Acta Cardiol Sin 2015;31:136–143
Original Article
doi: 10.6515/ACS20140526B

Coronary Artery Disease

Impact of Aortic Stiffness Evaluated by Aortic Pulsatility on Fractional Flow Reserve

Serkan Duyuler,[1] Pınar Türker Bayır,[2] Ümit Güray,[2] Belma Kalaycı,[3] Orhan Maden,[4] Süleyman Kalaycı[4] and Halil Lütfi Kısacık[4]

Background: Fractional flow reserve (FFR) is a highly reproducible, accurate and lesion-specific index to indicate inducible ischemia for a particular coronary artery lesion. Invasively measured aortic pulsatility (AP) is an indicator of aortic stiffness. In this study we aimed to evaluate the possible impact of AP in terms of aortic stiffness on FFR measurement.

Methods: In this study, we reviewed the FFR evaluation of 90 patients who had intermediate lesions (40-70% stenosis measured with quantitative coronary analysis) at the left anterior descending artery (LAD). AP was calculated as the ratio of aortic pulse pressure (systolic-diastolic pressure) to mean pressure.

Results: Aortic systolic pressure, aortic diastolic pressure, aortic pulse pressure and also aortic pulsatility did not differ significantly between patients with FFR $\leq$ 0.80 and FFR > 0.80 (p = 0.44, p = 0.28, p = 0.93 and p = 0.41, respectively). In subgroups arranged according to the degree of luminal narrowing (40-50%, 51-60%, and 61-70%), we did not observe significant correlation between AP and FFR value in subgroups with 40-50% and 51-60% lesions (r = 0.03, p = 0.95 and r = 0.07, p = 0.69, respectively). However, a statistically significant negative correlation between FFR value and AP in the subgroup of patients with 61-70% lesions was detected (r = -0.54, p = 0.04).

Conclusions: These findings suggested that aortic stiffness might have a possible impact on FFR measurement in coronary lesions of 61-70% stenosis evaluated quantitatively.

Key Words: Aortic pulsatility • Fractional flow reserve • Stiffness

INTRODUCTION

The presence of inducible ischemia is an important prognostic factor in coronary artery disease, and revascularization of ischemia inducing lesions improves symptoms and outcomes.[1] However, conventional coronary angiography has a limited value in defining ischemia, particularly in lesions of visually intermediate severity.[2] Fractional flow reserve (FFR) is a highly reproducible, accurate and lesion-specific index to indicate inducible ischemia for a particular coronary artery lesion and is accepted to be almost independent of hemodynamic variables such as heart rate, systemic blood pressure and ventricular contractility. On the other hand, maximal hyperemic response to agents like adenosine is necessary for proper FFR evaluation, and the presence of some factors such as microvascular disease may affect FFR interpretation.[3]

Aortic stiffness is an independent predictor of adverse cardiovascular events, and evaluation of large artery stiffness in hypertensive subjects is recommended by current guidelines.[4] Aortic stiffness has also been shown to be associated with the presence and extent of

Received: September 16, 2013 Accepted: May 26, 2014
[1]Department of Cardiology, Hakkari State Hospital, Hakkari; [2]Department of Cardiology, Ankara Numune Education and Research Hospital; [3]Department of Cardiology, Çubuk State Hospital; [4]Department of Cardiology, Turkiye Yuksek Ihtisas Training and Research Hospital, Ankara, Turkey.
Address correspondence and reprint requests to: Dr. Serkan Duyuler, Hakkari Devlet Hastanesi, Kardiyoloji Kliniği, Dağgöl Mah, Hastane Cad, 30000, Hakkari, Turkey. Tel: 90 555 618 27 75; Fax: 90 0438 211 71 92; E-mail: serkanduyuler@yahoo.com

coronary artery disease and coronary microvascular dysfunction.[5,6] Invasively measured aortic pulsatility (AP) is thought to be an indicator of aortic stiffness, and increased AP has been found to be associated with adverse outcomes in patients following coronary interventions and with coronary slow flow and cardiac syndrome X.[7,8] Dividing pulse pressure to mean arterial pressure theoretically omits the effects of cardiac output and peripheral vascular resistance. Thus, AP indicates arterial stiffness better than pulse pressure. Furthermore, aortic stiffness has been shown to be related to a lower magnitude of hyperemic response induced by adenosine in coronary arteries.[9] However, no study to date has evaluated the possible impact of aortic stiffness on FFR, which is closely related to the microvascular structure and hyperemia induced by adenosine. In this study we aimed to evaluate the possible impact of AP in terms of aortic stiffness on FFR measurement.

METERIALS AND METHODS

Study population

We retrospectively reviewed 147 consecutive patients who had undergone FFR measurement at Turkiye Yuksek Ihtisas Training and Research Hospital between February 2010 and May 2011. Patients whose pressure recordings were not available, who had acute coronary syndrome or acute decompensated heart failure in the index hospitalization, who had pronounced left ventricle hypertrophy, severe valvular heart disease or severe arrhythmia were excluded from the study. Finally, 90 patients who had intermediate lesions (40-70% stenosis measured with quantitative coronary analysis) at the left anterior descending artery (LAD) were included in the analysis. All subjects provided written informed consent before FFR measurement and the study protocol was approved by the local Ethics Committee. Patient age, height, weight, fasting blood glucose, fasting lipid profile, presence of diabetes mellitus, hypertension and hyperlipidemia were obtained from the hospital records. Diabetes mellitus was defined as a history of anti-diabetic medication or fasting blood glucose above 126 mg/dl. Hypertension was diagnosed if the average of the three blood pressure measurement at the two clinic visits was consistently above 140 mmHg systolic and/or 90 mmHg diastolic. Furthermore, previously diagnosed and treated patients were also accepted as hypertensive. Hypercholesterolemia was defined as having low-density lipoprotein cholesterol level $\geq$ 100 mg/dl and/or being on a lipid-lowering drug. Diagnostic coronary angiography was performed through use of the radial or femoral percutaneous approach. Coronary angiography records of the patients were reviewed by two experienced invasive cardiologists, and quantitative coronary analysis (QCA) of the lesions was evaluated in conjunction with FFR. Lesion severity (% narrowing) and lesion length were measured for each patient. Then the patients were divided into three subgroups according to lesion severity in QCA as 40-50%, 51-60% and 61-70%. Correlation between AP and FFR was evaluated in these subgroups.

Quantitative coronary analysis

All coronary angiograms were analyzed at Turkiye Yuksek Ihtisas Training and Research Hospital's coronary angiography laboratory by quantitative angiography on digital angiograms (Vepro, Medimage, Pfungstadt, Germany). Angiograms with intermediate stenotic lesions in LAD were evaluated by two experienced physicians blinded to the study. For each lesion, an end-diastolic frame from angiograms was selected. The automatic edge detection program defined the vessel contours. Computer software automatically calculated the minimum lumen diameter, reference diameter, percent diameter stenosis, and stenosis length.

FFR measurement

A guiding catheter without side holes was routinely used to engage the coronary artery for FFR measurement. Special attention was paid to insure coaxial alignment with the coronary ostium to avoid damping. All patients received a bolus of heparin (5000 IU) before the procedure and an additional bolus of 2000 IU was given every hour if the procedure lasted more than 1 hour. A 0.014-inch pressure monitoring guide wire (PrimeWire, Volcano, San Diego, California, USA) was calibrated and advanced through the coronary artery until it was positioned distal to the stenosis. An intracoronary bolus of nitroglycerin (0.2 mg) was given at the start of the procedure and repeated every 30 min. After recording baseline distal intracoronary pressure,

intracoronary adenosine (90 to 300 μg) was administered to induce maximal hyperemia and FFR measurements were repeated at least two times. According to protocol of our institution, incremental bolus of intracoronary adenosine (90 μg, 120 μg, 180 μg and 300 μg) was administered if the previous FFR value was not significant. Each administration was performed in 5 to 10 seconds and rapidly flushed by saline solution. The next higher dose was not administered in case of an atrioventricular block lasting more than 5 seconds, hemodynamic compromise or FFR value was significant. The final recorded FFR was the lowest value obtained in the repeated measurements. FFR was calculated as the ratio of the mean distal intracoronary pressure to the mean aortic pressure at the time of peak hyperemia which is generated automatically by the software. An FFR value ≤ 0.80 was considered hemodynamically significant.

Measurement of hemodynamic parameters

Systolic and diastolic blood pressures of the ascending aorta were measured during FFR evaluation before administration of nitroglycerine and adenosine. Pressure tracings were obtained with a 0.014-inch pressure monitoring guide wire (PrimeWire, Volcano, San Diego, California, USA). The average of three pressure measurements was used for calculations to minimize the effect of blood pressure fluctuations during FFR measurement. Aortic mean blood pressure was calculated as 1/3 systolic + 2/3 diastolic blood pressure. AP was calculated as the ratio of aortic pulse pressure (systolic-diastolic blood pressure) to mean pressure.

Statistical analysis

Data were analyzed with the SPSS software version 17.0 for Windows (SPSS, Chicago, IL, USA). Continuous variables are expressed as mean ± SD and categorical variables are expressed as percentages. Comparison of categorical and continuous variables between the two groups was performed using the χ^2 test and two sample t-test, respectively. The relationship between AP and FFR was evaluated by multiple linear regression analysis. Variables included in the analysis were p value of < 0.1 in univariate comparisons. All tests of significance were two-tailed, and statistical significance was defined as a p value of less than 0.05.

RESULTS

We included 90 patients with intermediate (40-70%) stenosis at LAD (34 female, 56 male; mean age 60 ± 10.4 years) who had undergone FFR measurement at our clinic between February 2010 and May 2011. Baseline clinical features and laboratory parameters of the study patients are shown in Table 1. FFR value was found to be hemodynamically significant in 27 (30%) patients. Demographic, laboratory and anthropometric parameters did not differ significantly between patients with hemodynamically significant and insignificant lesions. There was no statistical significance between FFR and lesion severity according to QCA (p = 0.3, see Table 2).

Since our study was conducted retrospectively, the adenosine dosage was not constant. However, the amount of adenosine used in patients with and without hemodynamically significant lesions was similar (156.6 ± 42.4 μg vs. 175.0 ± 48.9 μg, p = 0.07) and a tendency to use higher adenosine doses for hemodynamically insignificant lesions.

No significant differences were noted in aortic blood pressure parameters including systolic blood pressure, aortic diastolic blood pressure, aortic pulse pressure and also aortic pulsatility between patients with FFR ≤ 0.80 and those with FFR > 0.80 (p = 0.44, p = 0.28, p = 0.93 and p = 0.405, respectively). In the whole group, there was no significant association between FFR value and AP.In order to perform analysis in more similar lesion severity groups, we arranged 3 subgroups according to their degree of luminal narrowing (subgroup 1: 40-50%, subgroup 2: 51-60%, and subgroup 3: 61-70%). We then evaluated the correlation between FFR and AP within subgroups separately, as postulated by previous similar studies.[10,11] Subgroup 1 consisted of 47, subgroup 2 consisted of 29 and subgroup 3 consisted of 14 lesions. In univariate analysis, we did not observe any significant correlation between AP and FFR in subgroup 1 (r = 0. 03, p = 0.95) and subgroup 2 (r = 0.07, p = 0.69). However, significant correlation was found between FFR value and AP in only patients with 60-70% lesion severity (subgroup 3 r = -0.54, p = 0.04, Figures 1A, B and C). The relationship between AP and FFR was evaluated also by multiple linear regression analysis. Variables included in the analysis were p value of < 0.1 in univariate comparisons. In the whole group, there were no significant

Table 1. Clinical and laboratory characteristics of study population

	All patients N = 90	FFR > 0.80 n = 63	FFR ≤ 0.80 n = 27	p value
Age (years)	60.0 ± 10.4	60.4 ± 11.3	59.8 ± 10.1	0.47
Female	34 (37.8)	22 (34.9)	12 (44.4)	0.39
Male	56 (62.2)	41 (65.1)	15 (55.5)	
BMI (kg/m^2)	28.6 ± 4.6	28.6 ± 4.2	28.7 ± 4.8	0.30
Diabetes mellitus	27 (30)	19 (30.1)	8 (29.6)	0.96
Hypertension	56 (62.2)	42 (66.6)	14 (51.9)	0.18
Hyperlipidemia	73 (81.1)	49 (77.7)	24 (88.8)	0.21
Total cholesterol (mg/dl)	192.5 ± 45.9	188.1 ± 45.9	202.9 ± 45.3	0.23
LDL (mg/dl)	119.9 ± 39.6	113.3 ± 39.1	135.2 ± 37.2	0.78
HDL (mg/dl)	42.7 ± 14.8	43.7 ± 21.6	42.3 ± 11.0	0.27
Triglyceride (mg/dl)	176.1 ± 96.0	188.5 ± 101.9	147.2 ± 74.8	0.40
Fasting blood glucose (mg/dl)	124.3 ± 54.3	127.5 ± 60.6	117.0 ± 45.0	0.54
Adenosine (μg)	169.5 ± 47.6	175.0 ± 48.9	156.6 ± 42.4	0.07
Lesion length (mm)	9.8 ± 4.5	9.0 ± 3.7	11.6 ± 5.6	0.01
Aortic systolic pressure (mmHg)	141.8 ± 28.2	145.6 ± 27.7	133.1 ± 27.7	0.44
Aortic diastolic pressure(mmHg)	73.6 ± 14.6	75.7 ± 12.9	68.5 ± 17.0	0.28
Aortic pulse pressure (mmHg)	68.2 ± 20.6	69.8 ± 21.4	64.5 ± 18.4	0.93
Aortic pulsatility	0.71 ± 0.18	0.70 ± 0.17	0.72 ± 0.19	0.40
ACEi/ARB	43 (47.8)	32 (50.8)	11 (40.7)	0.38
Antiagregant	68 (75.6)	47 (74.6)	21 (77.8)	0.75
Beta blocker/ca blocker	39 (43.3)	29 (46.0)	10 (37.0)	0.43
Statin/fibrate	56 (62.2)	37 (58.7)	19 (70.4)	0.30

Data are presented as number (percentage) or mean ± SD values.
ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; FFR, fractional flow reserve; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 2. Quantitative coronary angiographic lesion severity and hemodynamic significance

QCA	FFR		Total N = 90	p
	FFR > 0.80 N = 63	FFR ≤ 0.80 N = 27		
40-50 % lesions	36 (76.6)	11 (23.4)	47	
51-60 % lesions	19 (65.5)	10 (35.5)	29	0.3
61-70 % lesions	8 (57.1)	6 (42.9)	14	

Data are presented as number (percentage).
FFR, fractional flow reserve, QCA, quantitative coronary angiography.

associations between FFR and AP in multiple linear regression analysis; however, significant and independent correlation was found between FFR value and AP in patients with 60-70% lesion severity (p = 0.03). Variables included in the analysis were FFR value as dependent variable and age, lesion length, adenosine dosage and AP as independent variables.

In the whole group, lesion length of the evaluated luminal narrowing was found to be negatively correlated with FFR value (r = -0.28, p = 0.008, see Figure 2), but we did not observe a correlation between lesion length and AP (p = 0.42). AP also was found to increase with advance of age (r = 0.37, p < 0.001, see Figure 3).

In a separate analysis of all subgroups, the presence of diabetes mellitus (p = 0.2, p = 0.20, p = 0.85, respectively), hypertension (p = 0.33, p = 0.07, p = 0.85, respectively) or hyperlipidemia (p = 0.52, p = 0.36, p = 0.38, respectively) did not have a statistically significant impact on FFR value.

DISCUSSION

In this study, we found a statistically significant negative correlation between FFR value and AP in patients with coronary lesions with 61-70% narrowing,

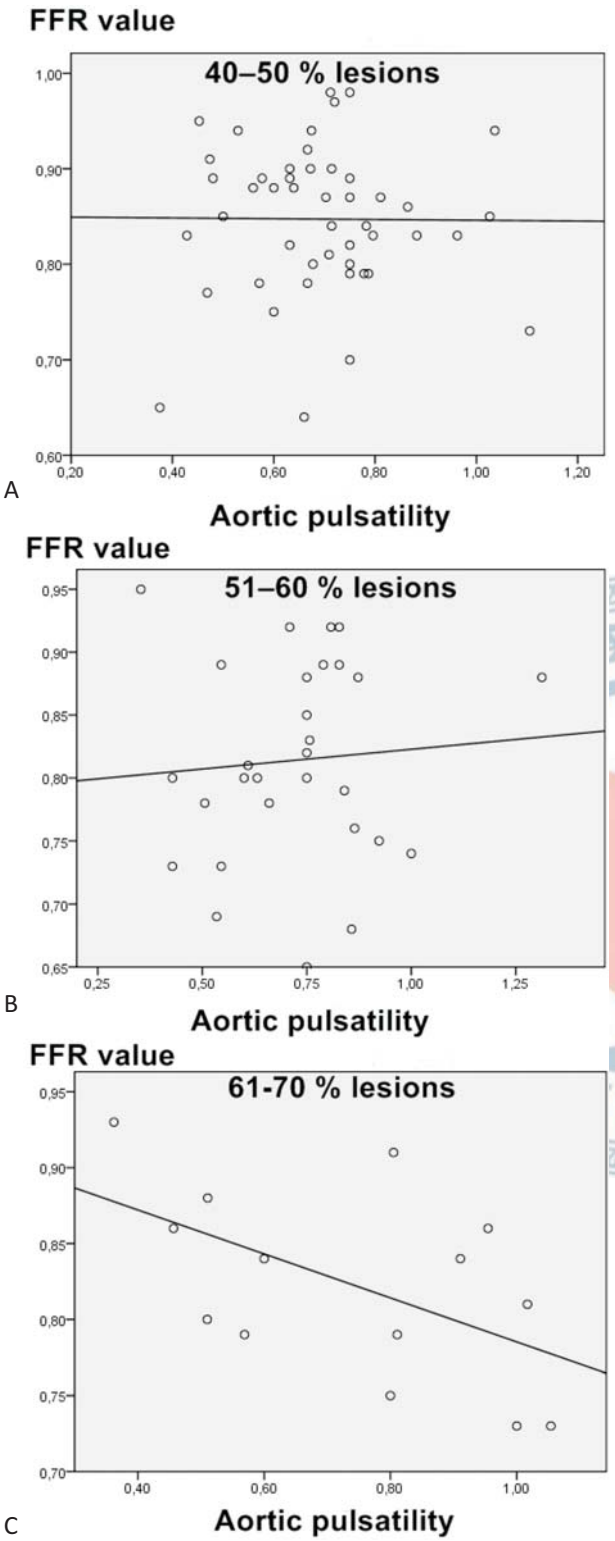

Figure 1. *Correlation between aortic pulsatility and FFR value in (A) 40-50% lesions (r = 0.03, p = 0.95), (B) 51-60% lesions (r = 0.07, p = 0.69) and (C) 61-70% lesions (r = -0.54; p = 0.04). FFR, fractional flow reserve.*

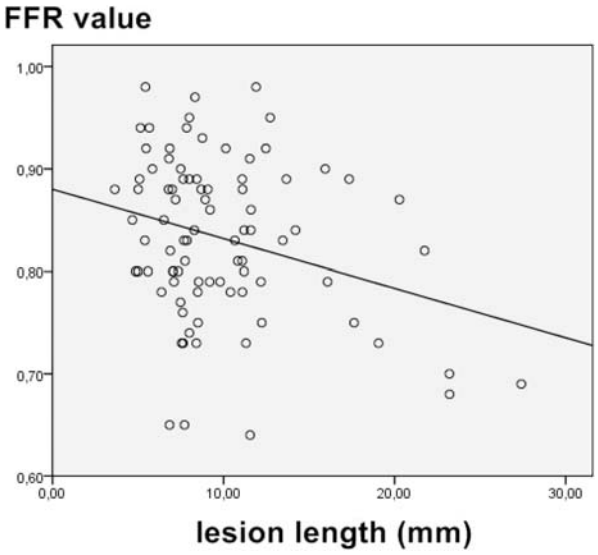

Figure 2. *Correlation between lesion length and FFR value (r = -0.28, p = 0.008). FFR, fractional flow reserve.*

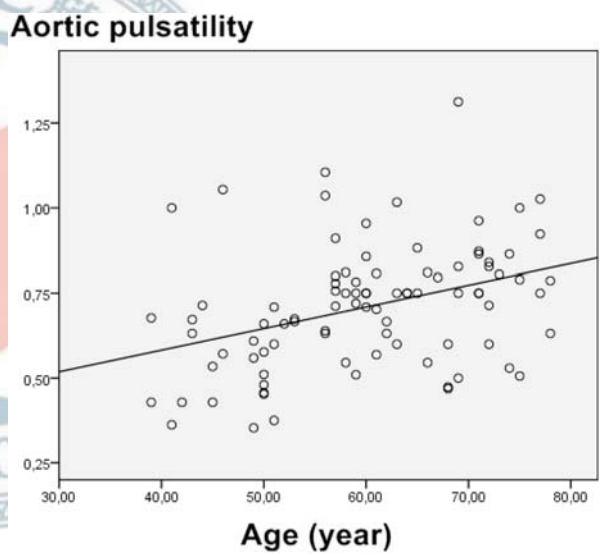

Figure 3. *Correlation between age and aortic pulsatility (r = 0.37, p < 0.001).*

according to QCA. However, this correlation was not observed in lesions with lesser narrowing according to QCA.

Pathologically, aortic stiffness includes increased medial hypertrophy and fragmentation of elastin and accumulation of collagen in the arterial wall that accompany aging and the disease processes. Many factors accelerating aortic stiffness are also related to atherosclerosis.[9,12] Aortic stiffness is regarded as a risk marker of vascular aging and cardiovascular disease.[13] Evalua-

tion of aortic stiffness can be performed invasively or non-invasively. Non-invasive evaluation of aortic stiffness by pulse wave velocity is more suitable for screening and risk stratification of large patient groups. However, invasively assessed indices of aortic stiffness showed a more robust association with the presence and extent of coronary artery disease.[14] Age, which is found to be closely related to aortic pulsatility in our study, is one of the main factors affecting blood pressure difference between invasive and non-invasive measurements.[15] Therefore, invasively measured aortic pressures and AP via catheterization is a more reliable and accurate indicator of aortic stiffness. In our study, we used the AP, which was a calculated from aortic pressure traces during FFR evaluation, as a surrogate of aortic stiffness.

In contrast to many other indices measured in the catheterization laboratory, FFR is considered almost independent of hemodynamic conditions. On the other hand, distal coronary artery pressure depends on flow across the stenosis, which is determined by both epicardial and microvascular resistance. Left ventricular hypertrophy, infarction, and microvascular disease also affect minimum coronary resistance to a certain extent.[16,17] Also, higher cut-off values for FFR have been suggested for patients having such conditions.[18] A number of studies have shown that increased aortic stiffness may stimulate left ventricular hypertrophy, remodeling and perturbations in microcirculation.[6,19] Additionally, in a parametric analysis, Siebes et al. concluded that the absolute value of FFR in intermediate lesions is more dependent on hemodynamic conditions than mild or severe lesions.[20] A current study conducted by Tok et al. demonstrated that impaired coronary flow reserve is independently related to increased aortic stiffness in patients with metabolic syndrome, which is closely related to microvascular dysfunction.[21] In this context, it would be expected that invasively measured AP (a possible indicator of aortic stiffness) might have an impact in FFR measurement directly (via hemodynamic effects) or indirectly (via microvascular dysfunction). Basically, we evaluate this potential correlation between AP and FFR measurement in patients with intermediate LAD lesions.

In our study, we found a statistically significant negative correlation between AP and FFR value in lesions with 61-70% narrowing. On the other hand, according to QCA, this correlation was not valid for lesions with lesser narrowing. Although the number of patients was relatively low in this subgroup (which is a particular drawback of the analysis), this analysis must be taken into consideration since these are the patients with most significant stenosis quantitatively among the study groups. Some factors such as ischemic burden of the lesion, microvascular dysfunction and fluid dynamics may interact on these results. One possible explanation is that a stiffer aorta may be more closely related to ischemic burden in the intermediate lesion group with 61-70% narrowing (compared to lesions with lesser narrowing) and thus AP and FFR correlation reaches statistical significance in this group. However, this correlation between aortic stiffness and FFR value is not pronounced and does not reach statistical significance in lesions with lesser narrowing. In clinical practice, for a given lesion with 61-70% lesion according to QCA, measurement of AP during coronary catheterization may provide additional information regarding the ischemic burden of the lesion, even in the absence of FFR. Since our study population did not include lesions > 70% luminal narrowing, extrapolation of our findings to more severe luminal stenosis would be only speculation requiring further investigation. However, according to our theory, it would be expected that AP would correlate more significantly with FFR in cases of more severe luminal narrowing.

In a dynamic coronary flow simulation based on measured coronary morphometric data and a physics-based computational model, independence from parameters such as aortic blood pressure, blood hematocrit, and stenotic vessel stiffness of all indexes including FFR is substantially compromised under changes in vasculature stiffness. This model also suggests a lesser FFR cut-off value in stiffer coronary vasculature for higher coronary intervention benefit.[22] Since mutual factors are affecting both aortic and coronary vasculature, it would be anticipated that a stiffer aorta is associated with stiffer coronary vasculature and a narrower lesion is expected to be stiffer compared to less narrow lesions. A blunted hyperemic response to adenosine secondary to aortic stiffness in addition to stiffer coronary vasculature may also accentuate the dependence of FFR to hemodynamic parameters such as aortic blood pressure. These findings are consistent

with our results; however, more in-depth studies are necessary for full picture of the mechanisms.

Study limitations

In addition to its retrospective manner, our study has several limitations. Although our study population was rather large in number as compared to similar studies, we believe it is still too limited in number. Also, although we excluded patients with comorbidities such as left ventricular hypertrophy which has a possible impact on FFR, microvascular dysfunction was not evaluated in our study. The addition of microvascular dysfunction with methods such as coronary flow reserve or index of microcirculatory resistance would further provide invaluable data for underlying mechanisms affecting our results.

CONCLUSIONS

We demonstrated a statistically significant negative correlation between FFR value and AP in coronary lesions with 61-70% narrowing according to QCA. However, this correlation was not present in lesions with lesser narrowing. Some factors such as ischemic burden of the lesion, microvascular dysfunction and fluid dynamics may be operative on these results. More in-depth studies are necessary to create a more comprehensive picture of the mechanisms.

CONFLICTS OF INTEREST STATEMENT

The authors state that they have no conflicts of interest.

ACKNOWLEDGEMENT

None declared.

REFERENCES

1. Shaw LJ, Berman DS, Maron DJ, et al. COURAGE Investigators. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. *Circulation* 2008;117:1283-91.
2. Topol EJ, Nissen SE. Our preoccupation with coronary luminology. The dissociation between clinical and angiographic findings in ischemic heart disease. *Circulation* 1995;92:2333-42.
3. Pijls NH, Sels JW. Functional measurement of coronary stenosis. *J Am Coll Cardiol* 2012;59:1045-57.
4. Mancia G, De Backer G, Dominiczak A, et al. The task force for the management of arterial hypertension of the European Society of Hypertension, The task force for the management of arterial hypertension of the European Society of Cardiology. 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2007;28:1462-536.
5. Danchin N, Benetos A, Lopez-Sublet M, et al. ESCAPP Investigators. Aortic pulse pressure is related to the presence and extent of coronary artery disease in men undergoing diagnostic coronary angiography: a multicenter study. *Am J Hypertens* 2004;17:129-33.
6. Mitchell GF, Vita JA, Larson MG, et al. Cross-sectional relations of peripheral microvascular function, cardiovascular disease risk factors, and aortic stiffness: the Framingham Heart Study. *Circulation* 2005;112:3722-8.
7. Guray U, Guray Y, Yilmaz MB, et al. Aortic pulse pressure and aortic pulsatility in patients with coronary slow flow. *Cardiology* 2007;107:233-8.
8. Cay S, Guray U, Korkmaz S. Increased aortic pulse and fractional pulse pressures in patients with cardiac syndrome X. *Blood Press* 2006;15:179-84.
9. Leung MC, Meredith IT, Cameron JD. Aortic stiffness affects the coronary blood flow response to percutaneous coronary intervention. *Am J Physiol Heart Circ Physiol* 2006;290:H624-30.
10. Bayir PT, Duyuler S, Güray U, et al. Impact of metabolic syndrome on fractional flow reserve. *Acta Cardiol* 2013;68:569-74.
11. Sahinarslan A, Kocaman SA, Olgun H, et al. The reliability of fractional flow reserve measurement in patients with diabetes mellitus. *Coron Artery Dis* 2009;20:317-21.
12. Lee SJ, Park SH. Arterial ageing. *Korean Circ J* 2013;43:73-9.
13. Willum-Hansen T, Staessen JA, Torp-Pedersen C, et al. Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. *Circulation* 2006;113:664-70.
14. Cho SW, Kim BO, Kim JH, et al. The relation of non-invasively and invasively assessed aortic pulsatile indices to the presence and severity of coronary artery disease. *Blood Press* 2011;20:309-16.
15. Kayrak M, Ulgen MS, Yazici M, et al. Comparison between brachial blood pressures obtained by aneroid sphygmomanometer and central aortic pressures: factors affecting the measurements. *Turk Kardiyol Dern Ars* 2008;36:239-46.
16. Duncker DJ, Bache RJ. Effect of chronotropic and inotropic stimulation on the coronary pressure-flow relation in left ventricular hypertrophy. *Basic Res Cardiol* 1997;92:271-86.

17. Uren NG, Crake T, Lefroy DC, et al. Reduced coronary vasodilator function in infarcted and normal myocardium after myocardial infarction. *N Engl J Med* 1994 331:222-7.
18. Blows LJ, Redwood SR. The pressure wire in practice. *Heart* 2007;93:419-22.
19. Nigam A, Mitchell GF, Lambert J, Tardif JC. Relation between conduit vessel stiffness (assessed by tonometry) and endothelial function (assessed by flow-mediated dilatation) in patients with and without coronary heart disease. *Am J Cardiol* 2003;92:395-9.
20. Siebes M, Chamuleau SA, Meuwissen M, et al. Influence of hemodynamic conditions on fractional flow reserve: parametric analysis of underlying model. *Am J Physiol Heart Circ Physiol* 2002;283:H1462-70.
21. Tok D, Özcan F, Kadife İ, et al. Impaired coronary flow reserve evaluated by echocardiography is associated with increased aortic stiffness in patients with metabolic syndrome: an observational study. *Anadolu Kardiyol Derg* 2013;13:227-34.
22. Algranati D, Kassab GS, Lanir Y. Flow restoration post revascularization predicted by stenosis indexes: sensitivity to hemodynamic variability. *Am J Physiol Heart Circ Physiol* 2013;305: H145-54.