

Characterization of Ventricular Myocardial Performance in the Fetus by Tissue Doppler Imaging

Sayaka Watanabe, MD; Ikuo Hashimoto, MD; Kazuyoshi Saito, MD; Kazuhiro Watanabe, MD; Keiichi Hirono, MD; Keiichi Uese, MD; Fukiko Ichida, MD; Shigeru Saito, MD*; Toshio Miyawaki, MD; Petra Niemann, MD**; David J Sahn, MD**

Background: Clinically useful indices of fetal cardiac function have not been fully delineated for tissue Doppler imaging (TDI).

Methods and Results: In the present study, 56 pregnancies between the 17th and 38th weeks of gestation included 38 normal fetuses, 6 cases of hydrops fetalis (HF), and 12 of intrauterine growth retardation (IUGR). Peak velocity in early diastole (E) was measured by pulsed-wave Doppler and the peak annular velocities in systole (Sa) and early diastole (Ea) were measured by TDI. The ratio between flow velocity and annular velocity in early diastole (E/Ea) and the ratio of the Sa of right ventricle to that of the left ventricle (RVSa/LV Sa) were estimated. In all fetuses with HF, LV Sa was <2 cm/s and LVE/Ea was >13. RV Sa/LV Sa in the HF group was significantly higher than that in the normal group, and RV Sa/LV Sa in the IUGR group was significantly lower than that in the normal group.

Conclusions: A combination of low LV Sa and high LVE/Ea shows reduced global myocardial performance of the LV, and would be one of the useful indices for quantitative assessment in high-risk pregnancies. Changes in the RV Sa/LV Sa ratio may reflect afterload changes in both ventricles and compensatory cardiovascular mechanisms occurring during the process of placental insufficiency and heart failure. (Circ J 2009; 73: 943–947)

Key Words: Fetal cardiac function; Hydrops fetalis; Intrauterine growth retardation; Peak annular velocity; Tissue Doppler imaging

The clinical application of echocardiography for prenatal imaging has the major advantage that it is non-invasive, easy accessible, and can be used in pregnancy to study the fetus in a truly physiological state. A wide variety of echocardiographic methods have been used for evaluation of fetal cardiac function, but validation of these indices in the prenatal population has been difficult, especially in the fetus with heart failure.

Tissue Doppler imaging (TDI) represents a new development of the Doppler technique, allowing direct measurements of regional myocardial velocities.^{1,2} In the adult, several studies have shown that the systolic myocardial velocity of the mitral valve annulus along the left ventricular long axis correlates closely with left ventricular (LV) pressure changes (dP/dt) and LV ejection fraction (EF) validated by angiography.^{3,4} The ratio between flow velocity (E) and annular velocity (Ea) in early diastole (E/Ea ratio) has also been shown to correlate strongly with filling pressures.^{5,6} Thus, it has been proposed that regional myocardial velocities reflect global cardiac function, and can be used to estimate systolic and diastolic function in both ventricles.

Recently, several studies reported the feasibility of TDI for assessing fetal cardiac function, demonstrating myocardial velocity changes in relation to advancing gestational age.^{7–10} In addition, it has been reported that the E/Ea ratio is significantly higher in fetuses with right ventricular (RV) heart failure.¹¹ However, there is a paucity of data with respect to abnormalities in the fetal heart. The aim of this study was to evaluate the characteristics of myocardial velocities in normal fetuses and those in high-risk pregnancies, and to determine specific indices for quantitative assessment of fetal cardiac function using TDI.

Methods

Study Subjects

The study population consisted of 56 healthy pregnant women between the 17th and 38th week of gestation. They were recruited from pregnant women referred to Toyama University Hospital for screening of fetal cardiac function between September 2003 and November 2005. Fetal cardiac anomalies on echocardiography, fetal arrhythmias, and the fetuses of diabetic mothers were excluded from our study. The study protocol was approved by the Ethics Committee of Toyama University Hospital. Written informed consent was given by all the pregnant women before study entry. A total of 38 normal fetuses were found to have growth appropriate for gestational age and were assigned as controls. The high-risk pregnancies included 12 fetuses with intrauterine growth retardation (IUGR) and 6 with hydrops fetalis (HF). IUGR was defined as an estimated fetal weight in the 10th percentile below the mean expected weight for the Japanese standard gestational age, based on biparietal diameter, abdominal circumference, and femur length determined by

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Department of Pediatrics, *Department of Obstetrics and Gynecology, School of Medicine, University of Toyama, Toyama, Japan and **Clinical Care Center for Congenital Heart Disease, Oregon Health and Science University, Portland, OR, USA

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Mailing address: Fukiko Ichida, MD, Department of Pediatrics, School of Medicine, University of Toyama, 2630 Sugitani, Toyama 930-0194, Japan. E-mail: fukiko@med.u-toyama.ac.jp

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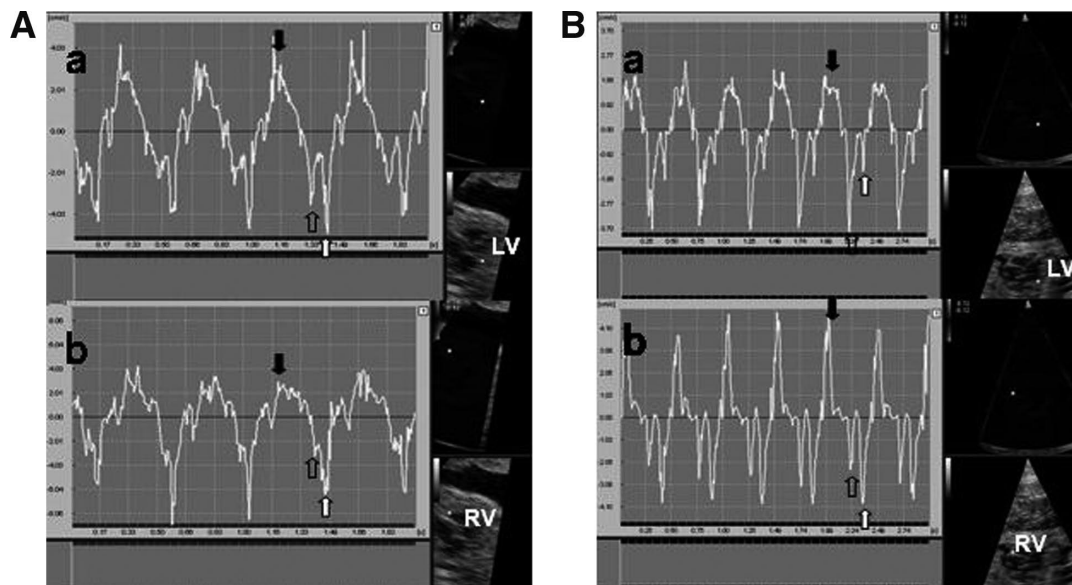


Figure 1. Representative TDI velocities in a normal fetus (A) and one with hydrops fetalis (B) (a, left ventricle (LV); b, right ventricle (RV)). Black arrows indicate Sa (peak systolic annular velocity), clear arrows indicate Ea (peak early diastolic annular velocity) and white arrows indicate Aa (peak late diastolic annular velocity). TDI, tissue Doppler imaging.

ultrasonographic evaluation. None of the pregnant women had any material complications. All fetuses had asymmetrical IUGR, and all fetuses were singletons, except for 2 cases of dichorionic diamniotic twins and triplets. HF was defined as the demonstration of skin edema and/or fluid accumulation in the serous cavities of the fetus.¹² HF diagnoses included non-immune HF, secondary to chylothorax, Down syndrome, twin-to-twin transfusions (TTTS), and unknown.

Echocardiographic Measurements

In this study, we used an ALOKA SSD-6500 digital ultrasound system (Tokyo, Japan) for 2-dimensional (D), pulsed wave Doppler and TDI scanning. Scanning was performed by an abdominal approach and with a 3.5–5.0 MHz phase-array transducer. Using pulsed wave Doppler, the mitral or tricuspid flow was measured longitudinally from the apex or atrium depending on the fetal position. Next, peak velocity during early diastole (E) was measured in both ventricles. The TDI sector was placed and limited to encompass the entire fetal heart. The TDI data for the mitral and tricuspid valve annuli were acquired with a pulse repetition frequency from 1.5 to 5.0 kHz without aliasing, and a frame rate ranging from 100 to 200/s, depending on the heart rate. TDI data for a cine loop of at least 3 s were stored digitally for offline analyses using the Pyramid 3.1 application software of the ALOKA SSD-6500. This software allowed us to determine and display simultaneously the tissue velocities of several different locations. In the 4-chamber view, sample volumes were placed on the lateral aspect of the annulus of each atrioventricular valve. We measured wall velocities without Doppler angle correlation. The ultrasonic Doppler beam was aligned as parallel to, or at angle of, $<60^\circ$ to each myocardial wall.

The peak annular velocities during systole (Sa) and early diastole (Ea) were measured (Figure 1). TDI data were taken from each wall location with a sample volume of 3×3 pixels. The average value of 3 consecutive beats was calculated. In addition, the E/Ea ratios of both ventricles and the Sa ratio of the RV to that of LV (RVSa/LV Sa) were

estimated. On the 2-D images, EF was measured in both ventricles by an area-length method from the 4-chamber view using an off-line cine loop analysis as follows:

$$\begin{aligned} \text{EDV} &= \{8.0 \times (\text{LAd})^2\} / (3\pi \times \text{Ld}), \\ \text{ESV} &= \{8.0 \times (\text{LAS})^2\} / (3\pi \times \text{Ls}), \\ \text{EF} &= (\text{EDV} - \text{ESV}) / \text{EDV}, \end{aligned}$$

where EDV is the end diastolic volume; LAd, the diastolic long-axis area; Ld, the diastolic long-axis dimension; ESV, the end-systolic volume; LAS, the systolic long-axis area; and Ls, the systolic long-axis dimension.

We used the area-length method even for RV estimation. The assessment of RV function is still a very difficult task because of its geometrical complexity. Helbing et al¹³ reported that the biplane area-length method for approximating a pyramidal model of RV geometry provided the best predictions of RV volumes, using MRI. However, they indicated that the RVEF could be calculated adequately with the relatively simple monoplane area-length method,¹³ so we used the simple method to measure fetal RV function.

All measurements and estimation were performed by 1 author (S.W.).

Statistical Analysis

Data are expressed as mean \pm SD. Linear regression analysis was used for comparison between gestational ages, EF and TDI-derived variables. The differences in the TDI values of the normal group and HF group were analyzed by Student's unpaired t-test. The RV Sa/LV Sa ratio was compared among the 3 groups using 1-way ANOVA followed by Dunnett's method. In a similar fashion, heart rate, birth weight, and gestational age were compared. A P-value less than 0.05 was regarded as statistically significant.

Results

In this study, we were able to obtain echocardiographic data from all subjects. The intra-observer correlation values for the TDI parameters and EF were determined in 15

Table 1. Characteristics of the 3 Groups of Fetuses

	Normal (n=38)	HF (n=6)	IUGR (n=12)
GA at study (weeks)	28.0±5.7	31.0±4.1	32.8±3.5
HR (beats/min)	146±10.7	144±18.7	142±11.8
GA at birth (weeks)	38.3±2.4	32.4±3.7**	36.3±4.3
Birth weight (g)	2,882±576	2,063±1,003*	1,922±623*

Values are mean ±SD.

*P<0.05, **P<0.01 vs normal group.

HF, hydrops fetalis; IUGR, intrauterine growth retardation; GA, gestational age; HR, heart rate.

Table 2. TDI and Conventional Echocardiographic Values in the 3 Groups of Fetuses

	Normal		HF		IUGR	
	LV	RV	LV	RV	LV	RV
TDI						
Sa (cm/s)	2.88±0.45	3.72±0.93	1.67±0.21***	4.22±0.58	3.77±0.78	3.57±0.85
Ea (cm/s)	2.92±0.72	3.93±1.22	2.70±0.60	4.95±3.18	3.57±0.85	3.98±1.00
RVSa/LVSa	1.29±0.20		2.58±0.64**		0.95±0.21*	
Doppler						
E (cm/s)	30.2±7.04	36.2±7.87	39.0±10.0	53.5±17.2	33.4±5.26	32.2±7.09
E/Ea ratio	10.6±1.58	9.58±2.05	14.4±1.71***	13.9±6.60	9.70±2.16	8.40±2.10
Conventional echocardiography						
EF	0.64±0.08	0.69±0.08	0.44±0.10***	0.53±0.08**	0.69±0.06	0.70±0.05

Values are mean ±SD.

*P<0.05, **P<0.01, ***P<0.001 vs normal group.

TDI, tissue Doppler imaging; LV, left ventricle; RV, right ventricle; Sa, peak systolic annular velocity; Ea, peak early diastolic annular velocity; RVSa/LVSa, ratio of Sa of RV to that of LV; E, peak early diastolic filling velocity; EF, ejection fraction.

patients (0.97 and 0.96, respectively), demonstrating high reproducibility.

Fetal Characteristics

Characteristics of the 3 groups are listed in **Table 1**. No significant differences were seen in gestational age and heart rate. However, gestational age at birth and birth weight were significantly lower in the HF group than in the normal group (P<0.01); birth weight was lower in the IUGR group than in the normal group (P<0.05). Of the 38 women in the normal group, 32 had a normal delivery with an uneventful perinatal course, except for 2 cases of mild asphyxia. Of the remaining 6, 5 were still pregnant, and 1 has aborted. Three cases in the HF group had TTTS, and 1 had intraventricular hemorrhage after birth, resulting in severely impaired neurological development. One of the fetuses with HF of unknown cause had periventricular leukomalacia after birth. The child with chylothorax died during the neonatal period because of the hypoplastic lung. Another child with Down syndrome survived beyond the neonatal period. Of the 12 cases in the IUGR group, 1 was revealed as Down syndrome after birth, and another was 1 of triplets and an extremely immature infant who died in the neonatal period. The remaining 10 IUGR cases survived with normal neurological development.

Comparison of TDI- and Conventional Echo-Derived Values in the Normal and HF Groups

In the HF group, the EF of both ventricles, especially that of the LV, decreased significantly compared with the normal group. Similarly, the Sa in the LV in the HF group was significantly lower than that in the normal group (**Table 2**). In the LV, the E/Ea ratio was significantly higher in the HF group than in the normal group. In the RV, however, TDI-derived values showed a wide variation and were not significantly different from those of the normal

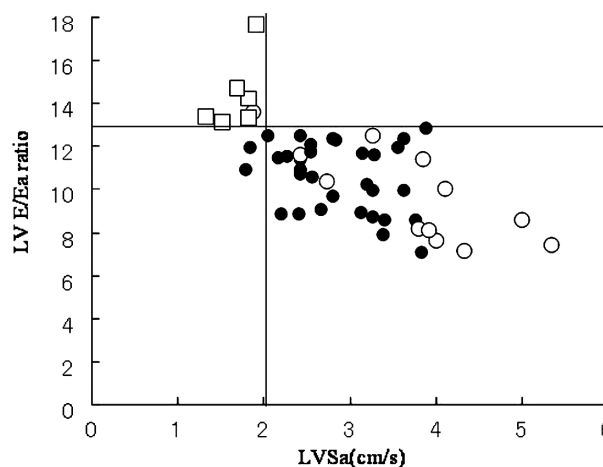


Figure 2. Relationship between LV Sa and the LV E/Ea ratio in normal (black circles), intrauterine growth retardation (clear circles), and hydrops fetalis (clear squares) fetuses. LV, left ventricle; Sa, peak systolic annular velocity; E/Ea, ratio of peak early diastolic filling velocity to peak early diastolic annular velocity.

group. **Figure 2** shows the relationship between LV Sa and the LVE/Ea ratio. LV Sa was <2 cm/s and the LVE/Ea ratio was >13 in each of the HF fetuses (sensitivity 100%, specificity 97.3%). In contrast, most of the normal fetuses had LV Sa values >2 and LVE/Ea ratios <13. Two fetuses from the normal control group had LV Sa values <2, when they were assessed prior to the 20th week of gestation. Most of the IUGR fetuses showed the same tendency as the normal fetuses, and shifted to the right. One case in the IUGR group existed in the left upper area with the HF fetuses. That fetus was 1 of triplets and an extremely immature infant who died in the neonatal period.

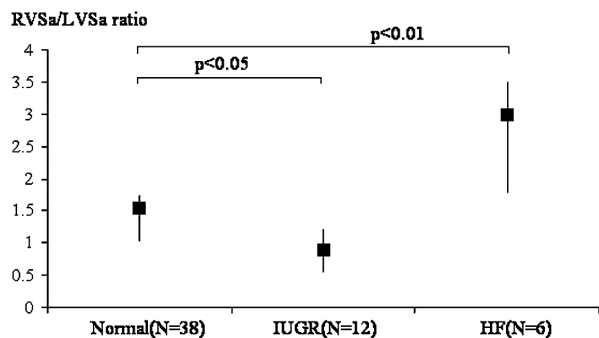


Figure 3. Comparison of the RVSa/LV Sa ratio among the 3 groups: IUGR (intrauterine growth retardation), HF (hydrops fetalis) and controls. RVSa/LV Sa, ratio of peak systolic annular velocity of the right ventricle to that of the left ventricle; HF, hydrops fetalis; IUGR, intrauterine growth retardation.

Comparison of the RVSa/LV Sa Ratio Among the 3 Groups

Figure 3 shows the RVSa/LV Sa ratio in the 3 groups. The RVSa/LV Sa ratio was significantly higher in the HF group (2.51 ± 0.68 , $P < 0.01$) and significantly lower in the IUGR group (0.95 ± 0.20 , $P < 0.05$) as compared with the normal group (**Table 2, Figure 3**).

We observed serial changes in the RVSa/LV Sa ratio in the fetus with chylothorax and progression of HF at 27, 28 and 30 weeks of gestation. On the first evaluation, severe bilateral chylothorax was seen in this fetus, a pericardial effusion had progressed on the second evaluation, and skin edema and elevation of the preload index ($=0.91$) were observed on the final prenatal evaluation. Concordant changes in the RVSa/LV Sa were observed at all 3 evaluations, and had declined by the final study, 2.56, 3.50 and 1.53, respectively. The LV Sa decreased from the first study (1.48, 1.33 and 1.50, respectively), while the RV Sa remained normal until the last study (3.79, 4.65 and 2.30, respectively). However, the pregnancy was terminated by cesarean section, but the fetus died of hypoxemia during the neonatal period because of the severely hypoplastic lung.

Discussion

Myocardial Velocities of the Ventricles in Normal Fetuses

In the fetus, the LV is dedicated to the coronary circulation and upper body, while the RV is the main distributor to the lower part of the body, the placenta and the lung. Because of this distribution, the afterload acts separately on each ventricle. In this study, Sa and Ea were higher in the RV than in the LV in normal fetuses, consistent with the RV being the dominant ventricle. This finding concurs with previous studies.⁹ Another possible reason for RV Sa dominance in the fetus is that we were limited to estimating the myocardial velocity along the long-axis, which measures the motion of longitudinal myocardial fibers only. Systolic myocardial velocities of the RV and LV walls may be strongly influenced by the anatomical arrangement of the myocardial fibers.^{14,15} LV function depends on the appropriate degree and timing of both shortening and lengthening of circumferential and longitudinal fibers, whereas the RV has a different myocardial fiber orientation and tends to contract along its long axis rather than along the short axis. Therefore, RV systolic function is probably better assessed

by the TDI value of Sa along the long axis, whereas LV function may be underestimated using myocardial velocity only along the long-axis.

Characteristics of Myocardial Velocities of the Fetus in High-Risk Pregnancies

The present study demonstrated that the RVSa/LV Sa ratio in the case of IUGR was lower than that in the normal fetus. As a consequence of uteroplacental insufficiency, RV afterload is elevated because of systemic vasoconstriction, and LV afterload declines because of cerebral vasodilatation, secondary to a brain-sparing effect.⁶ These selective changes resulted in a change in cardiac afterload, redistributing cardiac output towards the LV, thus providing increased coronary perfusion to the myocardium. A lower RVSa/LV Sa ratio in IUGR most likely reflects an increased RV/LV afterload ratio because of the redistribution of cardiac output. In this stage, myocardial contraction and relaxation remain normal, as our data showed normal Sa and E/Ea measurements even in the IUGR cases. While in the advanced stage of placental insufficiency, persistence of hypoxemia/ischemia may result in ventricular dysfunction, with a subsequent fall in the cardiac output of both ventricles and an increase in end-diastolic and central venous pressures. In this advanced stage, the TDI values of Sa and E/Ea will also change.

In the present study, we demonstrated a decrease in LV Sa, associated with a marked elevation of LVE/Ea in the HF group, suggesting both impairment of systolic function and elevation of filling pressures.^{11,17} End-stage heart failure results in HF. Several features are responsible for HF, but the final common pathway compromising the cardiovascular system is the elevation of ventricular end-diastolic pressure, atrial pressure and central venous pressure. The reduced ability of the fetal heart to contract, the lower myocardial compliance, the higher dependence of cardiac output on heart rate and the lack of adrenoreceptors all contribute to a decreased cardiac reserve in response to stress and to higher susceptibility for the development of fetal cardiac failure. Therefore, combined low LV Sa and high LVE/Ea shows reduced global myocardial performance of the LV and offers the potential of predicting the outcome of high-risk pregnancies.

Of interest, the present study demonstrated that in the HF group deterioration of longitudinal LV motion preceded the decrease in the RV motion. Consequently, the RVSa/LV Sa ratio in the HF group was higher than that in the normal control group. RV Sa remained normal in the HF group until the development of end-stage heart failure. One of the causative mechanisms is that the RV is the predominant ventricle anatomically and functionally in the fetus. In the fetus, both the RV and LV are systemic ventricles, so if there is increased afterload in 1 ventricle, the output of that ventricle will fall and the output of the contralateral ventricle will increase in a compensatory manner. However, decompensation of this protective mechanism leads to dysfunction of both ventricles and progressive deterioration of the fetal condition at advanced stages, as our cases with HF showed. Therefore, an elevated RVSa/LV Sa ratio in cases of HF might reflect compensatory RV function of the fetal circulation.

Thus, this index of RVSa/LV Sa reflects changes in the loading conditions in both ventricles, and might contribute to a better understanding of the compensatory cardiovascular mechanisms occurring during the process of placental insufficiency and heart failure.

Study Limitations

Inter-observer correlation was not determined in this study because all data were analyzed by the same author (S.W). Furthermore, the evaluation of myocardial velocities of the fetal heart was limited by the angle of the ultrasound beam and the fetal heart motion. In this study we were limited to estimating myocardial velocity along the long-axis from the 4-chamber view, because of the high feasibility and reproducibility of fetal echo studies. Therefore, contraction and relaxation of circumferential muscle fibers and ventricular function in the short axis were not estimated. This would bias our data. Finally, the value of the present study is limited by the relatively small number of samples, especially fetuses with HF. Further studies are needed to identify definite predictors of poor prognosis in high-risk pregnancies.

Conclusions

TDI allows insights into impaired cardiac function in fetuses that are not available with conventional echocardiography. HF shows low LV_{Sa} combined with high LVE/Ea, which would be a useful index of poor prognosis in fetuses.

Serial evaluation of the RV_{Sa}/LV_{Sa} ratio could also provide useful information about loading changes in both ventricles and compensatory cardiovascular mechanisms occurring during the process of placental insufficiency and heart failure.

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