While a number of research tools for assessing circulatory status in preterm infants have been investigated, none have so far proven reliable in assessing cardiac function or cardiac output. While important advances in understanding of physiology have been made using echocardiography, the technique has poor repeatability [3], and is unable to accurately determine how well the heart muscle is contracting.

Cardiac magnetic resonance (CMR) techniques have significantly advanced understanding of cardiovascular physiology and pathophysiology in adults. These non-invasive assessments of cardiac health are now being gained faster, in more detail and with greater sophistication than ever before [4]. Techniques currently available in adults can accurately and reliably assess both contractility of the heart muscle and volume of blood ejected by the heart. In addition, tagging of distinct areas of heart tissue has permitted the complex contractile and rotational movement of the heart to be interrogated. However, until now, technical challenges have prevented the use of CMR in vulnerable preterm infants.

Scanning facilities

In 1996 an MR scanner was installed in the Neonatal Intensive Care Unit at Queen Charlotte’s and Chelsea Hospital. This enabled the safe study of brain development and injury in thousands of even the smallest, sickest preterm infants. In 2006 the system was upgraded to a Philips Achieva 3.0T MR scanner with full cardiac capacity.

Full intensive care facilities are available within the scanning suite, enabling us to safely perform MR scans on infants requiring ventilatory and inotropic support. Since its installation our group has been developing functional CMR techniques for study of the preterm transitional circulation.
Scanning process/stability

Infants are scanned with oxygen saturation, heart rate and continuous temperature monitoring (Figure 1), with a pediatrician or trained neonatal nurse in attendance throughout each scan. Scans can be performed free-breathing, with the provision of nasal continuous positive airway pressure (NCPAP) or low-flow oxygen as clinically indicated.

In all cases cardiac MR images are obtained after infants have been allowed to fall into a natural sleep after a feed, with careful swaddling. Sedative medication has not been required. Protection from acoustic noise is achieved by applying moldable dental putty to the ears and covering them with neonatal ear muffs (Natus Minimuffs, Natus Medical Inc., San Carlos, CA, USA). To date we have performed cardiac MR imaging in over 100 newborn infants without any adverse events.

Image sequences and optimization

To give an idea of the challenges involved in obtaining satisfactory images of cardiac function in the extremely preterm neonate, Figure 2 shows same-scale images of a four-chamber cardiac view from an adult, and from a neonate weighing 590 grams at the time of scan.

Imaging at 3T provides a potential doubling of intrinsic signal-to-noise ratio (SNR) compared with conventional 1.5T platforms. This added signal confers a substantial benefit for imaging small neonates. This is certainly the case for neurological examinations, but there are challenges in realizing this potential for cardiac MR, as field inhomogeneities increase at higher field strengths and can degrade imaging performance. However, while this is a particular problem over larger structures such as the adult thorax, the smaller size of the neonatal chest appears to produce less inhomogeneity, and excellent image resolution at 3T [5].

Early difficulties with susceptibility artifacts have been minimized with appropriate shimming. Shorter TR sequences have reduced artifacts produced by through-plane blood flow, and the associated temporal resolution of around 10 milliseconds has allowed us to acquire 32 phases of imaging despite neonatal heart rates of around 180 beats per minute.

CMR is highly sensitive to movement artifacts, such that in adult and pediatric cardiac imaging most techniques require image acquisition to occur either during episodes of breath-holding, or by use of a navigator bar to coordinate image acquisition with diaphragmatic movement. Both such techniques have a significant impact on the time required for image acquisition.

A somewhat surprising advantage of neonatal cardiac imaging has been that high-quality images have been obtained without the need for such measures [5]. This improves the applicability of scanning in the neonatal population (by avoiding the need for intubation and ventilation) and reduces image acquisition time.

Imaging sequences

Balanced Fast Field Echo

Core information on global cardiac function can be obtained using rapid balanced Fast Field Echo (bFFE) sequences. The approximate...
imaging parameters used for bFFE sequences are TR 4 ms, TE 2 ms, flip angle 45°, FOV 220 mm, matrix 144, in-plane resolution 1.5 mm, slice thickness 3-5 mm, temporal resolution approx. 10 milliseconds, 32 phases/cycle.

**Four-chamber view**
The four-chamber view demonstrates the left and right atria and ventricles, and is similar to an echocardiographic apical four-chamber view (Figure 3). The view is used predominantly to allow tracking of atrioventricular valves through the cardiac cycle to eliminate inaccuracy from the through-plane motion of the base of the heart. This base-to-apex shortening may also potentially be quantified using myocardial tagging techniques.

**Short axis view**
The short axis view demonstrates the left and right ventricles, and is similar to an echocardiographic parasternal short axis view (Figure 4). This is a key view when examining cardiac function. Views taken at a single level allow analysis of wall thickness and thickening through the cardiac cycle. The position of this single slice can be determined from the previously acquired four-chamber view, allowing for constant positioning at the mid-ventricular level. This permits enhanced accuracy of CMR over traditionally echocardiographic assessments, where small variations in transducer positioning may lead to significant variations in quantitative measures in the tiny preterm heart. However, a "stack" of adjacent slices may also be acquired to allow assessment of global cardiac function. Short axis stacks therefore allow assessment of total left and right ventricular volumes at end-diastole and end-systole by tracing the endocardial border in each slice. Cardiac MR therefore provides enhanced accuracy over echocardiography as the two-dimensional nature of echocardiography means that assumptions, which are often inaccurate, have to be made about the shape of the ventricular cavities.

Assessments of global left and right ventricular function can be made either using Philips own Viewforum software, or with a number of commercially available packages. We are currently comparing quantitative data obtained from Viewforum analysis with that obtained from CMR Tools (Cardiovascular Imaging Solutions Limited, London) which allows modeling of a mesh of the endocardial or epicardial borders (Figure 5) and as mentioned above allows simultaneous tracking of the level of the atrioventricular valves, reducing inaccuracy from through-plane motion of the base of the heart.
Phase contrast imaging

Phase contrast imaging techniques allow quantification of volume of flow in any large blood vessel. The approximate imaging parameters used for bFFE sequences are TR 5 ms, TE 3 ms, flip angle 10°, FOV 250 mm, matrix 208, in-plane resolution 0.98 mm, slice thickness 4 mm, 20 phases per cardiac cycle.

Phase contrast measures of cardiac output at the level of the aortic and pulmonary valves allow internal validation of cardiac output (by comparing measurements taken by bFFE and phase contrast techniques). However, their particular value in the neonate lies in quantifying flow at multiple points in the circulation. The persistence of fetal shunt pathways in the preterm neonate means that neither left nor right ventricular output can necessarily be taken to represent true systemic or pulmonary perfusion. Cardiac MR allows quantification of flow in the superior vena cava (SVC) and descending aorta (DAO), both of which are considered to be markers of true systemic perfusion in the preterm neonate [3]. In Figure 6, static tissues are shown as mid-gray, flow in the head-foot direction is dark, flow in the foot-head direction is light.

By estimating velocity in each pixel covering the vessel throughout the cardiac cycle, a velocity-time graph is produced, with the area under the curve representing total volume of flow (Figure 7). Our initial data suggests that repeatability of phase contrast quantification of blood flow volume may be significantly improved when compared to echocardiography in neonates. Provisional data also suggests that measures of left ventricular output by bFFE and phase contrast techniques are closely related, so providing valuable internal validation of both techniques.

Comparison of CMR and echocardiography

While echocardiography has clear utility at the cotside, the technique is far from ideal. In particular, the relatively poor repeatability of echo flow measurements limits its use as an end-point in clinical trials of intervention.

Cardiac MR techniques have a number of advantages over echocardiography:
- Cardiac MR is less operator-dependent, enhancing repeatability
- Direct visualization of function in all areas of the heart obviates the need for assumptions of cardiac geometry, which are often overly simplistic
- Assessment of shortening in radial and axial planes (see below), along with assessment of rotational motion, provides multiple markers of contractility
- Multiple techniques allow internal validation of flow measurements
- Improved repeatability allows decreased subject numbers while maintaining the power of interventional studies
- Multiple assessments of intracardiac volumes, wall motion and blood flow will provide an enhanced appreciation of how clinical interventions impact on the three principal components of cardiac function – preload, contractility and afterload.

Placement of radial and axial plane slices

Placement of the radial and axial plane slices can be determined from orthogonal views, reducing error in quantitative measures from variability in image plane. This may be of particular value in assessment of velocity of circumferential fiber shortening, an afterload-correctable measure of “true” contractility taken from the short axis view. Afterload correction of functional measures is of particular significance in neonates, given the prominent role of peripheral vascular resistance in governing blood pressure in this population.

Future directions

Continuing rapid developments in MR technology mean that newborn infants will benefit from further advances in image quality, complexity and post-processing.

CMR-guided insights into neonatal circulatory function may in future be linked with the IUPS Physiome project [6] by registering neonatal
CMR images to computational models, potentially greatly advancing understanding of newborn circulatory physiology. We may also be able to investigate the importance of common genetic polymorphisms on neonatal circulatory function [7] and response to therapeutic interventions.

The key ultimate goals of the project are to use CMR biomarkers to improve understanding of neonatal cardiovascular function in health and disease, employ biomarkers as endpoints in clinical trials of existing and emerging therapies, and allow standardization of bedside echocardiographic techniques to apply improvements in patient care to the largest number of sick newborn infants. In the long term we hope that improved ability to monitor and support heart function in premature babies will help infants to survive, and survive free from disability.

References


