Left Ventricular Torsional Mechanics in Uncomplicated Pregnancy

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ABSTRACT

Background: Alterations in left ventricular (LV) twist (torsion) and untwist have been described for a variety of physiologic and pathologic conditions. Little information is available regarding changes in these parameters during normal pregnancy.

Hypothesis: Pregnancy is associated with significant changes in LV torsional mechanics.

Methods: Left ventricular twist and untwist was measured in 32 pregnant females (mean gestation 199 ± 48 d) and 23 nonpregnant controls using speckle-tracking echocardiography.

Results: Left ventricular ejection fraction ($68 \pm 5\%$ vs $66 \pm 5\%$) was similar between the groups (P not significant). There was a significant increase in peak LV twist from nonpregnant controls (9.4 ± 3.7 degrees) to second-trimester (12.0 ± 4.2 degrees) and third-trimester subjects (12.6 ± 5.9 degrees, all $P < 0.05$). Peak LV twist velocity was also increased in second- and third-trimester groups compared with controls (94 ± 24 degrees/sec and 93 ± 30 vs 64 ± 21 degrees/sec, respectively, both $P < 0.05$). Both peak untwist velocity and time to peak untwist velocity were not significantly different between groups (P not significant). Multiple regression analysis indicate that only systolic blood pressure ($r = 0.394$, $P = 0.005$) was an independent predictor for increased LV torsion.

Conclusions: There are significant changes in LV torsional indices during the course of pregnancy, whereas untwist parameters remain unchanged. Blood pressure is independently associated with increased torsion during pregnancy.

Introduction

Pregnancy is associated with reversible adaptations in maternal systolic and diastolic left ventricular (LV) function.^{1,2} Prior studies have shown increased preload and cardiac output,^{3–5} decreased systemic vascular resistance,^{2,6} and increased LV mass and wall thickness⁷ during pregnancy. Changes in LV fractional shortening are less well-defined, with the literature offering conflicting data.^{8–10} Little information is available concerning alterations in LV torsion (LV_{Tor}), the helical twisting motion of the LV about its longitudinal long axis.¹¹

Speckle-tracking echocardiography (STE) is a noninvasive method that allows for rapid, objective quantification of LV_{Tor} .¹² Numerous studies have demonstrated that STE can accurately quantify differences in LV_{Tor} associated with various pathophysiologic conditions.^{13–16} We used STE to measure LV_{Tor} in healthy pregnant women and nonpregnant controls.

Methods

Study subjects consisted of consecutive female patients referred for 2-dimensional (2D) transthoracic echocardiogram for the evaluation of heart murmur between July 2007 and July 2008. Pertinent clinical history and laboratory data were obtained via medical-record review. Patients with hypertension, diabetes, arrhythmias, cardiomyopathies, valvular disease including moderate or severe valvular regurgitation, high-risk pregnancies, severe pulmonary or systemic disease, and suboptimal echocardiographic images were excluded, leaving 55 subjects for analysis. Pregnant patients were healthy women with a singleton pregnancy (mean age, 25 ± 5 y) referred by the Bronx-Lebanon Hospital Center Prenatal Care Clinic. The control group comprised 23 nonpregnant females (mean age, 28 ± 6 y, P not significant), with subsequent medical-record review demonstrating that none were pregnant at the time of echocardiography. The protocol was approved by the Bronx-Lebanon Hospital Center Institutional Review Board.

The authors have no funding, financial relationships, or conflicts of interest to disclose.

Echocardiography Protocol

Standard 2D echocardiographic examination was performed using a commercially available ultrasound machine with a 2.5-MHz phased array probe (M3S probe, Vivid 7; GE Vingmed, Horten, Norway). Parasternal long-axis views were used to obtain LV end-systolic and end-diastolic dimensions, ventricular septal and posterior wall thicknesses, outflow tract diameter, and fractional shortening.^{17,18} Doppler examination included interrogation of the LV outflow tract, mitral leaflet tip inflow, and septal and lateral wall tissue velocities. Left ventricular ejection fraction was calculated using Simpson's method. Left ventricular mass was calculated using a necropsy-validated formula.¹⁹

Digital grayscale 2D cine loops from 3 consecutive beats were obtained from short-axis views at depths of approximately 16 cm. Short-axis recordings were obtained with transducer frequencies (1.7–2.0 MHz), sampling rates (86–115 frames per second), sector widths (as narrow as possible), and gain settings adjusted to optimize endocardial definition and speckle quality. The proper basal and apical levels were determined utilizing previously published criteria.²⁰ Offline analysis was performed on the digitally stored images using customized software on a personal computer workstation (EchoPAC; GE Vingmed, Noblesville, IN). All measurements of LV function and twist mechanics were made in a blinded fashion to exclude operator bias.

The images were analyzed for the frame-by-frame movement of speckles, natural acoustic markers formed by structures smaller than the wavelength of ultrasound.²¹ The endocardium was traced manually by a point-and-click method to generate a region of interest encompassing the entire myocardial cross-section, which could be manually adjusted as needed. The automated software then calculated the rotation and rotational velocities of the region of interest.^{22,23} The motion of the apex and base are conventionally described from an apex-to-base view down the longitudinal axis of the LV, with clockwise rotations measured in negative degrees and counterclockwise rotations measured in positive degrees (Figure 1). Left ventricular torsion is the sum of maximal instantaneous basal-to-apex angle difference, expressed in degrees. Normalized torsion (Tor_{Norm}) is defined as torsion corrected for LV length (degrees/cm). Left ventricular length was measured from the apical 4-chamber view. The duration of systole was obtained from pulsed-wave Doppler of the LV outflow tract, and measured from the peak electrocardiographic R wave. Time sequences were normalized to the percent of systole duration (ie, $t = 100\%$ at end systole).

Hemodynamic Data

Heart rate (HR) and blood pressure (BP) were recorded at the time of echocardiography. Stroke volume was Doppler-derived.²⁴ Cardiac output (L/min) was calculated as the product of stroke volume and HR. Systemic vascular resistance ($\text{dynes} \cdot \text{s} \cdot \text{cm}^{-5}$) was calculated as the ratio between cardiac output and the mean arterial pressure. Hematocrit (%) data were considered acceptable if measured within 3 weeks of the date of echocardiogram. Whole blood volume was calculated using a formula based on gender, height, weight, and deviation from ideal weight.²⁵

Figure 1. Schematic illustration of LV torsion. α = apical rotation, measured in degrees. β = basal rotation. Torsion = $\alpha + \beta$. h = distance between the basal and apical planes. The dotted rectangle indicates the original position of the apex and base in relation to the LV centroid. The arrows indicate the direction of rotation during systole. Abbreviations: LV, left ventricular.

Statistical Analysis

Data analysis was performed using SAS version 9.2 (SAS Institute Inc., Cary, NC). Clinical and echocardiographic data are presented as mean $\pm$ SD. A 2-tailed P value of <0.05 was deemed statistically significant. Differences between pregnant and nonpregnant subjects were assessed using Student t test for continuous variables; the χ^2 statistic was used to assess differences in categorical variables. Differences in variables among trimesters were tested by analysis of variance with linear orthogonal polynomials to assess a linear trend over time; all analyses were adjusted for age. Univariate analysis was performed on clinical, geometric, functional, and hemodynamic variables to identify candidate predictor variables for further analysis. Multiple linear regression analysis was then used to model LV_{Tor} as a function of the aforementioned predictor variables, both individually and in combination, using no more than 4 variables at a time due to total sample size considerations.

Results

The study group consisted of 55 women, of whom 32 were pregnant (mean gestation 199 ± 48 d) and 23 were not pregnant at the time of echocardiogram. No adverse fetal events or peripartum complications occurred in the pregnant subjects.

Left Ventricular Hemodynamics and Geometry in Pregnancy

Pregnant women had a higher HR ($P < 0.005$) and lower hematocrit ($P < 0.05$) than controls (Table 1). Left ventricular mass was also slightly higher in the pregnant subjects (149 ± 29 g vs 129 ± 22 g, $P < 0.01$), but LV mass index was similar between groups. Stroke volume and cardiac index were both higher in pregnant patients. Total peripheral resistance was lower in pregnant women than in controls ($P < 0.005$).

Table 1. Clinical, Geometric, Functional, and Hemodynamic Features of Nonpregnant and Pregnant Women

Variables	Nonpregnant Group (n = 23)	Pregnant Group (n = 32)	P Value
Systolic BP (mm Hg)	109 ± 8	113 ± 10	NS
Diastolic BP (mm Hg)	66 ± 10	66 ± 9	NS
Heart rate (bpm)	72 ± 11	83 ± 14	<0.005
Hematocrit (%)	36 ± 4	32 ± 4	<0.05
Whole blood volume (L)	4.6 ± 1	4.7 ± 1	NS
Septal wall thickness (cm)	0.83 ± 0.1	0.88 ± 0.1	<0.05
LV diastolic dimension (cm)	4.7 ± 0.3	4.8 ± 0.4	NS
Posterior wall thickness (cm)	0.83 ± 0.1	0.88 ± 0.1	<0.05
LV mass (g)	129 ± 22	149 ± 29	<0.01
LV mass index (g/m ²)	76 ± 11	77 ± 15	NS
LV length (cm)	7.6 ± 1	7.8 ± 1	NS
Relative wall thickness	0.35 ± 0.05	0.36 ± 0.04	NS
EF (%)	66 ± 5	68 ± 5	NS
Midwall shortening (%)	25 ± 3	26 ± 4	NS
Mitral E (cm/s)	98 ± 21	104 ± 17	NS
Mitral A (cm/s)	58 ± 16	70 ± 21	<0.05
Mitral E/A ratio	1.7 ± 1	1.6 ± 0.4	NS
IVRT (ms)	84 ± 16	84 ± 18	NS
E' (cm/s)	14 ± 3	14 ± 3	NS
E/E' ratio	7.3 ± 2	7.6 ± 2	NS
Stroke volume (mL)	62 ± 11	76 ± 20	<0.005
Cardiac output (L/min)	4.5 ± 1	6.4 ± 2	<0.0005
Cardiac index (min ⁻¹ · m ⁻²)	2.5 ± 1	3.5 ± 1	<0.001
Systemic vascular resistance (dynes · s · cm ⁻⁵)	1537 ± 470	1153 ± 465	<0.005

Abbreviations: A, peak late mitral diastolic filling; BP, blood pressure; E, peak early mitral diastolic filling velocity; E', tissue Doppler velocity of mitral annulus; EF, ejection fraction; HR, heart rate; IVRT, isovolumic relaxation time; LV, left ventricular; NS, not significant.

When the pregnancy group was divided into trimesters, HR demonstrated a progressive increase between nonpregnant women and second-trimester patients (72 ± 11 bpm vs 82 ± 10 bpm, $P < 0.05$) and third-trimester subjects (84 ± 16 bpm, $P < 0.005$) (Table 2). Stroke volume increased from 62 ± 11 mL in nonpregnant women to 80 ± 18 mL ($P < 0.001$) in the third trimester. Cardiac index increased from 2.5 ± 1 min⁻¹ · m⁻² in control subjects to 3.5 ± 1 min⁻¹ · m⁻² in the third trimester ($P < 0.001$). There was a 19% increase in LV mass in third-trimester

Table 2. Clinical, Geometric, Functional, and Hemodynamic Features by Trimester

Variables	Control Group (n = 23)	Second Trimester (n = 11)	Third Trimester (n = 21)
Systolic BP (mm Hg)	109 ± 8	110 ± 11	115 ± 9 ^a
Diastolic BP (mm Hg)	66 ± 10	65 ± 11	67 ± 8
HR (bpm)	72 ± 11	82 ± 10 ^b	84 ± 16 ^{a,c}
Hematocrit (%)	36 ± 4	33 ± 3	32 ± 4 ^a
Whole blood volume (L)	4.6 ± 1	4.3 ± 0.3	5.0 ± 1 ^c
LV diastolic dimension (cm)	4.7 ± 0.3	4.7 ± 0.3	4.9 ± 0.4 ^a
LV mass (g)	129 ± 22	138 ± 16	154 ± 33 ^a
LV mass index (g/m ²)	75 ± 11	78 ± 11	76 ± 17
LV length (cm)	7.6 ± 1	7.6 ± 1	7.9 ± 1
EF (%)	66 ± 5	68 ± 6	68 ± 5
Mitral E (cm/s)	98 ± 20	107 ± 19	102 ± 16
Mitral A (cm/s)	58 ± 16	67 ± 23	71 ± 21 ^a
Mitral E/A ratio	1.7 ± 0.5	1.7 ± 0.4	1.5 ± 0.5
E' (cm/s)	14 ± 3	15 ± 4	14 ± 3
E/E' ratio	7.3 ± 2	7.5 ± 2	7.6 ± 2
Stroke volume (mL)	62 ± 11	68 ± 22	80 ± 18 ^a
Cardiac output (L/min)	4.5 ± 1	5.6 ± 2	6.8 ± 2 ^a
Cardiac index (min ⁻¹ · m ⁻²)	2.5 ± 1	3.4 ± 1 ^b	3.5 ± 1 ^a
Systemic vascular resistance (dynes · s · cm ⁻⁵)	1537 ± 470	1248 ± 386	1103 ± 503 ^a

Abbreviations: A, peak late mitral diastolic filling; BP, blood pressure; E, peak early mitral diastolic filling velocity; E', tissue Doppler velocity of mitral annulus; EF, ejection fraction; HR, heart rate. ^a $P < 0.05$ for nonpregnant women vs third-trimester women. ^b $P < 0.05$ for nonpregnant women vs second-trimester women. ^c $P < 0.05$ for second-trimester women vs third-trimester women.

patients compared with nonpregnant females ($P < 0.005$). This difference was not significant when LV mass was indexed to body surface area. Whereas transmitral A-wave velocity increased 22% between control and third-trimester patients, the E/A ratio did not differ significantly between groups.

Torsional Mechanics in Pregnancy

Left ventricular torsion showed a trend for a progressive increase from controls (9.4 ± 3.7 degrees) to second-trimester (12.0 ± 4.2 degrees, $P = 0.08$) and third-trimester patients (12.6 ± 5.9 degrees, $P = 0.04$) (Figure 2) (Table 3). This change was wholly attributable to an increase in apical rotation. Basal rotation remained constant between study groups (P not significant). Measurement of Tor_{Norm} demonstrated a trend for increase during pregnancy (1.3 ± 0.5 degrees/cm in controls vs 1.6 ± 0.8 degrees/cm in third-trimester patients, $P = 0.07$). Peak torsion velocity also increased between controls and second-trimester patients (64 ± 21 degrees/sec vs 94 ± 27 degrees/sec, $P = 0.002$), but did not demonstrate further change between the second and third trimesters.

In nonpregnant women, the time to peak torsion occurred before aortic valve closure, at 92% of systole duration. However, the time to peak torsion showed a trend toward delay to 102% of systole duration by the third trimester ($P = 0.07$). There was no significant difference in either peak untwisting velocity or time to peak untwisting velocity between controls and women in either trimester of pregnancy.

Univariate analysis performed on all prespecified clinical, geometric, functional, and hemodynamic variables (Table 1) identified the following candidate predictor variables for further analysis: pregnancy status, body mass index, systolic BP, hematocrit, LV internal diastolic dimension, relative wall thickness, cardiac output, and HR. Multiple regression analysis was performed looking at these candidate variables individually and in combination to see if the candidate variables were modulated by other potential predictors. No multiple regression models were significant. Systolic BP was the only independent predictor of increased LV_{Tor} ($r = 0.394$, $P = 0.005$). Pregnancy status at the time of echocardiogram was not found to be independently associated with increased LV_{Tor} .

Table 3. Torsion Parameters in Pregnant Women by Trimester

Variables	Control Group (n = 23)	Second Trimester (n = 11)	Third Trimester (n = 21)
LV Torsion (°)	9.4 ± 3.8	12.0 ± 4.2^a	12.6 ± 5.9^b
Apical rotation (°)	5.5 ± 2.7	7.8 ± 3.3^a	8.8 ± 4.2^b
Basal rotation (°)	-4.9 ± 2.9	-5.1 ± 2.4	-4.9 ± 2.2
Normalized torsion (°/cm)	1.3 ± 0.5	1.6 ± 0.6	1.6 ± 0.8
Peak LV twist velocity (°/sec)	64 ± 21	94 ± 24^a	93 ± 30^b
Peak LV untwist velocity (°/sec)	67 ± 35	74 ± 29	61 ± 29
Time to peak torsion (% systole)	92 ± 20	100 ± 22	103 ± 16
Time to peak untwist rate (% systole)	116 ± 9	118 ± 8	120 ± 7

Abbreviations: LV, left ventricular. ^a $P < 0.05$ between control group and second trimester. ^b $P < 0.05$ between control group and third trimester.

Inter- and intraobserver variabilities for the measurement of LV_{Tor} were determined by 2 independent blinded cardiologists who analyzed 16 randomly selected patients. Interobserver variability showed a correlation coefficient of 0.92 (standard error of the estimate 1.6). In terms of intraobserver variability, a correlation coefficient was found to be 0.96 (standard error of the estimate 1.2). Bland-Altman analysis also showed good agreements for intra- and interobserver variabilities (limits of agreement 0.48 u [2.51 u] and 0.51 u [3.27 u], respectively).

Discussion

Our study characterizes the changes in torsion-related parameters during the second and third trimesters of pregnancy in comparison with nonpregnant controls. During the cardiac cycle, the LV undergoes systolic “twisting” and diastolic “untwisting.” The systolic twisting motion

Figure 2. Mean global torsion (solid line), mean apical rotation (dotted line), and mean basal rotation (dashed line) for all patients in the nonpregnant control group, all patients in the second-trimester group, and all patients in the third-trimester group, respectively. The horizontal axis represents 1 cardiac cycle, from 0% (end diastole) to 100% (end diastole).

stores potential energy in both intra- and extracellular structures.^{26,27} This stored energy is then released during diastolic untwisting and contributes to the formation of an intraventricular suction gradient that facilitates LV inflow.^{28–30} Numerous studies have suggested that LV_{Tor} adaptively changes in response to ventricular loading conditions.^{16,31–34} Only 1 prior study examined LV_{Tor} during human pregnancy. Tzemos et al demonstrated that peak torsion was increased during the second trimester in 10 normal healthy females, and that peak torsion returned to baseline levels in the postpartum period.¹¹

Our study extends these findings in a larger sample size and enhances them by illustrating both systolic twist and diastolic untwist parameters for the second and third trimesters. We found a significant increase in peak twist velocity during the second and third trimester of pregnancy. An increase in twist velocity alone would be expected to cause a premature time to peak torsion, not a delay as seen in our pregnant patients. Time to peak torsion is delayed past aortic valve closure in patients with chronic mitral regurgitation.³⁵ However, none of the pregnant patients in our study had significant mitral regurgitation, and a more plausible etiology for the observed delay is the chronic volume overload status. Increased preload has been reported to delay the time to peak twist in the absence of changes in contractility.^{30,31} Interestingly, systolic BP was the only independent correlate on multiple regression analysis for increased LV_{Tor} , indicating that pregnancy itself is not an independent predictor variable.

Our findings suggest that diastolic function is not impaired during the course of normal pregnancy despite the volume overload state. Most noninvasive measures of diastolic function are subject to pseudonormalization. Delayed untwisting despite normal or increased LV_{Tor} has been shown to occur with impaired myocardial relaxation.^{36–38} Rovner et al³⁹ demonstrated that untwist rate may be a more direct measure of diastolic function than conventional Doppler-derived indices. Dong et al³¹ have shown that untwist rate remains constant with volume loading, is independent of left atrial pressure, and is more closely correlated to τ (the time constant of relaxation) than the isovolumic relaxation time. We found no significant difference in time to peak untwist rate or untwist velocity between the control group and the pregnant patients.

Potential Limitations

Due to the cross-sectional nature of our study, we have no information regarding LV torsional changes during the first trimester. However, the LV geometric and hemodynamic changes that parallel changes in LV_{Tor} are progressive and sustained throughout pregnancy, and are reflected in the changes we observed in our subjects during the second and third trimesters.

Conclusion

Numerous studies have demonstrated that the STE method can accurately assess myocardial function in a variety of cardiovascular conditions.²³ Our analysis of LV torsion parameters confirms that normal pregnancy results in an increase in LV_{Tor} and peak torsion velocity, and that

this change is due to increased apical rotation. We have expanded on existing knowledge by providing torsion values for the third trimester of pregnancy, and have shown that systolic BP is an independent predictor of increased LV_{Tor} . Additionally, we are the first to report that untwist parameters, volume-independent measures of diastolic function, remain unchanged during pregnancy. Further studies are needed to prospectively validate our findings.

References

1. Duvekot JJ, Peeters LH. Maternal cardiovascular hemodynamic adaptation to pregnancy. *Obstet Gynecol Surv.* 1994;49:S1–S14.
2. Mesa A, Jessurun C, Hernandez A, et al. Left ventricular diastolic function in normal human pregnancy. *Circulation.* 1999;99:511–517.
3. Hennessy TG, MacDonald D, Hennessy MS, et al. Serial changes in cardiac output during normal pregnancy: a Doppler ultrasound study. *Eur J Obstet Gynecol Reprod Biol.* 1996;70:117–122.
4. Van Oppen AC, Stigter RH, Bruinse HW. Cardiac output in normal pregnancy: a critical review. *Obstet Gynecol.* 1996;87:310–318.
5. Katz R, Karliner JS, Resnik R. Effects of a natural volume overload state (pregnancy) on left ventricular performance in normal human subjects. *Circulation.* 1978;58:434–441.
6. Poppas A, Shroff SG, Korcarz CE, et al. Serial assessment of the cardiovascular system in normal pregnancy: role of arterial compliance and pulsatile arterial load. *Circulation.* 1997;95:2407–2415.
7. Hunter S, Robson SC. Adaptation of the maternal heart in pregnancy. *Br Heart J.* 1992;68:540–543.
8. Mabie WC, DiSessa TG, Crocker LG, et al. A longitudinal study of cardiac output in normal human pregnancy. *Am J Obstet Gynecol.* 1994;170:849–856.
9. Mone SM, Sanders SP, Colan SD. Control mechanisms for physiological hypertrophy of pregnancy. *Circulation.* 1996;94:667–672.
10. Desai DK, Moodley J, Naidoo DP. Echocardiographic assessment of cardiovascular hemodynamics in normal pregnancy. *Obstet Gynecol.* 2004;104:20–29.
11. Tzemos N, Silversides CK, Carasso S, et al. Effect of pregnancy on left ventricular motion (twist) in women with aortic stenosis. *Am J Cardiol.* 2008;101:870–873.
12. Yoon AJ, Bella JN. New options in noninvasive assessment of left ventricular torsion. *Future Cardiol.* 2009;5:51–61.
13. Helle-Valle T, Crosby J, Edvardsen T, et al. New noninvasive method for assessment of left ventricular rotation: speckle tracking echocardiography. *Circulation.* 2005;112:3149–3156.
14. Neilan TG, Ton-Nu TT, Jassal DS, et al. Myocardial adaptation to short-term high-intensity exercise in highly trained athletes. *J Am Soc Echocardiogr.* 2006;19:1280–1285.
15. Bansal M, Leano RL, Marwick TH. Clinical assessment of left ventricular systolic torsion: effects of myocardial infarction and ischemia. *J Am Soc Echocardiogr.* 2008;21:887–894.
16. Yoon AJ, Pokhare P, Nazari R, et al. Left ventricular torsion during adenosine-mediated ischemia measured by speckle tracking echocardiography. *J Am Soc Echocardiogr.* 2009;22:567.
17. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr.* 2005;18:1440–1463.
18. De Simone G, Devereux RB, Roman MJ, et al. Gender differences in left ventricular anatomy, blood viscosity and volume regulatory hormones in normal adults. *Am J Cardiol.* 1991;68:1704–1708.
19. Devereux RB, Pini R, Aurigemma GP, et al. Measurement of left ventricular mass: methodology and expertise. *J Hypertens.* 1997;15:801–809.
20. Notomi Y, Setser RM, Shiota T, et al. Assessment of left ventricular torsional deformation by Doppler tissue imaging: a validation study using tagged magnetic resonance imaging. *Circulation.* 2005;111:1141–1147.

21. Wagner RF, Smith SW, Sandrik JM, et al. Statistics of speckle in ultrasound B-scans. *IEEE Trans Son Ultrason*. 1983;30:156–163.
22. Kaluzynski K, Chen X, Emelianov SY, et al. Strain rate imaging using two-dimensional speckle tracking. *IEEE Trans Ultrason Ferroelectr Freq Control*. 2001;48:1111–1123.
23. Notomi Y, Lysyansky P, Setser RM, et al. Measurement of ventricular torsion by two-dimensional ultrasound speckle tracking imaging. *J Am Coll Cardiol*. 2005;45:2034–2041.
24. Ihlen H, Amlie JP, Dale J, et al. Determination of cardiac output by Doppler echocardiography. *Br Heart J*. 1984;51:54–60.
25. Feldschuh J, Enson Y. Prediction of the normal blood volume: relation of blood volume to body habitus. *Circulation*. 1977;56:605–612.
26. Waldman LK, Nosan D, Villarreal F, et al. Relation between transmural deformation and local myofiber direction in canine left ventricle. *Circ Res*. 1988;63:550–562.
27. Granzier H, Wu Y, Siegfried L, et al. Titin: physiological function and role in cardiomyopathy and failure. *Heart Fail Rev*. 2005;10:211–223.
28. Dong SJ, Hees PS, Siu CO, et al. MRI assessment of LV relaxation by untwisting rate: a new isovolumic phase measure of tau. *Am J Physiol Heart Circ Physiol*. 2001;281:H2002–H2009.
29. Rademakers FE, Buchalter MB, Rogers WJ, et al. Dissociation between left ventricular untwisting and filling: accentuation by catecholamines. *Circulation*. 1992;85:1572–1581.
30. Notomi Y, Popovic ZB, Yamada H, et al. Ventricular untwisting: a temporal link between left ventricular relaxation and suction. *Am J Physiol Heart Circ Physiol*. 2008;294:H505–H513.
31. Dong SJ, Hees PS, Huang WM, et al. Independent effects of preload, afterload, and contractility on left ventricular torsion. *Am J Physiol Heart Circ Physiol*. 1999;277:H1053–H1060.
32. Tibayan FA, Lai DT, Timek TA, et al. Alterations in left ventricular torsion in tachycardia-induced dilated cardiomyopathy. *J Thorac Cardiovasc Surg*. 2002;124:43–49.
33. Sandstede JJ, Johnson T, Harre K, et al. Cardiac systolic rotation and contraction before and after valve replacement for aortic stenosis: a myocardial tagging study using MR imaging. *Am J Roentgenol*. 2002;178:953–958.
34. Notomi Y, Martin-Miklovic MG, Oryszak SJ, et al. Enhanced ventricular untwisting during exercise. *Circulation*. 2006;113:2524–2533.
35. Borg AN, Harrison JL, Argyle RA, et al. Left ventricular torsion in primary chronic mitral regurgitation. *Heart*. 2008;94:597–603.
36. Stuber M, Scheidegger MB, Fischer SE, et al. Alterations in the local myocardial motion pattern in patients suffering from pressure overload due to aortic stenosis. *Circulation*. 1999;100:361–368.
37. Oxenham H, Sharpe N. Cardiovascular aging and heart failure. *Eur J Heart Fail*. 2003;5:427–434.
38. Takeuchi M, Borden WB, Nakai H, et al. Reduced and delayed untwisting of the left ventricle in patients with hypertension and left ventricular hypertrophy: a study using two-dimensional speckle tracking imaging. *Eur Heart J*. 2007;28:2756–2762.
39. Rovner A, Greenberg NL, Thomas JD, et al. Relationship of diastolic intraventricular pressure gradients and aerobic capacity in patients with diastolic heart failure. *Am J Physiol Heart Circ Physiol*. 2005;289:H2081–H2088.