non-contractile mass is only about 30 %, as compared to 60 % proportion of myofibrils in adults.

In other experiments, Friedman (1972) compared foetal and adult hearts in an isotonic afterloaded preparation. The results (Fig. 2C) show that the extent of muscle-fibre shortening in foetuses is smaller, at a given tension per unit of trans-sectional area, and they explain the poor tolerance of immature individuals to an increase in the afterload. The relation between tension and rate of shortening likewise shows a shift to the left (Fig. 2D). The intersection with the horizontal axis (i.e. isometric tension) is lower in foetuses and the velocity of contraction is also lower, at any tension. The smaller proportion of contractile material in foetuses again plays a role in these differences. If the contraction velocity is extrapolated to zero tension ( $V_{max}$ ), the differences compared with the adult myocardium disappear.

The curves expressing the relationship between ventricular pressure and ventricular size obtained in whole hearts were used to evaluate the compliance of the individual ventricles (Romero *et al.* 1972). Both the right and the left ventricle are less compliant in foetuses than in adults and in both groups the right ventricle is more compliant than the left. An increase in left ventricular filling pressure in foetuses significantly reduces the volume of the right ventricle, explaining why, in premature and newborn infants, defects with a volume or pressure overload of the left ventricle are always manifested in right-sided congestive failure.

Further ontogenetic differences exist in the sympathetic innervation of the heart, which is not complete even in newborn lambs. They are also reflected in pharmacological studies (Friedman 1972). Owing to the absence of uptake and binding, the foetal heart is hypersensitive to noradrenaline. At the same time, the same relative responsiveness to isoprenaline indicates that the sensitivity of beta-receptors is analogous. The contractility of the foetal heart may increase in response to circulating catecholamines released from the rich supply in the adrenals. The cholinergic fibres in the myocardium are already developed in the foetal period and the administration of acetylcholine reduces contractility in foetuses to the same extent as in adults.

Functionally important ontogenetic differences also exist in the calcium metabolism of myocytes. The sarcoplasmic reticulum is not adequately developed and the immature myocardium is therefore primarily dependent on the transsarcolemmal calcium flux, as demonstrated by its significantly greater sensitivity to calcium channel antagonists (Škovránek *et al.* 1986).

Considerably less information is available on the prenatal development of haemodynamics in human foetuses. Pathoanatomical studies of aborted foetuses show no differences in the weight of the right and the left ventricle or in the thickness of their walls (St. John Sutton *et al.* 1984). The dimensions of the tricuspid and pulmonary annulus are somewhat greater than those of the left heart valves (Alvarez *et al.* 1987). Echocardiographic studies demonstrate linear growth of the size of the ventricles and the thickness of their walls with gestational age (Allan *et al.* 1982). The ratio of right to left ventricular size in foetuses is 1.18 and the ratio of the width of the pulmonary artery and the aorta is likewise 1.18 (Sahn *et al.* 1980). The output of both ventricles, computed from echographic measurement of the areas of the atrioventricular orifices and from Doppler measurements of the mean flow velocities, shows that it increases exponentially during pregnancy. The ratio of right to left ventricular output falls in the second half of pregnancy from 1.3 to 1.1 in the late gestation phase (De Smedt *et al.* 1987). Right ventricular dominance thus also exists in human foetuses, but it is much less pronounced than in sheep, in association with the greater brain mass of human foetuses. The aortic isthmus is likewise not as narrow as in lambs. Judging from the flow velocities, the narrowest site on the great arteries is the ductus arteriosus.

The foetal heart differs from the adult heart as regards the filling of the ventricles. In foetuses, filling after contraction of the atria (i.e. wave A) is dominant in relation to the initial phase of passive filling (E). Such filling is typical of ventricles with poor compliance and is thus in agreement with animal experiments. During pregnancy, the A/E flow rate ratio falls and the compliance of both ventricles increases (Reed *et al.* 1986).

Electrophysiological ontogenetic differences are manifested in frequent - mostly supraventricular - premature beats with the danger of paroxysmal tachycardia. Chronic elevation of the heart rate to over  $200 \text{ min}^{-1}$  is tolerated badly and leads to the development of congestive heart failure and foetal hydrops. In spontaneous bradycardia of short duration, Doppler measurement of the flow velocities in the arteries show that the stroke volume does not increase and cardiac output falls as in experimental animals. The foetal heart is capable of adapting itself to early chronic bradycardia in the presence of a complete atrioventricular conduction block by compensatory growth of the heart chambers, as long as the ventricular rate is over  $60\text{--}70 \text{ min}^{-1}$ ; at lower heart rates hydrops may develop.

Foetal echocardiography allows documentation of the significance of intracardiac haemodynamics in the pathogenesis of certain cardiac defects appearing in the phase after organogenesis of the heart has been completed. Restriction of the flow through the foramen ovale can lead to obstructive defects of the left heart, including its hypoplasia (Fig.3, see Plate 2), while limitation of the flow in the right hearts leads to pulmonary stenosis or atresia.

It can thus be claimed that the foetal heart has limited reserves and that relatively small changes in the preload, afterload, heart rate and contractility can lead to heart failure. Recent developments in foetal echo-cardiography now make it possible to obtain data on the development of the heart and its haemodynamics which in human foetuses were once inaccessible.

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**Fig.3.**

*Above:* M-mode ECHO recording in the 27th week of pregnancy. Normal size of the right (RV) and left (LV) ventricle. *Centre:* Clear disproportion in the size of the ventricles in the 31st week of pregnancy. Restriction of the flow through the foramen ovale was demonstrated by Doppler technique. *Below:* Two-dimensional ECHO recording in the 38th week of pregnancy, showing severe hypoplasia of the left ventricle, a thickened hypoplastic mitral valve (arrow), a small left atrium (LA) and enlargement of the right atrium (RA) and right ventricle (ias - interatrial septum, s - interventricular septum, tv - septal leaflet of tricuspidal valve). Autopsy confirmed a diagnosis of a hypoplastic left heart with premature closure of the foramen ovale.

