Evaluation of Contraindications and Efficacy of Oral Beta-Blockade Prior to Computed Tomography Coronary Angiography

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Am J Cardiol. 2010;105:767-72
ABSTRACT

Multidetector computed tomography coronary angiography (CTA) image quality is inversely related to heart rate (HR). As a result beta-blocking medication is routinely administered prior to investigation. In the present study, the use, contraindications and efficacy of pre-scan beta-blockade with regards to HR reduction and CTA image quality were assessed. In a total of 537 patients referred for CTA, baseline HR and blood pressure were measured upon arrival and contraindications for beta-blockade were noted. Unless contraindicated, a single dose of metoprolol was administered orally one hour before data acquisition in patients with HR ≥ 65 beats per minute (bpm) according to a predefined medication protocol. After one hour HR was re-measured. In total 283 patients (53%) had a HR ≥ 65 bpm. In this group, beta-blockade was contraindicated in 46 patients (16%). Metoprolol was administered to the remaining 237 patients. However, 26 patients (11%) received suboptimal (lower dose than prescribed by protocol) beta-blockade due to contraindications. In patients receiving optimal beta-blockade, 27% (n=57) did not achieve target HR, whereas in patients with contraindications to beta-blockade 60% (n=43) did not achieve target HR. Compared to patients with optimal HR control, patients receiving no or suboptimal beta-blockade due to contraindications had significantly less examinations of good image quality (40% vs. 74%, p<0.001), and significantly more examinations of poor image quality (20% vs. 6%, p<0.001). In conclusion, most patients require HR reduction before CTA. Contraindications to beta-blockade are present in a substantial proportion of patients. This results in suboptimal HR control and image quality, indicating the need for alternative approaches for HR reduction.
INTRODUCTION

To achieve heart rate (HR) control, beta-blocking medication is routinely administered, either orally or intravenously, prior to multidetector computed tomography coronary angiography (CTA) examination. Beta-blocking medication lengthens the diastolic interval, during which the heart is relatively motion-free, and thereby reduces cardiac motion artifacts.\(^1\)\(^2\) In addition, beta-blockade reduces HR variability. At present, however, limited data are available concerning the prevalence of contraindications for beta-blockade as well as its efficacy in a general population referred for CTA. Therefore, this study assesses the use and contraindications of oral beta-blockade prior to CTA, and evaluates the effect on image quality.

METHODS

In consecutive patients clinically referred for CTA, information on HR prior and during CTA as well as beta-blocking medication were recorded. A total of 537 patients, 298 men and 239 women, with a mean age of 56 ± 18 years, were enrolled. Exclusion criteria for CTA investigation were: (1) (supra)ventricular arrhythmias, (2) renal insufficiency (glomerular filtration rate < 30 ml/min), (3) known allergy to iodine contrast material, (4) severe claustrophobia, and (5) pregnancy. The main clinical characteristics of the study population are listed in Table 1.

Table 1. Patient Characteristics (n=537)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male / female</td>
<td>298 / 239</td>
</tr>
<tr>
<td>Age (years)</td>
<td>56 ± 18</td>
</tr>
<tr>
<td>Current smoker</td>
<td>84 (16%)</td>
</tr>
<tr>
<td>Positive family history for coronary artery disease</td>
<td>194 (36%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>323 (60%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>249 (46%)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>128 (24%)</td>
</tr>
<tr>
<td>Prior percutaneous coronary intervention</td>
<td>49 (9%)</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>33 (6%)</td>
</tr>
<tr>
<td>Prior coronary artery bypass grafting</td>
<td>32 (6%)</td>
</tr>
<tr>
<td>Use of chronic medication</td>
<td></td>
</tr>
<tr>
<td>Beta-blockade</td>
<td>217 (40%)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>97 (18%)</td>
</tr>
<tr>
<td>Statin</td>
<td>187 (35%)</td>
</tr>
</tbody>
</table>
Baseline HR and blood pressure (BP) were evaluated manually in all subjects upon arrival, one hour prior to the scheduled CTA examination. Contraindications for beta-blockade were noted. Absolute contraindications were: low BP (defined as a systolic BP < 100 mmHg), severe chronic obstructive pulmonary disease (COPD) (defined as GOLD stage III or IV), severe aortic valve stenosis (defined as aortic valve area < 1.0 mm²), reduced left ventricular ejection fraction (defined as an ejection fraction < 35%), second or third degree atrio-ventricular (AV) block and known allergy to metoprolol. In addition, in patients already receiving high dose beta-blocking medication (defined as more than 100 mg metoprolol or an equivalent dose of another beta-blocking agent) as part of their baseline medication at the time of CTA, additional beta-blocking medication was contraindicated. Unless contraindicated, a single dose of metoprolol was administered orally one hour before data acquisition in patients with HR ≥ 65 beats per minute (bpm). The administered dose prior to CTA was determined based on a pre-defined beta-blocking medication administration protocol. Patients with a HR between 65 and 75 bpm received 50 mg metoprolol while patients with a HR ≥ 75 bpm received 100 mg metoprolol. However, patients already using low dose beta-blocking medication as part of their baseline medication (defined as less than 100 mg metoprolol or an equivalent dose of another beta-blocking agent) and patients with mild to moderate COPD (defined as GOLD stage I or II) were considered to have relative contraindications to beta-blockade. In these subjects, additional beta-blocking medication prior to CTA was administered at a lower dose, classified as a suboptimal dose of beta-blocking medication. Finally, in case of anxiety, 1 mg lorazepam was administered orally. After one hour HR was re-evaluated. The target HR, which was also the threshold for beta-blocker administration, was defined as an average HR < 65 bpm.

CTA studies were performed with two different systems: a 64-row scanner (Aquilion 64, Toshiba Medical Systems, Otawara, Japan) and a 320-row scanner (Aquilion ONE, Toshiba Medical Systems, Otawara, Japan) with 64 and 320 simultaneous detector rows, respectively (each 0.5 mm wide). The total amount of non-ionic contrast media (Iomeron 400; Bracco, Milan, Italy) injected into the antecubital vein was 60-100 ml (depending on body weight and scanner type) at a flow rate of 5.0 ml/s or 6.0 ml/s, followed by a saline flush of 25-50 ml. In order to synchronize the arrival of the contrast media, bolus arrival was detected using a real-time bolus tracking technique. All images were acquired during a single inspiratory breath-hold of maximally 12 seconds. During the scan, the electrocardiogram (ECG) was registered simultaneously for retrospective (64-row CTA) or prospective (320-row CTA) gating of the data. For 64-row CTA, additional scan parameters were: 400 ms gantry rotation time, 120 kV tube voltage and 300-350 mA (depending on body-weight and thoracic anatomy). For the 320-row system, scan parameters were: 350 ms gantry rotation time, 120-135 kV tube voltage and 400-580 mA.
Beta Blockade Before CTA

The average investigation time for the CTA acquisitions was approximately 20 minutes. There were no complications due to beta-blocker administration.

CTA reconstructions were transferred to a remote workstation with dedicated analysis software (for 64-row CTA reconstructions: Vitrea 2, Vital Images, Minnetonka, MN, USA; for 320-row CTA reconstructions: Vitrea FX 1.0, Vital Images, Minnetonka, MN, USA). Assessment of image quality of each CTA study was conducted on a per patient basis. When multiple reconstructions from different cardiac phases were available, the reconstruction with the best image quality was evaluated. Image quality was assessed using a 3-point grading scale: 1: good image quality (no artifacts), 2: moderate image quality (moderate image degradation), 3: poor image quality (severe image degradation) (Figure 1). CTA analysis was performed by two experienced observers blinded to medication and HR. Quantitative data were expressed as mean ± standard deviation (SD) and compared using the paired 2-tailed Student’s t test. Categorical variables were described as percentages. Comparison of CTA image quality between groups, as well as between CTA systems, was performed by Chi-Square analysis. A p-value < 0.05 was considered statistically significant.

Figure 1. CTA image quality was assessed using a three-point scale. Panel A shows an example of good image quality; Panel B shows an example of moderate image quality; Panel C shows an example of poor image quality.
RESULTS

In the total population referred for CTA (n=537), mean baseline HR was 67 ± 13 bpm. At arrival, a total of 254 patients (47%) had a baseline HR below the target HR and did not require HR reduction. Conversely, 283 patients (53%) had a baseline HR above target HR and thus required HR reduction. In this group, 98 patients (35%) were already using beta-blockade as part of their baseline medication. In all patients requiring HR reduction, beta-blockade was contraindicated in 46 patients (16%). Contraindications were: low BP (n=18), high dose beta-blockade as part of baseline medication (n=17), severe COPD (n=5), severe aortic valve stenosis (n=4) and reduced left ventricular ejection fraction (n=2).

Metoprolol was administered to the remaining 237 patients (84%) requiring HR reduction. A total of 157 patients received 50 mg metoprolol and 80 patients received 100 mg metoprolol. However, of patients receiving beta-blockade, 26 patients (11%) received suboptimal beta-blockade due to relative contraindications. Specific relative contraindications were: low dose beta-blockade as part of baseline medication (n=23) or mild to moderate COPD (n=3). There were no adverse effects from beta-blocking medication administration. In addition, 22 patients (4%) received 1 mg lorazepam.

Of patients with a baseline HR < 65 bpm, 37 patients (15%) did not remain below target HR at the time of investigation. In 9 of these patients, increased HR was caused by atrial fibrillation (AF). In patients receiving optimal beta-blockade in the absence of contraindications, 57 patients (27%) did not achieve the target HR. Conversely, in patients receiving no or suboptimal beta-blockade due to contraindications, 43 patients (60%) did not achieve the target HR.

Immediately before data acquisition, 25 patients (5%) were excluded from CTA examination due to: AF (n=14), inadequate HR reduction (n=9) or irregular HR due to frequent ventricular extra systoles (n=2). Accordingly, CTA was performed in 512 (95%) patients (64-row scanner n = 311; 320-row scanner, n=201). Mean HR at baseline and during CTA in patients with and without contraindications to beta-blockade are shown in Figure 2. Good or moderate image quality was achieved in 92% (n=472) of patients scanned, and 8% (n=40) of CTA studies were of poor image quality.

In the presence of contraindications to beta-blockade, overall CTA image quality was decreased as compared to patients without contraindications. In patients without contraindications to beta-blockade, 74% (n=334) of scans were of good image quality, 20% (n=88) were of moderate image quality and 6% (n=28) were of poor image qual-
Conversely, in the presence of contraindications to beta-blockade, 40% (n=25) of scans were of good image quality, 40% (n=25) were of moderate image quality and 20% (n=12) were of poor image quality. Thus, optimal HR reduction using beta-blocking medication was associated with a significant improvement in CTA image quality (Figure 3). In a separate analysis, results were compared between data obtained with 64-row and 320-row CTA, indicating no significant differences in distribution of image quality for patients with and without contraindications to beta-blockade (Chi-Square =1.786, p=0.41).
DISCUSSION

The present study evaluated the use and efficacy of beta-blockade one hour prior to investigation in 537 consecutive patients referred for CTA. In addition, the effect on CTA image quality was investigated. In conclusion, more than half of the patients presenting for CTA require HR reduction prior to examination. The current data suggest that oral beta-blocking administration one hour before CTA effectively reduces HR in the majority of cases. However, contraindications to beta-blockade are present in a substantial proportion of patients requiring HR control. As a consequence, in these individuals, mean HR during CTA was significantly higher leading to a decrease in overall image quality.

The prevalence of contraindications to beta-blockade in a general patient population referred for CTA has not been extensively investigated. In a recent study by Shapiro and colleagues, investigating 150 consecutive patients referred for CTA, intravenous beta-blocker (5-20 mg) was administered to patients with a baseline HR ≥ 65 bpm, and contraindications to beta-blockade were recorded. The target HR was defined as an average HR < 65 bpm without a single measurement above 68 bpm. Similar to the present study, contraindications to beta-blocker administration included asthma, advanced AV block, severe left ventricular systolic dysfunction, severe aortic stenosis and known allergy to metoprolol. Roughly in line with the current results, approximately half of the patients (45%) required HR reduction prior to investigation. However, 24% of patients did not receive intravenous beta-blockade due to the presence of contraindications. Similarly, 16% of patients in the present study did not receive beta-blockade due to contraindications. These data suggest that contraindications to beta-blocking medication are common in a general population referred for CTA.

Furthermore, the study by Shapiro and colleagues illustrated that, of patients receiving beta-blockade prior to investigation, only 35% achieved the target HR. In our study, however, 77% of patients receiving optimal beta-blockade achieved the target HR at the time of CTA investigation. Conversely, only 40% of patients with contraindications to beta-blockade, whom received no or suboptimal beta-blockade, achieved adequate HR control. These differences are most likely explained by differences in beta-blocking strategy and suggest that aggressive beta-blockade is important in achieving optimal HR control. However, more aggressive beta-blocker strategies may also increase the risk of complications. Particular care needs to be taken in patients with low blood pressure or in the presence of comorbidities, such as moderate asthma or other obstructive pulmonary diseases, first degree AV-block and aortic stenosis. Careful individual assessment is important and alternatives should be considered (such as verapamil or ivabradine)
in consultation with the referring medical specialist. Aggressive beta-blockade should invariably be performed under strict clinical supervision.

Lastly, similar to our results, in the study by Shapiro et al. HR remained below target HR during CTA investigation in only 75% of patients with a baseline HR < 65 bpm, illustrating that a substantial proportion of patients with a low baseline HR are unable to maintain a low HR at the time of CTA investigation. Accordingly, these observations may indicate the necessity of beta-blockade even at low HR, to avoid procedural increase in HR as well as HR variability, which are common in the presence of anxiety.

A recent study by Maffei and colleagues evaluated the efficacy, timing and safety of several pharmacological treatments (including a no-treatment group, oral beta-blockade with metoprolol, intravenous beta-blockade with atenolol and intravenous atenolol plus nitrates) in 560 patients before CTA. The authors concluded that HR control may be most adequately achieved with intravenous beta-blockers without nitrates, with a mean HR reduction of 16 ± 8 bpm. An additional advantage of intravenous beta-blocking administration was effective timing, allowing for faster patient preparation as compared to oral beta-blocking administration (with mean time of 8 vs. 62 minutes between patient arrival and CT investigation, respectively).

Multiple previous studies have demonstrated an inverse relationship between HR and CTA image quality. In a study using 16-row CTA, Hoffmann and colleagues reported that nondiagnostic image quality in 6.4% of segments was mainly attributable to increased HR. However, several studies have reported that, with increased temporal resolution, image quality becomes less dependent on HR. Indeed, in a study by Leschka et al. using 64-row CTA, only a weak effect of HR on image quality was demonstrated. On the other hand, Brodoefel and colleagues, using 64-row CTA, demonstrated a persistent inverse correlation between image quality and patient HR. Importantly, however, this effect did not translate into decreased diagnostic accuracy. Nevertheless, in nearly all CTA studies reporting on 64-row CTA, beta-blocking medication has been used for patient preparation. Also using novel 320-row CTA, Rybicki et al. found that the most common cause of image degradation was cardiac motion. In the present study, a clear relationship between image quality and increased HR using 64-row and 320-row CTA was demonstrated. Although the effect of image quality degradation due to increased HR on overall diagnostic accuracy still needs further investigation, in the present study the number of examinations with poor image quality was higher in patients with contraindications to beta-blockade. These findings imply that, also using 64-row and 320-row CTA, HR control remains important in optimizing CTA image quality. However, dual-source CTA, with superior temporal resolution, may eliminate the problem of motion...
artifacts at increased HR. Indeed, a recent randomized comparison between 64-row single source and dual source CT showed that HR control significantly improves image quality using 64-row single-source CT, while image quality and diagnostic accuracy remain unaffected in dual-source CT angiography. In patients with a HR < 65 bpm, however, diagnostic accuracy on a per-patient basis is comparable between the two scanner types.

Importantly, with the introduction of prospective ECG triggering for the purpose of radiation dose reduction, adequate HR control may be even more relevant. Using this protocol, image acquisition is performed during a small pre-defined portion of the cardiac cycle which reduces the possibility to reconstruct images during other cardiac phases. Low HR widens the diastolic phase, allowing for optimal image acquisition. Using this novel approach a significant decrease in radiation dose has been reported in patients with low HR. As previously mentioned, also using novel prospectively triggered 320-row CTA, HR control remains an important topic of concern. Moreover, Steigner et al. using prospectively gated 320-row CTA, demonstrated that patients with decreased HR had significantly more diagnostic phases available for image reconstruction. Thus, even when imaging in a single heart beat using state of the art 320-row CTA, HR control using beta-blockade is essential for optimizing image quality as well as reducing radiation exposure.

The following limitations to the present study should be acknowledged. Firstly, immediately before CTA, it was decided not to proceed with contrast enhanced CTA examination in a number of patients due to AF, inadequate HR reduction or irregular HR. This may have slightly affected the results. Furthermore, only an oral beta-blockade protocol was evaluated. Two scanner types and acquisition techniques were used: 64-row CTA was performed using retrospective ECG gating, while 320-row CTA was performed using prospective ECG triggering. Moreover, 320-row CTA allows image acquisition in a single heart beat, whereas 64-row CTA uses helical scanning techniques to image the heart in multiple heart beats. The difference in acquisition techniques may have yielded a slight difference in CTA image quality between the two scanners, although not significant.
REFERENCES