Heart rate reduction with ivabradine prevents the global phenotype of left ventricular remodeling

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Submitted 30 November 2009; accepted in final form 14 October 2010

Cardiac remodeling is defined as a series of genome expression, molecular, biochemical, electrophysiological, and interstitial modifications following myocardial injury, which progressively lead to changes in cardiac size, shape, function, and energetic metabolism (15). Remodeling can occur in different physiological and pathological conditions and most often after severe myocardial infarction (MI). Clearly, progressive left ventricular (LV) dysfunction leading to cardiac remodeling is a multifactorial process, and there is much evidence to support the hypothesis that impaired energy metabolism plays a major role post-MI. This concept is based on the demonstration of energy deprivation in failing myocardium and on a series of metabolic changes that have been found in this condition, including abnormalities in substrate utilization, oxidative phosphorylation, and high-energy phosphorylation (25, 35).

Heart rate (HR) is an important determinant of myocardial oxygen supply and demand, and therefore direct control of HR could be expected to influence the progression toward myocardial dysfunction and prevent or even reverse remodeling. Accordingly, β-blockade prevents further deterioration of post-MI remodeling, both in experimental preparations and in the clinical setting (12, 21, 27, 39). As β-blockers have actions other than HR reduction (e.g., negative inotropism, blood pressure reduction, and/or prevention of the deleterious effects of catecholamines in the cardiomyocyte), it is unclear whether their antiremodeling effect is attributable to HR reduction or to their other effects. Ivabradine, the only agent presently available whose sole effect is HR reduction (5), provides an opportunity to test the effects of “pure” HR reduction on remodeling.

Ivabradine inhibits the pacemaker hyperpolarization-activated current (IHyperpolarization) that controls spontaneous diastolic depolarization in the sinus node and regulates HR (5, 8) with no effect on intra-atrial, atrioventricular, or intraventricular conduction times, myocardial contractility, or ventricular repolarization (40, 45, 46). Clinically, ivabradine is indicated in stable angina pectoris (6, 37, 42). A preliminary study in patients with reduced LV ejection fraction (LVEF) showed improvement in LV systolic and diastolic dimensions, suggesting containment of the remodeling process (26). There are a few studies on the effects of ivabradine in a rat model of post-MI LV dysfunction induced by coronary artery ligation (18, 30, 31, 34). Although these studies demonstrated beneficial cardiac effects of ivabradine, in terms of improvement in LV systolic and diastolic function and decreased interstitial and perivascular fibrosis, they did not address the impact of ivabradine on cardiac energy metabolism and ex vivo electrophysiological remodeling at the cellular level.

The aim of the investigations described here was to assess whether HR reduction with ivabradine can modulate the global phenotype of post-MI LV remodeling. To this end, we used a well-known animal model of cardiac remodeling in the rat to investigate the effect of ivabradine on a wide range of parameters associated with this phenotype, including LV dimension and dysfunction, hemodynamics, electrophysiological and interstitial remodeling, neuroendocrine activation, and energy metabolism.

MATERIALS AND METHODS

Study design. All animals were fed a standard rat chow diet and drinking water ad libitum and were maintained in an artificial 12-h:12-h light/dark cycle. The study was conducted in compliance with the Guide for the Care and Use of Laboratory Animals published by NIH (publication no. 85–23, revised 1996). According to the local laws, the study was approved by the local Ethics Committee in Ferrara and Gussago and submitted to the Italian Ministry of Health.
The experimental design is presented in Fig. 1. Male anesthetized (Zoletil + xylazine) Wistar rats (Charles River, Milan, Italy) (n = 106, aged 8–10 wk) underwent left anterior descending (LAD) coronary artery ligation according to Pfeffer et al. (36). In 20 rats, the suture was tied loosely so as not to obstruct flow (sham rats; 14 for cardiac function and metabolism; 6 for electrophysiology). In the remaining 86 rats, the LAD was ligated to induce MI; 37 rats died within 24 h, 1 rat within 1 wk, and 6 rats were excluded because asynergy did not involve more than one segment. Seven days after surgery, animals with trivial infarct (<2 segments and normal LV dimensions) were discarded. The remaining 42 animals were allocated sequentially to two groups and received either no treatment (MI rats; 15 for cardiac function and metabolism; 5 for electrophysiology) or ivabradine (10 mg·kg⁻¹·day⁻¹ in vehicle drinking water ad libitum) (MI+IVA rats; 17 for cardiac function and metabolism; 5 for electrophysiology) for 90 days. There was no between-group difference for heart weight/bodyweight ratio or cell membrane capacitance (Cm) in sham: 182.8 ± 10.1 pF (n = 20); Cm in MI: 206.6 ± 16.1 pF (n = 30); Cm in MI+IVA: 206.7 ± 10.8 pF (n = 28).

At 90 days, the animals were anesthetized by pentothal (30 mg/kg ip), weighed, and killed by guillotine. Liquid effusions in the pleural and peritoneal space were measured with a syringe. Heart and chambers (left and right ventricles and septum) were separated, weighed, and stored before analysis. Great caution was used to sample the intact muscle, away from the fibrotic border by inspection.

Echocardiography. Echocardiography was performed according to standard literature methods (33, 48) using a Vivid I echocardiograph (GE Medical Systems, Milan, Italy) equipped with 10S-RS and 8L-RS probes and 3S-RS transducer, in anesthetized rats at time 0 (start of treatment, i.e., 7 days after ligation) and 30 and 90 days. Posterior end-diastolic and end-systolic LV posterior wall thickness was measured, and volumes (LVESV and LVEDV), diameters (LVEDD and LVESD), and LVEF were calculated. This information was used to calculate stroke volume (SV = AoVTI × (π × LVOD³/2), where AoVTI is the aortic velocity time integral and LVOD is the LV outflow diameter) and cardiac output (CO = SV × HR). LV wall motion score index (LVWMSI) was calculated as the ratio of the sum of wall motion scores over total segments scored; the standard 16-segment model of the LV was applied (23).

Cardiac biomarkers. After solid-phase extraction (Strata C-18-E; Waters, Milford, MA) (9) with spectroscopic detection at 205 nm for hydroxyproline, cardiac hydroxyproline was measured spectroscopically at 560 nm (3). Further details are included in the supplemental material, which is available online at the American Journal of Physiology Heart Circulatory Physiology website.

Whole cell configuration patch-clamp technique. The excised hearts were mounted on a Langendorff apparatus for immediate isolation of single ventricular cardiomyocytes by enzymatic procedures, as described elsewhere (10). The whole cell configuration of the patch-clamp technique was used to record action potential (AP) and ionic currents in the isolated myocytes (in at least 8 cells per group per parameter), according to literature methods (10, 29) using a patch amplifier (Axopatch-200B; Axon Instruments, Sunnyvale, CA). APs were elicited at the rate of 0.2 Hz and sampled at 2 kHz. Cells were superfused with normal Tyrode solution (in mM: 140 NaCl, 5.4 KCl, 1.8 CaCl₂, 1.2 MgCl₂, 10 d-glucose, and 5 HEPES adjusted to pH 7.5 with NaOH) to measure the AP or with properly modified Tyrode solution (normal Tyrode solution added with CdCl₂ 0.5) for the transient outward current (Iₒ). Iₒ was evoked by depolarizing steps for 750 ms from −35 to +55 mV from a holding potential of −70 mV, measured as peak outward current and normalized with respect to Iₒ.

Kv4.2 and KChIP2 expression by quantitative RT-PCR. LVs were frozen and stored at −80°C. Abundance of cardiac Kv4.2 and KChIP2 RNA transcription expression and an internal control transcript (GAPDH) was determined using quantitative RT-PCR. RNA was extracted using RNeasy Fibrous Tissue Mini Kit (cat. no 74704; Qiagen, Hilden, Germany), and first-strand cDNA synthesis was performed in a 100-μl volume (2 μg RNA and 2.5 μmol random hexamer primers). qRT-PCR reactions were performed using 10 μl of TaqMan Universal PCR Master Mix (Applied Biosystems, Foster City, CA) in a 20-μl volume containing 50 ng cDNA and TaqMan primers and probes (Applied Biosystems cat. nos. Kv4.2, Rn00581941_m1; KChIP2, Rn00581941_m1; GAPDH, 452338E). Reactions were performed in triplicate using an ABI Prism 7500 Sequence Detection System (Applied Biosystems). Relative quantification of mRNA was determined using the 2⁻ΔΔCt method (28).

Cardiac energy metabolism. Creatinine phosphate (CP) and purine nucleotides (ATP, ADP, and AMP) were extracted with 0.4 N HClO₄ from frozen LV biopsies, as described elsewhere (47). Supernatants were assayed by high-pressure liquid chromatography (600 E multisolvent delivery system and a model 990 photodiode array detector; Waters, Milford, MA) (9) with spectroscopic detection at 205 nm for CP and 260 nm for nucleotides. The nucleotide levels were used to

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Fig. 1. Experimental design. Echo, echocardiography; IVA, ivabradine; LAD, left anterior descending; MI, myocardial infarction.
calculate energy charge, which is proportional to the mole fraction of ATP plus half the mole fraction of ADP.

Statistical methods. Data by group and time are represented as mean, standard error, median, minimum, maximum, and/or N. Parameters were treated differently according to whether they related to model validation (MI vs. sham) or interpretation of treatment effect (MI+IVA vs. MI).

For parameters related to cardiac echocardiography and body weight, two-way analysis of variance was performed with repeated measures on time with SAS Mixed Procedure (with repeated statements; the correlation matrix selected by the Akaike and Schwarz’s Bayesian information criteria, the restricted maximum likelihood estimation method, and the Satterthwaite estimation method for degrees of freedom). For interpretation, the threshold for significance was fixed at 10% for interaction and 5% for principal effects. If the model (or treatment) multiplied by time interaction was significant, the model (or treatment) effect was considered at each fixed time. Otherwise, model (or treatment) effect was considered at all pooled times.

The distribution of the parameters CP, ATP, ADP, AMP, energy charge, remodeling index, hydroxyproline, body weight, and heart weight (all measured at time of death) was considered as Gaussian. In other cases, the MI rats were compared with MI+IVA rats; MI rats vs. sham; MI rats vs. MI+IVA rats; MI+IVA rats vs. sham. §§§P < 0.001, all times pooled, MI vs. MI+IVA.

Correlations between HR and each of CP, LVEF, ADP, hydroxyproline, and ANP, as well as between hydroxyproline and infarct area, were studied for MI and MI+IVA animals. Because of small sample sizes and because those animals came from two different groups (MI and MI+IVA), a nonparametric correlation was performed with Spearman correlation coefficient.

RESULTS

Hemodynamic cardiac remodeling. LAD ligation resulted in MI-induced phenotypic changes typical of LV remodeling (Fig. 2, A and B). In untreated ligated animals (MI rats), there were constant increases in LVEDV and LVESV, which were significant at 90 days (P < 0.05 and P < 0.01, respectively, MI vs. sham). As expected, this resulted in a significant reduction in LVEF (P < 0.001, all times pooled, MI vs. sham, Fig. 2C). HR was slightly elevated at randomization, most likely as a result of a compensatory mechanism following the acute damage of ligation (Fig. 2D). In MI rats, HR was normalized by 30 days, returning toward sham levels. The MI rats also presented evidence of cardiac dysfunction with the development of heart failure (HF) (Table 1), as indicated by the changes in the

![Fig. 2. Left ventricular (LV) end-diastolic volume (LVEDV) (A), LV end-systolic volume (LVESV) (B), LV ejection fraction (LVEF) (C), and heart rate (D) at 7, 30, and 90 days in sham rats (●, dotted line) and in ligated rats with no treatment (MI rats; ▲, solid line) or treated with 10 mg·kg⁻¹·day⁻¹ ivabradine in drinking water (MI+IVA rats; ■, solid line). Values are means ± SE. **P < 0.01 all times pooled, MI+IVA vs. MI. §§P < 0.05, §§§P < 0.01, MI rats vs. sham. §§§§P < 0.001, all times pooled, MI rats vs. sham.](http://ajpheart.physiology.org/)
Table 2. Action potential parameters in isolated LV cells of sham rats and ligated rats

<table>
<thead>
<tr>
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<th>Sham Rats (n = 18)</th>
<th>MI Rats (n = 29)</th>
<th>MI IVA Rats (n = 25)</th>
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<td>MPD, mV</td>
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<td>−69 ± 1</td>
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<td>APA, mV</td>
<td>98 ± 4</td>
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<td>32 ± 6</td>
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<td>58 ± 13</td>
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<td>APD70, ms</td>
<td>51 ± 7</td>
<td>108 ± 18*</td>
<td>96 ± 18</td>
</tr>
<tr>
<td>APD90, ms</td>
<td>88 ± 12</td>
<td>177 ± 34*</td>
<td>154 ± 26</td>
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</tbody>
</table>

Values are means ± SE. Data are from sham rats and ligated rats with no treatment (MI rats) or treated with 10 mg·kg⁻¹·day⁻¹ ivabradine in drinking water (MI+IVA rats). MPD, maximum diastolic potential; APA, action potential amplitude; APD30, APD50, APD70, and APD90, action potential duration at 30%, 50%, 70%, or 90% repolarization, respectively. *P < 0.05 vs. sham.

following parameters vs. sham: 1) the presence of pleural effusion (14/15 MI rats, range 50–2,000 µl), 2) an increase in plasma ANP (150%; P < 0.001 vs. sham), and 3) an increase in cardiac hydroxyproline, a marker of fibrotic tissue modification with collagen deposition (300%, P < 0.05 vs. sham).

As expected, ivabradine induced a HR reduction of 12% from 30 days, which continued to the end of the study (P < 0.01 all times pooled vs. MI rats) (Fig. 2D). HR reduction with ivabradine also resulted in reductions in LVEDV and LVESV, which occurred by 30 days of treatment and continued to 90 days (−17%, P = NS and −30%, P = NS vs. MI rats after 90 days) (Fig. 2, A and B). At 90 days, LVEF was significantly improved by ivabradine treatment (15%, P < 0.01 vs. MI rats, Fig. 2C), and the CO maintained (165 ± 7 ml/min sham and 178 ± 12 ml/min MI+IVA, NS). There was no difference in cardiac function parameters for ivabradine-treated ligated animals vs. sham. Interestingly, there was a close relationship between HR and LVEF in all ligated animals (r = −0.3971, P < 0.05). This improvement in cardiac function induced by treatment with ivabradine also resulted in less evidence for development of HF, as indicated by reductions in pleural effusion (5/17 rats, range 50–300 µl, P < 0.01 vs. MI rats), plasma BNP (−21%, P = NS), ANP (33%, P = 0.052), and cardiac hydroxyproline (33%, P = NS) (Table 1). No change was observed in LVWMSI between MI rats (1.81 ± 0.07 in untreated MI vs. 1.75 ± 0.06 with MI rats treated with ivabradine), in line with the fact that ivabradine was administered after a week, with no effect, therefore, expected on infarct size.

Electrophysiological cardiac remodeling. In isolated LV cells of untreated ligated animals (MI rats), AP duration (APD) was homogeneously and significantly prolonged vs. sham (Table 2). This effect was attenuated with ivabradine at all points on the repolarization curve. $I_{\alpha}$ density at 50 mV was significantly reduced in MI rats vs. sham (from 9.5 pA/pF in sham to 5.1 pA/pF in MI rats, P < 0.05) (Fig. 3, A and B). This effect was partially, but significantly reversed by the administration of ivabradine (7.2 pA/pF in MI+IVA; P < 0.05 vs. MI rats). Figure 3C shows that quantitative expression of mRNA Kv4.2, the major isofrom coding for the $\alpha$-subunit channel

![Image](http://ajpheart.physiology.org/) Fig. 3. Typical transient outward current ($I_{\alpha}$) recordings in LV myocytes from sham rats and from ligated rats with no treatment (MI rats) or treated with 10 mg·kg⁻¹·day⁻¹ ivabradine in drinking water (MI+IVA rats) showing reverse remodeling in the ivabradine-treated animals (A). Average current-voltage relationship for peak $I_{\alpha}$ density (n = 20 to 30 individual cells per group) (B). qRT-PCR measurement of messenger RNA Kv4.2 (C) and KChIP2 (D) gene expression (n = 5 per group). Kv4.2, the major isoform coding for the $\alpha$-subunit channel underlying the transient outward potassium current ($I_{\alpha}$); KChIP2, auxiliary $\beta$-subunit of the channel. $\dagger P < 0.05$, MI vs. sham; *P < 0.05, MI+IVA vs. MI; †P = 0.06, MI+IVA vs. MI.
underlying the transient outward potassium current \( I_{o} \) in the rat, is significantly decreased in untreated ligated MI rats (−43%, \( P < 0.05 \) vs. sham) and partially recovered with ivabradine (\( P = 0.057 \) vs. MI rats). mRNA expression for KChIP2 (β-subunit of the channel) was markedly and significantly (\( P < 0.05 \)) enhanced in MI rats vs. sham with a trend to recover the control value in MI+IVA (Fig. 3D).

**Cardiac energy metabolism.** As expected, cardiac energy metabolism was profoundly affected by MI (Fig. 4). Accordingly, CP was significantly decreased by 37% vs. sham (\( P < 0.001 \)) and ATP by 18%. As a consequence, there was accumulation of ADP and AMP, which increased by 34% (\( P < 0.05 \) vs. sham) and 92% (\( P = 0.097 \)), respectively. This translated into a reduction in energy charge (−10%, \( P < 0.01 \) vs. sham). Treatment with ivabradine restored CP content by 33% (\( P < 0.001 \) vs. MI rats) and ATP by 15%; it reduced ADP content by 16% (\( P < 0.05 \)) and tended to reduce AMP content (37%). Energy charge was maintained at the sham level with ivabradine (+9%, \( P < 0.05 \) MI+IVA vs. MI rats).

**Correlation with HR.** A number of parameters were investigated for correlation with HR (Fig. 5). Thus despite the relatively small number of experiments, a significant inverse correlation was found between CP and HR (\( r = -0.69, P = 0.013 \)) and a positive significant correlation between ADP and HR (\( r = 0.77, P = 0.003 \)), constituting further evidence that the effect on cardiac metabolism is attributable to the HR-reducing properties of ivabradine. Positive correlations with HR were also found for hydroxyproline (\( r = -0.57, P = 0.055 \)) and ANP (\( r = -0.52, P = 0.003 \)), and a negative correlation was found between HR and LVEF (\( r = -0.40, P < 0.05 \)).

**DISCUSSION**

We found that HR reduction with ivabradine prevents at least some of the post-MI maladaptations leading to remodeling and, eventually, HF. We made an effort to determine in the same animal model the global phenotype of post-MI remodeling, including hemodynamic, electrophysiological, structural, and energetic changes, as well as markers of HF.

HR is a major determinant of myocardial oxygen delivery and consumption. HR reduction optimizes energy balance by prolonging diastolic duration and improving diastolic coronary flow and oxygen supply, while simultaneously reducing cardiac work and oxygen demand (16). The cardiac effects of ivabradine are highly specific to HR reduction, as it has no inotropic effects or impact on peripheral vascular resistance. This implies that HR reduction is the only active mechanism for ivabradine in our experimental model (40).

The present data demonstrate that HR reduction improves the energetic state of the heart in terms of maintenance of the high-energy phosphate content (CP and ADP), and energy charge. In a similar model of post-MI animals, Christensen et al. (13) found that coronary reserve was improved with ivabradine but not with atenolol. This indicates a complementary mechanism by which ivabradine may improve oxygen supply and demand.

The improved myocardial energetics are concomitant to changes in cellular electrophysiological remodeling. As the main current to be modified in post-MI LV dysfunction, \( I_{o} \) current density constitutes an excellent electrophysiological marker of LV remodeling (2, 44). Moreover, despite a large regional variability, a homogeneous reduction of \( I_{o} \) density in all ventricular compartments (LV free wall and apex, septum, and right ventricle) has been reported in MI rats (1). Electrophysiological adaptation to post-MI LV dysfunction has been previously studied in human cardiomyocytes and, like in our experiments, shown to lead to a prolongation of APD and a reduction in \( I_{o} \) current density (4). Our results demonstrate that HR reduction with ivabradine improves \( I_{o} \) current density in the failing rat heart and prevents LV remodeling. We also

![Fig. 4. Evaluation of cardiac energy metabolism parameters creatine phosphate (CP) (A), ATP (B), energy charge (C), ADP (D), and AMP (E), in LV at 90 days in sham rats and in ligated rats with no treatment (MI rats) or treated with 10 mg·kg⁻¹·day⁻¹ ivabradine in drinking water (MI+IVA rats).](http://ajpheart.physiology.org/) by 10220.33.2 on June 8, 2017
observed a shortening of APD with ivabradine vs. the MI rats, which returns toward normal (sham) values. Whereas a small fraction of $I_{to}$ is attributable to Kv1.4, a large portion of the current is carried by channels in the Kv4 family. These channels are multimeric complexes consisting of pore-forming Kv4.2 and/or Kv4.3 proteins and auxiliary KChIP2 subunits. The Kv4.2 mRNA level appears to correlate well with the size of $I_{to}$ across the LV walls of rat and mouse hearts (19, 23). Indeed, this recovery of APD was, at least in part, regulated at a transcriptional level because $Kv4.2$, one of the major genes encoding for the transient outward potassium channel in the rat, was also increased. Also, the $\alpha$-subunit $K$ChIP2, which is thought to modulate transient outward current kinetics, was increased in MI and normalized to control values in MI/IVA.

A full appreciation of this result is impossible because to date the role of KChip subunits has not been fully elucidated; however, KChIP2 overexpression in rat hypertrophied hearts seems to negatively modulate $I_{to}$, by slowing down current inactivation (22).

The energetic and electrophysiological improvements occur concomitant to a positive impact of ivabradine on LV function, with decreased LV volumes and increased EF. However, the effect of HR reduction on structural remodeling is large but less prominent on systolic function, as would be anticipated given that ivabradine was administered in the chronic phase and not acutely (therefore not reducing infarct size). There was also maintenance of CO with ivabradine, suggesting that HR reduction improves hemodynamics. Previous studies have shown that HR reduction with ivabradine also reduces wall stress (30), leading to improved myocardial oxygen supply and demand (17). Moreover, in our study, significant correlations were found between HR and markers of cardiac metabolism (CP and ADP) as well as markers of HF, such as hydroxyproline and ANP. Treatment with ivabradine also reduced plasma BNP levels, but this did not reach statistical significance. This indicates a direct link between HR reduction, energy consumption, interstitial remodeling, and neuroendocrine activation.

Our results appear to contradict those of ivabradine in a rat model of HF induced by pressure overload (14). Banding of the ascending aorta induces a stenosis that increases the afterload on the heart and prevents any modification of SV. The elevated wall stress in such a model also increases myocardial oxygen consumption; under these conditions, HR reduction can only further reduce CO, increasing neuroendocrine activation and the progression of remodeling (14). On the other hand, LAD ligation, as performed in our study, is a better model for investigation of the effects of HR reduction post-MI LV dysfunction because the afterload is not fixed, allowing the full benefits of HR reduction to be observed.

The effects of $\beta$-blockers are well known and constitute a premise to this study. The effects of HR reduction only with ivabradine should have been compared with those of $\beta$-blockers, which are known to improve HF via, at least in part, a HR-lowering effect (24). The pharmacodynamic action of $\beta$-blockade, however, is more complex, as these agents also have negative inotropic and other metabolic effects, which together are most likely responsible for the long-term beneficial effects. In this context, pure HR reduction with ivabradine has been previously compared with atenolol in a canine model of myocardial ischemia and stunning (32). Our results appear to further substantiate the role of HR reduction alone in the progression of LV dysfunction.

In the present study, the positive action of ivabradine on LV volumes and LVEF are not as immediate as in the canine model of stunning (32); they are evident at 90 days but not at 30 days. This suggests that the impact of ivabradine is not immediate like in stunning. Stunning and remodeling are, however, two different phenomena. Stunning refers to a delayed functional recovery of the ischemic myocytes after a short period of reversible ischemia without necrosis (7). In
contrast, remodeling describes functional, biochemical, and structural changes occurring in the still viable myocytes following an acute (and usually large) MI with necrosis. Furthermore, in the stunning experiments, ivabradine was administered acutely either before ischemia and/or at the time of reperfusion (32). This effect represents a cardioprotection against ischemia and/or reperfusion insult. In the present experiments, ivabradine was provided in the drinking water a week after coronary ligation to avoid any possible interference attributable to its cardioprotective effect on acute ischemia. The change in phenotype in the chronic phase of remodeling is not expected to be immediate, and HR reduction with ivabradine most likely requires time to exert a full beneficial antiremodeling effect. The ligated rat model correlates well with results in patients with coronary artery disease who are prone to develop remodeling and progression to HF. Interestingly, in a preliminary study in HF patients, ivabradine reduced ventricular volumes and improved LVEF (26). A sub-study of the MorBidity-mortality EvAilUaTion of the I_{f} inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction (BEAUTIFUL) trial (20) is presently investigating the effect of ivabradine on remodeling measured in terms of centralised echocardiographic parameters in a subgroup of almost 1,000 patients participating in that study and may provide the clinical equivalent of our experiments. We should also note that the BEAUTIFUL patients had a long history of MI, on average 6 years previously (43), whereas our experimental conditions demonstrate a beneficial effect for ivabradine on early post-MI remodeling. The recent results of the systolic HF treatment with the I_{f} inhibition ivabradine (SHIFT) trial demonstrate an advantage of ivabradine on HF-related outcomes (41). Our results may constitute a pathophysiological basis for these effects in humans.

There are a number of limitations to the study. One could be the age of the rats because young rats continue to grow and mature, and cardiac responses to ivabradine may be significantly different from those in older animals. On the other hand, available data support the notion that 2.5-mo-old rats may be considered as “young adult” rather than “young” animals from an electrophysiological point of view. For example, electrophysiological maturation is complete within 1 mo of age (11, 38).

In conclusion, myocardial injury and necrosis induce several changes in the still viable myocytes, normally referred to as remodeling. In the post-MI rat with LV dysfunction, the HR-reducing properties of ivabradine prevent the changes in the global phenotype of LV remodeling, optimize energy consumption, and avoid electrophysiological and structural modification.

DISCLOSURES

A. Mugelli, C. Cecconi, and R. Ferrari have served as speakers for Servier, and have received research grants from Servier. M. Bouly is an employee of the Institut de Recherches Internationales Servier. All authors had full access to the data, and participated in the decision to submit the final version of the manuscript.

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