Diltiazem as an Alternative to Beta-blocker in Coronary Artery Computed Tomography Angiography

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Abstract

Background: Reducing heart rate (HR) in CT angiography of the coronary arteries (CTACor) is critical to image quality. The effectiveness of calcium channel blockers as alternatives for patients with contraindications to beta-blockers has not been established.

Objectives: To compare the efficacy in the reduction of HR and RR variability of metoprolol and diltiazem in CTACor.

Methods: Prospective, randomized, open study that included patients with clinical indication of CTACor in sinus rhythm with HR > 70 bpm and no use of agents that could interfere with HR. Fifty patients were randomized to the groups: metoprolol IV 5-15 mg or up to HR ≤ 60 bpm (M), and diltiazem IV 0.25 to 0.60 mg/kg or up to HR ≤ 60 bpm (D). Blood pressure (BP) and HR were measured at baseline, 1 minute, 3 minutes and 5 minutes after the agents, at the acquisition and after CTACor.

Results: HR reduction in absolute values was higher in group M than in group D (1, 3, 5 min, acquisition and post-test). The percentage reduction of HR was significantly higher in group M only 1 min and 3 min after the start of the agents. There was no difference in 5 min at acquisition and after examination. The percentage RR variability in group D was lower than that in group M during acquisition (RR variability/mean HR of acquisition). A single case of AVB, 2:1 Mobitz I occurred, which was spontaneously reverted (group D).

Conclusion: We conclude that diltiazem is an effective and safe alternative to beta-blockers in the reduction of HR when performing computed tomography angiography of coronary arteries. (Arq Bras Cardiol 2012;99(2):706-713)

Keywords: Diltiazem; calcium channel blockers; coronary angiography; tomography; coronary vessels.

Introduction

Coronary artery imaging is a key element for decision management in patients with known or suspected coronary artery disease (CAD). The classical method for obtaining images of the coronary arteries is invasive catheterization or coronary angiography, which, as an invasive procedure, has a non-negligible risk of complications and thus is indicated in specific cases of high suspicion of CAD or situations of acute disease presentation[1].

Recently, a new method for noninvasive assessment of coronary arteries using computed tomography (CT) equipment, is able to visualize the lumen and the wall of the coronary arteries[2-5]. This method was developed with the advent of multiple-detectors computed tomography (MDCT), which allowed a much faster image acquisition, and therefore, the visualization of the coronary arteries as static images without significant motion artifacts.

While publications of international and multicenter studies have validated this technology[6-8], demonstrating the high accuracy in relation to catheterization, several national[9] and international[10] guidelines and consensus documents corroborate that computed tomography angiography of coronary arteries (CTACor) has important current clinical indications, including: patients with intermediate pretest probability of CAD unable to exercise; patients with previous imaging results that are doubtful or discordant with the clinical picture[11]; evaluation of chest pain in emergency department patients with low or intermediate pre-test probability and

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Manuscript received August 20, 2011; manuscript revised August 23, 2011; accepted February 24, 2012.

normal or doubtful ECG and normal or doubtful markers of myocardial necrosis ("enzymes"); evaluation of suspected coronary anomalies, among others of great clinical relevance.

Despite, however, the best temporal resolution of current CT equipment, the heart rate (HR) of the patient during image acquisition of ATCCor still needs to be around 60 beats per minute (< 65 bpm) for the optimal quality of picture and/or for the radiation dose to be the lowest possible[12,13]. In addition, the RR interval should also be regular for optimal image quality, and irregular heartbeats, such as in atrial fibrillation and extrasystole, can be extremely damaging to image acquisition in CTACor[14,15]. In the current routine use of this test, HR reduction is obtained through the preferential use of beta-blockers, either by oral or intravenously administration. Intravenous use has been preferred by the majority of services in Brazil as it is ease of use, safe and fast-acting, allowing a rapid flow of patients at the equipment.

In the reduction of HR for CTACor, calcium-channel blockers are an alternative to beta-blockers in patients with contraindications to the latter[16]. Beta-blockers, even those with B1-selective effect, are contraindicated in patients with severe asthma or severe chronic obstructive pulmonary disease, especially with episodes of bronchoconstriction or use of bronchodilators[17,18]. The acute use of beta-blockers is also contraindicated in cases of decompensated CHF, hypotension (systolic BP < 100 mmHg, advanced atrioventricular block, severe aortic stenosis, diabetes at risk of hypoglycemia and severe peripheral arterial disease (e.g., intermittent claudication, or Raynaud's disease). Of all mentioned contraindications, lung diseases are the most commonly found in clinical practice and complications of severe bronchoconstriction crisis associated with the acute use of beta-blockers are among the most feared.

One alternative to beta-blockers for HR reduction in CTACor and that does not have contraindications in patients with bronchoconstriction pulmonary disease are non-dihydropyridine calcium-channel blockers, such as verapamil (fenyl-alquilamines) and diltiazem (benzothiazepines)[19]. However, although mentioned in many texts as an alternative to beta-blockers, the efficacy of calcium-channel blockers used in the decrease of HR prior to the CTACor has not been clearly defined and comparative data are still unavailable. Another potential drug for HR reduction in this clinical situation is ivabradine, which is only available for oral administration in Brazil, as its intravenous form is not yet available for clinical use. We participated in an international study with intravenous administration of ivabradine, and it showed good results in the decrease of HR when performing the CTACor[20].

In the present study, therefore, our objective was to evaluate the effectiveness of diltiazem to decrease HR and the RR interval variability, when compared to metoprolol in patients referred to undergo CTACor.

Methods

We designed a prospective, randomized (1:1) and open study. Patients with clinical indication of CTACor in sinus rhythm and with HR > 70 bpm were included and randomized to receive intravenous metoprolol or diltiazem. Metoprolol (metoprolol tartrate, Seloken ®) was used at a dose of 5 mg in slow intravenous injection, repeated until HR ≤ 60 bpm or up to a maximum dose of 15 mg. Diltiazem (diltiazem hydrochloride, Balcor ®) was used at a dose of 0.25 mg / kg in 2 minutes and HR > 60 bpm, with an additional dose of 0.35 mg / kg in 2 minutes. We excluded patients using agents that interfere with the HR. Thus, we excluded those who had prior use of beta-blockers, calcium blockers or any other agent that would interfere in the conduction of the AV node or that could alter HR. All patients signed a free and informed consent form and the study was approved by the institutional Ethics Committee.

Basal HR, as well as systolic, diastolic and mean blood pressure (BP) were measured before and 1 minute, 3 minutes and 5 minutes after infusion of agents. All measurements were repeated after the completion of CTACor. The RR variability was measured during the examination acquisition using the electrocardiographic tracing of beats recorded during image acquisition provided by tomography equipment, in general an ECG tracing during 8-12 seconds of the acquisition (8-12 beats). The absolute RR variability was defined as the difference between the highest and lowest HR, or the largest and smallest RR interval and expressed as beats per minute (bpm). Thus, a lower variability indicates less difference between the minimum and maximum HR during acquisition. The percentage RR variability was calculated as the absolute RR variation divided by the mean HR during the acquisition of CTACor.

Patients were followed up to 30 minutes after the examination to assess the effects of agents and safety in case of possible side effects caused by the examination or its preparation.

As mentioned earlier, HR and BP were measured at baseline, before administration of any drug. The assessment of HR and BP were repeated 1 minute, 3 minutes and 5 minutes after the start of agent infusion. Additionally, HR was measured during CTACor acquisition (at this moment, it was not possible to measure BP), and finally both HR and BP were measured again 10 minutes after CTACor. HR was measured by the monitor of the electrocardiogram tracing and BP was measured with a sphygmomanometer, using the traditional auscultatory method. The measurements were performed with the patient in the supine position on the table of MDCT equipment.

We also calculated the percentage reduction of HR in relation to basal HR of each patient, thus normalizing the effects of drugs for initial HR of each patient, which showed significant variation.

The CTACor used a standard protocol for image acquisition in MDCT equipment with 64-detector columns (Aquilion 64, Toshiba Medical Systems, Otawara, Japan) and injection of nonionic iodinated contrast at the time of acquisition. This protocol was described in a previous study[21].

The statistical analysis used the Shapiro-Wilk test to determine whether the distribution was normal. For variables with normal distribution, Student's *t* test for two means with similar variance was used to compare the HR in both groups of agents at each moment in time. For variables with nonparametric distribution, the Kruskal-Wallis test was used.

Results

We selected 126 consecutive patients referred to the Department of Magnetic Resonance and Cardiovascular Computed Tomography of our institution with CTACor clinical indication. Seventy-six patients were excluded due to some exclusion criteria: current use of any agent that could cause bradycardia or interfere with the conduction of the AV node; cardiac rhythm other than sinus, HR < 70 bpm. Thus 50 consecutive patients were included, 38 men (76%) and 12 women (38%) with a mean age of 57.8 ± 6.7 years. Patients were randomized to the metoprolol (M) or diltiazem (D) group, with 25 patients in each group.

Only six patients (24%) from group D received 0.25 mg/kg of diltiazem and the other 19 patients (76%) received a total dose of 0.6 mg/kg. The mean dose of diltiazem was 0.15 ± 0.516 mg/kg. In group M, eight patients received 5 mg, eight patients received 10 mg and nine patients received 15 mg of metoprolol. The mean dose of metoprolol was 10.2 ± 4.2 mg.

No patient developed symptoms during or after the infusion of agents. Two patients had frequent ventricular extrasystoles at baseline, both from group D. After the infusion of agents and during or after the acquisition of CTACor, four patients had ventricular extrasystoles (the same two patients who had them at baseline and two patients without prior arrhythmia, also from group D). One patient from group M showed significant worsening of sinus arrhythmia during acquisition, with significant RR variability of 10 beats, thus impairing image acquisition. One patient from group D showed second-degree AV block, Mobitz I 2:1, without any symptoms or hemodynamic effects, which reverted spontaneously during patient follow-up (after 10 minutes).

Basal HR was similar between groups. HR at 1 minute, 3 minutes, 5 minutes, acquisition and post-CTACor were significantly lower in group M, when compared with group D, especially at 1 minute, 3 minutes and 5 minutes (Table 1). Minimum and maximum HR values are shown in Table 1. Figure 1 shows all points of all patients with the temporal evolution of HR, in both groups. Figure 2 shows the curve of predicted HR using fractional polynomial fit, for each point and its confidence interval, for both groups.

If we consider the percentage reduction in relation to basal HR, we will normalize the data for initial HR of each patient, which showed significant variation. Thus, the percentage reduction in HR was higher in group M when compared to group D, only at the first and third minutes, no longer significant at the fifth minute, acquisition and post-CTACor (Table 2). The absolute RR variability showed a trend toward less variability in group D, while the percentage variability (RR variability / mean HR of the acquisition) was statistically lower in group D when compared to group M during the acquisition (Table 3).

BP behavior is shown in Tables 4, 5 and 6. After the start of intravenous drug injection, the BP decreased and recovered in the post-acquisition period. The BP decreases were slight and did not result in any hypotension symptoms in any patient. In general, the D group showed lower BP even at baseline and remained more hypotensive throughout the monitoring period when compared to group M.

Discussion

The CTACor by intravenous injection of nonionic iodinated contrast allows the detailed anatomical visualization of the coronary arteries, vascular grafts (mammary and saphenous vein bypass grafts) and intra- and extracardiac structures, such as valves, thrombi and pericardium. As mentioned earlier, the acquisition and reconstruction of CTACor images are performed synchronously with the electrocardiographic signal. Therefore, the optimized image acquisition depends on the HR control of patients, to improve the diagnostic quality and the use of the lowest possible radiation dose[14,15].

In 64-detector devices, the patients must have regular HR, as data is obtained in different heartbeats (usually six to eight), and then combined into a single volume. Thus, if there are irregularities between RR intervals, the combined data that were acquired at different phases of the cardiac cycle result in "steps" and/or movement artifacts. In addition, a low and regular HR allows the use of dose modulation algorithms connected to the ECG, where the higher dose of X-ray is released only during diastole, or even the use of prospective acquisition (with fewer images from the device), which can reduce the radiation dose by 60%. In more modern devices, which are still rare in our country, image acquisition is performed during only one or two beats.

Nevertheless, the use of negative chronotropic agents is important. Although less critical, controlling the HR is still used almost universally in order to take full advantage of its dose reduction capacity, which can become smaller than

Table 1 – Minimum, mean and maximum Heart Rate (HR) – temporal evolution in the groups

Mean HR (bpm)	Basal	1 min	3 min	5 min	Acquisition	Post
Metoprolol	80.0 ± 6.1	69.3 ± 6.2	65.3 ± 5.7	63.6 ± 6.6	62.6 ± 8.5	70.2 ± 6.6
Diltiazem	83.4 ± 8.4	76.8 ± 7.7	73.0 ± 7.2	68.7 ± 6.4	68.5 ± 9.1	75.0 ± 9.3
p	0.11	0.0004	0.0001	0.0071	0.0215	0.0396
HR Min-Max (bpm)						
Metoprolol	70 - 96	58 - 86	56 - 80	54 - 79	50 - 81	60 - 82
Diltiazem	72 - 108	58 - 90	56 - 86	55 - 82	54 - 96	61 - 102

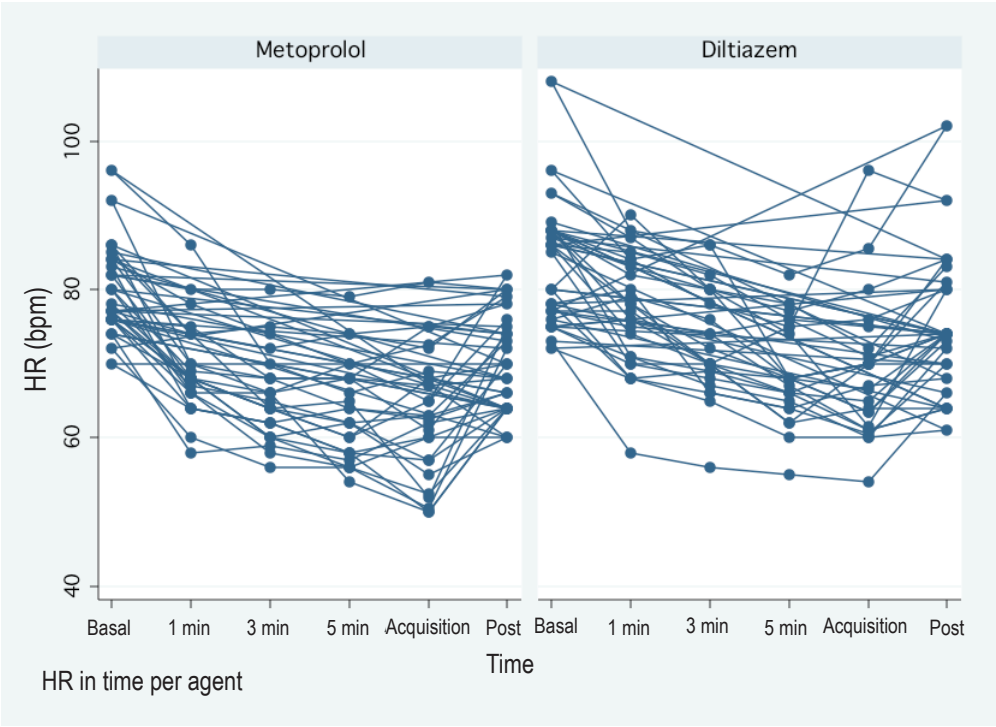

Figure 1 – *Line graph illustrating the temporal evolution of heart rate for all patients in both groups, metoprolol, and diltiazem.*

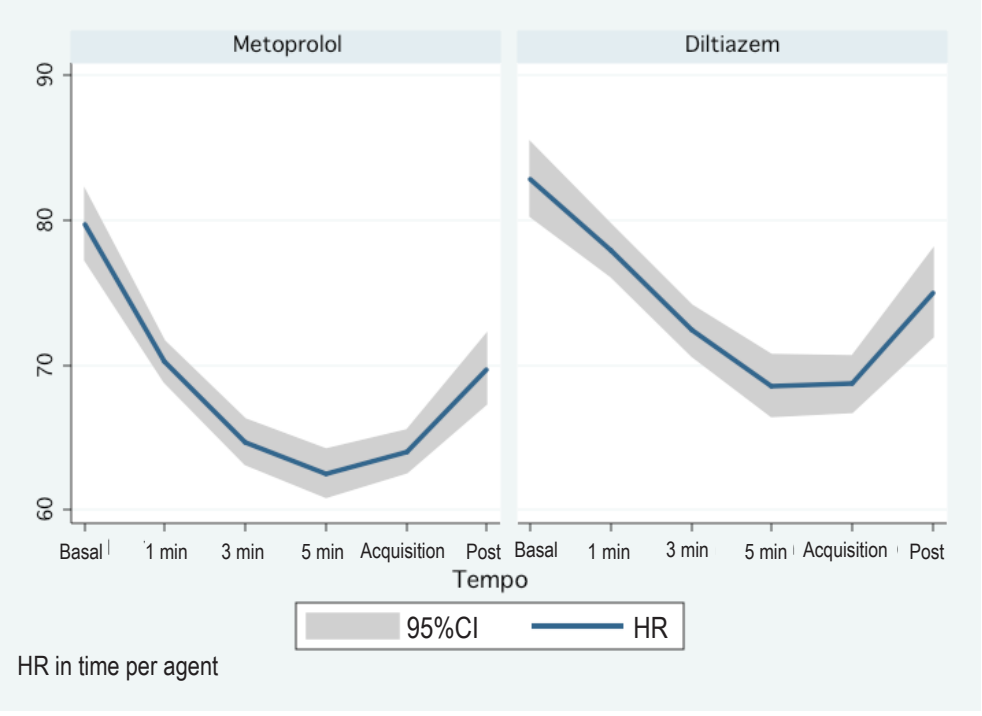

Figure 2 – *Gráfico demonstrando a evolução temporal da frequência cardíaca predita e o intervalo de confiaça de 95%, num ajuste de curva utilizando um polinomial fracional, em ambos os grupos, metoprolol e diltiazem.*

Table 2 – Percentage decrease in heart rate in relation to basal HR

Decrease / basal HR (%)	1 min	3 min	5 min	Acquisition	Post
Metoprolol	13.2 ± 6.1	18.1 ± 6.7	20.4 ± 6.9	21.7 ± 8.9	12.0 ± 7.6
Diltiazem	7.6 ± 8.2	12.2 ± 6.6	17.3 ± 6.3	17.7 ± 7.7	9.9 ± 7.8
p	0.0085	0.003	0.1012	0.0964	0.3266

Table 3 – Variability of the RR interval – absolute and percentage of mean HR of acquisition

RR Variability	Absolute, mean [min-max] (bpm)	% of mean HR of Acquisition
Metoprolol	5.7 ± 2.8 [2 - 11]	9.4 ± 5.2
Diltiazem	4.3 ± 2.9 [0 - 12]	6.2 ± 4.0
p	0.0891	0.0174

Table 4 – Systolic Blood Pressure (SBP) – temporal evolution in the groups

SBP (mmHg)	basal	1 min	3 min	5 min	Post
Metoprolol	139.2 ± 25.0	132.0 ± 23.1	128.5 ± 23.1	125.9 ± 24.0	129.4 ± 21.5
Diltiazem	130.4 ± 16.0	116.5 ± 10.0	116.7 ± 10.7	117.0 ± 8.9	119.4 ± 15.2
p	0.1428	0.0035	0.0247	0.0876	0.0685

Table 5 – Diastolic Blood Pressure (DBP) – temporal evolution in the groups

DBP (mmHg)	basal	1 min	3 min	5 min	Post
Metoprolol	85.2 ± 10.1	82.2 ± 11.2	80.3 ± 11.1	78.9 ± 9.9	80.5 ± 10.5
Diltiazem	78.7 ± 9.4	72.7 ± 10.6	73.6 ± 8.8	73.0 ± 8.5	75.2 ± 9.9
p	0.0222	0.0035	0.0228	0.0279	0.0762

Table 6 – Mean Arterial Pressure (MAP) – temporal evolution in the groups

MAP (mmHg)	basal	1 min	3 min	5 min	Post
Metoprolol	103.2 ± 14.1	98.8 ± 14.1	96.2 ± 14.3	94.5 ± 13.7	97.7 ± 13.7
Diltiazem	95.9 ± 10.1	87.4 ± 9.0	87.9 ± 8.0	87.6 ± 6.9	89.8 ± 10.0
p	0.0395	0.0017	0.0148	0.0279	0.0486

1mSv (approximately 10 plain chest X-rays)[22]. Protocols vary depending on the services, but the target HR on acquisition is below 65 bpm. When the patient arrives for the examination with a HR > 65 bpm, invariably he or she will receive medication to control HR.

The group of agents initially used to control HR is the beta-blockers, by premedication, by oral route, approximately one hour before the examination, or intravenously immediately prior to it. However, some studies that analyzed the performance of this strategy found surprisingly high rates (27% to 34%) of patients who did not reach the target HR, even after oral premedication and the use of maximum dose (20 mg) of the most commonly used intravenous beta-blocker, metoprolol. Furthermore, there was a high number (16%) of patients with some degree of contraindication to the use of this class of agents.

All this contributes to the poorer quality of diagnostic images and explains the need for alternative strategies and drugs[23,24]. The following are contraindications to beta-blockers, selective or not: presence of advanced atrioventricular block, hypotension, asthma, Chronic Obstructive Pulmonary Disease (COPD) and clinical

instability [16]. Although there have been studies demonstrating the safety of chronic use of low-dose selective beta-blockers by oral administration in patients with COPD[25], the acute intravenous use for CTACor, especially in patients using beta-adrenergic agents such as bronchodilators, is still considered a contraindication from the clinical and pharmacological point of view, and literature studies that tested this particular situation are not available.

Calcium-channel blockers, particularly diltiazem, may be used in cases of patients with pulmonary disease, being a simple, efficient and widely available alternative to control HR[16]. Calcium-channel blockers decrease conduction through the AV node and to a lesser extent, in the sinoatrial node[26]. Due to this mechanism, they are the group of choice for pre-examination control of patients with atrial fibrillation[27]. They do not induce bronchospasm, but have a less intense negative chronotropic effect. Among them, diltiazem should preferably be chosen, as it has a lower negative inotropic effect.

The recommended dose of diltiazem is 0.25 mg/kg, IV route, in 2 minutes, and a second dose of 0.35 mg/kg, may be administered if the target HR is not attained. Our results suggest that the second dose is usually required to achieve the target HR. Thus, the first dose can be administered in the preparation room and the second in the examination room. In some cases in clinical practice, when the patient arrives at the service with high HR (> 90 bpm), to facilitate management strategy we calculate a maximum dose of 0.6 mg/kg and infuse the medication for 15-20 minutes, diluted with 100 mL of saline solution.

The present study was one of the first to investigate, in a controlled manner, the use of diltiazem for ATCCor and to compare results with beta-blockers. A direct comparison between the major drugs, metoprolol and diltiazem, is scarce in the literature. In this study we observed a significant reduction in HR after 1, 3 and 5 minutes of drug infusion, both in patients who received beta-blockers and those who received diltiazem, with a higher reduction in the first group; however, statistical significance was observed only in the third minute and not at the end of infusion. We also observed the safety when using diltiazem in the context of CTACor. Blood pressure after the test was similar in both groups (despite the theoretical greater vasodilation with calcium-channel blockers) and there were no reports of major disturbances in heart rhythm.

A very important and original data investigated in this study was that patients receiving diltiazem had significantly lower variability of the RR interval during CTACor acquisition, which is an extra advantage for the quality of acquired images at the coronary angiography, particularly in equipment with 64-detector columns.

The combined use of beta blockers and diltiazem is not recommended for routine use, due to the potential to cause bradyarrhythmias. However, in some specialized centers and in selected patients, when the highest dose of beta-blockers is achieved and HR remains well above the target, a dose of 0.25 mg/ kg of diltiazem has been associated, allowing the acquisition below 70 bpm, with no record of problems. In this case, the patient remains under observation after the examination during the half-life of diltiazem elimination, which is 3.5 to 4.5 hours (authors' personal experience). Every center that carries out the examination should be prepared with equipment and personnel trained in advanced life support in cardiology to treat potential complications such as hypotension and bradycardia. Basic treatment includes high volume administration and lower-limb elevation. The antidotes glucagon (for beta-blockers) and calcium gluconate or chloride should also be available, in addition to atropine and vasopressors for cases of extreme gravity, which fortunately are very rare.

In short, there was effective decrease in HR in both groups, with a greater reduction in the metoprolol group. In turn, the smaller RR variability during the examination acquisition with diltiazem, associated with its coronary vasodilator effect is an inherent characteristic of the drug, which can offer advantages over the classical use of beta-blockers. It is noteworthy, however, that in the present study we did not perform a direct evaluation of the quality of images obtained in both groups. As there have been several studies showing a direct association between the degree of HR reduction and the final quality of the images[13-15], in the present study we chose to restrict our investigation to an indirect assessment of the effect of HR control agents on the final quality of images.

Nevertheless, it is important to recognize that this issue represents an important limitation, and that further studies should be performed in order to more specifically clarify the association between the type of drug used to control HR and the final quality of images. Therefore, we would have definitive proof that diltiazem is an effective alternative to beta-blockers in this clinical context.

Finally, the present randomized clinical trial showed that, in the clinical situation of CTACor examinations, HR reduction was greater with diltiazem, when compared to metoprolol. Diltiazem showed lower RR variability during image acquisition when compared to metoprolol, which is also associated with better image quality. Overall, diltiazem showed to be an effective and safe alternative to beta-blockers in reducing HR prior to angiography by computed tomography of the coronary arteries.

Potential Conflict of Interest

I declare that there are no relevant conflicts of interest, exception made to the authors Drs. Carlos Rochitte and Dr. Guilherme Santana Nunes Azevedo, who were paied by the Laboratory Baldacci to prepare a text, named Coronary Computed Tomography. Baldacci produces the drug Balcor (Diltiazem).

Sources of Funding

This study was partially funded by Fundação Zerbini. Dr. Rochitte is an established researcher of National Counsel of Technological and Scientific Development, CNPq, and was partially funded by a grant-in-aid, number 305569/2007-4.

Study Association

This study is not associated with any post-graduation program.

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