The development of, and future for, fetal functional cardiac imaging techniques

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Structural evaluation of the fetal heart has now become an accepted component of the modern morphology scan, and increasingly cardiac structural evaluation is being performed in the first trimester along with evaluation of risk at the nuchal translucency scan. While a number of complex cardiac anomalies still elude 100% detection, and others may be subtle at the time of morphological evaluation and evolve later in gestation, prenatal detection and accurate diagnosis of fetal structural cardiac abnormalities and integrated multidisciplinary care has become a standard part of tertiary care.

Within the fetal medicine community and in the international literature, there has for over a decade been an increasing demand for measures to non-invasively and accurately evaluate fetal cardiac function. There are numerous conditions that may be associated with fetal cardiac impairment, either intrinsic to the heart itself, or extrinsic, such as the heart strain seen in intrauterine growth restriction (IUGR) or twin-twin transfusion syndrome (TTTS), the overload of sacrococcygeal teratomas, vascular compression of congenital diaphragmatic hernia or chest masses etc. This has resulted in a relative explosion of publications with a plethora of novel functional indices and techniques, the majority of which been extrapolated from adult applications.

For two of the more common conditions in fetal medicine practice (IUGR and TTTS), fetal evaluation is serially performed to determine timing of intervention or delivery. Additionally, when counselling regarding long-term outcome, one of the major determinants in these conditions is potential cardiac dysfunction, though in the absence of validated Doppler indices, evaluation for this remains relatively crude. Most practitioners will be familiar with 'eyeballing' the fetus to evaluate cardiac orientation, size, shape, rate and rhythm and to a crude degree evidence of effective contractility. The enlarged, 'floppy' and hypo-contractile heart may be visually determined, but this may be a late appearance, as may signs of heart failure with development of hydrops. Attempts have been made to even quantify the 'floppiness' or irregularity of the heart using a pseudo-scientific 'sphericity index' though one might anticipate that alterations in cardiac dimensions would be a relatively late feature and represent at least some degree of cardiac failure. It is the time period before this failure, when there is subclinical cardiac dysfunction and cardiac remodelling, that is the target of indices of fetal cardiac function, and it is here that interventions may be optimally directed.

Functional and unique circulatory properties of the fetal heart

A starting point for evaluation of fetal cardiac function is to consider basic cardiac functions. Simplistically, the heart fills, pauses, contracts, then perfuses, moving blood effectively and appropriately around the body to provide adequate tissue perfusion. As has been previously described, ideal function involves preservation of both systolic and diastolic function, with synchronised time events leading the heart through the phases of: Isovolumetric relaxation; Early (passive) diastole; Atrial contraction; Isovolumetric relaxation; Ejection.[1]

The fetal heart has two parallel circuits with the two ventricles contributing to perfusion of the systemic circulation, with three shunts (foramen ovale, ductus arteriosus and ductus venosus) connecting them. The right ventricle predominantly supplies the subdiaphragmatic circulation and placenta while the left ventricle is responsible for supplying highly oxygenated blood to the brain and coronary arteries. Between these lies the Aortic Isthmus, an important watershed that may give valuable information about the relative function of the two sides of the heart. The fetal heart is accepted to show a right heart dominance with 52–65% of cardiac output going through the right ventricle, 75–90% of which shunts through the ductus arteriosus to the systemic circulation.[2]

Perfusion is dependent upon stroke volume, determined in turn by preload, afterload and contractility. The cerebral and subdiaphragmatic/placental vascular beds determine ventricular preload and afterload. Venous return is the main factor determining preload which influences ventricular filling. In conditions of volume overload such as recipient TTTS, there will be dilatation of the cardiac chambers. Afterload is determined by the pressure in the outflow vessels, whether aorta or pulmonary artery, against which the heart must contract. Whilst it may appear simple to deconstruct cardiac function into individual factors such as preload, afterload, electrical activity and myocardial contractility, the picture is of course not this clear with each of these factors showing a strong inter-dependence. The result of this is that any test that appears to evaluate one of these components will of course be influenced by the others. This may be one of the reasons why researchers have proposed complex 'scoring' systems to more comprehensively evaluate cardiac function, though underlying inadequacies and poor standardisation for each of the components of these scores reduce their potential impact.[3,4]

Table 1: Key two-dimensional image-based functional cardiac tests.

Cardiac parameter	Description	Method
Systolic function		
Blood volume estimation: ejection fraction or cardiac output.	Indicative of the volumetric fraction of blood ejected from the ventricle with each heartbeat, though may only show changes late in progression of some diseases.[1] Volume measurements notoriously prone to inaccuracy of vessel diameter measurement.	M-mode, speckle tracking.[1]
Myocardial deformation: strain and strain rate	Strain and strain rates represent the magnitude and rate respectively of myocardial deformation.[11] Disagreements remain on how strain and strain rate alter with gestation,[1] and whether frame rates are too low for reliable fetal measurement.[12]	Tissue Doppler or speckle tracking.[1]
Left ventricular shortening fraction	The difference in ventricular chamber diameter between end-diastole and end-systole divided by the end-diastolic diameter.[8] Longitudinal motion uses endocardial longitudinal fibres,[8] furthest from the epicardial blood supply so sensitive to hypoxia. This can be challenging to acquire in the fetus because it depends on the fetal lie to obtain the required transverse view of the heart.[13]	M-mode.[8]
Myocardial motion: fetal tricuspid annular plane systolic excursion (f-TAPSE) – also mitral (f-MAPSE)	A modified method to measure the vertical movement of the tricuspid valve annulus for assessment of right heart function, providing a quantification of ventricular contraction.[14] As a parameter reflecting longitudinal function, the f-TAPSE typically shows changes earlier in disease progression.[1]	M-mode, speckle tracking.[1]
Diastolic function		
E/A ratio	Ratio of the two peaks in flow velocity observed over the atrioventricular valves in diastole, during early (E) passive diastolic filling and during the atrial (A) 'kick' or contraction'.[5,15] This provides an independent assessment of both sides of the heart.[10] However, results for the E/A ratio have been mixed[10] as respiratory and body movements may have a lot of influence and the fast fetal heart rate may fuse these waveforms.	Pulsed-wave Doppler.[10]
Global function		
Myocardial performance index (MPI)	A measure of global myocardial function using a ratio of isovolumetric to ejection time intervals. Most commonly performed using the valvular clicks as landmarks[16] using pulsed-wave Doppler with one plane for the left heart and two separate planes for the physically separated tricuspid and pulmonary valves. Alternatively performed using tissue Doppler, especially for the right ventricle[7] where otherwise dual pulsed-wave Doppler strips are required.	Pulsed-Doppler, tissue Doppler.

Modified from Crispi, *et al*.[1]

Available techniques for evaluation of fetal cardiac function

Numerous parameters have been proposed to quantify fetal cardiac function, from measurements including Doppler flow mapping, heart biometry and timing of cardiac events.[2] The basis of many of the novel indices of fetal cardiac function include techniques familiar to most fetal medicine practitioners and cardiologists such as pulsed wave,[5] M-mode,[6] and tissue Doppler[7] as well as the relatively new technique of speckle tracking.[8] Traditionally, cardiologists have been trained in, and fetal medicine practitioners have shied away from M-mode though it is a very sensitive tool for cardiac measurements. Speckle tracking involves tracking bright points of myocardium that are generated by natural acoustic reflections. When these individual points are followed, it is possible to evaluate the overall deformation of the myocardium, and when a time integral is introduced this generates velocity vectors, that can be used to calculate displacement, velocity, deformation (strain) and velocity of deformation (strain rate) in the cardiac wall.[9] Readers are directed to a number of extensive reviews of techniques for evaluating fetal cardiac function,[2,10] one of which was contained within a focussed fetal cardiac function edition of the journal Fetal Diagnosis and Therapy from 2012 that can be accessed at the following location: http://www.karger.com/Book/Home/257215.

Table 1 briefly summarises some of the key two-dimensional ultrasound techniques that are now available for evaluation of fetal cardiac function.[11-16]

Pitfalls and limitations of fetal cardiac functional evaluation

It is important to note that each of the functional imaging methods may have inherent methodological limitations, and these may be the reasons why they have not fully translated from research to clinical tools. One of the major issues that functional fetal cardiac imaging has suffered from has been a lack of precision, uniformity and consistency of adopted technique by different research groups. This is not solely a problem for fetal cardiac imaging. Too frequently, new techniques and technologies are enthusiastically grasped, a flurry of papers is produced that contribute to academic careers, and the authors move on to the next area of whim or interest. In their wake they may well leave a potentially useful tool that has been poorly evaluated and discarded as useless. Equally, many new proposed software techniques may generate a multitude of multi-coloured graphs though on close analysis be little more than 'random

number generators' with limited repeatability or reproducibility. Therefore prudence and caution are necessary. It is becoming increasingly difficult to publish 'boring' repeatability studies in influential imaging journals, when in fact it may be this work that is of most value to those attempting to translate imaging research into clinical practice.

Our own group at UNSW has focused for the last five years on the Myocardial Performance Index. This tool was introduced into medicine nearly 20 years ago, extrapolated to the fetus 15 years ago, and then refined as the 'Modified MPI' by use of valvular clicks in 2005[16] followed by a wide output of research papers into its clinical utility. Soon, the enthusiastic 'first adopters' realised that they were generating differing normal ranges, so moved on to new fields. When we evaluated this carefully we realised that the published literature at that stage showed huge variation in normal mean MPIs from different research groups.[17] Subsequent evaluation of these studies showed widely differing techniques that would result in over- or under-estimation of true Mod-MPI. We have since published a number of technical papers working towards a unified methodology,[18] and have now developed an automated system that will ensure at least that all researchers can be using the same tool. In the meantime, five years of MPI research and publications have taken place with a relatively subjective user-dependent tool. Only with a standardised, and we feel automated, tool can a detailed evaluation of its utility be considered, though it may be too late to convince the enthusiastic first adopters to revisit MPI.

So where to in the future?

So what does the future hold for functional fetal cardiology? There is no doubt that the drive for this will continue to come from the fetal medicine practitioner, striving to determine which Stage I TTTS case requires laser, or when the IUGR fetus at 28 weeks with redistribution and absent end-diastolic frequencies in the umbilical artery should be optimally delivered. Fetal cardiology services in Australia will benefit from diversifying from structural evaluation to more functional tools. Ideally these services will follow the lead of international practitioners and literature, evaluating tools that are superior to 'eyeballing', while equally learning from the mistakes of the early-adopters who may have overlooked tools with true clinical utility. There must be a continued focus on the laborious and seemingly tedious process of determining the following: repeatability; influence of machine settings; normal range estimation with optimised settings; then finally evaluation of pathology. Those publishing results for pathology must only do so with equally valid normal ranges from their own group against which to compare. Methodology needs to be explicitly detailed in order for others to repeat their findings and thus ascribe meaning, and standardised techniques should be adopted internationally.

In the ultrasound literature over the last few years, there has been a strong focus upon the optimal tools for demonstrating test repeatability. Repeatability may be defined as 'variation in repeat measurements made on the same subject under identical conditions', whereas the more commonly used (and probably inaccurate) terminology is reproducibility which refers to the variation in measurements made on a subject under changing conditions, whether different methods or instruments or over a period of time.[19,20] Measures favoured to best demonstrate repeatability are the Intraclass Correlation Coefficient (specifically the two-way mixed model) and the Bland-Altman plot for 95% limits of agreement. For this work we need the support of appropriately funded PhD students who will make that particular 'pinhead of science' the focus of up to four years of their life.

There is no doubt that there will be a clinically useful Doppler ultrasound tool for fetal functional cardiology, but the exciting point is that we do not know yet what that will be. Our own group feels that as well as a focus on global cardiac or individual ventricular function there is great benefit in evaluating differential ventricular/cardiac strain, as numerous fetal pathologies show a strain on one side before the other (e.g. right ventricular strain in TTTS recipients or IUGR), that may not be so clearly determined by measurement of individual ventricular function. We are in the process of publishing the normal range and early pathological findings for one such measure, the 'Delta' MPI, though it is likely that others will emerge.[21]

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