Fetal and Neonatal Diastolic Myocardial Strain Rate: Normal Reference Ranges and Reproducibility in a Prospective, Longitudinal Cohort of Pregnancies

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Background: Normative fetal diastolic strain rate values have not been comprehensively reported. The aims of this study were to report normative data for diastolic strain rate parameters across gestation and upon delivery, determine the effect of advancing gestational age on these measures, and compare interobserver variability at multiple gestational age time points.

Methods: Sixty gravid women were enrolled before 20 weeks' gestation. The following measures were obtained by two blinded observers at five time points across gestation and at 4 to 8 weeks' postnatal age: global left ventricular circumferential strain rate peak E and A waves, global left and right ventricular longitudinal strain rate peak E and A waves, and mitral and tricuspid valve E/A ratios. Reproducibility was assessed using intraclass correlation and Bland-Altman analysis. Least square means analysis was used to evaluate for changes across gestational age.

Results: Left ventricular longitudinal and circumferential diastolic strain rate values decreased across gestation, while right ventricular longitudinal values remained stable. With delivery, left ventricular values remained fairly stable, while right ventricular values increased. Intraclass correlations for diastolic strain rate values were 0.68 to 0.94 at ≥24 weeks' gestation and 0.25 to 0.82 for values at 20 to 21 weeks' gestation. Intraclass correlations ranged from 0.49 to 0.90 for mitral valve and tricuspid valve E/A ratios across gestation.

Conclusions: Fetal measures of diastolic strain rate have acceptable reproducibility after 24 weeks' gestation. The described changes across gestation likely reflect intrinsic myocardial adaptation to loading conditions. These reference ranges can be used to assess effects of various disease states on fetal myocardial deformation. (J Am Soc Echocardiogr 2016;■:■-■.)

Keywords: Fetal echocardiography, Myocardial deformation, Strain rate, Pediatric, Cardiac function, Diastolic function, Normative values

Fetal cardiovascular function can be affected by multiple factors, including intrinsic cardiac disease and extracardiac pathology. Regardless of the etiology, fetal cardiovascular dysfunction tends to manifest diastolic abnormalities before systolic dysfunction.[1,2] Fetal echocardiographic parameters of diastolic function such as the presence of abnormal intracardiac and extracardiac Doppler patterns are the mainstay for assessment of fetal cardiovascular function.[3] However, these parameters are often imprecise and subjective. Quantitative measures of fetal diastolic function are lacking.

Over the past 10 years, the assessment of fetal cardiac function has advanced dramatically. As technology advances, techniques such as myocardial deformation analysis, which requires adequate spatial and temporal resolution, can now be applied to the fetus. Multiple studies have been published that describe normal systolic values for myocardial deformation.[4-10] Two previous studies have reported normative values and reproducibility for peak diastolic strain rate in the fetus.[5,9] These two studies, however, were limited by cross-sectional design, focus on regional as opposed to global measures, and other technical limitations. To date, no study of which we are aware has characterized diastolic deformation properties of fetal adaptation to postnatal life.

In this study, we applied a standardized protocol to measure longitudinal and circumferential peak early and late diastolic strain rate in a prospectively enrolled, longitudinal cohort of normal fetuses across pregnancy and after delivery. We sought to report normative data for these measures across gestation and upon delivery, determine the effect of advancing gestational age (GA) on these measures, and compare the interobserver variability of these measures at multiple GA time points.

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Abbreviations

CSr-LVa = Global circumferential late peak left ventricular strain rate

CSr-LVe = Global circumferential early peak left ventricular strain rate

GA = Gestational age

ICC = Intraclass correlation coefficient

LSr-LVa = Global longitudinal late peak left ventricular strain rate

LSr-LVe = Global longitudinal early peak left ventricular strain rate

LSr-RVa = Global longitudinal late peak right ventricular strain rate

LSr-RVe = Global longitudinal early peak right ventricular strain rate

LV = Left ventricular

RV = Right ventricular

METHODS

Subjects were enrolled from a recently completed prospective study that evaluated longitudinal changes and interobserver variability of systolic myocardial deformation values.[4] The participants were identical between the two studies. Mothers who were undergoing routine obstetric ultrasonography at Texas Children's Hospital Pavilion for Women were invited to enroll in this institutional review board–approved study at the time of the routine second-trimester ultrasound scan. Informed consent was obtained, and participants were compensated for parking and time spent participating in the study. Criteria for inclusion in the study included acceptable visualization of the fetal heart, absence of cardiac abnormalities during the screening examination, and body mass index < 30 kg/m^2. Only mothers in whom the fetal heart could be adequately visualized for clinical care on the routine second-trimester ultrasound were offered participation in the study. The determination of whether the fetal heart was adequately visualized was made at the discretion of the staff obstetrician, as per clinical routine. Exclusion criteria were preexisting or history of gestational diabetes, maternal hypertension, growth restriction, thyroid disease, and other significant chronic disease or obstetric complication.

The sample size for this study was predetermined on the basis of the aforementioned prior study of systolic measures of myocardial deformation. In that study, a total sample size of 53 patients was chosen to obtain a 99% CI ($\alpha = 0.01$). The type I error rate was assumed to be 0.01 for sample-size considerations to allow multiple hypothesis testing and control the overall probably of a type I error. Additional patients were enrolled because of a presumed attrition rate of about 10%. To confirm that the sample size was large enough to adequately power the present study, a post hoc power analysis was performed. We found that a sample size of 42 would be needed to find a difference of 0.4 sec^{-1}, assuming an SD of 0.67.

Image Acquisition and Analysis

Image acquisition for measuring fetal strain and strain rate was performed by one of two American Registry for Diagnostic Medical Sonography–certified fetal sonographers with ≥7 years' experience performing fetal echocardiography. Image acquisition for measuring neonatal strain and strain rate was performed by one of two certified pediatric cardiac sonographers. Images were obtained using a GE Vivid E9 ultrasound system using a 5- or 6-MHz phased-array probe and stored as raw data. Although it was possible to use the curvilinear probe, we found that the phased-array probes provided the best combination of acoustic signal and temporal resolution. Echocardiograms were obtained at the following time points for each fetus: 20 to 21 weeks' gestation, 24 to 25 weeks' gestation, 28 to 29 weeks' gestation, 32 to 33 weeks' gestation, 36 to 37 weeks' gestation, and 4 to 8 weeks' postnatal age, with particular attention paid to optimal spatial resolution and signal and with a minimal frame rate of 100 frames/sec. The 4- to 8-week postnatal age time frame was chosen to ensure transition to postnatal circulation. A larger window (4 weeks) was chosen to ensure compliance. Raw, uncompressed data were then sent to an independent workstation for analysis, which uses speckle-tracking for the measurement of strain and strain rate (EchoPAC version 110.0.2; GE Healthcare, Milwaukee, WI). For each measure, in all study subjects, offline image analysis was performed by two examiners, each blinded to the results of the other: a pediatric cardiologist with expertise in fetal imaging (S.A.M.) and a sonographer with substantial experience in the measurement of myocardial deformation who serves as the research sonographer for our group. To ensure adequate blinding, data from each observer were saved in separate folders on a research server. Observers analyzed data obtained on the same acquisition and were free to choose which cardiac cycle in the particular acquisition to analyze.

In lieu of an available electrocardiogram, mechanical events were used to time the cardiac cycle, as previously described.[4] The time cursor typically used to mark the beginning of the QRS complex was placed at mitral valve closure. Aortic valve opening and closure were manually identified on spectral Doppler interrogation of the aortic valve. The following measures of diastolic strain rate were obtained: global circumferential early peak left ventricular (LV) strain rate (CSr-LVe), global circumferential late peak LV strain rate (CSr-LVa), global longitudinal early peak LV diastolic strain rate (LSr-LVe), global longitudinal late peak LV strain rate (LSr-LVa), global longitudinal early peak right ventricular (RV) diastolic strain rate (LSr-RVe), global longitudinal late peak RV strain rate (LSr-LVa), and mitral and tricuspid Doppler inflow pattern E/A ratios. For longitudinal strain, a U-shaped region of interest was traced in the four-chamber views. Separate acquisitions optimized specifically for LV or RV analysis were used. Whereas the analysis of global longitudinal strain on transthoracic echocardiography uses four-chamber, two-chamber, and three-chamber acquisitions, studies of prenatal echocardiography have used a single four-chamber acquisition. Therefore, for the purposes of this and other reports of fetal myocardial deformation, the term *global* refers to an average of the regional values obtained in the four-chamber plane. For circumferential strain, a circle-shaped region of interest was traced in the short-axis view at

Table 1 Mathematical equations for the expected values and variances of fetal measurements by GA

Parameter (P)	Expected value of $\log_e$(P)	Variance of $\log_e$(P)
CSr-LVe	1.3702 + (−0.01809 × GA)	0.008835* + 0.09989†
CSr-LVa	1.2356 + (−0.02862 × GA)	0.008908* + 0.2102†
LSr-LVe	0.9570 + (−0.00389 × GA)	0.004639* + 0.07606†
LSr-LVa	1.1122 + (−0.01436 × GA)	0.008844* + 0.1164†
LSr-RVe	1.0426 + (−0.00964 × GA)	0.01355* + 0.06866†
LSr-RVa	0.7718 + (−0.00485 × GA)	0.005965* + 0.1248†
MV E/A ratio	−0.7702 + (0.01378 × GA)	0.006462* + 0.03864†
TV E/A ratio	−0.6518 + (0.009869 × GA)	0.003489* + 0.01483†

MV, Mitral valve; *TV*, tricuspid valve.
*Intercept variance.
†Error variance.

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