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Improvements in Left Ventricular Hypertrophy and Diastolic Function Following Renal Denervation

Effects Beyond Blood Pressure and Heart Rate Reduction

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Objectives This study sought to investigate the interaction between blood pressure (BP) and heart rate (HR) reduction and changes in left ventricular (LV) structure and function following renal sympathetic denervation (RDN).

Background Hypertension results in structural and functional cardiac changes. RDN reduces BP, HR, and LV mass and improves diastolic dysfunction.

Methods We evaluated LV size, mass, and function before and 6 months after RDN in 66 patients with resistant hypertension and analyzed results in relation to systolic BP (SBP) and HR.

Results SBP decreased by 11 ± 3 mm Hg in the first, 18 ± 5 mm Hg in the second, and 36 ± 7 mm Hg in the third tertile of SBP at baseline ($p < 0.001$). HR decreased by 13 ± 4 beats/min, 8 ± 3 beats/min, and 11 ± 6 beats/min in tertiles of SBP (p for interaction between tertiles $= 0.314$). In all SBP tertiles, LV mass index (LVMI) decreased similarly (LVMI -6.3 ± 2.2 g/m$^{2.7}$, -8.3 ± 2.1 g/m$^{2.7}$, and -9.6 ± 1.9 g/m$^{2.7}$; p for interaction $= 0.639$). LVMI decreased unrelated to HR at baseline (p for interaction $= 0.471$). The diastolic parameters E-wave deceleration time, isovolumetric relaxation time, and E′-wave velocity improved similarly in all tertiles of SBP and HR. Changes in LV mass and function were also unrelated to reduction in SBP or HR. Vascular compliance improved dependently on BP but independently of HR reduction.

Conclusions In patients with resistant hypertension, LV hypertrophy and diastolic function improved 6 months after RDN, without significant relation to SBP and HR. These findings suggest a direct effect of altered sympathetic activity in addition to unloading on cardiac hypertrophy and function. (J Am Coll Cardiol 2014;63:1916–23) © 2014 by the American College of Cardiology Foundation

Pressure overload in arterial hypertension leads to maladaptive myocardial remodeling associated with cardiac hypertrophy and later development of heart failure with preserved or reduced ejection fraction (1). Antihypertensive drugs reduce cardiac remodeling (2) and progression to heart failure (3). Resistant arterial hypertension is defined as insufficient office blood pressure (BP) control despite the use of ≥3 antihypertensive drugs at maximal tolerated doses, one being a diuretic (4). Renal artery sympathetic denervation (RDN) is a novel technique that has been shown to reduce BP and heart rate (HR) in patients with resistant hypertension (5–7). HR is associated with outcomes in hypertension (8) and heart failure (9), and HR reduction improves left ventricular (LV) remodeling (10) and outcomes (11) in heart failure. RDN has also been shown to reduce LV hypertrophy (LVH) and to improve diastolic and systolic LV function, also achieving a decrease of LV mass in some office BP nonresponders (<10 mm Hg decrease 6 months after RDN) (12). These findings

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attracted our attention to a possible BP-independent effect of RDN. In the present study, we thus investigated cardiac structure and function before and 6 months after RDN using transthoracic echocardiography and analyzed results in relation to BP and HR reduction.

Methods

Patient selection. This study was approved by the institutional medical ethics committee (No. 67/11) in accordance with the declaration of Helsinki. Sixty-six consecutive patients scheduled for RDN for treatment of resistant arterial hypertension (defined as office systolic BP [SBP] ≥140 mm Hg) were prospectively included using a prespecified analysis protocol (Symplicity extension NCT00664638, NCT00888433, and NCT01888315) if they were in sinus rhythm and did not suffer from systolic heart failure (ejection fraction <50%) or severe renal dysfunction (estimated glomerular filtration rate <45 ml/min/1.73 m^2 as measured by cystatin C). Patients suffering from secondary causes of hypertension were excluded.

BP and HR. Following 10 min of supine rest, BP was measured in triplicate with an automatic oscillometric monitor and HR was obtained from a 12-lead electrocardiogram. Ambulatory BP monitoring (ABPM) was performed to exclude pseudoresistant hypertension (mean 24-h SBP <130 mm Hg) (13).

Echocardiography. Transthoracic echocardiography was performed by the same operator (M.M.Y.A.S.), who was blinded to BP data and patient status, on a Vivid E9 (General Electric, Frankfurt, Germany) before and 6 months after RDN. The investigation included regular 2-dimensional echocardiography, Doppler, and tissue Doppler imaging according to the guidelines of the American Society of Echocardiography (14). All studies were read offline by an investigator blinded to patient status (S.H.S.). LV size was measured as left ventricular end-diastolic diameter (LVEDD) using M-mode. LV mass was calculated from the end-diastolic diameters of the interventricular septum (IVSd), left ventricular posterior wall (LVPWd), and LV cavity using the Devereux formula (15). Body surface area was calculated according to the Mosteller formula (16), and LV mass was indexed to height to the 2.7th power. Relative wall thickness was calculated as the sum of IVSd and LVPWd divided by LVEDD. LV diastolic function was assessed according to standardized criteria (17), using pulsed-wave (PW) Doppler of the mitral inflow and measuring deceleration time (DT) of the E-wave, E- to A-wave ratio (E/A), and isovolumetric relaxation time (IVRT) (time between closure of the aortic and opening of the mitral valve). Tissue Doppler was used for measurements of E′ septal and E′ lateral wave (peak early diastolic septal and lateral mitral annular velocities) and calculation of the ratio of the maximum E-wave velocity and the mean E′-wave. Other hemodynamic parameters were calculated as follows: stroke volume = $\pi \times VTI_{LVOT} \times (diameter_{LVOT}/2)^2$, for which VTI is velocity time integral and LVOT is LV outflow tract. Peripheral arterial compliance = stroke volume/(SBP − DBP), for which DBP is diastolic blood pressure. HR-corrected LV circumferential fiber shortening (VCFc) = FS/ET × $(60/HR)^{1/2}$, for which FS is fractional shortening and ET is ejection time. End-systolic meridional wall stress (EsMWS) was calculated according to Grossman et al. (18) and Reicheck et al. (19) as follows: (0.334 × SBP × LVESD)/(LVPWs × [1 + LVPWs/LVESD]), for which LVESD is LV end-systolic diameter and LVPWs is LV posterior wall during systole.

RDN procedure. Following renal artery angiography, RDN was performed using the Flex catheter system (Medtronic, Santa Rosa, California), as previously reported (7). In both renal arteries, radiofrequency ablations at a maximum power of 8 W lasting 2 min each were performed.

Statistical analysis. Data are presented as mean ± SEM. Data were analyzed for normal distribution using the Kolmogorov-Smirnov test. Normally distributed parameters were compared between baseline and 6-month follow-up using a paired Student *t* test or a Wilcoxon matched-pairs test if not normally distributed. Linear regression analyses were used to calculate the correlation between the change in BP and the change in echocardiographic parameters. Analysis of variance was performed with post-hoc testing for trend when the change in the 3 groups was compared. The Fisher exact test was used for testing associations in 2 × 2 contingency tables. Differences were considered significant if p was <0.05. SPSS version 18.0 (SPSS Inc., Chicago, Illinois) was used for statistical calculations.

Abbreviations and Acronyms

- **ABPM** = ambulatory blood pressure monitoring
- **BP** = blood pressure
- **DBP** = diastolic blood pressure
- **DT** = deceleration time
- **E/A** = E- to A-wave ratio
- **EsMWS** = end-systolic meridional wall stress
- **FS** = fractional shortening
- **HR** = heart rate
- **IVRT** = isovolumetric relaxation time
- **LV** = left ventricular
- **LVEDD** = left ventricular end-diastolic diameter
- **LVESD** = left ventricular end-systolic diameter
- **LVH** = left ventricular hypertrophy
- **LVMI** = left ventricular mass index
- **LVOT** = left ventricular outflow tract
- **LVPWs** = left ventricular posterior wall during systole
- **RDN** = renal sympathetic denervation
- **SBP** = systolic blood pressure
- **VCFc** = heart rate–corrected left ventricular circumferential fiber shortening

Results

Baseline characteristics. Patients in the treatment group had a mean age of 63.5 ± 1.2 years. Thirty-six of the 66 study patients (54.5%) were male. Average body mass index was 29.4 ± 0.6 kg/m^2. Patients were receiving 4.3 ± 0.1 antihypertensive drugs (Online Table 1). The RDN procedure was performed without complications in all patients.