Novel Echocardiography Methods in the Functional Assessment of the Newborn Heart

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Key Words

Neonatology · Echocardiography · Cardiac function · Deformation · Tissue Doppler · Strain

Abstract

Echocardiography in the neonatal intensive care unit has led to improvements in our ability to assess the neonatal heart in health and disease. Advances in neonatal cardiac imaging have provided the capability to obtain quantitative information that often supersedes the qualitative information provided by conventional methods. Novel quantitative measures of function include the assessment of the velocity of muscle tissue movement during systole and diastole using tissue Doppler velocity imaging, and evaluation of deformation and rotational characteristics of the myocardium utilizing speckle tracking echocardiography or tissue Doppler-derived strain imaging. A comprehensive understanding of these novel functional modalities, their predictive value, and limitations can greatly assist in managing both the normal and maladaptive responses in the newborn period. This article discusses the novel and emerging methods for assessment of left and right heart function in the neonatal population.

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The role of functional echocardiography in the neonatal intensive care unit for the evaluation of infant cardiovascular well-being has significantly expanded over the last 10 years [1–3]. The use of echocardiography in the neonatal intensive care unit, also referred to as targeted neonatal echocardiography, has been shown to identify cardiovascular compromise earlier, guide therapeutic intervention, monitor treatment response, and improve overall outcome [4–6].

Advances in neonatal cardiac imaging have provided the capability to obtain quantitative information that often supersedes the qualitative information provided by conventional methods. Conventional function measures, such as shortening (SF) and ejection fraction (EF), assess the changes in cavity dimensions. Newer quantitative measures assess the velocity of muscle tissue movement during systole and diastole in one image using colour tissue Doppler velocity imaging (cTDI), and evaluate deformation and rotational characteristics of the myocardium utilizing speckle tracking echocardiography (STE) or tissue Doppler-derived strain imaging. In addition, there is

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Table 1. Recommendations for the echocardiographic assessment of LV and RV function in neonates

Echocardiographic imaging	Recommended methods	Populations studies in neonates	Reference ranges	Advantages	Limitations
Tissue Doppler	Longitudinal myocardial motion velocity is measured at the mitral valve annulus, tricuspid valve annulus, and the base of the septum	Preterm [25, 26, 29, 30, 44, 57, 58] Healthy [22] PDA [31] BPD [74] PRBC tx [32, 33] Term Healthy [22–24, 28, 30] Encephalopathy [36] Sepsis [38] CDH [35]	Dependent on GA and postnatal age	Improved accuracy compared to SF and EF Less effected by paradoxical septal wall motion Simultaneous assessment of muscle wall velocity across different myocardial segments	Influenced by loading conditions
<i>Deformation</i> cDTI	The region of interest is placed at the basal area of the wall of interest	Preterm [44, 50, 60, 61] CLD [50] Term Healthy [46, 75] CHD [48]	Dependent on GA and postnatal age	Very suitable in neonates with baseline fast HR Less dependent on loading conditions	Angle dependent
STE	LV global longitudinal strain is calculated from a 17- or 18-segment model by segmental averaging of the three apical views, apical 4-, 3-, and 2-chamber views Circumferential and radial strains are obtained from the parasternal short-axis view at the level of the papillary muscle (base) mitral valve (mid-ventricular), and apex Rotational mechanics is derived from the parasternal short-axis view at the base and apex	Preterm [41, 49, 57, 58] Healthy [62] CLD [62] Term [59] Healthy [52] Hypothermia [14] Preterm [27, 65] Term [45, 76]	Dependent on GA and postnatal age Different for RV and LV strain imaging Dependent on GA and postnatal age	Angle independent Used to assess torsion Assess global and regional function of both ventricles Established prognostic value	Lower reproducibility with diastolic strain rate values Inter-vendor/software variability
<i>RV function</i> TAPSE	Derived from M-mode, cTDI, or STE analysis of the lateral tricuspid annular ring	Preterm [68] Term [28, 68, 70]	Dependent on GA and postnatal age >0.9 mm	Correlates with RV ejection fraction on MRI Unaffected by heart rate	Not indexed to RV length Angle dependent Influenced by loading and tricuspid regurgitation No imaging of the outflow tract
FAC	Calculated by tracing the RV endocardium from the lateral tricuspid annulus along the free wall to the apex and back to medial tricuspid annulus, along the interventricular septum in end-diastole (RV EDA) and end-systole (RV ESA) Trabeculations are considered part of the cavity by tracing RV EDA and RV ESA between RV trabeculations and the compact layer of the ventricle $FAC = 100 [RV\ EDA\ (cm^2) - RV\ ESA\ (cm^2)] / RV\ EDA\ (cm^2)$	Preterm [44, 65] Term Healthy [28]	Dependent on GA and postnatal age [73] 35% [28]	Utilizes standard echocardiographic equipment Less affected by RV geometry	Influenced by loading conditions Less reproducible

Table 1 (continued)

Echocardiographic imaging	Recommended methods	Populations studies in neonates	Reference ranges	Advantages	Limitations
<i>Novel methods</i>					
3D STE	Strain is derived from the 3D full-volume data sets with the apical four-chamber, two-chamber, long-axis view, and short-axis views 3D strain is calculated as the vector sum of the longitudinal and circumferential strain components, ignoring the radial component		Normal data does not exist for neonates	Correlates with cardiac MRI	Not validated for radial shortening
3D EF	Volumetric semi-automated border detection approach is the recommended method for the assessment of RV EF		Normal data does not exist for neonates	Ability to assess RV ejection fraction Measure of overall RV performance	Load dependent Interventricular changes affecting septal motion Poor acoustic windows

an emerging set of validated measures to assess right ventricular (RV) function in neonates that includes percent fractional area change (FAC) and tricuspid annular plane systolic excursion (TAPSE). This expanding body of literature details methodology (feasibility and reproducibility), reference ranges, and diagnostic/predictive ability of all these parameters with respect to neonatal cardiopulmonary health and disease (table 1).

Conventional Methods of Assessment of Function

Monitoring the cardiovascular status of sick and/or premature newborn infants remains a challenge due to the insensitivity of conventional echocardiographic measures to assess cardiac output and myocardial performance [7, 8]. Assessment of left ventricular (LV) output and RV output as a surrogate for systemic blood flow is challenged by the presence of shunts in early neonatal life. Superior vena cava flow is also suggested as a surrogate of blood flow from the upper body circulation. However, there are challenges with the reproducibility of this measurement and no information is provided by superior vena cava flow on blood flow to the lower body [9, 10].

SF can assess LV function using M-mode from either a long parasternal axis or short-axis view of the left ventricle, and is dependent on the change in cavity dimensions in one plane. SF is inaccurate in the presence of septal wall paradoxical motion, which often occurs with high RV pressures during the transitional period or with per-

sistent pulmonary hypertension [11]. EF may provide a better assessment of LV function in the presence of paradoxical septal motion, but both SF and EF are heavily influenced by ventricular preload as they assess cardiac function by measuring changes in cavity dimension rather than by directly analyzing muscle wall properties. The Simpson's biplane method for EF measurement is recommended as an alternative to M-mode in the presence of regional wall motion abnormalities [2]. It involves manual tracing of the LV cavity endocardium from the 4-chamber view and a modified 2-chamber view at end-systole and end-diastole (fig. 1).

The prognostic value of EF and SF has been shown to be inferior to novel quantitative measures for predicting major adverse cardiac events in adults [12]. In neonates, SF and EF lack the sensitivity to detect subtle or preclinical changes in myocardial function when compared with newer methods such as TDI and STE [8, 13, 14]. SF and EF are also not suitable for the assessment of RV function due to the complex geometry of the right ventricle [15]. The limitations of these conventional echocardiography methods have hindered the assessment of myocardial performance in many critical neonatal conditions.

Tissue Doppler Velocity Imaging

Tissue Doppler velocity imaging (TDI) is a quantitative echocardiographic modality that measures the velocity of muscle movement directly from the myocardi-

Fig. 1. Simpson's biplane method for EF measurement. The apical 4-chamber (4C) view is used as a starting point. Most modern echocardiography machines have an option to measure EF using Simpson's biplane method. The LV cavity in the 4C view is traced at the end of diastole (maximal area) and then at the end of systole (minimal area). The probe is then angled *anti-clockwise* until the RV chamber is no longer visible to obtain the 2-chamber (2C) view. The LV cavity is traced again in systole and diastole. The machine's software should then calculate the EF.

um by filtering out high-velocity signals obtained from the movement of blood to focus on the lower velocity Doppler signals of the muscle walls. Longitudinal myocardial motion velocity (from base to apex in systole and the reverse in diastole) can be measured at the mitral and tricuspid valve annuli and the base of the septum. With TDI, systolic function is obtained by measuring the peak systolic velocity of the myocardial muscle (s' wave) [16, 17] and diastolic function is measured at two time points [18]: (1) the peak early diastolic velocity (e'), and (2) the peak late (or atrial phase) velocity (a'). TDI can be performed in pulsed-wave (pw) and colour (c) modes (fig. 2a, b). pwTDI is used to measure peak myocardial velocities and has high temporal resolution, but does not permit simultaneous analysis of multiple myocardial segments. Compared with pwTDI, cTDI increases spa-

tial resolution and provides visualization of multiple segments of the heart from one single view. The velocities obtained from cTDI are 20% lower than those obtained from pwTDI, so the two methods are not interchangeable [17, 19].

TDI has been validated in adult [17, 20], paediatric [16, 21], and neonatal populations [22, 23], as well as in foetuses [24], and has demonstrated acceptable reliability. Normative reference values now exist for preterm and term infants [25–28]. Lower gestational age preterm infants have lower myocardial velocities in both systole and diastole [26, 29, 30]. Reduced myocardial velocity is also present during the transitional period from the foetal to the neonatal circulation, and increases over the first few weeks. TDI provides a more accurate assessment of myocardial dysfunction than SF and EF [8, 31–33]. TDI can

Fig. 2. a Tissue Doppler velocity measurement using pulsed waves. Diagram 1 shows the apical 4-chamber view with colour tissue Doppler. A colour-coded representation of myocardial velocities is superimposed on gray-scale 2D or M-mode images to indicate the direction and velocity of myocardial motion. The three small yellow boxes (colour in online version only) indicate the place where the pulsed-wave Doppler cursor is placed to measure velocity (from left to right: tricuspid annulus, septum, mitral valve annulus). Diagram 2 shows the corresponding pulsed-wave Doppler signal with the y-axis showing the velocity in cm/s: s' is the peak systolic velocity, e' is the peak early diastolic velocity, and a' is the peak late diastolic velocity. Diagram 3 shows the pulsed-wave Doppler signal from a premature infant. Notice the e'/a' wave reversal indicative of abnormal diastolic function. **b** Colour tissue Doppler velocity assessment. This mode facilitates simultaneous assessment of muscle wall velocity across different myocardial segments. This method can only be derived offline. The 4-chamber view image (in colour Doppler and gray scale) illustrates the region of interest where the velocities were obtained. RV systolic velocity (red line) starts before septal (yellow line) and LV (green line) velocities (colour in online version only).

assess both global and regional myocardial performance and is less affected by paradoxical septal wall motion [34]. TDI is more sensitive in detecting and monitoring myocardial dysfunction in critically ill preterm infants and term infants with congenital diaphragmatic hernia and neonatal sepsis [35–38]. TDI may also provide functional haemodynamic data to assist in outcome prediction models [35–39]. TDI is positively influenced by increasing preload, and negatively influenced by increasing afterload [24, 31].

Deformation Imaging

Deformation refers to a change in the shape of the myocardium in multiple planes from its baseline shape at end-diastole to its deformed shape at end-systole. LV and RV deformation patterns are different and are based on their own unique architectural patterns. The LV myocardium consists of longitudinal fibres in the endocardial and epicardial layers, and circumferential fibres in the mid-wall layer [40]. LV deformation during systole comprises longitudinal shortening, circumferential shortening, and radial thickening. Compared with the left ven-

Fig. 3. Tissue Doppler-derived measurement of strain and SR. The region of interest used for this technique is placed at the basal area of the wall of interest. During aortic valve opening (AVO), the wall segment strain is at baseline. Peak systolic strain is identified at the time of aortic valve closure (AVC). Peak systolic SR occurs in mid-systole (SRS). The early (SRE) and late (SRA) diastolic SR occur between mitral valve opening (MVO) and mitral valve closure (MVC).

tricle, the shape of the thin-walled RV cavity is more complex and the RV myofibre architecture is composed of superficial oblique and dominant deep longitudinal layers. Longitudinal shortening is the dominant deformation of the RV that provides the major contribution to stroke volume during systole [41].

Myocardial strain (ϵ) and strain rate (SR), which describe the longitudinal, circumferential, and radial deformation in the left ventricle and the longitudinal deformation in the right ventricle under an applied force, have been demonstrated to be feasible and sensitive quantitative measures of LV function in neonates [31, 42–46]. Strain is a measure of absolute tissue deformation during systole and is expressed as a percentage change from baseline. It is assigned a negative sign for shortening (in longitudinal and circumferential planes) and a positive sign for thickening in the radial plane. Strain is influenced by preload (which increases wall strain) and afterload (which reduces wall strain) [8]. SR measures the time course of deformation (velocity of shortening/time unit), and provides one value in systole representing the rate at which

the deformation occurs, and two values in diastole representing the early and late phase rates of return to baseline. It is thought to be less dependent on loading conditions [47], and may be a closer reflection of contractility. Strain and SR may be used to assess global and regional function in both ventricles [48]. There are two different echocardiographic methods used to measure tissue deformation: (1) cDTI and colour Doppler myocardial imaging and (2) two-dimensional (2D) STE

cDTI measures the velocity gradient of two points over a segment with a fixed distance in the myocardium. Strain is described as a displacement gradient (spatial derivative of displacement) and SR as the velocity gradient (spatial derivative of velocity) (fig. 3). Strain is calculated as a spatial derivative of SR, is measured along the beam of the ultrasound, and is insonation angle dependent. cDTI is better suited for measurement of SR values in neonates (with a higher baseline heart rate) as it employs a natural SR calculation method with much higher frame rates (high temporal resolution) [49, 50]. This technique is highly feasible and reproducible, but

Fig. 4. Speckle tracking method for calculation of strain. The top panel shows the assessment of the left ventricle by the offline analysis software in six segments (4-chamber view). The speckle tracking algorithm divides the LV myocardium into 6 segments (basal septum, mid-septum, apical septum, basal lateral, mid-lateral, and apical lateral) and generates 7 curves, 6 specific myocardial segments, and 1 global value representing the combined strain from

all segments; the LV global longitudinal strain from a 17- or 18-segment model is calculated from segmental averaging of the three apical views: apical 4-, 3-, and 2-chambers. The bottom panel demonstrates circumferential and radial strains obtained from the parasternal short-axis view at the level of the mitral valve. AVC = Aortic valve closure.

the disadvantages of this approach are the dependence on the angle of insonation ($>20^\circ$ results in a significant underestimation of values) and loading conditions [51]. Strain values obtained with the cDTI are not interchangeable with those derived by STE [52]. This is particularly true if the extent of the deformation is large [51]. Basal longitudinal cDTI measurements of strain and SR in the RV and septum provide better reproducibility than LV measurement in preterm infants. This may relate to the angle of insonation of the LV free wall or due to the left lung often obstructing a clear view of the LV free wall base [44].

2D-STE imaging uses standard B-mode images for speckle tracking analysis [12]. The speckle patterns are the result of acoustic backscatter generated by the reflected ultrasound beam. Speckles represent fixed tissue markers, or 'natural acoustic markers', that are randomly distributed throughout the myocardium and have their own unique signature or 'fingerprint' [52]. The movement of this speckled pattern follows myocardial tissue motion as it tracks the defined region of speckles, frame by frame and eventually over the entire heart cycle, and extracts the displacement (the movement of those speckles), velocity (the speed at which this movement occurs), strain (the

Fig. 5. Left ventricle rotational mechanics. The base of the left ventricle rotates in a clockwise fashion (depicted as a negative rotation) and the apex of the left ventricle rotates in an anticlockwise fashion (depicted as a positive rotation). The net difference between those opposing rotational movements is LV twist. The rate of twist ($^{\circ}/s$) in systole and early untwist in diastole are illustrated as well.

relative change in distance between those speckles), and SR (the speed at which the change in distance occurs) of a defined myocardial segment (fig. 4). STE is angle independent and gives true longitudinal strain, as the movement of speckles can be followed in any direction [53]. In the three apical image views, STE allows for calculation of longitudinal and transverse parameters. In short-axis images, both circumferential and radial parameters can be calculated for all myocardial segments [42, 54, 55]. STE-derived LV and RV strain demonstrates high clinical feasibility and reproducibility in term and preterm infants

with appropriate frame rate:heart rate ratios [8, 31, 41, 44, 56]. However, STE (as compared to TDI) employs relatively lower frame rates to derive SR measurements and the assessment of SR parameters in preterm infants using STE currently has lower reproducibility [41].

There is an expanding body of literature on strain and SR in term and preterm infants using both cDTI and STE techniques [8, 31, 44, 49, 56–58]. Current research is evaluating the ability of ϵ and SR to characterize the physiological and pathological changes in diseases such as hypoxic ischaemic encephalopathy, pulmonary hypertension, li-

Fig. 6. TAPSE measurement. Assessment of the movement of the annular plane towards the apex can be carried out in Tissue Doppler (a) and 2D M-mode (b). TAPSE is acquired with the cursor optimally aligned along the direction of the tricuspid lateral annulus in the RV-focused apical 4-chamber view and measured between end-diastole and peak systole.

gation of a patent ductus arteriosus, and chronic lung disease. [14, 28, 31, 41, 43, 59–61]. Furthermore, longitudinal reference ranges of LV and RV strain and SR (including the septum) in term and preterm infants are emerging and are a necessary prerequisite to evaluating cardiopulmonary health and disease in neonates [62].

LV Rotational Mechanics

LV twist describes the wringing motion of the LV during systole, and is the net result of the contrasting rotation of the apex (in an anticlockwise direction, depicted as a positive rotation) and the base (in a clockwise direction, depicted as a negative rotation) along the long axis of the left ventricle; both are expressed in degrees. LV torsion is the term given to LV twist indexed to its length. This wringing motion, which is also expressed in degrees, improves the ejection of blood from the LV cavity during systole. LV untwist contributes directly to early diastolic

filling and is influenced by muscle fibre compliance and elastic recoil properties. The speed at which LV twist occurs (LV twist rate) and LV untwist occurs (LV untwist rate) can also be measured and expressed as degrees per second (fig. 5). These rotational parameters add important information on myocardial performance [63]. The twisting motion of the LV is aided by the helical arrangement of the subepicardial (left handed) and subendocardial (right handed) fibres [7]. Untwist is facilitated by the kinetic energy stored in those twisted fibres which is released during diastole due to elastic recoil. Therefore, the LV untwist rate in early diastole is highly influenced by LV twist in systole. Reduced LV twist will therefore translate to a reduced LV untwist rate [27]. Increased afterload appears to decrease the LV twist and untwist rates in experimental animal models and human adults [64]. Similarly, in the preterm neonatal population, increased afterload appears to negatively impact those measurements [65].

Fig. 7. Calculation FAC. RV FAC is calculated by tracing the RV endocardium in EDA and end-systole ESA. Trabeculations are considered part of the cavity by tracing RV EDA and RV ESA between RV trabeculations and the compact layer of the ventricle. $FAC = 100 [RV\ EDA\ (cm^2) - RV\ ESA\ (cm^2)] / RV\ EDA\ (cm^2)$.

Rotational mechanics can be assessed by STE in a similar fashion to the method described above and demonstrates acceptable agreement with twist measured by magnetic resonance imaging (MRI) [63, 66]. Twist as a marker of cardiac function has been validated in adults and children [45, 67]. Rotational mechanics data in term neonates during the early transitional period is lacking. There are limited studies of those parameters in preterm infants [27, 65]. Our group has recently demonstrated the feasibility and acceptable reproducibility of measuring LV twist in the premature population, in addition to the changes occurring over the first week of age [27]. We have also demonstrated that increased systemic vascular resistance over the first day of age has a negative impact on LV twist and untwist [65].

RV-Specific Markers of Cardiac Performance

Accurate assessment of RV performance can be challenging [15], but RV function is a critical prognostic determinant of cardiopulmonary pathologies in term and preterm infants. RV-specific markers of function have recently emerged. These include TAPSE and FAC [19, 46, 68].

TAPSE measures movement of the tricuspid annulus from base to apex during systole and reflects global RV systolic function (fig. 6). This is an absolute measurement

of the distance travelled by the annulus during systole and is not indexed to the length of the right ventricle. It has been validated as an accurate measure of RV function in adult and pediatric patients [69, 70] with further research on term and preterm infants demonstrating its acceptable reliability [28, 44, 68]. The impact of lower gestation and postnatal age reveals a reduction in annular displacement which is consistent with other modalities [30]. TAPSE has been proven to show better reproducibility than other methods of RV assessment [71] and has shown a correlation with RV EF determined by MRI. It is not influenced by heart rate, which is of importance for its use in preterm infants [72]. In order to compare TAPSE across different gestations and heart size, some advocate indexing the measurement to RV length.

RV FAC is a quantitative measurement of RV function. RV FAC expresses the percentage change in the RV chamber area between end-diastole (EDA) and end-systole (ESA). Calculation of FAC can be easily performed using standard echocardiographic equipment and does not require any geometric assumptions (fig. 7). Although FAC is affected by loading conditions, it is less sensitive to abnormal geometry and regional abnormalities. RV FAC measurements in term and preterm infants are highly reproducible [28, 44, 73]. Reference values for RV EDA, RV ESA, and FAC have been identified in the neonatal population for both term and preterm infants [73]. As expected, there is an increase in RV areas and FAC

with gestational age and a linear increase with weight [28]. In the transitional period, RV areas and RV FAC remain relatively stable in healthy term infants. However, in preterm infants the RV ESA and RV FAC increase in the transitional period, while RV EDA remains stable. This increase in FAC is most likely because of a smaller RV ESA (compared with healthy term infants), 'which likely reflects the decreased afterload imposed on the RV by a slowly decreasing pulmonary vascular resistance' [44].

Conclusion

The methods to diagnose and manage cardiac function with echocardiography in term and preterm infants must be firmly understood and established before routine clinical adoption can be implemented and incorporated into neonatal guidelines. The novel echocardiography methods to assess cardiac function that are now available have been validated in stable preterm infants and healthy term infants. Despite the push to standardize the acquisition of these measures and reduce intervender differences and

ambiguities, it is important for the reader to review any details of hardware settings, manual settings, and local imaging protocols to get a better understanding of the values presented. The next phase is to determine the applicability of these novel measures of myocardial performance as a means for assessing the efficacy of patient management strategies in health and disease. We need to understand their ability to direct management, monitor treatment response and predict outcomes to optimize the care we deliver to term and preterm infants. In addition, exploring further novel methods of functional assessment, including 3D-STE and 3D-echocardiography-derived RV volume and EF is warranted.

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Disclosure Statement

The authors report no conflicts of interest.

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