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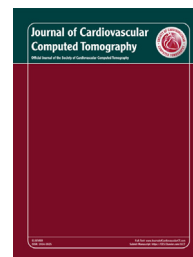
Original Research Article

Esmolol is noninferior to metoprolol in achieving a target heart rate of 65 beats/min in patients referred to coronary CT angiography: A randomized controlled clinical trial

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Pál Maurovich-Horvat MD, PhD, MPH, FSCCT*, Mihály Károlyi MD,
Tamás Horváth MD, Bálint Szilveszter MD, Andrea Bartykowszki MD,
Ádám L. Jermendy MD, Alexisz Panajotu MD, Csilla Celeng MD,
Ferenc I. Suhai MD, Gyöngyi P. Major MD, Csaba Csobay-Novák MD,
Kálmán Hüttl MD, PhD, DSc, Béla Merkely MD, PhD, DSc

MTA-SE Lendület Cardiovascular Imaging Research Group, Heart and Vascular Center, Semmelweis University,
68 Varosmajor ut, Budapest 1122, Hungary

ABSTRACT

Background: Coronary CT angiography (CTA) is an established tool to rule out coronary artery disease. Performance of coronary CTA is highly dependent on patients' heart rates (HRs). Despite widespread use of β-blockers for coronary CTA, few studies have compared various agents used to achieve adequate HR control.
Objective: We sought to assess if the ultrashort-acting β-blocker intravenous esmolol is at least as efficacious as the standard of care intravenous metoprolol for HR control during coronary CTA.
Methods: Patients referred to coronary CTA with a HR >65 beats/min despite oral metoprolol premedication were enrolled in the study. We studied 412 patients (211 male; mean age, 57 ± 12 years). Two hundred four patients received intravenous esmolol, and 208 received intravenous metoprolol with a stepwise bolus administration protocol. HR and blood pressure were recorded at arrival, before, during, immediately after, and 30 minutes after the coronary CTA scan.
Results: Mean HRs of the esmolol and metoprolol groups were similar at arrival (78 ± 13 beats/min vs 77 ± 12 beats/min; P = .65) and before scan (68 ± 7 beats/min vs 69 ± 7 beats/min; P = .60). However, HR during scan was lower in the esmolol group vs the metoprolol group (58 ± 6 beats/min vs 61 ± 7 beats/min; P < .0001), whereas HRs immediately and 30 minutes after the scan were higher in the esmolol group vs the metoprolol group (68 ± 7 beats/min vs 66 ± 7 beats/min; P = .01 and 65 ± 8 beats/min vs 63 ± 8 beats/min; P < .0001;

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respectively). HR ≤65 beats/min was reached in 182 of 204 patients (89%) who received intravenous esmolol vs 162 of 208 of the patients (78%) who received intravenous metoprolol ($P < .05$). Of note, hypotension (systolic BP <100 mm Hg) was observed right after the scan in 19 patients (9.3%) in the esmolol group and in 8 patients (3.8%) in the metoprolol group ($P < .05$), whereas only 5 patients (2.5%) had hypotension 30 minutes after the scan in the esmolol group compared to 8 patients (3.8%) in the metoprolol group ($P = .418$).

Conclusion: Intravenous esmolol with a stepwise bolus administration protocol is at least as efficacious as the standard of care intravenous metoprolol for HR control in patients who undergo coronary CTA.

1.   Introduction

Coronary CT angiography (CTA) with its high sensitivity and high negative predictive value is an established diagnostic tool for the evaluation of coronary artery disease.[1,2] Despite the great advances in scanner technology, the image quality remains highly dependent on heart rate (HR) and the regularity of cardiac rhythm.[3–5] Current guidelines recommend that HR should be <65 beats/min and optimally <60 beats/min to achieve excellent image quality and low effective radiation dose.[6] Metoprolol is the first-line intravenous (IV) β-blocker for HR lowering in patients undergoing coronary CTA.[7–9] However, a recent survey has revealed that 50% of centers allow an HR >70 beats/min for coronary CTA, mainly because of concerns regarding potential side effects of β-blocker administration (mainly hypotension and bradycardia).[10] The half-life of IV metoprolol is approximately 3 to 7 hours; therefore, if adverse effect occurs as a result of the HR-lowering medication, it may debilitate the patient for hours.[11] These data indicate the need for a safe, short-lasting HR control in the scanner rooms.

Esmolol is an ultrashort-acting cardioselective IV β-receptor blocking agent with a rapid onset (within 2–3 minutes) and ultrashort duration of action (mean half-life [$t_{1/2}$] = 9 minutes).[11,12] The rapid onset and offset of effects of esmolol provide an element of safety not previously available with longer-acting β-adrenoceptor antagonists.[13] During coronary CTA, short and effective HR control is desirable; therefore, esmolol might be a good alternative to the standard of care metoprolol. Currently, esmolol is routinely administered in the intensive care unit for the treatment of acute supraventricular arrhythmias; however, administration before coronary CTA for HR reduction is an "off-label" indication. In an observational study, Degertekin et al[14] used 50 mg of oral β-blocker (atenolol) in combination with IV esmolol 1 to 2 mg/kg (range, 50-300 mg) and reported a 65% responder rate with regard to achieving a HR of <65 beats/min. There is a lack of evidence regarding the efficacy and safety of IV esmolol administered in a body weight-independent, stepwise bolus protocol. Furthermore, no direct comparison of esmolol vs metoprolol administration for HR control during coronary CTA is available.

We sought to investigate if the ultrashort half-life IV esmolol is at least as efficacious as the standard of care IV metoprolol for HR reduction during coronary CTA. Therefore, the primary objective of this clinical trial was to compare the proportions of patients who achieve the target HR of ≤65 beats/min during the coronary CTA image acquisition in the esmolol vs metoprolol groups. As the secondary objective, we sought to estimate the incidence of bradycardia (defined as HR <50 beats/min) or hypotension (defined as systolic blood pressure [BP] <100 mm Hg) as an effect of β-blockers in the esmolol and metoprolol groups.

2.   Materials and methods

The study complied with the Declaration of Helsinki. The National Institute for Pharmacy and the institutional review board approved the study. Informed consent was obtained from all patients. The authors had full control of the data and the information submitted for publication. The study was designed and implemented in accordance with the CONSORT statement, elaborated for randomized, controlled trials.[15]

2.1.   Study design

This is a randomized single-center noninferiority phase III clinical trial comparing two IV β-adrenergic receptor blockers to reduce HR in patients who undergo coronary CTA because of suspected coronary artery disease (European Union Clinical Trials Register number: 2013-000048-24). The noninferiority margin was set on 10% because we assumed that the difference between the two groups in proportion of responder patients (patients achieving ≤65 beats/min) less than this is clinically irrelevant. The primary endpoint was the proportion of patients who reached HR ≤65 beats/min in the esmolol group. The secondary endpoint was the proportion of patients who experienced bradycardia (HR <50 beats/min) and/or hypotension (systolic BP <100 mm Hg) as an effect of β-blockers. We have performed an interim analysis after 45 days to ensure adequate enrollment rate and to assess toxicity as well as adverse events. An adverse event was defined as a change in health condition resulting from the administration of β-blockers, which is not resolving with observation and requires medical intervention.

2.2.   Study population

Patients who were referred to coronary CTA because of suspected coronary artery disease and had an HR >65 beats/min despite oral metoprolol pretreatment were enrolled in the

study. Patients with history of a coronary intervention and an implanted stent with a diameter ≥3 mm or previous coronary artery bypass surgery were eligible to participate in the study.[16] Individuals with a heart rhythm other than sinus rhythm, any contraindication against β-blocker (asthma bronchiale, chronic obstructive pulmonary disease, any type of documented atrioventricular block, severe aortic valve stenosis, severe left ventricular dysfunction characterized by ejection fraction below 30%), or a systolic BP <100 mm Hg before the coronary CTA scan were excluded from the study.

2.3. Drug administration protocol and HR monitoring

Patients received 50-mg oral metoprolol at arrival if the HR was >65 beats/min. If the HR was ≥80 beats/min, 100-mg oral metoprolol was administered. The HR was re-evaluated 60 minutes after the oral β-blockade, immediately before the coronary CTA examination. Patients presenting with an HR >65 beats/min on the CT table were randomized to IV esmolol or IV metoprolol administration. In both the investigational (esmolol) and the active control (metoprolol) groups, the IV drug was administered by the physician performing the coronary CTA scan. To achieve randomization, we administered IV esmolol on even weeks and metoprolol on odd weeks in an alternating fashion. The IV metoprolol (Betaloc; 1 mg/mL; AstraZeneca, Luton, United Kingdom; 5-mg ampoule) was titrated in 5-mg doses in every 3 minutes until the target HR (≤65 beats/min) or the maximum dose of metoprolol (20 mg) was achieved.[1] The IV esmolol (Esmocard; 2500 mg/10 mL; AOP Orphan Pharmaceuticals AG, Vienna, Austria) was diluted to 500 mg/10 mL and titrated in ascending 100-, 200-, 200-mg doses in every 3 minutes until the target HR (≤65 beats/min) or the maximum dose of esmolol (500 mg) was achieved. BP was monitored before every administered drug bolus. If hypotension (defined as systolic BP <100 mm Hg) or bradycardia (defined as HR <50 beats/min) was measured, the administration of the β-blocker agent was suspended. Two puffs of sublingual nitroglycerine were given to each patient 3 to 5 minutes before the CT scan to ensure the proper visualization of the coronaries. The HR was recorded at arrival (T1), immediately before coronary CTA (T2), during breathhold, contrast injection, and scan (TS), immediately after scan (T3), and 30 minutes after coronary CTA scan (T4). BP was measured at T1, T2, T3, and T4 time points. The study flow chart is summarized in Figure 1.

2.4. Scan protocol

All examinations were performed with 256-slice CT (Brilliance iCT 256; Philips Healthcare, Best, the Netherlands). Contrast-enhanced image acquisition was performed in inspiration during a single breathhold in craniocaudal direction. Imaging parameters were used as follows: slice collimation of 128 mm × 0.625 mm, rotation time of 270 ms, tube voltage of 80 to 120 kV, and tube current of 150 to 300 mAs depending on patients' body mass index. The images were acquired using prospective electrocardiogram triggering at 75% to 81% phase (3% padding). The iodinated contrast agent (Iomeron 400; Bracco Ltd, Milan, Italy) was injected into an antecubital vein via an 18-ga cannula using a dual-syringe technique, at a flow
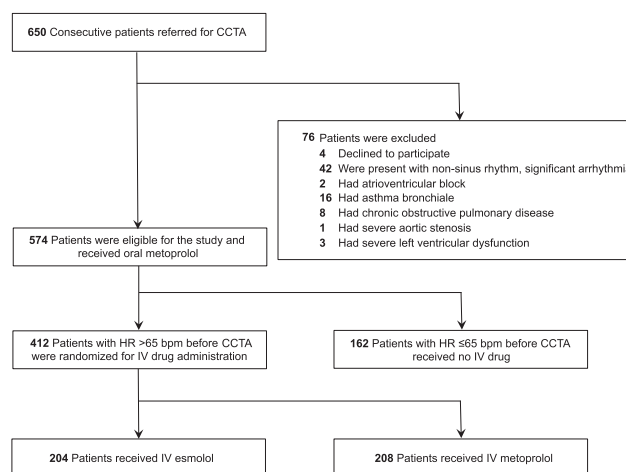

Fig. 1 — **Flow chart of the study. bpm, Beats/min; CCTA, coronary CT angiography; HR, heart rate; IV, intravenous.**

rate of 3.5 to 5.5 mL/s depending on patients' body mass index and the tube voltage. Bolus tracking was used with a region of interest placed in the left atrium. Images were reconstructed with a slice thickness of 0.8 mm and 0.4-mm increment.

2.5. Statistical analysis

The sample size calculation was based on a recently published study, which showed that 83% of patients who received metoprolol premedication achieved an HR of ≤65 beats/min during coronary CT angiography.[17] The noninferiority margin was set to 10% because we have assumed that this is a clinically acceptable maximum difference between the responder proportions of the two treatment groups. Degertekin et al[14] reported that 65% of the patients achieved the target HR of ≤65 beats/min after administration of intravenous esmolol. However, Degertekin et al administered smaller doses; thus, our primary aim to achieve at least 73% responder proportion seemed to be realistic. Dedicated software was used for sample size calculation (East, version 5.4.1; Cytel Inc, Cambridge, Massachusetts). A total of 595 patients, 297 to 298 patients on each treatment arm, were needed to show that the difference between proportion of responders in metoprolol group vs esmolol group is less than the noninferiority margin set at 10% with a power of 90% using a 1-sided $P = .025$ level test. The sample size calculation was based on an intention to treat analysis.

Continuous variables were reported as mean ± standard deviation. Categorical variables are given in frequency. According to the Shapiro-Wilk tests, some of the parameters showed mild deviation from normal distribution. To deal with the non-normality, the groups were compared by robust t tests using 20%-trimmed means with bootstrapping.[18] Differences of categorical variables between treatment groups were analyzed by chi-square tests. With respect to all statistical tests, a 2-sided P-value of <.05 was considered significant. Statistical analyses were performed with R, version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

3.   Results

We have stopped the patient enrollment early as the interim analysis indicated that IV esmolol is clearly noninferior to IV metoprolol, and in fact, esmolol showed superiority characteristics compared to IV metoprolol in reducing HR during coronary CTA. Between April 2013 and September 2013, in total, 650 consecutive patients referred to coronary CTA were screened, and of these, 574 patients were eligible to participate in the study. In 162 patients no IV drug was administered because the HR before scan was ≤65 beats/min. In total, 412 patients (with HR >65 beats/min before the scan) were enrolled and randomized into either esmolol or metoprolol group; 204 received IV esmolol and 208 patients received IV metoprolol. There was no difference between the two groups regarding the clinical characteristics (Table 1).

In the esmolol group, 53 of 204 patients (26.0%) received 1 bolus (100 mg), 73 of 204 (35.8%) received 2 boluses (300 mg), and 78 of 204 (38.2%) received 3 boluses (500 mg) of esmolol. In the metoprolol group, IV metoprolol was administered in a similar fashion as in the esmolol group but in 5-mg increments. Eighty-three of 208 patients (39.9%) received 1 bolus (5 mg), 45 of 208 patients (21.6%) 2 boluses (10 mg), 53 of 208 (25.5%) 3 boluses (15 mg), and 27 of 208 (13.0%) 4 boluses (20 mg) of metoprolol.

Oral metoprolol administration was similar in the esmolol and metoprolol groups (51.2 ± 33.1 vs 52.4 ± 33.6; P = .71). On average, 325.6 ± 158.4 mg IV esmolol and 10.7 ± 6.3 mg IV metoprolol were administered.

The mean HRs of the esmolol and metoprolol groups were similar at the time of arrival (T1: 78 ± 13 vs 77 ± 12 beats/min; P = .65) and immediately before the coronary CTA examination (T2: 68 ± 7 vs 69 ± 7 beats/min; P = .60). However, HR during the scan was significantly lower among the patients who received IV esmolol vs patients who received IV metoprolol (TS: 58 ± 6 vs 61 ± 7 beats/min; P < .0001). On the other hand, HRs immediately after the coronary CTA and

Table 2 – Heart rate.

Time point	Esmolol (n = 204)	Metoprolol (n = 208)	P
	Mean ± SD	Mean ± SD	
T1	78 ± 13	77 ± 12	.652
T2	68 ± 7	69 ± 7	.599
TS	58 ± 6	61 ± 7	<.0001
T3	68 ± 7	66 ± 7	<.01
T4	65 ± 8	63 ± 8	<.0001

Heart rate measured (in beats/min) at T1 (arrival), T2 (before scan), TS (during scan), T3 (after scan), and T4 (emission). Statistics: robust, independent t test.

30 minutes after the coronary CTA were higher in the esmolol group than in the metoprolol group (T3: 68 ± 7 vs 66 ± 7 beats/min; P < .01; and T4: 65 ± 8 vs 63 ± 8 beats/min; P < .0001, respectively; Table 2; Fig. 2). Systolic and diastolic BPs showed no difference between the 2 groups measured at any time point (Table 3).

HR of ≤65 beats/min was reached in 182 of 204 (89%) of patients in the esmolol group vs in 162 of 208 (78%) of patients in the metoprolol group (P < .05), whereas HR ≤60 beats/min was reached in 147 of 204 (72%) of the patients who received esmolol vs in 117 of 208 (56%) of patients who received metoprolol (P < .001; Fig. 3).

None of the patients developed bradycardia (defined as HR <50 beats/min) after β-blocker administration (minimum HR in group esmolol was 53 beats/min; minimum HR in group metoprolol was 52 beats/min). However, hypotension (defined as systolic BP <100 mm Hg) was observed in 19

Table 1 – Demographic characteristics of study groups.

Characteristic	Esmolol (n = 204)	Metoprolol (n = 208)	P
Age (y), mean ± SD	56.9 ± 10.8	57.6 ± 12.2	.390
Male/female	100/104	111/97	.377
BMI (kg/m²), mean ± SD	28.4 ± 4.9	28.2 ± 4.7	.956
Hypertension (%)	67	66	.889
Diabetes (%)	16	14	.603
Dyslipidemia (%)	48	55	.154
AMI (%)	5	10	.076
PCI (%)	5	7	.455
CABG (%)	4	6	.287
PAD (%)	9	8	.801
Stroke (%)	4	1	.072
Smoking (%)	25	26	.845
β-Blocker (%)	47	48	.795

AMI, acute myocardial infarction; BMI, body mass index; CABG, coronary artery bypass graft; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention. Statistics: robust, independent t test and chi-square test.
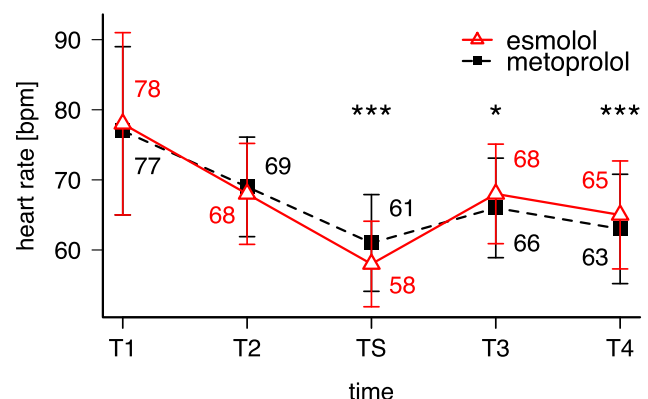

Fig. 2 – The figure represents the mean heart rates and their standard deviations in the esmolol and metoprolol groups at different time points. The red triangles represent the mean heart rates in the esmolol group, whereas the black squares indicate the mean heart rates in the metoprolol group. T1, time of arrival; T2, time point before the coronary CT angiography (CTA) scan; TS, coronary CTA scan; T3, time point immediately after the coronary CTA; T4, 30 minutes after the coronary CTA. *P < .01; ***P < .0001. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 3 – Blood pressure.

Time point	Esmolol (n = 204)	Metoprolol (n = 208)	P
	Mean ± SD	Mean ± SD	
T1			
Systole	142 ± 22	146 ± 21	.195
Diastole	87 ± 12	87 ± 12	.819
T2			
Systole	144 ± 21	145 ± 20	.918
Diastole	86 ± 13	87 ± 12	.945
T3			
Systole	128 ± 20	131 ± 19	.053
Diastole	74 ± 12	75 ± 12	.522
T4			
Systole	132 ± 20	134 ± 21	.414
Diastole	79 ± 11	80 ± 12	.589

Blood pressure (in mm Hg) measured at T1 (arrival), T2 (before scan), T3 (after scan), and T4 (emission).
Statistics: robust, independent t test.

patients (9.3%) in the esmolol group and in 8 patients (3.8%) in the metoprolol group right after the scan (T3; P < .05). Importantly, only 5 patients (2.5%) had a systolic BP <100 mmHg 30 minutes after the scan (T4) in the esmolol group, whereas the number of patients with hypotension remained 8 (3.8%) in the metoprolol group (P = .418). None of the patients required hospitalization or medical intervention due to hypotension and the systolic BP normalized after a short (maximum 2 hours) observation in every case. Of note, the absolute time spent in the CT unit (T3–T2) did not differ between the esmolol and metoprolol group (21.1 ± 7.5 vs 21.8 ± 7.9 minutes; P = .428).
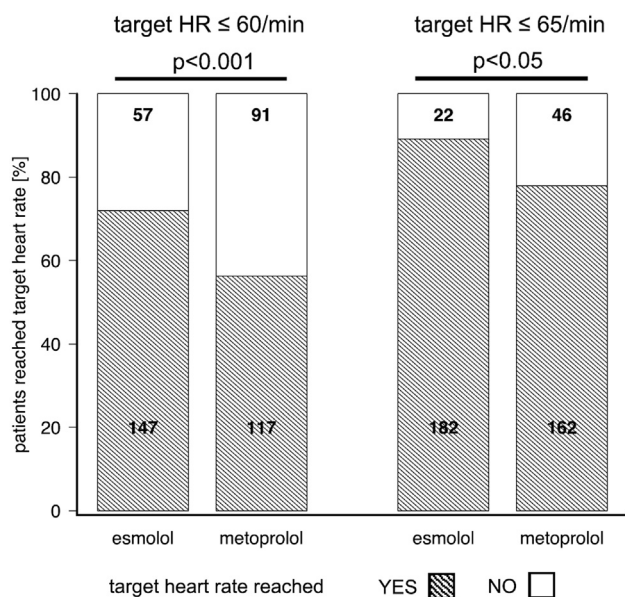

Fig. 3 – **The bar charts illustrate the proportion of patients that reached a heart rate ≤60 beats/min (*left side*) and the proportion of patients that reached a heart rate ≤65 beats/min in the esmolol and metoprolol groups.**

4.   Discussion

In this randomized, single-center clinical trial we compared IV esmolol vs IV metoprolol for HR control in patients who underwent coronary CTA because of suspected coronary artery disease. We showed that esmolol with a stepwise bolus administration protocol is at least as efficacious as the standard of care metoprolol to achieve the optimal HR (<65 beats/min) during coronary CTA. Furthermore, we have demonstrated that IV esmolol allows a safe HR control for coronary CTA examination even if it is administered in relatively high doses with a dosage scheme independent of body weight.

Esmolol is an ultrashort-acting intravenous β-blocker. The rapid onset and offset of effects of esmolol make this intravenous drug a potential alternative of the standard of care metoprolol in the daily routine coronary CTA service. Especially, coronary CTA services with no access to cardiology or intensive care background might benefit most of this ultrashort-acting medication. The recommended administration protocol of IV esmolol with infusion pump is relatively complex and precluded its widespread use in the diagnostic facilities. Different dosage schedules have been developed depending on clinical setting and diagnosis. Generally, a loading dose of <500 μg/kg/min over 1 minute is administered followed by a continuous infusion of 25–300 μg/kg/min.[17] We showed that esmolol is safe and efficacious if administered in boluses without the subsequent continuous infusion. The "bolus only" administration protocol of esmolol would make this IV β-blocker a real life alternative of IV metoprolol. In this clinical trial we used a body weight–independent administration protocol with stepwise increments in dose in every 3 minutes. Importantly, the timing of the administration of the IV esmolol boli was similar to the metoprolol administration protocol; therefore, it did not slow down our routine clinical cardiac CT workflow. Our choice of 100-mg IV esmolol for the initial bolus is based on a previous observational study that showed that the dose of 2 mg/kg (for a 70-kg patient this equals 140-mg esmolol) is safe to administer before the coronary CTA examination.[14] If 100-mg dose proved to be ineffective, thus the patient's HR did not reach the predefined ≤65 beats/min in 3 minutes, we have increased the bolus to 200-mg IV esmolol. Finally, if the HR did not change after an additional 3-minute period (testing during a Valsalva maneuver as well), we administered the third, once again 200-mg, bolus of IV esmolol. We have not added further boluses; thus, the maximum administered IV esmolol was 500 mg during an approximately 6- to 7-minutes time period. Of note, only about one-third of patients have received the full dose of esmolol and two-thirds of patients have reached the target HR with ≤300-mg esmolol dose. We have stopped the patient enrollment early as the interim analysis indicated that esmolol is clearly noninferior to metoprolol; in fact, it showed superiority characteristics as the responder proportion in the esmolol group was 89% vs the metoprolol group's 78%.

Degertekin at al[14] demonstrated the safety and efficacy of IV esmolol in 391 patients. In this prospective study, HR was reduced from 80 ± 11 beats/min to 63 ± 7 beats/min and HR <65 beats/min was achieved in 65% of the patients. Four of the 391 patients (1%) have experienced a final HR

of <50 beats/min; however, all 4 remained asymptomatic and the bradycardia resolved in minutes without any intervention with atropine or temporary pacing. Moreover, Degertekin et al[14] reported a 0.5% incidence of transient hypotension (systolic BP <100 mm Hg). In our clinical trial, we have reached a higher responder proportion (89.2%) probably because of a more aggressive dosing scheme. Importantly, none of the 204 patients who received esmolol had severe bradycardia (minimum HR was 53 beats/min). On the other hand, transient hypotension (systolic BP <100 mm Hg) was observed in 9.3% of the patients immediately after the scan in the esmolol group, which was significantly higher compared to the metoprolol group's 3.8%. Importantly, 30 minutes after the scan this decreased to 2.5% in the esmolol group, whereas in the metoprolol group the percentage of patients with hypotension did not change (3.8%). None of the patients had clinically significant adverse event. Thus, the stepwise bolus administration of esmolol is safe and it is well tolerated among patients with normal left ventricular function scheduled to undergo coronary CTA examination. Furthermore, our data show that IV esmolol is at least as efficacious as IV metoprolol to reach optimal HR during coronary CTA.

Many centers are reluctant to administer IV medication for HR control during coronary CTA owing to the fear from potential side effects. A recent study by Kassamali et al[19] reported minor complications (transient hypotension) related to IV metoprolol administration only in 1.47% and major complications (not resolving with observation of analgesia) in 0.44% of patients who underwent coronary CTA. These results demonstrate that IV metoprolol is a safe drug to use for this purpose in patients with normal left ventricular function although the study was underpowered to assess for rare major complications.

Esmolol is metabolized via rapid hydrolysis by red blood cell esterases, independent of the hepatic and renal function.[20] It is routinely administered during perioperative intensive care and before laryngoscopy and tracheal intubation procedures to prevent hypertension and tachycardia.[21,22] In this clinical trial, we have excluded patients with contraindications to β-blockers such as asthma. However, it has been demonstrated previously that esmolol is safe in bronchospastic diseases.[23]

There are some limitations of our study we have to consider. This is a single-center study; therefore, the efficacy and safety of the described esmolol bolus protocol has to be evaluated in a multicenter randomized controlled trial. As the administration protocols and the injected volumes were different for the IV metoprolol and IV esmolol groups, it was not feasible to blind the physicians to the drug they were administering. The combined use of oral and IV β-blocker protocols for HR control might limit the generalizability of our results for IV-only protocols. Owing to the oral metoprolol pretreatment, our findings do not demonstrate that esmolol IV alone vs metoprolol IV is as or more effective for HR control. However, it is important to note that the combined use of oral and IV β-blockers is a widely used and effective strategy for HR lowering before coronary CTA.[6,24] In this scenario, esmolol is at least as efficacious as IV metoprolol. The response rate to oral metoprolol was relatively low in our study (162 of 574 [28%]), which might have been higher with the use of a more

aggressive administration regime (eg, 100-mg oral metoprolol if HR >65 beats/min).[17] Furthermore, we did not test smaller doses of esmolol (eg, 50–100 mg), which might be equally efficacious. Moreover, it is important to note that esmolol is more expensive than IV metoprolol. However, the effective and short duration of HR control achievable with esmolol might result in wider usage of this IV β-blocker in cardiac CT labors, which would increase the percentage of patients scanned with optimal HR and improve the diagnostic performance of CTA. A larger multicenter trial is warranted to adequately explore the cost-effectiveness of esmolol use in the coronary CTA laboratories.

Acknowledgment

REFERENCES

1. Schroeder S, Achenbach S, Bengel F, et al. Cardiac computed tomography: indications, applications, limitations, and training requirements: report of a writing group deployed by the Working Group Nuclear Cardiology and Cardiac CT of the European Society of Cardiology and the European Council of Nuclear Cardiology. *Eur Heart J*. 2008;29:531–556.
2. Achenbach S, Raggi P. Imaging of coronary atherosclerosis by computed tomography. *Eur Heart J*. 2010;31:1442–1448.
3. Stolzmann P, Goetti RP, Maurovich-Horvat P, et al. Predictors of image quality in high-pitch coronary CT angiography. *AJR Am J roentgenology*. 2011;197:851–858.
4. Matt D, Scheffel H, Leschka S, et al. Dual-source CT coronary angiography: image quality, mean heart rate, and heart rate variability. *AJR Am J roentgenology*. 2007;189:567–573.
5. Dewey M, Zimmermann E, Deissenrieder F, et al. Noninvasive coronary angiography by 320-row computed tomography with lower radiation exposure and maintained diagnostic accuracy: comparison of results with cardiac catheterization in a head-to-head pilot investigation. *Circulation*. 2009;120:867–875.
6. Abbara S, Arbab-Zadeh A, Callister TQ, et al. SCCT guidelines for performance of coronary computed tomographic angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. *J Cardiovasc Comput Tomogr*. 2009;3:190–204.
7. Mahabadi AA, Achenbach S, Burgstahler C, et al. Safety, efficacy, and indications of beta-adrenergic receptor blockade to reduce heart rate prior to coronary CT angiography. *Radiology*. 2010;257:614–623.
8. Pannu HK, Alvarez Jr W, Fishman EK. Beta-blockers for cardiac CT: a primer for the radiologist. *AJR Am J Roentgenol*. 2006;186(6 Suppl 2):S341–S345.
9. Maffei E, Palumbo AA, Martini C, et al. "In-house" pharmacological management for computed tomography coronary angiography: heart rate reduction, timing and safety of different drugs used during patient preparation. *Eur Radiol*. 2009;19:2931–2940.
10. Johnson PT, Eng J, Pannu HK, Fishman EK. 64-MDCT angiography of the coronary arteries: nationwide survey of patient preparation practice. *AJR Am J Roentgenol*. 2008;190:743–747.

11. Westfall TC, Westfall DP. Beta adrenergic receptor antagonists. In: Brunton LL, ed. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. New York, NY: The McGraw-Hill; 2011.

12. Wiest D. Esmolol. A review of its therapeutic efficacy and pharmacokinetic characteristics. *Clin Pharmacokinet*. 1995;28:190–202.

13. Wiest DB, Haney JS. Clinical pharmacokinetics and therapeutic efficacy of esmolol. *Clin Pharmacokinet*. 2012;51:347–356.

14. Degertekin M, Gemici G, Kaya Z, et al. Safety and efficacy of patient preparation with intravenous esmolol before 64-slice computed tomography coronary angiography. *Coron Artery Dis*. 2008;19:33–36.

15. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet*. 2001;357:1191–1194.

16. Taylor AJ, Cerqueira M, Hodgson JM, et al. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 Appropriate Use Criteria for Cardiac Computed Tomography. A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. *J Cardiovasc Comput Tomogr*. 2010;4:407.e1–407.e33.

17. Roberts WT, Wright AR, Timmis JB, Timmis AD. Safety and efficacy of a rate control protocol for cardiac CT. *Br J Radiol*. 2009;82:267–271.

18. Wilcox RR. *Introduction to Robust Estimation and Hypothesis Testing*. Waltham, MA: Elsevier; 2012.

19. Kassamali RH, Kim DH, Patel H, et al. Safety of an i.v. beta-adrenergic blockade protocol for heart rate optimization before coronary CT angiography. *AJR Am J Roentgenol*. 2014;203:759–762.

20. Reynolds RD, Gorczynski RJ, Quon CY. Pharmacology and pharmacokinetics of esmolol. *J Clin Pharmacol*. 1986;26(Suppl A):A3–A14.

21. Oxorn D, Knox JW, Hill J. Bolus doses of esmolol for the prevention of perioperative hypertension and tachycardia. *Can J Anaesth*. 1990;37:206–209.

22. Parnass SM, Rothenberg DM, Kerchberger JP, Ivankovich AD. A single bolus dose of esmolol in the prevention of intubation-induced tachycardia and hypertension in an ambulatory surgery unit. *J Clin Anesth*. 1990;2:232–237.

23. Sheppard D, DiStefano S, Byrd RC, et al. Effects of esmolol on airway function in patients with asthma. *J Clin Pharmacol*. 1986;26:169–174.

24. Jimenez-Juan L, Nguyen ET, Wintersperger BJ, et al. Failed heart rate control with oral metoprol prior to coronary CT angiography: effect of additional intravenous metoprolol on heart rate, image quality and radiation dose. *Int J Cardiovasc Imaging*. 2013;29:199–206.