

Original Article

Physiological adaptation of the left ventricle during the second and third trimesters of a healthy pregnancy: a speckle tracking echocardiography study

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Abstract: Background: During a healthy pregnancy women experience cardiovascular and hemodynamic changes and normal ranges of left ventricular (LV) function on two-dimensional speckle tracking echocardiography (STE) are not well defined. The aim of this study was to describe the cardiovascular changes that occur during the second and third trimesters of a healthy pregnancy using STE. Methods: Pregnant subjects were enrolled retrospectively if they underwent a transthoracic echocardiography (TTE) between 2011-2014. Subjects with abnormal TTE findings, hypertension, diabetes, preeclampsia, prior cardiac surgery, poor imaging quality or in the 1st trimester were excluded. A total of 74 pregnant subjects were categorized into the 2nd or 3rd trimesters. Twenty-one healthy age-matched females were selected as a control group. Results: The heart undergoes extensive remodeling during pregnancy with increased LV septal thickness, posterior wall thickness, cavity size and mass ($p=0.045$, $p=0.002$, $p<0.001$, $p=0.018$, respectively). However, myocardial mechanical function measured by: global longitudinal strain, radial strain, circumferential strain, systolic and diastolic global longitudinal strain rate (GLSR), global radial strain rate (GRSR) and global circumferential strain rate, remains preserved. Only time to peak strain rate corrected for heart rate for diastolic GRSR and diastolic GLSR were significantly increased in the third trimester ($p=0.016$ for both). Conclusion: Despite extensive heart remodeling, many STE derived parameters of LV function in healthy pregnant women remain unchanged and valid for women in the 2nd and 3rd trimester. Future studies investigating early detection of pregnancy related heart disease can refer to these parameters as reference ranges.

Keywords: Two-dimensional speckle tracking echocardiography, strain, pregnancy

Introduction

The cardiovascular system of women during pregnancy undergoes a unique set of physiological changes. There is a decrease in systemic vascular resistance leading to a decrease in left ventricular (LV) hemodynamic afterload, and an increase in blood volume leading to an increase in venous preload [1, 2]. These hemodynamic changes are accompanied by cardiac remodeling including: an increase in LV wall thickness, an increase in LV cavity size and an increase in LV mass [3, 4]. However, LV systolic and diastolic strain function remains poorly characterized during a normal pregnancy [3]. Two-dimensional speckle track-

ing echocardiography (STE) allows for in-depth quantification of global and regional LV mechanical function and reference values for healthy non-pregnant individuals have been reported [5-8]. Yet for women during a healthy pregnancy, previous studies have reported conflicting unchanged or decreased systolic strain function [9, 10]. Establishing reference values for systolic and diastolic strain function during a healthy pregnancy is critical for the evaluation of pregnancy-related heart disease. Therefore this study was undertaken to explore the strain function of the LV in healthy pregnant women and define normal reference values for the second and third trimesters.

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Table 1. Population demographics and comorbidities

Variables	A) Female controls	B) Second trimester	C) Third trimester	p value
Demographics				
N	21	37	37	
Age (years)	30±6	29±6	29±6	0.556
Gestational week (week)	-	21±6	33±4	
BSA (m ²)	1.76±0.17	1.80±0.20	1.84±0.16	0.162
BMI (kg/m ²)	27±6	29±7	31±7	0.152
Mean daytime SBP (mmHg)	115±11	108±11	110±15	0.150
Mean daytime DBP (mmHg)	72±10 ^{bb,cc}	64±9 ^{aa}	64±9 ^{aa}	0.003
Mean daytime PP (mmHg)	44±9	44±8	48±9	0.107
Twin pregnancy	-	4 (11)	2(5)	0.674
C-section	-	8 (22)	13 (35)	<0.001
Comorbidities, n (%)				
Hyperlipidemia	0	2 (5)	1 (3)	0.522
Gestational diabetes mellitus	0	0	2 (4)	0.562
BSA: Body surface area, BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, PP: Pulse pressure.				
Key	p<0.05	p≤0.01	p≤0.001	
a- vs Controls	a	aa	aaa	
b- vs 2 nd Trimester	b	bb	bbb	
c- vs 3 rd Trimester	c	cc	ccc	

Methods

Study design and patient population

In this retrospective cohort study pregnant subjects who were referred for transthoracic echocardiography (TTE) were identified using Montefiore Medical Center's echocardiography database between April 2011 and May 2014. Healthy pregnancy was defined as pregnant women without pre-eclampsia, seizure disorder, hypertension, non-gestational diabetes and renal disease. Subjects with suboptimal imaging quality for STE, a history of hypertension, non-gestational diabetes, sickle cell disease, pre-eclampsia, in first trimester or have abnormal findings on TTE were excluded. Abnormal TTE was defined as: 1) dilation of at least one of the 4 cardiac chambers beyond normal reference dimension [11] 2) LV ejection fraction (LVEF) <55% or right ventricular dilation or hypokinesis, 3) moderate or worse valvular disease, 4) presence of a pathological (more than small amount) pericardial effusion, 5) corrected or uncorrected cyanotic or non-cyanotic congenital heart disease, 6) presence of diastolic dysfunction. First, second and third trimester were defined as 1-12 weeks, 13-26 weeks and 27-42 weeks, respectively.

Twenty-one age-matched, non-pregnant female subjects without history of hypertension, diabetes, hyperlipidemia, smoking or other comorbidities were selected as a healthy control population. All medical information was retrospectively obtained through electronic medical record system. The Montefiore Medical Center and Albert Einstein College of Medicine Institutional Review Board approved the study.

Transthoracic echocardiography

All subjects underwent standard TTE (Philips IE-33, Philips Medical, Andover, MA). All images were recorded according to the American Society of

Echocardiography guidelines [12]. Parasternal long axis, short axis and 2, 3 and 4-chamber apical views were recorded with the patient at left lateral position. LV systolic and diastolic diameter, inter-ventricular septal thickness and posterior wall thickness were measured at the parasternal long axis view. Doppler images were used to measure mitral inflow deceleration time (DT) and E/A at appropriate views. Tissue Doppler imaging was used to measure E/e'. LV mass was calculated using the Devereux formula [13]. Relative wall thickness (RWT) was calculated as 2 x (LV posterior wall thickness/LV end-diastolic diameter). It was considered increased when it was RWT >0.42 [11]. Pulmonary artery pressure was obtained by adding the central venous pressure to 4 x (maximum velocity of tricuspid regurgitation)² [14]. Augmentation index was calculated as stroke volume index/pulse pressure [15]. All images were digitally stored to Xcelera R3.1L1 workstations (Philips, Andover, MA) and all measurements were performed by physician echocardiographers.

Speckle tracking echocardiography

Offline analysis was performed with Syngo Velocity Vector Imaging software version 3.5

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Table 2. Echocardiographic measurements

Variables	A) Female controls	B) Second trimester	C) Third trimester	p value
Dimensions				
Interventricular septum (cm)	0.77±0.12 ^c	0.81±0.10	0.84±0.11 ^a	0.045
Posterior wall thickness (cm)	0.75±0.14 ^c	0.82±0.10	0.86±0.10 ^a	0.002
LV Dimension, diastole (cm)	4.5±0.3	4.8±0.4	4.7±0.4	0.05
LV Dimension, systole (cm)	2.8±0.3 ^{bb,c}	3.2±0.3 ^{aaa}	3.0±0.4 ^a	<0.001
DT (sec)	0.20±0.03	0.20±0.04	0.21±0.04	0.706
LV Mass index (g/m ²)	63±12 ^{b,c}	71±9 ^a	72±14 ^a	0.018
Relative wall thickness	0.34±0.07	0.35±0.07	0.37±0.05	0.145
LVEF (%)	62±3	62±4	63±4	0.302
Volumes				
LA Volume (ml)	36±7 ^{bb,c}	44±14 ^{aa}	44±13 ^a	0.006
LAVI (LAV/BSA, ml/m ²)	20±4 ^{bb,c}	25±6 ^{aa}	24±7 ^a	0.010
Doppler				
RSVP (mmHg)	28±5	30±5	30±5	0.573
E/A	1.7±0.5	1.7±0.5	1.5±0.4	0.706
E/e'	5.4±1.4	5.6±1.4	6.1±2.3	0.323
Arterial impedance				
SVR (dynessec·cm ⁻⁵)	1690±520 ^{bbb,ccc}	1294±303 ^{aaa}	1152±351 ^{aaa}	P<0.001
AI (%)	54±24	55±15	47±19	0.176
LV: Left ventricular, DT: deceleration time, LVEF: Left ventricle ejection fraction, LA: Left atrium, RVSP: Right ventricular systolic pressure, LAVI: Left atrium volume index, SVR: Systemic vascular resistance, AI: Augmentation index.				
Key	p<0.05	p≤0.01	p≤0.001	
a- vs Controls	a	aa	aaa	
b- vs 2 nd Trimester	b	bb	bbb	
c- vs 3 rd Trimester	c	cc	ccc	

(Siemens Healthcare, Erlangen, Germany). Strain analysis for pregnant and non-pregnant subjects was performed by two blinded observers. The endocardium of the LV was manually traced at the end-diastolic phase using simultaneous electrocardiography monitoring. Tracing of the epicardium was automatically performed by the software and was manually corrected when appropriate to maximize tracking accuracy. STE was deemed sufficient when all 6 segments were considered to be adequate in apical and parasternal views.

Global radial strain (GRS) and strain rate (GRSR), global circumferential strain (GCS) and strain rate (GCSR) were calculated from the six segments of the parasternal short axis view at the papillary muscle level. Global longitudinal strain (GLS) and strain rate (GLSR) were calculated from the 18 segments of the 2, 3 and 4-chamber apical views. Time to peak (TTP) values were recorded for each strain measurement. STE analysis was performed with imaging

stored in digital imaging and communications in medicine (DICOM) format at 30 frames/sec.

Statistical analysis

All continuous variables are reported as mean ± standard deviation. All categorical variables are reported as a number (percentage). Comparison of categorical variables was performed using the Chi-squared and if significant difference was detected, then the two-tailed Fischer exact test was used in post-hoc analysis. All continuous variables were confirmed to be normally distributed using the Shapiro-Wilk test. Comparison of continuous variables was performed using the ANOVA test; and if significant difference was detected, then a two-tailed Tukey test was used in post-hoc analysis. A *p*-value <0.05 was considered significant. Intraclass correlation coefficients (ICC) were calculated to assess intra-observer and inter-observer variability of the strain measurements GLS, GLSR, GCS, GCSR, GRS and GRSR by per-

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Table 3. Comparison of strain based on trimester

Variable	A) Female Controls	B) Second Trimester	C) Third Trimester	p value
Longitudinal Strain				
Basal Strain (%)	-18.4±3.4	-18.3±3.6	-18.2±4.8	0.983
Medial Strain (%)	-18.7±3.7	-18.4±3.7	-18.0±3.7	0.756
Apical Strain (%)	-24.0±4.2	-23.1±4.8	-23.6±4.2	0.750
GLS (%)	-20.3±3.4	-19.9±3.2	-19.9±3.4	0.884
GLS TTP/HR	0.35±0.05	0.35±0.5	0.37±0.04	0.489
GLSR- systolic (1/s)	-1.31±0.24	-1.25±0.21	-1.31±0.24	0.512
GLSR TTP/HR- systolic	0.23±0.04	0.22±0.04	0.24±0.12	0.619
GLSR- diastolic (1/s)	1.48±0.34	1.46±0.29	1.49±0.30	0.941
GLSR TTP/HR- diastolic	0.56±0.08	0.56±0.08 ^c	0.61±0.07 ^b	0.016
Circumferential Strain				
GCS (%)	-28.5±6.6	-25.3±5.2	-25.7±4.3	0.070
GCS TTP/HR	0.40±0.07	0.41±0.06	0.41±0.07	0.746
GCSR- systolic (1/s)	-2.00±0.46	-1.76±0.41	-1.88±0.41	0.114
GCSR TTP/HR- systolic	0.22±0.04	0.23±0.04	0.23±0.04	0.773
GCSR- diastolic (1/s)	2.18±0.63	1.93±0.53	1.98±0.54	0.234
GCSR TTP/HR- diastolic	0.55±0.09	0.56±0.08	0.59±0.08	0.157
Radial Strain				
GRS (%)	28.7±11.7	25.8±7.6	26.4±8.5	0.492
GRS TTP/HR	0.39±0.08	0.40±0.06	0.41±0.07	0.620
GRSR- systolic (1/s)	1.45±0.44	1.35±0.51	1.35±0.41	0.631
GRSR TTP/HR- systolic	0.19±0.05	0.20±0.06	0.18±0.06	0.460
GRSR- diastolic (1/s)	-1.53±0.56	-1.46±0.45	-1.48±0.63	0.876
GRSR TTP/HR- diastolic	0.54±0.09 ^c	0.58±0.09	0.62±0.10 ^a	0.016
GLS: Global longitudinal strain, GLSR: Global longitudinal strain rate, TTP: Time to peak, HR: Heart rate, GCS: Global circumferential strain, GCSR: Global circumferential strain rate, GRS: Global radial strain, GRSR: Global radial strain rate.				
Key	p<0.05	p≤0.01	p≤0.001	
a- vs Controls	a	aa	aaa	
b- vs 2 nd Trimester	b	bb	bbb	
c- vs 3 rd Trimester	c	cc	ccc	

forming duplicate strain analysis on ten randomly selected patients. Statistical analysis was performed using SPSS Ver. 19 (IBM, Chicago, IL).

Results

Patient characteristics

222 pregnant subjects who were referred for TTE were identified during the study period. Of this population, 115 patients were excluded for abnormal TTE results, 10 for suboptimal STE imaging, 4 for hypertension, 1 for type 1 diabetes, 1 for sickle cell disease, 2 for pre-eclampsia, 6 for being in the first trimester and 9 for missing relevant clinical information, therefore leaving 74 normal pregnant patients for analy-

sis. Twenty-one non-pregnant women without comorbidities were selected as an age-matched control group from the same time period.

The 74 pregnant subjects had a mean age of 29±6 years, a mean body mass index (BMI) of 30±6.9 kg/m², a mean body surface area (BSA) of 1.82±0.18 m² and were in a mean gestational week of 26 weeks. Thirty-seven patients were in the second trimester and 37 patients were in the third trimester. There were no statistical differences between pregnant and control groups regarding age, BSA, BMI, heart rate (HR) or pulse pressure (**Table 1**). Pregnant subjects did have a significantly lower mean diastolic blood pressure compared to controls (p=0.03).

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Table 4. Intraclass correlation coefficients

Variables	Intra-observer ICC	Inter-observer ICC
GLS (%)	0.948	0.819
GLS TTP/HR	0.665	0.665
GLSR-systolic (1/s)	0.849	0.857
GLSR TTP/HR- systolic	0.849	0.857
GLSR- diastolic (1/s)	0.706	0.828
GLSR TTP/HR- diastolic	0.969	0.950
GRS (%)	0.801	0.807
GRS TTP/HR	0.842	0.892
GRSR- systolic (1/s)	0.885	0.372
GRSR TTP/HR- systolic	0.518	0.390
GRSR- diastolic (1/s)	0.908	0.792
GRSR TTP/HR- diastolic	0.822	0.907
GCS (%)	0.958	0.743
GCS TTP/HR	0.899	0.873
GCSR- systolic (1/s)	0.965	0.381
GRSR TTP/HR- systolic	0.715	0.423
GCSR- diastolic (1/s)	0.690	0.830
GCSR TTP/HR- diastolic	0.912	0.952

Cardiac remodeling

Pregnant subjects were found to have significantly increased interventricular septal thickness ($p=0.002$), significantly increased posterior wall thickness ($p<0.001$), significantly increased LV mass index ($p=0.018$) and significantly increased left atrial volume ($p=0.006$) as compared to non-pregnant controls (**Table 2**). No significant difference was detected in dimensional measurements between the second and third trimester patient groups.

Systolic and diastolic mechanical function on strain analysis

Table 3 summarizes the results of STE-derived values for systolic and diastolic mechanical function. Overall, pregnant women in both trimesters had preserved cardiac function similar to non-pregnant healthy controls. GRS, GCS, GLS, systolic and early diastolic GRSR, GCSR and GLSR were unchanged from the control group. Early diastolic GLSR time to peak (TTP) corrected for HR (GLSR TTP/HR) was found to be increased in pregnant women in the third trimester compared to controls or the second trimester patients (0.56 ± 0.08 vs 0.61 ± 0.07 , respectively, $p=0.016$). Diastolic GRSR TTP cor-

rected for HR (GRSR TTP/HR) was also significantly increased in the third trimester compared to controls (0.54 ± 0.09 vs 0.62 ± 0.10 , respectively, $p=0.016$).

Inter-observer analysis

Inter and intra-observer analysis evaluated by ICC generally showed good correlation (**Table 4**). Systolic GRSR TTP/HR for both inter and intra ICC showed fair correlation ($ICC<0.7$ for all). Diastolic GCSR intra-observer correlation and systolic GRSR TTP/HR inter-observer correlation showed poor agreement ($ICC=0.690$ and $ICC=0.423$, respectively).

Discussion

In this study, we made three important clinical observations: first, the heart undergoes extensive remodeling during the second and third trimester of pregnancy. Second, despite this remodeling, cardiac systolic and diastolic mechanical function remains preserved. Third, an increase in GLSR and GRSR TTP/HR was detected and may reflect an adaptation mechanism not yet reported. Previous studies have mainly focused on systolic strain, our study has extended our knowledge to diastolic strain properties of myocardial adaptation in healthy pregnant subjects. Furthermore, we categorized the subjects based on real-world gestational week many previous studies did not do, making our results more applicable to daily practice.

Remodeling and mechanical function during healthy pregnancy

We detected remodeling of the left ventricle, expressed as an increase in septal and wall thickness, cavity size and mass, which was consistent with previous reports (3, 4). It is thought that this remodeling is due to the increase in preload received by the heart from the increase in blood volume that occurs with pregnancy [1, 2]. Regarding the STE derived parameters, past studies have shown a decrease in systolic-GLS and systolic-GLSR in the third trimester [9, 10]. However, the present study did not detect this change. This discrepancy is possibly a result of different inclusion criteria. We included patients in the second

and third trimesters, while the aforementioned study included patients only in weeks 32-36 of pregnancy. On post-hoc analysis of the present study we compared strain variables between patients in 32-42 weeks of pregnancy to non-pregnant controls. Only GLSR TTP/HR-diastolic and GRSR TTP/HR-diastolic were found to be significantly prolonged. Jianwen et al. demonstrated that early mitral diastolic velocity/strain rate ratio during the isovolumetric relaxation period is strongly dependent on left ventricular relaxation and can be used to assess diastolic function [16]. Koliass et al. recently reported that patients with diastolic dysfunction had significantly lower longitudinal and circumferential diastolic strain rate [17]. In addition, they found that global longitudinal strain was a sensitive parameter that was able to distinguish patients with diastolic dysfunction [17]. In our study, pregnant subjects did not have significantly decreased diastolic GLSR or GCSR and therefore were considered to not have diastolic dysfunction based on STE analysis. This is consistent with TTE data that there was no difference in E/A and E/e' between study subjects and healthy controls. Prolongation of early diastolic GLSR and GRSR TTP/HR is considered to reflect increased left ventricle filling time and may simply reflect the increase in preload that occurs in healthy pregnancy. Diastolic function during pregnancy has been reported in the past with mixed results [10, 18, 19].

Utility of speckle-tracking echocardiography in pregnancy

There are several opportunities where STE could be utilized in evaluating cardiac conditions during pregnancy. Peripartum cardiomyopathy is a rare but potentially devastating non-ischemic cardiomyopathy of unknown etiology. It mainly occurs in the last month of pregnancy to within six months postpartum [20]. Pre-eclampsia is characterized by increased blood pressure after 20 weeks of gestation and its pathophysiology is considered mainly as endothelium dysfunction [21]. Shahul et al. reported a decrease in GLS, GCS and GRS in women with pre-eclampsia compared with normal healthy women [22]. The role of STE in these pathologic cardiovascular conditions is expected to be further investigated in the future once reliable reference ranges have been established.

Limitations

There are several limitations in our study that need to be mentioned. First, this is a retrospective study that enrolled pregnant subjects who were referred for TTE for clinical indications and therefore does not totally represent healthy pregnant women. However, we have excluded subjects with abnormal findings on TTE with strict protocol and subjects with other comorbidities that would influence the STE derived values. Second, first trimester pregnant data were excluded because of a small sample size and were not explored in our study. However, the most profound cardiovascular changes during pregnancy occur during the second and third trimester and little change is seen in the first trimester. Third, the TTE data in each trimester was not serially obtained from the same subjects that may limit the power of this study. Some STE parameters had sub-optimal ICCs values in inter-observer analysis and so those parameters should be interpreted with caution.

Conclusion

Our study showed that despite extensive left ventricular remodeling, mechanical strain function remained unchanged in women in the second and third trimester of a healthy pregnancy. Therefore it is valid to use the same normal STE parameters defined in non-pregnant women when studying pregnant women. Future studies using strain parameters to evaluate heart disease in pregnant women can now be performed and are warranted.

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Disclosure of conflict of interest

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