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Effect of Sublingual Nitro-Glycerine Premedication On Image Analysis of Using 256 Multidetector Computed Tomography Coronary Angiography

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Abstract

Background: Multidetector Computed Coronary Tomography (MDCT) has limited spatial and temporal resolutions. Systematic pre-medication with nitrates may improve coronary MDCT analysis.

Objective: The aim of this study was to evaluate the effect of systematic use of nitroglycerin prior to acquisition using the 256 MDCT on safety, hemodynamics and Image quality.

Method: We prospectively enrolled 72 consecutive patients with probable coronary artery disease who underwent image acquisition using 256 MDCT. Patients were randomized into 2 groups according to sealed envelopes determination; One group (36 patients) received 2 doses of 30 mg of sublingual nitroglycerin prior to acquisition (TNT group) while the other group (36 patients) did not receive the pre-acquisition nitrates (non-TNT group). Hemodynamic parameters were measured in both groups (before and after TNT in the TNT group). Global imaging quality assessment, number of analyzable segments, geometric measurements and contrast attenuation of each segment were performed and compared between the 2 groups.

Results: There was no demographic or clinical difference between the two groups. The use of beta-blockers was similar in both groups. There was a significant decrease of blood pressure without changes in the heart rate in the TNT group compared to the non-TNT group ($p<0.002$). Global imaging quality assessment was equal in both groups. A better signal-to-noise ratio (SNR) and contrast -to-noise ratio (CNR) were observed in the TNT group for distal and secondary segments. The number of non analyzable segments was higher in non-TNT group (15 segments, corresponding to 3 % vs. 4 segments, corresponding to 1%, $p<0.05$). Per segment mean diameter and area was greater in TNT group for the main coronary arteries and their secondary segments.

Conclusion: Sublingual nitroglycerin significantly improves coronary arteries geometry analysis, especially in secondary segments, without any adverse hemodynamic side effect, which might improve the coronary CT diagnostic accuracy.

Keywords: Coronary scanner; 256 slices; Sublingual TNT; Image quality; SNR CNR

Introduction

Coronary MDCT has become a valuable diagnostic tool for ruling out significant CAD in patients with stable and unstable angina syndromes especially in patients with low to moderate likelihood of cardio-vascular diseases (CAD) [1,2]. However, despite the improvements of both spatial and temporal resolutions, and the use of prospective acquisition, the visualization of distal segments and or the secondary branches is still a technical challenge. This mainly stems from limitation in spatial resolution resulting in poor image quality in small vessels [3,4]. The difficulty in analyzing these coronary segments affects the diagnostic accuracy of this tool and hence its clinical usefulness [5]. Thus, exploring the factors which may increase the vessel caliber without affecting image quality is worthwhile and has the potential to improve diagnostic accuracy of MDCT [6,7].

Sublingual nitroglycerine (TNT) produces a significant and fast epicardial coronary arteries vasodilatation [1,8,10], and could improve the visualization of coronary arteries secondary branches. However this effect could be negatively counterbalanced by the hemodynamic effects of TNT (increase in heart rate and decrease in blood pressure), which has the potential to influence image quality and the diagnostic accuracy of the test [12-14]. Therefore, we sought to conducted this study to evaluate the feasibility, safety and the effect on image analysis of systematic use of sublingual nitroglycerine before the acquisition of a coronary CT angiography specifically focusing on secondary coronary segments.

Methods

We prospectively enrolled 72 consecutive patients referred to Antony private hospital, Antony, France for MDCT for a possible coronary artery disease between March 1st 2010 and April 30th 2010. Inclusion criteria included age >18 years old, both males and females with a possible coronary artery disease based on evidence of Ischemia in clinical history or non-invasive tests. Exclusion criteria included, Patients presented with acute myocardial infarction, history of Coronary Artery Bypass Graft (CABG), history of coronary stents, patients with hypertrophic cardiomyopathy, patients with hemodynamic instability, sever aortic valve stenosis, history of TNT or contrast allergy. Patients were randomized ½ into 2 groups, the first group (TNT group) received sub-lingual TNT prior to the acquisition and the second group (non-

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TNT group) did not receive pre-medication with TNT according to sealed envelopes randomization. The same CT machine (Brilliance 256 iCT, Philips Healthcare, Cleveland, Ohio, USA) was used and the same acquisition protocol has been applied for all patients. In the TNT group, all patients received 0.30 mg of sublingual nitroglycerin (Natispray®Teofarma) before starting the acquisition. As a part of the acquisition protocol, intra-venous beta-blockers were routinely administered for all patients of both groups if the heart rate exceeds 65 beats/minute. In the TNT group Heart rate (HR) and mean arterial pressure (MAP) were measured after the sublingual TNT and 3 minutes later. The study was approved from the hospital research committee and all patients gave consent to participate in the study.

Acquisition protocol

All acquisitions were performed using a 256-multi detectors scanner (Brilliance iCT, Philips Healthcare, Cleveland, Ohio, USA, with 270 milliseconds rotation time, cover detector 80 mm (128×0.625 mm)). Charges in the borders of the tube were between 400 and 600 mAs, and voltage across the tube was 120 Kv. Biphasic contrast injection was used as follows: a bolus of 1 ml/kg of iodinated contrast (Omnipaque 350, GE healthcare, France) at 5.5 mL/ second followed by a 50-75 ml of physiological saline was injected into the ante brachial vein via a 16 gauge catheter using a double body injector (DStellant, Medrad Europe, the Netherlands). A base line scanning started by defining a region of interest (ROI) in the descending thoracic aorta, and image acquisition was automatically started when the signal attenuation reached a threshold of 110 Hounsfield units (HU). The scan was performed in the cranio-caudal direction.

Images analysis

All the examinations were analyzed by two independent experts (MH and PD). The Coronary artery tree was divided into 17 segments according the ACC/AHA coronary segmentation classification [15]. The number of both analyzable and non-analyzable segments was determined for each coronary artery and its corresponding secondary branches.

Quantitative measurements

For each coronary segment mean coronary diameter and luminal areas were calculated from three points (proximal, meddle and distal), using a specialized software (Comprehensive Cardiac Analysis version 2.1, Philips, Amsterdam, The Netherland). Coronary stenosis defined as >50% narrowing in luminal diameter compared to the reference segment.

Attenuation measurements

To determine the homogeneity of the contrast material the mean attenuation of contrast medium was measured in the left ventricular cavity and myocardium [16] by a fixed circular region of interest (ROI) defined as 20 mm² for the left ventricle cavity placed at the apex in the four chambers view) and compared between patients and protocols.

For each coronary segment, attenuation of the contrast medium was measured by first calibrating a circular ROI in the middle segment. This standardized ROI was created to be as large as possible while still avoiding calcifications, plaques and stenosis [17-19]. Image noise was defined as the standard deviation within the ROI. The Signal- to- noise ratio (SNR) was defined as the ratio of attenuation in Hounsfield units (HU) in the coronary lumen to image noise. Contrast-to-noise ratio (CNR) was calculated by dividing the difference between the intra-vascular density and the perivascular density by the image noise.

Visual quality evaluation

The global Image quality was assessed by consensus of two independent operators (M Hakim, P Dupouy) and classified into 3 classes: good, average and non-interpretable.

Statistical study

Continuous variable were presented as the mean value ± SD and compared using paired or unpaired Student *t*-test as appropriate. Categorical variables were presented as numbers and percentage and compared with Chi-square or Fischer's exact test. A *P*-value<0.05 was considered statistically significant. Statistical analysis was performed with SPSS version 19 (SPSS, Chicago, Illinois).

Results

The base-line demographic and clinical characteristics of both groups are shown in Table 1. The mean dose of beta-blocker was 5.4 ± 0.6 mg in TNT group and 2.4 ± 0.6 mg in the non-TNT group, p=0.0005. The mean heart rate during acquisition was similar in both groups (61.2 ± 1.5 bpm vs. 61.9 ± 1.5 bpm in TNT and non-TNT group respectively, p=0.8). Sublingual TNT did not produce clinical side effects despite a mild decrease in the mean systemic blood pressure from 101 ± 8.2 mmHg to 95 ± 7.1 mmHg (p=0.002) and did not changed Heart rate (69.5 ± 0.4 bpm to 70.9 ± 0.4 bpm, NS). Prospective acquisition was used and images were reconstructed mainly at 75% phase of the cardiac cycle for both groups.

The overall image quality evaluation was comparable in both groups; 94.4% of images in the TNT group and. 91.7% in the non-TNT group (p=0.6) were judged of good quality.

Five subjects in the TNT group (13.8%) presented with coronary stenosis >50% in the TNT group versus 3 subjects (8.3%) in the non-TNT group (p=0.7)

A total of 536 and 531 segments were analyzed in the TNT and non-TNT groups respectively. The number of non-analyzable segments was higher in the non-TNT group compared with TNT group (4 segments vs. 15 segments, p=0.012). As regard the secondary segments 4 out of 199 of them were missed in TNT group versus 13 out of 180 in non-TNT group (p=0.019) (Tables 1 and 2).

Coronary segments evaluation

Table 3 shows measurements of the mean diameters and surface area of the main coronary arteries. Per segment average diameter and surface area were greater in TNT group than in non-TNT group 3.2 ± 0.1 mm vs. 2.8 ± 0.1 mm, p<0.0001 and 8.6 ± 0.3 mm² vs. 6.2 ± 0.3 mm²,

	TNT Group (n=36)	Non-TNT group (n=36)	p value
Age (y)	57 ± 2.2	57.9 ± 2.2	0.8
Men n(%)	11 (30.6)	15 (41.7)	0.5
BMI Kg/m²	27 ± 0.7	26 ± 0.7	0.3
Diabetes n (%)	2 (5.6)	3 (8.3)	1
Active smokers n (%)	9 (25)	6 (16.7)	0.6
Dyslipidemia n (%)	11 (30.6)	9 (25)	0.8
Hypertension n (%)	13 (36.1)	7 (19.4)	0.9
Oral beta blockers pre-treatment n (%)	8 (22.2)	5 (13.9)	0.54
DLP (mGy.cm)	431.8 ± 61	360.5 ± 65.7	0.43

Data are presented as mean ± SD, or numbers and percentage, BMI= body mass index, DLP=dose length product

Table 1: Patients demographic and clinical data.

	TNT Group (n=36)	Non-TNT (n=36)	Δ (%)	p
LM Diameter (mm)	4.6 ± 0.1	4.1 ± 0.1	+ 12.2%	<0.0001
LM Area (mm²)	16.8 ± 0.7	13.3 ± 0.7	+ 26.3%	0.0003
Proximal LAD diameter (mm)	4 ± 1.1	3.3 ± 0.5	+ 21.2%	<0.0009
Proximal LAD area (mm²)	11.4 ± 3,8	8.5 ± 2.9	+ 34.1%	0.0005
Mid LAD Diameter (mm)	3.3 ± 0.8	2.7 ± 0.8	+ 22.2%	<0.0001
Mid LAD Area (mm²)	8.3 ± 0.4	6 ± 0.4	+ 38.3%	<0.0001
Distal LAD diameter (mm)	1.8 ± 0.04	1.5 ± 0.04	+ 20%	<0.0001
Distal LAD Area (mm²)	3.1 ± 0.2	2.6 ± 0.2	+ 15.4%	0.0003
LCx Diameter (mm)	3.4 ± 0.9	3 ± 0.1	+ 13.3%	<0.0001
LCx Area (mm²)	9.3 ± 0,4	7 ± 0,4	+ 32.9%	0.0002
Proximal RCA Diameter (mm)	3.9 ± 0,1	3.4 ± 0,1	+ 14.7%	0.0007
Proximal RCA Area (mm²)	12,3 ± 0,6	8.9 ± 0,6	+ 38.2%	0.0003
Mean RCA Diameter (mm)	3.4 ± 0.1	2.9 ± 0.01	+ 17.2%	0.0015
Mean RCA Area (mm²)	9.5 ± 0.6	6.6 ± 0.6	+ 43.9%	0.0003
Distal RCA Diameter (mm)	2.9 ± 0.1	2.4 ± 0.1	+ 20.8%	0.0011
Distal RCA Area (mm²)	7 ± 0.5	4.9 ± 0.5	+ 42.9%	0.0019

Data are presented, as mean ± SD. LAD=left anterior descending, LCx=left circumflex, RCA=right coronary artery, Mg=marginal branch

Table 2: Computed tomography measurements of the main coronary arteries segments with and without TNT.

	TNT group (n=36)	Non-TNT group (n=36)	Δ (%)	P
Diagonal diameter (mm)	2.1 ± 0.1	1.7 ± 0.1	+ 23.5%	<0.0001
Diagonal Area(mm²)	4 ± 0.2	2.6 ± 0.2	+ 53.8%	<0.0001
Mg diameter (mm)	2.3 ± 0.1	1.9 ± 0.1	+ 21.1%	0.0010
Mg Area (mm²)	4.3 ± 0.3	3 ± 0.3	+ 43.3%	0.0031
PDA Diameter (mm)	2.1 ± 0.1	1.7 ± 0.1	+ 23.5%	<0.0001
PDA area (mm²)	3.8 ± 0.4	2.8 ± 0.4	+ 35.7%	0.05
PLA diameter (mm)	2.1 ±0.1	1.8 ± 0.1	+ 16.7%	0.0251
PLA Area (mm²)	3.8 ± 0.2	2.8 ± 0.2	+ 35.7%	0.0088

Data are presented, as mean ± SD. Mg=marginal branch, PDA=posterior descending artery, PLA=posterior lateral artery

Table 3: Computed tomography measurements of the secondary coronary arteries with and without TNT.

$p<0.05$ respectively. This remains true for segments of the secondary branches; mean diameters and surface areas were (2.2 ± 0.04 mm vs. 1.8 ± 0.04 mm, $p<0.0001$; 3.9 ± 0.2 mm² vs. 3.1 ± 0.2 mm², $p=0.001$) for both groups respectively (Table 3).

Attenuation measurement

SNR for the left ventricular Images was similar in the two groups (12.1 ± 5.9 vs. 10.5 ± 4; $p=0.19$). There was a non-significant difference between the two groups regarding the CNR (9.2 ± 5 vs. 8 ± 3.2; $p=0.27$).

A better SNR and CNR were observed in the TNT group. This difference was statistically significant for the distal LAD segments, proximal, distal and Lateral segments, as well as for the diagonal and posterior descending artery segments (Tables 4 and 5).

By analyzing all the segments, a trend to linear decrease of the SNR and CNR was observed from proximal to distal coronary segments, which reached statistical significance when focusing on right coronary artery ($p=0.003$)

Discussion

To the best of our knowledge the benefits of sublingual TNT has been previously described for 16 and 64 slices scanners [6,7,20], but remains inconsistently administered during cardiac MDCT acquisition. The main findings of this study can be summarized as

	TNT group (n=36)	Non-TNT group (n=36)	*p*
Signal to noise ratio			
LM SNR	12.6 ± 5.9	12.1 ± 6.6	0.781
LAD1 SNR	10.7 ± 6.7	8.9 ± 9.1	0.351
LAD 2 SNR	9.0 ± 7.1	6.5 ± 5.2	0.102
LAD 3 SNR	8.7 ± 5.8	6.2 ± 3.7	0.041
LCx 1 SNR	17.9 ± 11.2	10.8 ± 5.2	0.001
LCx 2 SNR	15.7 ± 13.2	9.1 ± 4.4	0.009
RCA 1SNR	20.3 ± 15.3	14.6 ± 11.9	0.092
RCA 2 SNR	14.4 ± 13.5	9.3 ± 7	0.055
RCA 3 SNR	14.5 ± 6.9	11.9 ± 7.5	0.147
Contrast to noise ration			
LM	14,1 ± 6,5	13.7 ± 7.3	0.813
LAD1	12.1 ± 7.4	10 ± 9.9	0.334
LAD 2	10.4 ± 7.9	7.6 ± 6.2	0,123
LAD 3	10.4 ± 7.9	7.6 ± 6.2	0.083
LCx 1	20.1 ± 12.5	12.3 ± 6	0.002
LCx 2	17.7 ± 14.5	10.7 ± 5.2	0.012
RCA 1	22.6 ± 16.6	16.5 ± 12.4	0.088
RCA 2	16.2 ± 14.9	10.6 ± 7.9	0.061
RCA 3	16.4 ± 7.6	13.8 ± 8.8	0.208
LM	14.1 ± 6,5	13.7 ± 7.3	0.813

Data are presented as mean ± SD. LV is left Ventricle, LM is left Main Artery, LAD is Left Anterior Descending Artery, LCx is left Circumflex, RCA is Right Coronary Artery

Table 4: SNR and CNR for main coronary segments.

	TNT group	Control group	*p*
Diagonal SNR	8.2 ± 5.6	5.4 ± 3	0.014
Diagonal CNR	9.4 ± 6.3	6.4 ± 3.4	0.017
Mg SNR	10.1 ± 6.4	8.4 ± 5.8	0.248
Mg CNR	11.6 ± 7.2	9.9 ± 6.7	0.321
PDA SNR	9 ± 4.8	6.3 ± 3.6	0.015
PDA CNR	10.4 ± 5.4	7.7 ± 4.2	0.024
PLA SNR	9.5 ± 6.2	9.4 ± 6.5	0.914
PLA CNR	11.2 ± 7	11.5 ± 7.7	0.871

Data are presented as mean±SD. Mg is Marginal Branch, PDA is Posterior Descending Artery, PLA is Posterior Lateral Artery

Table 5: SNR and CNR of secondary coronary segments.

follow; 1- systematic use of sub-lingual TNT before acquisition is well tolerated, does not compromise the image quality and substantially improve the geometry of the epicardial coronary arteries allowing with greater ease the evaluation of the main arteries and the secondary segments (Figure 1). 2-Our study emphasizes the fact that sublingual TNT should be systematically used with respect of contra-indications even with the use of a last generation machines.

The increase in the number of detectors does not really affect spatial resolution of the scanners, which remains between 0.5 and 0.8 mm depending on the machine. Variability in such technical characteristics hampered the study of vessels less than 2 mm in diameter. So far; the coronary segmentation in imaging scanner has been formally limited to vessels more than 2 mm in diameter [4,20,21], while the secondary branches less than 2 mm have always been under-evaluated with less favorable diagnostic accuracy when compared to angiography [4,12].

It is worth to know that the diagnostic accuracy of coronary CT angiography is less accurate compared with other diagnostic tools when it is used for evaluation of these secondary segments [4,5]. A number of studies showed the low diagnostic accuracy of CT scan in evaluating

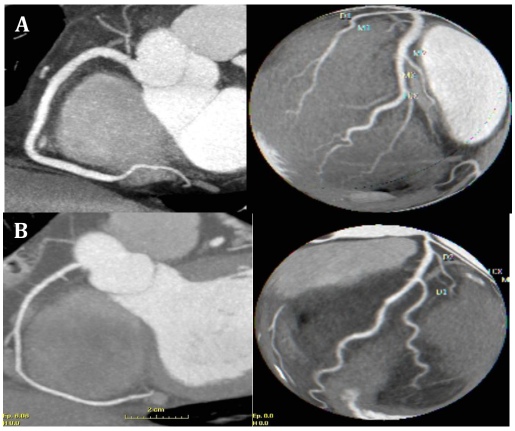

Figure 1: Direct comparison of coronary scanner coronary imaging with (A) and without (B) previous TNT used. Note the important size difference for RCA and proximal LAD.

the secondary segments compared with those evaluating only the main epicardial vessels. In a study using a 320 detectors machine, Nasis et al. [22] described a decreased image quality as segments progress from the proximal to distal part of the coronary arteries corresponding to poorer signal to noise ratio. In this study, two secondary branch lesions failed to be diagnosed because of their small diameters and poor image quality. On the same line, in another study by Chao et al. [23] found a decrease in the sensitivity and positive predictive value of the analysis of main segments compared to secondary segments analysis using a 256 detectors machine, taking into account that in this study they did not use systematic pre acquisition TNT.

Thus, TNT use has the potential to increase the accuracy of lesion detection by increasing the size of secondary and distal segments as described by Chun et al. on a 16 detectors machine [20]. Pre- treatment with TNT as discussed by Decramer et al. [6] has shown an improvement in the qualitative analysis of the septal and sino-atrial branches visibility however, it was of limited clinical relevance. More interestingly Chi-Ming Lee et al. concluded that sublingual TNT increased the number of visible secondary branches on a 64 slices scanner without affecting the image quality [2].

In the present study the vasodilatation effect of TNT seems to be equal or greater for secondary segments than for the main coronary epicardic arteries. Taking into consideration that the acquisition protocol was the same for all patients, this geometric impact might contribute to the observed increase of segmental SNR and CNR. This could result in an improvement of the number of analyzable segments and by consequence the diagnostic performances of the coronary scanner.

Notably, another point of interest is the hemodynamic impact of TNT, which can influence quality of the acquisition. As previously mentioned TNT induced slight hemodynamic modifications which did not influence neither the patient tolerance nor the imaging quality refuting argument which limit he systematic use of TNT before coronary CT acquisition. On the other hand, the pre-medication with TNT did mildly lower the mean BP while it did not increase the heart rate mainly due to its use in conjunction with beta blockers. Furthermore, the use of beta-blockers has resulted in a comparable acquisition heart rate in both groups, despite a higher beta-blockers dose in the TNT group. Meanwhile, Low heart rate (<65 bpm) facilitate prospective acquisition and guaranteed good image quality in both groups. In comparison to the present study, Chun et al. [20] described a TNT induced increase in heart rate of 1 ± 2.4 bpm and a BP decrease of 8.3 ± 14 mm Hg. In our study per protocol of acquisition beta-blockers were routinely used by intravenous injection just before the acquisition with no adverse side effect, while in the other studies the protocol of acquisition involved administration or oral beta blockers 1 hour or more before the test.

Study limitations

First, this is a single center with a small sample size comparatively lacking the statistical power. Second, it was not feasible, due to technical and radiological safety measures, to conduct the study by performing the test with and without TNT on the same patient. Therefore the TNT effect was evaluated by comparing two randomized groups of patients with and without pre-medication with TNT. Third, we did not compare the diagnostic accuracy of sublingual TNT prior to MDCT to another imaging modalities such as the angiography. Larger randomized studies with head to head comparison with coronary angiography could provide more accurate results.

Conclusion

This study showed that use of sublingual TNT before image acquisition using 256 MDCT can ameliorate image analysis especially in the secondary and distal coronary artery segments strongly supporting the systematic use of sublingual TNT before coronary scanner acquisition.

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