

## REVIEW

## Potential interests of heart rate lowering drugs

T Laperche, D Logeart, A Cohen-Solal, R Gourgon

**Cardiology**  
**Department, Hôpital**  
**Beaujon, 100 bd du**  
**Général Leclerc,**  
**Clichy, France**  
 T Laperche  
 D Logeart  
 A Cohen-Solal  
 R Gourgon

Correspondence to:  
 Dr T Laperche, Centre  
 Cardiologique du Nord,  
 32-36 rue des Moulins  
 Gêmeaux, 93200 Saint  
 Denis, France.

Accepted for publication  
 8 October 1998

Epidemiological studies have shown that a high heart rate at rest is a risk factor for global and cardiovascular mortality.<sup>1-3</sup> A rapid heart rate is associated with a variety of prognostic factors indicative of worse heart conditions (for example, hypoxaemia, anaemia, alcohol consumption, low physical training status). The link between a high resting heart rate and an increase in overall and cardiovascular mortality has, however, been shown to be independent of cardiac conditions that can contribute to an increase in the resting heart rate, and persists after adjustment for other classic variables (sex, arterial pressure, and alcohol consumption).<sup>2,3</sup>

Recently, an elegant study showed that, among mammals, the relation between the number of beats per lifetime and life expectancy was remarkably constant, and the provocative question was raised as whether human life could be extended by slowing the heart rate.<sup>4</sup> Of course, such a study using bradycardiac drugs has not yet been performed, but these data point to the potential beneficial effect of heart rate lowering drugs in patients with cardiac disorders. This review examines the impact on the cardiovascular system of treatments which lower the heart rate.

### Heart rate and vascular structure and function

#### VASCULAR FUNCTION

Arterial mechanical properties are determined by elastic, viscous, and inertial components of the vessel wall. The duration of the distension recoil cycle potentially affects arterial function. In vitro, the mechanical properties of the large arteries, particularly the incremental elastic modulus, index of arterial stiffness, are frequency dependent and may be influenced by the resting heart rate. In animal studies, pace induced tachycardia is associated with reductions in arterial compliance and distensibility, with a greater effect in carotid than in femoral arteries.<sup>5</sup> A recent clinical study in humans has shown a positive correlation between high heart rate and high arterial stiffness.<sup>6</sup> However, the beneficial effect of heart rate reduction on vascular function has not yet been demonstrated.

#### ATHEROGENESIS

Animal studies have shown that a reduction in heart rate delays the onset of coronary and carotid atheroma. In monkeys fed an athero-

genic diet after ablation of the sinoatrial node (in order to decrease the heart rate) or after sham surgical procedure, coronary atheroma was twice as severe in those with the higher heart rate (55.9% stenosis *v* 26.1% stenosis in the group with the low heart rate,  $p < 0.02$ ).<sup>7</sup> Later, focusing on carotid atheroma in monkeys, the same authors obtained similar results—atheromatous lesions were less in animals with a lower heart rate, independent of arterial pressure and blood cholesterol concentrations (30.7% stenosis in the group with a high heart rate *v* 15.2% stenosis in the group with a low heart rate,  $p < 0.002$ ).<sup>8</sup>

In humans, follow up of 56 patients with a history of myocardial infarction who underwent serial coronary angiographies showed a positive correlation between the minimum heart rate (detected by Holter ECG) and the angiographic severity score of atheroma, and also between the minimal heart rate and the progression of coronary atheroma, independent of cholesterol concentrations and  $\beta$  blocker treatment.<sup>9</sup>

One possible explanation for these observations is based on the mechanical theory of atherogenesis. Atherosclerosis does not affect the different arterial compartments to the same extent, but preferentially affects junctions and curves. These differences can be explained partly by local haemodynamic effects, enhanced by the pulsatile nature of the blood flow. It has been shown that oscillations in the direction of wall shear stress prolong the stagnation of blood particles, thereby increasing the time during which the endothelium is exposed to atherogenic particles and enhancing atherogenesis by blood wall interactions. Thus, areas of the intima exposed to stress fluctuations (of intensity and direction) are more exposed to the onset and progression of atherosclerotic lesions.<sup>10</sup> These fluctuations are mainly observed during systole.<sup>10</sup> While a heart rate acceleration increases the systolic component of the cardiac cycle (relative to diastole), a decrease in heart rate reduces it (particularly below 75 beats/min) (fig 1).<sup>11</sup> Thus, lowering the heart rate would appear to reduce detrimental interactions between the blood and vessel wall, and delay atherogenesis (as demonstrated in animal studies). In coronary arteries, if the bulk of flow occurs during diastole, then the systolic component is different from zero and comprises two acceleration-deceleration cycles. Reducing the

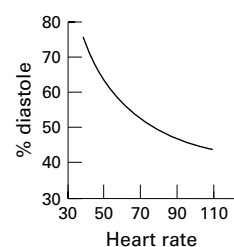


Figure 1 Relation between heart rate and percentage diastole. Because of the non-linearity of the relation, a small decrease in heart rate results, at lower heart rates especially, in a dramatic increase in the diastolic part of the cardiac cycle. (Reproduced from Boudoulas H, Rittgers SE, Lewis RP, et al. *Circulation* 1979;60:164-9, with permission of American Heart Association.)

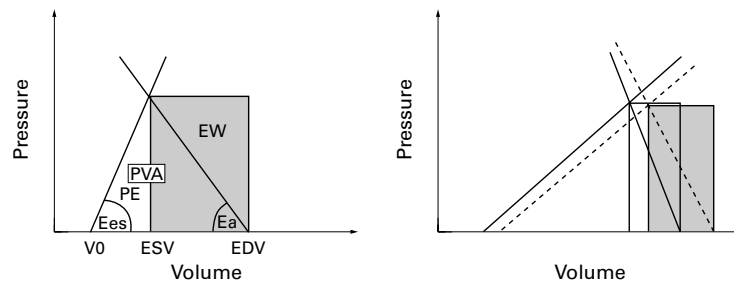


Figure 2 (Left) Work efficiency in normal subjects.  $E_{es}$  represents the slope of the left ventricular end systolic pressure–volume relation, and  $E_a$  the slope of the arterial end systolic pressure–stroke volume relation. External work (EW) (area in grey), the mechanical cardiac work, represents the area bounded by the pressure–volume trajectory of one beat. Pressure–volume area (PVA) represents the area bounded by the end systolic pressure–volume relation, the end diastolic pressure–volume relation, and the systolic pressure–volume trajectory of the contraction. Potential energy (PE) is the difference between PVA and EW.  $EW/PVA$  represents the work efficiency.  $ESV$ , end systolic volume;  $EDV$ , end diastolic volume;  $V_0$  is the volume axis intercept of the end systolic pressure–volume relation. (Right) Effect of a heart rate lowering drug on work efficiency in patients with heart failure. In comparison with basal conditions (solid lines and white area), negative chronotropic effect (dashed lines and grey area) considerably reduces  $E_a$  and  $E_{es}$  to a lower extent, resulting in a fall in the  $E_a/E_{es}$  ratio, so that  $EW/PVA$  significantly increases, meaning an increase in work efficiency. (Adapted from Yamakawa H, Takeuchi M, Takaoka H, et al. *Circulation* 1996;94:340–5, with permission of American Heart Association.)

heart rate would reduce pulsatile stress exerted on the arterial wall during systole.

Furthermore, there seems to be a link between heart rate and lipid abnormalities. A positive correlation has been observed between the resting heart rate and atherogenic lipid fractions.<sup>12</sup> This could partly be caused by atherosclerosis, but could also depend on neuroendocrine factors (catecholamines) influencing cardiac haemodynamics and lipid metabolism.

### Heart rate and ventricular function

#### MYOCARDIAL ENERGETICS

The ventricle is a generator of hydraulic energy, which transfers the mechanical energy of contraction to the blood accumulated in the ventricular chambers in order to eject it through the arterial system. Left ventricular oxygen consumption can be formulated as a function of a ventricular contractility index ( $E_{max}$ , the maximal value of the time varying left ventricular end systolic elastance) and a measure of ventricular total energy (systolic pressure–volume area (PVA), as defined in fig 2A). Left ventricular work efficiency is composed of two parts, one depending on mechanical cardiac work, and the other depending on the energy requirements for basal metabolism and inotropy.<sup>13</sup> In heart failure, for a given end diastolic volume, maximal work is obtained at the expense of decreased mechanical efficiency.<sup>14</sup>

Heart rate affects myocardial energetics. Experimental studies in closed chest dogs with normal left ventricular function showed that, when heart rate was increased, there was an increase in contractility but a decrease in efficiency caused by an increase in non-mechanical myocardial oxygen consumption.<sup>15</sup>

Such results have been observed in patients with heart failure.<sup>16</sup> The possibility that lowering heart rate results in greater energetic efficiency could explain the surprisingly good early tolerability of  $\beta$  blocker treatment in

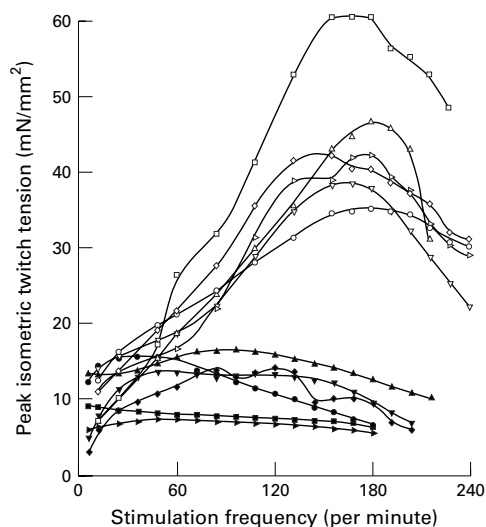
patients with heart failure.  $\beta$  blockers reduce myocardial oxygen expenditure. It is difficult to define clearly the respective roles of decreased heart rate, decreased myocardial contractility, improved perfusion of subendocardial layers or shift in substrate utilisation. The lower oxygen expenditure for non-mechanical work increases the efficiency of the working myocardium (fig 2B).<sup>17</sup> However, the beneficial effects of negative chronotropic properties of  $\beta$  blockers could be counterbalanced by their negative inotropic properties in patients with heart failure. A recent comparison between a  $\beta$  blocker (propranolol) and a specific bradycardiac agent (zatebradine) in patients with left ventricular dysfunction showed preserved efficiency with a  $\beta$  blocker but an improvement of efficiency with the bradycardiac agent.<sup>18</sup> Whether different  $\beta$  blockers share the same beneficial effects on myocardial energetic balance and work efficiency, and whether pure bradycardiac agents will be more effective in congestive heart failure, remains to be addressed.

In clinical studies of patients with heart failure, beneficial effects of  $\beta$  blockers and amiodarone on outcome have been observed and are associated with a reduction in heart rate.<sup>19–21</sup> The mortality reduction observed with carvedilol and amiodarone principally occurred in patients with higher basal heart rates, but this reduction was weak or not significant in patients with lower basal heart rate.<sup>19–21</sup> In the cardiac insufficiency bisoprolol (CIBIS) trial, patients receiving bisoprolol had a lower mortality risk than those receiving placebo, whatever their heart rate change over time.<sup>20</sup> It seems necessary to understand how heart rate modulation contributes to the beneficial effect of  $\beta$  blockers or amiodarone for an optimal identification of patients who need such drugs. Even if the relations between heart rate reduction, left ventricular function improvement, and prognosis in heart failure are complex, there is a possibility that the beneficial effects of these drugs are in part related to improved myocardial energetics secondary to heart rate reduction.

#### LEFT VENTRICULAR SYSTOLIC FUNCTION

At rest, heart rate changes have no major effect on cardiac output, because of parallel and inverse variations in stroke volume, at least within a certain range of frequencies. In contrast, during exercise, an increase in heart rate is essential to increase cardiac output when venous return and left ventricular filling are increased.

Independently of vagal or sympathetic tone change, a rise in heart rate increases the contractile force of the myocardium (positive inotropic effect) and accelerates myocardial relaxation (positive lusitropic effect). This effect is attributed to a rise in the rate of calcium transients and the rate of actin–myosin bridge activation during each cycle. In studies of isolated fibres, a rise in the frequency of stimulation increases the tension developed by the fibre during contraction. This effect is observed across a frequency range not exceeding 180 beats/min, above which the opposite effect occurs.<sup>22</sup>



*Figure 3 Force–frequency relation in human hearts. The figure displays the force–frequency relation developed by papillary muscles of six normal subjects and six patients with heart failure (cardiomyopathy) in response to a progressive increase in stimulation frequency. Force increases with the increase in stimulation frequency in normal subjects (open symbols), up to a critical frequency above which it decreases. In heart failure (filled symbols), the force–frequency slope is considerably decreased. Increasing the stimulation frequency does not produce a meaningful increase of force; furthermore, the point of inflexion occurs at a low frequency. This explains why, at high heart rates, the force of contraction of cardiac fibres of patients with heart failure is not increased, and may even be decreased. Negative chronotropic agents shift the operating frequencies during exercise to the left part of the axis, which may in part explain their beneficial effect on cardiac function. (Reproduced from Mulieri LA, Hasenfuss G, Leavitt B, et al. *Circulation* 1992;85:1743–50, with permission of American Heart Association.)*

Adrenergic stimulation potentiates the force–frequency effect.<sup>23</sup> A direct myocardial effect of  $\beta$  adrenergic receptor stimulation acting together with amplification of the force–frequency relation during exercise has been shown. In heart failure, a loss of the adrenergic control of the force–frequency relation and an alteration of the force–frequency relation are observed (fig 3).<sup>22, 23</sup> A rise in the stimulation frequency is accompanied by little or no increase in developed tension. Furthermore, the heart rate at which the force–frequency relation becomes negative is shifted leftward. Haemodynamic studies have shown that atrial or ventricular stimulation at increasing frequencies in patients with heart failure are not accompanied by a rise in the slope of the end systolic pressure–volume relation.<sup>24, 25</sup> A practical consequence of this is that, while tachycardia appears to have a beneficial effect during exercise in healthy subjects, contributing with adrenergic stimulation to increase myocardial contractile force, it has practically no effect or even a detrimental effect in subjects with heart failure, as contractile force is not increased or may be reduced at the frequencies generally seen during exercise.<sup>24</sup>

In summary, there are various explanations for the beneficial effect of heart rate reduction in patients with impaired left ventricular function: contractile force of the myocardium may increase; myocardial oxygen consumption decreases; time available for diastolic filling is

prolonged (up to a certain level above which deleterious effects could appear); and time available for coronary perfusion is prolonged.<sup>25</sup>

#### LEFT VENTRICULAR DIASTOLIC FUNCTION

Disorders of diastolic function account for a noteworthy proportion of heart failure cases. It is estimated that systolic function is normal in 40% of cases of heart failure, although this figure may be dependent on the age of the studied population.<sup>26</sup> Even if these forms of heart failure are associated with a lower mortality rate than systolic dysfunction, their consequences in terms of morbidity are far from negligible.

Experimental studies have demonstrated the importance of heart rate in ventricular filling. In animal experiments, the left ventricular pressure curve falls more rapidly at high frequencies, facilitating ventricular filling despite the shortening of the diastolic phase. In healthy subjects, the time constant of isovolumic pressure decay correlates negatively (and strongly) with the heart rate. The higher the heart rate, the lower the time constant, thereby avoiding an excessive increase of filling pressures during effort.<sup>27</sup> However, if the chronotropic response during exercise is inhibited in healthy subjects, the left ventricular end diastolic pressure and mean atrial pressure both increase, perhaps contributing to the onset of exertional dyspnea.<sup>28</sup> In case of abnormal relaxation, the fall in pressure is less at high heart rates. This is particularly clear in patients with coronary disease, in whom filling pressures increase in large part because of slower relaxation. The left ventricular diastolic pressure–volume relation shifts upward in patients with angina pectoris induced by exercise or pacing tachycardia.<sup>29</sup>

Abnormalities of diastolic function can be schematically summarised in reduction in diastolic compliance and altered relaxation, although they are often combined and associated with inappropriate tachycardia and/or loss of atrial function in clinical practice. The ultimate consequences are impairment in left ventricular filling, with an upward shift in the pressure–volume relation (fig 4). The abnormal increase in filling pressures can be present at rest but is clearer during effort, when diastole is reduced and other factors (such as myocardial ischaemia and an increase in arterial pressure) are superimposed. When an inappropriate heart rate is responsible for the expression of this diastolic abnormality, heart rate lowering treatment may be the treatment of choice, especially when it does not have a negative inotropic effect.<sup>30</sup>

However, heart rate lowering drugs could have deleterious effects in those heart failure patients with increased chamber stiffness, creating an important rise in pressure levels even for small volume variations, because of their steeper end diastolic pressure–volume relation (fig 4). This group of subjects usually comprise end stage heart failure patients. These patients have no more preload reserve, and an increase in their left ventricular filling is severely deleterious. A promising way to

identify these patients is by studying their Doppler mitral flow (restrictive filling pattern), eventually with loading manipulations.<sup>31</sup>

### Heart rate and ischaemia

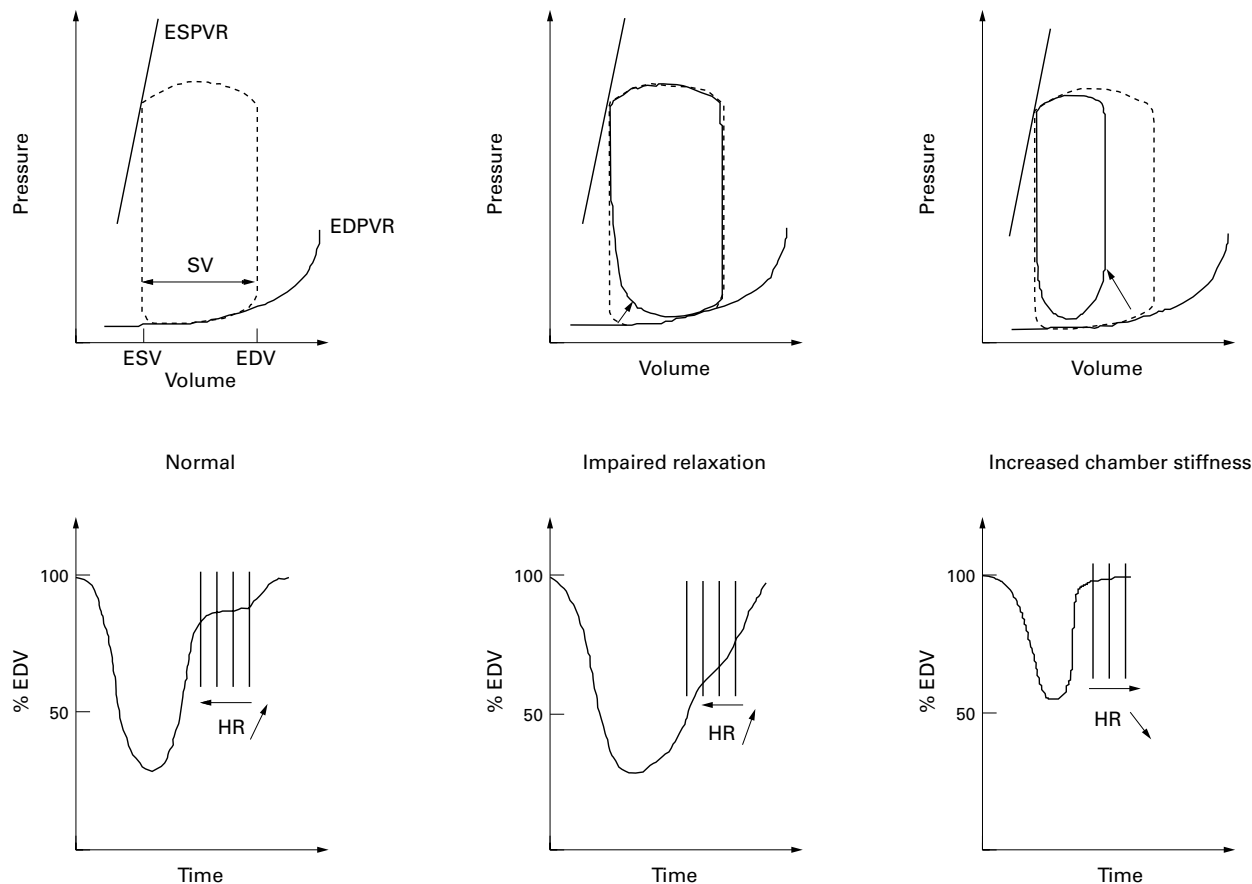
#### EXERCISE ISCHAEMIA

Experimental studies have shown that the prevention of exercise ischaemia by  $\beta$  blockers is caused by the heart rate lowering effect of these drugs, independently of their other properties.<sup>32</sup> When the reduction in heart rate is cancelled out by atrial stimulation, the anti-ischaemic benefit of the  $\beta$  blocker is lost. The two explanations are the decrease in myocardial oxygen consumption caused by the decrease in heart rate, and the prolongation in the myocardial perfusion time during diastole as observed with heart rate lowering drugs, with a redistribution of flow towards the subendocardial layers. This contributes towards delaying the onset of myocardial ischaemia.

As heart rate is considered the most important determinant of myocardial oxygen requirements, some authors have deduced that

drugs with a purely heart rate lowering effect might form the basis for a new approach to the treatment of myocardial ischaemia.

Experimental studies showed that such a drug effectively attenuated ischaemia induced by exercise and improved myocardial perfusion in the ischaemic area, without negatively affecting non-ischaemic zones or the overall contractile function of the left ventricle.<sup>33</sup> However, a recent placebo controlled trial of zatebradine (an inhibitor of sinus node activity) in patients with coronary heart disease treated with nifedipine failed to find improvement in exercise tolerance.<sup>34</sup> While onset of ST depression was significantly delayed relative to the placebo group during the first week, the effect disappeared thereafter. After four weeks of treatment, there was no difference in exercise tolerance between the two groups. Even if the methodology of this trial was criticised, another recent study has confirmed these findings.<sup>35</sup> It is possible that, because of the bradycardiac effect, ventricular preload and therefore contractility (via the



**Figure 4** Effects of heart rate increase on left ventricular filling (the same model applies for the three parts of the figure). Top of figure: pressure–volume relation (ESV, end systolic volume; ESPVR, end systolic pressure–volume relation; EDV, end diastolic volume; EDVPR, end diastolic pressure–volume relation; SV, stroke volume). Bottom of figure: left ventricular volume changes (expressed in percentage end diastolic volume (EDV)) during one cardiac cycle. Vertical lines summarise the consequences of heart rate (HR) variations on left ventricular filling volume. Depending on the context, various increases in heart rate (leftward displacement of arrow) result in modifications of left ventricular volume filling. In normal subjects (left part of the figure) with normal pressure–volume relation (dashed line loop), modifications of heart rate mainly affect diastasis. Volume changes during this period are minor, with most of the filling occurring in early and late diastole, so that tachycardia, up to a critical limit, does not significantly affect ventricular volume. In patients with impaired relaxation (middle part of the figure), because of the delayed early diastolic rapid filling phase (solid line loop in the top of the figure), diastasis is shortened or abolished and atrial systolic filling is increased in compensation for the reduced contribution of rapid filling. So, inappropriate tachycardia will significantly reduce ventricular filling. This explains the benefit of heart rate lowering drugs in patients with impaired relaxation and heart failure caused by inappropriate tachycardia. Finally, in patients with increased chamber stiffness (right part of the figure), stroke volume is reduced (solid line loop in the top of the figure) and there is a leftward and upward displacement of the end diastolic pressure–volume relation (arrow). So, tachycardia represents a compensatory response to reduced systolic ejection volume. In these patients, a heart rate lowering drug may have a deleterious effect, by creating an important increase of pressure levels even with small volume variations, caused by the steep end diastolic pressure–volume relation.

Frank-Starling mechanism) increased, leading to an increase in myocardial consumption. So, in the opinion of some authors, drugs with a purely heart rate lowering action do not provide a convincing clinical benefit in patients with stable angina, and bradycardiac agents with a negative inotropic action and/or a vasodilatory effect on the coronary vessels should thus be preferred.

#### SILENT ISCHAEMIA

Studies using 24 hour Holter recordings have shown the influence of heart rate in the mechanisms of onset of myocardial ischaemia.<sup>36,37</sup> An increased heart rate leads to increased oxygen requirements, and is therefore an important mechanism in the onset of ischaemia. Some  $\beta$  blockers can reduce the frequency of silent ischaemia considerably, partly through a reduction in heart rate and a resulting attenuation of ischaemic episodes.

#### MYOCARDIAL INFARCTION

A high heart rate has been recognised as a risk factor for mortality in postinfarction patients.<sup>38,39</sup> A high heart rate: suggests an enhanced sympathetic tone or a decrease in vagal activity, both being arrhythmogenic in myocardial infarction; increases oxygen consumption and may contribute to the appearance of ischaemic episodes; and facilitates adverse outcome in patients with ischaemic heart failure caused by the alteration of the force–frequency relation.

The beneficial effect of  $\beta$  blockers on post-infarct survival is widely documented.  $\beta$  Blocker treatment reduces oxygen consumption by lowering the heart rate and arterial pressure, and has antiarrhythmic effects. During the acute phase,  $\beta$  blockers reduce the size of the infarct and left ventricular wall stress, and prevent cardiac rupture. In the chronic phase, they reduce overall mortality, risk of sudden death, and heart failure rate. On the basis of studies in the acute and postacute phase, some authors have concluded that the reduction in the size of the infarct (and therefore the reduction in risk) correlates with the reduction in heart rate. It was subsequently suggested that  $\beta$  blockers with the strongest heart rate lowering effect also yielded the largest reduction in risk.<sup>40</sup> However, this was not borne out by a meta-analysis of randomised trials, or by the APSI (acebutolol et prévention secondaire de l'infarctus) study in which the largest reduction in postinfarct mortality of all such studies was obtained, despite the fact that the drug used had the weakest action on the heart rate, given its intrinsic sympathetic activity.<sup>41</sup> Furthermore, the beneficial effect of  $\beta$  blockers after myocardial infarction is only present in high risk patients, not in medium or low risk patients.<sup>42</sup> So, the apparent benefit of a reduction in heart rate in the postinfarct period and in patients with exertional angina may simply be caused by erroneous interpretation; the reduction in heart rate may have been only a clinical marker of adequate  $\beta$  blockade and negative chronotropic action rather than the direct cause of the benefit.<sup>43</sup>

#### Summary

We have therefore seen the impact of heart rate on the cardiovascular system and the potential benefit of heart rate lowering drugs. Other aspects remain to be more extensively studied. For example, the parasympathetic agonists, which also reduce heart rate, deserve to be investigated further, given that recent studies suggest their beneficial effect in heart failure. Heart rate seems to be a true cardiovascular risk factor, rather than a marker of cardiovascular risk, or simply a confounding factor (patients with severe heart disease having a compensatory increase in heart rate). However, no ideal target frequency has been determined. In fact, there is no threshold value, as the risk increases linearly with the resting heart rate. Conversely, an epidemiologic survey showed a J shaped survival–frequency curve, suggesting that a lower limit should be respected.<sup>44</sup>

However, even if the beneficial effect of heart rate lowering drugs is not demonstrated in normal patients, and remains speculative on the basis of epidemiological studies, there are convincing arguments for the use of such drugs in: hypertensive patients (allowing an enhancement in their left ventricular filling parameters, particularly relaxation parameters); patients with coronary diseases (because of the decrease in the myocardial oxygen consumption, the increase in the myocardial perfusion time during diastole, and the redistribution of coronary flow towards the subendocardial layers—the efficacy being clear if the drug also has a negative inotropic action and/or a vasodilatory effect); and high risk patients with heart failure (by restoring a positive force–frequency relation, and improving left ventricular efficiency), but with caution because of potential deleterious effects on filling pressures in those patients in which preload reserve has been exhausted.

Heart rate reduction is probably not indicated for all patients. Therefore, future studies using bradycardiac drugs will have to determine the precise potential benefit of optimal heart rate control in several categories of cardiac patients. The methodology of such studies and the choice of associated covariables have to be particularly well defined, because of the numerous interactions between heart rate and the cardiovascular system.

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