Relationship between Left Ventricular Twist and Circulating Biomarkers of Collagen Turnover in Hypertensive Patients with Heart Failure

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Background: Left ventricular (LV) twist may be a compensatory mechanism to preserve ejection fraction (EF). In patients with hypertension, twist varies depending on the left ventricle's degree of remodeling and systolic function; it is increased in those with hypertension with normal EF (HTNEF) and diminished in those with hypertension with low EF (HTLEF). The ratio of collagen-degradation biomarkers in patients with hypertension is higher in those with low EFs than those with preserved EFs and may contribute to remodeling and systolic dysfunction.

Methods: The aim of this study was to evaluate the relationship between these biomarkers and LV twist in 82 patients with hypertension, 41 with EFs < 50% (HTLEF group) and 41 with EFs ≥ 50% (HTNEF group). Net LV twist was measured using speckle-tracking echocardiography. Markers of collagen turnover, including serum concentrations of matrix metalloproteinase–1 (MMP1), tissue inhibitor of MMP1 (TIMP1), and the ratio of MMP1 to TIMP1, were measured.

Results: Log TIMP1, log MMP1, and log MMP1/TIMP1 ratio levels were higher in the HTLEF group than the HTNEF group (12.3 ± 0.3 vs 11.8 ± 0.1 [$P < .0001$], 9.1 ± 0.3 vs 8.0 ± 0.2 [$P < .0001$], and −3.3 ± 0.3 vs −3.8 ± 0.2 [$P < .0001$], respectively). Net LV twist was lower in the HTLEF group than the HTNEF group (3.3 ± 1.1 vs 11.7 ± 0.7, $P < .0001$). An inverse correlation existed between log MMP1/TIMP1 and net LV twist after adjusting for age, EF, duration of heart failure, systolic blood pressure, LV mass index, and LV sphericity index at end-diastole ($r = -0.43$, $P < .0001$).

Conclusions: This inverse correlation between twist and loss of myocardial collagen scaffolding in patients with hypertension with heart failure suggests that the integrity of the extracellular matrix may play an important role in preserving myocardial deformation. (J Am Soc Echocardiogr 2014;27:1064-71.)

Keywords: Twist, Speckle tracking, Heart failure, Hypertension, Matrix metalloproteinases, Tissue inhibitor of matrix metalloproteinase–1

Left ventricular (LV) twist is defined as the wringing motion of the heart during systole whereby the apex rotates in a counterclockwise direction with respect to the base, rotating in a clockwise direction.[1-5] It is an important contributing factor to the systolic function of the left ventricle in health and disease.[1-5] Evaluation of LV twist using speckle-tracking is a sensitive technique used to assess cardiac performance[1-5] and can be a better index of systolic function than ejection fraction (EF) in patients with hypertension. In patients with hypertension with normal EF (HTNEF), LV twist is increased while longitudinal strain is diminished, suggesting that LV twist may be a compensatory mechanism to preserve EF.[6] LV twist is diminished in patients with hypertension with low EF (HTLEF) who initially present with heart failure[7] and has been found to be more diminished in patients with hypertension with eccentric LV hypertrophy as opposed to concentric hypertrophy.[8] This suggests that LV twist varies with the degree of remodeling and systolic function caused by hypertension.

The remodeling process of the left ventricle in hypertension entails a complex interplay between myocyte hypertrophy and dysfunction, with qualitative changes in the extracellular matrix (ECM) contributing to progressive dysfunction.[9-12] Adverse LV remodeling and hypertrophy in patients with hypertension is associated with derangements in the dynamic balance between the accumulation and breakdown of collagen in the cardiac ECM.[9-12] Furthermore, increased matrix metalloproteinase 1 (MMP1) levels, reflecting

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Abbreviations

AR = Apical rotation

BR = Basal rotation

ECM = Extracellular matrix

EF = Ejection fraction

HTLEF = Hypertension with low ejection fraction

HTNEF = Hypertension with normal ejection fraction

LV = Left ventricular

LVIDd = Left ventricular internal diameter at end-diastole

MMP1 = Matrix metalloproteinase–1

PWTd = Posterior wall thickness at end-diastole

SWTd = Septal wall thickness at end-diastole

TIMP1 = Tissue inhibitor of matrix metalloproteinase–1

collagen degradation, may contribute to the development of LV dilatation and failure in patients with hypertension.[9-13] A greater excess of MMP1 relative to the tissue inhibitor of MMP1 (TIMP1) occurred in the myocardium of patients with HTLEF than those with HTNEF.[13] Moreover, circulating MMP1/TIMP1 ratio was associated with greater LV dilatation and systolic dysfunction.[13] The varying morphology and function in hypertensive heart disease could be related to the equilibrium of MMP1 and TIMP1 in maintaining collagen homeostasis.[13] Hypertension can cause systolic dysfunction as a consequence of adverse remodeling and LV hypertrophy, but given the multitude of factors involved in LV decompensation mediated by mechanical, neurohormonal, and cytokine routes, the exact mechanisms that contribute to the adverse remodeling and EF deterioration are not fully elucidated.[14,15]

We postulate that changes in the ECM as reflected by MMP1/TIMP1 ratio account for the varying morphology, EF, and LV twist in patients with hypertension who present with heart failure. The aim of this study was to evaluate LV twist mechanics and their relationship with biomarkers of collagen degradation in patients with hypertension.

METHODS

This cross-sectional study complies with the Declaration of Helsinki and was approved by the University of Witwatersrand Ethics Committee and the Institutional Review Board. Patients of African descent were recruited from the Chris Hani Baragwanath Hospital Heart Failure Clinic from January 2011 to June 2012. Inclusion criteria were documented prior diagnosis of hypertension (measurements on three separate occasions of systolic blood pressure $\geq$ 140 mm Hg or diastolic blood pressure $\geq$ 90 mm Hg, taken over a period of 2 months[16] at the Hypertension Clinic), documented heart failure using Framingham Heart Study criteria,[17] sinus rhythm, and normal epicardial coronary arteries. Exclusion criteria were previous myocardial infarction or history of ischemic heart disease, previous arrhythmia, anemia (hemoglobin $<$ 12 g/dL in women and $<$ 13 g/dL in men), excess alcohol intake (alcohol intake $>$ 40 g/d in men and $>$ 20 g/d in women), renal dysfunction (glomerular filtration rate $<$ 60 mL/min/1.73 m^2), documented diagnosis of diabetes and/or glycated hemoglobin $>$ 7%, any organic valvular disease, dilated cardiomyopathy of any etiology, cardiac infiltrative diseases, postviral myocarditis, any systemic illness (e.g., human immunodeficiency virus), thyroid disease, and any primary organ dysfunction or failure (e.g., chronic renal disease).

A total of 120 subjects who fulfilled the criteria and provided voluntary informed consent were enrolled and underwent detailed clinical and echocardiographic evaluations at baseline (Figure 1). After echocardiography, 25 patients were excluded as a result of inadequate image quality that did not allow complete segmental assessment of LV rotation at both the basal and apical left ventricle (e.g., poor transthoracic windows, inability to obtain true apical or basal views, or loss of more than one segment at any level for speckle-tracking analysis). Furthermore, patients with rigid body rotation were excluded from this study (n = 13). The remaining 82 patients with hypertension, 41 of whom had EFs $<$ 50% (the HTLEF group) and 41 of whom had EFs $\geq$ 50% (the HTNEF group), made up the study cohort and were given adequate doses of heart failure therapy per individual patient requirements. Twenty-eight of the 41 patients in the HTLEF group were included from a previous study.[7]

The control group (n = 41) from a prior publication[7] served as the healthy control subjects recruited from staff members at Chris Hani Baragwanath Hospital, patient escorts, and community members from Soweto. All controls were unrelated to patients in the study groups and were asymptomatic, were normotensive, had no evidence of cardiovascular or systemic disease, and had normal results on 12-lead electrocardiography before undergoing echocardiography for the study. The control group was age and sex matched with the HTLEF and HTNEF cohorts. Individuals $<$50 years of age were matched with a tolerance of 5 years in terms of age; individuals $>$50 years of age were allowed a tolerance of up to 10 years.

Echocardiography

Comprehensive transthoracic echocardiography was performed using a commercially available system (iE33 xMATRIX; Philips Healthcare, Best, The Netherlands) according to a standardized protocol. All echocardiographic measurements were averaged from three heartbeats. Measurements relating to chamber size and function were performed in accordance with the American Society of Echocardiography chamber quantification guidelines of 2006.[18] Severity of mitral and tricuspid regurgitation was analyzed in accordance with American Society of Echocardiography guidelines on native valvular regurgitation.[19] EF was calculated from LV volumes by using the modified biplane Simpson's rule in accordance with guidelines.[18]

The time interval between the peak of the R wave on the electrocardiogram and aortic valve opening and closure, as well as the time interval between the R wave and mitral valve opening and closure, was measured using pulsed Doppler acquired from LV outflow and inflow, respectively. LV mass was calculated using the formula LV mass = $0.8 \times \{1.04[(\text{LVIDd} + \text{PWTd} + \text{SWTd})^3 - (\text{LVIDd})^3]\} + 0.6$ g, where LVIDd is LV internal diameter at end-diastole, PWTd is posterior wall thickness and end-diastole, and SWTd is septal wall thickness at end-diastole, respectively.[18,20] Relative wall thickness was calculated using the formula $(2 \times \text{PWTd})/\text{LVIDd}$.[18,20] Concentric hypertrophy was defined as relative wall thickness $>$ 0.42 and LV mass index $>$ 95 g/m^2 in women and $>$ 115 g/m^2 in men, whereas eccentric hypertrophy was defined as relative wall thickness $<$ 0.42 and LV mass index $>$ 95 g/m^2 in women and $>$ 115 g/m^2 in men.[18,20] LV sphericity index was calculated by dividing the maximal long-axis internal dimension by the maximal short-axis internal dimension at end-diastole and end-systole[21] using apical four-chamber view.

Speckle-Tracking Analysis

Two-dimensional images were obtained at a rate of 50 to 80 frames/sec. Parasternal short-axis images at the LV basal level showing the tips of the mitral valve leaflets were obtained with the cross-section as circular as