Physiology of the fetal and transitional circulation

Anna Finnemore a,*, Alan Groves b

a Department of Perinatal Imaging and Health, King's College, London, UK
b Department of Pediatrics, Weill Cornell Medical College, New York, NY, USA

Keywords:
Fetal physiology
Neonatal critical care
Perinatal management

SUMMARY

The fetal circulation is an entirely transient event, not replicated at any point in later life, and functionally distinct from the pediatric and adult circulations. Understanding of the physiology of the fetal circulation is vital for accurate interpretation of hemodynamic assessments in utero, but also for management of circulatory compromise in premature infants, who begin extrauterine life before the fetal circulation has finished its maturation. This review summarizes the key classical components of circulatory physiology, as well as some of the newer concepts of physiology that have been appreciated in recent years. The immature circulation has significantly altered function in all aspects of circulatory physiology. The mechanisms and significance of these differences are also discussed, as is the impact of these alterations on the circulatory transition of infants born prematurely.

© 2015 Elsevier Ltd. All rights reserved.

1. Introduction

The fetal circulation is an entirely transient event, not replicated at any point in later life, and functionally distinct from the pediatric and adult circulations. An understanding of the physiology of the fetal circulation is core to accurate interpretation of hemodynamic assessments in utero.

Given that premature infants begin extrauterine life before the fetal circulation has finished its maturation, infants manifest many of the functional and structural characteristics of the fetal vasculature. Therefore awareness of the fetal physiology is also relevant for many aspects of postnatal circulatory care. Indeed in the absence of conclusive clinical trials determining the optimal clinical management of many common clinical presentations of the preterm infant (hypotension, patent ductus arteriosus, pulmonary hypertension), treatment decisions in the neonatal intensive care unit (NICU) frequently rely on applying knowledge of physiology and pathophysiology to identify optimal therapy.

This review aims to summarize the distinct features of the fetal and transitional circulations and to put forward the best current understanding of the functional significance of each of these factors.

2. Brief summary of cardiac anatomy

The workhorses of the cardiac musculature are cardiomyocytes – individual muscle units that split and recombine into a complex network, which is then encased in a collagenous extracellular matrix. The extracellular matrix both withstands and dissipates the forces created by the muscle fibers [1]. The cardiomyocytes are made up of myofibrils, themselves formed from chains of sarcomeres. Within each sarcomere, muscle filaments cross-link and relax to produce muscular contraction. Surrounding these fibers and linking them to the extracellular matrix is a cytoskeleton of protein or endomysium [1], the constituents of which have a crucial role in development and remodeling of the myocytes in response to mechanical and chemical signals [2].

The sarcoplasmic reticulum (SR) is a network of sleeve-like structures surrounding the myofibrils within a muscle fiber. Its role is the storage, release and reuptake of calcium that is crucial to the conversion of an action potential to a muscular contraction. When an action potential arrives at the plasma membrane of the muscle fiber, it is conducted via the T tubules to the sarcoplasmic reticulum, which releases calcium into the cytosol [3]. This binds to troponin, a complex of three regulatory proteins, I, C, and T, which control contraction and relaxation of the muscle in the presence of calcium (Fig. 1) [4]. When calcium levels increase, some binds to troponin, altering its shape and allowing actin–myosin cross-bridges to form and contraction to occur. Removal of the calcium

* Corresponding author. Address: Department of Perinatal Imaging and Health, 1st Floor, South Wing, St Thomas' Hospital, London SE1 7EH, UK. Tel.: +44 (0)20 7188 9145; fax: +44 (0)20 7188 9154.
E-mail address: anna.finnemore@kcl.ac.uk (A. Finnemore).
from troponin then restores the tropomyosin blocking action and the muscle relaxes.

3. The classical triad of circulatory physiology: preload, contractility, and afterload

3.1. Preload

This is the initial stretching of the cardiac muscle fibers prior to contraction. As preload increases and sarcomeres stretch, there is an increase in the number of actin–myosin bridges formed (up to a certain point) and therefore of the scope for force generation [5]. The association between increasing preload and increasing cardiac output is known as the Frank–Starling mechanism. However, whereas numbers of actin–myosin bridges were previously considered the central component of the Frank–Starling mechanism, awareness of cardiac anatomy and physiology continues to evolve. It is now clear that titin (also known as connectin), the largest known mammalian protein, plays a key role in myocyte function [5,6]. Titin links the Z-disc region of the thin filament to the myosin thick filament (Fig. 2) [7], and has an elastic structure which allows it to stretch. This makes it a key component of myocardial stiffness, but also enhances its role in force generation [5]. Although this is partly due to release of the kinetic energy stored as potential energy during stretch of the molecule during diastole, titin also mediates force generation by altering Ca$^{2+}$ release. At the time of writing, many aspects of titin’s function remain unknown or contentious. The properties of titin are complex, and highly variable across species, over time, within different layers of the heart, with altering isoforms (over days/weeks) and changing calcium concentrations (over milliseconds during the cardiac cycle). The characteristics of this complex molecule have been the subject of a number of excellent reviews [8,9].

3.2. Contractility

This is the ability of sarcomeres to change their inherent contractile force (independent of preload), a trait unique to cardiac muscle. Increased inotropy (or contractility) manifests as increased velocity of muscle fiber shortening and therefore increased ejection velocity of blood. As the time available for ejection of blood is relatively constant, increased ejection velocity over a constant time-period will result in increased ejection volume [10]. Contractility is determined largely by the interaction of the sympathetic and parasympathetic autonomic nervous systems [10]. Circulating catecholamines also have an impact, as do poorly understood interactions with heart rate (the Treppe effect) [10] and afterload (the Anrep effect) [11]. Most changes in cardiac contractility appear to be mediated by changes in intracellular calcium levels [10].

3.3. Afterload

This is the load against which the ventricle must eject blood and is probably best thought of in terms of vascular resistance, although it is not synonymous with this. As afterload increases, so does the wall stress in the ventricle, decreasing the rate at which muscle fibers contract and (with ejection time being relatively constant) decreasing the ejection volume. Changes in vessel diameter (particularly small arteries and arterioles) regulate blood flow within individual organs, and the total resistance created by each of these vascular beds is systemic vascular resistance (SVR) [10]. Vasoregulation is determined by intrinsic myogenic mechanisms, local vasoactive mediators and extrinsic factors including the autonomic innervation of blood vessels and circulating vasoactive hormones [10]. Blood pressure is the product of vascular resistance and blood flow and is therefore frequently closely associated with...
afterload. Particularly in the transitional circulation it is thought that systemic vascular resistance has a dominant influence over blood flow in determining blood pressure [12,13].

The separation of the effects of preload, contractility and afterload in hemodynamic physiology is somewhat artificial since the closed nature of the cardiovascular system means that any change in one component of the circulation will have ‘knock on’ effects elsewhere. For example, an increase in afterload will cause a reflex increase in myocardial inotropy, though this will only partly preserve stroke volume. Residual blood not ejected from the left ventricle will act to increase preload, also enhancing contractile force [10].

4. Additional components of circulatory physiology: recoil, torsion, and rotation

4.1. Recoil

The classical description of preload given in Section 3.1 conjures an entirely passive process. However, it is now known that diastolic function and cardiac filling are much more dynamic processes. In the early stages of diastole there is a rapid filling phase known as recoil, in which blood is effectively suctioned into the ventricles [14]. Titin again seems to play a key role here. Isolated sarcomeres have a resting length, or “slack length,” of around 1.9 µm. When stretched beyond that length, sarcomeres naturally contract down to their slack length in an energy-independent fashion. This process is now known to be due to stretching of subregions of titin. Similarly, when compressed to below 1.9 µm in length, sarcomeres will naturally lengthen back to their slack length when the contracting force is removed [15]. Although the exact mechanism of the process is uncertain, it may be that titin proteins are anchored such that titin has its shortest length when the sarcomeres measure 1.9 µm. Alternatively, titin might be further shortened at sarcomere lengths <1.9 µm, expanding back to its own resting length when the compressing force is removed, effectively acting as a molecular coiled spring [6]. In either case, titin is the principal determinant of this recoil [15], and the extent of the expansile force at lengths <1.9 µm is equivalent to the contractile force at length >1.9 µm (Fig. 3) [16].

4.2. Torsion

The contraction of the myocardium in the healthy human heart is not simply a circumferential movement. Innate to the efficiency of the myocardium is the structure of differently oriented fibers to maximize contractile efficiency. The role of these oblique layers has become more clearly defined in recent years and the concept of a wringing motion of contraction has been introduced. In adult hearts, the apex rotates in a counter-clockwise direction to the base, so twisting the ventricle and squeezing blood up towards the outflow tract [17]. Sub-epicardial and sub-endocardial fibers move

---

**Fig. 2.** Schematic arrangement of myofilaments in an extended and contracted sarcomere. The upper, middle, and lower panels illustrate the highly extended, shortening, and shortened sarcomere, respectively. Reproduced with permission from Nagy et al. [7].

**Fig. 3.** Predicted force developed by single titin molecule as a function of sarcomere length (SL). Titin develops restoring force below the slack SL (1.9 µm) and passive force above the slack SL. Reproduced with permission from Lahmers et al. [16].
in opposite directions to increase the efficiency of this wringing motion [1]. The systolic twist not only assists with the ejection of blood, but also stores further energy, augmenting recoil as described above [14].

4.3. Rotation

Another contributor to this early ventricular filling phase may be the complex intracardiac rotational flow blood patterns that are consistently seen, at least in the adult heart [18]. As blood enters the left atrium from the pulmonary veins, or the right atrium from the superior and inferior venae cavae, it does not spill randomly into the chamber, and then wait idly for opening of the atrioventricular valves. Instead it forms highly reproducible rotational flow patterns. These patterns were initially proposed to maintain the kinetic energy of inflowing blood, allowing it to ‘slingshot’ into the ventricles in early diastole [18]. However, the degree of kinetic energy conserved by this process has been debated [19], and the role of the process in the healthy or sick heart is currently difficult to quantify [20].

5. Unique aspects of the fetal and transitional circulation

5.1. Structural/flow path differences in the fetal circulation

The central unique feature of the fetal circulation is that gas exchange occurs not in the lungs, but via the placenta. Relatively well-oxygenated blood returns to the fetus from the placenta via a single umbilical vein. This blood has a partial pressure of oxygen of around 3.7 kPa (27 mmHg), at which 70–80% of fetal hemoglobin is saturated [21–23]. Blood flows from the umbilical vein into the umbilical recess where it mixes with a small volume of blood from the portal vein. Around 50% of this blood passes through the ductus venosus to bypass the liver and join with the inferior vena cava and left and right hepatic veins immediately before entering the right atrium [24].

Oxygenated blood from the ductus venosus is preferentially diverted into the left atrium by the Eustachian valve. Passage into the left atrium is possible since higher pressure in the right atrium (due to high volume venous return) stents open the valve over the foramen ovale [25]. This relatively well-oxygenated blood joins with a small volume of pulmonary venous return to flow into the left ventricle before being ejected into the ascending aorta. Thus the brain, heart, and upper body are preferentially supplied with relatively highly oxygenated blood (oxygen saturation around 65%) [25].

The remainder of the venous return to the right atrium, from the inferior vena cava, hepatic veins and superior vena cava, flows into the right ventricle before being ejected into the pulmonary artery. However, only a small proportion (10–25%) of the right ventricular output reaches the lungs to supply the lung tissue’s basic metabolic needs [26], with the proportion increasing at higher gestations [27]. The remainder of the right ventricular output is diverted through the ductus arteriosus into the descending aorta. In addition to perfusing the abdominal organs and lower limbs of the fetus, this deoxygenated blood (oxygen saturation around 35%) flows to the low-resistance placenta to collect oxygen and dispose of carbon dioxide and other waste products.

5.2. The placental circulation

The development of an adequate placental circulation, providing a low-resistance vascular bed for efficient gas and nutrient exchange between maternal and fetal blood, is vital to the development of the fetus and to the formation of a functional fetal cardiovascular system. Its impairment has been shown to correspond to the development of some congenital heart defects [28,29] as well as to cardiovascular dysfunction later in life, as proposed in the Barker hypothesis [30].

From the onset of the fetal heartbeat at around 22 days of gestational age, until the cessation of organogenesis at 9 weeks, both the vitelline circulation from the yolk sac and the umbilico-placental circulation are functional. At the end of this period, the yolk sac regresses and the umbilico-placental circulation becomes dominant. At around 10–12 weeks of gestational age, trophoblastic invasion of the placenta begins. This appears to be influenced by hypoxia, cytokines, growth factors, enzymes, and other angiogenic substances [31]. Under the control of these biochemical modulators, fetal trophoblastic cells from the surface of the blastocyst invade the uterine spiral arteries, lining them with fetal endothelial cells, increasing their diameter and reducing impedance. This produces a low-resistance, high-flow, low-velocity vascular bed, allowing copious maternal blood flow and efficient gas and nutrient exchange. Dysfunction of the placenta and assessment of the placental circulation using Doppler ultrasound is discussed in detail by Pruetz et al. in this issue of Seminars. Processes such as poor trophoblast invasion or maternal ischemia lead to high placental impedance and hypoxic vasodilatory adaptation in the fetus to ensure adequate oxygenation of vital organs. This in turn produces a raised right ventricular pre- and afterload, exacerbated by abnormal retrograde diastolic flow in the aortic isthmus secondary to cerebral vasodilation, and eventually failing coronary perfusion with potential myocardial damage. Many factors may affect placental development and trophoblast invasion, such as maternal diet, blood pressure, and ingestion of alcohol, lithium, or cigarettes [28].

6. Magnetic resonance imaging (MRI) quantification of fetal blood flow

Advances in MRI technology, particularly the development of metric optimized gating, have recently allowed quantification of blood flow in the great vessels of near-term fetuses in utero [27]. Metric optimized gating is retrospective processing of non-electrocardiogram-gated MRI data where over-sampled data are sorted with a range of possible heart rates until artifacts are minimized and the true heart rate is identified. Despite the technical challenges of this process, the measurements are relatively robust. These studies therefore provide normative ranges for flow volumes and distributions, and allow verification of true physiology, matching closely with values taken from instrumented animal models. Prsa et al. have shown that the mean combined ventricular output in the near-term fetus is 465 mL/kg/min, with around 55% of this output coming from the right ventricle, and 45% coming from the left. In the near-term fetus, around 25% of the right ventricular output (15% of the combined ventricular output) reaches the lungs through the right and left pulmonary arteries; the remaining 75% of the right ventricular output flows through the ductus arteriosus to supply the abdomen, lower body and the placenta. Around 75% of the relatively well-oxygenated left ventricular output (30% of the combined ventricular output) perfuses the head, neck, and arms, with the remaining 25% joining the ductus arteriosus flow in the descending aorta. Around 50% of the descending aortic flow (30% of the combined ventricular output) flows to the placenta [27].

7. Functional differences in the fetal circulation

The fetal heart also has significant functional differences relative to the adult heart, which profoundly alter its function.
7.1. Compliance

How the compliance of the fetal heart compares to the more mature circulation is contentious. It had previously been accepted that the premature myocardium is a less compliant structure than that of the term infant and that this has an impact on preload and contractility [32]. However, more recent data [33] have suggested that fetal compliance may be significantly higher (more than double) than in the adult. This increased compliance appears to be predominantly due to differences in titin subtypes. The fetal (N2BA) isoform represents nearly all cardiac titin throughout gestation, then rapidly disappears after birth [16,33]. Compared to the adult (N2B) isoform the fetal isoform has a high intrinsic compliance and this provides the fetal myocardium with a low passive tension and reduced myocardial stiffness (Fig. 3).

It is thought that these variations in the protein structure of the myocardium enable the fetal heart to produce an adequate output even at the reduced filling pressures (3–4 mmHg [34]) seen in utero [33]. The high compliance may also be important to allow intrinsic stretch of the sarcomeres, which is thought to trigger their proliferation and hence the growth of cardiac structures [33]. Maturational changes in collagen make-up and rate of calcium extrusion are also likely to contribute to altered ventricular compliance in the fetus [35].

7.2. Passive versus active ventricular filling

Ventricular filling is biphasic, consisting of phases traditionally referred to as passive and active. In the adult circulation, ‘passive’ filling predominates, though as discussed above this is more complex than simple relaxation of the ventricle, and is governed by recoil of titin, untwisting of ventricular torsion, rotational flow patterns in the atria, and likely many other factors. Ventricular filling in late diastole is then augmented by atrial contraction. The relative contributions of these phases are readily studied by Doppler echocardiography in both adults and fetuses. In the fetal circulation the maximum velocity of passive filling (E wave) is consistently lower than the peak of active filling (A wave), producing an E/A ratio of < 1 [36]. As gestation advances, E/A ratio increases, but is rarely > 1, so active filling predominates throughout gestation.

As with compliance, multiple factors are likely influencing E/A ratio. Low E/A ratio was previously cited as an indicator of low compliance – a stiffer ventricle being less likely to fill spontaneously [35]. However, with the increasing awareness of the actions of titin, it could also be argued that a low E/A ratio is a marker of higher compliance. As shown in Fig. 3, a highly compliant fetal myocardium will have a shallow slope of the length/force curve, such that, as the sarcomere is stretched, little additional force is generated. But similarly, at lengths below the slack length (as seen at end systole), a compliant myocardium will also have low recoil. Less recoil could then manifest as less passive filling, and a lower E/A ratio.

Second, the venous return to the left atrium is low throughout gestation since pulmonary blood flow is minimal, such that filling volumes of the left side of the heart depend almost entirely on foramen ovale shunt. Low preload is known to be strongly associated with poor passive ventricular filling and low E/A ratio. Since the pulmonary blood flow – and therefore the left atrial venous return – increases through gestation, this could partly explain the rise in E/A ratio seen with advancing maturity.

Third, the normal rotational flow patterns, which may maintain the kinetic energy of inflowing atrial blood, have been shown to be disrupted in the neonatal heart [37], and may also therefore be inefficient in the fetal heart.

7.3. Heart rate

The normal fetal heart rate is between 110 and 160 beats per minute. This means there is less time available for diastolic filling. In addition, as at higher heart rates, ejection time is relatively well preserved, whereas filling time is disproportionately reduced.

7.4. Contractility

The fetal heart has a reduced inherent contractility. Less of the fetal myocardium is made up of contractile elements [32,38]. The sarcoplasmic reticulum and the T tubules are immature in the fetus and the calcium shifts for contraction and relaxation are more reliant on the extracellular levels [35]. Perhaps to counteract this immaturity, the fetal heart displays a higher percentage of a fetal troponin I isoform, which raises calcium sensitivity [39]. However, troponin C, which is responsible for maximum force generation in response to calcium levels, is low through much of gestation, only increasing in late gestation. The fetal left ventricle is also likely to have fewer β-adrenoceptors [40], a prime driver of contractility in response to circulating catecholamines. Similarly, sympathetic innervation of the fetal heart is significantly reduced [41].

8. The transitional circulation in the preterm infant

Immediately prior to birth the placenta is a low resistance vascular bed ensuring that low pressure deoxygenated blood can return for exchange, while the lungs represent an area of high resistance and the pulmonary flow is therefore diverted. If born at term, a healthy baby’s first few breaths inflate the lungs, rapidly dropping the resistance they present to the circulatory system and increasing pulmonary blood flow. At around the same time (see Kluckow and Hooper in this issue of Seminars for a detailed discussion of the importance of ventilation around the time of cord clamping), the umbilical cord is cut, blocking the low-pressure placental bed. Due to a sharp increase in left atrial return from the pulmonary veins, left-sided atrial pressure rises rapidly, functionally closing the septal layers of the foramen ovale [42]. The ductus arteriosus will then gradually close under the influence of oxygen and the metabolism of prostaglandins in the fully functioning lungs. At the end of this transition the full return of deoxygenated blood from the body to the right heart is directed to the lungs for oxygenation, and the full return of oxygenated blood from the lungs to the left heart is now directed to the body to supply the tissues [42].

There are multiple reasons why this process can be disrupted whenever infants are born prematurely. The key factors are discussed below.

8.1. Low inherent contractility

The immature myocardium has impaired contractility due to a decreased proportion of contractile elements, altered calcium release, altered titin function, decreased β-adrenoceptor number and decreased sympathetic innervation [39–41]. Animal and human studies conclusively show that the innate contractility of the preterm myocardium is impaired [32,43]. Preterm infants also have higher levels of serum troponin T, a marker of myocardial injury. The rise in troponin T is particularly marked in those who have suffered from hypoxia either in utero or at birth or in infants with continuing respiratory distress syndrome [44]. This suggests that there may be a level of myocardial damage or even programmed apoptosis occurring in these infants that may affect the contraction and relaxation properties of their hearts.
8.2. Poor tolerance of high systemic vascular resistance

The left and right ventricles both face an abrupt rise in vascular resistance at the time of cord clamping. Unless born after cho-
rioamnionitis or with sepsis, high resting α-adrenergic tone in the peripheral vasculature in preterm neonates maintains constriction of the capacitance arterioles in many vascular beds, further accentuating high vascular resistance. Echocardiographic studies in preterm infants have shown that the immature myocardium not only has reduced contractility, but that it is also particularly sen-
tive to increases in afterload [45].

8.3. Impaired diastolic filling

As seen in the fetus, the low compliance of fetal isoforms of titin mean that early diastolic recoil is ineffective [33]. Rotational flow patterns are disrupted, potentially having an effect on preservation of kinetic energy of inflowing blood during atrial filling [37]. High heart rate means that there is limited time available for ventricular filling. Most inotropes and vasopressor-inotropes are also chrono-
tropic, and will therefore further limit the time available for ven-
tricular filling [46]. Although the reliance of ventricular filling on atrial contraction reduces through gestation, it is still significantly more important for diastolic filling in neonates than in older chil-

8.4. Persistence of fetal shunt pathways

High prostaglandin levels, relatively low oxygen levels and the inherent immaturity in the muscular wall of the ductus arteriosus are among the leading factors delaying effective ductal closure in preterm infants. In the vast majority of preterm infants pulmonary vascular resistance drops to below systemic levels within minutes/ hours of birth, such that direction of blood flow within the ductus reverses to become left to right [42]. Particularly in the current era of antenatal steroids and surfactant administration there is good evidence that high volume left-to-right ductal shunt can occur even on the first day of postnatal life [50]. This causes significant pul-
monary hyperperfusion, giving a risk of pulmonary hemorrhage, and in a number of preterm infants will also cause systemic hypoperfusion. For a comprehensive discussion of the hemody-
namic role of the ductus arteriosus, see the article by Evans in this issue of Seminars. The foramen ovale can also remain patent in many premature infants. Due to the large amount of blood returning to the left atrium in many preterm neonates with pul-
monary overcirculation caused by the sustained ductal patency, the direction of shunting reverses to become left to right, potentially worsening their pulmonary hyperperfusion and systemic hypoperfusion.

9. Long-term effects of preterm delivery on heart development

It is becoming clear that the consequences of the immature heart undergoing the circulatory transition do not end in the newborn period. When the hearts of ex-preterm infants are studied in early adulthood, they have significantly reduced chamber length, increased myocardial mass, and impaired systolic and diastolic function [51]. Provisional work in the newborn period suggests that these changes may be even more marked in the extremely preterm infants who currently survive to discharge from the neonatal unit.

When studied by cardiac MRI, extremely preterm infants have in-
creases in left ventricular mass of more than 50% compared with term controls [52].

That pathologic remodeling occurs following preterm birth is to be expected given the requirement for cardiac growth in the healthy fetus. Fetal myocytes are in mononucleated form, and respond to stress by hyperplasia as opposed to the pattern seen later in life when the mature binucleated myocytes respond with hypertrophy. Lamb models show that the hearts of animals born preterm have a five- to seven-fold increase in extracellular matrix, a 20% increase in cardiomyocyte volume, and a significant increase in the proportion of myocytes remaining in the mononucleated proliferative state, even at term-corrected age [53].

The triggers for and functional significance of the remodeling seen following preterm birth are currently largely unknown, but it is feasible that cardiac remodeling puts surviving ex-preterm infants at risk of heart failure and ischemic heart disease.

10. Conclusion

The developing cardiovascular system has functionally signifi-
cant alterations in preload, contractility, afterload, diastolic filling, and intracardiac flow patterns. Whereas these changes occur under physiological circumstances in utero, they become rapidly patho-
logical in the setting of preterm birth. Abnormal physiology is then further compounded by persistence of the fetal shunt pathways. An understanding of the development of the circulatory physiology can assist the practising clinician with management of circulatory failure in the premature infant.

Practice points

- The fetal and neonatal circulations differ significantly from the circulation seen at any other point in development; interpretation of clinical and imaging findings should be made in that context.
- Therapeutic interventions during the transitional circula-
tions should target specific pathologies in preload, contractility, systolic function, diastolic function, after-
load, and shunting through the fetal pathways.
- As inter-individual differences in circulatory physiology are broad, response to therapeutic interventions should be regularly reassessed in every patient with evidence of circulatory failure.

Research directions

- Technological advances, particularly in fetal imaging, should examine the changes in fetal circulatory function in the presence of diseases such as placental failure, congenital heart disease, and twin–twin transfusion syndrome.
- Improvements in clinical assessment of circulatory physiology after birth are urgently required; a range of invasive and non-invasive methodologies are entering the clinical arena including but not restricted to echocar-
diography, MRI, impedance electrical velocimetry moni-
toring, near-infrared spectroscopy, and stroke volume variability.
Conflict of interest statement

None declared.

Funding sources

None.

References