Beneficial Effects of Heart Rate Reduction on Cardiac Mechanics and Energetics in Patients With Left Ventricular Dysfunction

Toshiro Shinke, MD; Motoshi Takeuchi, MD; Hideyuki Takaoka, MD; Mitsuhiro Yokoyama, MD

It has been shown recently that the force-frequency relationship is blunted in experimental heart failure models. Furthermore, tachycardia is thought to have adverse effects on the diseased heart for several reasons, one of which is an increase in myocardial oxygen consumption. Inversely, the oxygen-saving effects of bradycardia may be beneficial for the treatment of heart failure. The aim of this study was to elucidate how heart rate (HR) modulates cardiac mechanics and energetics in patients with left ventricular (LV) dysfunction. LV pressure-volume data and myocardial oxygen consumption (MVO2) was assessed using conductance and coronary sinus thermodilution catheters in 14 patients with moderate LV dysfunction (mean ejection fraction 34%) under 3 conditions: (a) basal, (b) HR increased by 20% using atrial pacing, and (c) HR decreased by 16% using a specific bradycardic agent, zatebradine (7.5 mg po). Atrial pacing decreased external work (EW) (from 0.39 to 0.31 J beat\(^{-1}\) m\(^{-2}\), p<0.05) at a comparable MVO2 per beat with a marginal increase in LV contractility index (E\(_{es}\)) (from 2.34 to 2.76 mmHg ml\(^{-1}\) m\(^{-2}\), p=0.08), resulting in a decrease in mechanical efficiency (EW/MVO2) (from 25.9 to 22.1%, p<0.05). In contrast, zatebradine did not decrease E\(_{es}\) (from 2.34 to 2.24 mmHg ml\(^{-1}\) m\(^{-2}\), NS), but increased EW (from 0.39 to 0.42 J beat\(^{-1}\) m\(^{-2}\), p<0.05 vs basal level) without a change in MVO2 per beat, resulting in improved mechanical efficiency (from 25.9 to 29.7%, p<0.05 vs basal level). These results suggest that mild bradycardia is energetically advantageous and does not decrease myocardial contractility and performance, whereas pacing-induced tachycardia worsens cardiac mechanics and energetics in patients with LV dysfunction. Thus, the oxygen-saving effect of bradycardia may be beneficial for the treatment of heart failure. (Jpn Circ J 1999; 63: 957–964)

Key Words: Contractility; Heart rate; Left ventricular dysfunction; Oxygen consumption

Tachycardia is generally seen in patients with heart failure and is considered to be a marker of depressed left ventricular (LV) function, which reflects abnormal activation of the sympathetic nervous system. It has been shown in myocardial strips from end-stage heart failure that depression of systolic tension becomes more pronounced with increased heart rate (HR)\(^{1}\). Impaired force-frequency relations have also been demonstrated in patients with LV dysfunction\(^{2}\) and LV hypertrophy\(^{3}\). Although tachycardia may aid homeostasis by preserving cardiac output, it worsens the cardiac condition owing to an increase in myocardial oxygen consumption (MVO2) and a decrease in the time for myocardial relaxation and diastolic ventricular filling. Tachycardia itself may induce myocardial damage and hence aggravate heart failure\(^{4,5}\).

In contrast, modest bradycardia may have a beneficial effect in the treatment of heart failure if it reduces MVO2 and increases the myocardial capillary supply\(^{6}\). Many large, multicenter studies have suggested the beneficial effects of long-term \(\beta\)-blocker treatment in dilated cardiomyopathy and one of the underlying mechanisms of the beneficial effects is thought to be the reduction in HR, associated with a reduction in the harmful consequences of neurohormonal effects and retardation in the progression of LV dysfunction and ventricular remodeling\(^{7,8}\). An earlier study showed that the beneficial effect of \(\beta\)-blockade therapy is quantitatively related to a reduction in HR\(^{9}\). A beneficial effect of a reduction in HR has also been demonstrated for both ischemic regional dysfunction and catecholamine-induced myocardial damage\(^{10}\). Our previous study showed that in patients with LV dysfunction, acute \(\beta\)-blockade (negative inotropic plus negative chronotropic action) reduced MVO2 at the slower HR, whereas it did not reduce MVO2 when HR was kept constant with atrial pacing\(^{11}\). However, the influence of chronotropic action per se on cardiac energetics in patients with LV dysfunction has not been fully elucidated. Furthermore, most studies have focused on the alteration of mechanics by increasing HR with atrial pacing, not by decreasing HR below control conditions\(^{12}\). In the present study, we compared the alteration in cardiac mechanics and energetics during tachycardia (induced by atrial pacing) and bradycardia (induced by using a specific bradycardic agent).

Methods

Patient Population

Fourteen patients (mean age, 55±11 years; 11 males, 3...
females; 10 patients with previous myocardial infarction and 4 patients with idiopathic dilated cardiomyopathy) undergoing cardiac catheterization for the evaluation of heart disease were enrolled in this study (Table 1). All were in normal sinus rhythm and the LV ejection fraction (EF) was 34±12% (range, 23–53%). Nineteen patients with LV dysfunction (EF <55%) initially entered the study, but 5 did not complete the protocol because of unsuccessful pressure-volume (P-V) measurements during occlusion of the inferior vena cava or unstable coronary sinus thermodilution measurements. Patients with acute myocardial infarction, unstable angina pectoris, valvular heart disease, or high-risk hemodynamic instability were excluded. None of the patients had dyskinetic LV wall motion. Complete informed, written consent was obtained from each patient before the study. No unfavorable complications occurred as a result of this investigation. The study protocol was approved by the Institutional Committee on Human Research at Kobe University Hospital.

Catheterization Procedure

All diuretics and vasodilators were withheld for at least 24 h before the study. An 8F introducer sheath was placed into the right femoral artery and 8F and 9F introducer sheaths were placed into the right femoral vein using the Seldinger percutaneous technique. Patients underwent routine catheterization, including coronary angiography and left ventriculography. After completion of routine catheterization, a 2F thermocatheter (Swan-Ganz catheter (Goodtech Inc., USA) was advanced into the pulmonary artery and an 8F conductance (volume) catheter (CardioDynamics, Rijnsberg The Netherlands) was advanced into the left ventricle through the femoral artery. An 8F coronary sinus thermodilution catheter (Cordis Webster, Inc., USA) was advanced into the coronary sinus; the position of the catheter tip was confirmed by injection of contrast medium, as previously described.16 LV P-V relations were determined simultaneously using the conductance catheter attached to a stimulator/processor (Sigma-5, CardioDynamics) and a 2F Millar catheter (Millar Instruments, TX, USA) advanced into the left ventricle through the lumen of the conductance catheter. Continuous, slow infusion of heparinized saline solution through the lumen of the conductance catheter was maintained to prevent hemostasis. The calibration offset (parallel conductance) was corrected by matching the conductance catheter signal with the cineventriculographic volume data using the area-length method described in detail in our previous study.16 The stroke volume was defined as the difference between the LV end-diastolic volume and the LV end-systolic volume. The LVEF was calculated as the ratio of the stroke volume to the LV end-diastolic volume. The principle and accuracy of LV volume measurement using a conductance catheter have been described in earlier reports and in our previous study.18

Assessment of LV Contractility

After calibrations were completed, a balloon catheter (Baxter, CA, USA) was advanced to the right atrium just above the inferior vena cava to interrupt venous return. Pressure-volume loops for the sequence of beats after a reduction in preload resulting in a 30- to 40-mmHg decrease in LV systolic pressure were recorded over 8 to 10 beats. This procedure was repeated several times to exclude extrasystolic and postextrasystolic beats and obtain stable end-systolic P-V relations (Fig 1A).17 End-systolic P-V points were fitted using the linear least-squares technique during a transient decrease in LV pressure to determine

\[
\text{ESP} = \frac{E_{es} (\text{ESV} - V_0)}{\Delta} \quad (1)
\]

where ESP is the LV end-systolic pressure, E_{es} is the slope of the linear end-systolic P-V relation, ESV is the LV end-systolic volume, and V_0 is the intercept of the volume axis. E_{es} (mmHg/ml) has been applied to the LV of the intact animal and human as a relatively load-independent index of myocardial contractility.17,19-21 We normalized E_{es} (mmHg ml^{-1} m^{-2}) and V_0 (ml/m^2) for body surface area to permit comparison among patients in the present study, as described previously.21

Effective Arterial Elastance and Artery-Ventricule Coupling

We determined the effective arterial elastance (E_a), a variable that incorporates the values of Windkessel model elements and HR as the ratio of end-systolic pressure to stroke volume:22 Thus,

\[ E_a = \frac{\text{ESP}}{\text{SV}}, \]

where ESP is the end-systolic pressure, SV is the stroke volume, and E_a is the negative value of the slope of the diagonal line connecting the end-systolic P-V point and the end-diastolic point on the volume axis (Fig 1B). The dimensionless ratio of E_a to E_{es} (E_{es}/E_{es}) represents arterial-ventricular coupling.

Calculation of P-V Area

Systolic P-V area (PVA) (mmHg·ml) was calculated as the area that is bounded by the end-systolic and end-diastolic P-V relations and the systolic P-V trajectory of each beat (Fig 1B).19 It consists of potential energy (PE, the triangular area on the P-V plane) and external work (EW) and is considered to represent the total mechanical energy generated by contraction. EW was calculated as the area that is bounded by the P-V trajectory of one beat.15

Measurements of Myocardial Oxygen Consumption and Energy Conversion Efficiency

The coronary sinus catheter was advanced percutaneously through a right jugular vein to the great cardiac vein. In each instance, the catheter tip was angiographically verified to be beyond the origin of any visible intermediate or lateral branches and in proximity to the anterior cardiac

<table>
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<tr>
<th>Table 1  Baseline Characteristics of the Study Population</th>
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<tr>
<td>EF (%)</td>
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<tr>
<td>HR (beats/min)</td>
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<tr>
<td>MAP (mmHg)</td>
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<tr>
<td>LVSP (mmHg)</td>
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<td>EDP (mmHg)</td>
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<tr>
<td>RA (mmHg)</td>
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<tr>
<td>PAWP (mmHg)</td>
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<tr>
<td>CI (L/min⁻¹·m⁻²)</td>
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<tr>
<td>Peak + dP/dt (mmHg·s⁻¹)</td>
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<td>Peak – dP/dt (mmHg·s⁻¹)</td>
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<td>Tau (ms)</td>
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EF, ejection fraction; HR, heart rate; MAP, mean arterial pressure; LVSP, left ventricular peak-systolic pressure; EDP, end-diastolic pressure; RA, mean right atrial pressure; PAWP, mean pulmonary artery wedge pressure; CI, cardiac index; dP/dt, left ventricular pressure derivative; Tau, time constant of left ventricular pressure decay. Values are given as mean±SD.
Coronary sinus blood flow was measured at least twice using a coronary sinus catheter during a 30-s continuous injection of room-temperature indicator (5% glucose) through the catheter lumen at a rate of 40 ml/min using a Mark IV angiographic injector (Medrad, USA). Coronary venous blood was sampled from the distal lumen of the coronary sinus catheter for oximetry. MVO2 per min was calculated as the product of coronary sinus flow (ml/min) and the arterial-coronary sinus oxygen content difference (vol %), and was divided by HR to yield MVO2 per beat (ml O2/beat). We calculated mechanical efficiency as the ratio of EW (J/beat) to MVO2 per beat (J/beat), where 1 mmHg·ml of EW and 1 ml O2 of oxygen consumption correspond to 1.33·10–4 and 20 J, respectively. Thus, mechanical efficiency is dimensionless. Suga et al demonstrated that this efficiency can be divided into 2 stages: the efficiency of energy transfer from MVO2 to PVA (the conversion efficiency of metabolic energy to mechanical energy) and the energy transfer from PVA to EW (the conversion efficiency of mechanical energy to external work). We determined the energy conversion efficiency of these 2 stages and the mechanical efficiency as a measure of the overall energy conversion efficiency in each study protocol.

Study Protocol

Control Study At least 30 min after the routine heart catheterization, hemodynamic variables, P-V data, and coronary sinus blood flow were measured and blood gas samples were collected from the coronary sinus and femoral artery during spontaneous sinus rhythm. Then inferior vena cava occlusions were performed several times to obtain the end-systolic P-V relation (ESPVR). Pacing Study After control measurements were made, right atrial pacing was started to increase HR by 20% from control conditions and was continued for at least 15 min to achieve steady hemodynamic and contractile states. Then, we repeated the similar measurements to the control study. Zatebradine Study After all measurements under atrial pacing were completed, atrial pacing was stopped and hemodynamic variables were monitored for at least 15 min until they returned to the control values. Then 7.5 mg zatebradine (ULFS 49 CL) was administered orally. Zatebradine is a pure, sinus node inhibitor having negative chronotropic action without negative inotropic action.

Statistics

Results are presented as mean value±SD, unless otherwise indicated. We obtained end-systolic P-V relations by linear regression analysis. ANOVA was applied to compare the parameters in hemodynamics and energetics among the 3 studies. When ANOVA demonstrated statistical significance, the Wilcoxon method with Bonferroni correction was applied to compare the paired variables between the 3 studies. Differences were considered significant at a p value <0.05.

Results

Effects of Atrial Pacing on Hemodynamic Parameters (Table 2)

After atrial pacing at a rate of 20% above the control value (from 83±10 to 101±11 beats/min, p<0.01), the end-diastolic volume index (EDVI) and stroke volume index (SVI) decreased, whereas the end-systolic volume index (ESVI), cardiac index (CI), end-systolic pressure (ESP), end-diastolic pressure (EDP), peak positive dP/dt, peak negative dP/dt and tau remained unchanged.

Effects of Atrial Pacing on LV contractility and Myocardial Energetics (Table 3)

Ees, an index of left ventricular contractility, tended to increase during atrial pacing, whereas Es, an index of arterial afterload, increased. Consequently, Es/Ees tended to increase. As schematically shown in Fig 2A, the P-V loop shifted to the left, associated with a marginal increase in Ees and resulting in decreases in SV, EW and PVA. Coronary sinus flow (CSF) and MVO2 per min increased, depending on the increase in HR, but MVO2 per beat remained unchanged during atrial pacing. The ratio of EW to PVA tended to decrease from 39.5±15.0 to 37.4±15.5% (p=0.10), and the ratio of PVA to MVO2 decreased from...
### Table 2 Effect of Heart Rate on Hemodynamic Variables

<table>
<thead>
<tr>
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<th>Control</th>
<th>Pacing</th>
<th>Zatebradine</th>
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<tbody>
<tr>
<td>HR (beats/min)</td>
<td>83±10</td>
<td>101±11*</td>
<td>69±10**</td>
</tr>
<tr>
<td>PAWP (mmHg)</td>
<td>11±7</td>
<td>10±7</td>
<td>13±7</td>
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<tr>
<td>CI (L·min⁻¹·m⁻²)</td>
<td>3.04±0.66</td>
<td>3.14±0.63</td>
<td>2.81±0.68</td>
</tr>
<tr>
<td>ESP (mmHg)</td>
<td>141±16</td>
<td>137±21</td>
<td>135±21</td>
</tr>
<tr>
<td>EDP (mmHg)</td>
<td>24±9</td>
<td>26±9</td>
<td>26±9</td>
</tr>
<tr>
<td>Peak + dP/dt (mmHg·s⁻¹)</td>
<td>147±356</td>
<td>153±398</td>
<td>137±318</td>
</tr>
<tr>
<td>Peak – dP/dt (mmHg·s⁻¹)</td>
<td>-163±532</td>
<td>-169±539</td>
<td>-149±536</td>
</tr>
<tr>
<td>Tau (ms)</td>
<td>62±10</td>
<td>63±13</td>
<td>59±11</td>
</tr>
<tr>
<td>EDVI (ml·m⁻²)</td>
<td>71±32</td>
<td>71±30</td>
<td>74±32</td>
</tr>
<tr>
<td>SVI (ml·m⁻²)</td>
<td>33±9</td>
<td>26±8*</td>
<td>37±10*</td>
</tr>
<tr>
<td>EF (%)</td>
<td>34±12</td>
<td>32±15</td>
<td>36±13</td>
</tr>
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HR, heart rate; PAWP, mean pulmonary artery wedge pressure; CI, cardiac index; ESP, left ventricular peak-systolic pressure; EDP, end-diastolic pressure; + dP/dt and – dP/dt, positive and negative dP/dt, respectively; Tau, time constant of isovolumetric left ventricular pressure decay using the method of Raff and Glanz. Values are given as mean±SD. *p<0.05 compared with control, †p<0.05 compared with pacing.

### Table 3 Effect of Heart Rate on Cardiac Mechanics and Energetics

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Pacing</th>
<th>Zatebradine</th>
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<tbody>
<tr>
<td>Ees (mmHg·ml⁻¹·m⁻²)</td>
<td>2.34±1.21</td>
<td>2.76±1.85</td>
<td>2.24±1.10*</td>
</tr>
<tr>
<td>Ea (mmHg·ml⁻¹·m⁻²)</td>
<td>4.61±1.28</td>
<td>5.73±1.85*</td>
<td>3.81±1.05**</td>
</tr>
<tr>
<td>V0 (ml·m⁻²)</td>
<td>-2.7±25.5</td>
<td>2.9±25.0</td>
<td>1.6±28.5</td>
</tr>
<tr>
<td>EW (J·m⁻² per min)</td>
<td>31.7±11.2</td>
<td>31.5±12.4</td>
<td>28.3±9.7</td>
</tr>
<tr>
<td>PE (J·m⁻² per beat)</td>
<td>0.39±0.15</td>
<td>0.31±0.14*</td>
<td>0.42±0.15**</td>
</tr>
<tr>
<td>PVA (J·m⁻² per beat)</td>
<td>1.01±0.30</td>
<td>0.85±0.30*</td>
<td>1.01±0.28</td>
</tr>
<tr>
<td>CSF (ml·min⁻¹)</td>
<td>98.6±22.3</td>
<td>119.0±29.7*</td>
<td>79.8±22.9**</td>
</tr>
<tr>
<td>MVO2 (J·min⁻¹)</td>
<td>216±46</td>
<td>264±57*</td>
<td>174±46**</td>
</tr>
<tr>
<td>MVO2 (J·beat)</td>
<td>2.61±0.49</td>
<td>2.58±0.50</td>
<td>2.53±0.63</td>
</tr>
<tr>
<td>PVA/MVO2 (%)</td>
<td>68.0±27.7</td>
<td>58.7±24.7*</td>
<td>71.1±28.7</td>
</tr>
<tr>
<td>EW/PVA (%)</td>
<td>39.5±15.0</td>
<td>37.4±15.5</td>
<td>43.0±15.4*</td>
</tr>
<tr>
<td>EW/MVO2 (%)</td>
<td>25.9±11.5</td>
<td>22.1±11.5*</td>
<td>29.5±13.3**</td>
</tr>
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</table>

Ees, left ventricular contractility index; Ea, arterial afterload index; V0, volume intercept; EW, external work; PE, potential energy; PVA, pressure-volume area; CSF, coronary sinus flow; MVO2, myocardial O2 consumption. Values are given as mean±SD. *p<0.05 compared with control, †p<0.05 compared with pacing.

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**Fig 2.** Schematic representation of the chronotropic effect the pressure-volume relation. (A) Atrial pacing caused a leftward shift of the pressure-volume loop and decreased SV, EW, and PVA. (B) Heart rate reduction induced by the negative chronotropic effect of zatebradine caused a rightward shift of the pressure-volume loop and increased SV and EW with no significant change in PVA.

**Fig 3.** Changes in the ratio of EW/PVA (left panel), PVA/MVO2 (middle panel) and EW/MVO2 (right panel). Atrial pacing reduced the ratio of PVA/MVO2 and EW/MVO2. Zatebradine increased the ratio of EW/PVA and EW/MVO2. *p<0.05.
68.0±27.7 to 58.7±24.7% (p<0.05), resulting in a decrease in the mechanical efficiency from 25.9±11.5 to 22.1±11.5% (p<0.05) (Fig 3).

There was no change in ECG, which would indicate developing myocardial ischemia during atrial pacing.

Effects of Zatebradine on Hemodynamic Parameters (Table 2)

After administration of zatebradine, HR decreased by 16% from the control value (from 83±10 to 69±10 beats/min, p<0.01). EDVI and SVI increased without changes in ESVI and CI. EDP, ESP, peak positive dP/dt, peak negative dP/dt, and tau remained unchanged.

Effects of Zatebradine on LV Contractility and Myocardial Energetics (Table 3)

Zatebradine did not change Ees, but decreased Ea, resulting in a decrease in Ea/Ees. As schematically shown in Fig 2B, the P-V loop shifted to the right associated with an unchanged Ees, resulting in increases in SV and EW. CSF and MVO2 per min decreased depending on the decrease in HR, but MVO2 per beat remained unchanged. The ratio of EW to PVA increased from 39.5±15.0 to 43.0±15.4% (p<0.05), and the ratio of PVA to MVO2 tended to increase from 68.0±27.7 to 71.1±28.7% (p=0.12), resulting in an increase in the mechanical efficiency from 25.9±11.5 to 29.7±13.3% (p<0.05) (Fig 3).

Discussion

The principal findings of the present study were as follows.

(1) A 20% increase in HR by atrial pacing and a 16% decrease in HR by zatebradine did not change Emax and MVO2 per beat significantly.

(2) Atrial pacing decreased mechanical efficiency due to a decrease in EW and an unchanged MVO2 per beat.

(3) HR reduction with zatebradine increased mechanical efficiency due to an increase in EW and an unchanged MVO2 per beat in patients with LV dysfunction.

Influence of HR on LV Contractility

Frequency potentiation of contractile force is considered to be a major physiological mechanism for the intrinsic regulation of myocardial contractility.27 It has been well established that frequency potentiation of contractile force occurs in the intact human heart.28 In intact conscious dogs, Freeman et al demonstrated that Ees increased to 238% of control levels when HR increased from 100 to 200 beats/min (bpm); autonomic blockade did not influence the results.29 In contrast, reversal of the force-frequency relationship has been demonstrated in isolated papillary muscle and myocardial strips from animals30-32 and humans with end-stage heart failure.33-36 Asano et al showed an attenuated inotropic response to HR in conscious autonomic-blocked dogs with pacing-induced heart failure.37 These data suggest that the force-frequency relationship may be blunted in the human failing heart. However, there are few clinical data on the relation between HR and LV contractility in patients with LV dysfunction.

In the present study of patients with LV dysfunction, a 20% increase in HR induced by atrial pacing and a 16% reduction induced by zatebradine elicited a modest change in Ees that was not significant. Although we did not compare the effects of HR on LV contractility with that of a normal group, we observed a positive correlation between the changes in Ees during atrial pacing and baseline LVEF (Fig 4). Thus, frequency potentiation of contractile force should be blunted in patients with severe LV dysfunction. Similar results have been observed in patients with varying degrees of ventricular dysfunction2 and in patients with dilated cardiomyopathy compared with patients with normal LV function.2 The mechanism whereby the force-frequency relationship is altered has not yet been elucidated. However, ours is the first study to describe the effect of both increasing and decreasing HR on the ESPVR in patients with heart failure and demonstrated that HR-dependent augmentation of Ees was blunted in patients with severe LV dysfunction.

Effect of Atrial Pacing on Cardiac Mechanics and Energetics

In the present study, on a per min basis, MVO2 per min increased during atrial pacing, whereas EW per min did not change. On a per beat basis, MVO2 per beat did not change during atrial pacing, whereas EW per beat even decreased. Consequently, mechanical efficiency (ie, EW/MVO2) decreased significantly regardless of per min or per beat basis.

Changes in the EW per beat during atrial pacing could be influenced by LV inotropic responses to tachycardia, as well as inotropic responses. Previous investigators consistently observed impaired LV diastolic relaxation and filling dynamics in congestive heart failure;38,39 thus, increased HR may aggravate filling dynamics in the diseased heart. Although tachycardia did not change end-diastolic pressure and tau significantly in the present patients, it might have reduced early diastolic filling and total filling volumes depending on the duration of the diastolic period. The impaired filling dynamics during atrial pacing, which were not estimated, may partially contribute to the decrease in EW, as well as the inotropic responses in patients with LV dysfunction.

Although HR is one of the major determinants of MVO2, how HR modulates MVO2 per beat is controversial. Weber et al reported that MVO2 per beat decreased by 13–25% of control values as HR was increased from 120 to 180 beats/min by atrial pacing in the isolated dog heart.40 In contrast, Boerth et al observed a slight increase in MVO2 per beat as HR was increased from 100 to 200 beats/min.41 In the present study, MVO2 per beat remained unchanged.
whereas EW decreased during atrial pacing. Consequently, mechanical efficiency (EW/MVO₂) decreased significantly regardless of the per beat or per min basis.

The effects of pacing-induced tachycardia on mechanical efficiency can be assessed in terms of PVA as proposed by Suga.¹⁹ Mechanical efficiency can be expressed as the product of the ratio of EW to PVA and the ratio of PVA to MVO₂. As previously confirmed in conscious dogs and the human heart, the theoretical framework of PV plane analysis shows that the heart can transfer more mechanical energy from PVA to EW in proportion to a decrease in $E_a/E_s$. Our recent study also confirmed this theoretical framework in patients with moderate heart failure. In the present study, atrial pacing tended to increase $E_a/E_s$ and decreased the ratio of EW to PVA, although those did not reach statistical significance.

The total MVO₂ at a given PVA consists of the sum of the PVA-dependent MVO₂ and PVA-independent MVO₂ (the MVO₂ used for basal metabolism and excitation-contraction coupling). The increase in LV contractility, $E_s$, is accompanied by an increase in PVA-independent MVO₂ and shifts the PVA-MVO₂ relationship upward so that the production of the same PVA requires a larger MVO₂.¹⁹ Therefore, the ratio of PVA to MVO₂ decreases as PVA decreases or $E_s$ increases. In the present study, a decrease in PVA and a modest increase in $E_s$ during atrial pacing resulted in a significant decrease in the ratio of PVA to MVO₂. Therefore, pacing-induced tachycardia could aggravate the conversion efficiency of MVO₂ to PVA as well as that of PVA to EW.

Effect of Zatebradine on Cardiac Mechanics and Energetics

There are many clinical reports that support the beneficial effect of HR slowing on cardiac function and mortality in patients with congestive heart failure (CHF). In several multicenter trials with β-blockers, the beneficial effects included a reduction in HR, an increase in EF, a decrease in hospital admission due to progression of heart failure and a benefit trend toward improved survival in patients with heart failure. Moreover, β-blockers with intrinsic sympathomimetic activating effects (pindolol, xametol, practolol etc) were not effective in reducing HR, increasing EF or improving prognosis.

Besides β-blockers, a randomized trial of the low-dose, anti-arrhythmic agent, amiodarone, in severe CHF reported a 28% reduction in overall 2-year mortality.⁴⁵ In that study, amiodarone reduced mortality in patients with a baseline HR >90 beats/min. Moreover, patients with a higher baseline HR showed a more dramatic reduction during amiodarone treatment. Amiodarone slows the sinus HR as well as its anti-arrhythmic action. Thus, these findings suggest that amiodarone-induced HR slowing may be one of the mechanisms improving cardiac function and survival.

In the present study, a 16% reduction in HR induced by zatebradine (negative chronotropic action alone) increased EW in association with increases in EDV and SV due to the prolongation of the diastolic period and the resultant increases in filling volume. In spite of the preload augmentation, MVO₂ per beat remained unchanged, as reported by earlier studies.⁴⁶,⁴⁷ Thus, the 16% reduction in HR induced by zatebradine did not decrease $E_s$ or increase MVO₂, but increased EW, improving mechanical efficiency in patients with LV dysfunction. In contrast, in our previous study a 15% reduction in HR induced by propranolol (negative chronotropic and inotropic action) decreased $E_s$, but did not increase EW or mechanical efficiency.¹¹ Thus bradycardia per se may contribute to the improvement of mechanical efficiency in patients with LV dysfunction.

In the present study, HR reduction induced by zatebradine increased the ratio of EW to PVA in proportion to the decrease in $E_a/E_s$, but did not alter the ratio of PVA to MVO₂. Thus, in the moderately depressed heart, preload augmentation induced by heart rate reduction does not seem to worsen the conversion efficiency of MVO₂ to PVA. These mechanoenergetical advantages of HR reduction may be an important therapeutic target for the treatment of heart failure.

Study Limitations

There are several limitations in the present study. First, although HR is modulated by the autonomic nervous system, we performed this study without autonomic blockade. Thus, we could not exclude the effects of reflex sympathetic stimulation elicited by pacing-induced hypotension, which might augment the inotropic state.¹⁸ Second, we administered zatebradine to reduce HR. Zatebradine is a substituted benzazepinone that is structurally similar to verapamil and is believed to act selectively at the sinoatrial node, having only negative chronotropic effects without concomitant effects on cardiac contractility, conduction velocity, or refractoriness.²⁵–²⁶ The precise mechanism of its negative chronotropic action is somewhat controversial, but it has been proposed that zatebradine may work by inhibiting the hyperpolarizing current (If) at the sinoatrial (SA) node.³⁹ Third, the hearts of the patients studied were not severely depressed. The results might be different in patients with severe heart failure due to the greater adrenergic drive. Moreover, if patients with more severe heart failure have ‘stiff’ left ventricles and limited preload reserve, HR reduction could neither increase SV or EW nor improve mechanical efficiency. Therefore, our findings can be applied only to the patients with mild to moderate heart failure. Fifth, although a 16% reduction in HR did not decrease cardiac output owing to an increase in SV, whether further HR reduction would be beneficial for heart failure is not clear. Sixth, in the present study, a 20% increase and 16% reduction in HR did not change MVO₂ per beat. It needs to be elucidated whether MVO₂ might not alter over a wide range of changes in HR in patients with LV dysfunction. Finally, we focused on the short-term effects of atrial pacing and HR reduction on cardiac mechanics and energetics. The results of the present study do not imply that HR slowing by a sinus node inhibitor may improve long-term mortality in patients with CHF. Pharmacological attenuation of activated neurohormonal factors, including catecholamine, the renin-angiotensin-aldosterone system, endothelin etc, may play a central role in improving function and survival. Our results suggest that HR reduction may be an adjunctive and supportive therapy in the treatment of CHF using angiotensin-converting enzyme inhibitors and β-blockers. Further studies will be needed to examine prospectively whether HR reduction itself has a long-term effect in ameliorating cardiac dysfunction in patients with heart failure.

Clinical Implications

These findings suggest that, in contrast to pacing-induced tachycardia, HR reduction is energetically advan-
tageous in patients with mild to moderate heart failure. Because failing hearts are thought to be in a critical state of cardiac energetics, further energy consumption induced by tachycardia could be disastrous. Experimental studies have demonstrated that specific bradycardic agents, or bradycardial pacing, protect myocardium damaged by acute ischemia or high doses of norepinephrine. As the force-frequency relationship is altered in the failing heart, bradycardia has little depressive effect on LV contractility. Therefore, it is likely that the energy-saving effect of bradycardia would be beneficial in the failing heart.

Conclusions

In patients with heart failure, tachycardia caused cardiac energetics to deteriorate. In contrast, HR reduction was energetically advantageous without depressing cardiac mechanics. The oxygen-saving effect of bradycardia may be beneficial in the treatment of heart failure.

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