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# Quantitative Assessment of Cardiac Function in Fetuses of Women with Maternal Gestational Thyroid Dysfunction Using VVI Echocardiography

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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**Background:** The study aimed to investigate the clinical value of velocity vector imaging (VVI) in assessing heart function in fetuses of pregnant women with thyroid dysfunction. The inter-observer and intra-observer variability was assessed for all VVI parameters observed.

**Material/Methods:** The participants were enrolled from singleton pregnant women with gestational ages ranging $24^{+0}$ to $40^{+1}$ weeks who visited the Department of Obstetrics and Gynecology at the Affiliated Hospital of Qingdao University, China, for prenatal care from July 2011 to February 2014. Digital 2-dimensional (2D) dynamic 4-chamber images of the heart were collected. A total of qualified 226 images from 125 fetuses of pregnant women with normal thyroid (control group), 64 fetuses of pregnant women with hypothyroidism (hypothyroidism group), and 37 fetuses of pregnant women with hyperthyroidism (hyperthyroidism group) were interrogated offline using VVI software. The echocardiographic parameters including the myocardium peak systolic velocity (Vs), peak diastolic velocity (Vd), peak systolic strain (S), peak systolic strain rate (SRs), peak diastolic strain rate (SRd) of RV and LV, were obtained from the velocity curves of 2D myocardial motion. The heart rate was measured using a virtual M-mode algorithm built into the software.

**Results:** The study found that the longitudinal Vs and Vd of both ventricles in the control group gradually decreased from basal segments to apical segments and significantly increased over the gestation. S, SRs, and SRd of both ventricles remained stable after middle gestation. Compared with the control group, the hypothyroidism and hyperthyroidism groups exhibited significantly reduced S, SRs, and SRd, even for fetuses at 24-weeks gestation. There were no significant differences in global Vs and global Vd between the control group and the hyperthyroidism or hypothyroidism groups.

**Conclusions:** The thyroid dysfunction of pregnant women may damage fetal heart function, and VVI could be a sensitive technique to measure the variation of fetal heart function.

**MeSH Keywords:** Fetus • Heart Function Tests • Hyperthyroidism • Imaging, Three-Dimensional

**Full-text PDF:** http://www.medscimonit.com/abstract/index/idArt/894381

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## Background

Maternal thyroid function changes during pregnancy as a result of physiological alterations in some factors such as thyrotrophic effect of human chorionic gonadotropin (HCG), increased iodine clearance in the kidneys, and increased thyroid hormone-binding globulin (TBG) concentration [1,2]. Thyroid dysfunction, including hypothyroidism and hyperthyroidism, has substantial effects on the cardiovascular system. Research shows that overt hyperthyroidism is related to heart disease, for example, atrial fibrillation, and that subclinical hyperthyroidism leads to elevated resting pulse, increased left ventricular mass index, increased frequency of atrial and ventricular premature beats, and cardiac output [3,4]. Regarding to hypothyroidism, subclinical hypothyroidism may disturb the heart function [5,6], and overt hypothyroidism may increase risk of heart diseases such as bradycardia [7] and myocardial infarction [8]. Normalization of thyroid function by treatment is considered to protect cardiac function [6].

Thyroid dysfunction affects up to 5% of pregnant women [9,10]. Maternal thyroid dysfunction is associated with a number of adverse outcomes on intrauterine development and birth, for example, increased risk of pre-term birth, placental abruption, fetal death, and impaired neurological development in the child [11,12]. But relationships of maternal thyroid status to fetal cardiac function are unclear. Considering the characteristics of maternal gestational thyroid function and of fetal hypothalamus-pituitary-thyroid axis development, it would be reasonable to hypothesize that maternal gestational thyroid dysfunction might damage the heart function of the fetus. A recent study showed that maternal hyperthyroidism may alter fetal Tei index [13]. Electrocardiograms and echocardiograms analyses showed infants with congenital hypothyroidism suffered from the functional heart abnormalities, and thyroid replacement therapy rapidly reversed cardiac function problems in infants with congenital hypothyroidism [14], suggesting that it may be clinically important to explore the relationship between maternal gestational thyroid dysfunction and fetal cardiac functional abnormalities. In addition, the heart is a central organ in fetal adaptive mechanisms. The functional assessment of the fetal heart is important for predicting outcomes and monitoring fetal well-being in both cardiac [15,16] and extracardiac pathologies [17–19].

Unfortunately, the assessment of fetal cardiac function relies on echocardiography, which is challenging due to variability of fetal position, fetal movement, and the tiny fetal heart. Conventional M-mode or 2-dimensional (2D) techniques for the evaluation of myocardial mechanics only offer information on global ventricular function. More recently, velocity vector imaging (VVI) has been developed to overcome the limitations of M-mode and 2D imaging. This novel angle independent ultrasonic speckle tracking technique directly analyzes myocardial mechanics by integrating frame-to-frame changes with the geometric shift of each speckle, denoting tissue motion. It computes multiple derivative parameters, including myocardial velocity, strain, and strain rate [20]. These parameters reflect myocardial motion and deformation during systole and diastole, are able to detect fine distinctions of cardiac deformation in space distributions and time distributions among different myocardial segments, and, therefore, are valuable for evaluating regional cardiac function. VVI allows dynamic visualization and quantification of segmental and global myocardial function in the fetus [21]. Some studies have shown that VVI may be feasible for assessing fetal myocardial function [22–25]; however, much research still remains to be done for characterizing the VVI parameters in normal fetal hearts, especially for the Chinese population. Moreover, no published studies on characteristics of VVI parameters in fetal hearts with maternal gestational thyroid dysfunction have so far been provided. This paper aims to study myocardial mechanics of fetus with maternal gestational thyroid dysfunction by VVI, to evaluate the feasibility and clinical value of multiple parameters derived from VVI in the assessment of fetal myocardial performance with maternal gestational thyroid dysfunction.

## Material and Methods

### Ethics statement

The study was conducted with the approval of the Institutional Review Board (IRB) of the Affiliated Hospital of Qingdao University in China, in accordance with principles of Good Clinical Practice. All the participants were informed of the study details and gave written informed consent to participant in the study before participation.

### Subjects

The participants were enrolled from singleton pregnant women with the gestational ages ranging $24^{+0}$ to $40^{+1}$ weeks who visited the Department of Obstetrics and Gynecology at the Affiliated Hospital of Qingdao University, China, for prenatal care from July 2011 to February 2014. All of the pregnant women underwent the routine obstetric ultrasound examinations to detect fetal number, fetal size, developmental anomaly, and extracardiac malformations. Women were eligible to participate if they were certain about the dates of their last menstrual period, neither used drug nor smoked cigarettes, and had no pregnancy-associated complications such as hypertension and gestational diabetes. In addition, the fetal cardiac ultrasound examinations were done to check endocardial malformations, cardiac tumors, and irregular heartbeats using the





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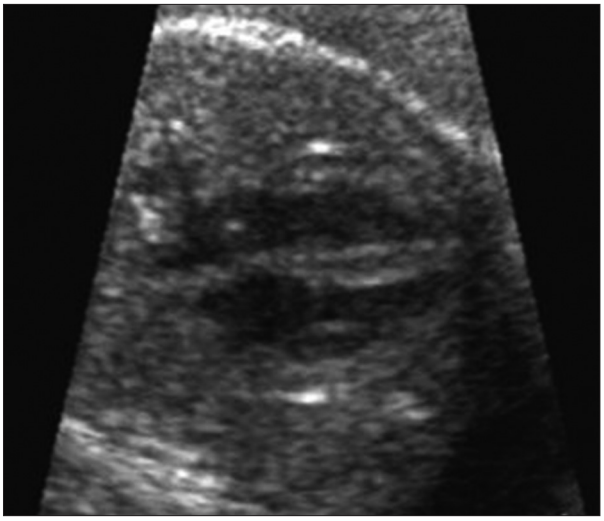

**Figure 1.** An apical 4-chamber view of fetal heart.

Sequential Segmental Analysis [26,27]. The fetuses had neither structural abnormalities nor arrhythmias.

Each pregnant woman was subject to laboratory examination of thyroid function at gestation. Laboratory diagnostic criteria for hypothyroidism and for hyperthyroidism were both based on our previous investigation on thyroid hormone levels in the pregnant women in the Shandong area in China. The criteria for hypothyroidism were: 1) thyroid-stimulating hormone (TSH) greater than 3 mIU/L (normal range is 0.4~3 mIU/L); 2) free thyroxine (FT4) greater than 9.0 pmol/L but smaller than 23.9 pmol/L (normal range is 9.0~23.9 pmol/L) for subclinical hypothyroidism, or FT4 no more than 9.0 pmol/L for hypothyroidism; and 3) free triiodothyronine (FT3) greater than 2.1 pmol/L but smaller than 5.4 pmol/L (normal range is 2.1~5.4 pmol/L) for subclinical hypothyroidism, or no more than 5.4 pmol/L for hypothyroidism. The criteria for hyperthyroidism were: 1) TSH smaller than 0.4 mIU/L, and 2) FT4 greater than 23.9 pmol/L and/or FT3 greater than 5.4 pmol/L.

### VVI Image acquisition and offline analysis

All patients underwent an ultrasonographic examination using a Siemens ACUSON Sequoia S2000 color Doppler ultrasound diagnostic apparatus with a 3~8 MHz convex array probe, which is equipped with VVI software. The examinations were carried out trans-abdominally by an experienced pediatric cardiology specialist. Briefly, the pregnant women were placed in the supine position and asked to hold their breath. The 2D images of the apical 4-chamber view were captured over 3 consecutive cardiac cycles during fetal quiescence (Figure 1). The apical 4-chamber view shows the right ventricle (RV), the left ventricle (LV), the right atria, the left atria, the ventricular septum, the atrial septum, and the foramen ovale. The magnification of the image was such that, in a transverse section of the fetal chest, the heart occupied 1/3~1/2 of the screen. Data were digitally stored for subsequent off-line analysis.

The study captured standard dynamic images of the 4-chamber view from 143 fetuses of pregnant women with normal thyroid (control group), 64 fetus of pregnant women with hypothyroidism, and 37 fetus of pregnant women with hyperthyroidism (hyperthyroidism group). Among them, 18 healthy cases were discarded due to vague endocardial borders, and the remaining 125 healthy cases were included for analysis. Fetal cardiac function gradually develops through pregnancy and may exhibit different characteristics at different gestational stages. To observe the dynamic process of VVI parameter values in fetal heart during pregnancy, each group was divided into 4 subgroups based on gestational ages (Table 1).

The captured images of the 4-chamber view were analyzed offline with the use of VVI software (VVI, syngo, US Workplace, Siemens Healthcare). At first, cardia cycles were determined based on anatomic M-mode ultrasound through mitral and tricuspid valve annulus. We set the initial frame at the beginning of systole, positioned a reference point at the apex of the heart, and started at mitral and tricuspid annulars; thereby, we manually tracked the endocardial borders. We set 8~10 points along the endocardial borders in each chamber. After the endocardial borders had been defined, VVI software automatically tracked endocardial borders throughout the cardiac cycles and the velocity vectors of all the trace points were established. Vector lengths represented the velocity of myocardial motion and vector direction represented the direction of local myocardial motion. The software automatically generated curves

**Table 1.** The distribution of gestational age of the control, hypothyroidism and hyperthyroidism groups.

| Subgroup | Subgroup | Control | Hypothyroidism | Hyperthyroidism |
|---|---|---|---|---|
| 1 | $24^{+0}$~$27^{+6}$ | 31 | 18 | 10 |
| 2 | $28^{+0}$~$31^{+6}$ | 38 | 16 | 7 |
| 3 | $32^{+0}$~$35^{+6}$ | 26 | 16 | 12 |
| 4 | $36^{+0}$~$40^{+1}$ | 30 | 14 | 8 |
| Total | $24^{+0}$~$40^{+1}$ | 125 | 64 | 37 |





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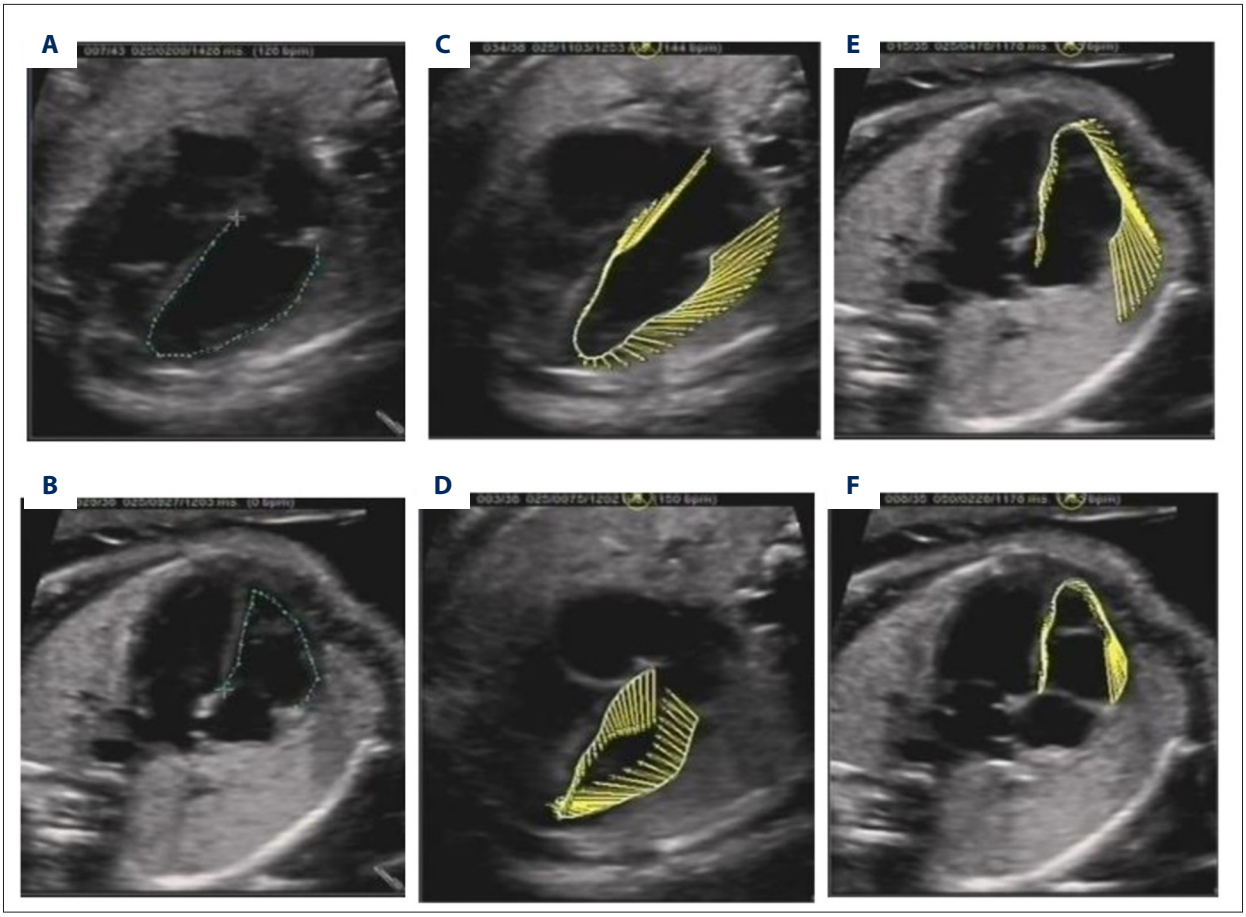


**Figure 2.** Cardiac VVI image of fetus of a pregnant woman with normal thyroid.

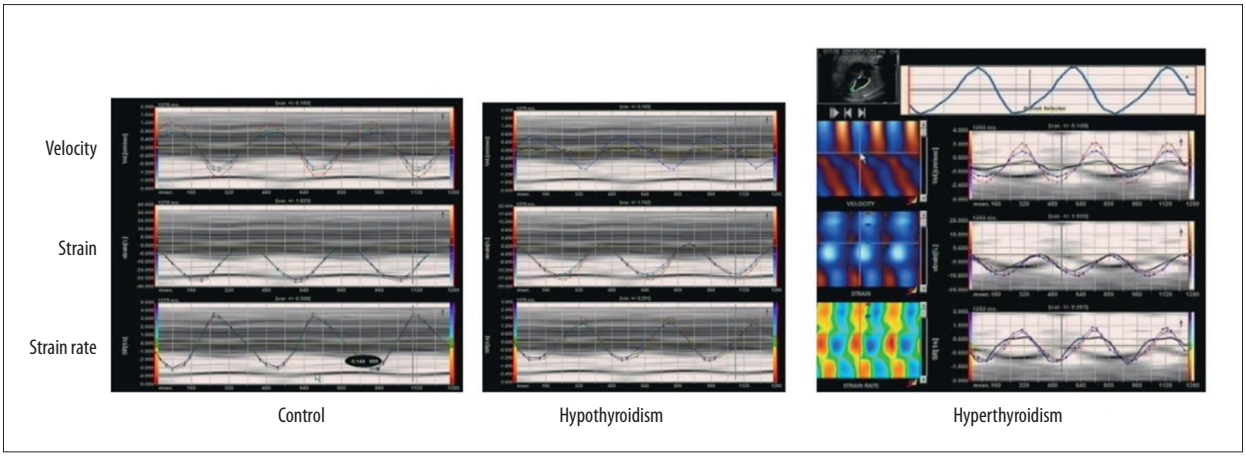


**Figure 3.** Velocity, strain, and strain rate curves in an apical 4-chamber view in the control, hypothyroidism, and hyperthyroidism groups.

of velocity of 2D myocardial motion, strain, and strain rate by calculating relative displacement within cardiac cycles. Left and right myocardial walls in fetal standard 4-chamber views were divided into the six segments, including basal, middle, and apical segments of the ventricular septum and free wall of the ventricles. All of the echocardiographic parameters, including the myocardium peak systolic velocity (Vs; cm/s), peak diastolic velocity (Vd), peak systolic strain (S; %), peak systolic strain rate (SRs; $S^{-1}$), peak diastolic strain rate (SRd) of RV and LV, were obtained from the velocity curves of 2D myocardial





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**Table 2.** Conventional ultrasonographic parameters in the control, hypothyroidism, and hyperthyroidism groups ($\bar{x}$±s).

| Group | Sub | N | LA | LV | RA | RV | IVS | LVLW | RVLW | HR |
|---|---|---|---|---|---|---|---|---|---|---|
| Control | 1 | 31 | 9.0±1.4 | 8.0±1.9 | 9.4±1.1 | 8.1±2.1 | 2.42±0.43 | 2.33±0.45 | 2.44±0.46 | 135±12.3 |
| | 2 | 38 | 10.2±1.8* | 10.0±2.1* | 10.6±1.9* | 10.2±2.5* | 2.85±0.64* | 2.65±0.57* | 2.70±0.62* | 135±9.0 |
| | 3 | 26 | 12.6±2.5* | 12.5±2.9* | 14.1±2.1* | 12.9±3.1* | 3.13±0.72* | 3.04±0.42* | 3.19±0.68* | 139±11.8 |
| | 4 | 30 | 14.4±1.9* | 14.2±2.7* | 15.7±3.1* | 14.3±3.3* | 3.55±0.53* | 3.33±0.78* | 3.48±0.49* | 140±13.6 |
| Hypo-thyroidism | 1 | 18 | 8.7±1.4 | 8.5±1.9 | 9.7±1.7 | 8.0±2.2 | 2.34±0.35 | 2.44±0.33 | 2.23±0.24 | 142±12.1 |
| | 2 | 16 | 10.3±1.8* | 11.0±2.5* | 10.0±2.7* | 10.0±2.7* | 2.61±0.45* | 2.75±0.40* | 2.67±0.52* | 135±14.3 |
| | 3 | 16 | 12.0±3.3* | 12.7±1.4* | 14.5±3.4* | 12.2±3.5* | 3.05±0.56* | 3.23±0.37* | 3.24±0.61* | 144±9.5 |
| | 4 | 14 | 14.7±2.9* | 14.7±3.1* | 16.0±4.2* | 14.7±3.7* | 3.67±0.42* | 3.48±0.40* | 3.57±0.46* | 138±6.9 |
| Hyper-thyroidism | 1 | 10 | 9.1±1.3 | 8.8±1.0 | 9.5±1.5 | 8.2±2.2 | 2.41±0.33 | 2.39±0.13 | 2.53±0.14 | 145±11.6 |
| | 2 | 7 | 10.7±1.6* | 11.2±2.7* | 10.6±2.4* | 10.4±2.0* | 2.81±0.37* | 2.68±0.29* | 2.79±0.27* | 138±8.1 |
| | 3 | 12 | 12.7±1.9* | 12.5±2.6* | 14.3±2.8* | 13.2±4.1* | 3.17±0.45* | 3.29±0.12* | 3.44±0.30* | 147±9.0 |
| | 4 | 8 | 14.8±1.7* | 15.1±3.1* | 16.4±3.6* | 14.4±2.6* | 3.54±0.39* | 3.45±0.20* | 3.62±0.26* | 144±11.9 |

LA – left atria; LV – left ven; RA – right atria; RV – right ven; IVS – ventricular septum; LVLW – left ventricular lateral wall; RVLW – right ventricular lateral wall, mm; HR – heart rate, times per minute; * $P<0.05$, compared to the parameters in the previous gestational ages.

**Table 3.** VVI parameters in the right ventricle in the control group with various maternal gestational ages ($\bar{x}$±s).

| Parameter | Sub | N | Free wall | | | Septum | | |
|---|---|---|---|---|---|---|---|---|
| | | | Basal | Middle | Apical | Basal | Middle | Apical |
| $V_s$ (cm/s) | 1 | 31 | 1.52±0.53 | 0.99±0.33* | 0.52±0.24*& | 1.55±0.42 | 0.89±0.34* | 0.51±0.20*& |
| | 2 | 38 | 1.62±0.54# | 1.22±0.42#* | 0.70±0.42#*& | 1.63±0.19# | 1.30±0.51#* | 0.59±0.33#*& |
| | 3 | 26 | 1.99±0.45# | 1.39±0.26#* | 0.81±0.52#*& | 1.80±0.39#* | 1.41±0.45#* | 0.68±0.28#*& |
| | 4 | 30 | 2.28±0.56# | 1.47±0.45#* | 0.98±0.37#*& | 2.31±0.27#* | 1.44±0.17#* | 0.86±0.17#*& |
| $V_d$ (cm/s) | 1 | 31 | –1.45±0.25 | –0.89±0.37* | –0.61±0.31*& | –1.50±0.36 | –0.79±0.54* | –0.50±0.25*& |
| | 2 | 38 | –1.76±0.57# | –1.33±0.41#* | –0.85±0.20#*& | –1.68±0.64# | –1.24±0.37#* | –0.69±0.28#*& |
| | 3 | 26 | –2.09±0.68# | –1.47±0.21#* | –0.91±0.17*& | –2.15±0.29# | –1.34±0.47#* | –0.76±0.41#*& |
| | 4 | 30 | –2.28±0.42# | –1.58±0.38#* | –1.11±0.35#*& | –2.27±0.33# | –1.51±0.16#* | –0.88±0.25#*& |
| S (%) | 1 | 31 | –22.58±4.56 | –21.56±5.29 | –21.74±5.11 | –22.89±5.18 | –21.26±4.17 | –23.88±5.03 |
| | 2 | 38 | –22.12±3.98 | –21.99±6.34 | –21.77±3.58 | –23.99±6.08 | –22.35±5.13 | –22.62±2.99 |
| | 3 | 26 | –23.05±4.29 | –22.12±4.26 | –22.53±4.17 | –22.01±3.94 | –20.58±3.17 | –23.82±3.67 |
| | 4 | 30 | –23.01±6.10 | –22.19±3.12 | –22.97±5.41 | –22.84±5.01 | –23.12±5.34 | –22.45±5.09 |
| $SR_s$ ($S^{-1}$) | 1 | 31 | –2.54±0.36 | –2.31±0.28 | –2.39±0.29 | –2.61±0.36 | –2.47±0.37 | –2.45±0.23 |
| | 2 | 38 | –2.43±0.19 | –2.47±0.31 | –2.35±0.48 | –2.56±0.37 | –2.52±0.27 | –2.59±0.34 |
| | 3 | 26 | –2.89±0.33 | –2.50±0.27 | –2.82±0.58 | –2.41±0.51 | –2.64±0.47 | –2.66±0.25 |
| | 4 | 30 | –2.48±0.29 | –2.45±0.39 | –2.90±0.47 | –2.62±0.34 | –2.76±0.51 | –2.74±0.42 |
| $SR_d$ ($S^{-1}$) | 1 | 31 | 2.19±0.37 | 2.19±0.45 | 2.23±0.26 | 2.12±0.39 | 2.27±0.35 | 2.12±0.48 |
| | 2 | 38 | 2.08±0.45 | 2.20±0.56 | 2.16±0.41 | 2.13±0.26 | 2.19±0.42 | 2.21±0.28 |
| | 3 | 26 | 2.17±0.49 | 2.24±0.27 | 2.07±0.59 | 2.19±0.25 | 2.14±0.36 | 2.31±0.42 |
| | 4 | 30 | 2.19±0.54 | 2.25±0.35 | 2.24±0.19 | 2.23±0.37 | 2.27±0.37 | 2.30±0.40 |

Sub – subgroup of gestational age; $V_s$ – peak systolic velocity; S – peak strain; $SR_s$ – peak systolic strain rate; $V_d$ – peak diastolic velocity; $SR_d$ – peak diastolic strain rate; # $P<0.05$, compared to the previous gestational age subgroups; * $P< 0.05$, compared to the basal segments; & $P<0.05$, compared to the middle segments.





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**Table 4.** VVI parameters in the left ventricle in the control group with various maternal gestational ages ($\bar{x}$±s).

| Parameter | Sub | N | Free wall | | | Septum | | |
|---|---|---|---|---|---|---|---|---|
| | | | Basal | Middle | Apical | Basal | Middle | Apical |
| $V_s$ (cm/s) | 1 | 31 | 1.32±0.53 | 0.81±0.41* | 0.48±0.18*& | 1.40±0.42 | 0.79±0.32* | 0.46±0.14*& |
| | 2 | 38 | 1.54±0.61# | 1.03±0.34#* | 0.59±0.33#*& | 1.51±0.23# | 1.10±0.44#* | 0.61±0.23#*& |
| | 3 | 26 | 1.83±0.39# | 1.23±0.45#* | 0.64±0.28#*& | 1.78±0.45# | 1.19±0.37#* | 0.59±0.31#*& |
| | 4 | 30 | 2.03±0.72# | 1.36±0.26#* | 0.77±0.21#*& | 2.14±0.57# | 1.28±0.39#* | 0.80±0.30#*& |
| $V_d$ (cm/s) | 1 | 31 | −1.29±0.45 | −0.75±0.38* | −0.43±0.16*& | −1.33±0.29 | −0.85±0.44* | −0.46±0.23*& |
| | 2 | 38 | −1.57±0.63# | −1.12±0.51#* | −0.59±0.36#*& | −1.47±0.66# | −1.20±0.47#* | −0.61±0.47#*& |
| | 3 | 26 | −1.91±0.80# | −1.23±0.60#* | −0.67±0.14#*& | −1.88±0.64# | −1.29±0.55#* | −0.68±0.30#*& |
| | 4 | 30 | −2.09±0.32# | −1.35±0.33#* | −0.73±0.25#*& | −2.11±0.41#* | −1.40±0.56#* | −0.77±0.35#*& |
| S (%) | 1 | 31 | −18.03±3.26 | −17.54±4.21 | −17.78±3.01 | −17.86±4.18 | −18.06±3.21 | −17.88±5.33 |
| | 2 | 38 | −18.29±4.02 | −18.09±5.34 | −18.23±4.27 | −18.34±5.14 | −18.01±4.23 | −18.42±4.77 |
| | 3 | 26 | −17.96±5.06 | −18.12±3.47 | −18.37±4.21 | −17.83±4.53 | −17.99±3.44 | −18.68±4.88 |
| | 4 | 30 | −18.20±4.56 | −18.33±6.12 | −18.59±4.12 | −18.03±4.12 | −18.54±6.01 | −18.03±5.69 |
| $SR_s$ ($S^{-1}$) | 1 | 31 | −1.99±0.46 | −2.09±0.38 | −2.17±0.41 | −2.04±0.56 | −2.11±0.45 | −2.31±0.58 |
| | 2 | 38 | −2.03±0.38 | −2.10±0.46 | −2.07±0.66 | −2.23±0.40 | −2.27±0.39 | −2.00±0.47 |
| | 3 | 26 | −2.10±0.41 | −2.22±0.50 | −2.41±0.27 | −2.07±0.38 | −2.17±0.44 | −2.19±0.20 |
| | 4 | 30 | −2.07±0.58 | −2.18±0.43 | −2.43±0.68 | −2.11±0.57 | −2.24±0.47 | −2.24±0.51 |
| $SR_d$ ($S^{-1}$) | 1 | 31 | 1.86±0.56 | 1.93±0.66 | 1.99±0.44 | 1.97±0.61 | 2.04±0.29 | 1.86±0.52 |
| | 2 | 38 | 1.79±0.39 | 1.85±0.45 | 1.85±0.45 | 1.85±0.47 | 1.97±0.51 | 1.97±0.38 |
| | 3 | 26 | 1.83±0.26 | 1.94±0.39 | 1.79±0.48 | 1.91±0.31 | 1.87±0.42 | 2.06±0.49 |
| | 4 | 30 | 1.80±0.51 | 1.89±0.25 | 1.96±0.46 | 1.95±0.49 | 2.10±0.39 | 2.01±0.55 |

Sub – subgroup of gestational age; $V_s$ – peak systolic velocity; S – peak strain; $SR_s$ – peak systolic strain rate; $V_d$ – peak diastolic velocity; $SR_d$ – peak diastolic strain rate; # $P<0.05$, compared to the previous gestational age subgroups; * $P< 0.05$, compared to the basal segments; & $P<0.05$, compared to the middle segments.

motion. The heart rate was measured using a virtual M-mode algorithm built into the software. Each parameter value was measured as the mean of 3 cardiac cycles. The global values of VVI parameter were measured as the means of the total values of the 6 segmental measurements in 3 cardiac cycles.

To assess the inter-observer variability for the VVI parameters, 60 cases, including 40 with healthy fetuses, 10 with maternal gestational hypothyroidism, and 10 with maternal gestational hyperthyroidism, were randomly selected and measured by a second pediatric cardiology specialist who was unaware of the previous results. To obtain the intra-observer variability, 60 cases, including 40 with healthy fetuses, 10 with maternal gestational hypothyroidism, and 10 with maternal gestational hyperthyroidism, were randomly selected from each group and measured again 2 weeks later by the same pediatric cardiology specialist.

### Statistical analysis

Statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). All data are expressed as mean ±SD. Student's t-test was used to compare 2 continuous variables. Analysis of variance was used to test differences between multiple continuous variables. Pearson's correlation coefficient test was used to compare relationships of various variables with gestational ages. P value <0.05 was considered as statistically significant.

## Results

### VVI images and conventional echocardiographic data

Figure 2 displays cardiac VVI images of fetus of pregnant woman with normal thyroid. Figure 3 shows velocity, strain, and strain rate curves in an apical 4-chamber view in the control, hypothyroidism and hyperthyroidism groups.





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**Table 5.** Global and regional VVI parameters in the both ventricles in the control, and hypothyroidism groups ($\bar{x}\pm s$).

| Parameter | Group | Free wall | | | Septum | | | Global value |
|---|---|---|---|---|---|---|---|---|
| | | Basal | Middle | Apical | Basal | Middle | Apical | |
| **Left ventricle** | | | | | | | | |
| $V_s$ | Hypo- | 1.50±0.35* | 0.95±0.27#* | 0.47±0.21#* | 1.47±0.28* | 0.91±0.42#* | 0.44±0.19#* | 0.91±0.26& |
| | Control | 1.81±0.31 | 1.29±0.54 | 0.66±0.32 | 1.84±0.41 | 1.20±0.39 | 0.70±0.50 | 1.34±0.42 |
| $V_d$ | Hypo- | −1.53±0.46* | −1.00±0.33#* | −0.44±0.12#* | −1.55±0.36* | −0.96±0.54#* | −0.49±0.28#* | −0.95±0.36& |
| | Control | −1.86±0.47 | −1.30±0.25 | −0.69±0.26 | −1.89±0.56 | −1.26±0.17 | −0.74±0.39 | −1.36±0.27 |
| S | Hypo- | −15.22±4.25* | −14.21±5.57* | −14.55±4.09** | −16.01±6.12* | −16.03±2.34* | −15.36±6.34* | −15.06±5.22& |
| | Control | −18.26±5.69 | −17.69±7.01 | −18.29±4.99 | −18.54±4.29 | −18.95±6.33 | −18.42±3.67 | −18.51±4.74 |
| $SR_s$ | Hypo- | −1.12±0.36* | −1.09±0.25* | −1.21±0.51* | −1.05±0.24* | −1.12±0.65* | −0.95±0.19* | −1.04±0.34& |
| | Control | −2.05±0.42 | −2.23±0.54 | −2.33±0.19 | −2.12±0.69 | −2.09±0.54 | −2.19±0.61 | −2.21±0.32 |
| $SR^d$ | Hypo- | 0.89±0.24** | 1.09±0.33* | 0.96±0.16** | 0.91±0.17** | 1.13±0.37* | 0.95±0.36** | 0.98±0.24& |
| | Control | 1.85±0.25 | 1.84±0.65 | 1.88±0.41 | 1.98±0.32 | 1.79±0.29 | 1.86±0.24 | 1.86±0.37 |
| **Right ventricle** | | | | | | | | |
| $V_s$ | Hypo- | 1.39±0.32* | 1.06±0.19#* | 0.56±0.22# | 1.27±0.25* | 1.05±0.28#* | 0.54±0.17#* | 1.29±0.25* |
| | Control | 1.86±0.25 | 1.36±0.29 | 0.71±0.18 | 1.89±0.46 | 1.33±0.24 | 0.76±0.35 | 1.42±0.36 |
| $V_d$ | Hypo- | −1.41±0.41* | −1.05±0.22#* | −0.58±0.14#* | −1.46±0.39* | −0.97±0.34#* | −0.54±0.27#* | −1.18±0.22* |
| | Control | −1.93±0.54 | −1.41±0.27 | −0.78±0.35 | −1.99±0.44 | −1.34±0.41 | −0.81±0.36 | −1.48±0.34 |
| S | Hypo- | −16.45±6.21* | −16.74±5.47* | −15.69±4.32* | −15.98±5.33* | −17.06±6.95* | −16.42±4.36* | −16.28±5.06* |
| | Control | −19.25±5.56 | −18.02±3.28 | −18.86±5.21 | −19.13±4.39 | −19.45±6.58 | −19.12±7.06 | −19.06±4.97 |
| $SR_s$ | Hypo- | −1.20±0.27** | −1.35±0.24** | −1.19±0.36** | −1.09±0.36** | −1.24±0.25** | −1.17±0.17** | −1.29±0.38& |
| | Control | −2.31±0.45 | −2.16±0.60 | −2.36±0.37 | −2.25±0.14 | −2.49±0.44 | −2.55±0.54 | −2.48±0.37 |
| $SR_d$ | Hypo- | 1.12±0.14** | 1.06±0.35** | 0.99±0.27** | 1.16±0.25** | 1.23±0.16** | 1.30±0.34** | 1.18±0.31& |
| | Control | 2.03±0.33 | 1.88±0.52 | 1.96±0.30 | 1.95±0.62 | 1.95±0.26 | 1.92±0.34 | 1.93±0.34 |

Hypo- – hypothyroidism group; $V_s$ – peak systolic velocity (cm/s); S – peak strain (%); $SR_s$ – peak systolic strain rate ($S^{-1}$); $V_d$ – peak diastolic velocity(cm/s); $SR_d$ – peak diastolic strain rate ($S^{-1}$); # $P<0.05$, compared to the previous segments. * $P<0.05$, ** $P<0.01$, compared to the control; & $P<0.01$, compared to the control.

In all 3 groups, atrial size, ventricular size, and ventricular wall thickness increased with the gestational ages ($P<0.05$), but there were no significant differences in heart rates between subgroups ($P>0.05$) (Table 2). In both the hypothyroidism and hyperthyroidism groups, atrial size, ventricular size, and ventricular wall thickness were not significantly different from those in the control group ($P>0.05$).

### Ventricular global and regional peak systolic strain, strain rate, and velocity in healthy fetuses

Vs and Vd of both lateral wall of the LV and left ventricular septal gradually decreased from basal segments to apical segments (Table 3). There were significant differences in Vs and Vd between different segments ($P<0.05$). No significant S, SRs, or SRd differences were observed between different segments ($P>0.05$). In the same segments, Vs and Vd increased with gestational ages. Vs and Vd showed significant differences between different gestational ages ($P<0.05$). However, No significant differences were observed in S, SRs, or SRd in various gestational ages between basal, middle, and apical segments ($P>0.05$).

Characteristics of right ventricular parameters were similar to those of right ventricular parameters (Table 4). Vs and Vd of both the RV lateral wall and right ventricular septal gradually decreased from basal segments to apical segments. There were significant differences in Vs and Vd between different segments ($P<0.05$). No significant differences were observed in S, SRs, and SRd between different segments ($P>0.05$). In the same segments, Vs and Vd increased with gestational ages. Vs and Vd revealed significant differences between different gestational ages ($P<0.05$). However, There were no significant differences in S in various gestational ages, SRs, and SRd between basal, middle, and apical segments ($P>0.05$).





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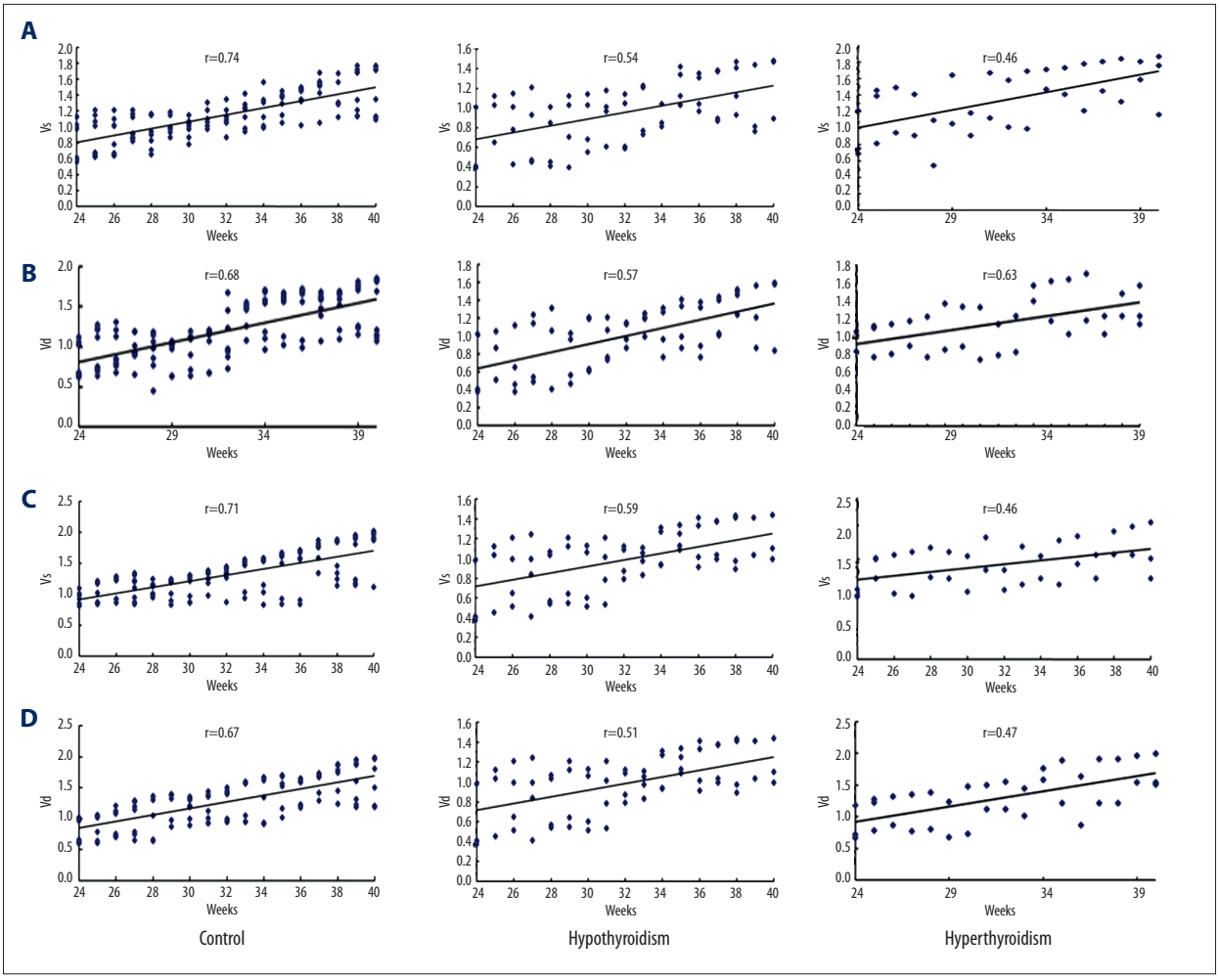


**Figure 4.** Correlation of peak velocities with maternal gestational ages in both ventricles in the control, hypothyroidism, and hyperthyroidism groups. The global Vs and Vd in RV and LV increased with the gestational ages, showing middle correlation. (**A**) Peak systolic velocity in left ventricle (cm/s); (**B**) peak diastolic velocity in left ventricle (cm/s); (**C**) peak systolic velocity in right ventricle (cm/s); (**D**) peak diastolic velocity in right ventricle (cm/s).

We compared the right ventricular parameters with the left ventricular parameters (Table 5). Vs in the basal and apical segments in free wall of RV and the middle segment of the right ventricular septum were significantly higher than those parameters in the left ventricular septum ($P<0.05$). Vd in the middle and apical segments in the RV were significantly higher than those in the left ventricular ($P<0.05$). S in the middle segments in the RV and the basal segments of the right ventricular septum were significantly higher than those in the left ventricular ($P<0.05$). SRs in the RV free wall were significantly higher than those in the left ventricular ($P<0.05$). All the global parameters in the RV were higher than in the LV ($P<0.05$).

We also analyzed the relationships of VVI parameters with the gestational ages. The global Vs and Vd in RV and LV increased with the gestational ages, showing middle correlation (Figure 4). After the middle pregnancy, the global S, global SRs, and global SRs in the RV and LV remained unchanged.

### Ventricular global and regional peak systolic strain, strain rate, and velocity in fetuses with maternal gestational hypothyroidism

Compared to the control group, VVI parameters revealed significant decreases in some LV segments in several gestational ages in the hypothyroidism group. For example, Vs was significant lower in the LV middle lateral wall in subgroup 3 and 4 when compared to the control group ($P<0.05$). Vd was significant lower in the middle and basal lateral wall in subgroups 2, 3, and 4 when compared to the control group ($P<0.05$). S was significant lower in all the 6 segments in all the gestational ages when compared to the control group ($P<0.01$ in the subgroups 1 and 2, $P<0.05$ in subgroups 3 and 4) (Table 6). SRs





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**Table 6.** VVI parameters in both ventricles in the hypothyroidism group with various maternal gestational ages ($\bar{x}$±s).

| Paramer | Sub | N | Free wall | | | Septum | | |
|---|---|---|---|---|---|---|---|---|
| | | | Basal | Middle | Apical | Basal | Middle | Apical |
| **Left ventricle** | | | | | | | | |
| $V_s$ (cm/s) | 1 | 18 | 1.07±0.42 | 0.68±0.31* | 0.33±0.14*# | 1.08±0.32 | 0.70±0.22* | 0.31±0.09*# |
| | 2 | 16 | 1.24±0.54& | 0.88±0.29&* | 0.42±0.26&*# | 1.30±0.23& | 0.85±0.33&* | 0.42±0.17&*# |
| | 3 | 16 | 1.45±0.17& | 0.99±0.51&* | 0.50±0.16&*# | 1.41±0.55& | 1.01±0.25&* | 0.51±0.24&*# |
| | 4 | 14 | 1.80±0.42& | 1.14±0.37&* | 0.69±0.30&*# | 1.95±0.27& | 1.12±0.40&* | 0.74±0.26&*# |
| $V_d$ (cm/s) | 1 | 18 | −1.01±0.41 | −0.65±0.25* | −0.29±0.13*# | −0.99±0.39 | −0.72±0.25* | −0.31±0.17*# |
| | 2 | 16 | −1.20±0.24& | −0.94±0.48&* | −0.40±0.22&*# | −1.14±0.41& | −0.84±0.19&* | −0.52±0.30&*# |
| | 3 | 16 | −1.39±0.36& | −1.01±0.54&* | −0.58±0.21&*# | −1.43±0.44& | −0.95±0.37&* | −0.59±0.26&*# |
| | 4 | 14 | −1.69±0.29& | −1.18±0.41&* | −0.77±0.18&*# | −1.81±0.39&* | −1.10±0.28&* | −0.54±0.24&*# |
| S (%) | 1 | 18 | −14.03±4.32 | −14.32±5.41 | −14.91±5.23 | −15.84±5.28 | −15.69±4.79 | −14.68±5.66 |
| | 2 | 16 | −14.54±5.69 | −15.20±6.01 | −14.63±5.62 | −14.24±6.53 | −15.07±5.47 | −15..16±7.01 |
| | 3 | 16 | −15.01±6.23 | −16.89±6.29 | −16.77±6.99 | −13.83±4.11 | −14.94±6.28 | −15.55±5.60 |
| | 4 | 14 | −16.89±3.58 | −17.17±5.89 | −15.61±6.26 | −16.43±5.17 | −14.70±5.46 | −16.73±4.21 |
| $SR_s$ ($S^{-1}$) | 1 | 18 | −1.02±0.41 | −1.23±0.45 | −0.96±0.36 | −1.12±0.42 | −1.14±0.63 | −1.33±0.62 |
| | 2 | 16 | −1.11±0.32 | −1.08±0.33 | −1.03±0.57 | −0.99±0.29 | −1.09±0.35 | −1.04±0.39 |
| | 3 | 16 | −0.84±0.45 | −1.14±0.56 | −0.97±0.38 | −1.04±0.42 | −0.92±0.37 | −0.89±0.47 |
| | 4 | 14 | −0.94±0.56 | −0.86±0.41 | −1.00±0.58 | −1.11±0.45 | −1.36±0.57 | −1.14±0.46 |
| $SR_d$ ($S_{-1}$) | 1 | 18 | 0.98±0.33 | 1.01±0.52 | 1.09±0.41 | 0.97±0.32 | 0.94±0.36 | 0.85±0.50 |
| | 2 | 16 | 0.89±0.45 | 1.12±0.44 | 1.14±0.37 | 0.95±0.46 | 0.97±0.30 | 1.07±0.43 |
| | 3 | 16 | 1.02±0.41 | 0.94±0.23 | 0.88±0.68 | 1.01±0.18 | 0.99±0.39 | 1.02±0.61 |
| | 4 | 14 | 1.14±0.26 | 1.10±0.35 | 0.96±0.57 | 0.94±0.54 | 1.10±0.63 | 1.19±0.42 |
| **Right ventricle** | | | | | | | | |
| $V_s$ (cm/s) | 1 | 18 | 1.04±0.33 | 0.61±0.19* | 0.36±0.18*# | 1.11±0.37 | 0.65±0.22* | 0.41±0.11*# |
| | 2 | 16 | 1.12±0.34& | 0.91±0.15&* | 0.51±0.18&*# | 1.24±0.27& | 1.11±0.54&* | 0.50±0.14&*# |
| | 3 | 16 | 1.46±0.16& | 1.15±0.16&* | 0.64±0.32&*# | 1.35±0.19&* | 1.29±0.17&* | 0.60±0.12&*# |
| | 4 | 14 | 1.85±0.35& | 1.33±0.29&* | 0.75±0.19&*# | 1.77±0.45&* | 1.34±0.27&* | 0.75±0.18&*# |
| $V_d$ (cm/s) | 1 | 18 | −1.02±0.15 | −0.67±0.25* | −0.41±0.27*# | −0.85±0.26 | −0.61±0.14* | −0.46±0.11*# |
| | 2 | 16 | −1.24±0.44& | −1.01±0.17&* | −0.51±0.17&*# | −1.12±0.43& | −0.84±0.25&* | −0.50±0.24&*# |
| | 3 | 16 | −1.47±0.56& | −1.17±0.35&* | −0.65±0.19&*# | −1.54±0.24& | −1.09±0.36&* | −0.67±0.37&*# |
| | 4 | 14 | −1.75±0.30& | −1.32±0.16&* | −0.89±0.25&*# | −1.85±0.16& | −1.28±0.33&* | −0.78±0.36&*# |
| S (%) | 1 | 18 | −16.35±5.62 | −16.47±4.13 | −16.58±5.02 | −16.18±5.44 | −16.87±6.03 | −16.71±6.12 |
| | 2 | 16 | −17.89±4.18 | −16.99±6.78 | −17.07±4.19 | −18.54±4.25 | −17.19±7.01 | −17.11±5.77 |
| | 3 | 16 | −15.72±4.52 | −17.13±3.69 | −15.65±8.17 | −16.01±5.14 | −18.39±4.58 | −16.35±6.74 |
| | 4 | 14 | −17.22±5.69 | −16.47±3.12 | −16.78±4.12 | −17.55±3.24 | −16.22±4.45 | −17.15±4.09 |
| $SR_s$ ($S^{-1}$) | 1 | 18 | −1.24±0.26 | −1.31±0.45 | −1.35±0.14 | −1.11±0.38 | −1.27±0.26 | −1.58±0.26 |
| | 2 | 16 | −1.33±0.25 | −1.24±0.11 | −1.22±0.38 | −1.39±0.12 | −1.02±0.17 | −1.29±0.34 |
| | 3 | 16 | −1.04±0.38 | −1.17±0.37 | −1.42±0.76 | −1.41±0.34 | −1.36±0.27 | −1.34±0.16 |
| | 4 | 14 | −1.27±0.45 | −1.27±0.21 | −1.16±0.27 | −1.07±0.16 | −1.37±0.16 | −1.10±0.39 |
| $SR_d$ ($S_{-1}$) | 1 | 18 | 1.13±0.47 | 1.34±0.35 | 1.33±0.18 | 0.97±0.48 | 1.32±0.45 | 0.99±0.52 |
| | 2 | 16 | 1.21±0.56 | 1.27±0.64 | 1.03±0.24 | 1.15±0.26 | 1.16±0.53 | 1.11±0.16 |
| | 3 | 16 | 1.17±0.35 | 1.19±0.38 | 1.10±0.47 | 1.29±0.46 | 1.34±047 | 1.30±0.22 |
| | 4 | 14 | 1.07±0.37 | 1.36±0.21 | 1.05±0.38 | 1.17±0.38 | 1.10±0.49 | 1.04±0.19 |

Sub – subgroup of gestational age; $V_s$ – peak systolic velocity; S – peak strain; $SR_s$ – peak systolic strain rate; $V_d$ – peak diastolic velocity; $SR_d$ – peak diastolic strain rate; # $P<0.05$, compared to the previous gestational age subgroups; * $P<0.05$, compared to the basal segments; & $P<0.05$, compared to the middle segments.





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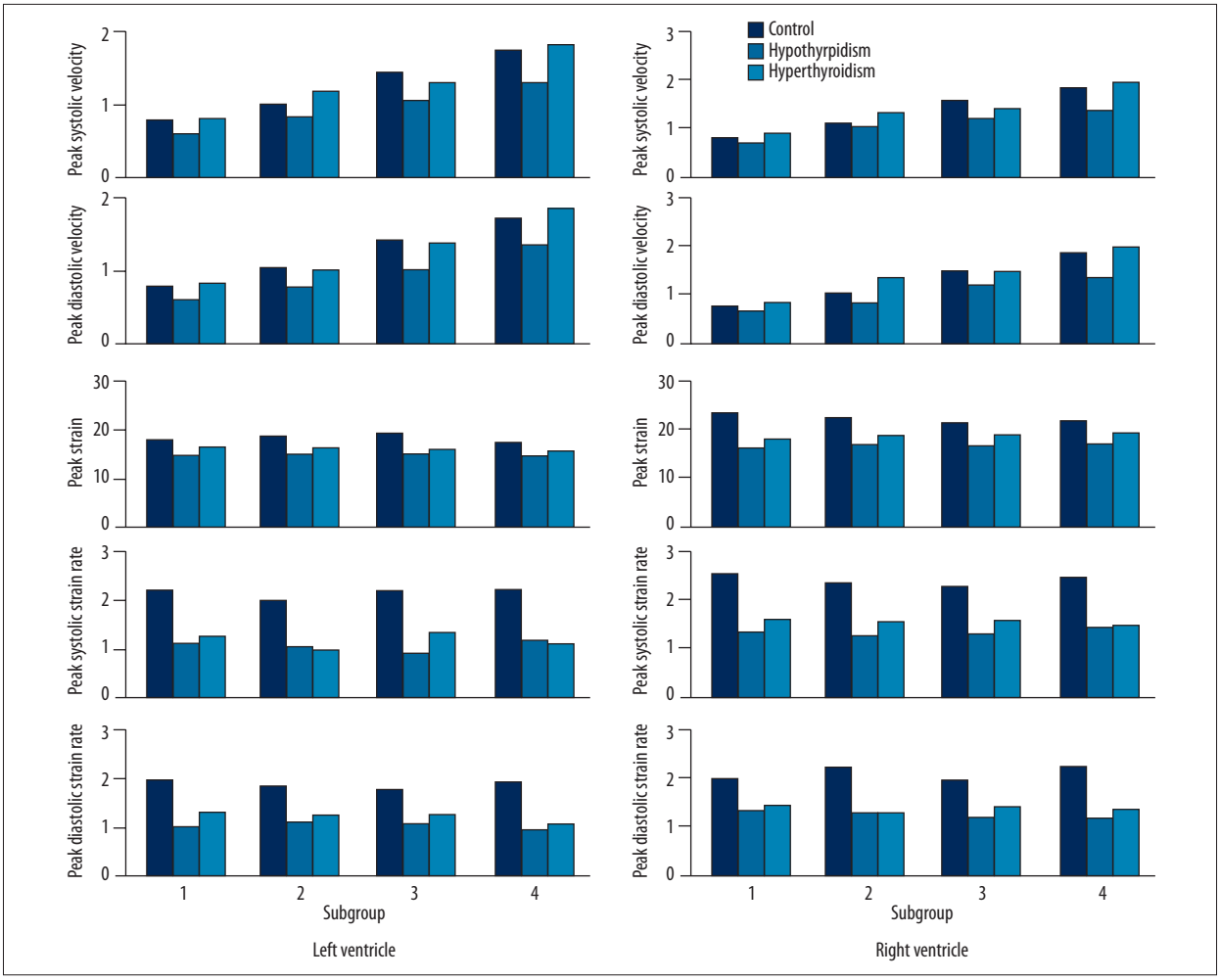


**Figure 5.** Peak velocities (cm/s), strains (%) and strain rates ($S^{-1}$) in both ventricles in the control, hypothyroidism, and hyperthyroidism groups. SRs and SRd were significantly lower in all 6 segments in all gestational ages when compared to the control group (P<0.01). The global S, the global SRs, and the global SRd revealed significant decreases in the hyperthyroidism group when compared to the control group (*P*<0.05). The study suggests the maternal gestational hypothyroidism and hyperthyroidism may have damaged fetal cardiac function.

and SRd were also significant lower in all 6 segments in all the gestational ages when compared to the control group (*P*<0.01) (Figure 5), suggesting the maternal gestational hypothyroidism may have damaged fetal cardiac function.

Similarly, VVI parameters also showed significant decreases in several LV segments in some gestational ages in the hypothyroidism group when compared to the control group. Vs was significant lower in the middle and apical free walls and the middle segments of the right ventricular septum in subgroup 3 and 4 when compared to the control group (*P*<0.05). Vd was significant lower in the middle and basal free wall and the middle segments of the right ventricular septum in subgroup 2, 3, and 4 when compared to the control group (*P*<0.05). S, SRs and SRd were significant lower in all 6 segments in all gestational ages when compared to the control group (*P*<0.01) (Figure 5).

In the hypothyroidism group, Vs and Vd gradually decreased from the basal segment to the apical segment, showing statistical significance of differences between the different segments (*P*<0.05). Except for Vs in the apical segment of the right ventricular septum, the study showed that Vs and Vd in the various segments, the global V, the global SRs, and the global SRd were significantly decreased in LV and RV in the hypothyroidism group, relative to the control group (*P* <0.05) (Figure 5).

### Ventricular global and regional peak systolic strain, strain rate, and velocity in fetuses with maternal gestational hyperthyroidism

The global Vs and global Vd were slightly higher in the hyperthyroidism group than those in the control group, but there were no statistically significant differences (*P*>0.05). The global





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**Table 7.** Global and regional VVI parameters in the both ventricles in the control and hyperthyroidism groups ($\bar{x}\pm s$).

| Sub | Group | N | Vs(cm/s) | Vd(cm/s) | S (%) | $SR_s$ ($S^{-1}$) | $SR_d$ ($S^{-1}$) |
|---|---|---|---|---|---|---|---|
| **Left ventricle** | | | | | | | |
| 1 | Hyper | 10 | 0.81±0.36$^{\#}$ | −0.84±0.21 | −16.54±3.62$^{\#*}$ | −1.26±0.16$^{\#\&}$ | 1.33±0.25$^{\&}$ |
| | Control | 31 | 0.78±0.25 | −0.82±0.36 | −18.04±5.16 | −2.21±0.43 | 1.98±0.27 |
| 2 | Hyper | 7 | 1.18±0.39$^{\#}$ | −1.02±0.19$^{\#}$ | −16.53±6.39$^{\#*}$ | −1.02±0.37$^{\#\&}$ | 1.26±0.14$^{\#\&}$ |
| | Control | 38 | 1.02±0.30 | −1.06±0.27 | −18.69±5.95 | −2.02±0.55 | 1.86±0.19 |
| 3 | Hyper | 12 | 1.39±0.16$^{\#}$ | −1.39±0.35$^{\#}$ | −16.02±2.51$^{\#\&}$ | −1.36±0.25$^{\#\&}$ | 1.25±0.34$^{\#\&}$ |
| | Control | 26 | 1.46±0.21 | −1.41±0.24 | −19.24±3.20 | −1.99±0.36 | 1.79±0.45 |
| 4 | Hyper | 8 | 1.81±0.33$^{\#}$ | −1.86±0.28$^{\#}$ | −15.54±4.42$^{\#*}$ | −1.13±0.47$^{\#\&}$ | 1.09±0.29$^{\#\&}$ |
| | Control | 30 | 1.75±0.29 | −1.73±0.16 | −17.41±6.51 | −2.44±0.26 | 1.96±0.26 |
| Global vaule | Hyper | 37 | 1.41±0.25$^{\#}$ | −1.30±0.36$^{\#}$ | −16.15±5.21$^{\#*}$ | −1.27±0.26$^{\#\&}$ | 1.32±0.34$^{\#\&}$ |
| | Control | 125 | 1.34±0.42 | −1.26±0.27 | −18.01±4.74 | −2.21±0.32 | 1.86±0.37 |
| **Right ventricle** | | | | | | | |
| 1 | Hyper | 10 | 0.90±0.19 | −0.86±0.16 | −18.24±6.21$^{\&}$ | −1.62±0.36$^{\&}$ | 1.46±0.29$^{\&}$ |
| | Control | 31 | 0.83±0.29 | −0.79±0.29 | −23.65±4.36 | −2.54±0.39 | 2.02±0.34 |
| 2 | Hyper | 7 | 1.36±0.37 | −1.36±0.32 | −18.95±5.46$^{\&}$ | −1.56±0.28$^{\&}$ | 1.33±0.22$^{\&}$ |
| | Control | 38 | 1.13±0.38 | −1.04±0.19 | −22.37±2.16 | −2.35±0.25 | 2.25±0.37 |
| 3 | Hyper | 12 | 1.43±0.22 | −1.48±0.29 | −19.26±4.39* | −1.59±0.38$^{\&}$ | 1.40±0.36$^{\&}$ |
| | Control | 26 | 1.57±0.34 | −1.52±0.20 | −21.49±5.93 | −2.29±0.61 | 1.99±0.59 |
| 4 | Hyper | 8 | 1.95±0.36 | −1.99±0.23 | −19.59±4.43* | −1.49±0.24$^{\&}$ | 1.39±0.29$^{\&}$ |
| | Control | 30 | 1.84±0.27 | −1.88±0.16 | −21.95±5.27 | −2.47±0.47 | 2.29±0.34 |
| Global value | Hyper | 37 | 1.70±0.47 | −1.75±0.28 | −19.06±6.33* | −1.56±0.29$^{\&}$ | 1.46±0.34$^{\&}$ |
| | Control | 125 | 1.61±0.36 | −1.68±0.34 | −22.36±4.97 | −2.48±0.37 | 2.17±0.34 |

Hypo- – hypothyroidism group; $V_s$ – peak systolic velocity; S – peak strain; $SR_s$ – peak systolic strain rate; $V_d$ – peak diastolic velocity; $SR_d$ – peak diastolic strain rate; $^{\#}$ $P<0.05$, compared to the right; * $P<0.05$, compared to the control; $^{\&}$ $P<0.01$, compared to the control.

S, the global SRs, and the global SRd revealed significant decreases in the hyperthyroidism group when compared to the control group ($P<0.05$) (Table 7, Figure 5).

### Reproducibility of VVI data

There were no significant mean differences between paired measurements by the same pediatric cardiology specialist, including all the regional and global parameters in all 3 groups. The values in paired measurements by 2 different pediatric cardiology specialists were not significant ($P>0.05$).

## Discussion

It remains unknown whether maternal gestational thyroid dysfunction will damage fetal cardiac function, partly because functional assessment of the fetal heart is challenging. VVI permits angle-independent measurements and is robust to maternal breath and fetus motion. Since the pioneering work by Younoszai et al., who first applied VVI to study myocardial mechanics in the normal fetal heart [20], several reports have demonstrated the feasibility of VVI in the functional evaluation of fetus [21,23–25,28–31]. However, there are limited data available for establishing reference values used to assess fetal cardiac function. In this study, we used this novel technology and analyzed cardiac function of fetuses of Chinese pregnant women with and without thyroid dysfunction. We found that the longitudinal Vs and Vd of both ventricles in the control group gradually decreased from basal segments to apical segments, but significantly increased over the gestation. S, SRs, and SRd of both ventricles remained stable after middle gestation. These results are in accordance with the reports by Younoszai et al. [20], but different from the studies by Paladini et al. [32] and Harada et al. [33].

Compared with the control group, the hypothyroidism and hyperthyroidism groups exhibited significantly reduced S, SRs,





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and SRd, even for fetuses at 24-weeks gestation. The hypothyroidism in the pregnant women may have exerted harmful influences on early development of fetal heart [34,35]. It is worth noting that there were no significant differences in global Vs and global Vd between the control group and the hyperthyroidism or hypothyroidism groups. These results demonstrate that S and SR are more sensitive parameters than cardiac velocity.

Interestingly, conventional echocardiographic parameters remained within normal ranges. Our findings demonstrate that thyroid dysfunction in pregnant women may impair the fetal cardiac function. VVI could be a sensitive technique to assess global and regional cardiac function of fetus. The specificity and sensitivity of global strain and global strain rate were better than Vs and Vd. To the best of our knowledge, this is the first application of VVI used to quantify global and regional function of fetus with maternal gestational thyroid dysfunction.

Early discovery of cardiac abnormality in the fetuses of pregnant women with gestational thyroid dysfunction has important clinical significances, because thyroid replacement therapy can efficiently treat fetal cardiac abnormality caused by thyroid dysfunction in pregnant women [14]. Unfortunately, this study did not observe whether correction of maternal thyroid dysfunction would reverse the fetal cardiac VVI parameter variations. In addition, the study did not analyze the quantitative relationship between fetal cardiac parameters and maternal thyroid dysfunction nor the relationship between the fetal cardiac pathologic changes and functional changes. All these are important limitations of this study. In the future we intend to further explore whether VVI can be used to monitor the changes of cardiac function of fetus of pregnant women with gestational thyroid dysfunction who receive thyroid replacement therapy.

## Conclusions

Thyroid dysfunction in pregnant women may impair the fetal cardiac function. Global strain and global strain rate may be useful parameters to quantitate fetal cardiac function.

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