Lowering of Heart Rate before Computed Tomographic Coronary Angiography: Improvement in Image Quality and Role of Ivabradine

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Abstract

Heart rate during coronary computed tomographic angiography (coronary CTA) has a direct correlation with image quality and detection of coronary artery disease. Beta blocking agents are the most commonly used drugs to lower the heart rate, but their use is limited due to adverse effects and contraindications. Ivabradine (IVA) is a novel drug that selectively acts on cardiac pacemaker cells and lowers heart rate. This brief review article emphasizes the importance of slow heart rate for coronary CTA image quality and pre-treatment with IVA as a negative chronotropic agent. We compared the role of other drugs used for this purpose.

Keywords — Ivabradine, Coronary CT angiography, Hear rate

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USE OF CORONARY COMPUTED TOMOGRAPHIC ANGIOGRAPHY

Coronary computed tomographic angiography (CTA) is a non-invasive modality used to: 1) evaluate the presence or absence of the coronary artery disease (CAD) in intermediate risk patients; 2) to detect congenital coronary artery anomalies; 3) to assess the patency of coronary artery stents and bypass grafts; and 4) defining the pulmonary vein anatomy before atrial fibrillation ablation. Coronary CTA has a specificity of 93 and 96% respectively in detecting coronary artery stenosis and has shown a high negative predictive value of 93-100% in ruling out significant coronary artery stenosis in symptomatic patients with intermediate risk of ischemic heart disease. Coronary CTA thus enhances the efficiency of clinical decision-making in acute chest pain in the emergency department.

Factors Affecting Image Quality

The quality of increased temporal resolution imaging, such as that obtained by Dual-source coronary CTA, is less dependent upon heart rate (HR) than regular CTA. Although there have been improvements in the image quality with the advent of 320-row coronary CTA, the detection of CAD and accurate description of the plaque are dependent on image quality, which is affected by multiple factors, including HR.

Studies have demonstrated an inverse relationship between image quality of coronary CTA, HR and HR variability. A lower HR lengthens the diastolic phase of the cardiac cycle, effectively increasing the time when the heart and coronary arteries are motion free. Lower HR thus decreases the need for image reconstruction during other phases of the cardiac cycle, consequently improving image quality and decreasing radiation dose (Fig 1). Due to their close proximity to the right and left atria respectively, the right coronary artery and left circumflex artery (LCx) are more prone to motion artifacts.

Pharmacological Interventions to Lower Heart Rate

Several pharmacological interventions have been implemented to decrease the pre-scanning HR. These include oral and intravenous administration of beta-blockers, nitrates, and non-dihydropyridine calcium channel blockers (CCB). Beta-blockers are the most widely used pre-medication to reduce HR and IV form has faster bioavailability. However, their use is limited due to possible contraindications in certain clinical situations. Although data is sparse, nitrates (nitroglycerin and glycerol trinitrate) have been used to improve angiography image quality. These drugs dilate coronary arteries by smooth muscle relaxation but cause reflex tachycardia and have significant side effects including headache, tachycardia and vasovagal symptoms. Concomitant use of 5-Phosphodiesterase inhibitors.

Beta-blockers improve the image quality both by reducing HR and increasing HR regularity. Metoprolol is the most widely used beta-blocker in clinical settings, as well as in various trials. Metoprolol is used in both IV and oral formulations: IV administration being quick acting and easy to administer but requiring greater monitored (e.g., presence of radiologist and patient may need to stay longer after the imaging is complete).

Major Clinical Trials

Shapiro et al prospectively studied the role of IV beta-blockers in patients with baseline HR >65 bpm. A significant percentage of patients (45%) required HR reduction before coronary CTA. The target HR (<65 bpm) was achieved in 35% of subjects by IV metoprolol administered 5 min prior to coronary CTA. About 24% of patients with a HR above the target could not receive beta-blockers due to various contraindications. The study did not consider arrhythmias and beat-to-beat variability, which can result in stair step artifacts.

Maffei et al divided patients into groups based on baseline HR: above goal group (>65 bpm) and below goal group (<65 bpm). HR above the goal was controlled with or above the target could not receive beta-blockers due to various contraindications. The average time before intervention was 44 ± 25 min. In the overall
population 81.8% of patients attained the target HR of ≥65 bpm with the best response being achieved with IV β-blockers that allowed quicker administration compared with oral pre-medication. Nitrates actually increased the HR in most cases. One of the many limitations of the study was a lack of comparison between different intervention strategies. Patients were prepared only on the day of the scan and the target HRs were different for the various groups, making comparison difficult.

Graaf et al. administered oral metoprolol and/or lorazepam 60 min before coronary CTA in patients with HR ≥65 bpm. In 16% of the patients with HR above the goal there was some contraindication to the use of β-blockers. They found that 73% of the patients reached the target HR (≤65 bpm) before coronary CTA.

Leschka et al. showed that HR reduction and variability was reduced in patients receiving β-blockers and that this was significantly correlated with improved image quality for all coronary arteries. About 63% of the patients were receiving β-blockers as baseline medication and the average HR was 63.7 ± 13.1 bpm with a beat-to-beat variability of 3.2 ± 2.1 bpm. No additional premedication was used before 64-s coronary CTA. The influence of HR on diagnostic accuracy was not analyzed.

Table 1. Cardiovascular and non-cardiovascular side effects of Ivabradine, β-blockers and calcium channel blockers.

| Name of drug | Cautions to be taken when starting medication | Non-cardiovascular side effects |
|--------------|---------------------------------------------|---------------------------------|
| Ivabradine | Symptomatic bradycardia (5%) QT prolongation | Luminous phenomenon (phosphenes); enhanced brightness in visual field. |
| β blockers | Hypotension | Severe aortic stenosis |
| | Bradycardia (contraindicated in sick sinus syndrome, degree heart block) | Hypertension | Severe aortic stenosis |
| | Bradycardia (contraindicated in sick sinus syndrome, degree heart block) | Bradycardia (contraindicated in sick sinus syndrome, degree heart block) |
| | Adrenergic mediated coronary spasm on sudden withdrawal | Adrenergic mediated coronary spasm on sudden withdrawal |
| Calcium channel blockers | Hypotension | Bradycardia |
| | Bradycardia | Constipation |
| | Bradycardia | Drowsiness |

Table 2: Uses of Ivabradine

| Uses | STEMI (VIVIFY trial) | Chronic stable angina pectoris | Congestive heart failure | Coronary artery disease | Inappropriate sinus tachycardia | Postural tachycardia |
|------|----------------------|-------------------------------|--------------------------|-------------------------|-------------------------------|----------------------|
| Cardiovascular uses (HCN 2 and HCN 4) | | | | | | |
| Non-Cardiovascular uses (HCN 1) | Epilepsy | Chronic pain | |

In a major trial Roberts et al. used oral metoprolol to reduce HR in most of the patients and IV verapamil in 4 patients, where metoprolol was contraindicated due to asthma. Verapamil was ineffective in reducing HR but this finding was inconclusive due to the relatively small sample size (n=4). Similar results were reported by Maffei et al revealing poor HR control with CCB and benzodiazepines.

ROLE OF IVABRADINE IN CONTROLLING HEART RATE

IVA has beneficial effects on coronary artery disease (CAD) and congestive heart failure (CHF) and has been approved in Europe for use in chronic stable angina pectoris (CSAP).  

MECHANISM OF ACTION OF IVABRADINE

The rationale for using IVA stems from it being a selective hyperpolarization-activated cyclic nucleotide-gated (HCN) cation channel-blocking agent. It acts at sino-atrial node (SAN) and blocks the I_{f} current (funny current) leading to bradycardia by reducing the slope of slow diastolic depolarization (Fig. 1).

Due to its site of action, IVA is effective in patients with sinus rhythm but does not affect other cardiac ionic currents nor have unwanted hemodynamic effects, such as reduction of blood pressure or cardiac contractility, which often limit the use of β-blockers. IVA has a good safety profile and does not affect atrioventricular conduction, corrected QT interval or peripheral vasomotion. In addition, there is no rebound effect with drug cessation or development of tolerance with prolonged use.

IVA does not negatively affect coronary circulation or ventricular function, which is particularly important in patients with myocardial ischemia. Small randomized control studies have shown superiority of IVA over other drugs in controlling HR.
Fig 1: Mechanism of action of Ivabradine and its effect on image quality

MAJOR CLINICAL TRIALS TESTING IVABRADINE

Celik et al.\(^{32}\) (n=125) considered the efficacy of one time 15 mg oral IVA or single dose of IV metoprolol in patients on long term CCB. The HR reported prior to the coronary CTA was lower in the IVA group (65 ± 7 vs. 69 ± 6; \(p<0.002\)). Similarly, a significant effect was noted concerning HRs during the scanning process (62 ± 7 vs. 66 ± 6; \(p<0.001\)). This favorable variation in HR was also evidenced by the IVA group achieving a greater overall HR reduction than the IV metoprolol group (18 ± 7 vs. 15 ± 4; \(p<0.003\)). Sinus bradycardia (HR <60 bpm) was also more evident amongst patients (33%) in the IVA group and in 12 patients (19%) in the metoprolol 5-10 mg IV group. The study was limited because of the low \(\beta\)-blocker dose used. In addition, patients with arrhythmia were not excluded and the finally image quality was not studied.

Lambrechten et al.\(^{33}\) (n=312) studied the outcome of twice daily dosing of oral IVA, which revealed a significant effect on the average resting HR of the group on no other pre-medication for HR reduction. Groups receiving 5 and 7.5 mg oral IVA twice daily at 2 and 16 h before coronary CTA were also compared. HR reduction was 70 ± 12.9 bpm, 64.9 ± 9.8 bpm and 63.2 ± 10.6 bpm in the no pre-medication, 5 mg IVA and 7.5 mg IVA groups respectively (\(p<0.001\)). Ultimately, the results of this study lead to a significantly decreased use of IV \(\beta\)-blocker to lower HR. In this study the IV group was not compared with the use of \(\beta\)-blockers.

Guaricci et al.\(^{30}\) (n=123) revealed that IVA, when delivered orally twice per day for five days prior to the coronary CTA, showed valuable HR reductions, both in groups that were designed to either receive \(\beta\)-blocker or not. However, when IVA and \(\beta\)-blockers were combined, this yielded the greatest HR reduction when compared to the other groups; control, only \(\beta\)-blockers, and only IVA groups (14.7 ± 7.1%, 12.0 ± 10.2%, 18.6 ± 9.6%, and 24.0 ± 10.4% respectively [\(p<0.001\)]). Additionally, target HR was maintained prior to and during the study. When results were compared to the study by Celik et al.\(^{32}\), it suggested that greater HR control with IVA was achieved with a twice daily dosing schedule than with a single dose on the day of examination.

Pichler et al.\(^{36}\) (n=120) conducted a randomized, prospective, comparative, single blinded trial to evaluate the efficacy of a single oral dose of either 50 mg metoprolol or 15 mg IVA. When comparing the patients with long-term \(\beta\)-blockade therapy, IVA 15 mg lowered the HR by 15.62 bpm vs. the 10.04 bpm reduction induced by metoprolol (\(p=0.048\)). Alternatively, while examining patients not on permanent \(\beta\)-blocker therapy, metoprolol reduced the HR by 15.62 bpm vs. Ivabradine’s reduction of 10.79 bpm (\(p=0.038\)). During the coronary CTA, IVA was significantly more successful in maintaining the HR at <60 bpm, which was achieved in 76% of the group, compared to 54% in the oral metoprolol group (\(p<0.05\)). Overall, in patients receiving IVA, lower HR was achieved in those on long term \(\beta\)-blocker therapy than those without \(\beta\)-blocker therapy but the values did not show significance. The number of patients included was small and maximum suboptimal dose of \(\beta\)-blocker was used.
Adile et al.\textsuperscript{34} (n=100) demonstrated that 5 mg oral IVA, administered 48 h prior to the coronary CTA was useful in reducing HR before (68.34 ± 6.75 bpm vs. oral metoprolol 77.98 ± 6.88 bpm; \( p=0.0001 \)) and during the examination (58.77 ±1.25 vs. oral metoprolol 63.20 ± 1.4; \( p=0.0001 \)) respectively. The average reduction in HR was greater with IVA (23.89 ± 6.95\%o) than that with metoprolol (15.20 ± 4.20\%; \( p=0.0001 \)) when given 48 h prior to examination. All patients assigned to the metoprolol group required additional doses of \( \beta \)-blocker on the day of examination, while only 52\% of the IVA group required extra doses of \( \beta \)-blocker to maintain a HR \( \leq 60 \) bpm.

Bayraktutan et al.\textsuperscript{31} (n=110) randomized 19 patients with a HR of >70 bpm to either receive a \( \beta \)-blocker IV on the day of the study or 5 mg IVA orally twice per day for three days prior to the study. The mean pre-scan HR in the IVA group was 59 ± 4.1 bpm compared to the 64 ± 6.7 bpm for the IV \( \beta \)-blockade group (\( p<0.05 \)). This trend was also noticed when greater reduction from baseline HR was observed in the IVA group (14 ± 8 and 9 ± 5 bpm; \( p<0.001 \)). Due to the reduced HR, coronary CTA image quality was superior in the IVA group, producing a higher number of images (95.5 vs. 89.8\%) with either minor artifacts or no artifacts. HR variability was not observed in this study.

In a prospective study conducted by Patel et al.\textsuperscript{35}, 100 consecutive patients received either oral IVA for 1-2 days prior to CTA, or oral \( \beta \)-blocker. IVA cases had a greater reduction of HR compared to \( \beta \)-blockers (20.00 vs. 15.58\%) in this middle age male dominant study. They also reported lower incidences of requiring any additional doses before the CTA in the IVA arm.

Conclusions

Control of HR and HR variability has a pivotal role in improving image quality during coronary CTA.Ivabradine is a novel drug that has been used to lower HR in patients undergoing CT angiography of the coronary arteries and is able to improve the image quality and decrease the need for additional drugs. Three oral doses have been studied in the clinical trials; 15, 7.5 and 5 mg. The greatest HR reduction, as shown by Celik and Pichler, was from a 15 mg single dose of oral IVA. Also, the convenience of a one-time dose may be more advantageous than a twice daily dosing for multiple days. IVA did not significantly alter the other hemodynamics. Here we highlight several limitations in the clinical trials performed so far: 1) The impact of treatment on image quality is not assessed in most of these studies; 2) The \( \beta \)-blocker dose could have been higher to achieve similar results. Large scale randomized double blind trials, comparing IVA with \( \beta \)-blockers are required to obtain verifiable results that are free from any bias.

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