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Original Article

Relation Between Microvascular and Macrovascular Hemodynamics in Normal Epicardial Coronary Arteries

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ABSTRACT

Background Cardiovascular risk factors affect both macrovascular and microvascular systems, resulting in negative results on the entire vascular tree. Aortic stiffness causes augmented systolic pressure, increased pulse pressure, increased myocardial oxygen demand, and consequently, coronary blood flow diminishes because of decreased diastolic augmentation. Deterioration in arterial stiffness and increased pressure pulsatility were shown in association with microvascular dysfunction. We investigated the relation between macrovascular parameters expressed by carotid-femoral pulse wave velocity (PWV), augmentation index (AI), and coronary microvascular parameters expressed by coronary flow reserve (CFR), index of microvascular resistance (IMR), and subendocardial viability ratio (SEVR)

Material and Methods We have included 58 consecutive patients (29 male, age 54 [34-71]) without any epicardial coronary stenosis in coronary angiography. Macrovascular and microvascular parameters were calculated with the measurements of tonometry, coronary flow reserve, and microvascular resistance.

Results PWV and SEVR had an inverse correlation (r=-0.328, p=0.007). The main reason for this correlation was a priorly positive correlation between PWV and systolic pressure-time integral (SPTI) (r=0.465, p<0.001).A positive correlation was noted between augmentation index (AI) and PWV (r=0.352, p=0.010); and an inverse significant correlation was noted between AI and SEVR (r=-0.383, p=0.003). PWV had a positive correlation with diastolic/systolic coronary flow velocity (r=0.42, p=0.04) and microvascular resistance (MR) (r=0.44, p=0.03) and a negative correlation with hyperemic mean coronary flow velocity (r=-0.416, p=0.043) and coronary flow reserve (CFR) (r=-0.419, p=0.04) in diabetic patient group (n=27). AI was inversely related to CFR (r=-0.41, p=0.04) in diabetic patient group. SEVR and CFR were well correlated in the same direction (r=0.569, p<0.001). SEVR was significantly lower in the patients with lower CFR (1.41±0.23 vs.1.58±0.24, p=0.01). SEVR had a significant negative correlation with MR (r=-0.321, p=0.016). SEVR was associated with arteriolar resistance index (r=0.413, p=0.002).

Conclusions Arterial stiffness is associated with coronary microvascular dysfunction in normal epicardial coronary arteries. The relation between the stiffness of the aorta, subendocardial myocardial perfusion, and coronary microvascular dysfunction in our study suggests that central arterial stiffness modulation may be a target for the treatment of coronary microvascular dysfunction.

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Introduction

Cardiovascular diseases are rapidly progressing in patients with risk factors, and the coexistence of these factors leads to more negative outcomes. Cardiovascular risk factors affect both macrovascular and microvascular systems, resulting in negative results on the entire vascular tree. A typical example of a macrovascular effect is an increase in arterial stiffness, and a typical example of a microvascular effect is remodeling in small-sized resistance arteries and a reduction in the vascular dilatation capacity.

In long-term epidemiological studies, increased arterial stiffness is an independent predictor of cardiovascular adverse events.[1] In many studies of arterial stiffness modeled by carotid-femoral pulse wave velocity (PWV) measurements in patients with hypertension, PWV is associated with all-cause and cardiovascular mortality.[2] As the aorta stiffens, the reflected wave returns in the systole rather than the diastole. Consequently, aortic stiffness causes augmented systolic pressure, increased pulse pressure, and increased myocardial oxygen demand. Coronary blood flow diminishes because of the decreased diastolic augmentation. Although there is no significant stenosis in coronary arteries, this decrease in coronary flow may cause impairment in the coronary microcirculation. The relation between arterial stiffness and coronary microcirculation has been investigated in experimental studies.[3-5] In the Framingham Heart Study, deterioration in arterial stiffness and increased pressure pulsatility were shown in association with microvascular dysfunction.[6] In another study, higher arterial stiffness was related to lower flow reserve calculated by flow-mediated dilatation beyond traditional risk factors.[7] Cooper et al.[8] also showed that a higher incidence of cardiovascular events was seen in patients with increased arterial stiffness and decreased hyperemic flow velocity.

We investigated the relation between macrovascular parameters expressed by carotid-femoral PWV, augmentation index (AI), and coronary microvascular parameters expressed by coronary flow reserve (CFR), index of microvascular resistance (IMR), and subendocardial viability ratio (SEVR).

Material and Methods

We included 58 patients who underwent elective coronary angiography because of stable angina or inducible ischemia in imaging studies and had no epicardial coronary artery stenosis. Non-invasive coronary flow reserve, coronary microvascular resistance, and arterial stiffness measurements were performed in all patients. CFR and IMR could not be calculated in one patient, and PWV could not be measured in 3 patients due to technical difficulties. We excluded patients with a history of myocardial infarction or coronary revascularization, cardiomyopathy, myocarditis, left ventricular systolic dysfunction (left ventricle ejection fraction <55%), moderate-severe valvular heart disease, chronic kidney and liver failure, active malignancy, active infection, and chronic obstructive pulmonary disease.

Patients with fasting blood sugar above 126 mg/dL and treated for known diabetes mellitus were considered diabetic. Patients with a systolic blood pressure above 140 mmHg, diastolic blood pressure above 90 mmHg, or those with a history of antihypertensive use were considered hypertensive. A fasting LDL level greater than 130 mg/dL or a history of statin use and a fasting triglyceride level above 150 mg/dL or with a history of antilipidemic drug use was considered as hyperlipidemia. All patients were included in the study after their written consent was obtained. The local ethics committee approved the study (2015/1283).

Measurement of Coronary Flow Reserve and Microvascular Resistance

CFR and coronary microvascular resistance studies were performed with VIVID 7 echocardiography device (GE, General Electronic). The mid-distal flow of the left anterior descending artery (LAD) was imaged with colored doppler with an optimal velocity of 12-15 cm/sec in the left ventricular apical 2-space long-axis view of the fourth or fifth left intercostal space in the left lateral decubitus position. Baseline diastolic average peak velocity (APVb), and diastolic deceleration time (DTb) of coronary flow were measured with pulsed-wave doppler, firstly. Then a dipyridamole infusion of 0.56 mg/kg was administered for 4 minutes. If the heart

rate increases less than 10% compared to baseline, an infusion of 0.28 mg/kg dipyridamole was added for 2 minutes. Then, hyperemic diastolic average peak velocity (APVh) and hyperemic diastolic deceleration time (DTh) were measured 2 minutes after the dipyridamole infusion was completed. Pre-and post-infusion blood pressures were measured at frequent intervals. CFR was calculated with the formula of APVh/APVb *(Figure 1).*

Resistance in arteries can be calculated with pressure difference divided by arterial flow (Resistance=ΔP/blood flow). The mean blood pressure measured from the peripheral artery is the same as the pressure that can be measured in any coronary area since it is studied in patients with proven absence of epicardial coronary artery stenosis. Coronary flow can be measured directly by doppler echocardiography from LAD. Microvascular resistance (MR), which is routinely calculated invasively, can be calculated by dividing mean blood pressure measured from the brachial artery by average peak velocity of coronary flow measured by echocardiography in patients with normal coronary arteries non-invasively. MR was calculated in baseline (MRb) and hyperemia (MRh) with the formula below:

Mean blood pressure (MBP)=diastolic blood pressure (DBP)+(systolic blood pressure [SBP]–DBP)/3

MR (cm.sn-1.mmHg)=MBP (mmHg)/average peak coronary flow velocity (cm/sec)

Arteriolar resistance index (ARI) is a significant indicator of resistance at the arterial level. ARI was calculated by the difference between the hyperemic and basal values of MR.

ARI=MRb – MRh

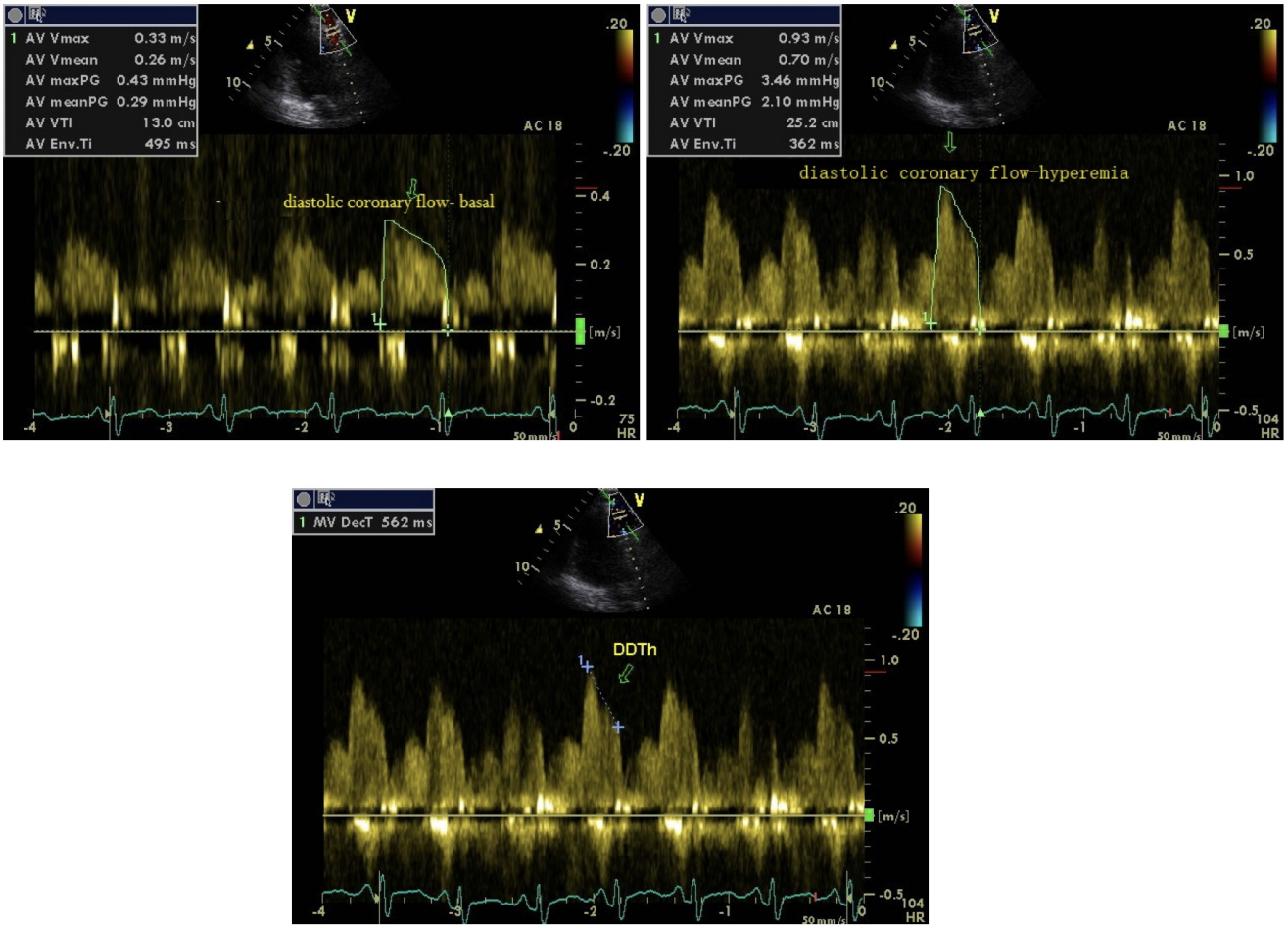

Figure 1. Hyperemic diastolic flow pattern, hyperemic diastolic deceleration time (DTh) and basal diastolic flow pattern obtained by pulsed wave doppler echocardiography from the mid-distal LAD in transthoracic echocardiography.

Measurement of Arterial Stiffness Parameters

Measurements were taken using SphygmoCor (AtCor Medical Pty. Ltd., Sydney) tonometry device. All measurements were made in ideal room conditions at the same time of the day, ten minutes after rest and lying in the supine position. Measurements were obtained by the applanation tonometry method. In this method, pressure trace was recorded pressing gently to the peripheral artery with a pressure transducer. Measurements were made on the radial artery because the pulse waveforms obtained from the superficial arteries were almost identical to the intra-arterial pressure waves. Pressure waveforms were transferred to the computer. SBP, DBP, mean arterial pressure (MAP), pulse pressure (PP), heart rate, augmentation index (AI), diastolic pressure-time integral (DPTI), systolic pressure-time integral (SPTI) parameters were calculated using "Pulse Wave Analysis (PWA)" with dedicated software of the device *(Figure 2)*.

PWV: The distance between the carotid artery and femoral artery was measured. The distance was calculated by the "direct measurement" method (direct carotid-femoral artery distance X 0.8) as indicated in the published consensus report.[9] PWV was calculated by dividing the time difference between the carotid artery and femoral artery by this distance.

Subendocardial viability ratio: The area under the systolic and diastolic portions of the central aortic pulse wave can be determined by pulse wave analysis. DPTI and SPTI were measured as the area under the diastolic and systolic portions of the pulse waves, respectively. SEVR was calculated from the ratio of DPTI to SPTI.

AI: AI was calculated from the central aortic waveform record as follows: Augmentation pressure (SBP – pressure at the first peak shoulder of the aortic pulse wave)/PPx100. AI was corrected for heart rate at 75 bpm as defined before.[10]

Statistical Analysis

Statistical analyses were performed using the computer software Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, version 21.0 released 2012, IBM Corp., Armonk, New York, USA). Kolmogorov-Smirnov test was performed to detect the distribution of the variables. Normally distributed variables are presented as mean±standard deviation, and

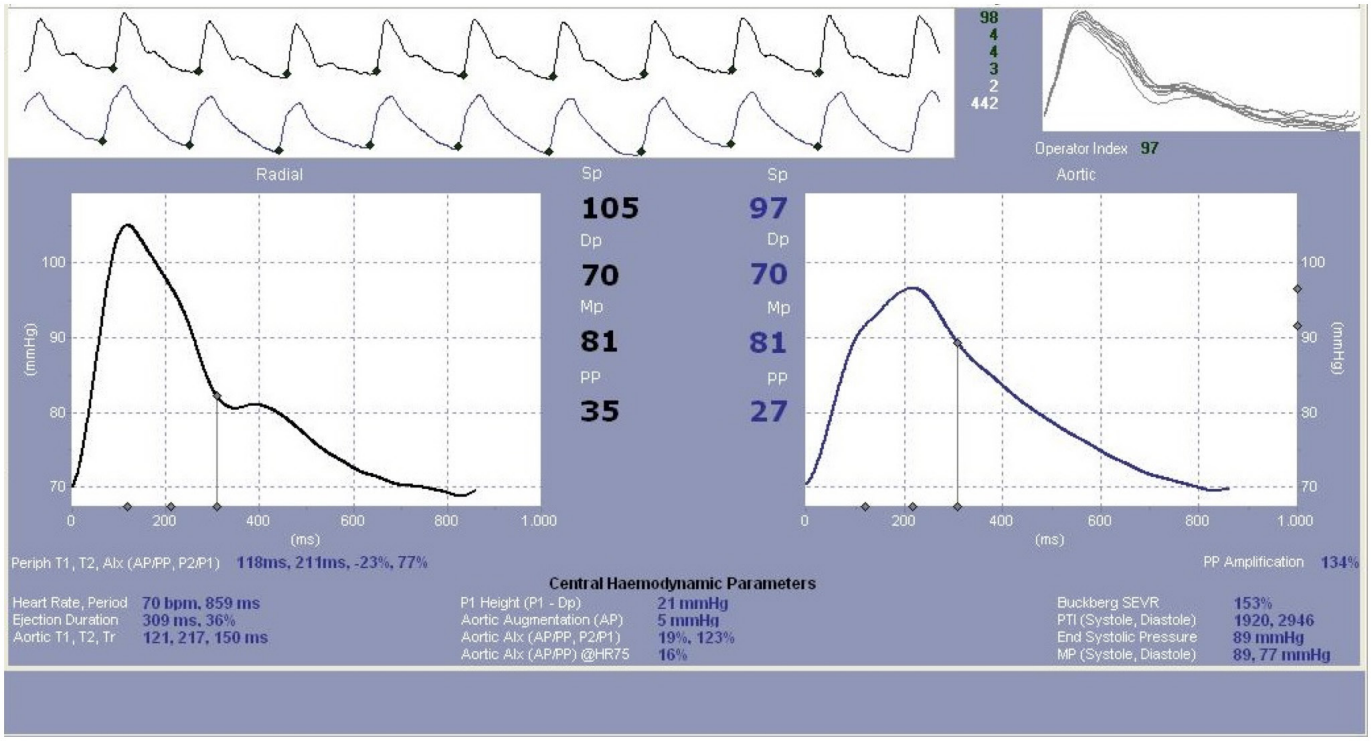

Figure 1. Central aortic pressure waveforms and hemodynamic parameters obtained by these waveforms

nonnormally distributed variables are presented as median (25^{th} to 75^{th} percentile). Categorical variables are expressed as numbers (%). The Student t-test was used to compare quantitative variables with normal distribution, and the Mann-Whitney U test was used to compare quantitative variables without normal distribution. The Pearson's chi-square and Fisher's exact tests were performed for categorical variables. Relations between coronary hemodynamic parameters and arterial hemodynamic parameters were assessed using Pearson or Spearman correlation analysis where appropriate. A p-value of <0.05 was considered significant.

Results

A total of 58 patients (29 males, mean age 54 [34-71]) were included in the study. 63% of the patients had hypertension (HT), 48% had diabetes mellitus (DM), 41% had hyperlipidemia (HL), and 17% had a smoking history. The general characteristics of the patients are shown in Table 1, measured microvascular parameters in Table 2, and macrovascular parameters in Table 3.

Relation Between Arterial Stiffness Parameters and SEVR

An inverse correlation was noted between PWV and SEVR (r=-0.328, p=0.007). This relationship was basically determined by the relationship of PWV and SPTI (r=0.465, p <0.001). A positive

Table 1. Patients' general characteristics

Variables	All study population (n=58)
Age (years)	54.97±8.5
Male	29 (50)
Hypertension	37 (63.8)
Diabetes Mellitus	28 (48.3)
Hyperlipidemia	24 (41.4)
Smoking	10 (17.2)
Body mass index (kg/m^2)	30.3±5.2
HbA1c (%)	7.06±1.4
Microalbumin/Creatinine (mg/g)	22.5±27.1
Creatinine (mg/dL)	0.84±0.19
Hemoglobin (g/dL)	13.2±1.3
HDL-Cholesterol (mg/dL)	45.3±12.3
LDL-Cholesterol (mg/dL)	132.5±27.8
Systolic blood pressure (mmHg)	125.4±15.2
Diastolic blood pressure (mmHg)	73.86±9.01
Carotid intima-media thickness (mm)	0.69±0.16
Ejection fraction (%)	68.9±2.7

Data are presented as number (%) or mean±SD. HbA_{1c}: glycosylated hemoglobin, SD: standard deviation.

Table 2. Microvascular parameters.

Parameters	Mean± SD
APVb (cm/sn)	23.93±5.60
DDTb (msn)	993±206
APVh (cm/sn)	51.74±13.31
sAPVh (cm/sn)	26.33±6.61
DDTh(msn)	743±197
CFR	2.19±0.48
MRb ($cm.sn^{-1}.mmHg$)	3.96±0.83
MRh ($cm.sn^{-1}.mmHg$)	1.76±0.47
Delta MR ($cm.sn^{-1}.mmHg$)	2.19±0.64

APVb: baseline average peak velocity, APVh: hyperemic average peak velocity, CFR: coronary flow reserve, DDTb: baseline diastolic deceleration time, DDTh: hyperemic diastolic deceleration time, MRb: baseline microvascular resistance, MRh: hyperemic microvascular resistance, sAPVh: systolic hyperemic average peak velocity.

Table 3. Macrovascular parameters.

Parameters	Mean±SD
PWV (m/sn)	8.37±2.06
AI (%)	25±11.01
DPTI (mmHg x sec)	3251.18±503.029
SPTI (mmHg x sec)	2261.12±414.813
SEVR (%)	1.46±0.22
Mean blood pressure (mmHg)	90.95±9.96
Pulse pressure (mmHg)	51.53±12.43

AI: augmentation index, DPTI: diastolic pressure-time integral, PWV: pulse wave velocity, SPTI: systolic pressure-time integral, SEVR: Subendocardial viability ratio.

correlation was noted between AI and PWV (r=0.352, p=0.010); and an inverse significant correlation was noted between AI and SEVR (r=-0.383, p=0.003).

Relation Between Coronary Microvascular Parameters and Arterial Stiffness Parameters

PWV and AI were not correlated with microvascular parameters in all groups or non-diabetic patients. PWV has a positive correlation with diastolic/systolic coronary flow velocity (r=0.42, p=0.04) and MR (r=0.44, p=0.03) and a negative correlation with diastolic deceleration time (DDT) (r=-0.399, p=0.05), hyperemic mean coronary flow velocity (r=-0.416, p=0.043) and CFR (r=-0.419, p=0.04) in diabetic patient group (n=27). AI was inversely related to CFR (r=-0.41, p=0.04) in diabetic patient group.

Relation Between SEVR and Coronary Microvascular Parameters

When the relation between SEVR and CFR was evaluated in the whole group, it was seen that the two parameters were well correlated in the same direction (r=0.569, p <0.001). SEVR was significantly lower in the patients with lower CFR (1.41±0.23 vs. 1.58±0.24, p=0.01) when CFR values were divided into two groups according to 2, which was considered categorically significant.[11] When SEVR and MR were evaluated, it was seen that the two parameters were significantly correlated in the opposite direction (p=0.016, r=-0.321). Delta MR (arteriolar resistance index-ARI), which is a significant indicator of resistance at the arterial level -calculated by the difference between the hyperemic and basal values of MR- and SEVR were shown to correlate significantly in the same direction (p=0.002, r=0.413).

Discussion

In this study, the effect of aortic stiffness, assessed by central hemodynamic parameters (PWV and AI) on myocardial supply/demand balance (SEVR) and coronary microcirculation hemodynamics (CFR and IMR), were investigated in patients with normal epicardial coronary arteries. The main findings of our study are as follows:

1. An increase in the severity of aortic stiffness determined by central hemodynamic parameters is associated with decreased subendocardial

perfusion (SEVR) despite normal coronary perfusion pressure (patients with normal coronary arteries). So, central aortic hemodynamic properties affect subendocardial microvascular perfusion.

2. PWV, an expression of the degree of arterial stiffness, is related to the structural and functional status assessed by objective parameters of coronary microcirculation in the diabetic patient group (CFR, ARI, MR). Increased aortic stiffness in diabetic patients affects microvascular hemodynamic parameters negatively despite normal epicardial coronary arteries.

3. A decrease in subendocardial perfusion ratio is associated with increased coronary microvascular resistance and a decrease in coronary flow reserve.

CFR is a measure of how much of the maximum flow quantity the microvessel can adapt to during myocardial rest.[12] Although the reduction in CFR is often considered a decrease in the dilatation capacity of the coronary microvasculature and, therefore, called microvascular dysfunction, another important indicator of the need for coronary flow during rest is energy the left ventricle consumes during systole. Any condition that causes the left ventricle to experience more hydraulic load during blood transfer to the aorta will increase baseline blood requirement and, therefore, a decrease in coronary flow reserve. Aortic stiffness, depending on age and various pathologies, causes blood to be drawn during systole to cause more aortic pressure elevation due to decreased aortic compliance.[13] This increase in hydraulic work, which is the product of pressure and stroke volume, requires more coronary flow (as shown in our work, PWV is related to SPTI). This causes the heart to use more quantity of CFR during the rest. Therefore, the increase in aortic stiffness is associated with a decrease in CFR, as demonstrated by the diabetic patient group. This situation, which leads to more dilatation of the prearteriolar sphincters during rest, also explains why there is a correlation between deltaMR and SEVR in our study (delta MR or ARI is a measure of the dilatation capacity of the prearteriolar sphincter, which represents the difference between baseline and hyperemic states of coronary microvascular resistance).[14] Essentially, in this situation, there is not any primary problem in the dilatation capacity of the coronary microvascular bed, and there is not any primary microvascular dysfunction. In accordance with our trial, Muroya et al.[15] showed that increased arterial stiffness is associated with microvascular dysfunction in non-obstructive coronary arteries.

Another disadvantage of aortic stiffness is increased systolic-diastolic fluctuation and pulsatile organ flow.[16] This creates a bigger problem, especially for coronary beds that are fed in the diastole. SEVR, which is an indicator of myocardial supply/demand balance and, therefore particularly, subendocardial perfusion, is related to the structural (MR) and functional (ARI) characteristics of the coronary microcirculation.[17] DPTI (mmHg x sec) accounts for the coronary diastolic pressure and diastolic time. Thus, it potentially indicates subendocardial blood flow supply. Reduced compliance with the lower diastolic flow (or lower DPTI) may cause objective ischemia because of supply/demand imbalance during exercise despite normal coronary arteries. In a previous study in normal coronary arteries, low CFR was associated with decreased SEVR as in our study.[18]

Another negative effect of arterial stiffness is that the pressure wave transmitted to the periphery during systole returns more rapidly than observed in the normal aorta.[19] In the optimal case, the reflected wave reaches the proximal aorta in the diastole and is less noticeable; but in the stiffened aorta, this wave returns in the systole and becomes more prominent. This means that more myocardial energy is needed to provide the same amount of cardiac output. Previous studies have demonstrated that lower levels of CFR in diabetic patients compared to non-diabetic patients in normal coronary arteries are explained with increased basal coronary flow rate, which is an indicator of increased myocardial energy requirement.[20-23]

One of the interesting findings of our study is the inverse relationship between hyperemic MR and SEVR. Since MR in resting is associated with coronary blood requirement, it is expected that there will not be a direct connection between the maximal dilatation capacity of the coronary bed -even if it is related to the afterload increase due to aortic stiffness. This association may be interpreted as an increase in the hyperemic

coronary microvascular resistance because of 1) aortic stiffness increasing microvascular resistance by microvascular destruction in various ways or 2) the mechanism causing the aortic stiffness leading to an increase in coronary resistance. First, a mechanism may be suggested that increased pulsatile stress has an adverse effect on the coronary bed. Mitchell et al.[16] investigated the effect of arterial stiffness on brain structure and function. Carotid pulse rate, pulsatility index, and carotid-femoral PWV increase were associated with an increase in silent subclinical infarcts detected by MRI. At the same time, increased pulsatility index was associated with lower total brain volume, lower memory scores, and decreased cognitive function. In another trial, the increased arterial pulsatile flow was associated with coronary microvascular dysfunction and cardiovascular events in non-obstructive coronary arteries.[24] Second, the similarities between the pathological changes in the micro and macrovascular structures can be suggested. Due to the elastic properties of the large arteries, the pulsatile flow is converted to continuous flow, and the microvascular structure provides metabolite and oxygen flow to the tissues. The microvascular structure is not only related to vascular resistance. At the same time, there are regions where wave reflections occur; especially in the elderly, these wave reflections are associated with an increase in the central aortic pressure. In a study by Safar et al.[25], the relation between the resistance of small subcutaneous arteries and blood pressure values in normotensive and hypertensive patients was evaluated. The most important determinants of small artery structure were clinical SBP, DBP, MBP, cardiac output, and PP, which indicated the compliance of the large arteries.

Conclusions

As a result, central aortic and coronary microvascular hemodynamics cannot be considered separately. Arterial stiffness is associated with coronary microvascular dysfunction in normal epicardial coronary arteries. The relation between the stiffness of the aorta, subendocardial myocardial perfusion, and coronary microvascular dysfunction in our study suggests that central arterial stiffness modulation may be a target for the treatment of coronary microvascular dysfunction.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: IG, MTA, SC; Study Design: IG, MTA, SC; Supervision: IG, MTA, SC; Materials: MTA, IG; Data Collection and/or Processing: IG, MTA; Statistical Analysis and/or Data Interpretation: IG, SC; Literature Review: IG, MTA, SC; Manuscript Preparation: SC, IG; and Critical Review: MTA.

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