CLINICAL RESEARCH

Effect of ivabradine on left ventricular remodelling after reperfused myocardial infarction: A pilot study

Effet de l’ivabradine sur le remodelage ventriculaire gauche après un infarctus du myocarde reperfusé : étude pilote

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KEYWORDS
Ivabradine; Myocardial infarction; Left ventricular remodelling; Magnetic resonance imaging

Summary
Background. — Heart rate is a major determinant of myocardial oxygen demand; in ST-segment elevation myocardial infarction (STEMI), patients treated with primary percutaneous intervention (PPCI), heart rate at discharge correlates with mortality. Ivabradine is a pure heart rate-reducing agent that has no effect on blood pressure and contractility, and can reverse left ventricular (LV) remodelling in patients with heart failure.

Aims. — To evaluate whether ivabradine, when added to current guideline-based therapy, improves LV remodelling in STEMI patients treated with PPCI.

Abbreviations: AMI, acute myocardial infarction; b.p.m., beats per minute; CMR, cardiovascular magnetic resonance imaging; HR, heart rate; LV, left ventricle/ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; PPCI, primary percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction.

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Methods. — This paired-cohort study included 124 patients between June 2011 and July 2012. Ivabradine (5 mg twice daily) was given promptly after PPCI, along with beta-blockers, to obtain a heart rate < 60 beats per minute (ivabradine group). This group was matched with STEMI patients treated in line with current guidelines, including beta-blockers (bisoprolol), according to age, sex, infarct-related coronary artery, ischaemia time and infarct size determined by initial cardiac magnetic resonance imaging (CMR) (control group). Statistical analyses were performed according to an intention-to-continue treatment principle. CMR data at 3 months were available for 122 patients.

Results. — Heart rate was lower in the ivabradine group than in the control group during the initial CMR (P = 0.02) and the follow-up CMR (P = 0.006). At the follow-up CMR, there was a smaller increase in LV end-diastolic volume index in the ivabradine group than in the control group (P = 0.04). LV end-systolic volume index remained unchanged in the ivabradine group, but increased in the control group (P = 0.01). There was a significant improvement in LV ejection fraction in the ivabradine group compared with in the control group (P = 0.04).

Conclusions. — In successfully reperfused STEMI patients, ivabradine may improve LV remodelling when added to current guideline-based therapy.

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Background

Acute myocardial infarction (AMI) induces scar formation and changes in the surviving myocardium, designated as post-AMI ventricular remodelling [1]. Adverse left ventricular (LV) remodelling, defined as an increase in LV end-systolic volume (LVESV) is associated with progression to heart failure and poor outcome. The therapeutic effects of beta-blockade, angiotensin-converting enzyme inhibition and mineralocorticoid receptor antagonist (MRA) inhibition have been linked to their beneficial effects on cardiac remodelling [2–4]. Thus, oral treatment with beta-blockers should
Ivabradine and left ventricular remodelling after STEMI

be considered during hospital stay and continued thereafter in all patients with ST-segment elevation myocardial infarction (STEMI) [5]. Heart rate (HR) is a major determinant of myocardial oxygen demand. Furthermore, in STEMI patients treated with primary percutaneous intervention (PPCI), HR at discharge has been found to correlate with mortality [6].

Ivabradine is a pure HR reducing agent that has no effect on blood pressure and contractility. The results of the Sys-tole Heart failure treatment with the iβ inhibitor ivabradine Trial (SHIFT) showed that an HR decrease with ivabradine reversed LV remodelling in patients with heart failure [7]. In the same way, ivabradine improved the LV pressure-volume relationship, decreased interstitial collagen content and increased capillary density in young adult rats with AMI and congestive heart failure [8]. Only one trial has investigated the effects of ivabradine versus beta-blockers in early phases of anterior STEMI with impaired LV function treated with PPCI [9]. In this study, at 2-month follow-up, patients treated with ivabradine had a significant increase in LV ejection fraction (LVEF), with concomitant reduction in LVESV and LV end-diastolic volume (LVEDV). However, to our best knowledge, no study has evaluated the additional value of ivabradine in STEMI patients treated with successful PPCI and optimal medical therapy. Therefore, our study was designed specifically to evaluate whether ivabradine improves LV remodelling after AMI when added to current guideline-based therapy, including beta-blockers, in STEMI patients treated with successful PPCI.

Methods

We decided to conduct a non-randomized study because we felt we did not have enough strong preliminary scientific data on the use of ivabradine in humans during the acute phase of myocardial infarction. However, in view of the experimental data, we wanted to conduct a pilot study to assess the feasibility and impact on LV remodelling of adding ivabradine to standard pharmacological therapy following PPCI in patients presenting with STEMI.

Patients

This paired-cohort study was approved by the ethics committee of our institution and all patients gave their written informed consent before inclusion. Between June 2011 and July 2012, all consecutive patients presenting with a STEMI were considered eligible for participation. Among them, two matched groups were formed: the ivabradine group and the control group. Inclusion criteria were: the presence of an inaugural STEMI, defined by prolonged chest pain, troponin T concentration higher than twice the upper limit (> 0.01 mg/mL) and electrocardiogram changes on at least two contiguous leads with pathological Q waves (> 0.04 seconds) and/or persisting ST-segment elevation (> 0.1 mV); and successful reperfusion (Thrombolysis in Myocardial Infarction [TIMI] flow grade 3 in the infarct-related artery). Exclusion criteria were: unsuccessful myocardial reperfusion (TIMI flow grade ≤ 2); thrombolysis; haemodynamic instability; atrial arrhythmia; HR < 70 beats per minute (b.p.m.) 1 hour after coronary angioplasty; and contraindications to cardiac magnetic resonance imaging (CMR). The ivabradine group was matched with a control group of STEMI patients according to age, sex, infarct-related coronary artery, ischaemia time and infarct size determined by initial CMR.

Emergency care and percutaneous procedure

During transport for percutaneous coronary intervention (PCI), all patients received intravenous low-molecular-weight heparin (enoxaparin; 0.5 mg/kg), intravenous aspirin (≥ 250 mg) and loading doses of clopidogrel (≥ 600 mg) or prasugrel (≥ 60 mg). All patients underwent PPCI with bare-metal and/or drug-eluting stent implantation in the culprit artery. A glycoprotein IIb/IIIa inhibitor (abiximab) was administered during the procedure, at the discretion of the operator. Thrombus aspiration before stent implantation of the infarct-related coronary artery was performed, according to the guidelines [10]. Coronary flow before and after revascularization was graded according to the TIMI study group classification [11] by two blinded observers (25 and 10 years of experience in coronary angiography, respectively). A successful procedure was defined when both TIMI grade 3 and residual diameter stenosis < 30% were obtained.

Study plan and treatments

Patients were assigned to a treatment group, according to the decision (free choice) of the cardiologist in charge at admission to the intensive care unit after the coronary angioplasty. The study plan is presented in Fig. 1. Between 1 and 3 hours after angioplasty, patients in the ivabradine group and presenting with HR ≥ 70 b.p.m., received a 5 mg test dose of ivabradine to evaluate their tolerance; ivabradine was then given orally at the 5 mg dose, twice daily. A concomitant beta-blocker (bisoprolol) was given and uptitrated to 10 mg to reach the target HR i.e. < 60 b.p.m. during hospitalization. Other therapies, including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and MRAs if considered appropriate, were

![Figure 1](image-url)
optimized in accordance with contemporary guidelines. If the resting HR was < 50 b.p.m. or the patient experienced symptoms related to bradycardia, the dose of ivabradine was reduced to 2.5 mg, twice daily. LV volume and mass, LVEF, myocardial wall thickness in infarct and remote non-infarcted myocardium and infarct size were assessed in all patients by performing CMR during hospitalization. The control group included patients treated according to current guidelines [5], including beta-blockers (bisoprolol in our centre), to obtain a HR < 60 b.p.m. at discharge. In our institution, all these patients were evaluated using initial CMR a few days after AMI and follow-up CMR at 3 months.

**CMR protocol and analysis**

CMR studies were performed on a 1.5T clinical scanner equipped with a 32-channel cardiac coil (Avanto; Siemens Medical Solutions, Forchheim, Germany). Cine imaging was performed to acquire a stack of short-axis slices covering the whole of the left ventricle (LV) from base to apex, using an electrocardiogram-gated balanced steady-state free-precession breath-hold sequence with the following parameters: repetition time/echo time 20–30/1.4 ms; flip angle 60°; slice thickness 6 mm; pixel size 1.6 × 1.6 to 1.8 × 1.8 mm; 20 frames per cardiac cycle. Late gadolinium-enhanced imaging was performed to acquire a stack of short-axis slices covering the whole LV from base to apex. Acquisition was initiated 15 minutes after the injection of 0.2 mmol/kg gadoterate meglumine (Dotarem; Guerbet, Aulnay-Sous-Bois, France) using an inversion-recovery-prepared three-dimensional turbo fast low-angle shot breath-hold sequence with the following parameters: TR/TE 700/1.4 ms; flip angle 10°; slice thickness 6 mm; pixel size 1.8 × 1.4 mm. Inversion time was optimized on a previously-acquired TI-scanning sequence [12]. Data were exported to a separate workstation for analysis using a commercially available software package (MASS version 7.0; Medis Medical Imaging Systems, Leiden, The Netherlands). Image segmentation was performed by two observers (with 12 and 2 years of experience in CMR, respectively) blinded to clinical data, including the treatment with ivabradine. Endocardial and epicardial contours were segmented on end-diastolic and end-systolic frames at each short-axis location. LV trabeculae and papillary muscles were included in the ventricular volume [13]. LVEDV and LVEF were computed in millilitres using the modified Simpson’s rule [14] and were used to calculate LVEF, expressed as a percentage. Adverse LV remodelling was defined as an increase in LVESV ≥ 15% at follow-up [15]. LV mass (in grams) was calculated from the total volume of myocardium at end diastole multiplied by the myocardial density of 1.05 g/mL. LV volumes were indexed to body surface area. Delayed-enhanced short-axis images were segmented at a different time point by the same observers. Endo- and epicardial contours were manually traced and myocardial scar was automatically segmented, with a threshold set at 50% maximal signal intensity [16].

**Statistical analysis**

Continuous data are expressed as means ± standard deviations when they followed a normal distribution and as medians (interquartile ranges) when they did not. Categorical data are expressed as absolute values (percentages). Statistical analyses were performed according to an intention-to-continue treatment principle. When follow-up CMR data were missing, they were replaced by values reflecting: increased LVEDV and LVEF of 20%; decreased myocardial wall thickness in infarct myocardium and decreased LV mass of 10%. Clinical and paraclinical characteristics were compared between the two groups using two-sample t tests (or their non-parametric equivalents, i.e. the Mann-Whitney test and the signed-rank Wilcoxon’s test). Two-sample t tests were also used to compare changes in continuous variables from initial CMR to follow-up CMR between the two groups. Comparison of categorical variables was achieved using the chi-square test or Fisher’s exact test. All statistics were calculated using NCSS and PASS software (NCSS 2001; NCSS Statistical Software, Kaysville, Utah). P values < 0.05 were considered significant.

**Results**

**Population**

Of 456 STEMI patients screened, 170 patients satisfied all the inclusion and exclusion criteria. These patients, according to the decision of the cardiologist in charge, were assigned to either the ivabradine group or the control group. Among them, 124 Caucasian patients were matched, to form two groups (Fig. 2). The final analysis included 124 patients whose characteristics are reported Table 1.

**Ivabradine group**

The first examination was carried out 6.1 ± 1.9 days after AMI. Five patients had to stop ivabradine treatment. Six days after the AMI, one patient developed acute cholecystitis requiring surgery. Seven days after AMI, one patient had a syncpe secondary to torsades de pointes and this patient had bradycardia (i.e. HR < 50 b.p.m.) associated with severe hypokalemia (2.7 mmol/L). During the time between the initial and follow-up CMRs, three patients presented excessive bradycardia (i.e. HR < 45 b.p.m.) that required cessation of ivabradine treatment. For three patients, the dose of ivabradine was reduced to 2.5 mg, twice daily; among them, one patient did not undergo follow-up CMR. Another patient was unable to complete the follow-up CMR because he had gained 8.2 kg in body weight.

**Control group**

The first examination was carried out 6.3 ± 1.7 days after the AMI. No adverse events were noticed in this group. As reported in Table 1, there were no significant differences between the ivabradine and control groups in terms of co-morbidities, ischaemia time, coronary angiography characteristics at admission and medical treatment at 3 months, including beta-blocker dosage. At 6 days, the infarct size in the control group was 15.6 ± 6.8% of the LV mass and did not differ from the infarct size in the ivabradine group, which was 16.3 ± 7.5% of the LV mass (P = 0.56). LVEF was 56.4 ± 9.1% and 57.9 ± 9.8% in the control and ivabradine groups, respectively (P = 0.35).
Changes in HR in the two groups

HR showed a significant reduction between 1 hour after angioplasty and 3 months of treatment in both groups (from 76.7 ± 7.0 to 54.7 ± 5.8 b.p.m. in the ivabradine group and from 76.0 ± 6.2 to 57.6 ± 6.5 b.p.m. in the control group; \( P < 0.001 \)) (Table 2). Furthermore, HR was lower in the ivabradine group than in the control group during initial CMR (56.2 ± 4.8 b.p.m. vs 58.8 ± 6.0 b.p.m.; \( P = 0.02 \)); this difference increased during follow-up CMR (54.7 ± 5.8 b.p.m. vs 57.6 ± 6.5 b.p.m.; \( P = 0.006 \)).

Changes in LV volumes and function between initial and follow-up CMR

At the initial CMR, there were no significant differences in LVEDV index, LVESV index and LVEF between the two groups (\( P = 0.96, P = 0.43 \) and \( P = 0.35 \), respectively). Late microvascular obstruction on late gadolinium-enhanced imaging was present in 29 patients (46.8%) in the ivabradine group; 27 patients (43.5%) in the control group also demonstrated late microvascular obstruction (\( P = 0.59 \)). Follow-up CMR data were missing for two patients in the ivabradine group. At the follow-up CMR, the increase in LVDESV index was smaller in the ivabradine group than in the control group (\( P = 0.04 \)) (Table 3). The LVESV index remained globally unchanged in the ivabradine group, whereas it increased in the control group (\( P = 0.01 \)). Adverse LV remodelling occurred in 14 (21.8%) patients in the ivabradine group and 20 (31.3%) patients in the control group (\( P = 0.23 \)). Regarding LVEF changes, there was a significant (\( P = 0.04 \)) improvement in the ivabradine group compared with the control group. Furthermore, there was an inverse relationship (\( r = -0.19, P = 0.04 \)) between the change in HR (between initial and follow-up CMR) and the change in LVEF. In contrast, there was no significant relationship between changes in HR and changes in LV volumes for all patients (\( r = 0.10, P = 0.24 \) for LVEDV index variation [%] and \( r = 0.14, P = 0.10 \) for LVESV index variation [%]).
Table 1  Study population baseline characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Ivabradine (n = 62)</th>
<th>Control (n = 62)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>56.7 ± 11.7</td>
<td>58.2 ± 10.5</td>
<td>0.45</td>
</tr>
<tr>
<td>Men</td>
<td>56 (90.3)</td>
<td>55 (88.7)</td>
<td>0.77</td>
</tr>
<tr>
<td>Family history of premature heart disease</td>
<td>25 (40.3)</td>
<td>28 (45.2)</td>
<td>0.59</td>
</tr>
<tr>
<td>Hypertension a</td>
<td>23 (37.1)</td>
<td>26 (41.9)</td>
<td>0.58</td>
</tr>
<tr>
<td>Smokers</td>
<td>43 (69.3)</td>
<td>42 (67.7)</td>
<td>0.85</td>
</tr>
<tr>
<td>Hyperlipidaemia b</td>
<td>42 (67.7)</td>
<td>40 (64.5)</td>
<td>0.45</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.7 (24.5–29.0)</td>
<td>26.2 (23.4–28.4)</td>
<td>0.23</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14 (22.6)</td>
<td>12 (19.3)</td>
<td>0.66</td>
</tr>
<tr>
<td>Ischaemia time (minutes)</td>
<td>294 ± 182</td>
<td>291 ± 169</td>
<td>0.79</td>
</tr>
<tr>
<td>Coronary angiography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infarct-related artery</td>
<td></td>
<td></td>
<td>0.81</td>
</tr>
<tr>
<td>LAD</td>
<td>29 (46.8)</td>
<td>27 (43.5)</td>
<td></td>
</tr>
<tr>
<td>LCx</td>
<td>12 (19.4)</td>
<td>15 (24.2)</td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>21 (33.8)</td>
<td>20 (32.3)</td>
<td></td>
</tr>
<tr>
<td>Single-vessel disease c</td>
<td>22 (35.5)</td>
<td>23 (37.1)</td>
<td>0.91</td>
</tr>
<tr>
<td>Double-vessel disease c</td>
<td>23 (37.1)</td>
<td>23 (37.1)</td>
<td>1.0</td>
</tr>
<tr>
<td>Triple-vessel disease c</td>
<td>17 (27.4)</td>
<td>16 (25.8)</td>
<td>0.73</td>
</tr>
<tr>
<td>TIMI flow grade ≥ 2 before PCI</td>
<td>16 (25.8)</td>
<td>12 (19.4)</td>
<td>0.39</td>
</tr>
<tr>
<td>Medication at follow-up (3 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>62 (100)</td>
<td>62 (100)</td>
<td>1.0</td>
</tr>
<tr>
<td>ADP receptor inhibitors</td>
<td>62 (100)</td>
<td>62 (100)</td>
<td>1.0</td>
</tr>
<tr>
<td>ACEI or A2 receptor blockers</td>
<td>61 (98.4)</td>
<td>59 (95.2)</td>
<td>0.31</td>
</tr>
<tr>
<td>MRA</td>
<td>9 (14.5)</td>
<td>10 (16.1)</td>
<td>0.80</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>62 (100)</td>
<td>62 (100)</td>
<td>1.0</td>
</tr>
<tr>
<td>Beta-blocker dosage (mg/day) d</td>
<td>4.0 (2.5–5)</td>
<td>4.2 (2.5–5)</td>
<td>0.84</td>
</tr>
<tr>
<td>Statins</td>
<td>62 (100)</td>
<td>62 (100)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation, number (%) or median (interquartile range). A2: angiotensin II receptor blocker; ACEI: angiotensin-converting enzyme inhibitor; ADP: adenosine diphosphate; LAD: left anterior descending artery; LCx: left circumflex artery; MRA: mineralocorticoid receptor antagonist; PCI: percutaneous coronary intervention; RCA: right coronary artery; TIMI: Thrombolysis In Myocardial Infarction.

a Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg.
b Hyperlipidaemia was defined as total cholesterol > 6.5 mmol/L, low-density lipoprotein cholesterol > 4.0 mmol/L or high-density lipoprotein cholesterol < 1.2 mmol/L.
c A lumen reduction of > 50% diameter stenosis was considered significant.
d Bisoprolol, the beta-blocker of preference, according to the local institutional protocol.

Changes in regional wall thickness between initial and follow-up CMR

We found no significant difference in global LV mass index between the two groups of patients at initial CMR (P = 0.15) (Table 3). At follow-up CMR, there was a significant (P = 0.02) trend towards a reduction in LV mass index in the control group.

Table 2  Changes in heart rate at baseline, day 1 and during initial and follow-up cardiac magnetic resonance imaging.

<table>
<thead>
<tr>
<th>Heart rate (beats per minute)</th>
<th>Ivabradine (n = 62)</th>
<th>Control (n = 62)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 hour after angioplasty</td>
<td>76.7 ± 7.0</td>
<td>76.0 ± 6.2</td>
<td>0.79</td>
</tr>
<tr>
<td>Day 1</td>
<td>65.9 ± 5.5</td>
<td>64.4 ± 7.7</td>
<td>0.21</td>
</tr>
<tr>
<td>Initial CMR</td>
<td>56.2 ± 4.8</td>
<td>58.8 ± 6.0</td>
<td>0.02</td>
</tr>
<tr>
<td>Follow-up CMR</td>
<td>54.7 ± 5.8</td>
<td>57.6 ± 6.5</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation. CMR: cardiac magnetic resonance imaging.

In the infarcted myocardium, there was a non-significant (P = 0.31) trend toward less reduction of end-diastolic wall thickness in the ivabradine group (from 7.6 ± 1.4 to 7.1 ± 1.5 mm) compared with the control group (from 7.7 ± 1.1 to 6.8 ± 1.4 mm). Furthermore, there was a non-significant (P = 0.40) trend toward less reduction of end-systolic wall thickness in the ivabradine group (from 9.1 ± 2.2 to 8.4 ± 2.4 mm) compared with the control group.
can be seen in Table 3. In the myocardium remote to the infarct, there was a significant effect of ivabradine on end-diastolic or end-systolic wall thickness at initial and follow-up CMR. In both groups, there was a trend towards a moderate increase in end-diastolic and end-systolic wall thickness between initial and follow-up CMR.

### Discussion

This study shows that ivabradine improves LV remodelling after AMI when added to current guideline-based therapy, including beta-blockers, in STEMI patients treated with successful PPCI. The ivabradine group showed a significant reduction in LVEDV and LVEF indexes compared with the control group after 3 months (P = 0.04 and P = 0.01, respectively). Regarding LVEF, there was a significant (P = 0.04) trend toward greater improvement in the ivabradine group. A significant reduction in HR was observed in ivabradine group at initial and follow-up CMR (P = 0.02 and P = 0.006, respectively). Furthermore, the use of ivabradine promptly after angioplasty appeared to be feasible.

To our knowledge, this study is the first to evaluate ivabradine added to current guideline-based therapy, including beta-blockers, in STEMI patients treated with successful PPCI. Thus far, only one study using echocardiography has been performed in patients after anterior myocardial infarction, demonstrating that the ivabradine group showed a significant reduction in LVEDV and LVEF indexes compared with the metoprolol group at 2 months [9]. However, in this randomized trial, the ivabradine group were not given beta-blockers and ivabradine was delivered late after angioplasty (i.e., 12 hours) [9]. The results of this study suggest that the early introduction of ivabradine in the context of AMI is a promising therapeutic strategy.

Clinical and experimental studies have revealed several mechanisms that may explain the beneficial effects of ivabradine on cardiac remodelling. First, ivabradine does not have negative inotropic or lusitropic effects; thus haemodynamic and myocardial contractility are not impaired [17,18]. Ivabradine leads to a decrease in HR, which reduces myocardial oxygen demand and simultaneously improves oxygen supply by prolonging diastole, which allows increased coronary flow and myocardial oxygenation. Second, Mulder et al. [8] observed in adult rats with AMI and congestive heart failure that ivabradine

### Changes in infarct size between initial and control CMR

In both groups, infarct size was significantly reduced at 3 months compared with baseline (P < 0.001). As shown in Table 3, there was no significant effect of ivabradine on infarct size at follow-up CMR compared with the control group, whether expressed as an absolute value (P = 0.48) or as a percentage of LV mass (P = 0.97).
improves the LV developed pressure-volume relationship, prevents LV systolic dysfunction and increases capillary density. In the same way, Dedkov et al. have documented several effects of ivabradine in middle-aged rats with AMI, including reduced periarterial and interstitial collagen content, attenuation of the increase in end-diastolic pressure and attenuation of the decrease in LVEF [19]. These beneficial effects of ivabradine after AMI have been investigated in models of permanent coronary ligation. Third, in a rabbit model of ischaemia reperfusion, Couvreur et al. observed that ivabradine reduced myocardial stunning [20].

In our study, the addition of ivabradine to the beta-blocker induced a significant reduction in HR compared with the control group. This difference increased with time and may be related to a ‘delayed effect’ of the molecule. We also noticed that the bisoprolol dose did not differ between both groups at follow-up CMR. We can suppose that the dose of beta-blocker could have been increased in the control group during follow-up, which may have attenuated the results. Therefore we propose that the magnitude of HR reduction by ivabradine, administered in addition to beta-blockers, rather than the background beta-blocker dose, explains partially the effects on LV remodelling. In the same way, similar findings have been observed in the SHIFT study [21]. In an experimental study, Christensen et al. compared the effects of atenolol versus ivabradine on myocardial perfusion, coronary reserve, and LV function after AMI in middle-aged rats [22]. They observed that ivabradine induced more favourable remodelling via greater LV hypotrophy and lower LVEDV-to-mass ratio. In the same way, in our study, there was a significant trend toward less reduction of LV mass index ($P=0.02$) in the ivabradine group. Furthermore, the additional effect of ivabradine on LV remodelling in our study was not explained by the reduction of infarct size, which was similar between both groups.

In this pilot study, ivabradine treatment appears to be feasible and well tolerated by the patients, except in some cases of excessive bradycardia. HR reduction with ivabradine reverses LV remodelling in patients with heart failure and documented LV systolic dysfunction (LVEF ≤35%) [7]. In view of our preliminary results, we believe that this treatment should be evaluated in association with beta-blockers in STEMI patients presenting with severe LV dysfunction and high HR.

This pilot study showed that ivabradine was associated with a moderate reduction in LV volumes and increase in LVEF compared with standard therapy. However, further larger trials are required to determine whether a rather small reduction in LV volumes with ivabradine added to standard care translates into benefit in terms of clinical outcomes. Adverse LV remodelling occurred in 14 (21.8%) patients in the ivabradine group and 20 (31.3%) patients in the control group ($P=0.23$). Given these results, the sample size necessary for a randomized placebo-controlled trial to demonstrate a significant difference between both groups in adverse LV remodelling using the chi-square test can be computed using PASS software. If the cut-off value for adverse LV remodelling is 15% (yielding a size effect of 0.1085), the total sample size should be 894 patients. Thus, many studies [7] have clearly demonstrated an improvement in haemodynamics, LV remodelling and mortality with angiotensin-converting enzyme inhibitor treatment.

Furthermore, the EPHESUS study [4] of over 6600 patients with AMI complicated by evidence of systolic LV dysfunction (LVEF ≤40%) showed that selective aldosterone blockade with eplerenone resulted in 15% reduction in total mortality. In the same way, Hayashi et al. [23] showed that MRA spironolactone combined with an angiotensin-converting enzyme inhibitor can prevent postinfarct LV remodelling in association with the suppression of a marker of collagen synthesis.

This study is not a randomized trial. However, we chose a non-randomized observational study design to evaluate the advantages and disadvantages of ivabradine in a possible new indication (i.e. its effectiveness in STEMI patients treated with successful PPCI). Thus, larger randomized double-blind multicentre studies, including particularly patients with unsuccessful reperfusion (TIMI flow grade ≤2), are required. Moreover, a longer follow-up period of 6 months or 1 year would provide additional interesting data. Finally, postconditioning, which reduces infarct size by 30–40% with a significant improvement in contractile function continuing 1 year after AMI [24], was not performed in this study.

Conclusions

We observed in this pilot study that in TIMI 3 reperfused STEMI, the early administration of ivabradine may improve LV remodelling when added to current guideline-based therapy, including beta-blockers. Given these promising results, larger randomized studies are necessary to confirm our findings.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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