REVIEW

Methods for prenatal assessment of fetal cardiac function

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Fetal cardiac function is increasingly recognized as a marker of disease severity and prognosis in selected fetal conditions. Magnetic resonance imaging (MRI) has been used in experimental (animal) fetal cardiology but the lack of a noninvasive fetal electrocardiogram (ECG) to trigger image acquisition remains a major limiting factor precluding its application in humans. Fetal medicine specialists are therefore limited to ultrasound to evaluate human fetal cardiac function. In this review, we aim to provide a complete overview of the different ultrasound techniques that can be used for fetal cardiac function assessment and we discuss their (theoretical) strengths and shortcomings. Conventional methods include M-mode assessment of ventricular contractility and Doppler assessment of the precordial veins and cardiac output (CO). More recent techniques such as the measurement of the myocardial performance index (MPI), myocardial motion analysis with tissue Doppler, speckle tracking and three-dimensional (3D) ultrasound techniques are also discussed. Copyright © 2009 John Wiley & Sons, Ltd.

KEY WORDS: echocardiography; cardiac function; ultrasound; fetal heart

INTRODUCTION

Postnatally, several imaging methods for measuring cardiac function are available, of which most are based on ultrasound, but more recently also on magnetic resonance imaging (MRI). They play an important role in the assessment of the severity of certain diseases and in the planning of further management (Krishnamurthy, 2009). It is no more than logic to transpose these methods to fetal cardiology, yet important differences hamper a simple extrapolation. First, the fetus is surrounded by amniotic fluid and maternal tissues, which increases the distance from the measuring probe to the fetal heart, which interferes with image quality and which precludes electric signal capture (ECG) for image triggering. Second, the fetal position is not fixed with regards to the measuring probe leading to varying angles of view at the fetal heart during a single assessment. Third, the fetal heart rate is two to three times faster than the adult heart rate and the fetal blood pressure is considerably lower (Struijk et al., 2008). Moreover, the fetal heart at 20 weeks’ gestation is only about 1/10th the size of the adult heart (Voogd et al., 1984; Shapiro et al., 1998), changes in cardiac loading conditions occur over gestation (Gardiner, 2005) and fetal cardiac wall movement is different from the adult as there is a small displacement of the interventricular septum during the cardiac cycle due to the slightly higher right ventricular pressure. Finally, over gestation maturational changes occur within the myocardium (Gardiner et al., 2006). All these factors have to be taken into account when measuring and interpreting fetal cardiac function.

Despite this, fetal cardiac function is increasingly being recognized as a marker of disease severity and even prognosis in a number of prenatal conditions including intrauterine growth restriction (Crispi et al., 2008; Mäkikallio et al., 2008), twin-to-twin transfusion syndrome (TTTS) (Raboison et al., 2004; Rychik et al., 2007; Van Mieghem et al., 2009b), sacrococcygeal teratomas (Wilson et al., 2008), congenital heart defects (Mäkikallio et al., 2006; Gardiner et al., 2008), (idiopathic) hydrops (Hofstaetter et al., 2006) and fetal arrhythmia (Veille and Covitz, 1994). Perinatologists managing these patients should therefore have a basic knowledge of the available methods for fetal cardiac function evaluation. The aim of this review is to provide a comprehensive overview of these methods, including their (theoretical) strengths and shortcomings.

MAGNETIC RESONANCE IMAGING

In postnatal cardiology, MRI is a useful adjunct to echocardiography for the evaluation of the pathologic heart (Krishnamurthy, 2009). Two factors, however, limit the introduction of MRI in fetal cardiology. First, there is the fast movement of the fetal heart and the presence of fetal body movements. In postnatal cardiology, this can be corrected for by taking image sequences during breath hold and by triggering image acquisition based on the electrocardiogram (ECG). In an experimental fetal setting, this can also be done in a catheterized fetus (Yamamura et al., 2009). Invasive access to the fetus however cannot be obtained in clinical situations and noninvasive registration of the fetal ECG is still in an experimental phase (Taylor et al., 2003; Van
Mieghem et al. (2009c). The second factor precluding fetal cardiac MRI is its image resolution (with typically 3–4-mm-thick slices in fetal imaging protocols; Cannie et al., 2008; Saleem, 2008), which is limited compared to ultrasound. However, with the ongoing development of higher power MRI magnets, newer scanning protocols (Saleem, 2008), new postprocessing software and tools to record the fetal ECG noninvasively, fetal cardiac MRI will probably be technically feasible in the not-so-far future (Holmes et al., 2008).

CARDIAC OUTPUT

For now, fetal medicine specialists have to resort to ultrasound to assess fetal cardiac function. Using this technology, the most obvious way to determine the hemodynamic function of the heart is by measuring the cardiac output (CO), which is the blood volume expelled by the ventricle over a given unit of time. One has to be cautious, however, not to confound CO with myocardial function. Indeed, in conditions such as fetal anemia or arteriovenous fistula, the CO is elevated yet the myocardium can be dysfunctional (‘high output cardiac failure’; Bond et al., 1990). The opposite is also true: a low output can be generated by a normally functioning myocardium due to a decreased ventricular preload.

By definition, the CO is obtained by multiplying the heart rate by the ventricular stroke volume (SV). The latter can be measured using Doppler, M-mode, two- or three-dimensional (2D, 3D) gray-scale ultrasound images.

Doppler estimation of SV

Doppler-based estimation of SV relies on the measurement of the outflow valve diameter (which allows to calculate the valve area; Table 1) combined with the blood flow velocity over the aortic or pulmonary valve (Kenny et al., 1986). Although this seems straightforward, different factors limit its feasibility and reproducibility:

- Doppler velocity measurements are strongly angle dependent and the ultrasound beam must be perfectly aligned with the vessel to obtain reliable velocity estimations (Friedman, 2009). When this is impossible, mathematical angle corrections can be used to correct for minor variations (Ruma et al., 2009) but this method is more prone to error (Yamamoto et al., 2006).
- Physiologic fetal changes such as breathing and other movements influence cardiac flow considerably (Rizzo et al., 1990). Therefore, care must be taken to obtain all measurements during fetal inactivity and apnea and a series of multiple consecutive uniform velocity waveforms with a high signal-to-noise ratio at a stable heart rate should be obtained when measuring. Despite these limitations, carefully performed Doppler measurements from an experienced observer have a coefficient of variation of less than 10% (Reed et al., 1986; Simpson and Cook, 2002).
- The error induced by valve area calculations based on valve diameter measurements adds to the Doppler error in the final calculation of CO. Indeed, owing to the limited spatial resolution of current routine ultrasound devices, vessel diameter measurements are prone to a considerable error (Kiserud and Rasmussen, 1998), especially when the vessel is small. As the aortic valve at 20 weeks’ gestation is only 3 mm wide, a 0.5-mm error already results in a 17% error in measurement. As the vessel dimensions are squared in the formula to calculate the valve area, the error is even more amplified. Repeated measurements (with a minimum of three), however, can reduce errors (Kiserud and Rasmussen, 1998). Similarly, optimization of the insonation angle for valve measurement (lateral view on the vessel) increases precision. On average, the error in vessel area for the cardiac outflow tracts at 20 weeks’ gestation ranges between 9–21%, whereas at 40 weeks it is 2–10% (Sutton et al., 1991).
- As the end diastolic LV volume at 20 weeks ranges around 0.7 mL, a 20% error would be 0.14 mL. Although this is very low in absolute values, it might strongly impact on the inter- and intraobserver variability.

Table 1—Formulas for the calculation of different indices of cardiac function. References are provided in the text

<table>
<thead>
<tr>
<th>Index</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output (CO)</td>
<td>CO = stroke volume × heart rate</td>
</tr>
<tr>
<td>Stroke volume (SV) − Doppler</td>
<td>SV = velocity time integral × valve area</td>
</tr>
<tr>
<td>Valve area</td>
<td>Valve area = π × (diameter/2)^2</td>
</tr>
<tr>
<td>SV − M-mode/B-mode</td>
<td>SV = end diastolic volume − end systolic volume</td>
</tr>
<tr>
<td>Ventricular volume (VV) − M-mode (Dodge)</td>
<td>VV = (VD)^3</td>
</tr>
<tr>
<td>Ventricular volume (VV) − M-mode (Teicholz)</td>
<td>VV = (7 × VD^3)/(2.4 + VD)</td>
</tr>
<tr>
<td>Ejection fraction (EF)</td>
<td>EF = SV/end diastolic volume</td>
</tr>
<tr>
<td>Shortening fraction (SF)</td>
<td>SF = (end diastolic VD − end systolic VD)/end diastolic VD</td>
</tr>
<tr>
<td>Myocardial ejection force (F)</td>
<td>F = (1.055 × valve area × velocity time integral of acceleration) × (PSV/AT)</td>
</tr>
<tr>
<td>Myocardial performance index (MPI)</td>
<td>MPI = (ICT + IRT)/ET</td>
</tr>
<tr>
<td>Pulsatility index for veins (PIV)</td>
<td>PIV = PSV − PDV/PSV</td>
</tr>
<tr>
<td>Inferior vena cava preload index (PLI)</td>
<td>PLI = peak velocity during atrial contraction/peak velocity s-wave</td>
</tr>
</tbody>
</table>

VD, ventricular diameter; PSV, peak systolic velocity; PDV, peak diastolic velocity; AT, acceleration time ICT, isovolumetric contraction time; IRT, isovolumetric relaxation time; ET, ejection time.

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M-mode and 2D estimation of SV

To overcome the limitations of Doppler techniques and vessel measurements, direct estimations of ventricular volume have been proposed. The SV can be calculated as the difference between the end diastolic and the end systolic volume (Table 1). When assuming that the ventricle is ellipsoid in shape and that there is a fixed relationship between the ventricular width and length, its volume can be calculated using Dodges ‘cubed’ formula (Dodge et al., 1960) or Teichholz’s formula (Teichholz et al., 1976; Table 1). Both formulas rely on M-mode ventricular diameter measurements. To obtain these, the M-mode cursor must be positioned perpendicular to the interventricular septum and just below the atrioventricular valves (Figure 1). This is difficult to standardize and often impossible to obtain due to fetal position (DeVore et al., 1984). Second, the geometric assumptions that are valid for a healthy adult ventricle are not necessarily valid for a fetal heart that is not functioning normally (Kleinman and Donerstein, 1985; Simpson and Cook, 2002). Finally, small measurement errors due to suboptimal positioning are amplified due to the multiplications in the formulas.

To alleviate some of the geometric assumptions, Schiller (Schiller et al., 1979) introduced a method based on Simpson’s rule in which, after tracing the endocardial border on two perpendicular 2D B-mode images, the ventricle is partitioned in 20 discs of identical thickness (‘method of discs’). The volume of each of these discs is subsequently calculated on the basis of its diameter and height (Figure 2). Summation of all individual disc volumes then yields the ventricular volume. This postnatal technique was later transposed to fetal echocardiography by Schmidt (Schmidt et al., 1995) and does not rely on the fixed relationship between ventricular width and length anymore. It, however, still assumes that the ventricle is ellipsoid in form, which is acceptable for a healthy left ventricle but much less so for the right ventricle, even if it is not affected by disease (Chen et al., 2006). The combined left and right ventricular CO (which is often the measurement of choice in fetal medicine) can therefore not be determined using M-mode or 2D techniques for volume calculations.

3D estimation of SV

With the advent of 3D and 4D ultrasound, more complex but more sophisticated methods to determine ventricular volume are now available (Chaoui and Heling, 2005). When a 3D ‘sweep’ of the beating heart is acquired during a certain time period, the acquired 2D images can be rearranged within the heart cycle according to the time point within that cycle they were obtained using spatiotemporal image correlation (STIC) technology. This generates a hypothetical heart cycle (Chaoui and Heling, 2005). Using mathematical volumetric methods, ventricular volume estimations can be made during systole and diastole, either by tracing the ventricular endocardial border on multiple frozen 2D-images (Rizzo et al., 2007; Molina et al., 2008; Uittenbogaard et al., 2009) or by using a kind of automated cavity recognition based...
on on inversion of the doppler signal (also called ‘inversion mode’) (Messing et al., 2007). As 3D techniques do not make any assumption about ventricular geometry, they can be used for both left and right ventricular stroke volume determination. One limitation, however, is that a STIC clip is an artificial reconstruction of multiple cardiac cycles, hence it is only an estimation of the true cardiac cycle. Second, imaging conditions have to be optimal to use this technique. These are as follows: (1) an ultrasound window allowing visualization of the entire ventricle and (2) fetal quiescence during a minimum period of 7.5 s necessary for the acquisition of the volume. Therefore, satisfactory images cannot be obtained in 15–30% of patients (Bhat et al., 2004; Uittenbogaard et al., 2009). Furthermore, validation on in vitro models showed that, under optimal visualization conditions, the relative error on volume estimations was higher at smaller ventricular sizes and ranged between 12–36% for volumes as small as 5 mL (Bhat et al., 2004). Taking into account that visualization in clinical situations is far less optimal and that fetal cardiac volumes range between 0.03 mL at 12 weeks and 3.43 mL at 30 weeks (Uittenbogaard et al., 2009), accuracy in real life conditions is probably even less good. In a clinical setting, Molina reported an inter- and intraobserver error of less than 18.4% for examinations where good quality images were available (Molina et al., 2008).

The different methods for CO calculation are sufficiently comparable, with 95% limits of agreement between −20 and +20% when comparing STIC and Doppler (Rizzo et al., 2007). Also, absolute differences between Doppler and ‘method of disc’ CO estimates are <10% (Schmidt et al., 1995). M-mode-based measurements coincide with Doppler measurements until 32 weeks’ gestation. Thereafter, however, they diverge strongly (Veille et al., 1990). On average, grayscale methods (M-mode, 2D and 3D) yield slightly lower COs than Doppler-based methods (Table 2). As CO increases over gestation, the use of reference curves is mandatory. Alternatively, the CO can be adjusted for fetal weight. In the second half of gestation, when assessed using Doppler estimation of SV, the combined CO per fetal weight remains stable around 400–450 mL/min/kg.

### EJECTION FRACTION

The ejection fraction is a quantification of short-axis ventricular function and is often used in adult cardiology. This index makes abstraction of the true ventricular volumes because it expresses the SV as a ratio to the end diastolic ventricular volume (Hsieh et al., 2000). Yet, the formula still relies on M-mode- (Hsieh et al., 2000), 2D- or 3D-based (Esh-Broder et al., 2004) volume calculations with the inherent limitations mentioned above. Moreover, it does not always truly reflect the cardiac function. For instance, when the heart rate is high, a small SV, hence a small ejection fraction, can result in a CO comparable to that from a larger SV at a slower heart rate. Also, when the ventricle is dilated, a normal SV will seem artificially small in terms of ejection fraction as it is expressed as a ratio of the enlarged end diastolic volume. In conclusion, measurement of the ejection fraction has largely been abandoned in fetal medicine.

### Table 2—Reference values for CO (in mL/min) determined with different methods

<table>
<thead>
<tr>
<th>First author/year</th>
<th>Method</th>
<th>N</th>
<th>20 weeks</th>
<th>25 weeks</th>
<th>30 weeks</th>
<th>CCO/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kenny et al. (1986)</td>
<td>Doppler and inner outflow tract area</td>
<td>80</td>
<td>131.8</td>
<td>117.5</td>
<td>199.5</td>
<td>182.0</td>
</tr>
<tr>
<td>Allan et al. (1987)</td>
<td>Doppler and inner outflow tract area</td>
<td>120</td>
<td>93.1</td>
<td>69.5</td>
<td>196.1</td>
<td>146.5</td>
</tr>
<tr>
<td>Chang et al. (2000)</td>
<td>Doppler and inner outflow tract area</td>
<td>212</td>
<td>97.1</td>
<td>88.2</td>
<td>269.1</td>
<td>194.0</td>
</tr>
<tr>
<td>Mielke and Benda (2001)</td>
<td>Doppler and inner outflow tract area</td>
<td>210</td>
<td>88.9</td>
<td>49.0</td>
<td>176.3</td>
<td>130.0</td>
</tr>
<tr>
<td>Kiserud et al. (2006)</td>
<td>Doppler and inner outflow tract area</td>
<td>212</td>
<td>67.2</td>
<td>48.5</td>
<td>154.2</td>
<td>124.0</td>
</tr>
<tr>
<td>Rasanen et al. (1996)</td>
<td>Doppler and outflow tract area</td>
<td>63</td>
<td>95.0</td>
<td>102.0</td>
<td>287.5</td>
<td>244.5</td>
</tr>
<tr>
<td>De Smedt et al. (1987)</td>
<td>Doppler and AV valve area</td>
<td>113</td>
<td>117.0</td>
<td>112.0</td>
<td>181.7</td>
<td>166.7</td>
</tr>
<tr>
<td>Veille et al. (1990)</td>
<td>M-mode and Teichholz formula</td>
<td>80</td>
<td>100.9</td>
<td>87.1</td>
<td>186.3</td>
<td>158.6</td>
</tr>
<tr>
<td>Schmidt et al. (1995)</td>
<td>2D and method of discs</td>
<td>50</td>
<td>72.2</td>
<td>51.8</td>
<td>151.9</td>
<td>118.1</td>
</tr>
<tr>
<td>Molina et al. (2008)</td>
<td>3D-STIC</td>
<td>140</td>
<td>46.7</td>
<td>43.5</td>
<td>126.2</td>
<td>120.4</td>
</tr>
<tr>
<td>Uittenbogaard et al. (2009)</td>
<td>3D-STIC</td>
<td>202</td>
<td>53.3</td>
<td>46.8</td>
<td>146.5</td>
<td>131.9</td>
</tr>
</tbody>
</table>

STIC, spatiotemporal image correlation; CO, cardiac output; CCO, combined cardiac output; RV, right ventricle; LV, left ventricle; AV, atriopulmonary.

*Data derived from graph.

Area derived from measurement from lead edge to lead edge of outflow tract thus yielding an overestimation of vessel area.
SHORTENING FRACTION

Assessment of fetal systolic cardiac function without the need for volume calculations can be done by subjective ‘eyeballing’ of systolic contractility. This method however requires extensive training (Picano et al., 1991) and is associated with a high interobserver variability (Hoffmann et al., 1996). Moreover, it does not allow to identify and quantify more discrete changes during longitudinal follow-up. A more objective quantification can be obtained by measuring the ‘shortening faction’ (SF), which is the systolic decrease in ventricular diameter expressed as a ratio of the end diastolic diameter (Wladimiroff and McGhie, 1981; Table 1).

The SF can either be measured in the minor axis plane thereby evaluating the circumferential contractility, or along the long axis of the heart for longitudinal ventricular function (Carvalho et al., 2001). Another, more simple way to assess longitudinal function is by measuring the maximal displacement of the atrioventricular ring. Long axis function measurements are probably the most useful for assessing the right ventricle where, due to myocardial fiber orientation, longitudinal function prevails over circumferential shortening. Standardization of the measurement of the end diastolic and the end systolic diameter is difficult due to problems with M-mode alignment as mentioned above. As a result, interobserver limits of agreement range around ±15% (Simpson and Cook, 2002). Moreover, the information obtained from M-mode measurements cannot be objectively timed in the cardiac cycle as no concomitant ECG is available. The SF nevertheless remains a widely used parameter of cardiac function. There are several reasons for that. One is that the SF does not make any assumptions about ventricular geometry. Second, SFs stay relatively stable over the second half of gestation (around the value of 31 ± 6%; Sikkel et al., 2005), allowing easy interpretation without need for reference curves. This could however also be a reflection of the fact that the SF is only a very crude estimation of ventricular contractility. The main criticism nevertheless remains that, using M-mode technology, the displacement of only a single point in the myocardium is evaluated. This problem has been alleviated by the introduction of the area SF (Harada et al., 1997; Goldinfeld et al., 2004), which assesses the contraction of the whole ventricular wall by expressing the ventricular cavity area in systole as a ratio of its diastolic area.

VENTRICULAR EJECTION FORCE

Another way to express myocardial systolic performance is by quantifying the force the ventricle develops to expel blood into the vascular bed. On the basis of Newton’s second law of motion, myocardial force is the product of the mass of the expelled blood during systole and its acceleration (Sutton et al., 1991). Both variables in this formula can be derived from Doppler flow measurements in the ventricular outflow tract and the valve area (Table 1). Ejection force and ejection fraction are correlated (Isaaz et al., 1989) and both increase over gestation (Sutton et al., 1991). The reproducibility of ventricular ejection force measurements is theoretically compromised by the limitations of Doppler-derived measurements as mentioned for the evaluation of the SV. However, formal validation studies on this issue are lacking.

MYOCARDIAL PERFORMANCE OR ‘TEI’-INDEX

An indirect reflection of systolic cardiac function is the time required by the heart to obtain an intraventricular pressure exceeding the systemic blood pressure. This time interval of myocardial contraction without expulsion of blood into the systemic circulation is called the isovolumetric contraction time (ICT). Conversely, the isovolumetric relaxation time is the time needed by the ventricle to relax after the expulsion of blood and before ventricular filling starts. As a consequence, the IRT is a reflection of cardiac diastolic function. Evaluation of both ICT and IRT is combined in the myocardial performance index (MPI) or ‘Tei-index’ (Tei et al., 1995; Table 1). As one can expect from the above, the MPI is not only dependent on myocardial function but is also strongly influenced by systemic arterial and venous pressure and atrial function. The measurement of the left ventricular MPI can be performed on a single Doppler trace of the left ventricular in- and outflow pattern, which can be obtained by positioning the Doppler sample volume on both the mitral and the aortic valve combined in an apical five-chamber view of the fetal heart (Hernandez-Andrade et al., 2005). The spikes generated in the Doppler trace by valve opening and closure serve as clear demarcations for the ICT and IRT and thus guarantee high reproducibility of this method (Hernandez-Andrade et al., 2005, Van Mieghem et al., 2009a). This method has recently been used quite often for assessment of cardiac function in TTTS where cardiac dysfunction is a common problem in the recipient fetus. This leads to the establishment of separate nomograms for monochorionic twins. Normal MPI values differ only slightly between singletons and monochorionic twins and increase over gestation (Hernandez-Andrade et al., 2007; Van Mieghem et al., 2009b). The MPI allows to differentiate monochorionic twin pregnancies complicated by selective growth restriction from cases complicated by TTTS (Raboisson et al., 2004). Whether the MPI, or to a wider extent, cardiac dysfunction will allow for a better prognostic evaluation, and hence become a management tool in the evaluation of TTTS remains to be demonstrated (Harkness and Crombleholme 2005; Ville 2007). The same is true for intrauterine growth restriction (Crispi et al., 2008).

ATRIOVENTRICULAR FLOW

The ventricular inflow pattern is characterized by an early E-wave, which reflects active ventricular
relaxation, followed by an A-wave caused by atrial contraction. This pattern can easily be documented using pulsed Doppler with the sample box set just below the valve in an apical or basal four-chamber view (DeVore, 2005). In healthy adults, the E/A ratio is $>1.0$ (Benjamin et al., 1992); conversely, in normal fetuses, the E/A ratio is $<1.0$. The E/A ratio increases over gestation almost exclusively due to an increase in the E-wave velocity, which correlates with a physiologic improvement in ventricular relaxation. (Carceller-Blanchard and Fouron 1993; Fernandez Pineda et al., 2000) Although some relation exists between the E/A ratio and fetal diastolic ventricular function, its correlation with the isovolumetric relaxation time is weak (Thomas and Weyman, 1991; Van Mieghem et al., 2009a). When severe cardiac constraint is present in conditions such as TTTS (Rychik et al., 2007) and aortic stenosis (Mäkikallio et al., 2006), the typical E and A waves disappear and a monophasic atrioventricular flow pattern is seen (Figure 3). Care, however, has to be taken not to confuse this sign of ventricular pathology with the physiologic fusion of the E- and the A-wave, which can occur at high heart rates.

**COLOR M-MODE PROPAGATION VELOCITY**

Fetal diastolic cardiac function can be quantified using the propagation velocity (Vp) of blood in the ventricle: the more compliant the ventricle, the lower is its intracavitary pressure, the faster the propagation of fluid in early diastole (De Boeck et al., 2005). Vp can be measured as the slope of the ventricular inflow pattern by combining M-mode and color Doppler assessment of ventricular inflow. (Moon-Grady et al., 2008) (Figure 4). Adult human and animal validation studies have shown that Vp is inversely correlated to the duration of the isovolumetric relaxation time and that significant alterations in filling pressure do not influence Vp, suggesting the index to be preload independent (Garcia et al., 2000). Measurement of the index is however seriously hampered in situations where the ventricular inflow pattern is altered such as in mitral stenosis, ventricular remodeling or intracavitary obstructive lesions. Although intraobserver variability is slightly better (95% limits of agreement $<41\%$), 95% interobserver limits of agreement can reach values as high as 85% (Moon-Grady et al., 2008), precluding application of this technique in a clinical setting with multiple observers.

**PRECORDIAL VENOUS BLOOD FLOW DOPPLER WAVEFORMS**

The first-level precordial veins (ductus venosus, inferior vena cava, hepatic vein and pulmonary veins) are in almost direct continuity with the atria, hence their multiphasic flow patterns reflect the atrial pressure gradients (Baschat and Harman, 2006; Lenz and Chaoui, 2006). The typical flow phases observed in these veins are the S- (ventricular systole) D- (ventricular diastole) E- (early ventricular filling) and A-wave (atrial contraction; Figure 5). When assessing the ductus venosus, care has to be taken to obtain a signal without superposition of flow patterns from adjacent vessels (most importantly the hepatic veins), which could falsely give the impression of reversal of the A-wave. Different methods have been proposed to quantify the mutual relation of the different waves observed in the venous flow pattern (preload index, pulsatility index for veins and peak velocity index; Table 1) (Kanzaki and Chiba, 1990). Abnormalities in precordial venous Dopplers are relatively aspecific, that is, they can reflect abnormal cardiac relaxation, abnormal ventricular contraction, increases in afterload or any combination of these factors. Yet, each
of the different indices has its specific characteristics. The vena cava pulsatility index is most influenced by cardiac afterload, whereas the preload index is the most afterload independent parameter (Baschat et al., 2003).

Assessment of the duration of the ductus venosus E-wave allows to estimate ventricular relaxation. When relaxation is impaired, the isovolumetric relaxation time increases, leading to a subsequent decrease in E-wave duration (Bensouda et al., 2007). This indirect E-wave measurement at the level of the ductus venosus is particularly helpful in cases of cardiac failure where atrioventricular flow patterns are disturbed and hence not usable for direct E-wave measurements at the level of the atrioventricular valves. Formal validations studies are however lacking and reproducibility of this technique might be poor due to a lack of clear delimitations of the time period.

The umbilical vein is a second-level precordial vein as its connection with the atrium is buffered by the ductus venosus. This leads in physiologic conditions to a continuous flow pattern in the intraabdominal part of the umbilical vein from 13 weeks’ gestation onward (Rizzo et al., 1992). However, when assessed at the level of a free cord loop, monophasic pulsations occur in up to 5–15% (Nakai et al., 1995). Quantification of these pulsations can be done using the umbilical vein resistance index (Russell et al., 2008). In the presence of severe cardiac failure, bi- or triphasic flow patterns appear (Figure 5).

Doppler assessment of the precordial veins allows to quantify cardiac function objectively (yet aspecifically) and has found widespread use in fetal medicine owing to its high reproducibility from early gestation onward (Prefumo et al., 2001). As such, it is now clinically applied in the surveillance of intrauterine growth restriction (Baschat et al., 2007), TTTS (Quintero et al., 1999), congenital heart defects (Baenz et al., 2005; Lenz and Chaoui, 2006) and (idiopathic) fetal hydrops (Hofstaetter et al., 2006).

**MYOCARDIAL MOTION ANALYSIS**

Where the earlier work in fetal functional cardiology mainly focused on blood flow as a measure of myocardial contractility, direct assessment of myocardial motion has recently become available. Using pulsed Doppler assessment of the myocardial wall (‘Pulsed Wave Tissue Doppler Imaging’ or PW-TDI), tissue velocities can be measured in the myocardium (Harada et al., 1999). In an apical four-chamber view, the velocity measured at the ventricular base reflects the integral of the myocardial shortening velocities from apex to base. This technique has been shown to be feasible in fetal echocardiography, even with conventional obstetric ultrasound devices and has the advantage to yield a high temporal resolution (Tutschek et al., 2003). Unfortunately, tissue velocities are not very sensitive to distinguish fetuses with heart failure from healthy fetuses (Aoki et al., 2004). Moreover, PW-TDI does not allow the calculation of cardiac function in different regions of the heart simultaneously, as it only provides information on one region at a time. When using color tissue Doppler imaging (C-TDI) on the other hand, a velocity signal is obtained for each pixel of the image. From these velocities, the deformation (strain) and deformation rate (strain rate) of each segment of the myocardial wall can be calculated off-line (Sutherland et al., 2004). A positive strain rate indicates lengthening of the tissue, whereas a negative strain rate indicates shortening. C-TDI has the advantage of allowing simultaneous assessment of different regions in the fetal myocardium (Larsen et al., 2006), yet its use is limited as the Doppler signal is angle dependent and only 1D motion (toward and away from the probe) can be quantified.

More recently, a technique called ‘speckle tracking’ has solved these typical Doppler-dependent problems. In brief, the method identifies myocardial ‘speckle patterns’, which are patterns in the acoustic backscatter generated by the reflected ultrasound beam on a
Figure 6—Speckle tracking: (A) Apical four-chamber view of the fetal heart with velocity vectors superposed on the ‘tracked’ myocardium. (B) Strain curves for different regions in the myocardial wall plotted on an M-mode trace of the atrioventricular valve. Note that strain is negative (myocardial shortening during contraction).

Table 3—Comparison of peak systolic strain and strain rate assessed with color-tissue-Doppler- and speckle-tracking-based methods

<table>
<thead>
<tr>
<th>First author, Year</th>
<th>Technique</th>
<th>Median GA (range)</th>
<th>Strain (%)</th>
<th>Strain rate (s(^{-1}))</th>
<th>Evolution over gestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Di Salvo et al. (2005)</td>
<td>C-TDI</td>
<td>75 (17–40)</td>
<td>−19 ± 8</td>
<td>−2.1 ± 0.8</td>
<td>Increase</td>
</tr>
<tr>
<td>Perles et al. (2007)</td>
<td>C-TDI</td>
<td>98 (13–40)</td>
<td>−32.7 ± 10.7</td>
<td>−2.9 ± 1.2</td>
<td>No change</td>
</tr>
<tr>
<td>Ta-Shma et al. (2008)</td>
<td>C-TDI</td>
<td>27 (20–38)</td>
<td>—</td>
<td>−2.5 ± 1.4</td>
<td>—</td>
</tr>
<tr>
<td>Di Salvo et al. (2008)</td>
<td>Speckle tracking</td>
<td>100 (20–32)</td>
<td>−24 ± 4</td>
<td>—</td>
<td>Increase</td>
</tr>
<tr>
<td>Ta-Shma et al. (2008)</td>
<td>Speckle tracking</td>
<td>28 (20–38)</td>
<td>−21 ± 5</td>
<td>−2.3 ± 0.5</td>
<td>No change</td>
</tr>
<tr>
<td>Younoszai et al. (2008)</td>
<td>Speckle tracking</td>
<td>27 (18–39)</td>
<td>—</td>
<td>—</td>
<td>No change</td>
</tr>
<tr>
<td>Barker et al. (2009)</td>
<td>Speckle tracking</td>
<td>33 (17–38)</td>
<td>−18.0 ± 6.4</td>
<td>−1.9 ± 0.8</td>
<td>—</td>
</tr>
</tbody>
</table>

GA, gestational age; RV, right ventricle; LV, left ventricle; C-TDI, color tissue Doppler imaging.

Good correlation exists between strain rate assessment with C-TDI and speckle tracking (Ta-Shma et al., 2008) yet strain and strain rate values are on average slightly lower when assessed by C-TDI than by speckle tracking (Table 3) due to the angle dependency of the former method.

**VASCULAR WALL MOTION ANALYSIS**

Another way to assess cardiac function is to evaluate the impact of the ejected blood on the peripheral vessel wall motion. Indeed, when the heart expels blood under high pressure, the arteries normally dilate. On the other hand, when the atrium fills, a negative pressure empties the veins and the venous diameter decreases. These diametrical changes can be measured...
using specific phase-locked ultrasound systems that automatically follow vessel wall movement. (Stale et al., 1991; Fujita et al., 2002; Mori et al., 2007). Akira and colleagues have shown that changes in inferior vena cava motion correlate with Doppler findings in the same vessel (Akira et al., 2008). Strong clinical data to support the use of these methods is still lacking and the value of these measurements will certainly be influenced by fetal blood pressure and vessels stiffness. On the other hand, however, the technique has the advantage of being Doppler (and thus angle) independent, making it potentially valuable. Further results are eagerly awaited.

CONCLUSION

Different ultrasound methods are available for the assessment of fetal cardiac function, each with their own specificities. Considerable inter- and intraobserver variability is the major limiting factor for most techniques. Moreover, many of the herein presented methods require extensive training, specific ultrasound hardware and/or laborious postprocessing. These factors impede introduction of fetal cardiac function assessment in general practice. Nevertheless, some of the techniques have found their application in specific pathologies or in research settings. As long as a ‘gold standard’ technique is missing, good knowledge of the wide range of techniques will allow the echocardiographer to select the most optimal (combination of) methods for each individual situation. In our eyes, M-mode measurement of the ventricular shortening fraction and Doppler assessment of the precordial veins are the only methods that should be mastered by every clinical perinatologist interested in fetal cardiology.

ACKNOWLEDGEMENTS

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REFERENCES


Friedman Z. 2009. The physics of ultrasound imaging. In
Fetal
Gardiner HM. 2005. Response of the fetal heart to changes in load:
Hofstaetter C, Hansmann M, Eik-Nes SH, Huhta JC, Luther SL.
Kanzaki T, Chiba Y. 1990. Evaluation of the preload condition of the
Kleinman CS, Donnerstein RL. 1985. Ultrasonic assessment of