Assessment of the Evolution of Normal Fetal Diastolic Function During Mid and Late Gestation by Spectral Doppler Tissue Echocardiography

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Objective: **To establish gestational age–specific reference values in healthy singleton fetuses, we prospectively assessed the evolution of diastolic longitudinal wall-motion velocities by spectral Doppler tissue imaging.**
Methods: **Early (Ea) and late diastolic (Aa) peak Doppler tissue imaging velocities were analyzed in 114 fetuses (age range: 14-42 weeks) at the base of right ventricular free wall, ventricular septum, and left ventricular free wall and compared with early (E) and late (A) diastolic peak Doppler inflow velocities.**
Results: **A linear increase in Ea, Aa, and Ea/Aa ratio was documented at all sites with advancing gestation. Likewise, the peak E flow velocities of both atrioventricular valves and the tricuspid peak A flow velocity increased. The ratio of peak E/Ea velocities decreased exponentially as a result of a more rapid increase in Ea than E, to reach a stable E/Ea relationship only in the early third trimester.**
Conclusions: **There was a strong positive correlation between Ea and Aa velocities and gestational age indicating improved diastolic myocardial lengthening with advancing gestation. Reference charts for Doppler tissue imaging velocities were established that will allow identification of fetal diastolic function abnormalities.** (J Am Soc Echocardiogr 2006;19: 1431-1437.)

Until recently, fetal diastolic function assessment has mainly relied on the analysis of systemic venous and atrioventricular (AV) flow recordings obtained by pulse wave Doppler echocardiography, including left ventricular (LV) isovolumic relaxation time and the ratio of early (E) and late (A) diastolic inflow velocities.[1-4] Diastolic inflow velocity profiles are primarily caused by changes in pressure gradients between atriums and ventricles and are affected by factors other than intrinsic myocardial properties including loading conditions and heart rate. This may be of particular relevance for the fetal circulation, which is characterized by an exponential increase in cardiac volume load throughout the course of gestation. Moreover, abnormal loading characterizes a number of pathologic conditions of pregnancy such as twin-twin transfusion.

The measurement of ventricular long-axis contraction and relaxation velocities directly from the myocardium using Doppler tissue imaging (DTI) is now widely accepted as a useful tool to quantify diastolic function in children and adults.[5-14] DTI frame rates of at least 140 frames/s are required to adequately analyze peak wall-motion velocities of cardiac events.[15,16] In fetal cardiology, a small number of reports have shown the feasibility to assess diastolic cardiac function by instantaneous pulse wave DTI,[17-20] including a recent report focusing on normal reference data.[21] Technical limitations of these fetal studies include the use of ultrasound equipment with low DTI frame rates (20-40/s) and consequently poor temporal resolution (>25 milliseconds). Assuming a heart rate of 150/min and a frame rate of 40/s only 15 data points will be available to study longitudinal shortening and lengthening velocities of myocardial fibers during each cardiac cycle. Yet, by means of spectral pulse wave DTI, which has recently become available in commercially available ultrasound systems, frame rates exceeding 200/s with temporal resolutions less than 5 milliseconds are possible.

Using this approach, the purpose of this study was to establish reference values for: (1) diastolic longitudinal wall-motion velocities; (2) AV Doppler in-

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flow; and (3) early diastolic flow/wall-motion velocity ratios in a population of healthy fetuses between 14 and 42 weeks of gestation.

METHODS

The study consisted of 114 healthy fetuses (range: 14-42 weeks) that were prospectively enrolled between August 2003 and December 2004. Inclusion criteria were singleton pregnancies with normal fetal-maternal examinations and normal outcomes. Each fetus was only scanned once. The institutional research ethics board approved this cross-sectional study and written informed consent was obtained from each participating woman.

Echocardiographic Examinations

All echocardiographic recordings were videotaped and digitally stored for review. To rule out fetal cardiovascular anomalies, each participant underwent a detailed 2-dimensional, color, and pulse wave Doppler fetal echocardiographic examination using VingMed Vivid-7 (GE Medical Systems, Milwaukee, Wis) or HDI-5000CV (Philips ATL, Bothell, Wash) ultrasound systems with 3.5- to 7.0-MHz curved-array transducers. Biparietal diameter and femur length ultrasound measurements were used to establish the gestational age. Two-dimensionally guided color-coded DTI recordings were obtained from a 4-chamber view of the fetal heart using a multifrequency phased-array transducer (central frequency, 3.5 MHz; range, 2.25-5.0 MHz). For the DTI recordings, the sector width, depth, and Nyquist limits (16-19 cm/s) were optimized to obtain highest possible frame rates (mean $\pm$ SD: 230 $\pm$ 28 frames/s). For all measurements, the Doppler beam was aligned parallel (<20 degrees) to the blood flow or parallel to the longitudinal wall-motion direction, respectively. No angle correction was used. Data were excluded if acquired during episodes of fetal movement or breathing.

Pulse Wave Doppler Measurements

Doppler inflow velocities of the mitral valve and tricuspid valve (TV) were obtained from a 4-chamber view by placing a 2-mm sample volume with a wall filter setting of 200 to 400 Hz immediately distal to the tips of the AV valve leaflets. Tracings were recorded at a sweep speed of 200 mm/s. E and A diastolic peak inflow velocities were obtained from 3 consecutive cardiac cycles and averaged.

Tissue Doppler Measurements

Digitally recorded cineloops of 10 or more consecutive cardiac cycles were analyzed offline using software (EchoPAC PC, Version 3.1.3, GE Medical Systems). Tissue velocity curves were obtained at the cardiac base from 3 locations: the right ventricular (RV) free wall, the ventricular septum (VS), and the LV free wall. Care was taken to keep the 1- $\times$ 1-mm Doppler sample volume within the center of the myocardial wall throughout the interrogated cardiac cycle. Data points were smoothed with a 3-point moving average filter. Peak early (Ea) and late diastolic (Aa) wall-motion velocities were measured on 3 consecutive cardiac cycles and subsequently averaged.

Reproducibility of Measurements

The interobserver and intraobserver variability in offline measurements was assessed in 20 randomly selected studies by the Bland-Altman method. DTI velocities were measured by two independent observers and subsequently 1 week later by one of these two observers.

Statistical Analysis

Data are expressed as median with range, mean with SD or 95% confidence interval, as appropriate. Correlation between dependent and independent variables was evaluated by linear and nonlinear regression. Stepwise multivariate linear regression analysis was used to evaluate the effects of gestational age and cardiac cycle length on wall-motion velocities. Comparison of mean DTI velocities in different wall segments was performed by analysis of variance with Bonferroni correction as a post hoc test. Linear and nonlinear regression analyses are expressed as the percent of variation in the dependent variables explained by the independent variable (R^2). Interobserver and intraobserver reproducibility of measurements was calculated as the difference between two independent observations and expressed as percent of average values. A P value less than .05, and F greater than 2.0 was considered significant. All data analysis was performed with commercially available statistical software packages (Prism for Windows, Version 4, Graph-Pad Software Inc, San Diego, Calif; and Statcel, Version 1998, OMS, Saitama, Japan).

RESULTS

Technically accurate Doppler recordings were obtained in 107 of 114 studies (94%) for LV inflow, 105 of 114 (92%) for RV inflow, 109 of 114 (96%) for RV free wall, 106 of 114 (93%) for VS, and 109 of 114 (96%) for LV free wall.

Tissue and Pulsed Doppler Velocities

To better characterize the impact of gestational age on diastolic variables, the study population was divided into 5 representative subgroups (14-19, 20-24, 25-29, 30-34, and ≥35 weeks) (Table 1). With advancing age, linear increases in peak Ea and Aa velocities were demonstrated in all 3 wall segments (Figures 1 and 2). Likewise, the peak E flow velocities of both AV valves and the peak A flow velocity of the TV increased with gestational age, whereas the peak A velocity of the mitral valve was not

Table 1 Diastolic pulse wave and tissue Doppler velocities in normal fetuses by gestational age group

Demographics	14-19 wk	20-24 wk	25-29 wk	30-34 wk	35-42 wk
Case No.	26	24	21	20	23
TV E velocity, cm/s	33.0 ± 3.7	35.5 ± 5.9	40.7 ± 6.6	48.3 ± 5.5	50.3 ± 6.5
TV A velocity, cm/s	51.2 ± 6.4	54.9 ± 6.4	55.7 ± 5.9	63.4 ± 6.4	63.1 ± 9.2
TV E/A ratio	0.65 ± 0.06	0.65 ± 0.06	0.73 ± 0.12	0.76 ± 0.08	0.81 ± 0.11
MV E velocity, cm/s	29.7 ± 5.1	33.0 ± 5.3	39.5 ± 8.0	44.2 ± 8.1	41.9 ± 5.9
MV A velocity, cm/s	49.6 ± 6.4	53.8 ± 6.1	55.8 ± 6.2	58.2 ± 8.3	50.1 ± 6.5
MV E/A ratio	0.60 ± 0.06	0.61 ± 0.07	0.71 ± 0.12	0.77 ± 0.14	0.84 ± 0.08
RV Ea velocity, cm/s	1.58 ± 0.42	2.57 ± 0.67	3.73 ± 0.80	4.94 ± 1.45	5.47 ± 1.47
RV Aa velocity, cm/s	4.52 ± 0.93	5.61 ± 1.09	6.63 ± 1.17	6.90 ± 1.47	7.55 ± 2.11
RV Ea/Aa ratio	0.35 ± 0.06	0.47 ± 0.11	0.57 ± 0.10	0.73 ± 0.19	0.74 ± 0.16
VS Ea velocity, cm/s	1.34 ± 0.41	1.79 ± 0.42	2.65 ± 0.59	3.00 ± 0.67	3.18 ± 0.53
VS Aa velocity, cm/s	3.02 ± 0.68	3.67 ± 0.73	4.03 ± 0.96	4.50 ± 0.80	4.50 ± 0.83
VS Ea/Aa ratio	0.44 ± 0.09	0.49 ± 0.08	0.67 ± 0.14	0.68 ± 0.15	0.72 ± 0.13
LV Ea velocity, cm/s	1.17 ± 0.41	1.77 ± 0.46	2.76 ± 0.79	3.79 ± 0.73	4.17 ± 1.04
LV Aa velocity, cm/s	3.02 ± 0.84	4.19 ± 0.86	4.79 ± 0.92	5.26 ± 1.01	4.94 ± 1.52
LV Ea/Aa ratio	0.39 ± 0.10	0.42 ± 0.07	0.59 ± 0.20	0.74 ± 0.19	0.92 ± 0.38

A, Late diastolic inflow; *Aa*, late diastolic wall-motion; *E*, early diastolic inflow; *Ea*, early diastolic wall-motion; *LV*, left ventricle; *MV*, mitral valve; *RV*, right ventricle; *TV*, tricuspid valve; *VS*, ventricular septum.
Data are expressed as mean ± SD.

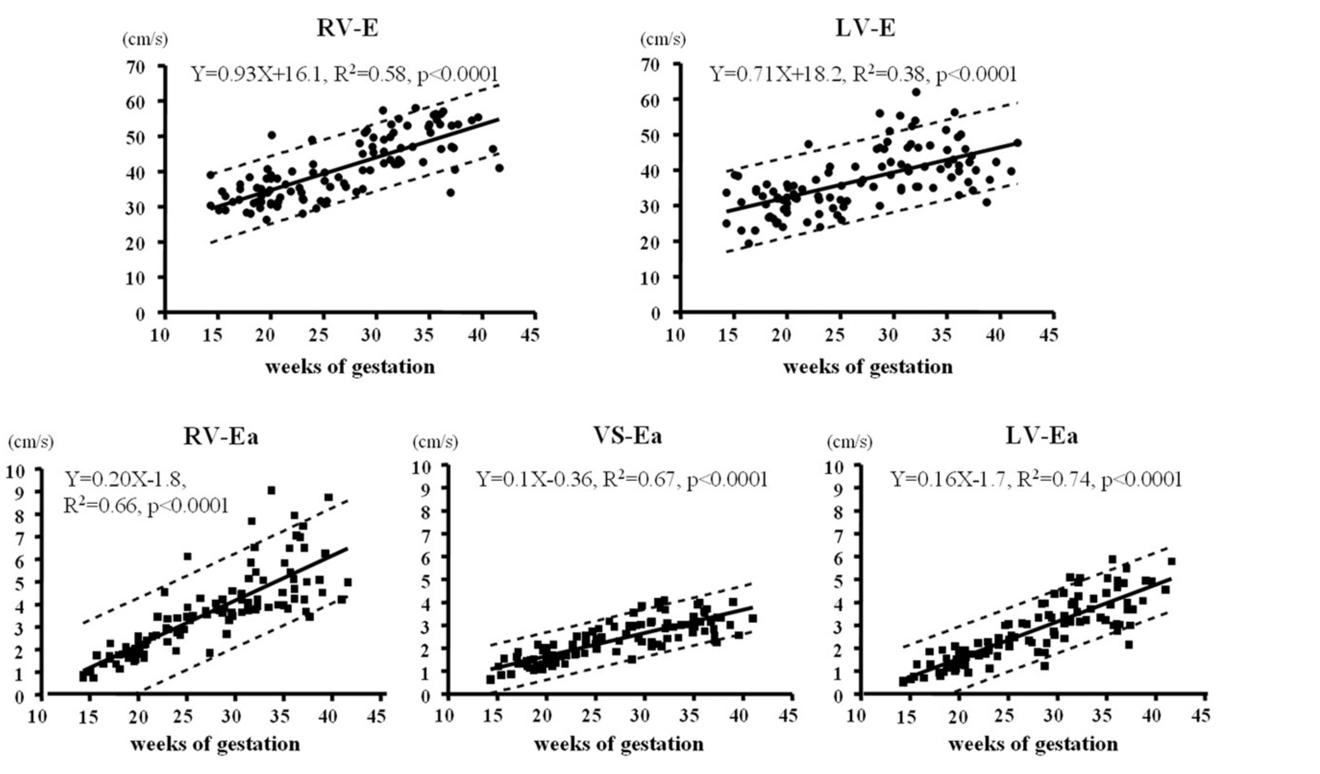

Figure 1 Impact of gestational age on early diastolic flow and ventricular wall-motion Doppler velocities (cm/s). Data are expressed as mean with 95% confidence interval. *E*, Early diastolic ventricular filling; *Ea*, early diastolic wall-motion velocity; *LV*, left ventricle; *RV*, right ventricle; *VS*, ventricular septum.

affected (Figure 2). Ea/Aa and E/A ratios increased with gestational age at all sites (Figure 3).

The influence of gestational age and cardiac cycle length on the diastolic wall motion is shown in Table 2. Stepwise regression analyses showed that gestational age correlated with all velocities with the exception of LV peak A flow velocity. Cardiac cycle length also significantly correlated with RV Ea, LV E, and LV Aa velocity amplitudes.

Comparison among DTI sites. Table 3 illustrates significant and consistent differences between age-matched diastolic RV, VS, and LV wall-motion veloc-

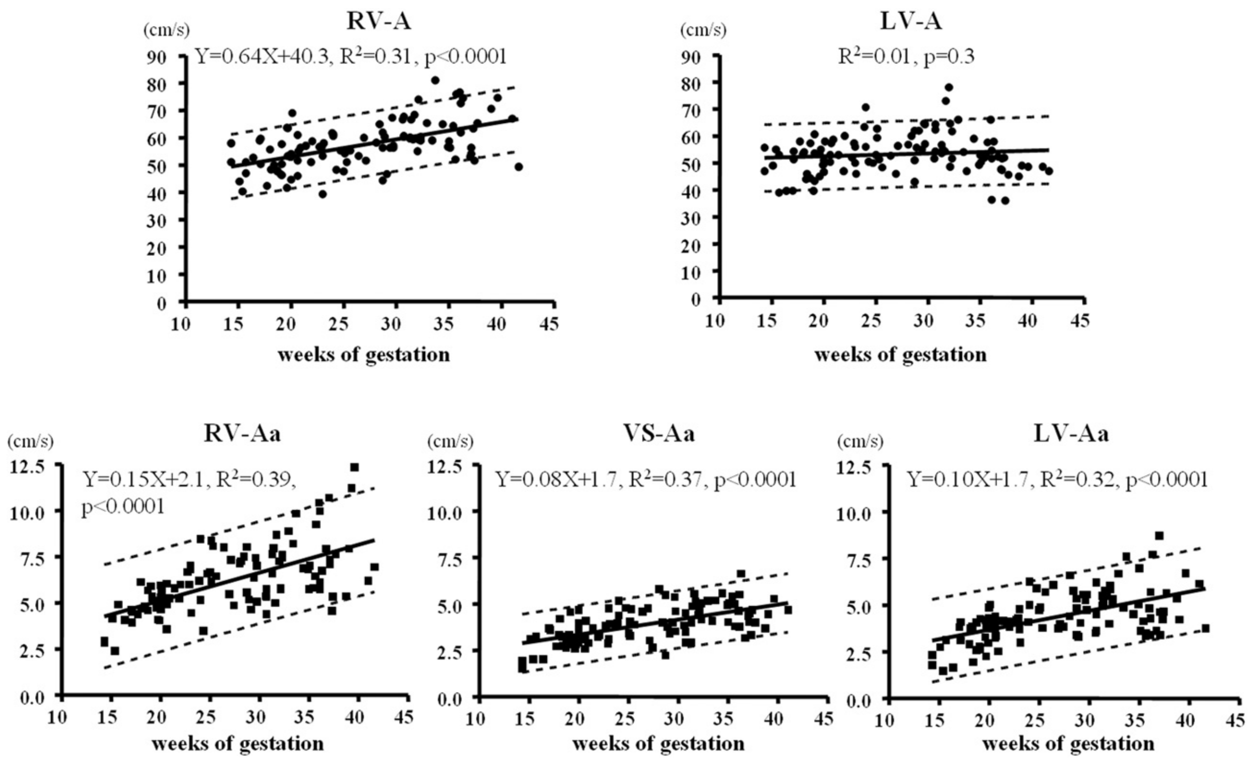

Figure 2 Impact of gestational age on late diastolic flow and wall-motion Doppler velocities (cm/s). Data are expressed as mean with 95% confidence interval. *A*, Late diastolic ventricular filling; *Aa*, late diastolic wall-motion velocity; *LV*, left ventricle; *RV*, right ventricle; *VS*, ventricular septum.

ities. For example, RV peak Ea and Aa velocities remained persistently higher when compared with gestational age–matched septal and LV free wall velocities (Table 1). When compared with septal Ea, LV Ea was significantly lower before 19 weeks and higher after 30 weeks of gestation. LV Aa was higher than VS Aa only transiently between 20 and 34 weeks.

Peak E/Ea and A/Aa ratios. Figure 4 shows the age-dependent relationship between E and Ea along with A and Aa velocities. An exponential decline in E/Ea ratio because of a proportionally greater increase in Ea velocity was observed for both ventricles up to 24 weeks. Thereafter, the E/Ea relationship leveled for the remainder of the pregnancy course. Similarly, A/Aa ratios decreased rapidly until about 20 weeks, whereas this relationship remained stable thereafter until term. This was caused by a greater increase in Aa than A velocities.

Reproducibility. The interobserver variability for DTI measurement was 0.5% with a 95% confidence interval of −1.3 to 2.2% (P = not significant). The intraobserver variability was 0.5% with a 95% confidence interval of −2.0 to 3.1% (P = not significant).

DISCUSSION

The primary purpose of this study was to establish gestational age–specific DTI reference data that may be useful for fetal diastolic functional assessment and as it is affected by disease. However, these data also shed light on to the natural history of evolving myocardial mechanics during fetal development.

Our study findings demonstrate that spectral DTI recordings are easily obtainable and provide reproducible information on segmental longitudinal wall-motion velocities as early as 14 weeks of gestation. With advancing age, early and late diastolic flow and wall-motion velocities evolve in a similar fashion in the healthy fetus. The ratios of E/A and Ea/Aa increase as a function of more rapid augmentation in early when compared with late diastolic velocities. The increase in E velocity has previously been explained by an improvement in active myocardial relaxation rather than a change in ventricular filling pressure,[2] a concept that is largely supported by our findings. In this study, we showed that Ea not only increased progressively with advancing fetal age, but did so at a faster rate than E. As a consequence, peak ventricular E/Ea ratios, which reportedly correlate well

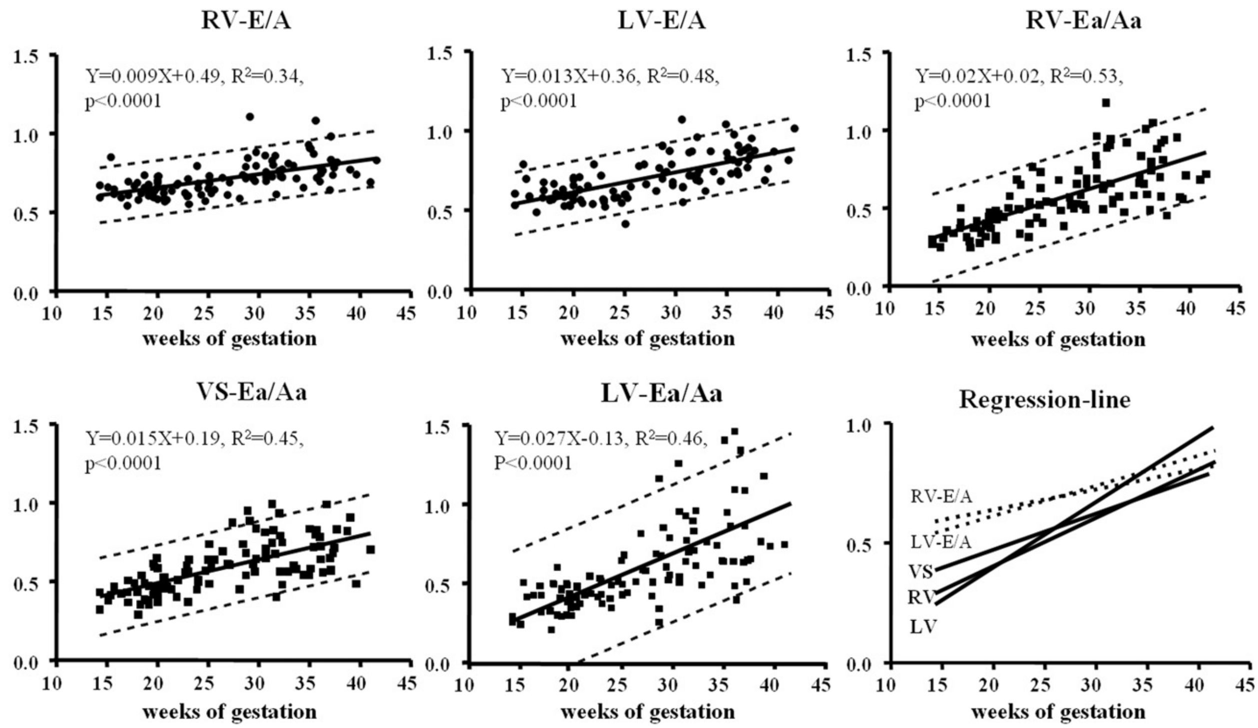

Figure 3 Impact of gestational age on early/late diastolic ventricular filling (*E/A*) and early/late diastolic wall-motion velocity (*Ea/Aa*) ratios. Data are expressed as mean with 95% confidence interval. *LV*, Left ventricle; *RV*, right ventricle; *TDI*, tissue Doppler imaging; *VS*, ventricular septum.

Table 2 Influence of gestational age and cardiac cycle length on diastolic inflow and wall-motion velocities

Variable	Tested factors	Equation of regression line
TV E velocity, cm/s	GW	Y = 0.9GW + 16.5; R^2 = 0.57, P < .0001
TV A velocity, cm/s	GW	Y = 0.6GW + 40.6; R^2 = 0.30, P < .0001
MV E velocity, cm/s	GW, CCL	Y = 0.6GW + 0.08CCL − 9.5; R^2 = 0.42, P < .0001
MV A velocity, cm/s	N/a	N/a
RV Ea velocity, cm/s	GW, CCL	Y = 0.2GW − 0.01CCL + 2.6; R^2 = 0.67, P < .0001
RV Aa velocity, cm/s	GW	Y = 0.2GW + 2.2; R^2 = 0.39, P < .0001
VS Ea velocity, cm/s	GW	Y = 0.1GW − 0.3; R^2 = 0.64, P < .0001
VS Aa velocity, cm/s	GW	Y = 0.08GW + 1.8; R^2 = 0.35, P < .0001
LV Ea velocity, cm/s	GW	Y = 0.2GW − 1.6; R^2 = 0.72, P < .0001
LV Aa velocity, cm/s	GW, CCL	Y = 0.1GW − 0.01CCL + 5.5, R^2 = 0.37, P < .0001

A, Late diastolic inflow; *Aa*, late diastolic wall-motion; *CCL*, cardiac cycle length; *E*, early diastolic inflow; *Ea*, early diastolic wall-motion; *GW*, gestational week; *LV*, left ventricle; *MV*, mitral valve; *N/a*, not applicable; *RV*, right ventricle; *TV*, tricuspid valve; *VS*, ventricular septum.

with ventricular filling pressure,[9,10] decreased exponentially to reach a stable E/Ea relationship only in the early third trimester. Thus, in spite of the tremendous increase in circulating fetal volume, and the known relatively constant atrial and umbilical venous pressures at gestational ages studied,[22,23] our data suggest that improvement in active myocardial relaxation is indeed the main contributor of the progressive increase in early diastolic filling seen throughout gestation. Although speculative, it may also be that estimation of filling pressures using E/Ea is useful only after 25 gestation weeks. We also found that the rate of relaxation differed significantly between ventricular segments. At any gestational age, the highest early diastolic flow and longitudinal wall-motion velocities were recorded from the TV and lateral RV wall, respectively, whereas the VS reached the lowest velocity of lengthening. This variation among tissue segments that persists after birth has been attributed to the predominance of longitudinal myofibers in the RV free wall, circumferentially oriented fibers in the VS, whereas both longitudinal and circumferential components prevail in the LV.[11,24]

Nevertheless, despite the improved ventricular relaxation rate, atrial systole remains the key con-

Table 3 Comparison between early and late diastolic peak wall-motion velocities among right ventricular free wall, ventricular septum, and left ventricular free wall basis

Gestational age, wk	Ea RV vs Ea VS	Ea RV vs Ea LV	Ea LV vs Ea VS	Aa RV vs Aa VS	Aa RV vs Aa LV	Aa LV vs Aa VS
14-19	<0.01	<0.001	<0.01	<0.001	<0.001	NS
20-24	<0.001	<0.001	NS	<0.001	<0.001	<0.05
25-29	<0.001	<0.001	NS	<0.001	<0.001	<0.01
30-34	<0.001	<0.01	<0.05	<0.001	<0.001	<0.05
35-42	<0.001	<0.01	<0.01	<0.001	<0.001	NS

Aa, Late diastolic wall-motion velocity; *Ea*, early diastolic wall-motion velocity; *LV*, left ventricle; *NS*, not significant; *RV*, right ventricle; *VS*, ventricular septum.

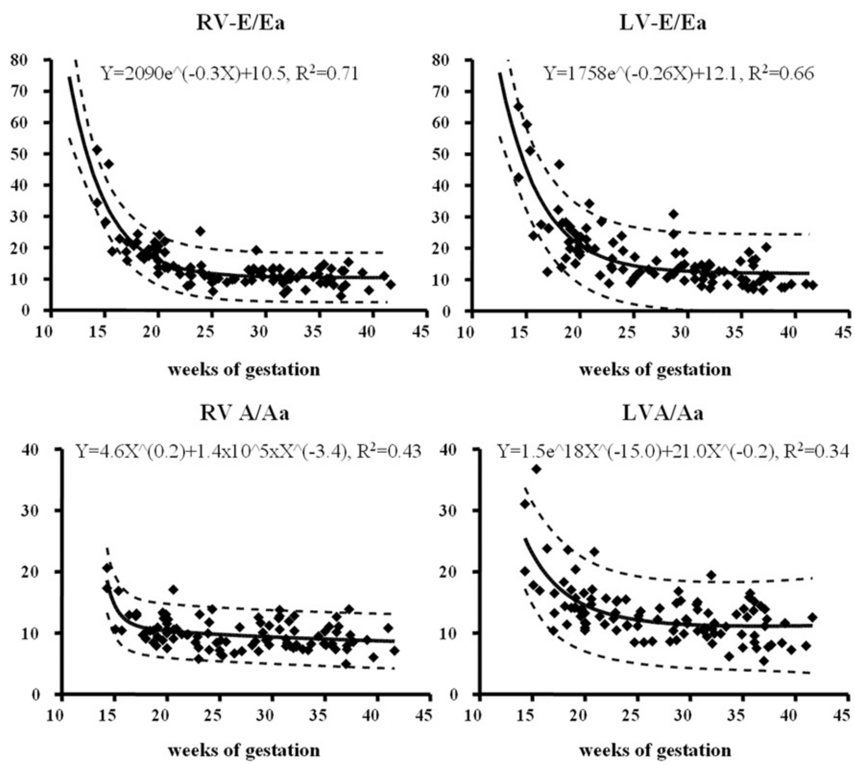

Figure 4 Impact of gestational age on early diastolic ventricular filling/wall-motion velocity (*E/Ea*) and late diastolic ventricular filling/wall-motion velocity (*A/Aa*) ratios. Data are expressed as mean with 95% confidence interval. *LV*, Left ventricle; *RV*, right ventricle.

tributor in ventricular filling to the very end of gestation. Various Doppler studies on the evolution of late diastolic flow velocities reported little or no change in A wave velocities with advancing gestation.[2,4] In this study, mitral A wave velocity remained largely unchanged whereas tricuspid A and all Aa velocities increased linearly. Similar to age-specific early diastolic velocities, the fastest late diastolic velocities were recorded in the RV free wall and TV, respectively. This is not surprising but emphasizes the dominant role of the fetal RV in the setting of a parallel-arranged circulation. The right heart contributes approximately 30% more than the left side to the combined fetal cardiac output[25] and, to accomplish this, privileged loading of the RV is essential. We assume that this is largely achieved as a result of preferential streaming of systemic venous blood toward the TV, superior relaxation and compliance characteristics of the RV myocardium, and increased atrial contractility consequent on its increased loading by a Starling mechanism.

In summary, spectral DTI is a feasible and reproducible imaging tool to quantify longitudinal myofiber lengthening in different regions of the fetal ventricular myocardium. There were strong positive correlations between gestational age and early and late diastolic wall-motion velocities suggesting maturational changes in ventricular relaxation and compliance. The ratio of maximal E/Ea velocities decreases exponentially with advancing gestation because of a more rapid increase in Ea than E. For the estimation of filling pressure, E/Ea becomes useful only after 25 weeks gestation.

Study Limitation

Spectral DTI averages the peak velocities of interrogated regions and measurements are 15% to 20% lower than similar peak velocity measurements obtained by instantaneous pulsed DTI.[16] Accordingly, Ea and Aa velocities are slightly smaller and E/Ea slightly higher when compared with previously published data.[17,20]

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