Coronary heart disease on coronary computed tomography angiography: in search of the vulnerable patient

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CHAPTER 5

Coronary Volume to Left Ventricular Mass Ratio in Patients With Hypertension

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Abstract

The coronary vascular volume to left ventricular mass (V/M) ratio assessed by coronary computed tomography angiography (CCTA) is a promising new parameter to investigate the relation of coronary vasculature to the myocardium supplied. It is hypothesized that hypertension decreases the ratio between coronary volume and myocardial mass via myocardial hypertrophy, which could explain the detected abnormal myocardial perfusion reserve reported in hypertensive patients. Individuals enrolled in the multi-center ADVANCE registry undergoing clinically indicated CCTA for analysis of suspected coronary artery disease (CAD) with known hypertension status, were included in current analysis. The V/M ratio was calculated from CCTA by segmenting the coronary artery lumen volume and left ventricular myocardial mass. In total, 2378 subjects were included in this study of which 1346 (56%) had hypertension. LV myocardial mass and coronary volume were higher in subjects with hypertension compared to normotensive individuals (122.7±32.8g vs. 120.0±30.5g, p=0.039, and 3105.0±992.0mm^3 vs. 2965.6±943.7mm^3, p<0.001, respectively). Subsequently, the V/M ratio was higher in patients with hypertension compared to those without (26.0±7.6mm^3/g vs. 25.3±7.3mm^3/g, p=0.024). After correcting for potential confounding factors, the coronary volume and ventricular mass remained higher in hypertensive patients (least square (LS)) mean difference estimate: 196.3 (95% CI: 119.9, 272.7)mm^3, p<0.001, and 5.60 (95% CI: 3.42, 7.78) g, p<0.001, respectively) but the V/M ratio was not significantly different (LS mean difference estimate: 0.48 (95% CI: -0.12, 1.08) mm^3/g, p=0.116). In conclusion, our findings do not support the hypothesis that the abnormal perfusion reserve would be caused by reduced V/M ratio in hypertensive patients.

Keywords: coronary artery lumen volume; left ventricular mass; volume to mass ratio; hypertension; coronary artery disease.

Introduction

Hypertension causes changes in the coronary circulation characterized by a reduction of the coronary vascular reserve.[1-10] Left ventricular (LV) hypertrophy, usually a complication of hypertension due to sustained elevated afterload, is associated with a reduction in maximal coronary vasodilator reserve[11-13] and an increase in myocardial oxygen demand.[14-16] The ratio of the total epicardial coronary artery lumen volume to left ventricular myocardial mass (V/M ratio) is considered a parameter capable of revealing a potential physiological imbalance between coronary blood supply and myocardial demand.[17] Low V/M ratios were associated with more advanced coronary artery disease (CAD), reduced myocardial blood flow and lesion-specific fractional flow reserve <0.80.[18,19] Based on previous studies observing reduced coronary flow reserve in patients with hypertension, we hypothesized that hypertensive patients may have a lower V/M ratio compared to normotensive patients.

Methods

ADVANCE (Assessing Diagnostic Value of Noninvasive FFRCT in Coronary Care) is a multinational (38 sites in Europe, North America and Japan) registry with prospective follow-up data of patients being investigated for clinically suspected CAD designed to understand the effect of CCTA-derived Fractional Flow Reserve on clinical practice. The study design has been described earlier in detail.[20] Summarized, subjects were enrolled from July 15, 2015 to October 20, 2017. Patients >18 years of age with documented stenosis of at least 30% on coronary computed tomography angiography (CCTA) were included. Patients with an insufficient CCTA image quality, an inability to comply with follow-up requirements and a life expectancy <1 year were excluded.

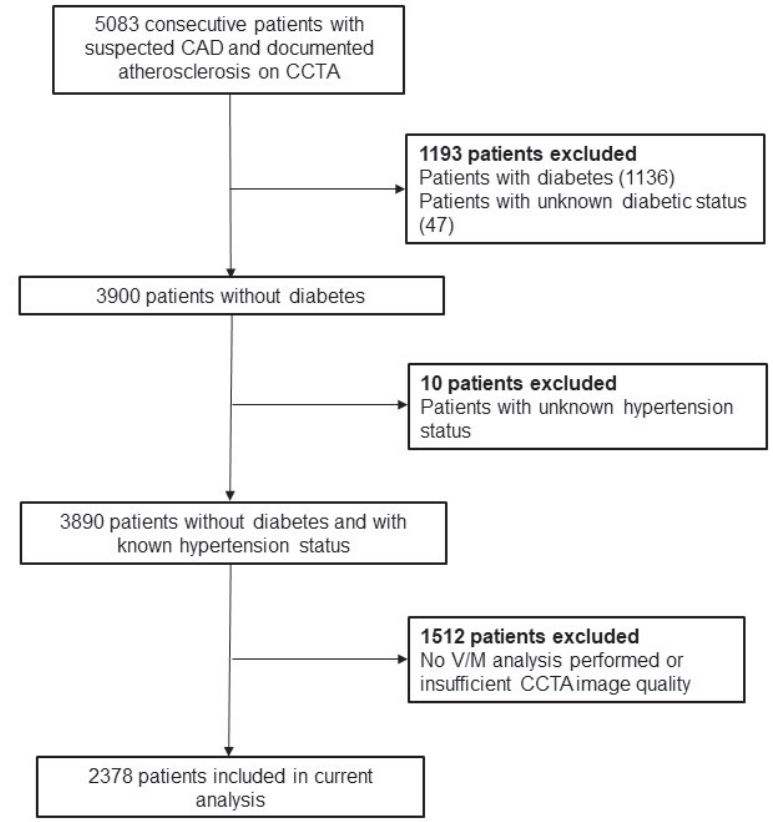
For the current analysis, patients with known hypertension status and available coronary artery lumen volume and LV myocardial mass analysis were included (Figure 1). Diabetic patients were excluded to reduce the confounding effects of diabetes on V/M.[21] The study was conducted in accordance with the Declaration of Helsinki. All individuals provided written consent following local Institutional Review Board review and approval.

Table 1. Baseline characteristics of the overall population and according to hypertension status.

	Total (N=2378)	Hypertension (N=1346)	No Hypertension (N=1032)	p-value
Age, (y)				
N	2272	1288	984	<0.001
Mean ± SD	66.1 ± 10.4	67.8 ± 9.6	63.9 ± 11.0	
Min, Max	15.0, 93.0	34.0, 93.0	15.0, 92.0	
Male sex	1564 (65.8%)	849 (63.1%)	(69.3%)	0.002
BMI, (kg/m²)				
N	2347	1332	1015	<0.001
Mean ± SD	26.1 ± 4.7	26.4 ± 4.9	25.6 ± 4.4	
Min, Max	14.9, 63.7	15.8, 63.7	14.9, 55.5	
Diamond Forrester CAD Likelihood				
N	2251	1281	970	0.544
Mean ± SD	50.9 ± 20.0	51.2 ± 19.9	50.6 ± 20.1	
Min, Max	5.3, 92.5	8.0, 92.5	5.3, 92.5	
Hyperlipidaemia				
Yes	1368 (57.5%)	888 (66.0%)	480 (46.5%)	<0.001
No	995 (41.8%)	448 (33.3%)	547 (53.0%)	
Unknown	15 (0.6%)	10 (0.7%)	5 (0.5%)	
Tobacco Use				
Current Smoker	364 (15.3%)	191 (14.2%)	173 (16.8%)	0.072
Ex-Smoker	815 (34.3%)	484 (36.0%)	331 (32.1%)	
Never Smoked	1020 (42.9%)	571 (42.4%)	449 (43.5%)	
Unknown	179 (7.5%)	100 (7.4%)	79 (7.7%)	
Angina Status				
Typical	465 (19.6%)	264 (19.6%)	201 (19.5%)	0.028
Atypical	868 (36.5%)	467 (34.7%)	401 (38.9%)	
Dyspnea	274 (11.5%)	148 (11.0%)	126 (12.2%)	
Non-cardiac Pain	150 (6.3%)	85 (6.3%)	65 (6.3%)	
None	604 (25.4%)	375 (27.9%)	229 (22.2%)	
Unknown	17 (0.7%)	7 (0.5%)	10 (1.0%)	
CCS Angina Class				
Grade I	109/ 465 (23.4%)	55/ 264 (20.8%)	54/ 201 (26.9%)	0.210
Grade II	264/ 465 (56.8%)	152/ 264 (57.6%)	112/ 201 (55.7%)	
Grade III	42/ 465 (9.0%)	27/ 264 (10.2%)	15/ 201 (7.5%)	
Grade IV	6/ 465 (1.3%)	5/ 264 (1.9%)	1/ 201 (0.5%)	
Unknown	44/ 465 (9.5%)	25/ 264 (9.5%)	19/ 201 (9.5%)	

Data are presented as mean ± standard deviation or number (percentage),as appropriate. BMI = body mass index; CAD = coronary artery disease; CCS = Canadian Cardiovascular Society.

Figure 1. Flowchart of study population.
CAD, coronary artery disease; CCTA, coronary computed tomography angiography; V/M, coronary volume and left ventricular mass



All CCTA scans were performed with ≥64-row multi-detector computed tomography (CT) scanners. If the pre-scan heart rate was above 60 beats per minute, patients received metoprolol before the CCTA scan, unless contraindicated. Sublingual nitrates was administered to all patients before scanning. Coronary arteries with a diameter of ≥ 2 mm were evaluated for stenosis severity in accordance with current guidelines according to the clinical site procedures.[22] HeartFlow Inc. (Redwood City, California, United States of America), a central core laboratory, computed the V/M analyses, which has been described previously.[20,23-26] In short, a patient-specific anatomic epicardial model of the coronary tree was derived from the CCTA images provided. The total coronary arterial lumen volume is calculated by the summation of all the segmented coronary arteries. The volume of the myocardium extracted from CCTA was multiplied by 1.05g/ml, an average value for myocardial tissue density, resulting in the left ventricle myocardial mass.[27] Subsequently, the ratio between the total coronary artery lumen volume and the LV myocardial mass was calculated. Because of software development during the study time period, the analysis of the V/M ratio could not be performed in all patients.

The diagnoses of hypertension were based on the medical history in the electronic case report forms and defined as systolic blood pressure values of ≥140 mmHg and/or diastolic blood pressure values of ≥90 mmHg requiring treatment. Among patients with anatomically obstructive and without obstructive CAD the coronary artery lumen volume and LV myocardial mass were separately analyzed. Obstructive CAD was defined as ≥50% diameter stenosis.

Statistical analyses were performed with SAS version 9.4 (SAS institute, Cary, North Carolina, USA). Continuous variables with a normal distribution are presented as mean ± standard deviation and were compared using the Student t-test or One-way ANOVA, as appropriate. Non-normally distributed continuous variables are presented as median with (25-75th interquartile range (IQR)) and were compared using the Mann-Whitney U test. Categorical variables are presented as absolute numbers and percentages and were compared using the χ^2 test. In order to correct for potential confounding effects on the coronary artery lumen volume, LV myocardial mass and V/M ratio, analysis of covariance models were used. Age, BMI, hyperlipidemia, sex, number of vessels with obstructive CAD and the degree of maximum stenosis were used as covariates in this analysis. The differences in total coronary artery lumen volume, LV myocardial mass and V/M ratio between hypertensive and normotensive patients are presented as Least Square (LS) mean difference estimate with corresponding 95% confidence intervals (CI). A two-sided p-value <0.05 was considered statistical significant.

Results

5083 individuals were enrolled in the ADVANCE registry. Of these, 2378 non-diabetic patients with known hypertension status and measured V/M ratio were included in current analysis. Hypertension was present in 1346 patients (60%). Baseline patient demographic and clinical characteristics of the enrolled patients are shown in Table 1. Patients with hypertension were older (67.8 ± 9.6 vs. 63.9 ± 11.0 years, p<0.001) and had a higher body mass index (BMI) (26.4 ± 4.9 vs. 25.6 ± 4.4 kg/m^2, p<0.001). Additionally, hypertensive patients had more frequently a history of hyperlipidemia (p<0.001) and were more likely to be female (p=0.002).

Hypertensive patients had more frequently obstructive CAD by anatomical CCTA evaluation (p=0.017) (Table 2). In the quantitative analysis, the volume of epicardial coronary arteries was higher in patients with hypertension (3105.0 ± 992.0 mm^3 vs. 2965.6 ± 943.7 mm^3, p=0.001). The LV myocardial mass was higher in hypertensive patients as well (122.7 ± 32.8 g vs. 120.0 ± 30.5 g, p=0.039). This resulted in a higher V/M ratio in patients with hypertension compared to patients without hypertension (26.0 ± 7.6 mm^3/g vs. 25.3 ± 7.3 mm^3/g, p=0.024). When correcting for the differences in baseline and CCTA characteristics, the coronary volume and myocardial mass remained significantly higher in hypertensive patients (LS mean difference estimate: 196.3 (95% CI: 119.9, 272.7) mm^3, p<0.001; LS mean difference estimate: 5.60 (95% CI: 3.42, 7.78) g, p<0.001, respectively) (Table 4 and Figure 2). Whereas the V/M ratio showed no significant difference between hypertensive and normotensive patients (LS mean difference estimate: 0.48 (95% CI: -0.12, 1.08) mm^3/g, p=0.116).

Table 2. Coronary computed tomography angiography parameters of patients according to hypertension status.

	Total (N=2378)	Hypertension (N=1346)	No Hypertension (N=1032)	p-value
CCTA anatomical finding				
Without obstructive stenosis < 50%	711 (29.9%)	376 (27.9%)	335 (32.5%)	0.017
Obstructive stenosis ≥ 50%	1663 (69.9%)	968 (71.9%)	695 (67.3%)	
Unknown	4 (0.2%)	2 (0.1%)	2 (0.2%)	
Non-severe stenosis ≤ 70%	1676 (70.5%)	943 (70.1%)	733 (71.0%)	0.596
Severe stenosis > 70%	698 (29.4%)	401 (29.8%)	297 (28.8%)	
Unknown	4 (0.2%)	2 (0.1%)	2 (0.2%)	
Degree stenosis				
Normal (0%)	15 (0.6%)	6 (0.4%)	9 (0.9%)	0.040
Minimal (0-30%)	136 (5.7%)	62 (4.6%)	74 (7.2%)	
Mild (30-50%)	560 (23.5%)	308 (22.9%)	252 (24.4%)	
Moderate (50-70%)	965 (40.6%)	567 (42.1%)	398 (38.6%)	
Severe (70-90%)	493 (20.7%)	288 (21.4%)	205 (19.9%)	
Sub-total/occluded (≥ 90%/ occluded)	205 (8.6%)	113 (8.4%)	92 (8.9%)	
Unknown	4 (0.2%)	2 (0.1%)	2 (0.2%)	
Number of vessels with anatomically obstructive CAD (> 50% DS)				
0	711 (29.9%)	376 (27.9%)	335 (32.5%)	0.004
1	1062 (44.7%)	592 (44.0%)	470 (45.5%)	
2	420 (17.7%)	259 (19.2%)	161 (15.6%)	
3	181 (7.6%)	117 (8.7%)	64 (6.2%)	
4	0	0	0	
Unknown	4 (0.2%)	2 (0.1%)	2 (0.2%)	
Rate of obstructive CAD per vessel				
LAD stenosis < 50%	1069 (45.0%)	584 (43.4%)	485 (47.0%)	0.080
LAD stenosis ≥ 50%	1309 (55.0%)	762 (56.6%)	547 (53.0%)	
LCX stenosis < 50%	1860 (78.2%)	1030 (76.5%)	830 (80.4%)	0.022
LCX stenosis ≥ 50%	518 (21.8%)	316 (23.5%)	202 (19.6%)	
RCA stenosis < 50%	1760 (74.0%)	963 (71.5%)	797 (77.2%)	0.002
RCA stenosis ≥ 50%	618 (26.0%)	383 (28.5%)	235 (22.8%)	
Coronary volume - myocardial mass				
Epicardial coronary artery volume (mm^3)				
N	2378	1346	1032	0.001
Mean ± SD	3044.5 ± 973.6	3105.0 ± 992.0	2965.6 ± 943.7	
Min, Max	704.6, 7891.2	732.1, 7891.2	704.6, 7198.4	

Table 2. Continued

	Total (N=2378)	Hypertension (N=1346)	No Hypertension (N=1032)	p-value
Left ventricle myocardial mass (g)				
N	2378	1346	1032	0.039
Mean ± SD	121.6 ± 31.8	122.7 ± 32.8	120.0 ± 30.5	
Min, Max	54.9, 324.1	54.9, 324.1	56.9, 308.9	
Coronary volume /mass (mm^3/g)				
N	2378	1346	1032	0.024
Mean ± SD	25.7 ± 7.5	26.0 ± 7.6	25.3 ± 7.3	
Min, Max	6.8, 62.5	6.8, 61.9	7.2, 62.5	

Data are presented as mean ± standard deviation or number (percentage), as appropriate. CAD = coronary artery disease; CCTA = coronary computed tomography angiography; DS = diameter stenosis; LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery;

As CAD has known effects on coronary volume, the groups with and without obstructive CAD were analyzed separately (Table 3). Obstructive CAD was present in 1663 subjects (69.9%), of whom 968 (58.2%) had hypertension. In individuals with obstructive CAD, patients with hypertension were more often male (p=0.009), were older (p<0.001), had a higher BMI (p=0.004) and had more frequently a history of hyperlipidemia (p<0.001) (Table 3). Coronary volume did not differ significantly between hypertensive and normotensive patients with obstructive CAD (3026.4 ± 971.5 mm^3 vs. 2937.5 ± 918.5 mm^3; p=0.058). Moreover, the LV mass was not significantly different between the two groups (123.6 ± 33.4 g vs. 121.8 ± 29.4 g; p=0.243). Accordingly, the V/M ratio was comparable between the two groups (25.2 ± 7.3 mm^3/g vs. 24.7 ± 7.2 mm^3/g, p=0.209). When we correct for potential confounding variables, the epicardial coronary artery volume and myocardial mass were significantly higher in hypertensive patients compared to normotensive patients (LS mean difference estimate: 135.21 (95% CI: 45.3, 225.1) mm^3, p=0.003 and LS mean difference estimate: 4.92 (95% CI: 2.30, 7.55) g, p<0.001 respectively) (Table 5 and Figure 2). However, the V/M ratio was not significantly different between the two groups (LS mean difference estimate: 0.15 (95% CI: -0.54, 0.84) mm^3/g, p=0.671).

Hypertension was present in 376 out of 711 (53%) patients without obstructive CAD. Hypertensive patients were more frequent female (p=0.024), older (p<0.001), had a higher BMI (p=0.006) and had more frequently a history of hyperlipidemia (<0.001) (Table 3). Coronary volume was higher in hypertensive patients compared to normotensive in patients without obstructive CAD (3305.8 ± 1019.1 mm^3 vs. 3023.8 ± 995.4 mm, p<0.001), while LV mass did not differ significantly between the groups (120.5 ± 31.1 g vs. 116.2 ± 32.4 g, p=0.074). Consequently, the V/M ratio was significantly higher (28.1 ± 7.9 mm^3/g vs. 26.5 ± 7.2 mm^3/g, p=0.007) in hypertensive patients compared to normotensive patients. Coronary artery volume remained significantly higher in patients with hypertension after correction for potential confounding variables (LS mean difference estimate: 352.20 (95% CI: 208.37, 496.04) mm^3, p<0.001) (Table 6 and Figure 2). The myocardial mass after correction for confounding variables was significantly higher in patients with hypertension as well (LS mean difference estimate: 7.24 (95% CI: 3.33, 11.14) g, p<0.001). The V/M ratio remained significant higher in the hypertensive patients (LS mean difference estimate: 1.33 (95% CI: 0.15, 2.51) mm^3/g, p=0.028) (Table 5).

Figure 2. Bar chart showing the Least Squares means, after correcting for potential confounding factors, of the coronary volume, left ventricular mass and V/M ratio for patients with and without hypertension.
A*: Total cohort
B*: Subjects with obstructive coronary artery disease
C: Subjects without obstructive CAD
* = The variable 'Number of vessels with obstructive coronary artery disease' is removed in current analysis due to collinearity with 'Maximum Stenosis %'. Inference did not change, but values changed slightly.
CAD, coronary artery disease; V/M, coronary volume and left ventricular mass

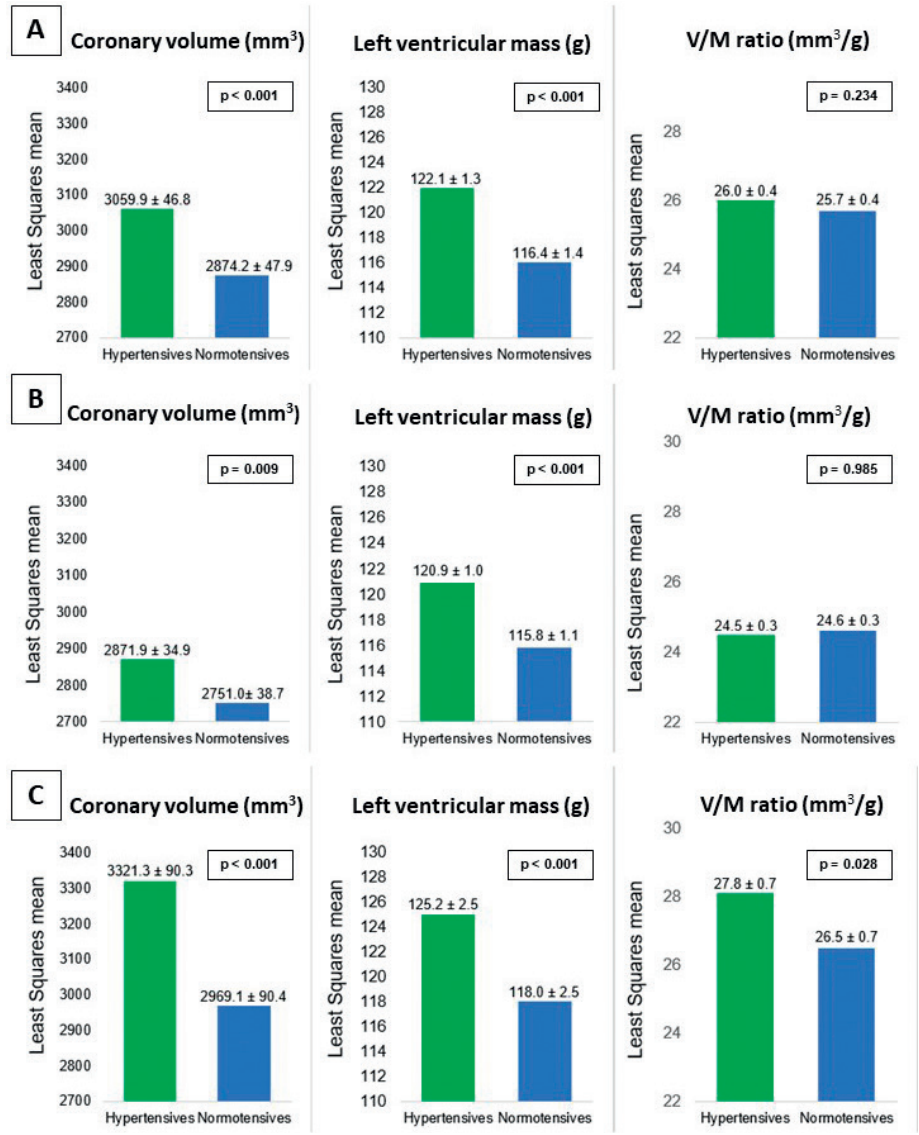


Table 3. Baseline characteristics and coronary computed tomography and coronary computed tomography angiography parameters of patients with anatomically obstructive and without obstructive CAD according to hypertension status

	Obstructive CAD (≥ 50% DS)				Without obstructive CAD (<50% DS)			
	Total (N=1663)	Hypertension (N=968)	No Hypertension (N=695)	p-value	Total (N=711)	Hypertension (N=376)	No Hypertension (N=335)	p-value
Baseline patient characteristics								
Age, (y)								
N	1597	930	667	<0.001	672	357	315	<0.001
Mean ± SD	66.6 ± 10.3	68.0 ± 9.6	64.6 ± 10.7		65.0 ± 10.7	67.2 ± 9.5	62.4 ± 11.4	
Min, Max	26.0, 93.0	40.0, 93.0	26.0, 92.0		15.0, 90.0	34.0, 89.0	15.0, 90.0	
Male sex	1150 (69.2%)	645 (66.6%)	505 (72.7%)	0.009	412 (57.9%)	203 (54.0%)	209 (62.4%)	0.024
BMI, (kg/m²)								
N	1648	960	688	0.004	695	370	325	0.006
Mean ± SD	25.9 ± 4.5	26.2 ± 4.6	25.5 ± 4.2		26.4 ± 5.2	26.9 ± 5.4	25.9 ± 4.8	
Min, Max	14.9, 53.1	15.8, 53.1	14.9, 42.6		15.9,63.7	18.0, 63.7	15.9, 55.5	
Diamond Forrester CAD Likelihood								
N	1585	926	659	0.656	663	354	309	0.206
Mean ± SD	53.2 ± 20.0	53.0 ± 20.0	53.4 ± 19.9		45.6 ± 19.0	46.5 ± 18.9	44.6 ± 19.2	
Min, Max	8.0, 92.5	8.0, 92.5	8.0, 92.5		5.3, 92.5	8.0, 92.5	5.3, 88.9	
Hyperlipidaemia								
Yes	959 (57.7%)	636 (65.7%)	323 (46.5%)	<0.001	406 (57.1%)	251 (66.8%)	155 (46.3%)	<0.001
No	697 (41.9%)	327 (33.8%)	370 (53.2%)		297 (41.8%)	120 (31.9%)	177 (52.8%)	
Unknown	7 (0.4%)	5 (0.5%)	2 (0.3%)		8 (1.1%)	5 (1.3%)	3 (0.9%)	

Table 3. Continued

	Obstructive CAD (≥ 50% DS)				Without obstructive CAD (<50% DS)			
	Total (N=1663)	Hypertension (N=968)	No Hypertension (N=695)	p-value	Total (N=711)	Hypertension (N=376)	No Hypertension (N=335)	p-value
Rate of obstructive CAD per vessel								
LAD stenosis < 50%	354 (21.3%)	206 (21.3%)	148 (21.3%)	0.995	NA	NA	NA	NA
LAD stenosis ≥ 50%	1309 (78.7%)	762 (78.7%)	547 (78.7%)		NA	NA	NA	
LCX stenosis < 50%	1145 (68.9%)	652 (67.4%)	493 (70.9%)	0.120	NA	NA	NA	NA
LCX stenosis ≥ 50%	518 (31.1%)	316 (32.6%)	202 (29.1%)		NA	NA	NA	
RCA stenosis < 50%	1045 (62.8%)	585 (60.4%)	460 (66.2%)	0.017	NA	NA	NA	NA
RCA stenosis ≥ 50%	618 (37.2%)	383 (39.6%)	235 (33.8%)		NA	NA	NA	
Coronary volume - myocardial mass								
Epicardial coronary artery volume (mm³)								
N	1663	968	695	0.058	711	376	335	<0.001
Mean ± SD	2989.2 ± 950.5	3026.4 ± 971.5	2937.5 ± 918.5		3172.9 ± 1017.1	3305.8 ± 1019.1	3023.8 ± 995.4	
Min, Max	704.6, 7415.5	732.1, 7415.5	704.6, 7055.6		889.6, 7891.2	1181.3, 7891.2	889.6, 7198.4	
Left ventricle myocardial mass (g)								
N	1663	968	695	0.243	711	376	335	0.074
Mean ± SD	122.9 ± 31.8	123.6 ± 33.4	121.8 ± 29.4		118.5 ± 31.7	120.5 ± 31.1	116.2 ± 32.4	
Min, Max	54.9, 324.1	54.9, 324.1	56.9, 247.1		58.3, 308.9	63.3, 264.6	58.3, 308.9	
Coronary volume / mass (mm³/g)								
N	1663	968	695	0.209	711	376	335	0.007
Mean ± SD	25.0 ± 7.3	25.2 ± 7.3	24.7 ± 7.2		27.3 ± 7.6	28.1 ± 7.9	26.5 ± 7.2	
Min, Max	6.8, 62.5	6.8, 59.2	7.2, 62.5		9.8, 61.9	10.7, 61.9	9.8, 51.0	

Discussion

The current study assessed the impact of hypertension on the V/M ratio. The hypothesis was that the known reduced myocardial perfusion reserve in hypertensive patients may be partially explained by an abnormally low V/M ratio, likely due to myocardial hypertrophy not accompanied by increase in vascular volume. The main results demonstrate that the V/M ratio was not decreased in hypertensive patients suggesting that the increased myocardial mass was compensated by increased vascular volume leading to preserved V/M ratio.

The V/M ratio has been shown to be reduced in patients with CAD.[18] This is expected as CAD typically affects the coronary lumen and the vasodilatory capacity. We recently found that V/M-ratio is reduced also in patients with diabetes, even when CAD was taken into account as a confounding factor.[21] In the current paper, we excluded patients with diabetes and also analyzed the patients with and without obstructive CAD separately. An interesting finding was that in patients without obstructive CAD, the V/M ratio was higher in hypertensive patients despite increased myocardial mass. In patients with obstructive CAD, V/M ratio was not significantly different between patients with and without hypertension, likely due to the confounding effect of CAD on the V/M ratio.

The concept of the V/M ratio was first described by Gould et al.[28] and the methodology of assessing the V/M ratio is based on allometric scaling laws. Allometric scaling laws provide a model to predict the functional and structural properties of the cardiovascular system of mammals.[29.] Choy et al.[30] investigated scaling laws of myocardial flow and mass in a porcine heart, and reported a very tight linear relationship between coronary artery lumen volume and myocardial mass. Previous studies investigating the V/M ratio, have shown that individuals with a low V/M ratio had reduced myocardial blood flow on positron emission tomography compared to patients with a high V/M ratio.[18] Furthermore, Taylor et al.[19] concluded that the V/M ratio was independently associated with a FFR below the ischemic threshold (≤0.80).

We hypothesized that the abnormal myocardial perfusion in patients with hypertension was caused by a reduced V/M ratio. LV hypertrophy is frequently associated with hypertension, increases the myocardial mass and is considered a mechanism contributing to abnormal myocardial perfusion. However, the present study shows a corresponding increase in coronary artery volume, leading to a preserved V/M ratio in patients with hypertension.

The increased coronary lumen volume in patients with hypertension we observed in the current study is in line with previous research, showing lumen enlargement of proximal elastic arteries.[31,32] Carotid and coronary arteries represent large vessels, often referred to as "elastic arteries" or "conducting arteries" and are both central, predominantly elastic and transport large volumes of blood away from the left ventricle to perfuse vital organs.[33] In addition, atherosclerotic disease and its potential confounding effect needs to be taken into account when calculating the V/M ratio, since the presence of atherosclerosis and reduced coronary volume has been linked. When the cohort is divided into patients with and without obstructive CAD, patients with obstructive CAD remain to

have no significant different V/M ratio between hypertensive and normotensive patients. However, we observed in hypertensive patients without obstructive CAD even a higher V/M ratio compared to normotensive patients. The increase in coronary lumen volume is apparently larger than the increase of the ventricular mass. This effect is diminished in patients with obstructive CAD by the presence of more extensive atherosclerosis. Zhou et al.[34] observed that the diameter of the coronary artery is inversely associated with the severity of CAD. In addition, endothelial dysfunction because of atherosclerosis, with a subsequent reduction of vasodilator capacity contributes to a reduced coronary volume in these patients as well.[35]

Table 4. Coronary volume, cardiac mass and coronary volume/mass ratio corrected for potential confounding variables

Model Effect	LS Mean Difference (95% CI)	p-value
Total Segmented Volume		
Hypertension (Yes/No)	196.3 (119.9, 272.7)	<0.001
Age		0.735
BMI		<0.001
Hyperlipidemia (Yes/No)		0.002
Sex (Male/Female)		<0.001
Number of Vessels with Obstructive CAD (0,1,2,3)		<0.001
Maximum Stenosis % (0, >0 - <30, ≥30 - <50, ≥50 - ≤70, >70 - ≤90, >90)		<0.001
Myocardial Mass		
Hypertension (Yes/No)	5.60 (3.42, 7.78)	<0.001
Age		<0.001
BMI		<0.001
Hyperlipidemia (Yes/No)		<0.001
Sex (Male/Female)		<0.001
Number of Vessels with Obstructive CAD (0,1,2,3)		0.047
Maximum Stenosis % (0, >0 - <30, ≥30 - <50, ≥50 - ≤70, >70 - ≤90, >90)		<0.001
Volume/Mass Ratio		
Hypertension (Yes/No)	0.48 (-0.12, 1.08)	0.116
Age		<0.001
BMI		<0.001
Hyperlipidemia (Yes/No)		0.629
Sex (Male/Female)		0.007
Number of Vessels with Obstructive CAD (0,1,2,3)		<0.001
Maximum Stenosis % (0, >0 - <30, ≥30 - <50, ≥50 - ≤70, >70 - ≤90, >90)		<0.001

BMI = body mass index; CAD = coronary artery disease; CI = confidence interval; LS = least squares.

The observational design of the study has inherent limitations including selection bias and unmeasured confounding. The registry may have been subject to referral bias inherent in local practices. In addition, information regarding the severity and duration of hypertension in the patients was lacking and in our population the increase of left ventricular mass was small, despite being statistically significant. Antihypertensive treatment has been associated with the reduction of LV hypertrophy and might have a favorable effect on the matching between myocardial mass and perfusion.[36] ACE-inhibitors were found to increase cardiac nitric oxide release and reduce oxygen consumption in coronary microvessels.[37,38] Lack of data regarding antihypertensive treatment, could be viewed as a limitation of the present study as well. Equally, this paper did not adjust for the presence or absence of other cardiac diseases that affect myocardial blood flow reserve, such as valvular disease and hypertrophic cardiomyopathy. Lastly, the lack of information regarding the total plaque burden can be considered a limitation.

Table 5. Coronary computed tomography angiography parameters corrected for potential confounding variables in patients with obstructive CAD

Model Effect	LS Mean Difference (95% CI)	p-value
Total Segmented Volume		
Hypertension (Yes/No)	135.21 (45.3, 225.1)	0.003
Age		0.790
BMI		<0.001
Hyperlipidemia (Yes/No)		0.002
Sex (Male/Female)		<0.001
Number of Vessels with Obstructive CAD (0, 1, 2, 3)		<0.001
Maximum Stenosis % (≥50 - ≤70, >70 - ≤90, >90)		<0.001
Myocardial Mass		
Hypertension (Yes/No)	4.92 (2.30, 7.55)	<0.001
Age		<0.001
BMI		<0.001
Hyperlipidemia (Yes/No)		<0.001
Sex (Male/Female)		<0.001
Number of Vessels with Obstructive CAD (0, 1, 2, 3)		0.031
Maximum Stenosis % (≥50 - ≤70, >70 - ≤90, >90)		0.002
Volume/Mass Ratio		
Hypertension (Yes/No)	0.15 (-0.54, 0.84)	0.671
Age		<0.001
BMI		<0.001
Hyperlipidemia (Yes/No)		0.371
Sex (Male/Female)		0.002
Number of Vessels with Obstructive CAD (0, 1, 2, 3)		<0.001
Maximum Stenosis % (≥50 - ≤70, >70 - ≤90, >90)		<0.001

BMI = body mass index; CAD = coronary artery disease; CI = confidence interval; LS = least squares.

Table 6. Coronary computed tomography angiography parameters corrected for potential confounding variables in patients without obstructive CAD

Model Effect	LS Mean Difference (95% CI)	p-value
Total Segmented Volume		
Hypertension (Yes/No)	352.2 (208.37, 496.04)	<0.001
Age		0.950
BMI		0.001
Hyperlipidemia (Yes/No)		0.239
Sex (Male/Female)		<0.001
Maximum Stenosis % (0, >0 - <30, ≥30 - <50)		0.352
Myocardial Mass		
Hypertension (Yes/No)	7.24 (3.33, 11.14)	<0.001
Age		0.014
BMI		<0.001
Hyperlipidemia (Yes/No)		0.043
Sex (Male/Female)		<0.001
Maximum Stenosis % (0, >0 - <30, ≥30 - <50)		0.352
Volume/Mass Ratio		
Hypertension (Yes/No)	1.33 (0.15, 2.51)	0.028
Age		0.002
BMI		<0.001
Hyperlipidemia (Yes/No)		0.731
Sex (Male/Female)		0.627
Maximum Stenosis % (0, >0 - <30, ≥30 - <50)		0.413

Conclusion

In contrast to our hypothesis, the V/M ratio was not decreased in patients with hypertension compared to patients without hypertension and the abnormal coronary flow reserve in hypertensive patients is not likely caused by a reduced arterial volume to myocardial mass. Further studies are required using different cohorts in order to investigate the relationship of flow reserve and V/M ratio.

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