Clinics in Surgery

Research Article
Published: 15 May, 2021

Myocardial Blood Flow Decreases in Hypertensive Patients with Non-Obstructive Epicardial Coronary Stenosis: New Evidence Provided by Dynamic Stress CT Myocardial Perfusion Imaging

Chenghu Guo[1#], Wei Yang[1#], Mei Dong[1], Peixin Lin[1], Lijuan Lv[1], Jichen Pan[1], Dexin Yu[2], Dumin Li[2], Junyan Sun[2], Yeming Han[2], Yongfeng Liang[2], Pengfei Zhang[1] and Mei Zhang[1]**

[1]Department of Cardiology, The Key Laboratory of Cardiovascular Remodeling and Function Research, Chinese Ministry of Education, Chinese National Health Commission and Chinese Academy of Medical Sciences, The State and Shandong Province Joint Key Laboratory of Translational Cardiovascular Medicine, Qilu Hospital, Cheeloo College of Medicine, Shandong University, China

[2]Department of Radiology, Qilu Hospital, Cheeloo College of Medicine, Shandong University, China

[#]These authors contributed equally to this work

OPEN ACCESS

Correspondence:
Pengfei Zhang and Mei Zhang, The Key Laboratory of Cardiovascular Remodeling and Function Research, Chinese Ministry of Education, Chinese National Health Commission and Chinese Academy of Medical Sciences, The State and Shandong Province Joint Key Laboratory of Translational Cardiovascular Medicine, Department of Cardiology, Qilu Hospital, Cheeloo College of Medicine, Shandong University, 107 Wenhuaxi Road, 250012, Jinan, China, Tel: +86531-82169257; Fax: +86531-86169356; E-mail: pengf-zhang@163.com; daixh@vip.sina.com

Received Date: *12 Apr 2021*
Accepted Date: *10 May 2021*
Published Date: *15 May 2021*

Citation:
Guo C, Yang W, Dong M, Lin P, Lv L, Pan J, et al. Myocardial Blood Flow Decreases in Hypertensive Patients with Non-Obstructive Epicardial Coronary Stenosis: New Evidence Provided by Dynamic Stress CT Myocardial Perfusion Imaging. Clin Surg. 2021; 6: 3170.

Abstract

Background: There is scarce information on the myocardial perfusion in hypertensive patients using dynamic stress CT Myocardial Perfusion Imaging (CT-MPI). Thus, this study attempted to quantify myocardial perfusion using dynamic stress CT-MPI to explain the association between myocardial perfusion, HTN, and hypertension-induced Left Ventricular Hypertrophy (LVH).

Methods: Subjects with stable chest pain or distress and non-obstructive Coronary Artery Disease (CAD) (<50% stenosis) were retrospectively selected and divided into the HTN and non-Hypertension (non-HTN) groups based on the office blood pressure. Hypertensive patients were further divided into the LVH and Non-Left Ventricular Hypertrophy (non-LVH) groups based on the Left Ventricular Mass Index (LVMI). Myocardial Blood Flow (MBF) and Myocardial Blood Volume (MBV) were quantified by CT-MPI.

Results: A total of 95 subjects were analyzed, including 31 subjects who had HTN, of which 11 individuals had LVH. MBF was lower in HTN than non-HTN [124 (114-146) *vs*. 151 (127-169) ml/100 ml/min, p=0.005]. Patients with LVH showed lower MBF than non-LVH [115 (95-129) *vs*. 131 (117-155) ml/100 ml/min, p=0.022]. Both sex and LVMI were independent predictors of MBF in all subjects (R=0.515 for combination, p<0.001) and in hypertensive patients (R=0.658 for combination, p<0.001). MBF was negatively correlated with LVMI in all subjects (r= -0.474, p<0.0001) and in HTN (r= -0.430, p=0.001). After normalized with sex and LVMI, the nMBF in the HTN group was remained lower than that of the non-HTN group (p=0.013). There was no significant difference in MBV among the above groups.

Conclusion: In hypertensive patients with non-obstructive CAD, MBF was decreased. CT-MPI could be used as a noninvasive modality to evaluate myocardial perfusion in hypertensive patients.

Keywords: CT myocardial perfusion imaging; Hypertension; Myocardial blood flow; CAD

Introduction

Hypertension (HTN) is often associated with myocardial ischemia and Major Adverse Cardiovascular Events (MACE). In particular, hypertension-induced Left Ventricular Hypertrophy (LVH) increased cardiovascular morbidity and mortality [1]. For patients with both HTN and non-obstructive Coronary Artery Diseases (CAD), studies have demonstrated that Coronary Flow Reserve (CFR) and hyperemic Myocardial Blood Flow (MBF) were decreased [2-4], which may be caused by Coronary Microvascular Diseases (CMVD).

The global prevalence of HTN was estimated to be 1.13 billion in 2015 and will increase to 1.5 billion by 2025 [5,6]. Therefore, there is an urgent need to explore an imaging modality that can evaluate both coronary artery stenosis and myocardial perfusion within one examination to

meet a huge clinical need. To obtain cardiac information on both coronary anatomy and myocardial perfusion, hybrid imaging techniques such as PET-CT and SPECT-CT were developed, but the biggest disadvantage was the larger dose of radiation, high cost, and time consuming [7]. It is hard to use these modalities to evaluate myocardial perfusion in large numbers of patients in clinical practice. A novel technology known as dynamic stress CT Myocardial Perfusion Imaging (CT-MPI) provides a new approach to absolutely quantify myocardial blood perfusion. CT-MPI improved the diagnostic accuracy for identifying flow-obstructing stenosis compared with coronary CT Angiography (cCTA) alone [8]. The advantages of CT-MPI are superior spatial resolution, cost-effective and fast, making it possible to popularize in clinical practice. Previous studies illustrated that HTN, especially with LVH, had a lower hyperemic MBF using different imaging modalities, such as PET [9], SPECT [4], and MRI [2,10]. However, there is scarce information on the myocardial perfusion acquired by CT-MPI. Thus, this study aimed to explore the feasibility of dynamic stress CT-MPI to detect the difference of myocardial perfusion between hypertrophic and non-hypertrophic HTN patients with non-obstructive coronary lesions.

Materials and Methods

Patient population

From October 2017 to February 2019, patients suspected of CAD and undergone a clinically indicated one-stop examination including cCTA and CT-MPI in sequences were enrolled retrospectively. Inclusion criteria was no evidence of coronary plaque or non-obstructive CAD (defined as stenosis <50% of the luminal diameter ascertained by cCTA in each coronary). The exclusion criteria included obstructive CAD, a history of acute or old myocardial infarction, cardiomyopathy (especially Hypertrophic Cardiomyopathy, HCM), and coronary revascularization, secondary HTN, atrioventricular block of second degree or more, atrial fibrillation, application of caffeine and antihypertensive drugs such as β-blockers 24 h before the examination. This study was approved by the Institutional Review Board, and informed consents were obtained from all participants.

Clinical data including age, sex, height, weight, Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Heart Rate (HR), and previous individual history were recorded. According to the 2018 ESC/ESH Clinical Practice Guidelines for the Management of Arterial Hypertension [5], HTN was defined as SBP ≥ 140 mmHg or DBP ≥ 90 mmHg. Patients with good control of HTN with treatment were also included in the HTN group. LVH was defined as Left Ventricular Mass Index (LVMI) of >115 g/m^2 for men or >95 g/m^2 for women [11]. Body Mass Index (BMI) and Body Surface Area (BSA) were calculated. BMI = weight/height^2; BSA = height 0.725 × weight 0.425 × 0.007184 [12].

Echocardiography

Echocardiographic parameters were collected using a Vivid E9 System (GE Vingmed Ultrasound, Horten, Norway). Septal Wall Thickness Diastole (SWTd), Left Ventricular End Diastolic Distance (LVEDd), and Post Wall Thickness Diastole (PWTd) were measured using Two-Dimensional (2D)-guided M-mode echocardiography on the parasternal projection of the long axis of the left ventricle [13]. Left Ventricular Mass (LVM) and LVMI were calculated with the following formula:

$$LVM = 0.8 \times 1.04 [(LVEDd+SWTd+PWTd)3-LVEDd3]+0.6$$

$$LVMI = LVM/BSA$$

Computed Tomography Myocardial Perfusion Imaging (CT-MPI)

Imaging protocol

CT-MPI was performed on a third-generation dual-source CT system (Somatom Force; Siemens Healthcare, Forchheim, Germany). Electrocardiography electrodes were fixed on the chest of patients, and 2 antecubital intravenous channels were established for contrast and adenosine infusion, respectively. A baseline non-contrast scan was performed at 70 kV with 20 mAs to confirm the Field Of View (FOV). After 3 min of adenosine infusion (at 140 μg/kg/min), stress dynamic CT-MPI was performed. It was initiated 4 seconds before the arrival of the contrast with an iodine concentration of 370 mg/ml (0.7 ml/kg at a flow rate of 5.0 ml/s, Ultravist 370 [Bayer HealthCare]) followed by a saline chaser (5.0 ml/s for 4 s) in the ascending aorta. CT-MPI scanning was performed in Electrocardiogram (ECG) -triggered shuttle mode (2 alternating z-positions of the heart table positions), resulting in an effective imaging coverage of 105 mm. Image acquisition was performed at 250 ms after the R-wave and lasted for more than 30 seconds. The scanning parameters were both X-ray tubes of 70 kV, gantry rotation time of 0.25 s, and total tube current with real-time dynamic tube current regulation. The acquired temporal resolution of perfusion scan was 66 ms, which was high enough to capture the contrast bolus passage. The entire scanning process was completed in breath-holding conditions. The inflow tube of the perfusion system was looped through the FOV of the perfusion scan and played a role in replacing the aorta. The arterial input function was derived from the substitute aorta.

After CT-MPI, the acquisition of cCTA scanning was performed after the sublingual application of nitroglycerin aerosol (0.5 mg per spray, total 2 sprays). The contrast dose was calculated at 0.7 ml/kg with an iodine concentration of 370 mg/ml and injected at 5.0 ml/s. The scanning parameters were both X-ray tubes of 100 kV, gantry rotation time of 0.25 s, and total tube current with real-time dynamic tube current regulation. Either retrospective ECG–gated acquisition or prospective ECG-triggered sequential acquisition was used according to the patient's heart rate. The former was applied for patients with a heart rate ≥ 70 bpm, while the latter was applied for patients with a heart rate <70 bpm.

Evaluation of cCTA

A section thickness of 0.5 mm and 0.5-mm increment was used to reconstruct the image for cCTA evaluation with a kernel (Bv36). A vessel was considered to have a significant stenosis if it contained non-assessable segments. Two experienced observers (6 years of experience with cCTA) conducted the cCTA evaluation using dedicated software (Circulation, Syngo MMWP workstation, Siemens Healthcare). If two observers disagreed, a third expert (10 years of experience with cCTA) evaluated it again, recording the consensus results.

Evaluation of CT-MPI data

Perfusion images were reconstructed with a section thickness of 1 mm and 1-mm increment using a smooth convolution kernel (Qr36). The myocardial perfusion parameters were quantified using dedicated software (Volume Perfusion CT Body, Syngo MMWP workstation, Siemens Healthcare). A dedicated parametric deconvolution technique, based on a two-compartment model of intra- and extravascular space, was used to fit the time-attenuation curves. MBF was calculated from the maximal slope of the fit model curve for every voxel, and Myocardial Blood Volume (MBV) was

derived from the peak enhancement of the model curve [14,15]. Endocardial and epicardial boundaries are automatically delineated by the software.

The left ventricular myocardium was segmented into 17 segmentations as recommended by the American Heart Association [16]. The sampling slices of the Region of Interest (ROI) were located on the middle site of every segment of the myocardium on the short axis section of the left ventricle. Then, an ROI was manually delineated, covering every myocardium segment except the 1-mm zone adjacent to the endocardial and epicardial boundary to avoid beam hardening influence. MBF and MBV are automatically calculated by the software. The perfusion parameters of each myocardium segment were measured 3 times, and the mean value of the 3 measurements was taken as the perfusion parameter of this segment. The MBF and MBV of the whole myocardium were taken from the average of 17 segments.

Statistical analysis

Statistical analysis involved the use of SPSS version 20.0 (IBM Corp., Armonk, NY) statistical software. Categorical variables are presented as Numbers (n) and percentages and compared using the $\chi 2$ test. The Shapiro-Wilk test was used to test the normality for continuous variables. Continuous normally distributed variables are presented as the mean ± SD and were compared using the independent samples t-test. Non-normally distributed variables are presented as the median and interquartile range (25 to 75 percentiles). For the non-normally distributed data of MBF and MBV, we transformed them to normally distributed data (nMBF and nMBV, respectively) using the normal score of case order, which were compared using the independent samples t-test. Both univariate linear regression analysis and multivariate stepwise linear regression analysis were performed to analyze the relationship between nMBF, nMBV, and general clinical variables or echocardiography data. Propensity score matching was used to correct confounders affecting nMBF and nMBV. Spearman correlation coefficients were calculated for the relationship between LVMI and MBF and MBV. A two-tailed $p<0.05$ was considered statistically significant for all statistics.

Results

The comparison of demographic parameters, clinical features, and echocardiography data

A total of 95 patients were enrolled, 31 individuals (33%) had HTN, of which 11 subjects showed LVH. The comparison of demographic parameters, clinical features, and echocardiography data between HTN and non-HTN groups are summarized. SBP and DBP in the HTN group were significantly higher than that in the non-HTN group (153 ± 11 *vs.* 123 ± 10 mmHg, $p<0.001$; 86 ± 10 *vs.* 76 ± 9 mmHg, $p<0.001$, respectively). Significant differences were not found between the HTN and non-HTN groups for sex, alcohol intake, diabetes mellitus, and family history of CAD. HTN group had higher age (p=0.010), BMI (p=0.045), smoking history proportion (p=0.039) and hyperlipidemia proportion (p=0.038) than non-HTN group. Both HTN and non-HTN groups had similar LVEDd. However, the HTN group showed significant increases in SWTd (11.32 ± 1.80 *vs.* 9.77 ± 1.38 mm, $p<0.001$), PWTd (9.96 ± 1.36 *vs.* 9.00 ± 1.91 mm, p=0.015), and LVMI (97.24 ± 19.75 *vs.* 82.18 ± 27.13 g/m^2, p=0.007) than the non-HTN group.

There were no significant differences in demographic and clinical features between the LVH and non-LVH group. It's worth noting that patients in the LVH group had higher but not significant BMI (p=0.069) and the proportion of family history of CAD (p=0.059) than the non-LVH group. No significant differences were found in angiotensin converting enzyme inhibitors/angiotensin receptor inhibitors, beta-blockers, and diuretics intake proportion, except Calcium Channel Blockers (CCB) intake proportion (45% *vs.* 5%, p=0.013) between LVH and non-LVH group. The LVH group had significantly higher LVEDd (48.64 ± 4.08 *vs.* 45.35 ± 3.82 mm, p=0.033), SWTd (12.71 ± 1.32 *vs.* 10.55 ± 1.57 mm, p=0.001) and PWTd (10.88 ± 1.35 *vs.* 9.45 ± 1.10 mm, p=0.003) than the non-LVH group, resulting in a higher LVMI (119.87 ± 12.92 *vs.* 84.80 ± 8.27 g/m^2, $p<0.001$). The mean effective radiation doses for CT-MPI and cCTA were 5.27 ± 2.10 mSv and 4.98 ± .37 mSv, respectively, and the total amount of contrast medium was 97.15 ± 16.37 mL.

The comparison of CT-MPI parameters between HTN and non-HTN group

The MBF in the HTN group was lower than that of the non-HTN group [124 (114 to 146) *vs.* 151 (127 to 169) ml/100 ml/min, p=0.005], but there was no significant difference in MBV. Univariate linear regression analysis revealed that nMBF was associated with age, sex, BMI, BSA, SBP, smoking, LVEDd, SWTd, PWTd, and LVMI, and that nMBV was associated with age and PWTd. Multivariate linear regression analysis showed that both Sex and LVMI (R=0.515 for combination, $p<0.001$) were the independent predictors of nMBF, of which LVMI had the largest effect on nMBF, while nMBV was only associated with age (R=0.343, p=0.001). MBF was significantly negatively correlated with LVMI (r= -0.474, $p<0.0001$) by Spearman correlation analysis, but no significant correlation between MBV and LVMI. Males showed significantly lower MBF than females [129 (112 to 153) *vs.* 150 (124 to 171) ml/100 ml/min, p=0.001] in all study populations, while no significant difference was found for MBV. After normalized with sex and LVMI, the nMBF in the HTN group was remained lower than that of the non-HTN group (p=0.013).

The comparison of CT-MPI parameters between LVH and non-LVH group

The LVH group showed significantly lower MBF than the non-LVH group [115 (95 to 129) *vs.* 131 (117 to 155) ml/100 ml/min, p=0.022], but there was no significant difference in MBV. In patients with HTN, univariate linear regression analysis showed that nMBF was associated with sex, BMI, smoking, SWTd, PWTd, and LVMI, but no factor was associated with nMBV. Multivariate linear regression analysis found that both sex and LVMI (R=0.658 for combination, $p<0.001$) were independent predictors of nMBF in subjects with HTN, of which LVMI had the largest impact on nMBF. The Spearman correlation analysis showed that MBF was significantly negatively correlated with LVMI (r= -0.499, p=0.004), but no significant correlation was found between MBV and LVMI. In addition, it was also found that males preserved significantly lower MBF than females [120 (101 to 145) *vs.* 129 (119 to 171) ml/100 ml/min, p=0.048] in the subjects with HTN, but not for MBV.

Discussion

The main finding of this study was that stress MBF decreased in hypertensive patients with non-obstructive CAD using CT-MPI. There was a significant correlation between sex, LVMI and MBF. CT-MPI could be used as a new noninvasive modality to evaluate myocardial perfusion in hypertensive patients.

CT-MPI, based on its superior spatial resolution and relative

cost-effectiveness, is increasingly widely used in the clinic. It provides an anatomic assessment of coronary and functional assessment of myocardial perfusion within one examination [17]. At present, PET is widely used as the gold standard for evaluating myocardial perfusion [18]. Studies explored the correlation between MBF derived from CT-MPI and from PET, these studies had proven a good correlation between the two imaging modalities [19,20]. The current reference standard for quantitative measurement of MBF in PET is that the normal stress MBF values are between 3 and 5 mL/min/g [21-23], while the MBF values reported by dynamic CT-MPI are between 1.0 and 1.4 mL/min/g, which is considered to be an underestimate of MBF [24-27]. A reason for the underestimation of MBF values based on CT-MPI is the lower sampling frequency; the other reason is that the nature of the Patlak-based method (VPCT software we used) is to calculate the transfer coefficient equivalent rather than the MBF [28].

In this study, we excluded the patients with obstructive epicardial coronary stenosis using the coronary anatomic assessment of cCTA, and made full use of the functional assessment of myocardial perfusion of CT-MPI to study the effect of HTN and HTN-induced LVH on myocardial perfusion after adenosine-induced myocardial hyperemia. HTN, as a risk factor of myocardial ischemia, is significantly correlated with MACE [29,30]. In particular, myocardial ischemia is more pronounced in hypertensive patients with LVH [1,9,31,32]. The absolute quantified MBF is affected by epicardial coronary stenosis, coronary microcirculation, use of β-blockers, intake of caffeine, and individual response to adenosine. Therefore, the quantified MBF, after reaching the state of maximal hyperemia using adenosine, excluding epicardial coronary stenosis and use of β-blockers and caffeine, can evaluate the myocardial ischemia. In this study, we found that although the MBF in the HTN group was statistically significantly lower than that of the non-HTN group [124 (114 to 146) *vs.* 151 (127 to 169) ml/100 ml/min, p=0.005], the box and plot in CT-MBF were partial overlapped between HTN and non-HTN group, the LVH and non-LVH group, respectively, it may be explained by the small sample size. The results of this study are similar to those of previous studies using MRI [33] and PET [34]. Furthermore, we found the HTN group had higher age, BMI, BSA, smoking, and hyperlipidemia proportion than the non-HTN group. These traditional CAD risk factors are associated with coronary microcirculation abnormalities leading to myocardial perfusion disorder [35]. Previous studies have also demonstrated the effects of traditional cardiovascular risk factors on coronary microcirculation [35-37]. In multivariate linear regression analysis, we also found that sex was an independent factor of nMBF, so we further investigated the difference in MBF between the females and males. The results showed lower MBF for males compared with that of females in all study populations and in the hypertensive subjects. This finding had been validated by a number of previous studies [38-40], and it may be related to lipid levels or hormone status [38]. Clinical observations found that CCB were responsible for the improvement of angina pectoris symptoms and exercise tolerance correlated with microvascular angina [36,41]. Although we found higher CCB intake in LVH group, MBF was significantly lower in LVH group than that in non-LVH group. These contradicting results have also been illustrated in one previous study, which may be resulted from the improvement of endothelial function, vasodilation of the pre arterioles and cardiac metabolism [42]. In our view, CCB may increase myocardial perfusion to improve angina pectoris by dilating the arterioles at rest state rather than stress state. We only measured myocardial perfusion parameters of left ventricle at stress state in our study, which may explain the contradicting findings.

Pathophysiologically, hypertension induced the development of interstitial fibrosis, the reduction of intra-myocardial capillary density, and thickening of the wall of small coronary arteries [4,9]. The remolding of the coronary arterioles significantly decreased the capacity of coronary vasodilation, resulting in impaired myocardial perfusion [43-45]. MBF reflects the blood flow per unit of myocardial tissue and per unit of time. In this study, we adopted ml/100 ml/min as the measurement unit of MBF. MBV is defined as the blood volume in the myocardium, which reflects the microvascular volume occupied by blood [17]. In the present study, unexpectedly, -LVH groups. The contradicted results were seemingly due to the criteria for individual inclusion, significant stenosis (stenosis >50%) of the epicardial coronary artery may produce the low MBV in patients with HTN.

For CT perfusion scanning, we found no differences in MBV between the HTN and non-HTN groups and between the LVH and none needed at least one time point that the flat-scan image is used to set the baseline value. If the scan time is too early, the patient will be exposed to unnecessary radiation, if the scan time is too late, the first scan will be already contrast scan, then the baseline value is inaccurate and the results will be affected, so a delay of 4 to 6 seconds is more appropriate based on the average time of human blood circulation. We decided the scan timing that 4 seconds before the arrival of the contrast in the ascending aorta. During the perfusion scans, the arterial input function curve and tissue attenuation curve were corrected for baseline differences and contrast build-up, and subsequently resampled to correct for non-uniform temporal sampling rates caused by heart rate variations. Considering that the end-diastole determined by CT scans is based on ECG–gated acquisition, which is not accurate enough, compared to artificially adjusted ultrasound images, we chose to measure LVMI using echocardiography rather than CT.

Study Limitations

There are several limitations in the present study. First, limited by the sample size, we analyzed the effect of LVMI but not relative wall thickness on myocardial perfusion parameters. Future studies may expand the sample size to analyze the difference of myocardial perfusion parameters between hypertensive patients with concentric hypertrophy and eccentric hypertrophy. Second, we measured the stress perfusion parameters of CT-MPI in this study, but no resting perfusion parameters were detected. Thus, CFR could not be obtained. Further studies can be performed to detect CFR and make it easier to elucidate the effects of HTN and LVH on CMVD. Lastly, the radiation dose increased must be taken into account.

Conclusion

Overall, we found that stress MBF decreased in hypertensive patients with non-obstructive epicardial coronary stenosis using dynamic stress CT-MPI. Both sex and LVMI are the independent predictors of MBF. Dynamic stress CT-MPI could be used as a promising noninvasive technique to evaluate myocardial perfusion in patients with HTN.

Acknowledgement

Special thanks and acknowledgements to all cardiology residents and radiology technicians of Qilu Hospital, Cheeloo College of Medicine, Shandong University who kindly helped with enrollment

and study examinations.

References

1. Devereux RB, Wachtell K, Gerdts E, Boman K, Nieminen MS, Papademetriou V, et al. Prognostic significance of left ventricular mass change during treatment of hypertension. JAMA. 2004;292(19):2350-6.
2. Kato S, Saito N, Kirigaya H, Gyotoku D, Iinuma N, Kusakawa Y, et al. Impairment of coronary flow reserve evaluated by phase contrast cine-magnetic resonance imaging in patients with heart failure with preserved ejection fraction. J Am Heart Assoc. 2016;5(2):e002649.
3. Tsiachris D, Tsioufis C, Dimitriadis K, Syrseloudis D, Rousos D, Kasiakogias A, et al. Relation of impaired coronary microcirculation to increased urine albumin excretion in patients with systemic hypertension and no epicardial coronary arterial narrowing. Am J Cardiol. 2012;109(7):1026-30.
4. Fu Q, Zhang Q, Lu W, Wang Y, Huang Y, Wang Y, et al. Assessment of coronary flow reserve by adenosine stress myocardial perfusion imaging in patients with hypertension. Cell Biochem Biophys. 2015;73(2):339-44.
5. Williams B, Mancia G, Spiering W, Rosei EA, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018;39(33):3021-104.
6. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: Analysis of worldwide data. Lancet. 2005;365(9455):217-23.
7. Beanlands RS, Chow BJ, Dick A, Friedrich MG, Gulenchyn KY, Kiess M, et al. CCS/CAR/CANM/CNCS/CanSCMR joint position statement on advanced noninvasive cardiac imaging using positron emission tomography, magnetic resonance imaging and multidetector computed tomographic angiography in the diagnosis and evaluation of ischemic heart disease--executive summary. Can J Cardiol. 2007;23(2):107-19.
8. Wang Y, Qin L, Shi X, Zeng Y, Jing H, Schoepf UJ, et al. Adenosine-stress dynamic myocardial perfusion imaging with second-generation dual-source CT: Comparison with conventional catheter coronary angiography and SPECT nuclear myocardial perfusion imaging. AJR Am J Roentgenol. 2012;198(3):521-9.
9. Akinboboye OO, Chou RL, Bergmann SR. Myocardial blood flow and efficiency in concentric and eccentric left ventricular hypertrophy. Am J Hypertens. 2004;17(5 Pt 1):433-8.
10. Gebker R, Mirelis JG, Jahnke C, Hucko T, Manka R, Hamdan A, et al. Influence of left ventricular hypertrophy and geometry on diagnostic accuracy of wall motion and perfusion magnetic resonance during dobutamine stress. Circ Cardiovasc Imaging. 2010;3(5):507-14.
11. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28(1):1-39.
12. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1916. Nutrition. 1989;5(5):303-11.
13. Marwick TH, Gillebert TC, Aurigemma G, Chirinos J, Derumeaux G, Galderisi M, et al. Recommendations on the use of echocardiography in adult hypertension: A report from the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE). Eur Heart J Cardiovasc Imaging. 2015;16(6):577-605.
14. Vliegenthart R, De Cecco CN, Wichmann JL, Meinel FG, Pelgrim GJ, Tesche C, et al. Dynamic CT myocardial perfusion imaging identifies early perfusion abnormalities in diabetes and hypertension: Insights from a multicenter registry. J Cardiovasc Comput Tomogr. 2016;10(4):301-8.
15. Mahnken AH, Klotz E, Pietsch H, Schmidt B, Allmendinger T, Haberland U, et al. Quantitative whole heart stress perfusion CT imaging as noninvasive assessment of hemodynamics in coronary artery stenosis: Preliminary animal experience. Invest Radiol. 2010;45(6):298-305.
16. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the cardiac imaging committee of the council on clinical cardiology of the American Heart Association. Circulation. 2002;105(4):539-42.
17. Feher A, Sinusas AJ. Quantitative assessment of coronary microvascular function: Dynamic single-photon emission computed tomography, positron emission tomography, ultrasound, computed tomography, and magnetic resonance imaging. Circ Cardiovasc Imaging. 2017;10(8):e006427.
18. deKemp RA, Yoshinaga K, Beanlands RS. Will 3-dimensional PET-CT enable the routine quantification of myocardial blood flow. J Nucl Cardiol. 2007;14(3):380-97.
19. Alessio AM, Bindschadler M, Busey JM, Shuman WP, Caldwell JH, Branch KR. Accuracy of myocardial blood flow estimation from dynamic contrast-enhanced cardiac CT compared with PET. Circ Cardiovasc Imaging. 2019;12(6):e008323.
20. Kikuchi Y, Oyama-Manabe N, Naya M, Manabe O, Tomiyama Y, Sasaki T, et al. Quantification of myocardial blood flow using dynamic 320-row multi-detector CT as compared with ^{15}O-H_2O PET. Eur Radiol. 2014;24(7):1547-56.
21. Kajander SA, Joutsiniemi E, Saraste M, Pietilä M, Ukkonen H, Saraste A, et al. Clinical value of absolute quantification of myocardial perfusion with (15)O-water in coronary artery disease. Circ Cardiovasc Imaging. 2011;4(6):678-84.
22. Bol A, Melin JA, Vanoverschelde JL, Baudhuin T, Vogelaers D, De Pauw M, et al. Direct comparison of [13N]ammonia and [15O]water estimates of perfusion with quantification of regional myocardial blood flow by microspheres. Circulation. 1993;87(2):512-25.
23. El FG, Kardan A, Sitek A, Dorbala S, Abi-Hatem N, Lahoud Y, et al. Reproducibility and accuracy of quantitative myocardial blood flow assessment with (82)Rb PET: Comparison with (13)N-ammonia PET. J Nucl Med. 2009;50(7):1062-71.
24. Pelgrim GJ, Dorrius M, Xie X, den Dekker M, Schoepf UJ, Henzler T, et al. The dream of a one-stop-shop: Meta-analysis on myocardial perfusion CT. Eur J Radiol. 2015;84(12):2411-20.
25. Kim EY, Chung WJ, Sung YM, Byun SS, Park JH, Ho Kim J, et al. Normal range and regional heterogeneity of myocardial perfusion in healthy human myocardium: assessment on dynamic perfusion CT using 128-slice dual-source CT. Int J Cardiovasc Imaging. 2014;30(Suppl 1):33-40.
26. Saraste A, Knuuti J. Dynamic perfusion CT: What is normal myocardial blood flow? Eur Heart J Cardiovasc Imaging. 2015;16(3):288-9.
27. Rossi A, Merkus D, Klotz E, Mollet N, de Feyter PJ, Krestin GP. Stress myocardial perfusion: Imaging with multidetector CT. Radiology. 2014;270(1):25-46.
28. Ishida M, Kitagawa K, Ichihara T, Natsume T, Nakayama R, Nagasawa N, et al. Underestimation of myocardial blood flow by dynamic perfusion CT: Explanations by two-compartment model analysis and limited temporal sampling of dynamic CT. J Cardiovasc Comput Tomogr. 2016;10(3):207-14.
29. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Himmelfarb CD, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;71(6):1269-324.
30. Rapsomaniki E, Timmis A, George J, Pujades-Rodriguez M, Shah AD, Denaxas S, et al. Blood pressure and incidence of twelve cardiovascular diseases: Lifetime risks, healthy life-years lost, and age-specific associations

in 1.25 million people. Lancet. 2014;383(9932):1899-911.

31. Tsai SH, Lu G, Xu X, Ren Y, Hein TW, Kuo L. Enhanced endothelin-1/Rho-kinase signalling and coronary microvascular dysfunction in hypertensive myocardial hypertrophy. Cardiovasc Res. 2017;113(11):1329-37.

32. Amanullah AM, Berman DS, Kang X, Cohen I, Germano G, Friedman JD. Enhanced prognostic stratification of patients with left ventricular hypertrophy with the use of single-photon emission computed tomography. Am Heart J. 2000;140(3):456-62.

33. Nakajima H, Onishi K, Kurita T, Ishida M, Nagata M, Kitagawa K, et al. Hypertension impairs myocardial blood perfusion reserve in subjects without regional myocardial ischemia. Hypertens Res. 2010;33(11):1144-9.

34. Rimoldi O, Rosen SD, Camici PG. The blunting of coronary flow reserve in hypertension with left ventricular hypertrophy is transmural and correlates with systolic blood pressure. J Hypertens. 2014;32(12):2465-71.

35. Tamis-Holland JE, Jneid H, Reynolds HR, Agewall S, Brilakis ES, Brown TM, et al. Contemporary diagnosis and management of patients with myocardial infarction in the absence of obstructive coronary artery disease: A scientific statement from the American Heart Association. Circulation. 2019;139(18):e891-e908.

36. Bairey MCN, Pepine CJ, Walsh MN, Fleg JL. Ischemia and No Obstructive Coronary Artery Disease (INOCA): Developing evidence-based therapies and research agenda for the next decade. Circulation. 2017;135(11):1075-1092.

37. Pasupathy S, Air T, Dreyer RP, Tavella R, Beltrame JF. Systematic review of patients presenting with suspected myocardial infarction and nonobstructive coronary arteries. Circulation. 2015;131(10):861-70.

38. Duvernoy CS, Meyer C, Seifert-Klauss V, F Dayanikli, I Matsunari, J Rattenhuber, et al. Gender differences in myocardial blood flow dynamics: lipid profile and hemodynamic effects. J Am Coll Cardiol. 1999;33(2):463-70.

39. Danad I, Raijmakers PG, Appelman YE, Harms HJ, de Haan S, van den Oever MLP, et al. Coronary risk factors and myocardial blood flow in patients evaluated for coronary artery disease: A quantitative [15O]H_2O PET/CT study. Eur J Nucl Med Mol Imaging. 2012;39(1):102-12.

40. Sunderland JJ, Pan XB, Declerck J, Menda Y. Dependency of cardiac rubidium-82 imaging quantitative measures on age, gender, vascular territory, and software in a cardiovascular normal population. J Nucl Cardiol. 2015;22(1):72-84.

41. Cannon RO, Watson RM, Rosing DR, Epstein SE. Efficacy of calcium channel blocker therapy for angina pectoris resulting from small-vessel coronary artery disease and abnormal vasodilator reserve. Am J Cardiol. 1985;56(4):242-6.

42. Sütsch G, Oechslin E, Mayer I, Hess OM. Effect of diltiazem on coronary flow reserve in patients with microvascular angina. Int J Cardiol. 1995;52(2):135-43.

43. Zhu XY, Daghini E, Chade AR, Rodriguez-Porcel M, Napoli C, Lerman A, et al. Role of oxidative stress in remodeling of the myocardial microcirculation in hypertension. Arterioscler Thromb Vasc Biol. 2006;26(8):1746-52.

44. Rizzoni D, Palombo C, Porteri E, Lorenza Muiesan M, Kozàkovà M, La Canna G, et al. Relationships between coronary flow vasodilator capacity and small artery remodeling in hypertensive patients. J Hypertens. 2003;21(3):625-31.

45. Rodriguez-Porcel M, Zhu XY, Chade AR, Amores-Arriaga B, Caplice NM, Ritman EL, et al. Functional and structural remodeling of the myocardial microvasculature in early experimental hypertension. Am J Physiol Heart Circ Physiol. 2006;290(3):H978-84.