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Cardiovascular Development

The incidence of congenital heart disease (CHD) is approximately 7 to 10 per 1000 live births. Most congenital heart defects are the result of an interaction of genetic predisposition and environmental factors. Environmental factors such as drugs, viral infection, maternal diabetes, or maternal alcohol abuse may account for specific lesions. Knowledge of cardiac development is a must to understand congenital heart lesions. This chapter reviews the embryology and cardiovascular physiology at birth.

Embryology

It is essential to understand the basic embryology and origin of the cardiac structures in order to appreciate the specific lesions described in the next section of the Handbook. It is beyond the scope of this Handbook to discuss the details of cardiac development, including : (i) cardiac sidedness or asymmetry; (ii) cardiac looping; (iii) formation of outflow tracts; and (iv) septation. The embryologic structures and their corresponding adult structures are listed in Table 1.1.

Cardiovascular Physiology

Circulatory changes occur at birth and continue over the first few days and the first months of life, and are considerable. They need to be appreciated in order to understand their profound effects on neonatal cardiovascular physiology. It is not coincidental that 50% of the neonates born with CHD will become ill enough during the first days or weeks of life to require medical or surgical intervention. Optimal perioperative and anesthetic management of the neonate with CHD must be based on a firm understanding of these developmental changes.

Fetal Circulation

Fetal circulatory channels shunt blood away from the lung such that both ventricles, in parallel, contribute to systemic oxygen delivery by pumping blood to the systemic arterial system. This parallel circulation permits normal fetal growth and development even in fetuses with cardiac malformations.

Oxygenated blood from the placenta returns to the fetus via the umbilical vein, which enters the portal venous system. The ductus venosus connects the left portal vein to the left hepatic vein at its junction with the inferior vena cava (IVC). This allows approximately 50% of umbilical venous blood to bypass the hepatic sinuses. The remainder of the umbilical venous flow passes through the liver and enters the IVC via the hepatic veins. Fetal IVC blood is a combination of blood from the lower fetal body, umbilical vein, and hepatic veins. The stream of blood from the ductus venosus has a higher velocity in the IVC than the stream from the lower body and hepatic veins. This higher velocity facilitates delivery

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Table 1.1 Cardiovascular embryologic structure and the corresponding structures in adults.

Embryologic structure	Adult structure
Truncus arteriosus	Aorta Pulmonary trunk
Bulbus cordis	Smooth part of right ventricle (conus arteriosus) Smooth part of left ventricle (aortic vestibule)
Primitive ventricle	Trabeculated part of right ventricle Trabeculated part of left ventricle
Primitive atrium	Trabeculated part of right atrium Trabeculated part of left atrium
Sinus venosus	Smooth part of right atrium (sinus venarum) Coronary sinus Oblique vein of left atrium
Aortic arches	
1	*
2	*
3	Common carotid arteries Internal carotid arteries (proximal part)
4	Right subclavian artery (proximal part) Part of the aortic arch
5	Regresses in the human
6	Pulmonary arteries (proximal part) Ductus arteriosus

of this higher-oxygen content blood across the foramen ovale (FO) into the left atrium (LA) (Figure 1.1).

The IVC blood enters the right atrium (RA) and, due to the position of the Eustachian valve, Chiari network and FO, enters the LA during 80% of the cardiac cycle. During the other 20% (atrial systole), IVC blood crosses the tricuspid valve and enters the right ventricle (RV). The overwhelming majority of superior vena cava (SVC) blood crosses the tricuspid valve and also enters the RV. Blood from the RV is ejected into the pulmonary artery (PA). Approximately 10–15% of blood from the PA passes through the lungs to reach the LA, and the rest is shunted to the distal aorta via the ductus arteriosus (DA). As a result, two-thirds of the total fetal cardiac output is provided by the RV, with the remaining one-third provided via the LV.

The dynamics of shunting at the level of the ductus venosus, FO, and DA result in a preferential delivery of the most highly oxygenated blood to the coronary and cerebral circulations. Obviously, this preferential delivery of oxygenated blood may be compromised *in utero* by cardiac lesions that prevent or reduce left ventricular output. At birth, a series circulation is established in which each ventricle pumps into a specific vascular bed (RV to pulmonary artery; LV to aorta). The removal of the placenta and the initiation of alveolar ventilation at birth have the immediate effect of establishing this series circulation. To maintain the adult series circulation, the fetal channels must be closed (Table 1.2). Complex neurochemical and hormonal influences affect the closing of these fetal shunts. Acidosis, sepsis, hypothermia, hypoxia and hypercarbia may cause a re-opening of the shunts and persistence of the fetal circulation (PFC). Most neonates that are critically ill from CHD have one or more of these inciting factors at the time of

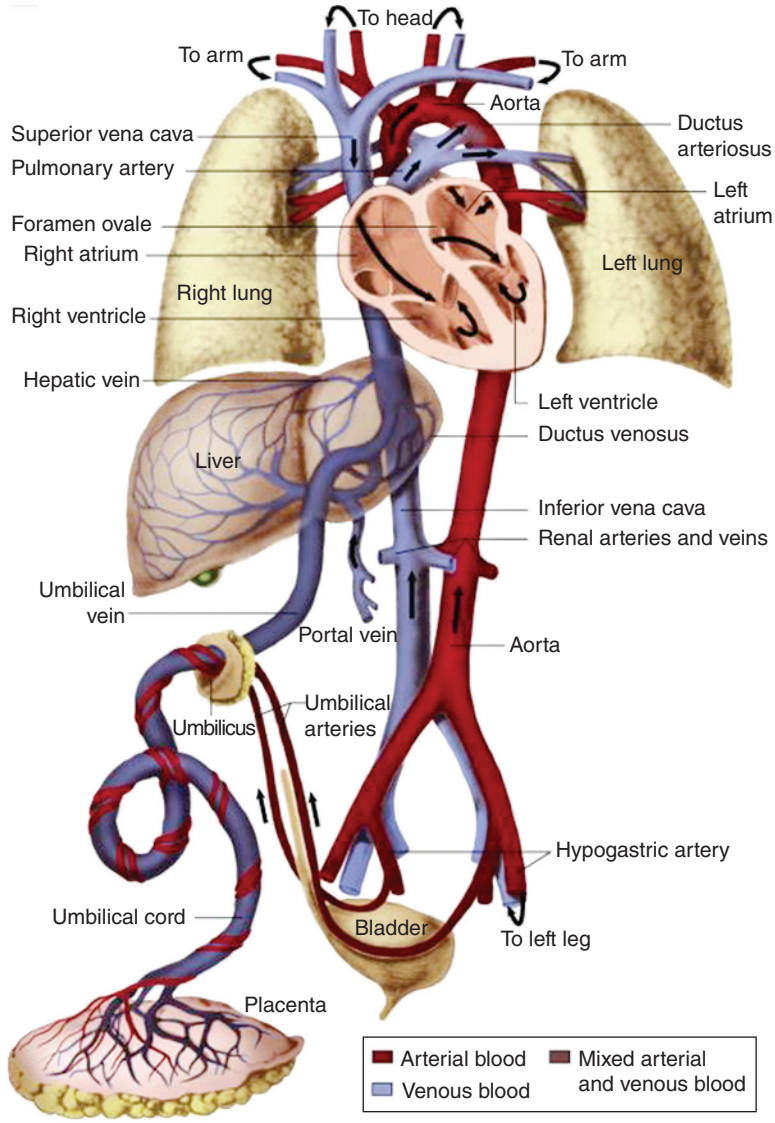

Figure 1.1 Course of the fetal circulation in late gestation. Note the selective blood flow patterns across the foramen ovale and the ductus arteriosus. Reproduced from Greeley, W.J., Berkowitz, D.H., Nathan, A.T. (2010) Anesthesia for pediatric cardiac surgery, in *Anesthesia*, 7th edition (ed. R.D. Miller), Churchill Livingstone, Philadelphia.

presentation. In some instances, the persistence of fetal circulatory channels may be beneficial or even mandatory for survival.

Closure of the Ductus Arteriosus

In the fetus, patency of the ductus arteriosus is maintained by high levels of prostaglandins (PGI_2 and PGE_1). There are two stages of ductal closure in the newborn: functional closure, and permanent anatomic closure. Functional closure occurs by contraction of the smooth muscle of the ductal wall and usually occurs within the first day of life. An increase in PO_2 and a decrease in prostaglandin levels contribute to functional closure. Oxygen is a dose-dependent ductal constrictor that acts

Table 1.2 Fetal structures and their corresponding structure in adults.

Fetal structure	Adult structure
Foramen ovale	Fossa ovalis
Umbilical vein	Ligamentum teres
Ductus venosus	Ligamentum venosum
Umbilical arteries	Medial umbilical ligaments, superior vesicular artery
Ductus arteriosus	Ligamentum arteriosum

by increasing the rate of oxidative phosphorylation within smooth muscle cells. In addition, the response to oxygen may be age-related; full-term neonates have a more dramatic response to oxygen than an immature newborn. Norepinephrine and epinephrine, by changing pulmonary and systemic vascular resistances, may secondarily contribute to ductal closure. Acetylcholine has a direct constrictor effect on ductal tissue. Permanent anatomic closure of the duct usually is accomplished by two to three weeks of life in the normal full-term neonate. The lumen is sealed by fibrous connective tissue, leaving the vestigial structure, known as the ligamentum arteriosum.

The survival of some neonates with congenital cardiac lesions is dependent on ductal patency. Because functional closure is a reversible event, the use of PGE_1 infusions ($0.01–0.05\ \mu g\ kg^{-1}\ min^{-1}$) has been one of the major medical advances in the stabilization of neonates with ductal-dependent heart lesions. Preterm neonates are at risk of delayed ductal closure. This may be due to a decreased degradation of PGE_1, an increased production of PGE_1, or a diminished sensitivity to the ductal-constricting effects of oxygen. In instances in which delayed ductal closure is disadvantageous, prostaglandin inhibitors such as indomethacin ($0.1–0.3\ mg\ kg^{-1}$ PO or IV) have been used successfully to promote ductal closure and establish normal patterns of pulmonary blood flow.

Closure of the Foramen Ovale

In utero, the right atrial pressure is higher than the left atrial pressure. IVC blood flows in such a manner as to keep the FO open. The cessation of umbilical vein flow causes a significant decrease in venous return to the right heart, leading to a decrease in right atrial pressure. In addition, ventilation causes a marked increase in pulmonary arterial and venous blood flows, resulting in an increase in left atrial pressure. This elevation of left atrial pressure relative to right atrial pressure causes the flap-like valve of the FO to functionally close. In instances in which right atrial pressure remains elevated, right-to-left shunting may persist. Functional closure usually progresses to anatomic closure. However, probe patency of the FO may persist in 30% of normal adults and in 50% of children younger than 5 years of age.

Closure of the Ductus Venosus

The umbilical vessels constrict strongly after mechanical stimulation, and a high oxygen tension facilitates this process. The resultant decrease in umbilical venous blood flow causes passive closure of the ductus venosus. The latter does not appear to be as sensitive as the ductus arteriosus to PaO_2, $PaCO_2$, or pH. The ductus venosus is functionally closed by one week of life and is anatomically closed by three months. The remaining structure is the ligamentum venosum. In addition to the establishment of the adult series circulation, dramatic alterations in pulmonary circulation, cardiac output and distribution, myocardial performance and myocardial cell growth and hypertrophy continue to occur during the first weeks, months, and even years of life. In the presence of CHD, these changes may be pathologically affected.

Pulmonary Vascular Changes

The fetus has a low pulmonary blood flow secondary to a high pulmonary vascular resistance. The minimal blood flow that reaches the

pulmonary bed has a very low PaO_2, which may cause hypoxic pulmonary vasoconstriction and contributes to the elevated pulmonary resistance seen in the fetus. Morphologic examinations of the small arteries of the fetal and newborn lung show a thick medial smooth muscle layer. The fetal pulmonary vasculature is reactive to a number of stimulants. Vasoconstriction is induced by decreases in PaO_2, pH, and leukotrienes. Acetylcholine, histamine, bradykinin, PGE_1, PGE_2, PGI_2 (prostacyclin), and prostaglandin D_2 and beta-adrenergic catecholamines are patent vasodilators of fetal pulmonary vessels.

At birth, alveolar ventilation commences. This reduces the mechanical compression of small pulmonary vessels and increases PaO_2, the result being a dramatic reduction in pulmonary vascular resistance (PVR). During the following weeks and months, remodeling of the pulmonary vessels occurs; the most notable change is a thinning of the medial smooth muscle layer. By six months of life this process results in a reduction of the PVR to near-normal adult levels. The normal process of postnatal pulmonary maturation may be altered significantly by pathologic conditions, such as those associated with CHD.

Myocardial Performance in the Neonate

In utero, the RV has a cardiac output of approximately 330 ml kg^{-1} min^{-1} compared to the left ventricular output of 170 ml kg^{-1} min^{-1}. At birth, both the RV and LV eject an output of approximately 350 ml kg^{-1} min^{-1}. This requires a minimal stroke volume increase for the RV but a considerable increase in stroke volume for the LV. The high output state of the newborn effectively limits further increases in cardiac output. This high output state decreases to about 150 ml kg^{-1} min^{-1} by eight to ten weeks of life.

Hemodynamic Changes at Birth

Myocardial morphology and performance is notably different in the neonate. These differences are summarized as follows and are listed in Table 1.3.

Table 1.3 Neonatal myocardial performance compared to the adult.

- Afterload mismatch
- Limited preload reserve
- Reduced contractile capacity
- Reduced ventricular compliance
- Increased intraventricular dependence
- Incomplete autonomic sympathetic innervation and dominance of parasympathetic
- Immature myocardial metabolism

- *Afterload mismatch:* The neonatal heart is more susceptible to afterload mismatch, and therefore the stroke volume is poorly maintained in the face of increasing outflow resistance (see Chapter 5).
- *Limited preload reserve:* The neonatal heart has a limited preload reserve. Augmentation of stroke volume via the Frank–Starling mechanism is limited compared with an adult.
- *Reduced contractile capacity:* Neonatal cardiac cells contain more water and fewer contractile elements than mature myocardium. In addition, there are fewer mitochondria and sarcoplasmic reticulum (SR) and poorly formed T tubules that make the myocardium more dependent on extracellular calcium. Development of the SR, T-tubular system and calcium-handling proteins appears to be rapid, and it has been suggested that they are relatively mature by three weeks in the neonatal heart.
- *Reduced ventricular compliance:* The compliance of the neonatal myocardium is reduced because a deficiency of elastic elements parallels the deficiency of contractile elements.
- *Increased intraventricular dependence:* Changes in ventricular pressure are transmitted to the opposite ventricle via the ventricular septum more readily in the immature myocardium. Left ventricular diastolic filling is disproportionately impaired in the neonate by a high right ventricular end-diastolic pressure. This is due to a leftward shift of the intraventricular septum and a reduction in

left ventricular distensibility. Right ventricular diastolic filling is impaired to an equal extent by high left ventricular end-diastolic pressures in neonates. This enhanced ventricular interaction is caused by reduced ventricular compliance and because, at birth, the LV and RV are of equal mass. The increased volume and pressure load experienced by the LV after birth produces relative left ventricular hypertrophy (LVH). The normal adult LV to RV mass ratio of 2:1 is not seen until several months after birth.

- *Incomplete autonomic innervations:* Sympathetic innervation, which is responsible for increasing the heart rate and contractility, is incompletely developed at birth. As a result, the local myocardial release of norepinephrine contributes less to increases in contractility than do increases in circulating catecholamine levels. For this reason, inotropic agents such as dopamine – the effects of which are partially mediated through release of norepinephrine from myocardial nerve endings – may have to be used at higher doses to be effective in younger patients. On the other hand, the parasympathetic system, which reflexly slows the heart, is fully functional at birth.
- *Immature myocardial metabolism:* The neonatal myocardium is more dependent on anaerobic metabolism than the adult heart, which uses carbohydrates and lactate as primary energy sources. This may have a somewhat protective effect, making the neonatal myocardium more tolerant to the effects of hypoxia.