Fetal Diagnosis and Therapy

Assessment of Fetal Cardiac Function Using Tissue Doppler Techniques

Montse Comas[a]   Fatima Crispi[b]

[a] Servei de Ginecologia i Obstetrícia, Corporació Sanitària Parc Taulí, Sabadell, and [b] Department of Maternal-Fetal Medicine, Institut Clínic de Ginecologia, Obstetrícia i Neonatologia (ICGON), Hospital Clinic, Fetal and Perinatal Medicine Research Group, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, and Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBER-ER), Barcelona, Spain

Abstract
Objective: Tissue Doppler echocardiography is being increasingly used in fetal medicine as a clinical and research tool. The objective of this study was to review the current status of tissue Doppler imaging (TDI) techniques applied to the fetus. *Methods:* Fetal cardiac function was evaluated using spectral and color TDI modes in normal fetuses and in several clinical conditions. *Results:* Annular peak velocities and their ratios as well as the myocardial performance index were evaluated using spectral TDI, and changes throughout gestation were described. Color TDI has several limitations in fetal life, particularly the use of low frame rates with current methods of acquisition and the lack of normal references for deformation parameters. *Conclusions:* Despite its limitations, TDI is a sensitive and promising method to evaluate fetal cardiac function.

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Background

Tissue Doppler imaging (TDI) is a consolidated and reproducible echocardiographic technique that was first described in 1989 [1] and permits accurate and direct quantitative assessment of myocardial motion. In adult echocardiography, this technique is useful in the early identification of subtle cardiac dysfunction in preclinical stages [2, 3] and as a prognostic tool in major cardiac diseases, such as heart failure, acute myocardial infarction, and hypertension. In these situations, peak annular velocities (PAV), the transmitral-to-mitral annular diastolic velocity ratio (E/E') , and intraventricular dyssynchrony have been shown to predict mortality and cardiovascular events [4]. Due to these properties, in fetal life, TDI could constitute a more sensitive tool than standard methods to detect the presence of cardiac dysfunction. Recently, several studies have applied and evaluated this echocardiographic technique in fetuses.

While conventional echocardiographic techniques are based on blood flow, TDI uses frequency shifts of ultrasound waves to calculate myocardial velocity, which is characterized by a lower velocity and a higher amplitude [5]. Because of these characteristics, TDI assessment has

Fatima Crispi
Department of Maternal-Fetal Medicine (ICGON)
Hospital Clínic, Universitat de Barcelona, Sabino de Arana 1
ES–08028 Barcelona (Spain)
Tel. +34 932 279 333, E-Mail fcrispi @ clinic.ub.es

Table 1. Web links to commercially available tissue Doppler echocardiography

Siemens ACUSON Antares™	http://www.medical.siemens.com/siemens/en_INT/gg_us_FBAs/files/brochures/Acuson/Antares_Cardiac.pdf
Siemens Sequoia	http://www.SequoiaUltrasound.com/pdf/sequoiaultrasound.com/Sequoia_512_Data_Sheet.pdf
General Electric Vivid-7	http://www.vivid7ultrasound.com/pdf/vivid7ultrasound.com/Vivid_7_2D_Strain_Brochure.pdf
Toshiba Aplio XG and Aplio MX	http://www.medical.toshiba.com/products/ul/aplioxg/cardiology-applications.php
Philips HD11 XE	http://www.healthcare.philips.com/in_en/products/ultrasound/systems/hd11xe/index.wpd
Aloka ProSound Alpha 10	http://www.aloka.com/products/view_system.asp?id=12

a lower load dependency than standard Doppler techniques. Table 1 lists the available echocardiography systems with tissue Doppler. TDI can be performed in spectral and color-coded modes.

Spectral TDI

In spectral TDI (S-TDI), Doppler information is sampled from a small sample volume (defined in 2D or color image) and presented on a timeline. Sampling is performed online though a preset system feature which adjusts the scale and velocity, similar to pulsed Doppler of blood flow. This technique is especially appropriate for measuring long-axis ventricular motion because the longitudinal fibers are more parallel to the ultrasound beam in the apical and basal views.

Technique and Measurements

In an apical or basal four-chamber view, the image is enlarged, the 2D scan area is reduced, and a sample volume between 2 and 4 mm is placed in the basal part of the ventricle or annulus. The insonation ultrasound beam is maintained at an angle of <30° to the ventricular wall or intraventricular septum. No angle correction should be applied. The velocity of myocardial movement toward the Doppler cursor is displayed as a spectrum [6] and waveforms are obtained (minimum 3) (fig. 1).

Measurements

The main outcome of S-TDI is PAV (fig. 1): (1) E' or Ea, early diastolic annular relaxation velocity, (2) A' or Aa, annular velocity during auricular contraction, and (3) S' or Sa, annular velocity during ventricular systole. Peak velocities are usually assessed in the valve annulus where long-axis ventricular motion of the myocardium is displayed as a measurement of global cardiac function. Regional function can be also assessed by evaluating myocardial peak velocities in any area on the myocardium.
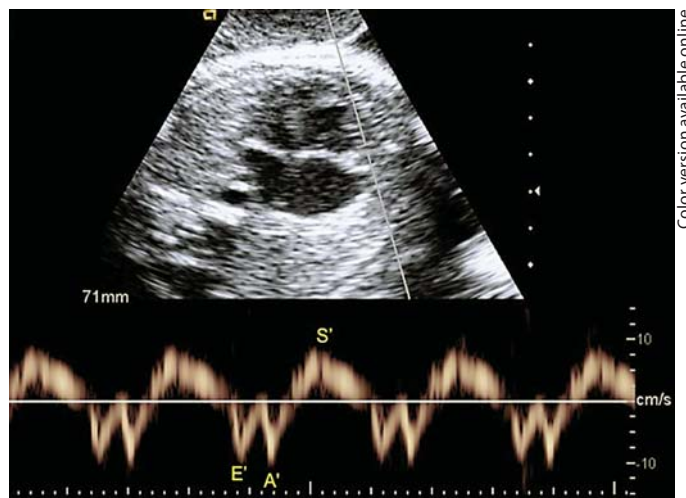

Fig. 1. Example of PAV obtained by spectral tissue Doppler in the right annulus. The sample volume is placed in the right annulus just below the tricuspid valve with an insonation angle of the ultrasound beam of <30° to the orientation of the ventricular wall. A tissue Doppler spectral waveform is displayed and PAV are obtained. E' = Annular velocity in early diastole; A' = annular velocity during atrial contraction; S' = annular velocity in systole.

Furthermore, several time periods can also be calculated to obtain the myocardial performance index (MPI'): isovolumic contraction time (ICT'), ejection time (ET'), and isovolumic relaxation time (IRT'). MPI' can be calculated as (ICT' + IRT')/ET'.

Feasibility and Reproducibility

TDI has been shown to be feasible in fetuses [7–9]. The first to show that TDI was technically possible in human fetuses were Harada et al. [7], who evaluated a group of 30 fetuses between 19 and 38 weeks of gestation using S-TDI. S-TDI evaluation was successfully performed in all fetuses and the tissue Doppler wave pattern was described, consisting of E', A', and S'. Subsequent studies [10–12] corroborated the high feasibility of this technique

(79–97% of the fetuses), being better at the right annulus than the left side or IVS. Several studies have evaluated the reliability of S-TDI in fetuses of at least 14 weeks and have shown acceptable reproducibility [7, 10, 11, 13]. Chan et al. [10] reported that reliability ranged from 0.91 to 0.97 using the intraclass correlation coefficient (ICC). Another recent study [13] showed similar, although lower, ICC values ranging from 0.66 to 0.88. Gardiner et al. [11] reported suboptimal interobserver reliability for PAV, which was explained by the presence of a small number of high outliers.

The reliability of left and right MPI' has also been evaluated by two recent studies [14, 15] reporting ICC values ranging between 0.70 and 0.94.

Limitations

Although fetal position and movements, the small fetal heart size, the high fetal heart rate, restricted physical access to the fetus, and the relatively low resolution of ultrasound equipment may limit the acquisition of S-TDI, several recent works have demonstrated that S-TDI is feasible and reproducible in most fetuses even from early on in the second trimester of pregnancy [7, 10–14]. The main disadvantage of this technique is that it only provides information on velocities [not strain (S) or strain rate (SR)] from one region of the heart at a time and does not allow multiple regions to be studied simultaneously.

Color TDI

In color TDI (C-TDI), velocimetry is presented as a color-coded overlay on top of a B-mode image. To perform C-TDI analysis, a cardiac cine loop with a high frame rate is acquired and the evaluation of TDI-derived parameters is performed offline.

Technique

C-TDI video clips are obtained during fetal quiescence with the ultrasound beam parallel to the region on interest (usually the septum or myocardial free walls in an apical or baseline four-chamber view). If needed, a sector tilt can be used to ensure that the angle between the probe and myocardial motion is <15°.

While recording the loop, the 2D scan area and the TDI color box should be kept as small as possible to obtain the highest number of frames per second (fps). It is critical to acquire images at a high frame rate (>200 fps). The color gain must be adjusted to avoid aliasing. For each acquisition, at least 5 s of noncompressed data

should be recorded. Analysis of TDI-derived parameters is performed offline. The velocity of myocardial movement toward the transducer is obtained for each pixel of the image. A color-coded representation of myocardial velocities, S, and SR is displayed offline (fig. 2). At least 3–5 cardiac cycles should be obtained with similar characteristics (slope <30°) to confirm good-quality acquisition. An advantage of C-TDI is that multiple segments can be evaluated in a single view, thus allowing segmental information of cardiac function to be obtained. Furthermore, deformation (S and SR) parameters can be also assessed.

Measurements

Apart from myocardial velocities, deformation indices such as S and SR can be evaluated offline using C-TDI. S represents the lengthening change of a myocardial segment from its original length. SR consists of the change of S during time. Velocity measurements cannot differentiate between active and passive motion related to translation or tethering of a myocardial segment. In contrast, deformation analysis allows discrimination between active and passive myocardial tissue movement [15] and could be more sensitive than myocardial velocities for noninvasive assessment of ventricular function.

Feasibility and Reproducibility

The reliability of C-TDI has been evaluated in fetuses. However, several limitations such as the frame rate and electrocardiogram (ECG) co-registration should be taken into account before drawing conclusions. The first report of C-TDI in fetal life was by Paladini et al. [16], who described high feasibility (84%) and reproducibility. However, these data were based on very low temporal resolution (20–40 fps), which strongly limits the validity of these findings. Subsequently, Nii et al. [17] obtained accurate TDI recordings in 96, 96, and 93% of cases in the left annulus, right annulus, and IVS, respectively, and also reported a good intra- and interobserver reproducibility of PAV measurements. In another study, Perles et al. [18] evaluated 98 fetuses by C-TDI and measurement of PAV, and S and SR was achieved in all cases. Deformation parameters such as SR were evaluated in four fetuses by Larsen et al. [19]. These authors highlighted the importance of collecting cardiac motion information with high frame rates (over 200 fps), which allows the fast events of the fetal heart to be correctly analyzed. A recent article by Crispi et al. [20] reported acceptable feasibility and reproducibility using a dummy ECG for the first time by manually indicating the onset of each cardiac cycle in
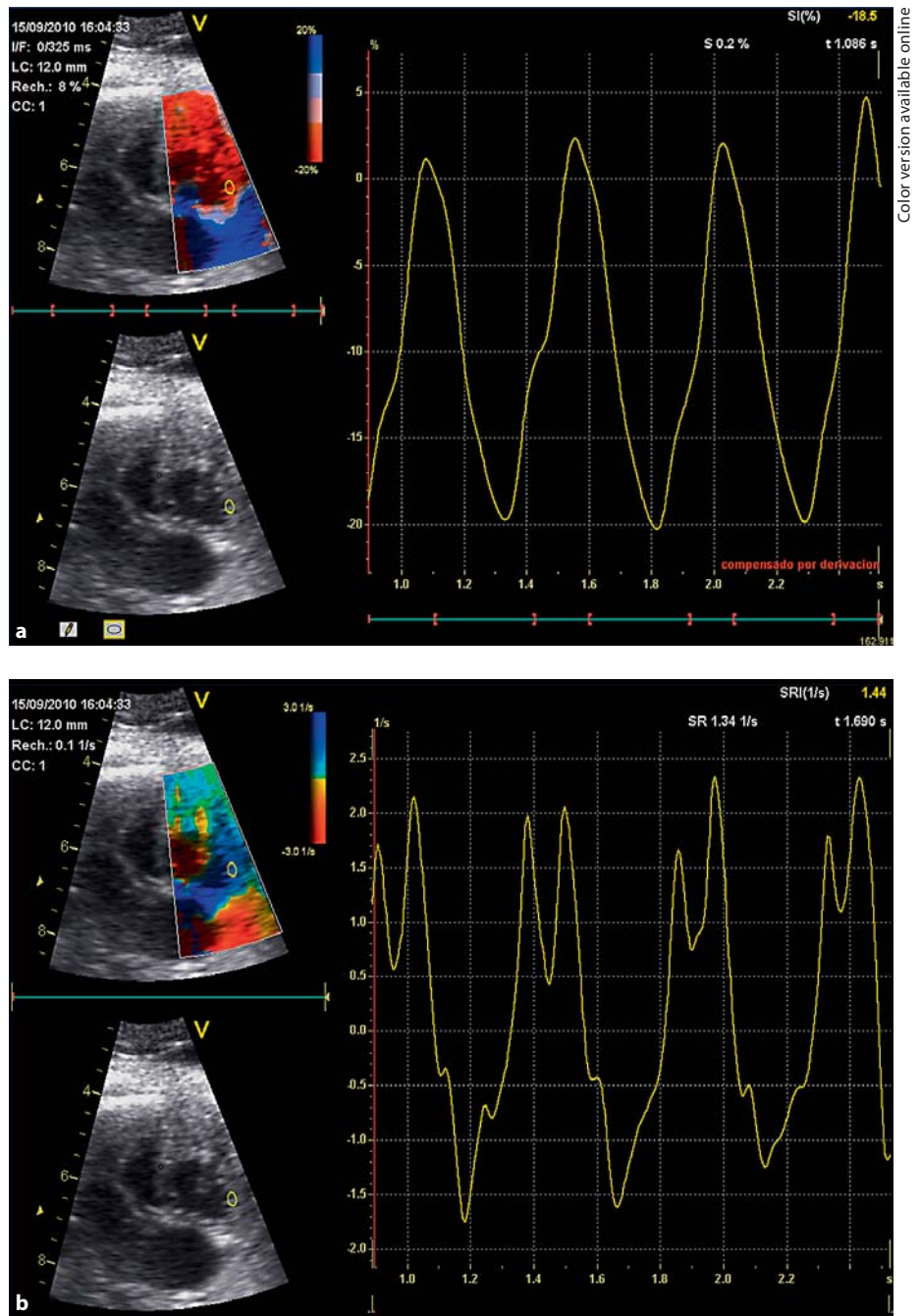
Fig. 2. Example of measurement of S (**a**) and SR (**b**) by color tissue Doppler. A four-chamber view with the right free wall aligned parallel to the Doppler beam is used and color tissue Doppler is superimposed. Offline analysis is performed displaying the S and SR of the right basal free wall.

the 2D clip based on valve motion. Feasibility and reproducibility during the first trimester of gestation have not yet been described.

Limitations

The use of C-TDI has several limitations in fetal life compared with the use of this technique in adults, which are listed below:

(1) Fetal position: during echocardiographic examination, the fetal position can vary, which sometimes does not allow a perfect apical four-chamber view to be obtained. Obtaining C-TDI recordings with a good angle is crucial to prevent underestimation of variables such as velocities.

(2) Fetal movements: recordings must be acquired during fetal quiescence, avoiding periods of fetal and respira-

tory movements that could interfere with the TDI algorithm.

(3) Frame rate: a high frame rate is critical to correctly analyze the fast events occurring throughout the cardiac cycle. Frame rates of at least 140 fps are required to adequately analyze myocardial events during each cardiac cycle in adults. Since the heart rate is higher in fetuses than in adults (110–180 beats per min), the temporal resolution permitted by the frame rate may limit this offline analysis. The technical limitations of some initial fetal studies using C-TDI include the use of ultrasound equipment with low TDI frame rates, which can lead to poor temporal resolution and sometimes result in underestimation of time-dependent variables such as velocities, MPI, and SR. Recently, frame rates exceeding 200 fps have become possible using some equipment [17, 20].

(4) Co-registration with ECG: in adult cardiology, C-TDI evaluation is usually carried out with simultaneous ECG registration to record myocardial events accurately. However, fetal ECG cannot be performed during gestation. The use of virtual fetal ECG has recently been shown to have good reproducibility [20].

(5) Resolution of ultrasound machines: most of the available transducers and equipment used to assess TDI in fetuses (table 1) were designed for adults and have not yet been adapted to obstetric ultrasound, which may limit proper evaluation of the fetal heart due to restricted physical access to the fetus and the small size of the fetal heart. Additionally, myocardial peak velocities are markedly lower in fetuses than in children and adults. Even the lowest available scale size of most ultrasound machines is often too large. In this case, waveforms are often displayed with suboptimal resolution, which may hamper accuracy.

(6) Low peak myocardial velocities: peak velocities obtained by C-TDI are always lower than those obtained by S-TDI, which may limit the accuracy of measurements.

Reference Ranges for Tissue Doppler Parameters during Normal Gestation

PAV and E'/A' E/E' Ratios

Reference charts for S-TDI parameters have been reported by several authors, showing similar values. PAV and E'/A' ratios seem to increase throughout gestation while a negative relationship between the E/E' ratio and

gestation has been described because of a greater increase in E' than in E [10–12].

For C-TDI, an increase in PAV and E'/A' ratios and a decrease in E/E' have also been reported in the left and right ventricles and IV septum [17]. Although these findings are consistent with S-TDI, peak velocity measurements were 15–20% lower than similar peak velocity measurements obtained by instantaneous S-TDI, which was attributed to the averaging at interrogated regions conducted with C-TDI. Accordingly, peak E' and A' were slightly smaller and E/E' was slightly higher when compared with previously published data obtained by S-TDI.

Moreover, differences could also be explained by the use of distinct echocardiographic equipment. The use of different echocardiographic TDI systems has yielded correlated but distinct values for myocardial velocities. Consequently, use of the same echocardiographic equipment during patient follow-up, as well as reference charts, has been recommended [21].

Time Intervals

MPI' values obtained by S-TDI are generally higher than those obtained by standard pulsed Doppler [14] and have shown a slight tendency to increase with gestational age [12]. In another study, Nii et al. [22] demonstrated the feasibility of C-TDI for measuring fetal atrioventricular time intervals and establishing gestational age reference data, which could be used to assess fetal atrioventricular conduction, particularly in cases of maternal anti-Ro and anti-La antibodies.

S and SR

Characterization of deformation parameters during gestation is still insufficiently known. While some authors suggest that S and SR increase with gestational age [23] others argue that these parameters remain stable [18] throughout gestation. Similar discordances have also been described in deformation analysis by 2D speckle tracking techniques; the first reports using a low frame rate reported no changes in S throughout gestation [24] while recent studies using more appropriate frame rates have demonstrated that S decreases with gestational age [25, 26]. Future studies in TDI using acceptable high frame rates to validate these parameters and their reproducibility are needed to study myocardial deformation properties in the fetus.

Table 2. Summary of most important spectral tissue Doppler studies

Reference	Echocardio-graphic system	Sample size	Population	GA range weeks	Annular location	Results	Other new information	Limitations
Harada et al. [7] (1999)	Aloka SSD-2200	30	Normal fetuses	19–38	Left, right, septum	E' < A', PAV and E'/A' increased with GA (except for A' and septal S')	Typical fetal tissue Doppler wave was provided	Small sample size
Tutscheck et al. [9] (2003)	Philips ATL HDI 5000	77	Normal fetuses	15–40	Left, right	PAV and E'/A' ratios increased with GA	Cardiac wall motion was detected by changing the Doppler settings but without specific TDI equipment	Small sample size
Aoki et al. [36] (2004)	Aloka SSD-5500	43	7 heart failure, 36 controls	16–39	Right	Increased E/E' and MPI' in fetuses with heart failure	E/E' and MPI' could be useful as indicators of right cardiac dysfunction	Small sample size Lack of reference ranges for MPI'
Chan et al. [10] (2005)	Philips HDI 5000	302	Normal fetuses	19–37	Left, right, septum	All PAV and E'/A' increased with GA. E/E' decreased with GA	Reference ranges for S-TDI parameters were provided	
Gardiner et al. [11] (2006)	Sequoia Siemens	159	Normal fetuses	15–38	Left, right, septum	PAV increased with GA (except for left A). Right PAV were higher than left PAV	PAV showed similar gestational rates of increase in both ventricles, suggesting similar maturational changes	Higher interoperator variation
Hátem et al. [33] (2008)	Philips HP Sonos 5500	62	47 diabetes, 15 controls	25–37	Left, right, septum	Higher PAV and lower E/E' in the fetuses of diabetic mothers	No differences between the fetuses of diabetic mothers with and without myocardial hypertrophy	Small sample size
Watanabe et al. [38] (2009)	Aloka SSD-6500	56	12 IUGR, 6 hydrops, 38 controls	17–38	Left, right	Right PAV were higher than left PAV. Lower left S' and higher left E'/A' in fetuses with hydrops	Right S'/left S' is a new index which was higher in IUGR and lower in hydrops	Small sample size Interobserver variability was not determined
Naujorks et al. [29] (2009)	Acuson Siemens	58	14 IUGR 13 AGA with hyperten-sion, 29 AGA	25–36	Left, right, septum	Higher left and septal E'/A' and lower left E/E' in IUGR		Small sample size
Comas et al. [13] (2010)	Antares Siemens	75	25 IUGR, 75 controls	26–34	Left, right, septum	Lower left and right PAV, higher left E'/A' and MPI' in early IUGR	Presence of both systolic and diastolic cardiac dysfunction in IUGR, detected by TDI	Small sample size. Uncertain correlation with perinatal and postnatal cardiovascular outcome
Comas et al. [12] (2011)	Antares Siemens	213	Normal fetuses	24–42	Left, right, septum	PAV and left and right E'/A' increase with GA. E/E' decreases with GA	Reference ranges for MPI' were first reported. Left MPI' increased with GA	Information limited to 24 weeks onwards
Comas et al. [30] (2011)	Antares Siemens	116	58 SGA 58 controls	34–41	Left, right, septum	Lower right E' and A' and higher MPI' in SGA	Presence of subclinical cardiac dysfunction in SGA with normal umbilical artery, detected by TDI	Significant changes only in the right ventricle that could be explained for higher PAV or better Doppler insonation

GA = Gestational age; E' = early diastolic annular relaxation velocity; A' = annular velocity during auricular contraction; S' = annular velocity during ventricular systole; MPI' = myocardial performance index measured by TDI.

Table 3. Summary of most relevant color tissue Doppler studies

Reference	Echocardio-graphic system	Sample size	Population	GA range weeks	Locations	Frame rate	Results	Limitations
Paladini et al. [16] (2000)	Toshiba Powervision	89	Normal fetuses	17–37	Left and right ventricular walls	20–40	PAV increased with GA. E'/A' was constant during gestation. Subendocardial velocities were higher than subepicardial velocities.	Low frame rate. Use of a transverse four-chamber view.
Rein et al. [35] (2002)	GE Vivid-5	31	Fetal arrhythmia	18–38	Left and right atrial wall and annulus	48–136	TDI could be useful in the evaluation of supraventricular and ventricular arrhythmias.	Low frame rate. Diagnosis of the arrhythmia could not always be confirmed after birth.
Di Salvo et al. [23] (2005)	GE Vivid-7	75	Normal fetuses	21–29	Mid wall (left, right, and septum)	40–90	Longitudinal myocardial deformation properties increased with GA and are homogeneous in left and right ventricles.	Limited reproducibility of S and SR.
Nii et al. [17] (2006)	GE Vivid-7	114	Normal fetuses	14–42	Annulus (left, right, and septum)	230 ± 28	E', A', and E'/A' increased with GA. E/E' decreased with GA and remained stable in the third trimester.	C-TDI velocities were lower than previously published S-TDI velocities.
Larsen et al. [19] (2006)	GE Vivid-7	4	1 aortic atresia, 3 normal fetuses	19–36	Annulus (left, right, and septum)	170–216	Reduced left and septal SR in the fetus with aortic atresia.	Small sample size.
Perles et al. [18] (2007)	GE Vivid-5	98	Normal fetuses	13–40	Left and right annulus	105–212	PAV increased with GA. S and SR were constant throughout gestation.	
Larsen et al. [27] (2009)	GE Vivid-7	62	20 IUGR 42 controls	26–34	Left and right annulus	175–215	Lower left S' in IUGR. Left S' and revered UA flow was associated with perinatal death.	Small subdivision groups by flow class.
Di Naro et al. [34] (2010)	Aloka Prosound Alpha 10	39	12 PPROM, 27 controls	24–34	Right annulus (velocity) and right ventricular wall (S and SR)	Not speci-fied	Higher E'/A' and early diastolic SR, lower systolic S and systolic SR in PPROM.	Small sample size.
Larsen et al. [28] (2011)	GE Vivid-7	53	15 IUGR 42 controls	24–34	Left and right annulus	175–215	Lower left and right A' and higher left E'/A' in IUGR.	Small sample size. Some fetuses had sequential examinations and others not.

Frame rates are expressed as ranges or means ± SD. GA = Gestational age; E' = early diastolic annular relaxation velocity; A' = annular velocity during auricular contraction; S' = annular velocity during ventricular systole; PPROM = preterm premature rupture of membranes.

Clinical Applications of TDI in Fetuses

In recent years, tissue Doppler studies have emerged to evaluate fetal cardiac function in several clinical conditions. Due to the higher sensitivity of this technique, TDI can be useful to detect cardiac dysfunction alone or in combination with conventional Doppler. The most important tissue Doppler studies are summarized in tables 2 and 3.

Intrauterine growth restriction (IUGR) has been clearly associated with cardiac dysfunction, explained by the major role of the heart as the central organ in fetal adaptive mechanisms to placental insufficiency. Several studies have demonstrated systolic and diastolic cardiac dysfunction in growth-restricted fetuses using S-TDI and C-TDI: decreased PAV [13, 27, 28], increased E'/A' ratios [13, 28, 29], decreased E/E' ratios [29], and higher values of MPI' [13]. The decrease in systolic peak velocities has

been proposed as a predictor of perinatal mortality in IUGR fetuses with reversed umbilical artery [27]. Changes in tissue Doppler parameters, with regards to PAV and MPI', have also been described in small-for-gestational-age (SGA) fetuses with a normal umbilical artery. In contrast with conventional echocardiography, TDI could detect significant differences between SGA fetuses and controls, supporting the higher sensitivity of this technique in detecting subclinical fetal cardiac dysfunction [30].

Maternal diabetes is the most common cause of fetal hypertrophic cardiomyopathy [31, 32]. Cardiac hypertrophy is reflected by increased values of PAV and leads to diastolic dysfunction measured by increased E'/A' and decreased E/E' ratios [33].

Changes in deformation parameters have been described in fetuses with preterm premature rupture of membranes and proven intraamniotic infection. Right ventricular function was evaluated in these fetuses using C-TDI and signs of diastolic and systolic dysfunction were demonstrated, characterized by increased E'/A', increased early diastolic SR, reduced systolic SR, and longitudinal myocardial dyskinesia [34].

Another potential application of C-TDI during fetal life is in the diagnosis and understanding of fetal arrythmias. Rein et al. [35] described a new method that allows simultaneous sampling of the right and left atrial and ventricular wall velocities to acquire temporal analysis of atrial and ventricular events. However, the low frame (48–136 Hz) used in this work strongly limits its validity.

Finally, fetuses with heart failure showed increased values of E/E' ratios and MPI' [36]. The transmitral to mitral annular diastolic velocity ratio (E/E') consists of the quotient between peak velocity during early diastole using conventional echocardiography and peak myocardial velocity during early diastole using TDI. This parameter was reported to correlate well with ventricular filling pressure [37] in adulthood. However, its value in fetal echocardiography is still unknown as no validation studies have demonstrated its significance and utility. Increased and decreased values of the E/E' ratio have been reported in altered fetal conditions, which supports the unknown value of this parameter in fetal life.

Conclusions

Tissue Doppler techniques represent a feasible method to evaluate fetal cardiac function. Reference ranges for TDI parameters have been reported for S-TDI and some clinical applications have recently been developed.

Tissue Doppler techniques were first designed to evaluate the adult heart, and their application in fetuses still has some limitations. The most important limitations are closely related to fetal characteristics during cardiac examination such as a variable position, fetal and respiratory movements, a higher heart rate, and the fact that simultaneous ECG cannot be performed. Although S-TDI requires formal training and special care with the angle of acquisition and the absence of fetal movements, in experienced hands, this technique is feasible and reproducible. However, these limitations are especially critical with the use of C-TDI because of the offline analysis. Application of C-TDI techniques requires further validation in fetuses and the establishment of normal references for deformation parameters. For example, the recently described decrease in S with gestational age needs to be corroborated. Therefore, studies using TDI should accurately describe the methodology used for the validity and applicability of this technique to be assessed.

Despite its technical limitations, in the future, TDI could constitute a promising and sensitive method to evaluate fetal cardiac function in several clinical conditions such as IUGR, maternal diabetes, and congenital heart diseases.

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