# Coronary Volume to Left Ventricular Mass Ratio in Patients With Hypertension

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**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 by way of myocardial hypertrophy, which could explain the detected abnormal myocardial perfusion reserve reported in patients with hypertension. Individuals enrolled in the multicenter ADVANCE (Assessing Diagnostic Value of Noninvasive FFRCT in Coronary Care) registry who underwent clinically indicated CCTA for analysis of suspected coronary artery disease with known hypertension status were included in current analysis. The V/M ratio was calculated from CCTA by segmenting the coronary artery luminal volume and left ventricular myocardial mass. In total, 2,378 subjects were included in this study, of whom 1,346 (56%) had hypertension. Left ventricular myocardial mass and coronary volume were higher in subjects with hypertension than normotensive patients (122.7 ± 32.8 g vs 120.0 ± 30.5 g, p = 0.039, and 3,105.0 ± 992.0 $mm^3$ vs 2,965.6 ± 943.7 $mm^3$, p <0.001, respectively). Subsequently, the V/M ratio was higher in patients with hypertension than those without (26.0 ± 7.6 $mm^3$/g vs 25.3 ± 7.3 $mm^3$/g, p = 0.024). After correcting for potential confounding factors, the coronary volume and ventricular mass remained higher in patients with hypertension (least square) mean difference estimate: 196.3 (95% confidence intervals [CI] 119.9 to 272.7) $mm^3$, p <0.001, and 5.60 (95% CI 3.42 to 7.78) g, p <0.001, respectively), but the V/M ratio was not significantly different (least square mean difference estimate: 0.48 (95% CI −0.12 to 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 patients with hypertension.**  **(Am J Cardiol 2023;199:100−109)**

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See page 108 for Declaration of Conflict of Interest.

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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 because of 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 luminal volume to LV myocardial mass (V/M ratio) is considered a parameter capable of revealing a potential physiologic 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 patients with hypertension may have a lower V/M ratio than 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 coronary computed tomography angiography (CCTA)-derived fractional flow reserve on clinical practice. The study design has been described earlier in detail.[20] In summary, subjects were enrolled from July 15, 2015 to October 20, 2017. Patients aged >18 years with documented stenosis of at least 30% on 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 present analysis, patients with known hypertension status and available coronary artery luminal volume and LV myocardial mass analysis were included (Figure 1). Patients with diabetes 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 informed consent after local institutional review board review and approval.

All CCTA scans were performed with ≥64-row multidetector computed tomography scanners. If the prescan heart rate was >60 beats/min, patients received metoprolol before the CCTA scan, unless contraindicated. Sublingual nitrates were administered to all patients before scanning. Coronary

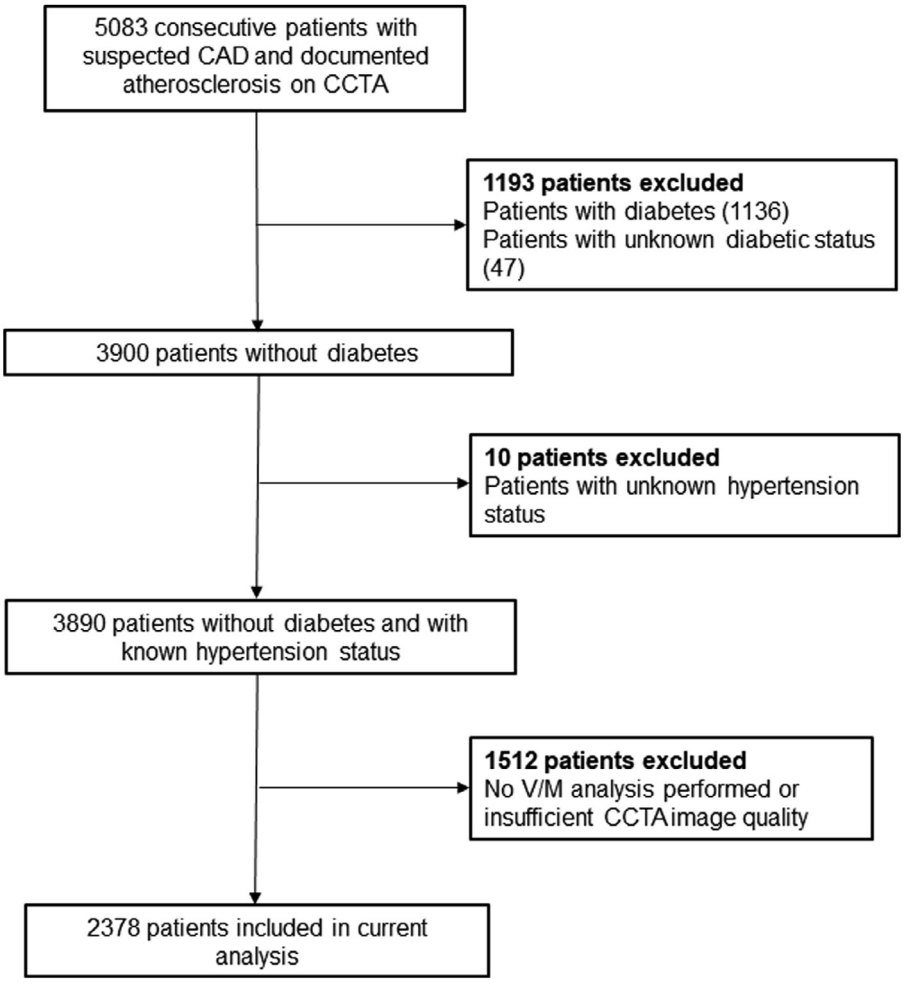


Figure 1. Flowchart of study population.

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), 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 luminal volume is calculated by the summation of all the segmented coronary arteries. The volume of the myocardium extracted from CCTA was multiplied by 1.05 g/ml, an average value for myocardial tissue density, resulting in the left ventricle myocardial mass.[27] Subsequently, the ratio between the total coronary artery luminal 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 mm Hg and/or diastolic blood pressure values of ≥90 mm Hg requiring treatment. Among patients with anatomically obstructive and without obstructive CAD the coronary artery luminal 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). Continuous variables with a normal distribution are presented as mean ± SD and were compared using the Student's *t* test or one-way analysis of variance, as appropriate. Non-normally distributed continuous variables are presented as median with (twenty-fifth to seventy-fifth interquartile range) and were compared using the Mann-Whitney *U* test. Categorical variables are presented as absolute numbers and percentages and were compared using the chi-square test. To correct for potential confounding effects on the coronary artery luminal volume, LV myocardial mass, and V/M ratio, analysis of covariance models were used. Age, body mass index (BMI), hyperlipidemia, gender, 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 luminal volume, LV myocardial mass,

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

| | Total (n=2,378) | Hypertension (n=1,346) | No hypertension (n=1,032) | p Value |
|---|---|---|---|---|
| **Age, (y)** | | | | |
| N | 2,272 | 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** | 1,564 (65.8%) | 849 (63.1%) | 715 (69.3%) | 0.002 |
| **BMI, (kg/m$^2$)** | | | | |
| N | 2,347 | 1332 | 1,015 | <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 | 2,251 | 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 | |
| **Hyperlipidemia** | | | | |
| Yes | 1,368 (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 | 1,020 (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.

and V/M ratio between hypertensive and normotensive patients are presented as least square (LS) mean difference estimate with corresponding 95% confidence intervals (CIs). A 2-sided p <0.05 was considered statistically significant.

## Results

A total of 5,083 individuals were enrolled in the ADVANCE registry. Of these, 2,378 patients without diabetes with known hypertension status and measured V/M ratio were included in present analysis. Hypertension was present in 1,346 patients (60%). Baseline patient demographic and clinical characteristics of the enrolled patients are listed 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 BMI (26.4 ± 4.9 vs 25.6 ± 4.4 kg/m$^2$, p <0.001). In addition, patients with hypertension had more frequently a history of hyperlipidemia (p <0.001) and were more likely to be female (p = 0.002).

Patients with hypertension had more frequently obstructive CAD by anatomic CCTA evaluation (p = 0.017; Table 2). In the quantitative analysis, the volume of epicardial coronary arteries was higher in patients with hypertension (3,105.0 ± 992.0 mm$^3$ vs 2,965.6 ± 943.7 mm$^3$, p = 0.001). The LV myocardial mass was higher in patients with hypertension 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

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

| | Total (n=2,378) | Hypertension (n=1,346) | No hypertension (n=1,032) | p Value |
|---|---|---|---|---|
| **CCTA anatomical finding** | | | | |
| Without obstructive stenosis <50% | 711 (29.9%) | 376 (27.9%) | 335 (32.5%) | 0.017 |
| Obstructive stenosis ≥50% | 1,663 (69.9%) | 968 (71.9%) | 695 (67.3%) | |
| Unknown | 4 (0.2%) | 2 (0.1%) | 2 (0.2%) | |
| Non-severe stenosis ≤70% | 1,676 (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%) | |
| 0 | 711 (29.9%) | 376 (27.9%) | 335 (32.5%) | 0.004 |
| 1 | 1,062 (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% | 1,069 (45.0%) | 584 (43.4%) | 485 (47.0%) | 0.080 |
| LAD stenosis ≥50% | 1,309 (55.0%) | 762 (56.6%) | 547 (53.0%) | |
| LCX stenosis <50% | 1,860 (78.2%) | 1,030 (76.5%) | 830 (80.4%) | 0.022 |
| LCX stenosis ≥50% | 518 (21.8%) | 316 (23.5%) | 202 (19.6%) | |
| RCA stenosis <50% | 1,760 (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 | 2,378 | 1346 | 1,032 | 0.001 |
| Mean±SD | 3,044.5±973.6 | 3,105.0±992.0 | 2,965.6±943.7 | |
| Min, max | 704.6, 7,891.2 | 732.1, 7,891.2 | 704.6, 7,198.4 | |
| Left ventricle myocardial mass (g) | | | | |
| N | 2,378 | 1346 | 1,032 | 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 | 2,378 | 1346 | 1,032 | 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 | |

Number of vessels with anatomically obstructive CAD (>50% DS). 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.

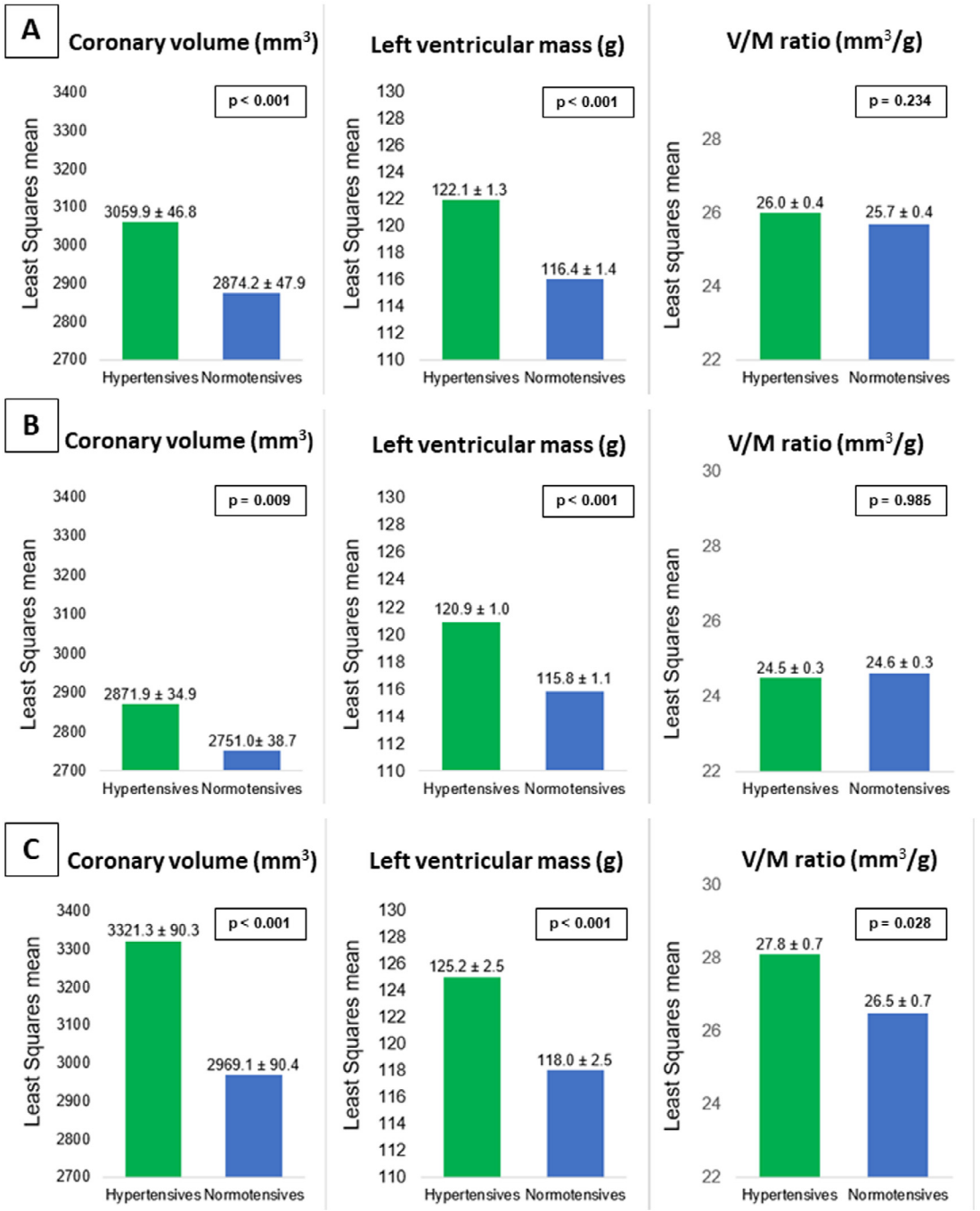


Figure 2. Bar chart showing the least squares means, after correcting for potential confounding factors, of the coronary volume, left ventricular mass and V/M ratio for patients with and without hypertension. *A*: total cohort. *B*: subjects with obstructive coronary artery disease. *C*: Subjects without obstructive CAD* = The variable "Number of vessels with obstructive coronary artery disease" is removed in current analysis because of collinearity with "maximum stenosis %." Inference did not change, but values changed slightly.

patients with hypertension than 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 patients with hypertension (LS mean difference estimate: 196.3 [95% CI 119.9 to 272.7] $mm^3$, p <0.001; LS mean difference estimate: 5.60 [95% CI 3.42 to 7.78] g, p <0.001, respectively; Figure 2, Table 3). Whereas the V/M ratio showed no significant difference between hypertensive and normotensive patients (LS mean difference estimate 0.48 [95% CI −0.12 to 1.08] $mm^3$/g, p = 0.116).

Because CAD has known effects on coronary volume, the groups with and without obstructive CAD were analyzed separately (Table 4). Obstructive CAD was present in 1,663 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

Table 3
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.

(p <0.001), had a higher BMI (p = 0.004), and had more frequently a history of hyperlipidemia (p <0.001) (Table 4). Coronary volume did not differ significantly between hypertensive and normotensive patients with obstructive CAD (3,026.4 ± 971.5 $mm^3$ vs 2,937.5 ± 918.5 $mm^3$, p = 0.058). Moreover, the LV mass was not significantly different between the 2 groups (123.6 ± 33.4 g vs 121.8 ± 29.4 g; p = 0.243). Accordingly, the V/M ratio was comparable between the 2 groups (25.2 ± 7.3 $mm^3$/g vs 24.7 ± 7.2 $mm^3$/g, p = 0.209). When we corrected for potential confounding variables, the epicardial coronary artery volume and myocardial mass were significantly higher in patients with hypertension than normotensive patients (LS mean difference estimate: 135.21 [95% CI 45.3 to 225.1] $mm^3$, p = 0.003 and LS mean difference estimate: 4.92 [95% CI 2.30 to 7.55) g, p <0.001 respectively]; Figure 2, Table 5). However, the V/M ratio was not significantly different between the 2 groups (LS mean difference estimate: 0.15 [95% CI −0.54 to 0.84] $mm^3$/g, p = 0.671).

Hypertension was present in 376 of 711 patients (53%) without obstructive CAD. Patients with hypertension 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 (p <0.001) (Table 4). Coronary volume was higher in patients with hypertension than normotensive patients without obstructive CAD (3,305.8 ± 1,019.1 $mm^3$ vs 3,023.8 ± 995.4 mm, p <0.001), whereas 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 patients with hypertension than 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 to 496.04) $mm^3$, p <0.001; Figure 2, Table 6). 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 to 11.14] g, p <0.001). The V/M ratio remained significant higher in the patients with hypertension (LS mean difference estimate: 1.33 [95% CI 0.15 to 2.51] $mm^3$/g, p = 0.028; Table 5).

## Discussion

This study assessed the impact of hypertension on the V/M ratio. The hypothesis was that the known reduced myocardial perfusion reserve in patients with hypertension may be partially explained by an abnormally low V/M ratio, likely because of myocardial hypertrophy not accompanied by increase in vascular volume. The main results demonstrate that the V/M ratio was not decreased in patients with hypertension, 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 because 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 this study, 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

Table 4
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=1,663) | 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 | 1,150 (69.2%) | 645 (66.6%) | 505 (72.7%) | 0.009 | 412 (57.9%) | 203 (54.0%) | 209 (62.4%) | 0.024 |
| **BMI, (kg/m$^2$)** | | | | | | | | |
| 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 | |
| **Hyperlipidemia** | | | | | | | | |
| 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%) | |
| **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% | 1,309 (78.7%) | 762 (78.7%) | 547 (78.7%) | | NA | NA | NA | |
| LCX stenosis <50% | 1,145 (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% | 1,045 (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 (mm$^3$)** | | | | | | | | |
| N | 1663 | 968 | 695 | 0.058 | 711 | 376 | 335 | <0.001 |
| Mean±SD | 2,989.2±950.5 | 3,026.4±971.5 | 2,937.5±918.5 | | 3,172.9±1,017.1 | 3,305.8±1,019.1 | 3,023.8±995.4 | |
| Min, max | 704.6, 7,415.5 | 732.1, 7,415.5 | 704.6, 7,055.6 | | 889.6, 7,891.2 | 1,181.3, 7,891.2 | 889.6, 7,198.4 | |
| **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 (mm$^3$/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 | |

Data are presented as mean±standard deviation or number (percentage), as appropriate.

BMI = body mass index; CAD = coronary artery disease; DS = diameter stenosis; LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery.

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 because of 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 method 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 the scaling laws of myocardial flow and mass in a porcine heart and reported a very tight linear relation between coronary artery luminal 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 with patients with a high V/M ratio.[18] Furthermore, Taylor et al[19] concluded that the V/M ratio was independently associated with a fractional flow reserve 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, this study shows a corresponding increase

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.

in coronary artery volume, leading to a preserved V/M ratio in patients with hypertension.

The increased coronary luminal volume in patients with hypertension we observed in this study is in line with previous research, showing luminal 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

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 (208.4, 496.0) | <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 |

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

because 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 patients with hypertension and normotensive patients. However, we observed in patients with hypertension without obstructive CAD an even higher V/M ratio than normotensive patients. The increase in coronary luminal 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 arter5y 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]

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 LV 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] Angiotensin-converting enzyme inhibitors were found to increase cardiac nitric oxide release and reduce oxygen consumption in coronary microvessels.[37,38] The lack of data regarding antihypertensive treatment could be viewed as a limitation of the present study as well. Equally, this study 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.

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

## Declaration of Competing Interest

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