Contributions of heart rate and contractility to myocardial oxygen balance during exercise

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Colin, Patrice, Bijan Gahleh, Xavier Monnet, Jinho Su, Luc Hittinger, Jean-François Giudicelli, and Alain Berdeaux. Contributions of heart rate and contractility to myocardial oxygen balance during exercise. Am J Physiol Heart Circ Physiol 284: H676–H682, 2003. First published October 24, 2002; 10.1152/ajpheart.00564.2002.—The respective contributions of heart rate (HR) reduction and left ventricular (LV) negative inotropy to the effects of antianginal drugs are debated. Accordingly, eight instrumented dogs were investigated during exercise at spontaneous and paced HR (250 beats/min) after administration of either saline, atenolol, or ivabradine (selective pacemaker current channel blocker). During exercise, atenolol and ivabradine (both 1 mg/kg iv) similarly reduced HR (~30% from 222 ± 5 beats/min), and LV mean ejection wall stress was not altered. LV dP/dtmax was reduced by atenolol but not ivabradine. Diastolic time (DT)3 was increased by atenolol versus saline (195 ± 6 vs. 123 ± 4 ms, respectively) and to a greater extent by ivabradine (233 ± 11 ms). Myocardial oxygen consumption (MV̇O2) was lower under ivabradine and atenolol versus saline (6.7 ± 0.6 and 4.7 ± 0.4 vs. 8.1 ± 0.6 ml/min, respectively, P < 0.05). Under pacing, DT and MV̇O2 were similar between ivabradine and saline but significantly reduced with atenolol. Thus HR reduction and negative inotropy equally contribute to the reduction in MV̇O2 during exercise in the normal heart. The negative inotropy limits the increase in DT afforded by HR reduction.

Although it is well known that reductions in heart rate and myocardial contractility are both major mechanisms involved in the antianginal effect of β-blockers, the relative contributions of these two parameters to the therapeutic properties of these drugs are still debated. Heart rate reduction is indeed critical to reduce exercise-induced ischemia by increasing subendocardial myocardial blood flows and diastolic perfusion time (12) and by decreasing myocardial oxygen consumption (MVO2). Accordingly, Guth et al. (13) abolished the anti-ischemic effect of atenolol through atrial pacing during exercise-induced ischemia, suggesting that the negative inotropic effect of this β-blocker was negligible in this setting. Furthermore, zatebradine and ivabradine, two selective heart rate-reducing agents devoid of any negative inotropic effect, afforded significant anti-ischemic effects during exercise-induced ischemia in conscious dogs (12, 18) and pigs (16). In contrast, Buck et al. (2) reported only a partial attenuation of the beneficial effects of β-blockade on myocardial blood flow distribution and dynamic severity of a proximal coronary artery stenosis after atrial pacing. Two clinical trials using zatebradine failed to reveal any antianginal activity secondary to the sole reduction in heart rate (8, 9). However, in these studies, reduction in heart rate might have induced changes in other determinants of MVO2, e.g., loading conditions. Furthermore, in these studies, the potential beneficial effects of heart rate reduction on diastolic time, i.e., one of the major determinants of myocardial oxygen supply, were not investigated.

In this context, the aim of the present study was to compare the effects of the β-blocker atenolol with those of the selective blocker of the sinus node pacemaker current channel ivabradine (18, 20, 21) on myocardial oxygen balance at rest and during treadmill exercise in conscious dogs with normal hearts. Myocardial oxygen supply (estimated by the diastolic time) and demand (heart rate, left ventricular contractility, and wall stresses) as well as MVO2 were simultaneously measured or calculated after administration of either saline, ivabradine, or atenolol. Drug-induced changes in heart rate were also corrected by atrial pacing both at rest and during exercise.

METHODS

The animal instrumentation and the experiments were performed in accordance with the official regulations of the French Ministry of Agriculture (approval n°A 94-043-12).

Instrumentation. Eight mongrel dogs (20–30 kg) were anesthetized with pentobarbital sodium (30 mg/kg iv), intubated, and ventilated with oxygen-enriched room air. A left thoracotomy was performed through the fifth intercostal space using sterile technique. Fluid-filled Tygon catheters...
were placed in the descending thoracic aorta and the left atrium. Silastic catheters were implanted in the pulmonary artery and in the coronary sinus. A solid-state pressure transducer (P7A, Konigsberg Instruments; Pasadena, CA) was introduced into the apex of the left ventricle (LV). A flow probe (Transonic Systems; Ithaca, NY) was placed on the left circumflex coronary artery for continuous measurement of coronary blood flow. Piezoelectric ultrasonic dimension crystals were implanted 1) on opposed anterior and posterior endocardial surfaces of the LV to measure LV internal diameter and 2) on opposed LV endocardial and epicardial surfaces to measure wall thickness. Finally, stainless steel wires were sewn to the left atrial appendage for subsequent electrical pacing. All catheters and wires were exteriorized between the scapulas, and the pneuemothorax was evacuated. Cefazolin (1 g iv) and gentamicin (40 mg iv) were administered before and during the first week after surgery. Bu- prenorphine (0.3 mg sc) was also administered during this period. The position of all catheters and crystals was confirmed at autopsy.

**Hemodynamic measurements.** All hemodynamic data were continuously recorded, digitized, and analyzed using HEM v3.2 software (Notocord Systems; Croissy sur Seine, France). Aortic and left atrial pressures were measured with a Statham P23 ID strain-gauge transducer (Statham Instruments; Oxnard, CA). Coronary blood flow was measured using a T206 blood flowmeter (Transonic Systems; Ithaca, NY). LV pressure (LVP), LV internal diameter, and LV wall thickness were digitized at 500 Hz. LVP was calibrated in vitro with a mercury manometer and in vivo with the left atrial and aortic pressures. The maximal change in LVP over time (LV dP/dt max) was computed from the LVP signal. LV end diastole was defined as the initiation of the upstroke of LVP tracing, and LV end systole was defined as the point of maximum negative LV dP/dt. LV end-systolic and end-diastolic wall stresses were calculated with a cylindrical model as

\[
\text{Stress} = 1.36 \times (\text{LVP} \times \text{ID}/2h)
\]

where ID is the internal short-axis diameter and h is wall thickness, each of these parameters being measured at end systole and end diastole. The LV peak systolic wall stress was computed as the maximal value of LV wall stress during the ejection period. The integral of the systolic wall stress-time curve so-called mean ejection wall stress was calculated during the ejection period, i.e., from the maximum positive LV dP/dt to the maximum negative LV dP/dt. Percent wall thickening was defined as end-systolic minus end-diastolic thickness divided by end-diastolic thickness times 100.

**LV oxygen consumption.** Measurement of oxygen content was made with a blood gas apparatus and a cooxymeter (BG III synthesis). Oxygen delivery to the LV myocardium was calculated as the product of mean coronary blood flow and arterial oxygen content. Oxygen consumption was calculated as the product of mean coronary blood flow and the arteriovenous difference in oxygen content. Oxygen extraction was calculated as the arteriovenous difference in oxygen content divided by the arterial oxygen content. Assumption was made that left circumflex coronary artery blood flow was proportional to the total LV coronary blood flow. Piezoelectric ultrasonic crystals were implanted at the end of this stage.

A second set of measurements and blood sample collection were performed 15 min after the onset of drug administration, both at spontaneous heart rate (Rest drug) and during a sequence of 5 min of atrial pacing at a rate of 125 beats/min (Rest drug paced). Treadmill exercise (10 km/h, slope 13%, 10 min) was then started. The first 5 min of exercise were performed at spontaneous heart rate with a set of measurements and blood samples collection being performed when a hemodynamic steady state was achieved (Exercise drug). The last 5 min of exercise were performed under atrial pacing at a rate of 250 beats/min (Exercise drug paced) with a last set of measurements and blood sample collection being performed at the end of this stage.

Each dog underwent three experimental sequences (saline, ivabradine, and atenolol), which were performed in random order 1 wk apart. Ivabradine and atenolol were administered through the pulmonary artery catheter as an intravenous bolus at a dose that induced equipotent reduction in heart rate at rest and during exercise, i.e., 1 mg/kg infused over 5 min in a volume of 10 ml saline. Saline was administered in the same conditions.

**Statistical analysis.** All results are means ± SE. Statistical analysis was performed with two-way (drug, n = 3; and time point, n = 5) ANOVA for repeated measures. When overall differences were detected, individual comparisons among drugs at each time point only were performed by paired Student’s t-test with Bonferroni’s correction. The statistical analysis was performed using Statview 5.0 software (Abacus Concept; Berkeley, CA). A value of P < 0.05 was considered as statistically significant.

**RESULTS**

**Hemodynamics at rest.** As shown in Table 1, baseline hemodynamic values were not significantly different among the three sequences of the protocol, and none of these parameters was altered at rest after saline administration. Atenolol and ivabradine decreased heart rate at rest compared with saline (−8 and −16%, respectively). Atenolol but not ivabradine significantly reduced LV dP/dt max compared with saline. Atrial pacing abolished the bradycardic effect of both drugs but not the negative inotropic properties of atenolol. LV end-diastolic pressure was significantly increased by both atenolol and ivabradine, and this effect was abolished by atrial pacing with ivabradine but not with atenolol.

As shown in Table 2, the increase in LV end-diastolic wall stress induced by atenolol and ivabradine was abolished by atrial pacing. Interestingly, none of the two drugs altered mean ejection wall stress compared with saline.

**Hemodynamics during exercise.** As shown in Table 1, both ivabradine and atenolol decreased the exercise-induced tachycardia to the same extent (151 ± 5 and 152 ± 4 beats/min, respectively, vs. 222 ± 5 beats/min under saline). Exercise-induced increase in LV dP/dt max was strongly and significantly reduced by atenolol but not by ivabradine. The effects of atenolol on LV dP/dt max were not corrected by atrial pacing. Exercise-induced increase in peak systolic LV pressure was not altered by ivabradine, whereas it was significantly reduced by atenolol. Both atenolol and ivabradine increased LV end-diastolic pressure, and this effect was
abolished by atrial pacing with ivabradine but not with atenolol.

As shown in Table 2, atenolol, but not ivabradine, reduced the exercise-induced increase in LV peak systolic wall stress. LV end-diastolic wall stress was significantly increased with ivabradine and atenolol compared with saline. This effect was the consequence of significant changes in LV end-diastolic pressure but also to significant increases in LV end-diastolic internal diameter and decreases in LV end-diastolic wall thickness, although not significant for ivabradine (significant for atenolol and a trend for ivabradine). Atrial pacing abolished the effects of ivabradine on LV end-diastolic wall stress but not those of atenolol. Importantly, the exercise-induced increase in LV mean ejection wall stress observed under saline was not significantly altered by atenolol and ivabradine.

Table 2. Effects of saline, ivabradine, and atenolol on loading conditions at rest and during exercise

<table>
<thead>
<tr>
<th>Drug</th>
<th>Baseline</th>
<th>Rest</th>
<th>Paced Rest</th>
<th>Exercise</th>
<th>Exercise Paced</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV mean ejection WS, g/cm²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline</td>
<td>349 ± 26</td>
<td>349 ± 26</td>
<td>351 ± 28</td>
<td>424 ± 37</td>
<td>409 ± 45</td>
</tr>
<tr>
<td>I vabradine</td>
<td>354 ± 24</td>
<td>383 ± 32</td>
<td>381 ± 31</td>
<td>444 ± 31</td>
<td>394 ± 28</td>
</tr>
<tr>
<td>Atenolol</td>
<td>356 ± 21</td>
<td>380 ± 28</td>
<td>373 ± 29</td>
<td>441 ± 19</td>
<td>399 ± 26</td>
</tr>
<tr>
<td>LV peak systolic WS, g/cm²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline</td>
<td>442 ± 29</td>
<td>452 ± 26</td>
<td>440 ± 20</td>
<td>618 ± 46</td>
<td>596 ± 58</td>
</tr>
<tr>
<td>I vabradine</td>
<td>449 ± 32</td>
<td>460 ± 36</td>
<td>466 ± 37</td>
<td>625 ± 42</td>
<td>581 ± 52</td>
</tr>
<tr>
<td>Atenolol</td>
<td>449 ± 37</td>
<td>482 ± 36</td>
<td>471 ± 38</td>
<td>554 ± 32†</td>
<td>493 ± 35†</td>
</tr>
<tr>
<td>LV end-diastolic WS, g/cm²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline</td>
<td>26 ± 2</td>
<td>26 ± 2</td>
<td>23 ± 3</td>
<td>66 ± 10</td>
<td>41 ± 8</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>26 ± 2</td>
<td>48 ± 7</td>
<td>23 ± 9</td>
<td>107 ± 13*</td>
<td>37 ± 7</td>
</tr>
<tr>
<td>Atenolol</td>
<td>28 ± 1</td>
<td>46 ± 4</td>
<td>36 ± 5</td>
<td>115 ± 5*</td>
<td>77 ± 8†</td>
</tr>
<tr>
<td>LV end-diastolic WT, mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline</td>
<td>8.8 ± 0.4</td>
<td>8.8 ± 0.4</td>
<td>8.5 ± 0.4</td>
<td>8.3 ± 0.5</td>
<td>8.3 ± 0.6</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>8.7 ± 0.4</td>
<td>8.2 ± 0.3</td>
<td>8.8 ± 0.4</td>
<td>8.5 ± 0.3</td>
<td>8.9 ± 0.5</td>
</tr>
<tr>
<td>Atenolol</td>
<td>8.7 ± 0.4</td>
<td>8.2 ± 0.3</td>
<td>8.6 ± 0.4</td>
<td>7.9 ± 0.3*</td>
<td>8.1 ± 0.5</td>
</tr>
<tr>
<td>LV end-diastolic ID, mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline</td>
<td>46.8 ± 1.3</td>
<td>46.8 ± 1.3</td>
<td>47.0 ± 1.3</td>
<td>47.6 ± 1.1</td>
<td>47.3 ± 1.2</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>46.8 ± 1.3</td>
<td>47.5 ± 1.4</td>
<td>46.7 ± 1.5</td>
<td>48.4 ± 1.3</td>
<td>47.3 ± 1.8</td>
</tr>
<tr>
<td>Atenolol</td>
<td>46.9 ± 1.5</td>
<td>48.5 ± 2.1</td>
<td>48.2 ± 2.2</td>
<td>51.2 ± 1.9*</td>
<td>49.0 ± 2.1</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 8. Dose for ivabradine and atenolol was 1 mg/kg. WS, Wall stress; WT, wall thickness; ID, internal diameter. *P < 0.05, significantly different from saline; †P < 0.05, atenolol significantly different from ivabradine.
diastolic time was significantly increased by atenolol and, to an even greater extent, by ivabradine. Under atrial pacing, these effects of ivabradine were abolished. In contrast, with atenolol, the diastolic time was significantly reduced under atrial pacing compared with saline, and LV ejection time was increased ($P < 0.05$) (Fig. 2). There was an average of 20 ms difference in the diastolic time, favoring ivabradine versus atenolol during exercise performed under atrial pacing. At spontaneous heart rate, this difference averaged 38 ms.

**LV oxygen consumption.** As shown in Table 3, neither saline, atenolol, nor ivabradine had any effect on resting coronary blood flow or myocardial oxygen handling at spontaneous and paced heart rates.

Both coronary blood flow and $MV_{O_2}$ increased during exercise after saline administration. In these conditions, the exercise-induced increase in $MV_{O_2}$ was reduced by 17% by ivabradine and by 42% by atenolol (Fig. 3). During atrial pacing, this effect of ivabradine was abolished, but atenolol still decreased $MV_{O_2}$ by 27%. The exercise-induced increase in coronary blood flow was reduced by 20% by ivabradine and by 43% by atenolol. During atrial pacing, this effect of ivabradine was abolished but atenolol still decreased coronary blood flow by 28%. Finally, compared with saline, ivabradine and atenolol similarly increased myocardial $O_2$ extraction during exercise, and this effect was abolished during atrial pacing.

**DISCUSSION**

In this study, the comparison between a β-blocker and a selective heart rate-reducing agent provides evidence for equal and additive contributions of the reduction in heart rate and in myocardial inotropy at limiting the exercise-induced increase in $MV_{O_2}$ in conscious dogs with normal heart. These changes in myocardial oxygen demand are accompanied by alterations in the diastolic time, the heart rate reduction resulting in a prolongation of this time interval. This effect is greater with ivabradine compared with atenolol, which increases the ejection time as a consequence of its negative inotropic properties.

On the basis of previous reports (4, 20), the doses of atenolol and ivabradine were chosen as those inducing a similar reduction in heart rate both at rest and during exercise. At the investigated doses, atenolol significantly reduced myocardial inotropy during exercise, whereas increases in LV $dP/dt_{max}$ observed under ivabradine were similar to those induced by saline, both at spontaneous and paced heart rates. Interestingly, LV end-diastolic wall stress was similarly affected by both drugs and LV mean ejection wall stresses, i.e., LV afterload, was not significantly different after saline, ivabradine, or atenolol. In agreement with previous studies (3, 15), atenolol decreased LV peak systolic wall stress, and this effect was accompanied by an increase in LV dimension (data not shown).
and a prolonged ejection time (Fig. 1). Because loading conditions were similar, it seems reasonable to consider that changes in time intervals and MV\(\dot{O}_2\) induced by both drugs were mainly due to heart rate reduction and/or to a negative inotropic effect in our experimental conditions. Finally, one should remind that stroke work is an important correlate of MV\(\dot{O}_2\) (19), but this was not evaluated in this study.

In these conditions, heart rate reduction was accompanied by a significant prolongation of the diastolic time as previously reported with other selective heart rate reducing agents (11). This phenomenon was significantly greater with ivabradine than with atenolol for a similar reduction in heart rate. Indeed, LV ejection time, a major determinant of diastolic time, was significantly increased by atenolol, probably as a consequence of its negative inotropic effect (6). The significance of diastolic time as a determinant of subendocardial perfusion has been well demonstrated in experimental studies performed in the normal heart showing that a 1% increase in diastolic time fraction by reducing heart rate increases subendocardial blood flow by 2.6 to 6% (1). Interestingly, it has been shown in patients with a marked reduction of the coronary diameter that a small reduction in diastolic time (~2–5 s/min) could induce myocardial ischemia (5, 7). Therefore, during exercise, compared with atenolol, a prolongation of ~5.7 s/min (151 beats/min × 38 ms) of diastolic time favoring ivabradine may be clinically relevant because Ferro et al. (7) previously indicated the relevant role of diastolic perfusion time in determining myocardial ischemia. These effects on myocardial oxygen supply were accompanied by simultaneous changes in MV\(\dot{O}_2\). Hence, ivabradine decreased MV\(\dot{O}_2\) at peak exercise, and this effect was solely related to heart rate reduction because it was abolished by atrial pacing. When heart rate reduction was combined with negative inotropy with atenolol, MV\(\dot{O}_2\) was reduced to a greater extent (~43%), and during atrial pacing, the sole reduction in LV dP/dt\(_{\text{max}}\) reduced MV\(\dot{O}_2\) by 27%. This result confirms that the negative inotropic properties of atenolol importantly participate to the MV\(\dot{O}_2\)-sparing effect of the drug. Therefore, in a normal heart, the combination of a reduction in heart rate and of a
negative inotropic effect appears to be additive at limiting the increase in \( MV_{O_2} \), and indexes that do not take into account LV contractility as a predictor of \( MV_{O_2} \) during an exercise underestimate the increase in energy cost arising from increased contractility.

The analysis of our results allows to quantify more precisely the relative contributions of heart rate and myocardial inotropy as determinants of \( MV_{O_2} \) during exercise. Indeed, when we compare the corresponding changes in \( MV_{O_2} \) after ivabradine and atenolol administration, one might conclude that a reduction of \( \sim 50\% \) in \( LV\ dp/dt_{max} \) is responsible for a decrease of \( \sim 25\% \) in \( MV_{O_2} \) at peak exercise. Concerning heart rate, when neglecting the difference in \( LV\ dp/dt_{max} \) secondary to the tresse effect, the comparison of ivabradine with saline indicates that a decrease of \( \sim 50\% \) in heart rate is accompanied by a reduction of \( \sim 20\% \) in \( MV_{O_2} \). In other words, the reductions in heart rate and myocardial inotropy almost equally participate to the decrease in myocardial oxygen demand during exercise in conscious dogs. Concerning the role of tachycardia in mediating the coronary hemodynamic response to severe exercise, our results are consistent with those of Vatner et al. (22), reporting that changes in heart rate accounted for about one-third of the increment in coronary blood flow during strenuous exercise. Regarding myocardial oxygen supply, a reduction of \( \sim 50\% \) in heart rate induces an increase of \( \sim 139\% \) in diastolic time but of only \( 92\% \) when \( LV\ dp/dt_{max} \) is concomitantly reduced by \( \sim 50\% \). Extrapolation of these quantifications to other situations than exercise should be cautious because we did not observe such responses at rest after administration of either atenolol or ivabradine, i.e., when sympathetic tone is low. In addition, these results obtained in the normal heart might partly explain the deleterious effects on regional myocardial blood flows observed by Guth et al. (13) during exercise-induced ischemia under atenolol when heart rate reduction was prevented by atrial pacing. The lack of stroke volume measurement might represent a limitation of these results as stroke work is an important correlate of \( MV_{O_2} \) (19).

In the present study, all changes in coronary blood flow induced by atenolol and ivabradine during exercises performed at spontaneous or paced heart rates were closely related to the variations in \( MV_{O_2} \). However, myocardial \( O_2 \) extraction was significantly and similarly increased by both drugs during exercise, and there was a trend for lower oxygen venous tension compared with saline, although the \( O_2 \) delivery to \( O_2 \) consumption ratio was similar. This would indicate that the increased metabolic requirements of the myocardium during exercise were not fully met by the increase in coronary blood flow. Because changes in myocardial \( O_2 \) extraction were abolished by atrial pacing, one might speculate that partial loss of flow-dependent vasodilation contributes to this phenomenon. Concerning atenolol, we cannot also exclude a role for the loss of \( \beta \)-adrenoceptor feedforward vasodilation and/or unopposed \( \alpha \)-adrenoceptor vasoconstriction (10, 17) because the relationship between coronary sinus PO\( _2 \) and \( MV_{O_2} \) was significantly steeper with atenolol compared with saline (data not shown). Such an effect has been previously reported with propranolol by Heyndrickx et al. (14) showing that, for a given level of exercise, the increases in coronary blood flow and oxygen extraction were respectively lower and higher than those expected if these parameters were only controlled through metabolic autoregulation.

In conclusion, it appears that changes in heart rate and myocardial contractility contribute almost equally to the increase in \( MV_{O_2} \) during exercise. Reducing heart rate and LV inotropy appears to be additive at limiting exercise-induced increase in \( MV_{O_2} \) in the normal heart. Conversely, heart rate reduction is of major importance at increasing myocardial oxygen supply, as estimated by diastolic time, but associated negative inotropy limited this beneficial effect. In patients with coronary artery disease, the decrease in \( MV_{O_2} \) and the improvement of coronary artery perfusion are two major goals to achieve. Some authors focused on oxygen supply rather than oxygen demand as a major determinant of exercise-induced myocardial ischemia (7). Further studies are thus needed to investigate the relevance of \( MV_{O_2} \) reduction versus diastolic time prolongation in the ischemic heart as well as the comparison of the effects of a heart rate-reducing agent to those of \( \beta \)-blockade on myocardial ischemia and stunning.

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