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Time-interval changes of cardiac cycles in fetal growth restriction

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ABSTRACT

Objective: The aims of this study were to investigate the time intervals of each component of cardiac flow velocity waveforms (FVWs) in fetuses with fetal growth restriction (FGR) and to compare these with those of normal fetuses using reference ranges.
Methods: The durations of atrioventricular (AV) valve opening (AVVO), AV valve closure (AVVC), total E- (total-E) and A- (total-A) waves, total ejection time (total-ET), acceleration time (acc-E for E-wave, acc-A for A-wave, and acc-ET for ejection time), and deceleration time (dec-E for E-wave, dec-A for A-wave, and dec-ET for ejection time) were measured in fetuses with FGR. All variables were analyzed using *z*-scores.
Results: Measurements of 17 growth-restricted fetuses were obtained. The time intervals between the last Doppler examination and delivery ranged from 0 to 6 days, with a median of 1 day. Significant increases were observed in AVVO, total-E, dec-E, and acc-A of the left heart. acc-E, acc-ET and AVVC of the left heart were significantly decreased. In the right heart, AVVO, total-E and dec-E were significantly increased.
Conclusion: A prolonged time interval between early ventricular inflow and atrial contraction, as well as increased duration of AV valve opening, may reflect hemodynamic alterations in FGR fetuses.

Introduction

Doppler assessment of the fetal circulation and cardiac function for the surveillance of fetal wellbeing is used clinically. Fetal growth restriction (FGR), which is one of the most challenging conditions in obstetrical management, needs to be assessed by sequential and detailed monitoring with Doppler methods, and the findings play a key role in perinatal decisions [1–4].

Using flow velocity waveforms (FVWs) obtained by Doppler methods, time-interval analysis has recently been introduced to examine fetal development and physiology. Nakagawa et al. showed that maturational changes appear in the time intervals of the fetal right heart, and the phenomena are reflected in those of the ductus venosus FVW [5]. These parameters were also found to show striking differences in the cases of recipients and donors of twin-to-twin transfusion syndrome [6]. Recently, we have constructed reference ranges of time intervals for mitral, tricuspid, aortic, and pulmonary FVWs, and characteristic differences between the right and left ventricles were seen in normal fetuses with progression of development and unequal blood volume owing to a unique shunt system [7]. The aims of this study were to investigate the time intervals of each component of cardiac FVWs in FGR fetuses and to compare them with those of normal fetuses using reference ranges.

Methods

This is a descriptive study using prior established reference ranges [7]. Pregnancies with FGR (n = 19) were recruited at Osaka City University Hospital and Osaka City General Hospital from April 2010 to December 2015. A total of 9 of these cases have already been included in a previous study [8]. FGR was defined as an estimated fetal weight below −2.0 SDs with an elevated

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umbilical artery pulsatility index above the 95th percentile of the reference range [9,10]. Gestational age was calculated from the last menstrual period and confirmed by the crown-rump length at 9–11 gestational weeks. In the FGR group, only the last examination within one week before delivery was obtained retrospectively for analysis. The indication for delivery was non-reassuring fetal status or fetal demise. Exclusion criteria for both the reference and FGR groups were multiple pregnancies, chromosomal abnormalities, or structural anomalies. All participants gave their written, informed consent, and the study protocol was approved by the Institutional Review Board.

Doppler studies were performed with Voluson E8 or E8 Expert (GE Healthcare, Milwaukee, WI, USA) ultrasound machines. All recordings were obtained in the absence of fetal breathing movements. The angle between the ultrasound beam and the direction of blood flow was less than 20°. The fetal heart rate was within the normal range of 120–160 beats per minute with normal sinus rhythm, and the difference between each Doppler measurement was <5 beats per minute. The FVWs of right and left ventricular inflow were recorded from a four-chamber view of the fetal heart. The Doppler sample volume was placed slightly distal to the valve annulus between the tips of the leaflets [11]. The following time-related components were measured [7]: time interval from atrio-ventricular (AV) valve opening to valve closure (AVVO); time interval from AV valve closure to valve opening (AVVC); total duration of the E-wave (total-E); total duration of the A-wave (total-A); time from the opening of the AV valve to the peak of the E-wave (acc-E); time from the peak of the E-wave to the nadir between the E- and the A-waves (dec-E); time from the nadir between the E- and A-waves to the peak of the A-wave (acc-A); and time from the peak of the A-wave to the closure of the AV valve (dec-A) (Fig. 1). The following intervals were also defined in FVWs through the pulmonary and aortic valves: total ejection time (total-ET); time from the beginning of ventricular systole to peak velocity (acc-ET); and time from peak velocity to the end of ventricular systole (dec-ET) (Fig. 2). The Doppler echo of the opening of each valve ('click') was used as a landmark to optimize measurements of the limits of the ejection period [12].

Measurements were transformed into *z*-scores for comparison to reference ranges [13], according to the following formula: *z*-score = $(X_{GA} - M_{GA})/SD_{GA}$, where X_{GA} is the measured value at a known gestational age, M_{GA} is the mean value according to the reference equation, and SD_{GA} is the standard deviation associated with the mean value at this gestational age. Non-parametric tests (Mann–Whitney *U*-test and Wilcoxon signed-rank test) were used for comparisons of not normally distributed variables. $P < 0.05$ was regarded as significant.

Results

Of the 19 FGR cases, two were excluded; one had a ventricular septal defect that was diagnosed postnatally, and the other one showed fetal tachycardia. Measurements were obtained from the right and left cardiac cycle in all 17 growth restricted fetuses. In the FGR group, all cases except for two with fetal demise were delivered by caesarean section due to non-reassuring fetal status. The time intervals between the last Doppler examination and delivery ranged from 0 to 6 days, with a median of 1 day.

Maternal and neonatal characteristics in FGR cases are shown in Table 1. All fetuses were severely restricted in growth.

Table 2 shows *z*-scores of each variable in FGR cases. Significant increases were observed in AVVO, total-E, dec-E, and acc-A of the left heart. On the other hand, acc-E, acc-ET and AVVC of the left heart were significantly decreased. In the right heart, AVVO, total-E and dec-E were significantly increased.

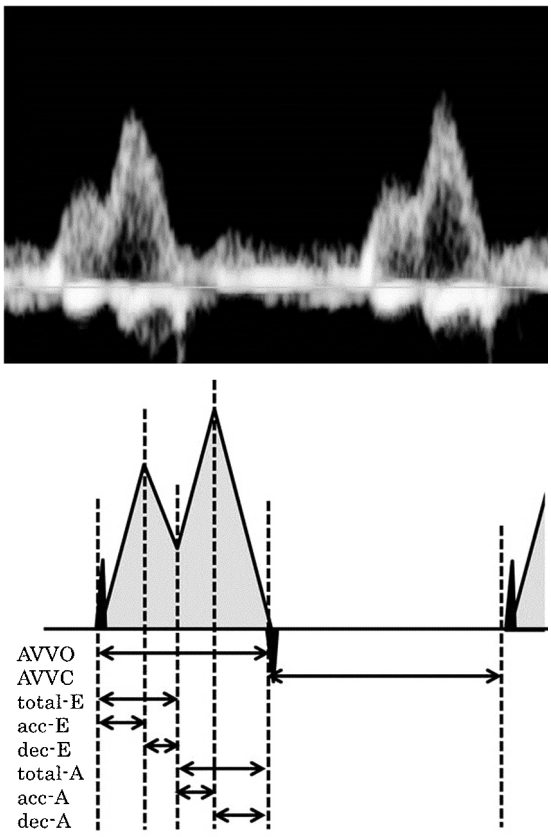

Fig. 1. Doppler tracing of the FVW of AV filling. (i) Duration of atrioventricular valve opening (AVVO), (ii) AV valve closing (AVVC), (iii) total duration of E-wave (total-E), (iv) time from opening of the AV valve to the peak of the E-wave (acc-E), (v) time from the peak of the E-wave to the nadir between the E- and A-waves (dec-E), (vi) total duration of the A-wave (total-A), (vii) time from the nadir between the E- and A-waves to the peak of the A-wave (acc-A), and (viii) time from the peak of the A-wave to closing of the AV valve (dec-A).

Discussion

Applying the recently constructed reference ranges [7], this study demonstrated the characteristic changes of FVW time-intervals in FGR cases. In the left heart, increased opening duration of the mitral valve (Lt-AVVO) was observed with decreased closure duration (Lt-AVVC). In addition, these phenomena result from the increased duration of the early ventricular relaxation time (total-E), especially from its deceleration time (dec-E). Significant increase of tricuspid valve (Rt-AVVO) was also observed, possibly caused by increases of total-E and dec-E of right heart.

Using other methods, Reed et al. measured human fetal tricuspid and mitral deceleration times in fetuses with growth restriction and the absence of end-diastolic Doppler velocities in the umbilical artery, and they found abnormally increased deceleration times across both ventricular valves in the FGR group [13]. Their results are partially in accordance with the present results, and the differences may be primarily due to methodological reasons, the number of cases, and the statistical methods. To overcome the fact that many of the time interval parameters are correlated with gestational age [7], the *z*-score was used to analyze the data, and significant increases were observed not only in the deceleration time of the E-wave, but also in the atrioventricular valve opening time. From the perspective of the phases of ductus venosus FVW, time interval differences between normal and FGR fetuses were demonstrated in our previous study, which suggests that time-interval alterations of the ductus venosus FVW, as well as cardiac cycles, may reflect the hemodynamic events caused by