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# Fetal right ventricular contraction and relaxation times at 11–13 weeks' gestation on speckle tracking imaging

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**KEYWORDS:** cardiac function; nuchal translucency; speckle tracking; tricuspid regurgitation; trisomy 21

## ABSTRACT

***Objective*** *To examine the contraction time and relaxation time of the right ventricle at 11–13 weeks' gestation in trisomy 21 and euploid fetuses by speckle tracking ultrasound imaging.*

***Methods*** *Measurement of fetal nuchal translucency (NT) thickness, Doppler assessment for tricuspid regurgitation and reversed A-wave in the ductus venosus (DV) and fetal echocardiography were performed immediately before chorionic villus sampling for fetal karyotyping at 11–13 weeks' gestation. Digital videoclips of the four-chamber view of the fetal heart were recorded and analyzed offline using speckle tracking imaging software. The contraction time, which is the time between the highest and lowest peaks in the right ventricular area, and relaxation time, which is the time between the lowest and the subsequent highest area peak, were measured and expressed as a percentage of the duration of the cardiac cycle. Values in trisomy 21 and euploid fetuses were compared.*

***Results*** *Mean contraction time and relaxation time in 119 euploid fetuses were 52.1% (95% CI, 51.6–52.8%) and 47.8% (95% CI, 47.2–48.4%), respectively. In 21 trisomy 21 fetuses, mean contraction time was significantly higher (57.0% (95% CI, 55.2–58.9%);* $P < 0.01$*) and relaxation time lower (42.9% (95% CI, 41.1–44.8%);* $P < 0.01$*) than in euploid fetuses. Multiple regression analysis showed that significant contributions to contraction time and relaxation time were provided by fetal karyotype, NT and tricuspid regurgitation, but not by reversed A-wave in the DV or the presence of a cardiac defect.*

***Conclusion*** *In first-trimester fetuses with trisomy 21 and in euploid fetuses with increased NT and tricuspid regurgitation there is evidence of increased right ventricular contraction time and shortening of the relaxation time.* 

## INTRODUCTION

Excessive nuchal fluid accumulation, tricuspid regurgitation and reversed A-wave in the ductus venosus (DV) are common sonographic findings in fetuses with cardiovascular compromise, and they can be found alone or in different combinations in a variety of conditions, such as severe fetal growth restriction, cardiac overload in the recipient fetus of twin-to-twin transfusion syndrome (TTTS) and fetal hydrops[1–3]. Extensive research has demonstrated that the prevalence of these findings is substantially higher in fetuses with trisomy 21 at 11–13 weeks' gestation than in euploid fetuses[4,5]. However, cardiac function in fetuses with trisomy 21 in the first trimester has been examined in very few studies, and these used pulsed-wave Doppler and M-mode ultrasound to measure atrioventricular and arterial blood flow velocities, cardiac output, stroke volume, shortening fraction and cardiac times[6–8].

Speckle tracking imaging is a relatively new ultrasound-based technique that is able to detect myocardial wall motion and to analyze several functional parameters, such as segmental and global myocardial velocities, deformation (strain), deformation rate (strain rate), ejection fraction and valve displacement[9,10]. Several studies have provided reference ranges for such measurements in normal fetuses in the second and third trimesters of pregnancy, and speckle tracking imaging was able to show differences in cardiac function between donor and recipient fetuses in TTTS and in fetuses with hypoplastic left heart[11–15].

The aim of this study was to examine contraction and relaxation times of the right ventricle at 11–13 weeks' gestation in trisomy 21 and euploid fetuses by speckle tracking ultrasound imaging.

## METHODS

Fetal echocardiography was performed on all consecutive patients attending our center over a 6-month period

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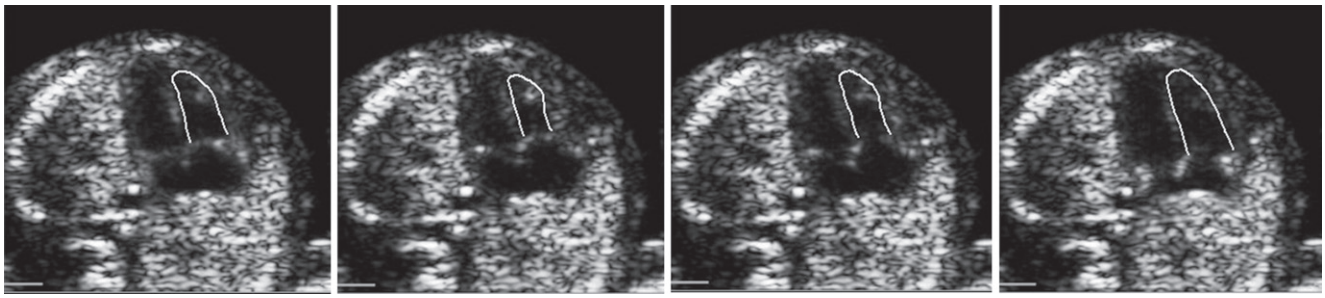

**Figure 1** Ultrasound images of the four-chamber view of the fetal heart at 12 weeks' gestation showing automatic tracing of endocardial borders by vector velocity imaging software during different phases of the cardiac cycle.

for chorionic villus sampling (CVS), which was carried out after risk assessment for chromosomal abnormalities by evaluation of a combination of maternal age, fetal nuchal translucency (NT) thickness, fetal heart rate and maternal serum free β-human chorionic gonadotropin and pregnancy-associated plasma protein-A[16]. In a minority of cases, CVS was carried out at maternal request or for genetic testing. Echocardiography was performed by obstetricians with extensive experience in second-trimester anomaly scanning and first-trimester ultrasound.

All examinations were carried out transabdominally using a 9-MHz linear transducer (9L, Acuson Sequoia 512, Imagegate, Siemens, Erlangen, Germany). In each case we aimed to demonstrate cardiac anatomy and to assess blood flow in the DV and across the tricuspid valve with the use of color and pulsed-wave Doppler ultrasound, as previously described[17].

In each case we recorded a videoclip showing the apical four-chamber view of the heart, of a duration of three to four cardiac cycles, during fetal quiescence. These clips were used for offline review by a fetal cardiologist. The magnification of the image was such that, in a transverse section of the fetal chest, the heart occupied most of the screen, with a frame rate of at least 30 frames/s. The videoclips of the four-chamber view were analyzed offline with the use of Vector Velocity Imaging™ (VVI) software (VVI, *syngo*®, US Workplace, Siemens Healthcare). The heart rate was measured using a virtual M-mode algorithm built into the software. Firstly, the video sequence was played back in order to identify a frame with clear delineation of the endocardial borders of the right ventricle, which were manually traced starting and ending at the atrioventricular valve plane and excluding the moderator band from the tracing. Secondly, the tracking algorithm was launched and the capacity of the software to follow cardiac wall motion was visually verified throughout the video sequence (Figure 1). When necessary, adjustments to the original tracing were made and cases in which a satisfactory endocardial tracking could not be obtained after several attempts were classified as inadequate and excluded from data analysis. Following successful myocardial motion tracking, average changes in the area of the right ventricle over time were calculated by the software. When the computer mouse is placed on the curve that describes the changes in ventricular area, the software returns the value of the area at that specific point in time. This allows definition of the beginning of systole as the point with the highest value in the area curve and that of diastole as the point with the lowest value. Contraction and relaxation times were measured by placing electronic time bars between the highest and lowest area peaks in a given cardiac cycle (Figure 2). Concordance between the video frame showing the beginning and end of systole and diastole and the area peaks calculated by the software was verified on the videoclip in each case. Measurements were performed by a single operator who was not aware of cardiac and extracardiac findings or fetal karyotype.

Outcome data included fetal karyotype and transabdominal fetal echocardiography findings at 18–22 weeks.

### Statistical analysis

The Mann–Whitney *U*-test was used to compare the means of continuous measurements between different groups. The Chi square and Fisher's exact tests were used to assess the differences in frequency distribution of categorical variables. Linear regression analysis was used to examine the relationship between cardiac times, fetal heart rate and crown–rump length (CRL). The measured NT was expressed as the difference from the expected normal mean for gestation (delta value)[18]. Multiple regression analysis was used to determine which of the factors among fetal karyotype, delta NT thickness, tricuspid regurgitation, reversed A-wave in the DV and the presence of a cardiac defect were significant predictors of contraction and relaxation times. Bland–Altman analysis was used to compare the agreement and bias for measurement of contraction and relaxation times for a single examiner and between two examiners[19]. The data were analyzed using the statistical software SPSS 18.0 (Chicago, IL, USA) and Excel for Windows 2003 (Microsoft Corp., Redmond, WA, USA), with statistical significance defined as $P < 0.05$.

## RESULTS

During the study period we carried out 219 ultrasound examinations. We excluded 16 cases with chromosomal abnormalities other than trisomy 21 (Figure 3). Satisfactory tracing and tracking of right ventricular wall motion was achieved in 140 (69.0%) of the remaining

 

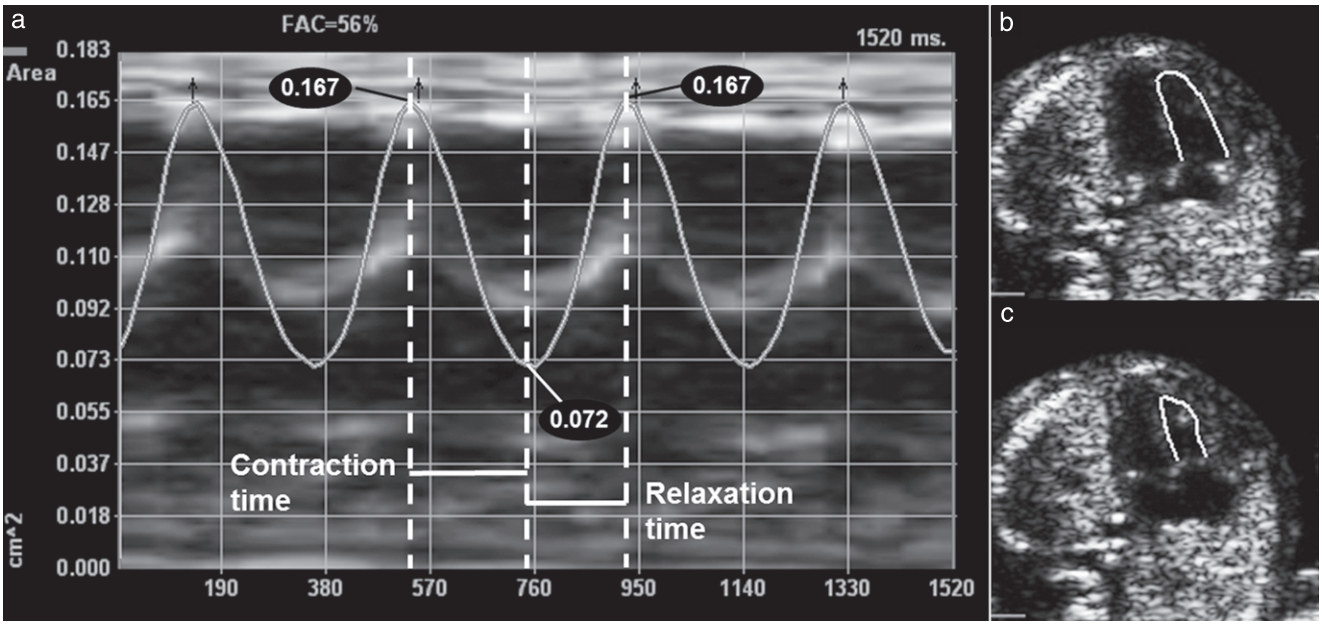


**Figure 2** (a) Output image from vector velocity imaging software showing variation in area of right ventricle with time (vertical dashed lines define contraction and relaxation times). (b,c) Concordance between highest and lowest area peaks calculated by software and video frames corresponding to end diastole (b) and end systole (c).

203 fetuses. Failure to obtain satisfactory results was the consequence of low frame rate, inadequate visualization of the endocardial borders of the right ventricle or fetal movement. In the study population of 140 cases, median maternal age was 35 (range, 19–46) years, median maternal body mass index was 23.9 (range, 18–32) kg/m$^2$ and median fetal CRL was 71.4 (range, 52–84) mm. There were 119 euploid fetuses and 21 cases of trisomy 21. In the trisomy 21 fetuses NT thickness and the prevalence of tricuspid regurgitation, reversed A-wave in the DV and cardiac defects were higher than in euploid fetuses, but there was no significant difference in CRL and fetal heart rate (Table 1). There was no significant difference in CRL, fetal heart rate and the prevalence of tricuspid regurgitation, reversed A-wave in the DV and cardiac defects between cases in which a satisfactory endocardial tracking was obtained and those in which the VVI software was not able to accurately follow cardiac wall motion, both in euploid and trisomy 21 fetuses (Table 1).

Regression analysis showed that contraction and relaxation times significantly decreased with increasing fetal heart rate ($r = 0.503$, $P < 0.01$, and $r = 0.611$, $P < 0.01$, respectively). Therefore, we expressed the values as a percentage of the cardiac cycle duration, derived by the sum of contraction and relaxation times in the same cycle. There was no significant change in contraction time/cardiac cycle duration (CT%) and relaxation time/cardiac cycle duration (RT%) with fetal heart rate ($r = 0.135$, $P = 0.112$ and $r = 0.134$, $P = 0.114$, respectively).

Mean CT% and RT% in the euploid fetuses were 52.1% (95% CI, 51.6–52.8%) and 47.8% (95% CI, 47.2–48.4%), respectively. In the trisomy 21 fetuses mean CT% was significantly higher (57.0% (95% CI, 55.2–58.9%), $P < 0.01$) and RT% lower (42.9% (95% CI, 41.1–44.8%), $P < 0.01$) than in euploid fetuses. Multiple regression analysis showed that significant contributions to CT% and RT% were given by fetal karyotype, delta NT thickness and tricuspid regurgitation but not by reversed A-wave in the DV or the presence of a cardiac defect (Table 2, Figure 4).

In order to verify the reliability of the VVI software in defining the duration of right ventricular contraction and relaxation, we compared the duration of the cardiac cycle calculated by the VVI software with that derived from the fetal heart rate calculated with conventional pulsed-wave Doppler on two consecutive cardiac cycles (cardiac cycle in ms = 60/fetal heart rate in beats per min × 1000). Paired samples *t*-test showed no significant difference in cardiac cycle length between the two methodologies ($P = 0.142$). The mean frame rate was 49 (range, 36–54) frames/s. There was no significant difference in frame rate between euploid fetuses and fetuses with trisomy 21 ($P = 0.974$).

The mean difference and the 95% limits of agreement between paired measurements of contraction time by the same observer were 0.740 (range, −8.860 to 10.340) ms and the values in paired measurements by two different observers were 1.120 (range, −14.199 to 16.439) ms (Figure 5). The values for measurements of relaxation time by the same observer were 0.120 (range, −9.281 to 9.521) ms and by two different observers they were −0.700 (range, −14.973 to 13.573) ms (Figure 6).

## DISCUSSION

This study showed that first, in euploid fetuses at 11–13 weeks' gestation, about half of the cardiac cycle is

 

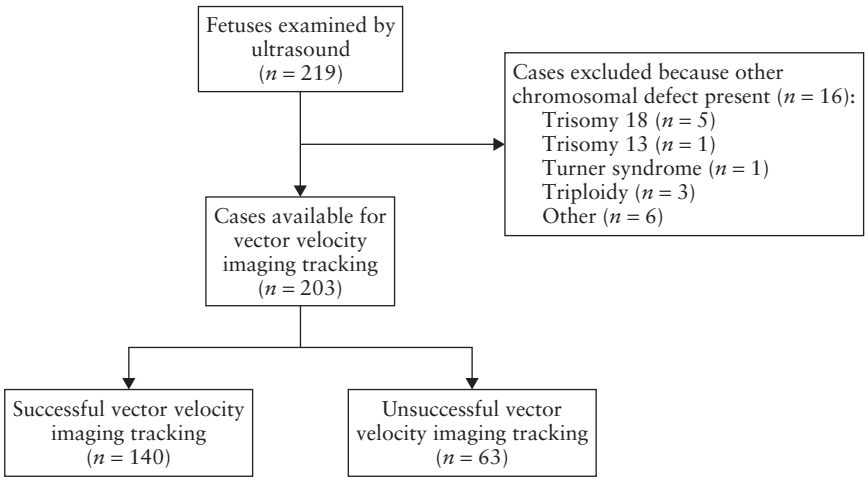


**Figure 3** Flow-chart of study population of all consecutive patients attending our center over a 6-month period for chorionic villus sampling ($n = 219$).

**Table 1** Main sonographic findings in euploid and trisomy 21 fetuses according to successful or unsuccessful vector velocity imaging (VVI) myocardial tracking

| | *Successful VVI tracking* | | | *Unsuccessful VVI tracking* | | | |
|---|---|---|---|---|---|---|---|
| *Parameter* | *Euploid (n = 119)* | *Trisomy 21 (n = 21)* | P | *Euploid (n = 59)* | P* | *Trisomy 21 (n = 4)* | P† |
| Crown–rump length (mm) | 71.4 (52–84) | 71.1 (54–84) | 0.791 | 69.9 (54–84) | 0.201 | 69.2 (60–76) | 0.630 |
| Fetal heart rate (beats per min) | 158 (140–188) | 157 (138–166) | 0.997 | 158 (100–178) | 0.822 | 161 (157–166) | 0.237 |
| NT thickness (mm) | 2.6 (1.3–9.8) | 4.4 (2.0–7.6) | < 0.01 | 2.5 (1.4–6.7) | 0.447 | 6.8 (3.2–12.1) | 0.532 |
| Tricuspid regurgitation | 25 (21.0) | 16 (76.2) | < 0.01 | 7 (11.9) | 0.152 | 3 (75.0) | 1.000 |
| Reversed A-wave in DV | 10 (8.4) | 6 (28.6) | < 0.01 | 6 (10.2) | 1.000 | 1 (25.0) | 1.000 |
| Cardiac defect | 3 (2.5) | 11 (52.4) | < 0.01 | 1 (1.7) | 1.000 | 1 (25.0) | 0.593 |
| Atrioventricular septal defect | 1 | 8 | — | 1 | — | 1 | — |
| Ebstein's anomaly | 1 | — | — | — | — | — | — |
| Disproportion of ventricles and great arteries | 1‡ | 3 | — | — | — | — | — |

Data given as *n*, *n* (%) or mean (range). *Comparison with euploid fetuses with successful VVI tracking. †Comparison with trisomy 21 fetuses with successful VVI tracking. ‡Coarctation of the aorta on follow-up scans. DV, ductus venosus; NT nuchal translucency.

**Table 2** Multiple regression analysis showing the contribution of different factors to contraction and relaxation times expressed as a percentage of the cardiac cycle

| *Independent variable* | *Contraction time coefficient* | P | *Relaxation time coefficient* | P |
|---|---|---|---|---|
| Karyotype | 2.387 | < 0.01 | −2.375 | < 0.01 |
| Delta NT | 0.594 | < 0.01 | −0.595 | < 0.01 |
| TR | 2.450 | < 0.01 | −2.467 | < 0.01 |
| Reversed A-wave in DV | 1.092 | 0.217 | −1.088 | 0.220 |
| Cardiac defect | −0.443 | 0.695 | 0.452 | 0.689 |

DV, ductus venosus; NT nuchal translucency; TR, tricuspid regurgitation.

occupied by contraction and the other half by relaxation of the right ventricle; second, in fetuses with trisomy 21 there is an increase in duration of ventricular contraction and shortening of relaxation time; and third, in both euploid and trisomy fetuses contraction and relaxation times are related to NT thickness and presence or absence of tricuspid regurgitation.

In the adult, with a heart rate of about 75 beats per minute (bpm), two thirds of the cardiac cycle is spent in ventricular relaxation[20]. Induced tachycardia to 150 bpm is associated with shortening of the relaxation time to half of the cycle[20]. This is consistent with our findings in early fetal life, when the heart rate is about 150 bpm. Similarly, in normal neonates and children an increase in heart rate is mainly achieved through shortening of the relaxation time[21].

Echocardiographic studies have shown that an increase in the ratio between systolic and diastolic times is a common finding in neonates and children with cardiac functional disorders, such as dilated and restrictive cardiomyopathy[22,23]. Consequently, our finding that in fetuses with trisomy 21 and in those with high NT and tricuspid regurgitation there is prolongation of contraction time and shortening of relaxation time could indicate the presence of cardiac dysfunction. There is evidence that, in postnatal life, trisomy 21 is associated with cardiac dysfunction[24–28], and a recent echocardiographic study found mild to moderate regurgitation in one or more heart valves in 106 (76.8%) of 138 adults with trisomy 21[29].

 

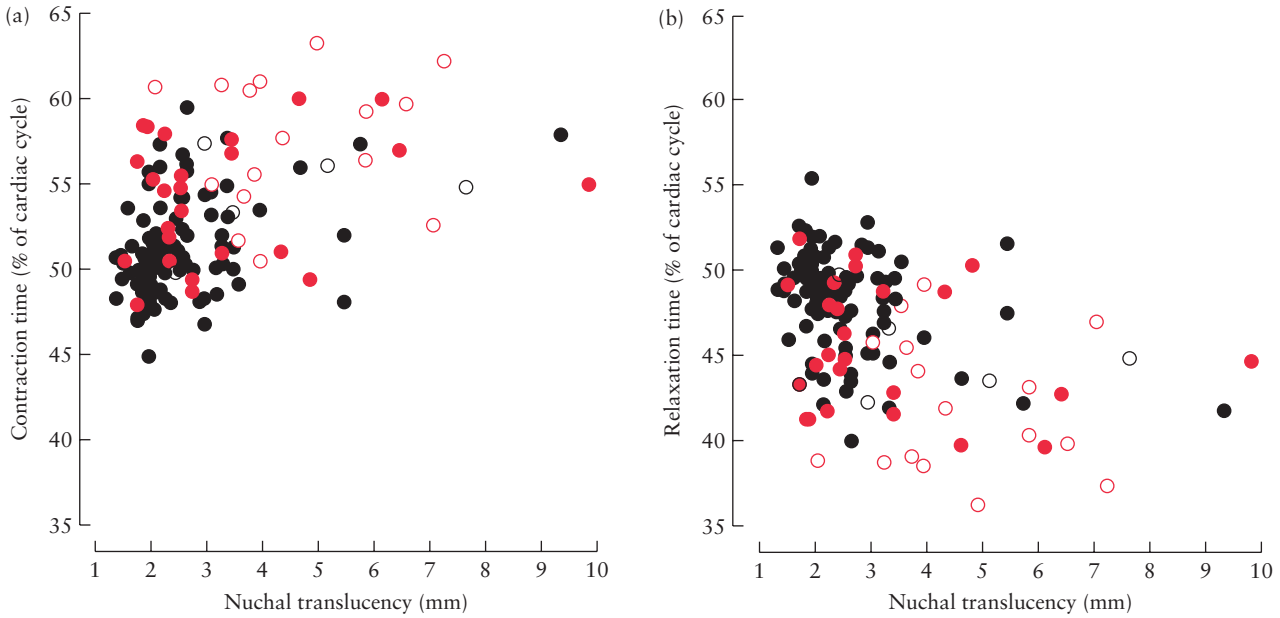


**Figure 4** Relationship of contraction time (a) and relaxation time (b) with nuchal translucency thickness in euploid fetuses (filled circles) and trisomy 21 fetuses (open circles) according to absence (black circles) or presence (red circles) of tricuspid regurgitation.

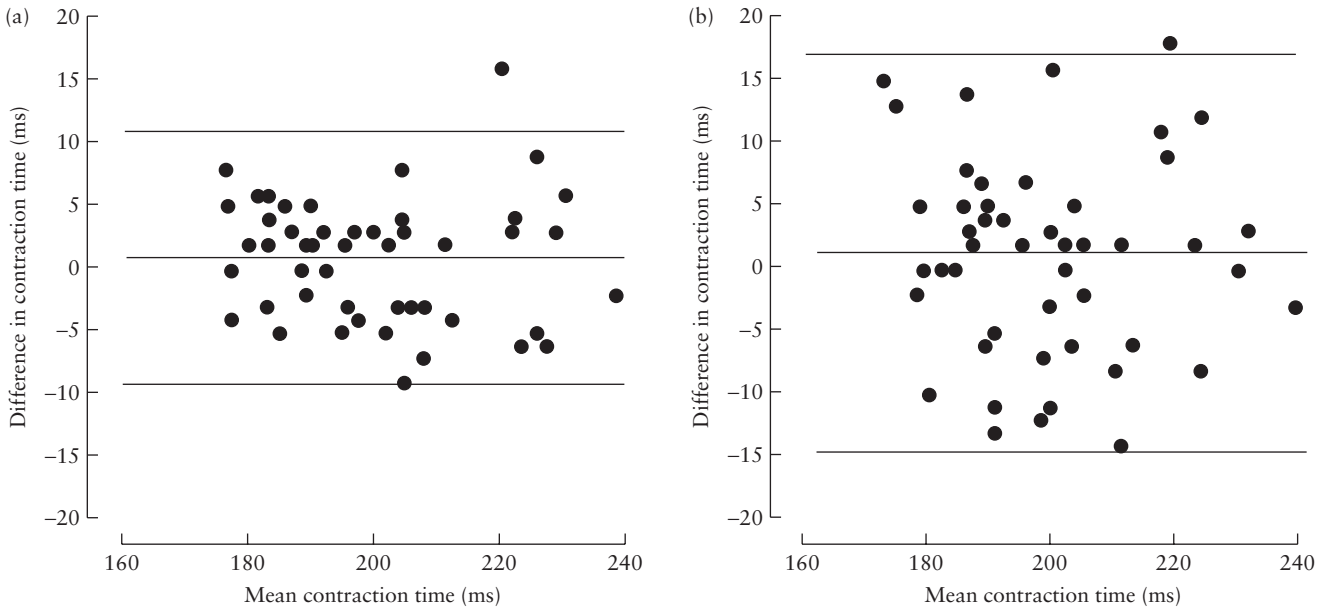


**Figure 5** Mean difference and 95% limits of agreement between paired measurements of contraction time as measured by vector velocity imaging by the same observer (a) and by two different observers (b).

Our findings are compatible with the results of animal studies. Gui *et al.*[30] measured cardiac time intervals using pulsed-wave Doppler in 20 mouse embryos with trisomy 16, which has been shown to be a good animal model for human trisomy 21 and is also associated with increased NT[31,32], and found that the ejection time, which accounts for most of the duration of ventricular contraction, was significantly longer than that in 129 normal mouse embryos.

Two previous first-trimester studies of human fetuses with trisomy 21 have examined cardiac time intervals using pulsed-wave Doppler measurement of the myocardial performance index (MPI), which is the sum of isovolumic contraction and relaxation times divided by the ejection time for each ventricle[6,7]. Although both studies found that in trisomy 21 right ventricular MPI was not significantly different from that of euploid fetuses, one study found that left MPI was increased but the other found that it was decreased[6,7]. One possible explanation for these discordant results is that, in both studies, measurement of MPI was subject to wide intra- and inter-observer variation. The ability of the VVI software to accurately analyze cardiac function depends strongly on the frame rate of the videoclip recording[33]. In this study, a mean rate of about 50 frames/s allowed clear separation of systole from diastole, but it was insufficient

 

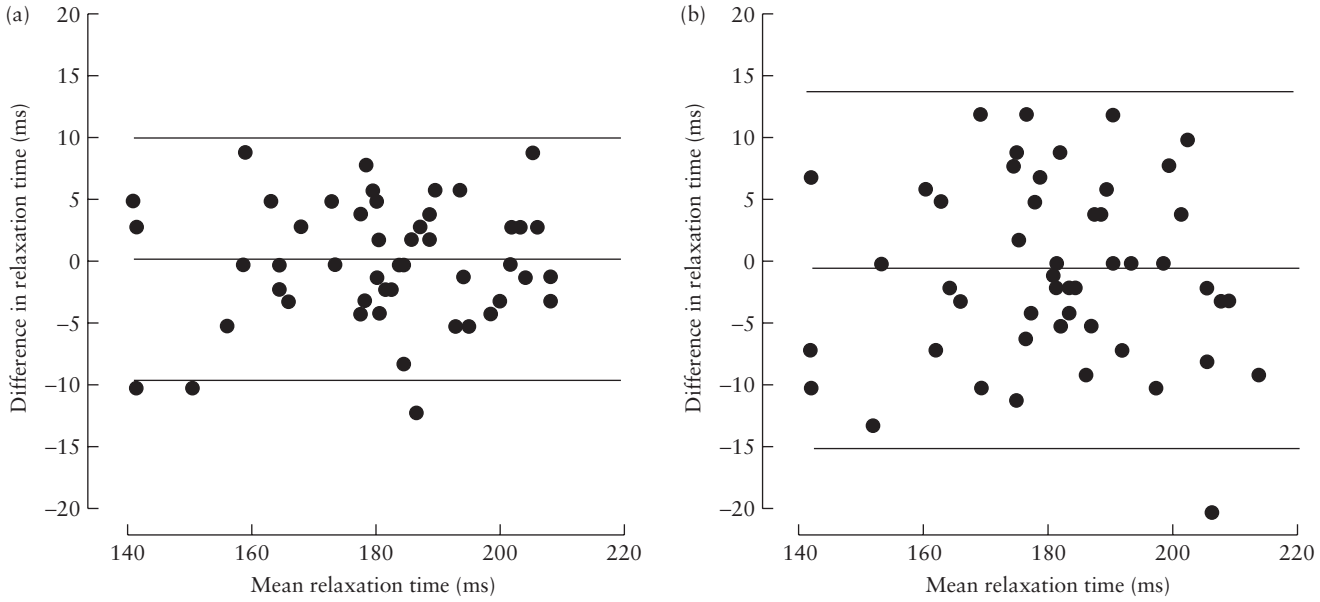


**Figure 6** Mean difference and 95% limits of agreement between paired measurements of relaxation time as measured by vector velocity imaging by the same observer (a) and by two different observers (b).

for a systematic detection of ventricular isovolumic times, which have a short duration and therefore require a higher number of frames/s.

The reliability of the VVI software in quantifying cardiac cycle length was verified in this study by showing no significant difference between it and the duration of the cardiac cycle calculated by pulsed-wave Doppler, which is known to reflect true fetal heart rate variations. In addition, the simultaneous display of the graph showing changes in the ventricular area during the cardiac cycle and the corresponding frame on the video sequence allowed verification of the ability of the algorithm to identify the beginning and end of systole and diastole. However, despite the use of high-frequency linear ultrasound, which provides detailed visualization of the fetal heart in the first trimester of pregnancy[17], the VVI software was not able to effectively track endocardial wall motion in about 30% of cases, mainly because of signal noise and fetal movement. For this reason, assessment of cardiac function by VVI in fetuses at 11–13 weeks' gestation is unlikely to be incorporated into routine screening, but it could be used to observe changes in cardiac functional parameters in selected populations for a better understanding of fetal cardiac pathophysiology.

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