Safety, Efficacy and Indications of β-Blockers to Reduce Heart Rate prior to Coronary CT Angiography-An Overview

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Abstract:

For selected indications, coronary computed tomographic (CT) angiography is an established clinical technology for evaluation in patients suspected of having or known to have coronary artery disease. In coronary CT angiography, image quality is highly dependent on heart rate, with heart rate reduction to less than 60 beats per minute being important for both image quality and radiation dose reduction, especially when single-source CT scanners are used. â-Blockers are the first-line option for short-term reduction of heart rate prior to coronary CT angiography. In recent years, multiple â-blocker administration protocols with oral and/or intravenous application have been proposed. This review article provides an overview of the indications, efficacy, and safety of â-blockade protocols prior to coronary CT angiography with respect to different scanner techniques. Moreover, implications for radiation exposure and left ventricular function analysis are discussed.

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Introduction:

Coronary computed tomographic (CT) angiography is an established clinical technology for the evaluation of coronary artery disease, with high sensitivity and high negative predictive value in selected patients. Furthermore, it has potential for the detection of coronary plaque burden.[1] Over the past decade, advances in scanner and post processing technology have led to substantial improvements in temporal and spatial resolution and hence image quality. Yet image quality remains highly dependent on both the regularity of the cardiac rhythm and the heart rate, especially when single-source CT scanners are used, which to date represent the vast majority of scanners in clinical practice. Current publications recommend a heart rate of ideally less than 60 beats per minute both for optimal image quality and for reduction of radiation exposure.[2] However, most patients seen in clinical practice have heart rates often much above 75 beats per minute at presentation.[3] Therefore, in the absence of contraindications, â-blockers should be routinely administered prior to coronary CT angiography to achieve sufficient reduction of heart rate prior to data acquisition. There many clinical trials support the need for more effective heart rate reduction in clinical practice.

In this article, we provide an overview of indications, safety, and efficacy of â-blockade prior to coronary CT angiography.

Pharmacologic Properties of â-Blockers

To reduce heart rate during coronary CT angiography, cardio selective β_1-blockers are the predominantly used agents. β-adrenergic antagonists reduce the heart rate by decreasing the frequency of the sinus node, by decreasing the spontaneous rate of depolarization of ectopic pacemakers, by slowing conduction in the atria and in the atrioventricular node, and by increasing the functional refractory period of the atrioventricular node.

Pharmacologic properties of short-term â-blockers, such as decreasing cardiac output and peripheral resistance, differ substantially from long-acting β-blockers, when total peripheral resistance returns to initial values, effects mediated by â-adrenoreceptors.[4] β -Blockers as a daily medication-for example, for heart failure-have only mild influence on resting heart rates and mainly reduce maximum heart rates achieved during exercise.[5] However, when administered as short-term medication in high doses, they also allow reduction of heart rate at rest, as desired for cardiac CT. As a trade-off, β-blockers can then cause substantial

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side effects because of their â$_1$ selectivity, intrinsic sympathomimetic activity, and membrane-stabilizing properties. These include hypotension, bradycardia, prolonged atrioventricular conduction times, and widened QRS complexes. Of importance, especially in high doses, cardio selective β-blockers also bind on β_2 receptors, which can cause a number of noncardiac side effects. Blockade of β_2 receptors with compensatory sympathetic reflexes that activate vascular β-adrenergic receptor can cause peripheral vasoconstriction, which reduces blood flow to most organs other than the brain, including a decrease in renal blood flow and glomerular filtration rate.[6] Fortunately, the decrease in peripheral blood flow is seen clinically only in the acral skin, usually without any pathologic relevance.

Selected Effects Mediated by β-Adrenergic Receptors Blocker

-Metoprolol (β_1 selective) is the most commonly used â-blocker for heart rate reduction. Its oral bioavailability is relatively low (40%) with high interindividual differences due to high first-pass metabolism with wide variation.[7] Therefore, intravenous administration (bioavailability 95%) is not only beneficial because it results in faster reduction of heart rate, but it also allows better dose titration. Intravenously, 2.5 or 5 mg metoprolol should be administered over 1-2 minutes, which can be repeated at approximately 2-5 minute intervals. Despite its half-life of 3-4 hours, it is usually intravenously administered immediately prior to the CT scan.

-Other used β-blockers are atenolol (oral bioavailability 40%–50%, half-life of 6–7 hours) and, less frequently, esmolol with a half-life of only 9 minutes, which can be applied as bolus injection immediately prior to the CT scan or as continuous infusion with careful titration of dose, until effective heart rate reduction is achieved.

Protocols for b-Blocker Administration prior to Coronary CT Angiography-

Several studies have addressed the effect of oral, intravenous, or combinations of oral and intravenous β-blocker administration in clinical practice.

Oral metoprolol administered 1 hour before scanning has been reported to be effective, especially in patients without prior medication, and therefore can help reduce the need of intravenous β-blocker administration.

If the target heart rate is not achieved, additional intravenous β-blocker administration should be performed prior to the scan.[8]

Some use intravenous metoprolol and others use esmolol[9] to a similar effect. The maximum dose of intravenous metoprolol for coronary CT angiography generally ranges from 10 to 30 mg.[10]

Overall, intravenous administration is associated with higher heart rate reduction. About 65% of subjects with heart rates greater than 65 beats per minute were reduced to less than 65 beats per minute by intravenous administration of esmolol at 1-3 mg per kilogram of body weight.

Only 1% had remaining heart rates greater than 80 beats per minute despite β-blocker administration.

Effectiveness of β-Blocker Protocols

â-Blockers may also diminish the increase in heart rate caused by nitroglycerine, which is routinely given prior to coronary CT angiography to improve the diagnostic accuracy of the examination[11].. Because of the simplicity of its use, its reported efficacy in many patients, its well-known safety profile in routine clinical practice, and the extensive experience with oral application in many institutions, oral â-blockade is a first-line option to reduce elevated heart rates, which should be supplemented by intravenous β-blockers as needed. Of importance, non–sustained-release forms of oral β-blockers should be used to obtain the desired short-term effect. Single or repeat intravenous injections of β-blockers have the advantage that the required dose can be titrated until the target heart rate is reached, and they are as safe as oral agents when administered appropriately. Use of intravenously administered β-blockers is therefore also considered an alternative first-line option.

Calcium-Channel Blockers in CT Angiogram

In many studies and clinical reports in the literature, a considerable number of patients (5%-11%) did not qualify for treatment with β-blockers owing to contraindications.[3] In these subjects, calcium-channel blockers such as verapamil or diltiazem are mentioned in the literature as potential alternatives. However, from clinical experience, the effectiveness of calcium-channel blockers for short-term heart rate reduction is considerably less than that of β-blockers. Calcium-channel blockers are not recommended as a useful means of sufficient heart rate reduction in cardiac CT. However, ivabradine may be an effective alternative.

Effects of Heart Rate on Image Quality

High heart rates during CT scanning limit the image quality. The higher the heart rate, the higher the likelihood of motion artifacts that can considerably diminish the diagnostic accuracy of the scan.[12]

Generally, motion artifacts are especially prominent in the mid right coronary artery, where the rapid translational movement of the vessel may be as much as five to six times its diameter during the twisting and torsion of the heart during the cardiac cycle.[13] Therefore, the need for â-blockade prior to multidetector CT scanning to lower the heart rate in most patients referred for coronary CT angiography has been acknowledged in recent statements by the American Heart Association, Society of Cardiovascular Computed Tomography, and American College of Radiology.[14]

If heart rate reduction is achieved, this usually translates into better image quality. With use of a 64-detector CT scanner, only 1% of subjects who reached a target heart rate of 60 beats per minute were reported to have relevant motion artifacts.

With improvements in temporal resolution on new scanner technologies such as dual-source CT or 320-detector CT, there is growing evidence that a restrictive heart rate reduction may not be needed, with reports of sufficient image quality even at heart rates of up to 110 beats per minute.[15] However, even for scanners with an effective temporal resolution less than 100 msec, slightly lower per-segment evaluability for high heart rates have been described, yet without decrease in overall diagnostic accuracy. Further studies showed that also in dual-source CT, accuracy and image quality are higher at lower heart rates.[16] Overall, to date there is an ongoing debate whether heart rate reduction is needed for retrospectively gated dual-source CT imaging. Further research is needed to better characterize the association between various target heart rates and heart rate variability with image quality in new scanner generations with improved temporal resolution.

Atrial Fibrillation and Frequent Ectopic Beats

In subjects with frequent ventricular or supraventricular ectopic heart beats; â-blockers are potentially useful due to their membrane-stabilizing properties and therefore their ability to decrease the spontaneous rate of depolarization of ectopic pacemakers. In subjects with atrial fibrillation, there are still conflicting data on the image quality even with new scanner generations with low temporal resolution. While initial experience suggested successful imaging in patients with atrial fibrillation,[17] others found a high number of segments with motion artifacts (27% with misalignment artifacts, only 12% free of artifacts) in patients with heart rate irregularities including atrial fibrillation, which resulted in limited overall accuracy despite the increased temporal resolution of dual-source CT. Likewise, a high rate of evaluable segments but significantly lower image quality has been reported for subjects with atrial fibrillation with use of 320-detector CT. Overall, more research is needed to further evaluate the diagnostic accuracy of coronary CT angiography in subjects with arrhythmias such as atrial fibrillation and to determine if reduction of heart rate and decrease of the rate of spontaneous depolarization of ectopic pacemakers by short-term â-blocker treatment may help to improve image quality in these patients.

Implications of Heart Rate Reduction on Radiation Exposure

In clinical practice, an increase in heart rate by 10 beats per minute was found to lead to a 5% increase in radiation exposure; this was reported in an international observational study with 50 sites that included a wide range of CT hardware.[19] Several algorithms have been developed to allow for direct or indirect reduction in radiation exposure, but all of these algorithms are more effective at lower heart rates.

Electrocardiographically Correlated X-ray Tube Current Modulation

When retrospective gating is applied for coronary CT angiography, x-ray data are acquired throughout the entire cardiac cycle, which allows reconstruction at any desired phase of the R-R interval. For coronary artery evaluation, which requires best image quality, phases during end diastole are usually reconstructed, while other phases are less frequently used for coronary CT angiography. Therefore, tube current can be reduced (typically by 80%) during remaining parts of the cardiac cycle. During this time, contrast-to-noise ratio is decreased but usually still allows sufficient image quality for function analysis at lower radiation exposure. However, effectiveness of tube current modulation decreases with increasing heart rates, since the relative length of the time during which tube current is reduced is shorter than with lower heart rates.[20]

Prospective Electrocardiographic Triggering ("Step-and-Shoot" Mode)

With prospective electrocardiographic triggering, the x-ray tube is turned on only during a certain previously defined phase of the R-R interval, and images can be reconstructed only at this one particular phase. Therefore, a low and regular heart rate is of particular importance to ensure diagnostic image quality, as variation in heart rates or ventricular ectopic beats would lead to severe stair-step artifacts and reconstruction at other phases is not possible if motion artifacts are present. The higher temporal resolution of dual-source CT scanners or scanners with high rotation speed theoretically allows for high-quality scans at higher heart rates. Yet, if prospective triggering is used, the likelihood of motion artifacts can also be reduced for dual-source CT scanners by using β-blockers, because the resultant reduction in heart rate and heart rate variability increases the phase window of the R-R interval during which artifact-free imaging is possible[21]. Therefore, β-blockers can help to achieve diagnostic image quality in radiation-saving prospectively triggered coronary CT angiography irrespective of the scanner type used.

Multisegment Reconstruction

The idea is to decrease the duration of the window used for image reconstruction by combining data from consecutive heart beats. With single-source CT scanners, data sets can retrospectively be reconstructed from several heart beats by using multisegment reconstruction. Therefore, retrospective electrocardiographically gated spiral modes at a low pitch are needed for image acquisition. In contrast to retrospective multisegment reconstruction, using 320-section CT, which allows for full volume scanning during a single heart beat at heart rates of less than 65 beats per minute, images can be prospectively acquired at heart rates greater than 65 beats per minute from up to four consecutive heartbeats and therefore reconstructed from up to four different segments of one tube rotation.[22] It has been suggested that this would reduce the need for routine β-blockade. However, multisegment reconstruction is associated with higher radiation exposure due to the required low pitch or multiple scans of the same volumes. It therefore may be preferable to lower the heart rate and avoid the necessity of multisegment reconstruction to limit radiation exposure.[9]

High-Pitch Spiral Acquisition

There are recent reports on high-pitch spiral acquisition ("flash spiral") with potential for further reduction of radiation exposure, resulting in a total effective dose of less than 1 mSv.[23] However, these protocols also require a stable and low heart rate (according to currently published data, <60 beats per minute) to achieve reliable triggering and to complete the entire data acquisition during the diastole of one cardiac cycle

Influence of â-Blocker Treatment on Ventricular Function Analysis

When coronary CT angiograms are acquired with retrospective gating, images throughout the cardiac cycle are available to the physician. These allow three-dimensional evaluation of systolic and diastolic left ventricular volume, left ventricular ejection fraction, left ventricular mass, and left atrial volume without additional radiation exposure or contrast agent administration.[24] However, in the context of high-dose β-blocker administration, findings from functional analysis could be altered, given its negative chronotropic and inotropic effect. Left ventricular end-systolic and end-diastolic volumes, ejection fraction, mass, stroke volume, and cardiac output from dual-source CT examinations were recently compared with and without β-blockers and cardiac magnetic resonance (MR) examinations. While left ventricular volumes and function analysis was not different in subjects without β-blockade during dual-source CT compared with MR imaging, the group receiving â-blockers (intravenous metoprolol, 5–30 mg) had significantly lower ejection fraction, stroke volume, and cardiac output with significantly increased end-systolic volume. Only end-diastolic volume and myocardial mass were not affected. Likewise, significantly lower stroke volume and ejection fraction at 16-section multidetector CT were found in comparison with those at MR imaging, when all subjects received β-blockers prior to CT and consecutively had lower heart rates. This finding is in good agreement with prior animal and patient studies that demonstrated the significant reduction of ejection fraction, stroke volume, and cardiac output with β-blocker treatment. Moreover, atenolol alters the relaxation process of the myocardium.[25] Taken together, these findings indicate that β-blocker application prior to coronary CT angiography may theoretically diminish the diagnostic value of left ventricular function analysis. However, all currently available reports are limited by the low number of subjects. Further studies are needed to evaluate the role of short-term high-dose β-adrenergic antagonist administration on global and regional ventricular function. Additionally, research is needed to assess whether β-blockers also effect left atrial volumes . If functional analysis is of special interest in addition to coronary CT angiography, ivabradine may be a useful alternative to β-blockers since it does not impair myocardial contractility.

Safety

When â-adrenergic blockers are administered as short-term high-dose medication prior to coronary CT angiography, safety is of concern, and screening for potential side effects can be mandatory even in the post procedural phase. For prevention of side effects, contraindications must be considered. In addition, â-blockers may trigger or aggravate symptoms of some medical conditions such as aortic stenosis, carotid stenosis, or pulmonary embolism. The latter is of particular relevance for triple-rule-out protocols. β-Blockers may further impair hemodynamic in severe pulmonary embolism, while being among first-line options in aortic dissection and acute coronary syndrome. The use of â-blockers has been reported for triple-rule-out protocols but should be considered individually, especially in the acute setting.[26] While indications for long-term â-blocker therapy in patients undergoing antidiabetic therapy need to be evaluated individually, there is no relevant contraindication for the short-term use of β-blockers in patients with diabetes. In summary, the use of â-blockers requires in-depth knowledge of contraindications, adverse effects, and interactions with other drugs, which have been well described in a recent review.

Overall, if contraindications are ruled out, side effects attributable to pharmacologic treatment are rare.

No adverse event could be attributed to â-blockers in subjects that received oral or intravenous β-blockers like metoprolol prior to multidetector CT examinations. The prolonged side effects of esmolol are avoided due to its short half-life. Following oral administration of β-blockers, post-CT monitoring is usually not required; following intravenous administration, surveillance of heart rate and blood pressure should be available and its use considered individually. If the patient develops symptoms due to bradycardia, a rapid intravenous injection of 0.5–1 mg of atropine is usually effective and can be repeated up to a maximum dose of about 3 mg. If the patient is symptomatic from hypotension, 10–20 mL of intravenous fluids per kilogram of body weight should be administered as a bolus dose. Clinically, side effects due to β-blocker application need to be distinguished from allergic reaction to iodinated contrast media.[27] The latter can present with mild symptoms such as skin rash, itching, nasal discharge, or nausea, but also can cause facial or laryngeal edema, bronchospasm, dyspnea, or heart rate irregularities that can lead to life-threatening conditions. Mild cases can be treated with oral or intravenous antihistamines, if necessary. In severe cases, securing the airway or administering intravenous epinephrine may become necessary.[27]

Frequently, combinations of different β-adrenergic blockers are used to achieve low heart rates. However, as there are only limited data on safety, the use of protocols combining different β-blockers should be considered individually.

Ivabradine

Ivabradine is a pure heart rate–lowering agent that acts by inhibiting I_f, an important ionic current involved in the pacemaker activity in cells of the SA node, with no effect on the duration or morphology of the action potential.[28] Ivabradine reduces the slope of spontaneous diastolic depolarization in these cells and lowers heart rate at rest and during exercise.[27] At therapeutic concentrations, ivabradine does not depress myocardial contractility or intracardiac conduction and has only minor effects on blood pressure.[27] Ivabradine shows"use dependence," that is, a more pronounced effect at higher heart rates. It is available at 5.0 or 7.5 mg per os and is given twice daily. Plasma levels peak after 1–2 hours with a bioavailability of 40%. At heart rates of more than 85 beats per minute, heart rate reduction is about 20 beats per minute, but reduction is only about five beats per minute at heart rates lower than 65 beats per minute.[29] Accordingly, symptomatic bradycardia is very rare, and the drug can also safely be used in the presence of concomitant â-blocker use.[27] Ivabradine therefore is a potential alternative or adjunct to β-blockade for heart rate reduction during cardiac CT scanning. Initial experience suggests that more than one dose may be required to sufficiently reduce heart rates. However, to date, little is known about safe and effective dosing intervals. Additionally, contraindications for the use of ivabradine also have to be considered, including acute myocardial infarction and unstable angina, heart failure (NYHA II-IV), severe hypotension, sick sinus syndrome or sinoatrial block, atrioventricular block of third degree, and severe hepatic insufficiency. Furthermore, ivabradine is currently not available for intravenous administration and, to date; information is lacking regarding which time intervals of application of ivabradine prior to the scan are necessary to most effectively reduce heart rate. Studies are ongoing to assess the effectiveness of ivabradine for short-term heart rate reduction prior to coronary CT angiography.

Take Home Massage

1. β-Adrenergic receptor blockade is the first-line treatment to reduce heart rate in subjects undergoing coronary CT angiography. In the absence of contraindications, short-term high-dose β-blocker administration is safe. It leads to effective heart rate reduction in the majority of patients.
2. Metoprolol and then atenolol are the most frequently used β-blockers. Oral and intravenous routes of administration are both first-line options. In case of oral administration, non–sustained release forms of â-blockers should be used. Oral application is easier and less invasive than intravenous administration but may not always sufficiently reduce heart rates. If target heart rates are not achieved, additional single or repetitive individually determined intravenous doses of â-blockers should be considered.
3. By virtue of their heart rate-lowering effect, â-blockers result in an improved image quality and diagnostic accuracy at coronary CT angiography.
4. Some scanning techniques and protocols, including dual-source CT, multisegment reconstruction, and increased rotation speed, may not necessarily require fixed target heart rates for optimal image quality. Yet, heart rate reduction allows for prospective triggering, tube current modulation, or single volume data acquisition, which significantly reduces radiation exposure.

References:

1. Miller JM, Rochitte CE, Dewey M, et al. Diagnostic performance of coronary angiography by 64-row CT. *N Engl J Med* 2008;359(22):2324–2336.
2. 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(3):190–204.
3. Shapiro MD, Pena AJ, Nichols JH, et al. Efficacy of pre-scan beta-blockade and impact of heart rate on image quality in patients undergoing coronary multidetector computed tomography angiography. *Eur J Radiol* 2008;66(1):37–41.
4. Mimran A, Ducailar G. Systemic and regional haemodynamic profile of diuretics and alpha- and beta-blockers. A review comparing acute and chronic effects. *Drugs* 1988;35(suppl 6):60–69.
5. Hoffman BB. Catecholamines, sympathomimetic drugs, and adrenergic receptor antagonists. *In:* Hardman JG, Limbird LE, Goodman L, Gilman A, *eds. Goodman*

Gilman's the pharmacological basis of therapeutics. New York, NY: McGraw-Hill, 2001.

6. Epstein M, Oster JR. Beta-blockers and the kidney. *Miner Electrolyte Metab* 1982;8(5):237–254.
7. Benfield P, Clissold SP, Brogden RN. Metoprolol: an updated review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy, in hypertension, ischaemic heart disease and related cardiovascular disorders. *Drugs* 1986;31(5):376–429.
8. Pannu HK, Sullivan C, Lai S, Fishman EK. Evaluation of the effectiveness of oral beta-blockade in patients for coronary computed tomographic angiography. *J Comput Assist Tomogr* 2008;32(2):247–251.
9. 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(10):867–875.
10. Raff GL, Gallagher MJ, O'Neill WW, Goldstein JA. Diagnostic accuracy of noninvasive coronary angiography using 64-slice spiral computed tomography. *J Am Coll Cardiol* 2005;46(3):552–557.
11. Chun EJ, Lee W, Choi YH, et al. Effects of nitroglycerin on the diagnostic accuracy of electrocardiogram-gated coronary computed tomography angiography. *J Comput Assist Tomogr* 2008;32(1):86–92.
12. Schroeder S, Kopp AF, Kuettner A, et al. Influence of heart rate on vessel visibility in noninvasive coronary angiography using new multislice computed tomography: experience in 94 patients. *Clin Imaging* 2002;26(2):106–111.
13. Budoff MJ, Achenbach S, Blumenthal RS, et al. Assessment of coronary artery disease by cardiac computed tomography: a scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention, Council on Cardiovascular Radiology and Intervention, and Committee on Cardiac Imaging, Council on Clinical Cardiology. *Circulation* 2006;114(16):1761–1791.
14. Jacobs JE, Boxt LM, Desjardins B, et al. ACR practice guideline for the performance and interpretation of cardiac computed tomography (CT). *J Am Coll Radiol* 2006;3(9):677–685.
15. Scheffel H, Alkadhi H, Plass A, et al. Accuracy of dual-source CT coronary angiography: first experience in a high pre-test probability population without heart rate control. *Eur Radiol* 2006;16(12):2739–2747.
16. Leber AW, Johnson T, Becker A, et al. Diagnostic accuracy of dual-source multi-slice CT coronary angiography in patients with an intermediate pretest likelihood for coronary artery disease. *Eur Heart J* 2007;28(19):2354–2360.
17. Oncel D, Oncel G, Tastan A. Effectiveness of dual-source CT coronary angiography for the evaluation of coronary artery disease in patients with atrial fibrillation: initial experience. *Radiology* 2007;245(3):703–711.
18. Leschka S, Wildermuth S, Boehm T, et al. Noninvasive coronary angiography with 64-section CT: effect of average heart rate and heart rate variability on image quality. *Radiology* 2006;241(2):378–385.
19. Hausleiter J, Meyer T, Hermann F, et al. Estimated radiation dose associated with cardiac CT angiography. *JAMA* 2009;301(5):500–507.
20. Weustink AC, Neefjes LA, Kyrzopoulos S, et al. Impact of heart rate frequency and variability on radiation exposure, image quality, and diagnostic performance in dual-source spiral CT coronary angiography. *Radiology* 2009;253(3):672–680.
21. Steigner ML, Otero HJ, Cai T, et al. Narrowing the phase window width in prospectively ECG-gated single heart beat 320-detector row coronary CT angiography. *Int J Cardiovasc Imaging* 2009;25(1):85–90.
22. Blobel J, Baartman H, Rogalla P, Mews J, Lembcke A. Spatial and temporal resolution with 16-slice computed tomography for cardiac imaging [in German]. *Rofo* 2003;175(9):1264–1271.
23. Lell M, Hinkmann F, Anders K, et al. High-pitch electrocardiogram-triggered computed tomography of the chest: initial results. *Invest Radiol* 2009;44(11):728–733.
24. Schlosser T, Pagonidis K, Herborn CU, et al. Assessment of left ventricular parameters using 16-MDCT and new software for endocardial and epicardial border delineation. *Am J Roentgenol* 2005;184(3):765–773.
25. Colin P, Ghaleb B, Hittinger L, et al. Differential effects of heart rate reduction and beta-blockade on left ventricular relaxation during exercise. *Am J Physiol* 2002;282(2):H672–H679.
26. Bastarrika G, Thilo C, Headden GF, Zwerner PL, Costello P, Schoepf UJ. Cardiac CT in the assessment of acute chest pain in the emergency department. *Am J Roentgenol* 2009;193(2):397–409.
27. Singh J, Daftary A. Iodinated contrast media and their adverse reactions. *J Nucl Med Technol* 2008;36(2):69–74; quiz 76–77.
28. DiFrancesco D. Funny channels in the control of cardiac rhythm and mode of action of selective blockers. *Pharmacol Res* 2006;53(5):399–406.
29. Tardif JC, Ponikowski P, Kahan T; ASSOCIATE Study Investigators. Efficacy of the I(f) current inhibitor ivabradine in patients with chronic stable angina receiving beta-blocker therapy: a 4-month, randomized, placebo-controlled trial. *Eur Heart J* 2009;30(5):540–548.
30. Savelieva I, Borer J, Camm A. Low incidence of severe bradycardia during therapy with ivabradine: the heart rate lowering effect is limited by baseline heart rate [abstr]. *Eur Heart J* 2007;28(suppl):219.