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Impact of sublingual nitroglycerin dosage on FFR_{CT} assessment and coronary luminal volume–to–myocardial mass ratio

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Abstract

Objectives Fractional flow reserve computed tomography (FFR_{CT}) depends upon nitroglycerin (NTG) inducing maximal hyperemia. However, the impact of NTG dosages on FFR_{CT} analysis including coronary volume–to–mass ratio (V/M) is unknown.

Methods Eighty patients with repeat coronary CT angiograms (CCTAs) with different sublingual spray NTG doses (0.4 mg and 0.8 mg) were retrospectively analyzed with 45 patients excluded. Patient and scan demographics, post-stenosis and nadir FFR_{CT} values, coronary volume, and coronary volume–to–mass ratio (V/M) were compared at initial CCTA (0.4 mg NTG) and follow-up CCTA (0.8 mg NTG). Differences were compared by Wilcoxon signed-rank test.

Results Thirty-five patients were included (time between CCTAs, 3.9 ± 1.6 years). Segment involvement score was 2.4 ± 3.3 and 2.8 ± 3.4 at initial and repeat CCTA (0.4 and 0.8 mg NTG), respectively ($p = 0.004$). There was similar image quality (4.1 ± 0.7 vs 4.1 ± 0.8; $p = 0.51$). Nadir FFR_{CT} values did not differ in the left (0.4 mg, 0.80 ± 0.08 vs 0.8 mg, 0.80 ± 0.03; $p = 0.66$), right (0.4 mg, 0.90 ± 0.04 vs 0.8 mg, 0.90 ± 0.06; $p = 0.25$), or circumflex coronaries (0.4 mg, 0.87 ± 0.06 vs 0.8 mg, 0.88 ± 0.06; $p = 0.34$). Post-stenosis FFR_{CT} values did not differ ($p = 0.65$). Coronary volume increased with 0.8 mg of NTG (2639 ± 753 mm^3 vs 2844.8 ± 827 mm^3; $p = 0.009$) but V/M ratio did not ($p = 0.20$).

Conclusions Use of 0.8 mg versus 0.4 mg of NTG in routine clinical CCTAs significantly increased coronary volume determined from FFR_{CT} analysis but did not alter FFR_{CT} or V/M. Further evaluation of repeat CCTAs in a more contemporaneous fashion using varied nitrate doses and disease severity is needed.

Key Points

- *Fractional flow reserve from computed tomography (FFR_{CT}) is a noninvasive method for evaluating the coronary arteries and relies on nitroglycerin (NTG) to induce coronary vasodilation, but the impact of different NTG dosages is unknown.*
- *Retrospective analysis evaluated use of different NTG doses on FFR_{CT}.*
- *Increased NTG dose increased coronary luminal volume on FFR_{CT} analysis, but did not change FFR_{CT} values.*

Keywords Nitroglycerin · Vasodilation · Coronary artery disease · Computed tomography angiography

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Abbreviations

CAD	Coronary artery disease
CAD-RADS	Coronary Artery Disease - Reporting and Data System
CCTA	Coronary computed tomography angiography
CT	Computed tomography
FFR	Fractional flow reserve
FFR_{CT}	Fractional flow reserve from computed tomography
LAD	Left anterior descending coronary artery
LCA	Left coronary artery system
LCx	Left circumflex coronary artery
NTG	Nitroglycerin

RCA	Right coronary artery
SCCT	Society of Cardiovascular Computed Tomography
SIS	Segment involvement score
SL	Sublingual
V/M	Epicardial coronary luminal volume–to–myocardial mass ratio

Introduction

Evaluation of the coronary arteries for flow-limiting stenosis has evolved with the clinical integration of fractional flow reserve (FFR) derived from computed tomography (FFR_{CT}). FFR_{CT} has been validated against traditional invasive FFR performed during coronary angiography and now serves as a noninvasive alternative [1–5]. FFR_{CT} analysis also allows for the determination of epicardial coronary luminal volume and myocardial mass, which can be expressed as a ratio of coronary volume–to–myocardial mass (V/M). V/M is proposed to be a quantitative metric of imbalance between coronary blood supply and myocardial demand [6–8]. FFR_{CT} and V/M analyses are both dependent upon the quality of the coronary CT angiography (CCTA) acquisition.

Sublingual (SL) nitroglycerin (NTG; $C_3H_4(NO_3)_3$) administration is recommended prior to CCTA acquisition according to recently published best practice guidelines; however, they do not specify NTG dose. This leaves the decision between 0.4 mg and 0.8 mg SL NTG to the discretion of the imager [9]. NTG is an organic nitrate that acts as an endothelial-independent vasodilatory agent with many studies proposing vasodilation to occur via the production of nitric oxide. NTG may cause side effects such as hypotension, headache, nausea, allergic response, and reflex tachycardia. NTG is contraindicated in patients including those who are hypotensive, taking soluble guanylate cyclase activators or phosphodiesterase 5 inhibitors, are severely anemic, have aortic stenosis, or preload-dependent cardiac pathologies [10–12].

The physiological impact of NTG is documented to be variable based on factors such as coronary vessel size, atherosclerotic burden, and dose and the importance of NTG for the evaluation of coronaries on CCTA is well established [13–23]. However, how this translates into clinical CCTA results used for FFR_{CT} analysis is unknown. Therefore, the study aimed to retrospectively analyze the impact of using 0.4 versus 0.8 mg of sublingual NTG prior to CCTA acquisition of FFR_{CT} analysis. The primary outcomes were determining if NTG dose changes FFR_{CT} values or coronary volume and V/M derived from FFR_{CT} analysis.

Materials and methods

Study design and patient population

In this retrospective study, 80 patients who underwent clinically indicated CCTA examinations at two separate time points between April 2010 and April 2018 but with different NTG administration protocols (0.4 mg vs 0.8 mg of sublingual NTG spray) at St. Paul's Hospital (Vancouver, Canada) were considered. Patients were excluded if their scans had dissimilar image quality or they had atherosclerotic plaque progression between CCTAs as described below. Patient data was collected from electronic medical records. No patients had an absolute contraindication for NTG administration and there were no documented side effects of NTG administration. Patients had been instructed to stop using phosphodiesterase 5 inhibitors prior to their CCTA, and the study population did not include patients with pulmonary arterial hypertension who may be taking soluble guanylate cyclase stimulators. The research ethics board at the University of British Columbia – Providence Health Care approved the study. This study was completed as a retrospective analysis and was completed under a retrospective waiver of consent by the research ethics board.

CCTA acquisition

All CCTA examinations were performed on CT scanners with ≥ 64 detector rows (GE Revolution, GE Discovery 750, or GE Lightspeed VCT) in accordance with optimal Society of Cardiovascular Computed Tomography (SCCT) acquisition guidelines [9]. Patients had been scanned on either scanner at initial or follow-up scan. Patients received oral and/or intravenous β-adrenergic receptor blocker at the discretion of the supervising imager to achieve a target pre-acquisition heart rate of less than 60 beats per minute. Sublingual NTG spray was administered 4–5 min prior to scan acquisition with patients receiving 0.4 mg in the initial scans and 0.8 mg in the follow-up scans. Scans were completed using either prospective or retrospective gating. A slice thickness of 0.625 mm was used.

CCTA assessment

CCTAs were evaluated by a level-three CT reader blinded to patient, NTG dose, scan order, and previously reported CCTA findings. CCTAs were evaluated in accordance with current guidelines [9, 24]. Image quality score was evaluated using a 5-point Likert scale, and patients with scans differing in image quality by greater than 1 in either direction (better or worse image quality at follow-up CCTA) point were excluded from further analysis. Segment involvement score (SIS) was used to quantify the atherosclerotic burden. SIS was computed as the

total number of the previously defined 16 coronary artery segments with atherosclerotic plaque involvement, regardless of stenosis severity [25, 26]. Patients with an increase in SIS score of greater than 2 at the follow-up CCTA were excluded. Stenosis severity was visually assessed and used to categorized patients according to the Coronary Artery Disease Reporting and Data System (CAD-RADS) [24]. Patients with a change in CAD-RADS score of 1 point or more at follow-up were excluded.

FFR_{CT} and V/M analysis

All included studies were assigned a random unique identifier to ensure blinded coronary segmentation and analysis and were transferred to Heartflow® for FFR_{CT} analysis and V/M quantification.

Briefly, FFR_{CT} analysis involved three-dimensional modeling of the aortic root and epicardial coronaries using semi-automated segmentation following which simulation of blood flow under conditions of maximal hyperemia was completed. From this, FFR_{CT} values were determined as the ratio of mean coronary pressure–to–mean aortic pressure at the specified point of interest. Each patient's FFR_{CT} models were restricted to regions conserved between both models. Nadir FFR_{CT} values were then defined as the lowest values observed in each of the RCA, LAD, and LCx. This was done to address potential discrepancies caused by differences in the size of model extracted from each scan. Nadir FFR_{CT} values were compared across all patients as well as within unaffected vessels (vessels without plaque). For each patient, FFR_{CT} values were also noted distal to the highest grade/greatest percentage stenosis. This value was defined as the FFR_{CT} value 2 cm distal to the site of the stenosis. Owing to having no stenosis, 13 patients with a CAD-RADS score of 0 were excluded from post-stenosis FFR_{CT} analysis. Cumulative 3-vessel FFR_{CT} values were calculated as the sum of nadir values in the LAD, RCA, and LCx.

V/M ratio was calculated from the CCTA dataset and FFR_{CT} analysis as previously described [6–8]; the coronary luminal volume was determined from the 3D model generated during the FFR_{CT} analysis which included branch points that can be determined from the CCTA to ~ 1 mm. The left ventricular myocardial volume was obtained from segmentation of the CCTA dataset, which was multiplied by an estimated average myocardial density value (1.05 g/mL) to calculate myocardial mass. Coronary luminal volume was calculated overall and for the RCA system and the left coronary artery system (LCA) inclusive of the left main, LAD, and LCx.

Statistical analysis

All statistical analyses were completed using IBM SPSS Statistics (IBM SPSS Statistics for Macintosh, Version 21.0). Demographic data are presented as means and standard deviations for continuous variables and as counts and percentages for categorical variables. Differences in demographic data between the initial and follow-up CCTAs were tested by Wilcoxon signed-rank test. Paired differences in FFR_{CT} and V/M ratio datasets were found to be not normally distributed as determined by the Shapiro-Wilk test. To assess for differences in FFR_{CT} between CCTAs using 0.4 mg or 0.8 mg of sublingual NTG, a Wilcoxon signed-rank test was performed for all collected measures, nadir FFR_{CT} in each epicardial coronary system, FFR_{CT} distal to the greatest percentage stenosis in each patient, total coronary volume, myocardial mass, and resultant V/M ratio. A p value less than 0.05 was considered significant. Nadir FFR_{CT} values, myocardial mass, total coronary volume, and V/M agreement were also compared by Bland-Altman plots.

Results

Patient population

In total, 80 patients with serial CCTAs were considered for inclusion in the study. Thirty-six patients were excluded for disparate image quality defined as having a difference of > 1 on the Likert scale or plaque progression consisting of a change in CAD-RADS or change in SIS of > 2. Eight patients were excluded as they had at least 1 CCTA that could not be processed for FFR_{CT} analysis. A single patient was excluded due to diagnosis of severe aortic valvular disease between scans. Therefore, overall, 35 patients were analyzed.

Demographic data for the included patients is outlined in Table 1. Patients had a mean age of 59.9 ± 10.0 years with a mean time to repeat CCTA of 3.9 ± 1.6 years. On CCTA, patients had a mean CAD-RADS score of 1.1 ± 1.0. Patients had a mean SIS of 2.4 ± 3.2 at initial CCTA (0.4 mg NTG) and 2.8 ± 3.4 at repeat CCTA (0.8 mg NTG) ($p = 0.004$), but had similar image quality scores between initial CCTA (4.1 ± 0.7) and repeat CCTA (4.1 ± 0.8) ($p = 0.51$).

FFR_{CT} analysis in all patients

Nadir FFR_{CT} values (the lowest FFR_{CT} values in the system) were compared between initial and repeat CCTAs at 0.4 mg and 0.8 mg NTG, respectively (Fig. 1; Table 2); nadir FFR_{CT} values at initial CCTA and repeat CCTA were not significantly different in the LAD ($p = 0.66$), the LCx ($p = 0.34$), or the RCA ($p = 0.25$). Cumulative nadir 3-vessel FFR_{CT} values did not differ significantly between NTG doses ($p = 0.69$). Bland-Altman plots comparing the differences of the paired measurements with the means of nadir FFR_{CT} in the RCA, LCx, LAD, and for 3-vessel FFR_{CT} are shown in Fig. 2 and confirm no systematic bias.

Table 1 Study population demographics

	$N = 35$		
Age (years)	59.9 (10.0)		
Time to follow-up (years)	3.9 (1.6)		
Male	16 (45.7)		
BMI (kg/m^2)	26.5 (5.2)		
Diabetes	7 (20.0)		
Hypertension	16 (45.7)		
Dyslipidemia	25 (71.4)		
Smoking history	7 (20.0)		
CAD-RADS	1.1 (1.0)		
	Initial CCTA (0.4 mg NTG)	Follow-up CCTA (0.8 mg NTG)	*p* value
SIS*	2.4 (3.2)	2.8 (3.4)	0.004
Image quality score**	4.1 (0.7)	4.1 (0.8)	0.51
Heart rate at scan	55.7 (5.2)	58.9 (7.7)	0.009

**SIS*, segment involvement score = total number of coronary segments with atherosclerotic plaque involvement

***Image quality score = image quality scored on a 5-point Likert scale; 5 = excellent, 4 = good, 3 = fair, 2 = poor, 1 = non-diagnostic

Difference in the initial and follow-up variables was tested by Wilcoxon signed-rank test

Values are expressed as mean (SD) or *n* (%) as appropriate

In patients with atherosclerotic plaque, post-stenosis FFR_{CT} values (2 cm distal to the greatest stenosis) did not differ significantly between initial and repeat CCTAs ($p = 0.65$).

FFR_{CT} in epicardial vessels without plaque

As the effects of an increased dose of NTG at repeat CCTA examination could potentially be counteracted by progression in atherosclerosis, possibly biasing the study towards a false negative result, an additional sub-analysis of nadir FFR_{CT} was performed. This was restricted to epicardial vessels with no evidence of atherosclerosis (SIS = 0) on CCTA. Among the disease-free vessels, nadir FFR_{CT} values at initial CCTA and repeat CCTA were not significantly different in the LAD ($p = 0.54$) or the RCA ($p = 0.24$), but significantly higher in the LCx (0.4 mg, 0.905 ± 0.041 vs 0.8 mg, 0.931 ± 0.030; $p = 0.004$).

Coronary luminal volume, myocardial mass, and V/M

Total coronary luminal volume increased significantly with increasing NTG (Table 3; 0.4 mg, 2639 ± 753 mm^3 vs 0.8 mg, 2844.8 ± 827 mm^3; $p = 0.009$) and mean differences are presented in Fig. 3a. Sub-analysis of the right and left coronary systems (RCA and LCA, respectively) showed that coronary luminal volume increased significantly in the LCA (Table 3; $p = 0.007$), but did not change significantly in the RCA ($p = 0.085$). Myocardial mass did not differ on initial and repeat CCTAs ($p = 0.098$).

V/M ratio values for each condition, 0.4 mg and 0.8 mg NTG, are summarized in Table 3, and mean differences are presented in Fig. 3c. Paired analysis of V/M ratio calculated in patients receiving 0.4 mg of NTG at initial CCTA and 0.8 mg of NTG at repeat CCTA yielded no significant difference (0.4 mg, 26.0 ± 5.6 mm^3/g vs. 0.8 mg, 27.4 ± 5.9 mm^3/g; $p = 0.201$). Bland-Altman analysis of total coronary volume, myocardial mass, and V/M is shown in Fig. 3.

Discussion

Sublingual NTG remains the pharmacological agent of choice for achieving maximal coronary vasodilation prior to CCTA. Such hyperemia is essential to FFR_{CT} analysis including V/M. Our study aimed to evaluate the impact of different NTG doses on FFR_{CT} analysis. This analysis demonstrated increased coronary luminal volume with increased dosage of sublingual NTG. Interestingly, despite the greater coronary volume, the nadir and post-stenosis FFR_{CT} values were unchanged between the two nitrate protocols.

To our knowledge, this is the first study to compare the effects of two accepted NTG doses listed within the SCCT acquisition guidelines [9]. Our findings suggest that within these guidelines, the dose of NTG administered prior to CCTA significantly impacts coronary volume. This is consistent with the literature establishing a dose-dependent effect of NTG on coronary arteries [13] and is additive to the literature regarding the importance of NTG administration prior to CCTA; Takx et al found that seven studies that evaluated coronary artery diameter all observed a significant increase

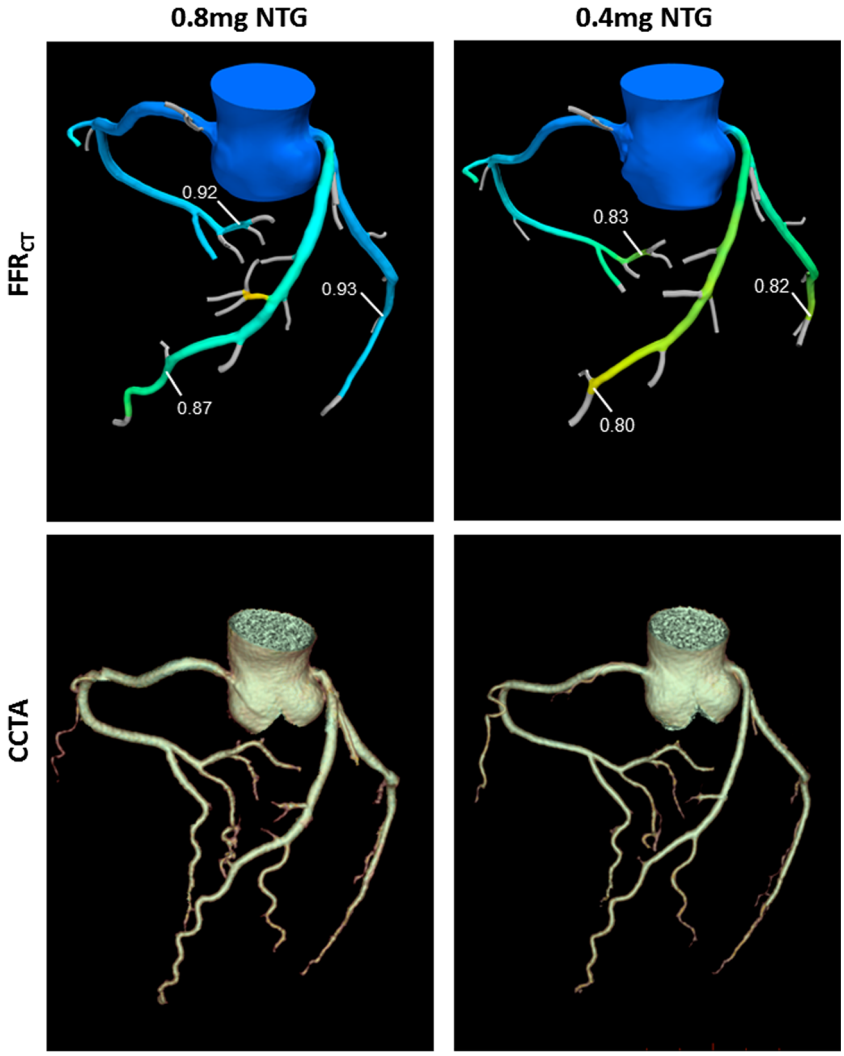

Fig. 1 Representative examples of CCTA and corresponding FFR_{CT} computational model in patients receiving 0.4 mg versus 0.8 mg of sublingual nitroglycerin. Examples of nadir FFR_{CT} values are marked in white

Table 2 Comparison of FFR_{CT} values

	0.4 mg NTG	0.8 mg NTG	*p* value
Nadir/lowest FFR_{CT} values (all patients)			
LAD	0.803 (0.083)	0.799 (0.029)	0.66
LCx	0.873 (0.062)	0.884 (0.060)	0.34
RCA	0.898 (0.042)	0.901 (0.057)	0.25
Cumulative 3-vessel	2.57 (0.123)	2.58 (0.114)	0.69
Post-stenosis FFR_{CT} (patients without plaque/CAD-RADS 0 excluded)			
	0.868 (0.109)	0.871 (0.067)	0.65
Nadir FFR_{CT} in unaffected vessels/vessels without plaque			
LAD	0.844 (0.062)	0.836 (0.073)	0.54
LCx	0.905 (0.041)	0.931 (0.030)	0.004
RCA	0.909 (0.038)	0.916 (0.035)	0.24

Values are expressed as mean (SD) and were compared by Wilcoxon signed-rank test

$N = 35$ for LAD, LCx, RCA, and 3-vessel. $N = 22$ for post-stenosis

In the sub-analysis of the unaffected vessels, $N = 11$ for LAD, $N = 19$ for LCx, and $N = 26$ for RCA

in diameter [16]. Among them, Klass et al demonstrated that the relative vessel diameter increase following administration of NTG is larger in distal vessel segments compared with proximal segments [17]. Meanwhile, Okada et al and Sato et al reported this observation for peripheral segments [18, 19]. Furthermore, sublingual NTG spray significantly dilates the coronary arteries and allows more septal branches to be visualized on coronary CT angiography without diminishing image quality or increasing the number of side effects [20].

Interestingly, this significant impact on coronary vasodilation had no effect on FFR_{CT} nadir or distal to stenosis values outcomes. Whether this simply reflects the modest burden of disease and significant changes would be present in the setting of more significant anatomical disease is not known. Further studies evaluating subjects with higher grade anatomical stenosis, in whom FFR_{CT} is more commonly used, would be important to determine the resultant impact of the more significant coronary vasodilation on FFR_{CT}.

In our study, 0.8 mg NTG was associated with a significant increase in coronary volume when compared with 0.4 mg.

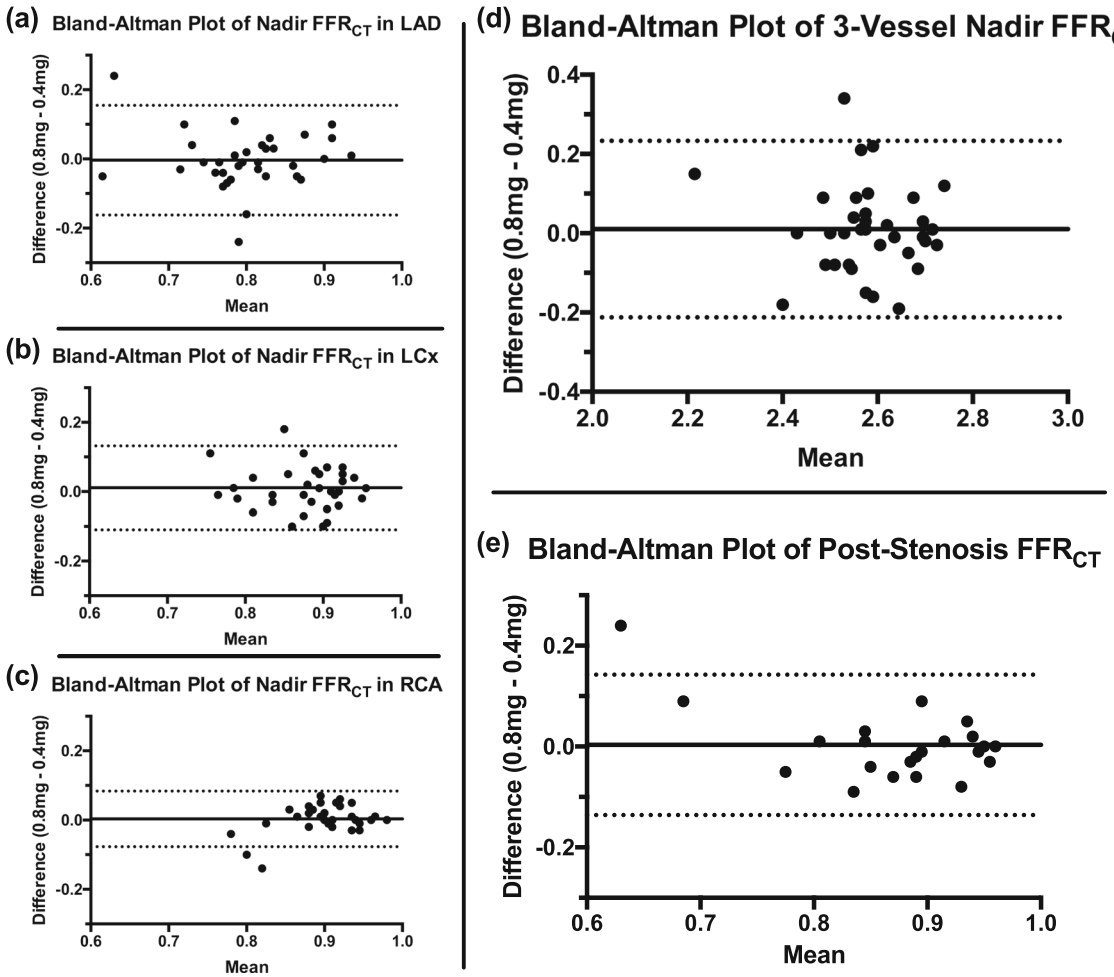

Fig. 2 Bland-Altman analysis of nadir FFR_{CT} values for the (**a**) LAD, (**b**) LCx, (**c**) RCA, (**d**) cumulative 3-vessel, and (**e**) post-stenosis analyses. Dotted lines indicated 95% limits of agreement. FFR_{CT} = fractional flow reserve computed tomography, LAD = left anterior descending artery, LCx = left circumflex artery, RCA = right coronary artery

However, we did not observe a significant increase in the V/M ratio under the same conditions. Possible explanations for this discrepancy are twofold. Firstly, mean myocardial mass modestly increased between scans, which reduced the difference in V/M observed between the groups. Secondly, the use of a Wilcoxon signed-rank test may account for the discrepancy between the coronary volume and V/M results, as the calculation of V/M may meaningfully alter the rank order of paired differences when compared with coronary volume that is not appreciable by examining the mean differences between groups.

The primary limitation of this study relates to the use of a retrospective analysis involving patients with serial CCTAs acquired as part of routine clinical practice at a single center. This study design inherently introduces the potential for bias caused by disease progression not captured by the exclusion

Table 3 Coronary volume, myocardial mass, and V/M ratio

	0.4 mg NTG	0.8 mg NTG	*p* value
Total coronary volume (V) (mm^3)	2639.7 (753.2)	2844.8 (826.6)	0.009
Left coronary volume (mm^3)	1573.9 (591.1)	1697.8 (636.0)	0.007
Right coronary volume (mm^3)	1065.8 (444.4)	1147.0 (477.8)	0.085
Myocardial mass (M) (g)	103.4 (27.0)	105.5 (27.2)	0.098
V/M ratio (mm^3/g)	26.0 (5.6)	27.4 (5.9)	0.201

Values are expressed as mean (SD). $N = 35$ for all measures and were compared by Wilcoxon signed-rank test. Myocardial mass = left ventricular myocardial volume × estimated average myocardial density

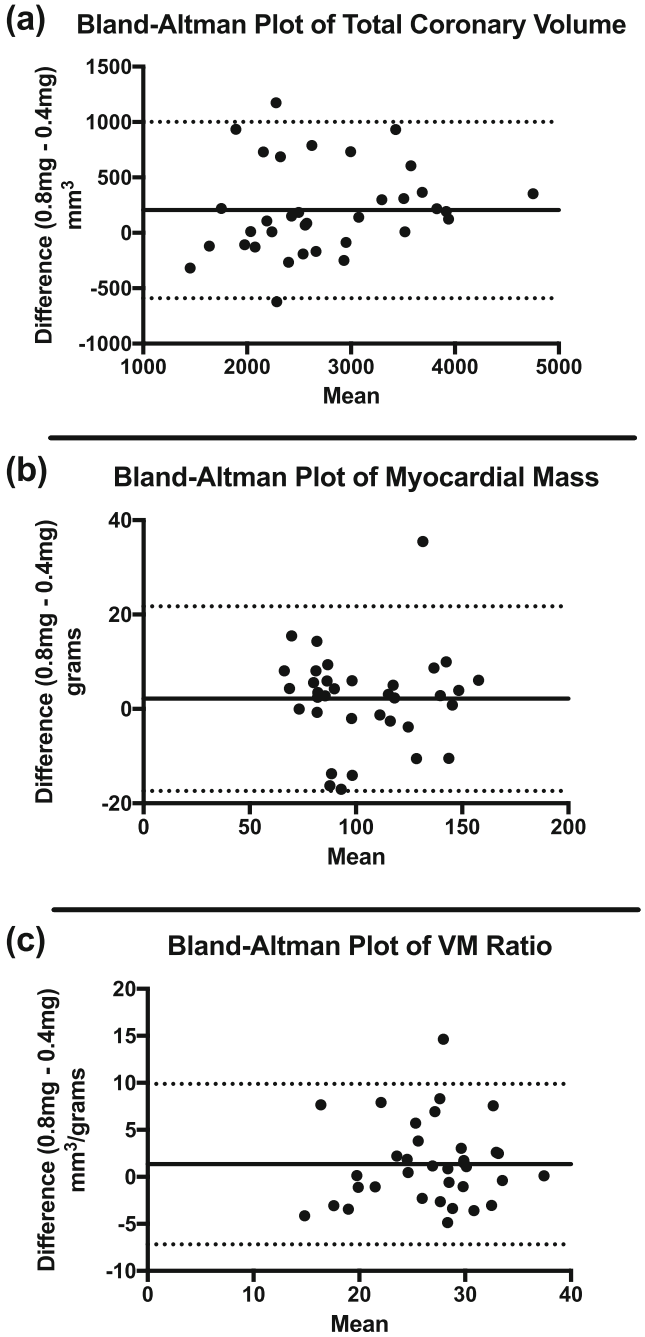

Fig. 3 Bland-Altman plots of (**a**) total coronary volume, (**b**) myocardial mass, and (**c**) V/M ratio

criteria used in the study and mean follow-up time between CCTAs. While notable criteria were used to exclude patients with meaningful disease progression in the intervening period, changes in plaque volume or characteristics would inevitably occur that could meaningfully reduce FFR_{CT} values. Furthermore, given that all scans using 0.8 mg NTG were acquired after those using 0.4 mg, disease progression is a potential factor that would increase the likelihood of a false negative result. Despite these limitations, we believe our findings remain valid as supported by the largely insignificant impact of NTG on FFR_{CT} values observed in vessels unaffected by CAD.

Another potential limitation of the study relates to the mild burden of disease in the study sample. Patients with significant disease will often receive interventions or experience significant disease progression between scans, which excludes them from further analysis. For this reason, patients included in the study tend to have mild to no disease as determined by CCTA. It is possible, however, that NTG dosage may have a significant impact on FFR_{CT} in the setting of severe stenosis.

Conclusion

Our study identifies a significant difference in coronary volume derived from FFR_{CT} analysis using 0.8 mg versus 0.4 mg of sublingual NTG without significant change in FFR_{CT} values or V/M. Future studies including more severe anatomical disease comparing the impact of NTG dose on FFR_{CT} analysis are needed.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Darra Murphy.

Conflict of interest J.A.L. and P.B. are consultants for Edwards Lifesciences and provide CT core lab services for Edwards Lifesciences, Medtronic, Neovasc, GDS, and Tendyne Holdings, for which no direct compensation is received. J.A.L. has stock options in, is a consultant to, and receives institutional research support from HeartFlow. D.T.M receives institutional research supported grants from HeartFlow. T.A.F. and C.T. are employees of HeartFlow Inc. The other authors report no disclosures.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- retrospective
- observational/experimental
- performed at one institution

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