REVIEW ARTICLE

Future perspectives on the use of deformation analysis to identify the underlying pathophysiological basis for cardiovascular compromise in neonates

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The assessment of the wellbeing of the cardiovascular status in premature infants has come to the forefront in recent years. There is an increasing realisation that myocardial performance, systemic blood flow and end-organ perfusion (particularly during the transitional period) play an important role in determining short and long-term outcomes in this population. The recent open access series on Neonatologist Performed Echocardiography (NPE) published in this journal outline the necessary techniques for image acquisition and analysis and provide a framework for the potential clinical applications of NPE in neonatal, and specifically preterm care. In this "Future Perspectives" review, we describe the important determinants of adequate cellular metabolism and myocardial performance (e.g. loading conditions, intrinsic contractility and morphological change), we discuss the maladaptive state of the preterm cardiovascular system, and highlight the emerging role that non-invasive echocardiography techniques, such as deformation analysis, serve in identifying the underlying physiological basis for cardiovascular instability.

INTRODUCTION

The cardiovascular system and the management of transitional circulatory physiology in premature infants is complex and challenging.[1–3] The cardiovascular determinants of cellular homoeostasis rely on the unique interface between cardiac performance, end-organ perfusion and oxygen delivery and consumption.[4] Coupled with immature intrinsic contractile reserve, the preterm myocardium is preconditioned to respond poorly to changes in preload (e.g. in states of hypovolemia or secondary consequences of positive pressure ventilation) and is poorly tolerant to elevated pulmonary vascular resistance (e.g. maladaptive transitional physiology). In addition, the presence of intra- and extra-cardiac shunts, the impact of perinatal events and emergence of antenatal interventions may all contribute to the delay in the postnatal transition and subsequent onset of haemodynamic insufficiency in this population. The haemodynamic assessment in the premature infant has historically been difficult, but echocardiography has significantly changed our view on hemodynamic transition of the extreme preterm infant.[5] Recently, evaluation of cardiac performance with myocardial deformation by two-dimensional speckle tracking echocardiography (2D STE) has gained greater acceptance as validation has been achieved postnatally in preterm and term neonates.[6] In this review, we describe the important determinants of adequate cellular metabolism and myocardial performance, discuss the maladaptive state of the unique preterm cardiovascular system, and highlight the emerging role that non-invasive echocardiography techniques, such as deformation analysis, serve in identifying the underlying physiological basis for cardiovascular instability.

DETERMINANTS OF ADEQUATE CELLULAR METABOLISM

The aim of treating low blood flow states is to ensure uninterrupted cellular metabolism. Adequate cellular metabolism involves a complex interplay between various components to sustain a normal cardiac output (and end organ perfusion) in addition to a normal blood oxygen (O_2) content (Fig. 1). Blood O_2 content is dependent on the oxygen carrying capacity of blood (haemoglobin) and lung function to ensure adequate gas exchange. Cardiac output (myocardial function) requires an intact myocardial pump to overcome vascular resistance and adequately fill the pump. Therefore, cardiac performance is dependent on the interaction between preload, afterload, intrinsic myocardial contractility and heart rate. Since 70% of the neonatal myocardium is non-contractile, the intrinsic contractility is likely further compromised in premature infants.[7] Contractility is further influenced by the *length–tension relationship*, the *force–velocity relationship and the force–frequency relationship* (Fig. 1). The length–tension relationship (also known as the Frank–Starling curve) governs the interaction between contractility and preload. Increased preload results in increased sarcomere length and tension leading to an increase in the force of contraction. Overstretching of those fibres however will compromise contractility and lead to myocardial dilatation. The force–velocity relationship governs the interaction between contractility and afterload. This is also referred to as ventricular–arterial coupling. An increase in afterload is usually coupled with an increase in myocardial contractility up to a certain point beyond which decoupling occurs and contractility is compromised. Premature infants suffer from early decoupling due to the maturational differences outlined above.[8] The force–frequency relationship

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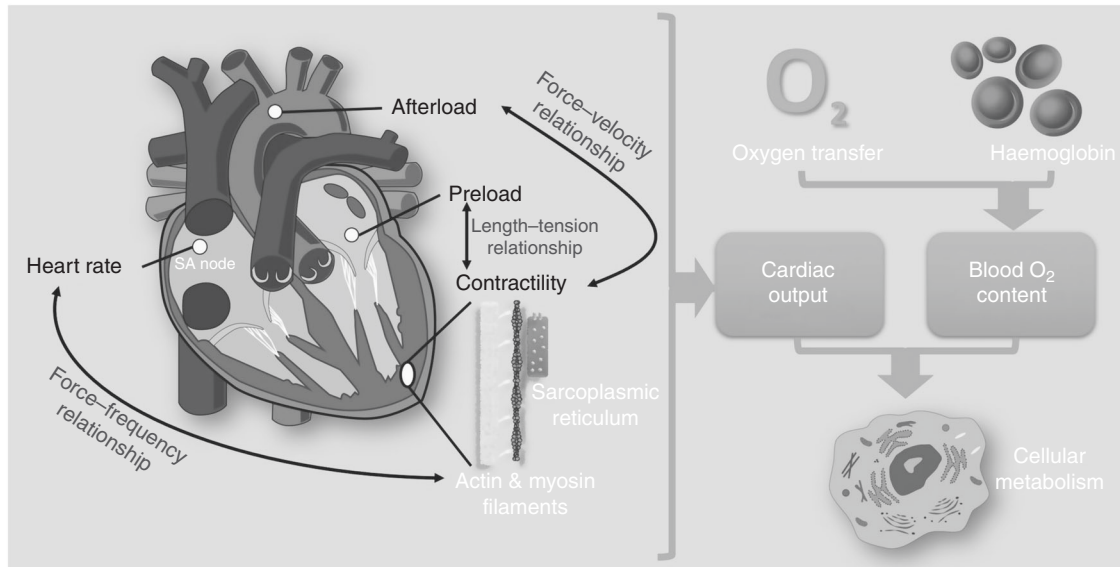Correspondence: Afif EL-Khuffash (afifelkhuffash@rcsi.ie)

Fig. 1 Determinants of cardiac output and adequate cellular metabolism

(FFR) governs the interaction between contractility and heart rate and describes the increase in contractile force with increasing chronotropy (heart rate) if there is adequate preload. "This involves neurohumoral effects on the interplay of calcium-flux modulating proteins in the myocyte membrane, which are influenced by changes in the frequency of stimulation. The exact mechanisms are complex and still not well understood".[9]

Understanding this complex mechanism necessary to maintain adequate circulation underpins the need for a more comprehensive appraisal of those components during cardiovascular compromise. The conventional use of blood pressure in isolation to determine inadequate blood flow is simplistic at best and should be abandoned in neonatal practise. A common misconception amongst clinicians is that arterial pressure is a reliable surrogate of systemic blood flow implying that a normal mean arterial pressure confirms the adequacy of blood flow to essential organs. This assumption fails to consider peripheral vascular resistance.[10] Several studies illustrated the lack of a relationship between arterial pressure and cardiac output.[11] A normal mean arterial pressure in the setting of a high resistance systemic circulation can only be explained by reduced systemic blood flow.[12] Conversely, a low blood pressure in the setting of low peripheral vascular resistance may imply normal or high systemic flow.

CHARACTERISTICS OF THE PREMATURE CARDIOVASCULAR SYSTEM
The premature myocardium is characterised by systolic dysfunction due to an immature and inefficient contractile apparatus and diastolic dysfunction due to the lack of elastic compliant tissue and a preponderance of stiff fibres.[13,14] These developmental differences drastically reduce the functional reserve of the premature heart in the face of postnatal stresses and increased afterload. During fetal life myocardial performance is preserved due to the low resistance placental circulation and the presence of fetal shunts which bypass the high resistance pulmonary circulation. However, the premature myocardium is ill equipped to deal with the high afterload, low preload state associated with the loss of placental circulation, prior to the establishment of adequate pulmonary circulation. The premature cardiovascular system is further characterised by important developmental differences that further contribute to cardiovascular instability.

Those include a lack of adequate adrenergic innervation and receptors potentially reducing the inotropic effect of medications. The immaturity of the hypothalamic–pituitary–adrenal axis further prevents the upregulation of adrenergic receptors and the production of glucocorticoids during times of stress.[15,16] There is a high resting peripheral vascular tone in preterm infants that is likely due to the higher number of peripheral vasoconstrictive (alpha) receptors and a reduction in the number of peripheral vasodilatory (beta) receptors.[17]

USING ECHOCARDIOGRAPHY TO DECIPHER THE PUZZLE
The use of echocardiography in the neonatal setting to assess the adequacy of the cardiovascular system remains largely dependent on either a subjective assessment of myocardial function, or the use of measurements of cavity change during the cardiac cycle (i.e. shortening fraction, SF and ejection fraction, EF). This approach fails to identify the determinants of myocardial performance. The term "myocardial function" is often used synonymously (but incorrectly) with "myocardial contractility". However, it is important to realise, as described above, that *myocardial contractility is only one of the determinants of myocardial function*, along with preload, afterload and heart rate. Tailoring therapy to target the predominant component responsible for myocardial dysfunction may result in a significant improvement in restoring cardiovascular instability while avoiding unnecessary exposure to medication. For example, reduced myocardial performance resulting from impaired preload is unlikely to respond to inotropic medication aimed to enhance contractility.

There is a need for an accessible, reliable, and a valid non-invasive tool with the ability to assess both intrinsic myocardial contractility and loading conditions in premature infants. The conventional echocardiography measures of SF and EF describe the change in a cavity dimension (SF assess change in diameter and EF assesses change in area). The reduction in function identified using SF or EF is likely to represent adverse loading conditions (e.g. impaired preload due to a reduction in left ventricular filling) rather than impaired contractility alone. In other words, you can have normal SF and EF without impaired contractility. However, it is also possible to have altered contractility that will lead to a reduction in function measured using SF and EF. Identifying the primary physiological cause for

dysfunction and separating out the contractile vs. loading components is challenging, as most of echocardiography measurements of function do not directly assess contractility, but are still highly dependent on preload and afterload.

The use of deformation analysis to categorise myocardial dysfunction

Characterization of ventricular performance with myocardial deformation by 2DSTE is a validated method to assess both ventricular contractility and loading conditions in preterm infants. Deformation analysis refers to a change in shape of a segment of the myocardium, or the myocardium as whole, from its baseline shape in diastole to its (deformed) changed shape in systole. Deformation occurs in three planes in the left ventricle (longitudinal, radial and circumferential) and predominantly in the longitudinal plane in the right ventricle. This results in the change in cavity dimensions leading to the ejection of blood during systole.[18] During diastole, the deformed myocardium returns to its baseline shape. Strain is the measure of the amount of deformation occurring and it is expressed as a percentage change from baseline. The speed at which this deformation occurs can also be measured and is termed systolic strain rate (SRs). The speed at which the deformed muscle wall returns to baseline is referred to as early (SRe) and late (SRa) diastolic strain rate.[4] Strain and strain rate measurements are feasible and reproducible in the premature and term neonates; normative values are now well established in this population.[19–23] Deformation analysis is more sensitive than SF and EF in detecting preclinical myocardial dysfunction, predict important short and long-term outcomes, and monitor response to therapeutic interventions.[20,24–26] In addition, deformation analysis provides an opportunity for the assessment of regional and global functional characteristics of the myocardial wall. In contrast to SF and EF that measures changes in cavity dimensions, strain and strain rate provides information on muscle wall characteristics. Strain, like SF and EF, is also highly influenced by loading conditions and therefore provides similar information regarding myocardial function, rather than intrinsic contractility. Increasing preload leads to a rise in the magnitude of strain while increasing afterload leads to a decrease in the magnitude of strain.[20,24] However, recent animal and adult human data have convincingly demonstrated that strain *rate* shows a close relationship with invasive measures of intrinsic contractility and exhibits observable properties further supporting load independency.[27] In a mouse model, both strain and strain rate measurements were reduced in mice with induced myocardial infarction (leading to compromised intrinsic contractility) when compared with controls; however, only strain and not strain rate was reduced in mice with transaortic constriction (leading to increased afterload). This suggests that strain rate is relatively uninfluenced by events leading to changes in afterload but is affected by events leading to compromised contractility. In addition, in a piglet model, strain rate is augmented with increasing heart rate thus demonstrating a FFR described above which is characteristic of invasive measures of contractility.[9]

Our group have replicated some of those observations in various neonatal populations.[28] In premature infants less than 29 weeks gestation, strain (but not strain rate) is positively influenced by increasing preload and is negatively influenced by increasing afterload.[29] We demonstrated that LV end diastolic diameter (LVEDD), a surrogate for preload, positively correlated with strain, and that an echocardiography-based measurement for systemic vascular resistance (SVR was determined by integrating blood pressure and left ventricular output as described by Noori et al.[30]) negatively correlated with LV strain. Conversely in the same population, we studied the relationship between heart rate and strain/strain rate and found that within a physiological range of heart rate, strain rate (but not strain) increases with increasing heart rate suggesting a reflection of intrinsic contractility and exhibiting a force–frequency relationship.[28] In summary these preclinical and clinical studies point to strain as highly influenced by loading conditions and strain rate as a mostly load independent measure, and therefore, more likely to represent myocardial dysfunction secondary to a reduction in intrinsic contractility (Fig. 2).

Characterization of adverse loading conditions and impaired contractility with advanced strain and strain rate measures provide a deeper understanding of myocardial performance phenotyping in preterm infants. For example, we have shown that premature
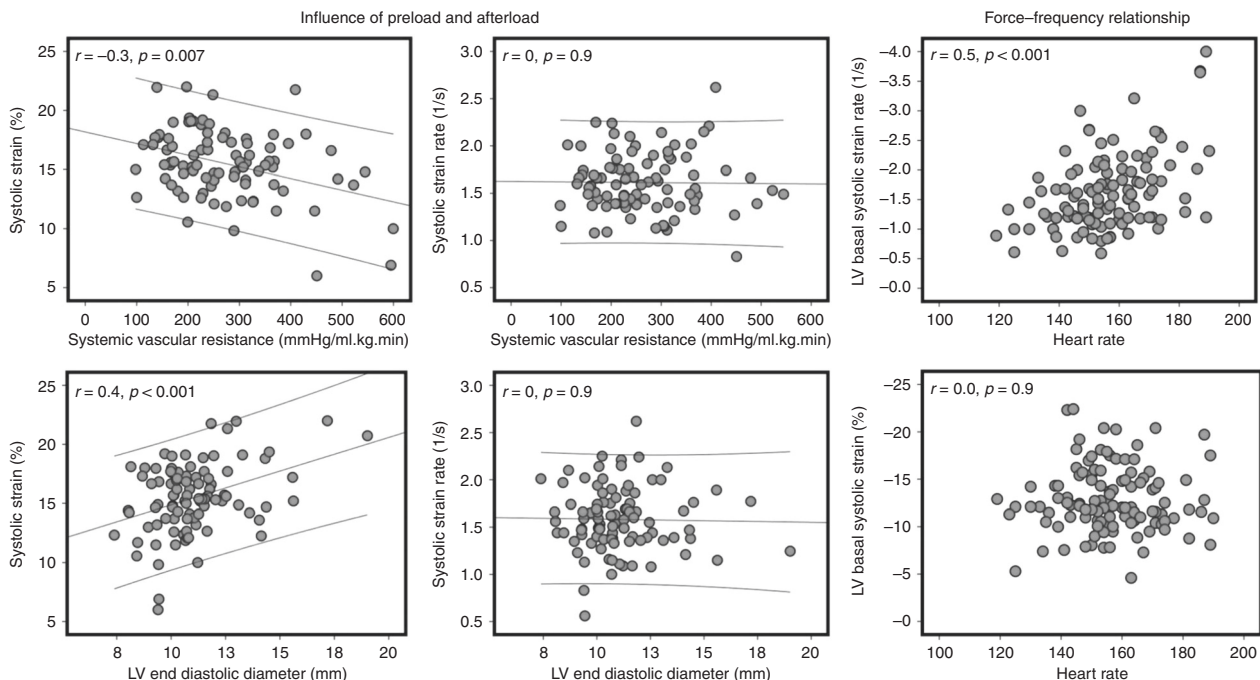

Fig. 2 Relationship between deformation measurements and loading conditions vs. intrinsic contractility

Table 1. Suggestions for integrating echocardiography and blood pressure measurements for assessment of cardiovascular instability

Underlying physiology	Ejection fraction	Strain	Strain rate	Systolic BP	Diastolic BP	Suggested management
Reduced preload	↓	↓	–	−/↓	↓↓	Fluid Resuscitation
Increased afterload	↓	↓	–	↓	↑	Vasodilator/Inotrope
Impaired contractility	↓	↓	↓	↓	−/↓	Inotrope

Legend: ↓ decreased; ↑ increased, − no change

infants assessed at 36 weeks post menstrual age (PMA) have lower magnitudes of strain with similar values of strain rate when compared to health term healthy term controls on day 1 of age.[25] These preterm infants demonstrate increased evidence of afterload at birth, that likely persists over the first year of age with preserved strain rate; the lack of difference in strain rate values supports the load dependency of strain and load independency of strain rate.[24,31] Finally infants with hypoxic ischaemic encephalopathy undergoing therapeutic hypothermia exhibit increased afterload due to increased SVR and impaired intrinsic contractility due to myocardial ischaemic damage.[32] We demonstrated a reduction in both strain and strain rate in this population when compared to healthy controls.[25]

PUTTING IT ALL TOGETHER IN A CLINICAL CONTEXT
Knowledge of the properties of the various echocardiography measurements and their relationship to the different determinants of myocardial function may provide the potential for a more intelligent and targeted approach to the management of haemodynamic compromise in neonates. Identifying the predominant underlying physiological cause of reduced myocardial performance and cardiac output: reduced preload, increased afterload, or reduced intrinsic contractility, can certainly help to move away from regimented protocols for the management of low blood flow states. Recently, Giesinger and McNamara proposed an approach to cardiovascular support based on disease pathophysiology.[33] In their review they "present a modern approach to cardiovascular therapy in the sick neonate based on a more thoughtful approach to clinical assessment and actual pathophysiology." The use of deformation measurement, along with the integration of blood pressure measurements can provide further means to support this (patho) physiological based approach (Table 1).

CONCLUSION
The causes of haemodynamic compromise are complex and unique to each infant. The underlying pathophysiology may be difficult to identify using blood pressure measurements in isolation and a thorough understanding of the various determinants of adequate cellular metabolism is essential. The use of echocardiography with knowledge of what functional measurements represent can enable a more targeted approach focusing on the underlying physiology. This approach required a systematic assessment to determine if improvement in short- and long-term outcome can be achieved.

AUTHOR CONTRIBUTIONS
N.B. wrote the first draft of the paper and performed the background literature search. A.K. organised the outline of the text, reviewed the manuscript and provided editorial input.

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