Safety and efficacy of oral ivabradine as a heart rate-reducing agent in patients undergoing CT coronary angiography

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Objective: To investigate the role of oral ivabradine as a heart rate reducing agent in patients undergoing CT coronary angiography (CTCA). Despite the routine use of β -blockers prior to CTCA studies, it is not uncommon to have patients with heart rates persistently above the target range of 65 bpm. Ivabradine is a selective inhibitor of the I_f current, which primarily contributes to sinus node pacemaker activity, and has no significant direct cardiovascular effects such as reduction of blood pressure, cardiac contractility or impairment of cardiac conduction.

Methods: We investigated 100 consecutive patients who had been referred for CTCA for the evaluation of suspected coronary artery disease (CAD). Patients were randomised to receive either of the following two pre-medication protocols: oral metoprolol or oral ivabradine.

Results: Ivabradine was significantly more effective than metoprolol in lowering the heart rate; the mean percentage reduction in heart rate with ivabradine vs metoprolol was 23.89±6.95% vs 15.20±4.50%, respectively ($p=0.0001$). Metoprolol significantly lowered both systolic and diastolic blood pressure while ivabradine did not. The requirement of additional doses to achieve a target heart rate of <65 beats per min was also significantly more frequent with metoprolol.

Conclusion: Ivabradine is a potentially attractive alternative to currently used drugs for reduction of heart rate in patients undergoing CTCA.

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Since the introduction of CT coronary angiography (CTCA) as a non-invasive tool for coronary artery imaging, its clinical utility has been established in various studies [1–3]. However, the presence of motion artefacts often prevents optimal reconstruction of individual coronary arteries, prompting use of pharmacological interventions (primarily β -blockers) during scanning to enhance image quality [4, 5]. A target heart rate of 65 beats per min (bpm) or less provides optimum image quality in most cases [6, 7]. Though calcium channel-blockers have also been used as alternatives to β -blockers [8], there still exists a subset of patients in whom the administration of these rate-lowering drugs may be hazardous (e.g. those with baseline blood pressure <100–110 mmHg, severe left ventricular dysfunction, peripheral vascular disease or severe obstructive airway disease). Moreover, despite the routine use of β -blockers prior to CTCA studies, it is not uncommon to have patients with heart rates persistently above the target range of 65 bpm [9–11].

There is a clear need for assessment of the potential role of alternative rate-lowering drugs in patients undergoing CTCA. Ivabradine, a novel heart rate-lowering agent, is a selective and specific inhibitor of the I_f current, which is one of the most important ionic currents for regulating pacemaker activity in the sinoatrial (SA) node [12–14]. This is primarily a mixed Na^+ – K^+ inward current activated

by hyperpolarisation and modulated by the autonomic nervous system, and ivabradine acts by selectively inhibiting the pacemaker I_f current and slowing the diastolic depolarisation slope of SA node cells, reducing both resting and exercise heart rate. Moreover, ivabradine inhibits the I_f current at concentrations that do not affect other cardiac ionic currents, resulting in a lack of haemodynamic effects such as reduction of blood pressure or cardiac contractility, which is often a limitation with β -blockers. It has a good safety profile without any effects on atrioventricular conduction, corrected QT interval and peripheral vasomotion, and there is no rebound effect with drug cessation or tolerance with prolonged use.

We investigated the safety and efficacy of oral ivabradine as a heart rate-lowering agent in patients undergoing CTCA at our institute. The aims of the study were (1) to assess the efficacy of ivabradine in achieving adequate heart rate control (defined as target heart rate <65 bpm), (2) to compare the differences (if any) between ivabradine and the β -blocker metoprolol in achieving target heart rate prior to CTCA and (3) to compare any difference in numbers of patients requiring additional doses of drugs prior to achieving the target heart rate.

Methods and materials

A total of 100 consecutive patients referred for CTCA for the evaluation of suspected coronary artery disease (CAD) were prospectively enrolled in the study, which conformed

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to the institutional ethical guidelines. Patients with atrial fibrillation, known arrhythmias, impaired renal function (serum creatinine $>1.5 \text{ mg dl}^{-1}$), known allergy to iodinated contrast media, pregnancy, baseline heart rate $<60 \text{ bpm}$, left ventricular ejection fraction $<30\%$, blood pressure $<100/70 \text{ mmHg}$, other known contraindications to β -blockers such as Mobitz, second- and third-degree atrioventricular block, congestive heart failure, severe peripheral vascular disease and chronic obstructive pulmonary disease were excluded from the study. All patients were initially assessed in the outpatient clinic and baseline heart rate (HR1), systolic (SBP1) and diastolic (DBP1) blood pressure, and a 12-lead electrocardiogram (ECG) were obtained. After obtaining informed consent, patients were randomised to receive either of the two pre-medication protocols: (1) oral β -blockers or (2) oral ivabradine.

Patient preparation and heart rate control

Patients allocated to the β -blocker group received oral metoprolol 50 mg bd while those randomised to oral ivabradine received 5 mg bd, started at least 48 hours before the scheduled CTCA examination. On arrival in the CT room, the heart rate and blood pressure were noted (HR2, SBP2, DBP2). Patients whose heart rate on arrival was $>65 \text{ bpm}$ were allocated to receive additional doses of the drugs (one dose of either 5 mg ivabradine or 50 mg of metoprolol); if the heart rate was still $>65 \text{ bpm}$ 3 h after the additional first dose, another dose of 5 mg ivabradine or 50 mg metoprolol was administered. The final heart rate (HR3) during the CTCA examination was also recorded in all patients. Patients whose heart rate could not be lowered below 65 bpm despite this protocol had their CTCA procedures rescheduled. (We did not allocate patients to receive intravenous (iv) β -blockers, to avoid skewed comparisons between the groups, as iv ivabradine is presently not available to us.)

CT coronary angiography protocol

All studies were performed on a 64-slice scanner (Brilliance; Philips Medical Systems, Cleveland, OH). Prior to CTCA, an unenhanced CT scan was performed in all patients with the aim of quantifying coronary artery calcification. The parameters for the unenhanced CT study were: gantry rotation time 400 ms, tube voltage 120 kV, tube current 55 mAs, slice thickness 2.5 mm, reconstruction increment 25 mm, field of view 160–180 mm and convolution kernel medium. For CTCA the following parameters were used: slices/rotation 64, individual detector width

0.6 mm, gantry rotation time 400 ms, pitch 0.2, tube voltage 120 kV, tube current 850 mAs, reconstruction increment 0.9 mm, field of view 160–180 mm and convolution kernel medium. A dose of 80–100 ml of non-ionic iodinated contrast material was administered at a rate of 5.5 ml s^{-1} with a power injector (Stellant; Medrad, Warrendale, PA) attached to an 18-gauge needle positioned in an antecubital vein. With the aim of optimising coronary artery enhancement, the bolus-tracking technique was used to synchronise the arrival of contrast material in the coronary arteries with the initiation of the scan. Images were obtained during a single breath-hold of 5–6 s. Retrospective reconstructions were performed based on the ECG signal to obtain images unaffected by motion artefacts. The time windows used were the mid-to-end diastolic phases (from 45% to 75% of the R–R interval). When performed (e.g. in the case of persistent and residual heart movement reducing the diagnostic quality of the image), additional reconstructions were analysed in different time windows during the cardiac cycle, generally between 25% and 35% of the R–R interval. Then, images were transferred to a remote dedicated workstation (Philips Brilliance) for post-processing.

Statistical analysis

All continuous variables are presented as mean $\pm$ standard deviation and categorical variables as percentages. The independent Student's *t*-test was used to assess differences in continuous variables. The χ^2 test was used to assess differences in categorical variables. A value of $p < 0.05$ was considered indicative of statistical significance. All hypothesis testing was done assuming a two-tailed test.

Results

The baseline characteristics of the patients are summarised in Table 1. The mean age was 54 ± 10 years, and 65% of the patients were males. The distribution of traditional risk factors such as hypertension, diabetes, dyslipidaemia, smoking and mean left ventricular ejection fraction as determined by ECG were comparable in the two groups. No adverse reactions to contrast material were noted during or after CTCA in any of the patients.

Efficacy of heart rate reduction

HR1, SBP1 and DBP1 in both groups were not significantly different (Figure 1). Both ivabradine and

Table 1. Patient characteristics in the ivabradine and metoprolol groups

Characteristics	Total (n=100)	Ivabradine group (n=50)	Metoprolol group (n=50)	p-value
Age (years)	54 ± 10	55 ± 9	56 ± 10	ns
Male, % (n)	65 (65)	64 (32)	66 (33)	ns
Diabetes, % (n)	30 (30)	28 (14)	32 (16)	ns
Hypertension, % (n)	20 (20)	18 (9)	22 (11)	ns
Smoking, % (n)	10 (10)	8 (4)	12 (6)	ns
Dyslipidemia, % (n)	66 (66)	68 (34)	64 (32)	ns
LVEF (echocardiography)	56 ± 6	54 ± 9	56 ± 11	ns

LVEF, left ventricular ejection fraction; ns, not significant.

Figure 1. Changes in heart rate following ivabradine and Metoprolol. p -values <0.001 for HR1 vs HR2 and HR2 vs HR3 for both ivabradine and metoprolol. p -values <0.001 for HR2_{ivabradine} and HR2_{metoprolol}. p -values <0.001 for HR3_{ivabradine} and HR3_{metoprolol}. HR, heart rate.

metoprolol were effective in lowering the heart rate, with ivabradine reducing the resting heart rate from 90.02 ± 7.02 (HR1) to 68.38 ± 6.73 bpm (HR2, $p < 0.0001$) and metoprolol reducing it from a HR1 of 91.92 ± 5.75 to HR2 of 77.98 ± 6.88 bpm ($p < 0.0001$). On comparing the two agents, ivabradine was significantly more effective in reducing the heart rates (HR2_{ivabradine} 68.34 ± 6.75 vs HR2_{metoprolol} 77.98 ± 6.88 bpm; $p < 0.0001$). After administering additional doses of ivabradine or metoprolol (whenever required, in the CT room, as per protocol), the final heart rates (HR3) in ivabradine group remained significantly lower than in the metoprolol group (58.77 ± 1.25 vs 63.20 ± 1.4 , respectively; $p < 0.0001$).

The mean percentage reduction in heart rate was also significantly greater with ivabradine than with metoprolol ($23.89 \pm 6.95\%$ vs 15.20 ± 4.50 , respectively; $p < 0.0001$; Figure 2).

Lack of significant blood pressure-lowering effects with ivabradine

In contrast to its significantly better heart rate-lowering properties as compared with metoprolol, there was no significant effect of ivabradine on systolic or diastolic blood pressure (SBP1/DBP1: $136.08 \pm 11.29/86.64 \pm 8.03$ and SBP2/DBP2: $135.28 \pm 11.52/86.32 \pm 7.50$; the p -value was not significant for both SBP1 and SBP2, and DBP1 and DBP2; Figure 3). On the other hand, metoprolol, apart from its heart rate-lowering effects, also, as expected, demonstrated a significant reduction in both systolic and diastolic blood pressure (SBP1 135.44 ± 14.30 to SBP2 116.40 ± 8.76 , $p < 0.0001$; and DBP1 88.04 ± 6.95 to DBP2 82.16 ± 4.38 , $p < 0.0001$). However, none of the patients experienced any adverse effects from the fall in blood pressure.

Requirement of additional doses of rate-reducing drugs

Of the 50 patients receiving ivabradine, 24 (48%) patients had a resting heart rate ≤ 65 bpm on the day of CTCA (HR1 ≤ 65 bpm); hence, these 24 patients did not require any additional dose of ivabradine (Table 2). Of the remaining 26 patients, 16 (32%) required one additional dose and 10 patients (20%) required two additional doses of ivabradine to achieve the target heart rate ≤ 65 bpm.

Figure 2. Mean percentage reduction in heart rate with ivabradine as compared with metoprolol. p -value <0.001 for mean percentage heart rate reduction between ivabradine and metoprolol.

Of the 50 patients receiving metoprolol, none of the patients had resting heart rates ≤ 65 bpm on the day of CTCA. 22 patients (44%) needed one additional dose and 28 patients (56%) required two additional doses of metoprolol to achieve the target heart rate ≤ 65 bpm.

Both drugs were well tolerated and no adverse effects to any of them were reported.

Discussion

CTCA has emerged as an excellent non-invasive tool for the diagnosis of CAD [1–3]. However, adequate image quality is essential to achieve optimal diagnostic accuracy, and having a heart rate of 60–65 bpm during imaging is recommended for this. An essential part of performing a successful CT CA examination is to optimise the patient's heart rate using β -blockers to limit motion artefacts in the coronary arteries. However, despite the routine use of β -blockers prior to CTCA studies, it is not uncommon to have patients with heart rates persistently above the target range of 65 bpm, despite using oral as well as iv β -blockers [9–11, 15].

Although calcium channel-blockers may be used as alternatives to β -blockers, overall they have been infrequently used as a pre-medication in patients undergoing CTCA [8]. There also exists a subset of patients in whom

Figure 3. Effect of ivabradine and metoprolol on systolic and diastolic blood pressure. No significant difference between SBP1 and DBP1 (ivabradine vs metoprolol). No significant difference between SBP1_{ivabradine} and SBP2_{ivabradine}, as well as DBP1_{ivabradine} and DBP2_{ivabradine}. p -values <0.001 for SBP1_{metoprolol} and SBP2_{metoprolol}, as well as DBP1_{metoprolol} and DBP2_{metoprolol}. SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 2. Patients requiring additional doses of heart rate-reducing drugs

Drug	No additional dose	One additional dose	Two additional doses
Ivabradine <i>n</i> =50	24 (48)	16 (32)	10 (20)
Metoprolol <i>n</i> =50	0 (0)	22 (44)	28 (56)

Data are given as number (percentage).

both β -blockers and calcium channel-blockers would be inadvisable, namely those with low baseline blood pressure (<100–110 mmHg), severe left ventricular dysfunction, severe aortic stenosis, etc. [15]. Moreover, patient response to β -blockers is often inadequate, which may be due to presence of polymorphisms in the β_1 -adrenoceptor or excessive adrenergic stimulation caused by anxiety, leading to persistent tachycardia [16]. Strategies that may be needed in such patients include (1) rescheduling the test and combining an anxiolytic such as diazepam with the β -blockers, (2) gradually up-titrating the β -blockers over several weeks and (3) administering higher doses of iv β -blockers [15]. However the safety and efficacy of all these strategies are unknown. Given the rapidly increasing clinical application of cardiac CT, there exists a real need to look at the potential role of alternative rate-lowering drugs.

Ivabradine is a novel heart rate-lowering agent that selectively inhibits the I_f current, which primarily contributes to sinus node pacemaker activity, without affecting other cardiac ionic currents [12–14]. Hence, there are no significant direct cardiovascular effects such as reduction of blood pressure, cardiac contractility or impairment of cardiac conduction. In fact, in contrast to β -blockers, I_f current inhibition increases stroke volume and may improve left ventricular function and ventricular remodelling [17]. The safety and efficacy of ivabradine in chronic stable angina and in patients with CAD with impaired left ventricular (LV) function, as monotherapy as well as add-on therapy to β -blockers, has been well demonstrated [18–20].

Ivabradine has been noted to be particularly beneficial in patients with high resting heart rates, a property that can be especially useful in patients undergoing CTCA. Side effects are infrequent and mostly restricted to dose-related visual disturbances, which are, however, rare if doses are kept to less than 10 mg bd [18, 21].

Given its pharmacological properties, the use of ivabradine as a heart rate-lowering agent promises to be an attractive therapeutic option. However, only a few studies have reported the use of ivabradine for reduction of heart rate in patients undergoing CTCA. Guaricci et al [22] reported the safety and efficacy of oral ivabradine in patients undergoing CTCA, and concluded that it significantly reduced the need for additional iv β -blockers in such patients. In patients considered non-eligible for iv β -blockers (primarily owing to pulmonary disease and history of heart failure), Bax et al [23] reported that a single iv bolus of ivabradine achieved a rapid, safe and sustained heart rate-lowering effect, significantly facilitating the performance of a satisfactory CTCA procedure.

We also found ivabradine an effective agent in lowering heart rates in patients undergoing CCTA. In the doses administered it was significantly more effective than metoprolol in lowering heart rates on the day of

the CTCA ($HR_{2,ivabradine} 68.38 \pm 6.73$ vs $HR_{2,metoprolol} 77.98 \pm 6.88$ bpm; $p < 0.001$). This was achieved without any associated adverse effects. Moreover, the mean percentage reduction in heart rate (HR1 to HR3) was significantly greater with ivabradine than with metoprolol, demonstrating the superiority of ivabradine. Ivabradine was also significantly more effective in improving the rates of patients achieving target heart rate (≤ 65 bpm) on the day of examination. While all patients in the metoprolol group required additional doses of the drug on the day of examination (22 requiring one additional dose and 28 requiring two additional doses), in the ivabradine group, 48% patients did not require any additional doses of the drug.

Importantly, ivabardine did not produce any significant change in the blood pressure (systolic or diastolic), while metoprolol, in the doses used, produced significant reduction in systolic (SBP1 135.44 ± 14.30 to SBP2 116.40 ± 8.76 ; $p < 0.0001$) and diastolic blood pressures (DBP1 88.04 ± 6.95 to DBP2 82.16 ± 4.38 ; $p < 0.0001$). This lack of significant blood pressure-lowering effect of ivabradine is likely to be of particular benefit in patients with low baseline systolic blood pressure who are undergoing CTCA.

It also needs to be kept in mind that, in contrast to β -blockers, ivabradine has no significant effect on LV function. Although measurement of LV function is rarely a primary indication for cardiac CT, ivabradine may be preferred in cases in which LV function needs to be quantified with simultaneous coronary assessment when there is a clear-cut need of heart rate-reducing medication.

Conclusion

Ivabradine, a novel heart rate-reducing agent, has the potential to be an attractive alternative to currently available drugs to achieve optimal heart rate control in patients undergoing CTCA. In the doses used in our study, ivabradine was safe and effective as a heart rate-reducing agent. It also produced a greater reduction in heart rate as compared with metoprolol. The number of patients requiring additional doses of the drugs prior to achieving target heart rates was also significantly reduced with ivabradine.

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