Cardiovascular adaptation to extra uterine life

Alice Lawford

Robert MR Tulloh

Abstract

The adaptation to extra uterine life is of interest because of its complexity and the ability to cause significant health concerns. In this article we describe the normal changes that occur and the commoner abnormalities that are due to failure of normal development and the effect of congenital cardiac disease. Abnormal development may occur as a result of problems with the mother, or with the fetus before birth. After birth it is essential to determine whether there is an underlying abnormality of the fetal pulmonary or cardiac development and to determine the best course of management of pulmonary hypertension or congenital cardiac disease. Causes of under-development, mal-development and mal-adaptation are described as are the causes of critical congenital heart disease. The methods of diagnosis and management are described to allow the neonatologist to successfully manage such newborns.

Keywords critical congenital heart disease; fetal circulation; nitric oxide; persistent pulmonary hypertension; pulmonary hypertension; sildenafil

Fetal life

Normal fetal circulation

In fetal life, the placenta supplies oxygenated blood via the umbilical vein to the circulation, 50% enters the hepatic circulation and 50% bypasses the liver via the ductus venosus and flows into the inferior vena cava, and then the right atrium. From here it flows through the foramen ovale to the left ventricle and hence to the cerebral and coronary circulation. Relatively deoxygenated blood flows from the cerebral and upper limb circulations to the right atrium but directed through the tricuspid valve, from the right ventricle to the pulmonary artery. Only 15% enters the fetal lungs, these are filled with fluid and mainly bypassed in the circulation because of the high pulmonary vascular resistance, blood flowing instead via the arterial duct to the feet. Then umbilical arteries supply the placenta ready for gas exchange to take place (Box 1).

Control of fetal pulmonary vascular tone

The pulmonary vascular tone is high in the fetus and maintained by the presence of fetal lung fluid, low oxygen tension, and vasoactive factors such as endothelin-1 (ET1), platelet activating factor (PAF), reactive oxygen species (ROS), and increased Rho A-Rho Kinase (RhoA-ROK) signalling. ET1 is the predominant Endothelin in the pulmonary vascular endothelial cells and binds to ET_A and ET_B receptors. Stimulation of ET_A causes vasoconstriction by elevating intracellular calcium and stimulation of ET_B causes vasodilatation, although a further complexity is added with a feedback loop. The hypoxic fetal condition also inhibits the production of vasodilating nitric oxide and prostaglandins.

Alice Lawford *MB ChB ST2 Bristol Royal Hospital for Children, Bristol, UK.*

Robert M R Tulloh *DM FRCPCH is Professor and Consultant in the Department of Congenital Heart Disease, Bristol Royal Hospital for Children, Bristol, UK.*

Abnormal fetal development

A number of maternal risk factors increase the likelihood of abnormal circulatory changes after birth. For example non-steroidal anti-inflammatory medication use tends to lead to premature closure of the ductus arteriosus with resultant pulmonary hypertension after birth and use of selective serotonin reuptake inhibitors (SSRI) can lead to persistent pulmonary hypertension. Maternal lithium use can lead to the structural congenital cardiac abnormality of Ebstein anomaly. Maternal diabetes leads to an increased risk of congenital heart disease; ventricular septal defect and transposition of the great arteries and also to hypertrophic cardiomyopathy (Box 2).

Antenatal diagnosis

Antenatal examination of the fetal heart can lead to the diagnosis of up to 70% of children who will require surgery in the first 6 months of life. In developed countries this examination is now a routine part of the fetal anomaly scan that takes place between 18 and 20 weeks' gestation. It is particularly important for fetuses that may be at an increased risk of CHD. These include those with suspected Down's syndrome or whose mothers or elder siblings have had CHD. In cases where a cardiac abnormality is detected, a paediatric cardiologist should perform detailed fetal echocardiography. Early diagnosis of CHD allows counselling to be provided for the parents and for antenatal management to be planned for the baby. In a minority of cases, the parents may decide to terminate the pregnancy. In the case of neonates with critical CHD and duct-dependent lesions who are likely to need

Fetal vascular structures that exist to direct blood flow

Fetal structure	Function
Arterial duct	Connects pulmonary artery to the aorta and shunts blood right to left; diverting flow away from fetal lungs
Foramen ovale	Opening between the two atria that directs blood flow returning to right atrium through the septal wall into the left atrium bypassing lungs
Ductus venosus	Receives oxygenated blood from umbilical vein and directs it to the inferior vena cava and right atrium
Umbilical arteries	Carrying deoxygenated blood from the fetus to the placenta
Umbilical vein	Carrying oxygenated blood from the placenta to the fetus

BOX 1

Maternal causes of congenital heart disease

Maternal disorders	
Rubella infection	Peripheral stenosis, PDA
Systemic lupus (SLE)	Complete heart block (anti-Ro and anti-La antibody)
Diabetes mellitus	
Maternal drug use	
Warfarin therapy	Pulmonary valve stenosis, PDA
Fetal alcohol syndrome	ASD, VSD, tetralogy of Fallot
Chromosomal abnormality	
Down's syndrome (trisomy 21)	Atrio-ventricular septal defect, VSD
Edward syndrome (trisomy 18)	Complex CHD
Patau syndrome (trisomy 13)	Complex CHD
Turner syndrome (45XO)	Aortic valve stenosis, coarctation of the aorta
Chromosome 22q11.2 deletion	Aortic arch anomalies, tetralogy of Fallot, common arterial trunk
Williams syndrome (7q11.23 microdeletion)	Supravalvular aortic stenosis, peripheral pulmonary artery stenosis
Noonan syndrome (PTPN11 mutation and others)	Hypertrophic cardiomyopathy, atrial septal defect, pulmonary valve stenosis

ASD, atrial septal defect; CHD, congenital heart disease; PDA, persistent ductus arteriosus; VSD, ventricular septal defect.

BOX 2

treatment within the first 2 days of life, parents may be offered the option of delivery at or close to the cardiac centre.

Changes that occur at birth

Normal circulatory changes at birth

The most dramatic physiological events related to birth are the switch from placenta to the lung as the organ of gas exchange. This is a highly co-ordinated process reliant on cortisol and vasoactive catecholamine to facilitate the transition (Figure 1).

Fetal breathing movements generate trans-pulmonary pressures of up to 30 cm of water, demonstrating that they are capable aerating the lungs after birth. Activation of chemoreceptors by an increase in arterial carbon dioxide and physical stimuli such as light, heat and handling, trigger the onset of regular inspiratory efforts. Hypoxia increasingly stimulates respiratory drive in the newborn due a change in oxygen sensitivity, which increases in the weeks after birth. The trans-pulmonary pressure gradients generated during inspiration are likely to be primarily responsible for the rapid clearance of airway liquid immediately after birth allowing further expansion of the alveoli and a further reduction in the pulmonary vascular resistance.

At birth with the first breath the lungs are filled with air and there is an abrupt increase in pulmonary blood flow, creating a shear stress with in the vessel wall. Shear stress and oxygenation stimulate endothelial nitric oxide synthase and up-regulate its expression. Oxygenation also inhibits the enzymatic activity of phosphodiesterase 5 (PDE5) that breaks down cyclic GMP in order to terminate its activity. This and other inhibitors of PDE5 therefore increase the effectiveness of endogenous nitric oxide to cause vasodilatation.

Another pathway of pulmonary vasodilatation is through the production of prostaglandins by the endothelium. Oxygenation stimulates production of prostaglandin (mostly prostacyclin PGI_2) from arachidonic acid with cyclooxygenase (COX) as the rate-limiting step. This causes vaso-relaxation but the decrease in PVR caused is less than that seen with NO. In addition to NO and PGI_2, oxygenation results in pulmonary dilatation via activation of potassium channel and reduction in calcium channel activity in pulmonary artery smooth muscles.

At the first breath, the decreased pulmonary vascular resistance (PVR) leads to increased pulmonary blood flow of deoxygenated blood from the right ventricle. This increased blood flow leads to a delivery of oxygen rich blood from pulmonary veins to the left atrium, with resultant closure of the foramen ovale as the septum primum rests against the septum secundum and separates the two atria. The high concentration of oxygen in the arterial blood along with a fall in prostaglandins causes constriction of the ductus arteriosus. The cardiac output nearly doubles corresponding to the marked rise in oxygen consumption.

The blood supply from the placenta is interrupted, both via vasoconstriction and from clamping of the cord that results in an increase in systemic vascular resistance. The ductus venosus closes as the flow dwindles in the umbilical vein. The right and left sides of the heart are now connected in series rather than in parallel. Although initially rapid, these changes consolidate over the next 2–3 weeks. Functional closure of the ductus occurs in the first 60 hours of life in the majority of term babies, but anatomic closure may not occur until 2–3 weeks of age because of prematurity, acidosis, and hypoxia.

Abnormal circulatory changes at birth

Congenital heart disease: the closure of a patent duct in critical congenital heart disease can precipitate rapid clinical deterioration, i.e. severe metabolic acidosis, seizures, shock, collapse and cardiac arrest.

Congenital heart disease (CHD) is the most common congenital disorder in newborns. It occurs when there is failure of normal cardiac development or persistence of the fetal circulation after birth. The incidence is reported at 8 per 1000 live births. 25% of those with CHD have critical CHD requiring life saving surgery or catheter based intervention in the first year of life. The challenge is detecting for which neonates this is. Cases are increasingly being detected antenatally with routine screening as imaging modalities enhance. However many are missed and not symptomatic until shortly after birth and even after discharge from the birth hospitalisation. A normal neonatal examination does not exclude life threatening cardiac malformation, especially those with ductal dependent lesions, where pulmonary or systemic circulation is supplied solely by flow through the duct.