Heart Rate–Dependent Left Ventricular Diastolic Function in Patients With and Without Heart Failure

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ABSTRACT

Background: Chronic heart rate (HR) reduction in the treatment of heart failure (HF) with systolic dysfunction is beneficial, but the immediate mechanical advantages or disadvantages of altering HR are incompletely understood. We examined the effects of increasing HR on early and late diastole in humans with and without HF.

Methods and Results: We studied force-interval relationships of the left ventricle (LV) in 11 HF patients and 14 control subjects. HR was controlled by right atrial pacing, and LV pressure was recorded by a micromanometer-tipped catheter. The time constant of isovolumic relaxation (tau) was calculated, and simultaneous sonographic images were analyzed for LV volumes. The end-diastolic pressure-volume relationship (EDPVR) was analyzed with the use of a single-beat method. Tau was shortened in response to increasing HR in both groups; the slope of this relationship was steeper in HF than in control subjects. The predicted volume at a theoretic pressure of 0 mm Hg (V30) increased at higher HRs compared with baseline, shifting the predicted EDPVR compliance curve to the right in HF patients but not in control subjects.

Conclusions: In HF, changes in HR affect early relaxation and diastolic compliance to a greater extent than in control subjects. Our study reinforces current recommendations for HR-lowering drug treatment in HF. (*J Cardiac Fail 2015;21:68–75*)

Key Words: Heart failure, diastole, left ventricle, heart rate.

High resting heart rate (HR) is a known marker of cardiovascular outcomes in patients with heart failure (HF) due to systolic dysfunction.[1] One-beat and 5-beat increases of resting HR increase the risk of cardiovascular death and HF hospitalizations by 3% and 16%, respectively.[1] The efficacy of cornerstone pharmacotherapeutic interventions, such as adrenergic antagonists, can be evaluated by reductions in HR. More recently, ivabradine, a nonselective inhibitor of the I_f channels in the sinoatrial node with purely negative chronotropic effects, has been clearly demonstrated to confer a survival advantage to HF patients.[2]

As such, current evidence-based ambulatory care for chronic HF mandates the acute manipulation of HR in these patients. Although the long-term benefits are clear, the immediate mechanical advantages or disadvantages of altering HR in HF patients are incompletely understood. It is well established that the left ventricular (LV) inotropic response to increases in HR (ie, force-frequency relationship) is blunted in the failing human myocardium.[3] However, less is documented regarding the acute effects of changes in HR on the LV diastolic response (ie, relaxation-frequency) in vivo in humans with and without HF. Such data arise from older studies that included relatively decompensated HF patients. There are few data assessing the

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relaxation-frequency response in contemporary cohorts of HF patients. Because diastolic dysfunction is a common feature of HF, investigating the mechanical effects of changes in HR on LV diastolic performance is of clinical relevance to the administration of therapies available to HF patients. Therefore, our purpose was to examine the effects of increasing HR on early and late diastole in a cohort of humans with and without HF.

Methods

Study Participants

The study population consisted of patients with normal systolic LV function (NLV) and patients with systolic HF who underwent elective diagnostic cardiac catheterization at the Cardiac Catheterization Research Laboratory of the Mount Sinai Hospital. Patients agreed to participate in the research experiment after the diagnostic procedure was completed. The study was approved by the Mount Sinai Ethics Review Board for experimentation involving human subjects, and every patient gave written informed consent. Patients with NLV enrolled in this protocol were referred from outpatient clinics for assessment of chronic chest pain syndrome. All patients underwent stress nuclear perfusion imaging or stress echocardiography, and those with ischemia at low or moderate stress were excluded. Briefly, inclusion criteria for the NLV group were LV ejection fraction (LVEF) $>55\%$, normal LV mass index documented by 2-dimensional (2D) echocardiography, no history or symptoms of HF, and LV end-diastolic pressure (LVEDP) ≤ 15 mm Hg at the time of catheterization. Patients in the HF group were recruited from a subspecialty HF clinic and were referred for right and left heart catheterization as part of the clinical evaluation. Similarly to the NLV patients, results of stress perfusion imaging or stress echocardiography were reviewed to exclude patients demonstrating ischemia at low or moderate stress. The etiology of patients with HF was nonischemic in all but 2 patients. Inclusion criteria for the HF group were LVEF $<35\%$ according to 2D echocardiography (confirmed on the day of the study) and stable symptomatic HF (New York Heart Association functional class II or III) of ≥ 3 months' duration. General exclusion criteria were acute coronary syndromes or revascularization procedures within the preceding 6 months, ventricular pace-dependency, any rhythm other than sinus, QRS >110 ms, uncontrolled hypertension, and inability to give informed consent.

Combined Cardiac Catheterization and Echocardiography Study Procedures

Our study procedure has been described previously.[4] All patients underwent selective coronary angiography, and HF patients underwent standard right heart catheterization from the femoral approach. Treatment with all oral medications was withheld on the morning of the investigation. Pharmacologic agents known to inhibit atrioventricular (AV) conduction were withheld 48 hours before the study day. To control HR, a 6-Fr bipolar pacing catheter was advanced to the high right atrium and aligned with a programmable stimulator (Prucka GE Cardiolab). A 7-Fr micromanometer-tipped catheter (Micro-tip Catheter; Millar Industries) was positioned in the LV for pressure measurement. A rest period was allotted after instrumentation, and a control condition was recorded. Two separate pacing protocols were then performed.

Pacing Protocol 1: Frequency-Dependent LV Pressure. Right atrial (RA) pacing was initiated $\geq 4-15$ beats/min above the intrinsic rate to a multiple of 10 beats/min. Thereafter, HR was increased by increments of 10 beats/min every 3 minutes to a maximum of 120 beats/min or until Mobitz type 1 or 2:1 AV block occurred. If AV conduction fell below 1:1, the pacing was reduced by increments of 5 beats/min until 1:1 conduction returned. After this pacing protocol was completed, a rest period was allotted to allow LV pressure and hemodynamics to return to control conditions.

Pacing Protocol 2: Combined Sonographic and Hemodynamic Study. In this pacing run, LV pressure was recorded at the same time that echocardiography images were acquired by a research sonographer, as previously described.[4] Four conditions were acquired: control and RA pacing at 80 beats/min, 100 beats/min, and 120 beats/min. Chronometers for the imaging system and hemodynamic recording system were synchronized to enable offline beat-to-beat simultaneous analysis of LV pressure and the time-stamped echocardiographic image frames. 2D and Doppler echocardiography imaging (GE Vivid 7 Imaging System, version BT03−5; GE Healthcare, Canada) and analyses were performed in accordance with the American Society of Echocardiography guidelines with the use of an M4S probe using optimized windows, and were analyzed offline with the use of a proprietary workstation (Echopac, version 7, GE Healthcare). Depending on the HR condition, images were acquired at 70−120 frames/s, with higher frame rates at higher HR conditions.

Hemodynamic Analysis

Electrocardiography (ECG) and LV pressure were continuously digitally recorded (1,000 Hz) online. For each study condition, LV peak positive dP/dt (LV $+dP/dt_{max}$), LV peak negative dP/dt (LV $-dP/dt_{min}$), LV end-diastolic pressure (LVEDP), minimum LV pressure (LV_{min}), and LV systolic pressure (LVSP) were calculated offline with the use of a customized software program (Labview version 5.0; National Instruments Corp). The time constant of isovolumic relaxation (τ) was also calculated by means of 2 separate methods: the monoexponential method with the use of a nonzero asymptote (τ_M),[5] and the pressure half-time ($\tau_{1/2}$) method.[6] Arterial pressure was acquired continuously from the sidearm of the femoral sheath. These analyses were performed by a research technician blinded to the clinical status of the patient and the purpose of the study.

Analysis of Frequency-Dependent LV Characteristics

Protocol 1. For each HR condition, 50 consecutive beats from the 2nd minute of RA pacing were selected. If the preceding R-R interval was not within 2% of the planned pacing cycle length, the specific beat and the subsequent 5 beats were discarded. Per beat, τ, LV $+dP/dt_{max}$, LV $-dP/dt_{min}$, LVEDP, and LV_{min} were measured. The mean of these 50 cardiac cycles are reported. The relationship between HR and LV $+dP/dt_{max}$ (the force-frequency relationship) as well as τ (the relaxation-frequency relationship) were plotted.

Protocol 2. At each HR condition, we used LV pressure recordings and sonographic images to estimate the end-diastolic pressure volume relationship (EDPVR) as described by Klotz et al.[7] The calculation of EDPVR is dependent on estimates of cardiac volumes by transthoracic echocardiography. We did not