

Left ventricle shortening fraction: a comparison between euploid and trisomy 21 fetuses in the first trimester

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Objectives Measurement of the shortening fraction of the left ventricle (SFLV) is an objective way to assess systolic performance. The aim of the study was to compare first trimester SFLV values in euploid fetuses to those in fetuses with trisomy 21.

Methods We measured SFLV in 56 fetuses from 11 weeks to 13 weeks 6 days. The left ventricular diastolic diameter (LVDD) and left ventricular systolic diameter (LVSD) were measured offline, and SFLV was calculated. The data were analyzed using Mann–Whitney *U* test.

Results We found a significant difference in the SFLV measurements between the group of 49 euploid fetuses and the 7 fetuses with trisomy 21 [38.00 (95% CI: 33.72–42.27) vs 49.93 (95% CI: 43.72–56.13)] ($p < 0.05$). There was also a significant difference in the nuchal translucency measurements between the two groups: 1.78 mm (95% CI: 1.08–2.48 mm) in the euploid population versus 5.06 mm (95% CI: 3.61–6.71 mm) in the fetuses with trisomy 21 ($p < 0.05$). There were no significant differences between the group of euploid fetuses and the group of trisomy 21 fetuses in the following parameters: CRL (chorionic villus sampling), LVDD and LVSD.

Conclusions SFLV is a well-defined, simple measurement of systolic function of the fetal myocardium. SFLV values in fetuses with trisomy 21 appear to be significantly higher than in euploid fetuses. Copyright © 2010 John Wiley & Sons, Ltd.

KEY WORDS: trisomy 21; first trimester; marker; shortening fraction of the left ventricle

INTRODUCTION

Shortening fraction of the left ventricle (SFLV) is felt to be an indicator of cardiac contractility. It may be measured in the fetus using M-mode ultrasound and has been shown to be fairly constant in the second and third trimesters (DeVore *et al.*, 1984; Agata *et al.*, 1991; Hsieh *et al.*, 2000; DeVore, 2005).

Studies comparing myocardial function in adults with Down syndrome to chromosomally normal individuals have shown major differences in myocardial function (Hamada *et al.*, 1993; Russo *et al.*, 1998). Indices of left heart function point to a better performance in individuals with Down syndrome: the end diastolic volume index (EDVI) and end systolic volume index (ESVI) tend to be decreased, and the ejection fraction (EF) and mean velocity of circumferential fiber shortening (mean Vcf) tend to be increased. Measurement of the SFLV is an objective way to assess systolic function (DeVore *et al.*, 1984; Agata *et al.*, 1991; Hamada *et al.*, 1993; Russo *et al.*, 1998; Hsieh *et al.*, 2000; DeVore, 2005).

The aim of the study was to assess whether SFLV values in euploid fetuses are different from those with trisomy 21 in the first trimester.

METHODS

The study population included consecutive first trimester fetuses between 11 weeks and 13 weeks 6 days of gestation in which the chromosomal status was determined by chorionic villus sampling (CVS). The ultrasound examination was performed either at the time of the first trimester combined screening test or prior to CVS. In each case, the decision to perform the CVS was based on an increased risk on the first trimester combined screen. The heart was imaged in one of two ways: the two ventricles were either viewed in the long axis with the face of the transducer being approximately parallel to the ventricular septum (Figure 1), or in the short axis view (Figure 2). The image of the heart was magnified, so it filled at least 75% of the image. An M-mode cursor was then placed through the two ventricles at a right angle to the ventricular septum beneath the level of the A–V valves (Figures 1 and 2). The appropriate M-mode images were obtained using a 7 MHz abdominal probe [M7C, Logic 9(GE)] by a single experienced operator (M.B.) and stored. We determined the time required to

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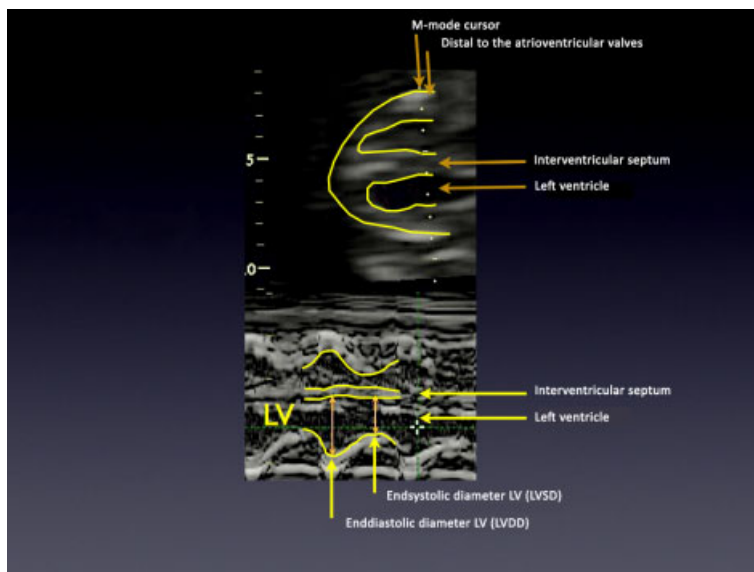


Figure 1—Fetal heart and the orientation of the M-mode cursor, placed perpendicular to the interventricular septum, just below the tips of the atrioventricular valves

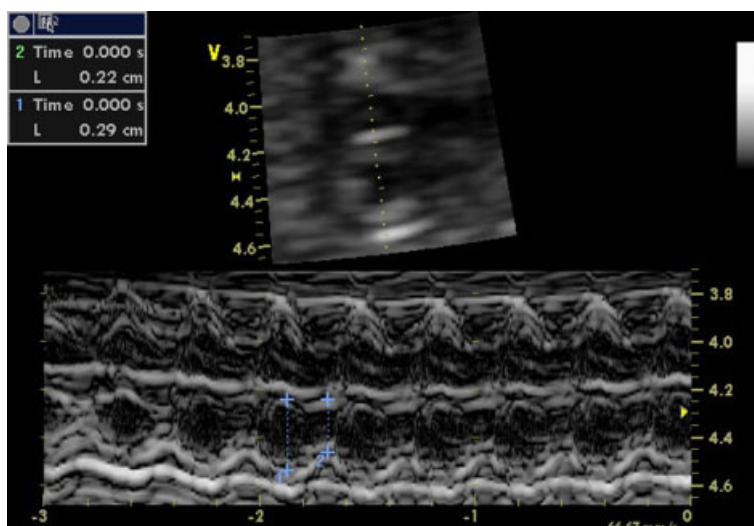


Figure 2—Fetal heart and the orientation of the M-mode cursor in the short axis view

obtain an appropriate image in the last 28 cases. The reason for using the most recent cases for this purpose was to allow a reasonable period to attain proficiency in this technique. The left ventricular diastolic diameter (LVDD) and left ventricular systolic diameter (LVSD) were measured offline. The SFLV was calculated using the following formula: $[(LVDD - LVSD)/LVDD] \times 100$. The fetal chromosomal status was not known at the time of the measurements. Multiple gestations and fetuses with an apparent heart defect were excluded from the study. Each patient signed a consent for the ultrasound examination.

RESULTS

Between September 2008 and February 2009, we examined 58 fetuses that fit the study criteria. In two

of the cases, appropriate images could not be obtained. Out of the 56 fetuses that were examined successfully, 49 were chromosomally normal and 7 had trisomy 21. The SFLV values in the euploid fetuses were statistically smaller than in fetuses with trisomy 21: 38.00 (95% CI: 33.72–42.27) versus 52.07 (43.72–56.13) ($p < 0.05$). There was also a significant difference in the nuchal translucency (NT) measurements between the two groups: 1.78 (95% CI: 1.08–2.48) in the euploid population versus 5.06 (95% CI: 3.61–6.71) in the fetuses with trisomy 21 ($p < 0.05$). The two groups did not differ in CRL measurements [euploid: 66.81 mm (95% CI: 58.28–75.35 mm) versus trisomy 21: 74.68 mm (95% CI: 65.23–79.59 mm) ($p = 0.05$)], LVDD measurements [euploid: 3.35 mm (95% CI: 2.67–4.03 mm) versus trisomy 21: 3.66 mm (95% CI: 2.69–4.06 mm) ($p = 0.19$)], and LVSD measurements [euploid: 2.09 mm (95% CI: 1.58–2.60 mm) versus

trisomy 21: 1.78 mm (95% CI: 1.17–2.20 mm) ($p = 0.28$).

Out of the 28 cases where the time to obtain the SFLV was measured, two cases (7.14%) required less than 60 s, 22 cases (78.57%) between 60 and 120 s, and in two cases (7.14%) 240 s were needed. Examination in the remaining two cases (7.14%) did not yield an acceptable M-mode image even after a prolonged examination.

STATISTICS

The statistical comparison was performed using Mann–Whitney U test. The null hypothesis was rejected for $p < 0.05$.

DISCUSSION

Background

The determinants of the systolic function are well known and include preload (initial sarcomere length), afterload (downstream resistance), efficiency of the contractility of the myofibrils, heart rate and the availability of calcium for binding to contractile proteins. Measurements of EDVI, ESVI, EF and SFLV in adults with Down syndrome appear to be different from chromosomally normal individuals, suggesting a difference in systolic function (Hamada *et al.*, 1993; Russo *et al.*, 1998). It is reasonable to investigate whether these differences exist during the fetal period as well. Accurate volumetric measurements of the cardiac ventricles would be difficult if not impossible to obtain in the first trimester; therefore, SFLV only was used in our study. The feasibility of performing of SFLV measurements has been demonstrated in the second and third trimesters (DeVore *et al.*, 1984; Agata *et al.*, 1991; Hsieh *et al.*, 2000; DeVore, 2005). The measurement is relatively simple as it involves measuring just the left ventricular diameter in diastole and in systole. The use of a ratio, rather than absolute distances, compensates for some of the variability of measurements that may result from slight differences in the angle of insonation.

In this study, we found that measurement of SFLV in the first trimester is feasible and, after allowing time to acquire experience with the procedure, adds very little time to the ultrasound examination. We also found a significant difference in the SFLV values between euploid fetuses and the fetuses with trisomy 21 at 11 weeks to 13 weeks 6 days of gestation, suggesting a difference in the left ventricular performance between the two groups. SFLV is increased in trisomy 21 fetuses, which suggests an improved left ventricular performance in that group. These findings are in line with those of Huggon *et al.* who studied 159 normal fetuses and 142 fetuses with Down syndrome at the same gestational age as in our study (Huggon *et al.*, 2004). In their study, the myocardial performance index (MPI) was found to be significantly decreased in trisomy 21 fetuses, also

suggesting better ventricular function (MPI is inversely proportional to SFLV). Similar findings are seen in individuals with Down syndrome postnatally (Hamada *et al.*, 1993; Russo *et al.*, 1998).

Theoretically, most of the known qualities of the myocardium in fetuses with trisomy 21 would be expected to lead to an impaired left ventricular performance. The myocardium contains both structural and ultrastructural abnormalities. There is an increase in cell size and a reduced cell number per unit area (Recalde *et al.*, 1986). The composition of the connective tissue in individuals with Down syndrome also differs from that in euploid individuals. Genes for several matrix-related proteins, particularly collagen VI and XVIII are located on chromosome 21 (Vis *et al.*, 2009). Gittenberger-de Groot *et al.* (2003) found higher concentrations of collagen VI in hearts of fetuses with trisomy 21 as compared to euploid fetuses. Carvalhaes *et al.* (2006) found that collagen XVIII is localized not only in various basement membranes but is also highly expressed throughout the connective tissue core of the endocardial cushions and forms A–V valve leaflets. It seems feasible that collagen XVIII, or one or more of its proteolytic fragments may play a role in the migration, proliferation and differentiation of connective tissue cells. It would be reasonable to expect that the changes in the composition of the extracellular matrix not only results in the congenital structural heart defects frequently seen in trisomy 21 (Freeman *et al.*, 2008) but may also adversely affect the contractile properties of the fetal myocardium.

It has been shown that adult individuals with Down syndrome have a consistently lower blood pressure, both systolic and diastolic (Richards and Enver, 1979; Russo *et al.*, 1998). It is hypothesized that the apparently better performance of the left ventricle found in adults with Down syndrome is due to this reduction in afterload. Whether the same mechanism is responsible for the findings in fetuses with trisomy 21 in our study is difficult to prove. However, this is a plausible theory that would reconcile the apparently contradictory findings of improved left ventricular performance in the setting of an abnormal myocardium. A physiologic finding that may support this assertion indirectly is the finding of slightly increased heart rate in first trimester fetuses with trisomy 21 (Liao *et al.*, 2000); decreased peripheral resistance may lead to tachycardia.

Limitations

This pilot study is designed to answer two basic questions: whether measuring SFLV in the first trimester is feasible, and whether there is a difference in SFLV measurements between euploid fetuses and fetuses with trisomy 21 based on evaluations of a single experienced operator. As such, it has a number of limitations. The study does not address the inter- and intra-observer variabilities of this measurement. It also does not determine whether the SFLV values change with gestational age, nuchal translucency measurement and fetal heart rate. Further studies are needed to address the outstanding

issues as well as the potential value of this measurement in screening for trisomy 21.

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