Aortic Elastic Properties, Carotid Intima-Media Thickness and Coronary Flow Reserve in Patients with Peripheral Artery Disease

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ABSTRACT

• **Objective:** *A non-invasive echocardiographic technique, coronary flow velocity reserve (CFR), could be used in the detection of coronary microvascular function. Our aim was to evaluate non-invasively micro-vascular circulation and endothelial function of epicardial coronary arteries in patients with peripheral artery disease (PAD).*

• **Material and Method:** *Twenty-seven patients with PAD (ankle-brachial index (ABI) <0.9) and 26 healthy subjects without claudication (ABI>1) were studied. Coronary diastolic peak flow velocities were measured baseline and after dipyridamole infusion. The ratio of hyperemic to baseline diastolic peak velocities (CFR), aortic strain and distensibility were calculated. The intima media tickness (IMT) of the carotid arteries were also measured.*

• **Results:** *Demographic parameters and risk factors of coronary artery disease were similar between the patient and control groups. Baseline diastolic peak and mean flow velocities were similar between the patients with PAD and healthy control subjects (p=0.56 and p=0.69 respectively).*

Hyperemic diastolic peak and mean flow velocities were significantly lower in the patient group compared to those in controls (45.64±14.21 cm/s vs 73.08±29.61 cm/s p<0.01 and 35.68±10.83 cm/s vs 54.31±22.28 cm/s p<0.01). CFR was 1.49±0.36 and 2.51±0.74 in patients and healthy control subjects respectively (p<0.01).

The IMT was significantly increased in patients with PAD (p<0.01). Both, aortic strain and distensibility were impaired in patients with PAD (p<0.01).

• **Conclusion:** *The present study showed that CFR, which establishes coronary microvascular and endothelial functions non-invasively, is significantly impaired in patients with PAD. The impaired CFR, increased carotid IMT, decreased aortic strain and distensibility, as early atherosclerotic changes, may have value in the prediction of coronary artery disease in patients at risk for coronary atherosclerosis.*

• **Key Words:** *Peripheral artery disease, coronary flow velocity reserve, aortic strain, aortic distensibility, carotid artery intima media thickness.* **Nobel Med 2009; 5(3): 58-64**

ÖZET

PERİFERİK ARTER HASTALARINDA AORTUN ELASTİK ÖZELLİKLERİ, KAROTİS İNTİMA-MEDYA KALINLIĞI VE KORONER AKIM REZERVİ

• **Amaç:** Girişimsel olmayan ekokardiyografik bir teknik olan koroner akım rezervi ölçümü, koroner mikrovasküler işlevin değerlendirilmesinde kullanılabilmektedir. Çalışmamızın amacı periferik arter hastalığı (PAH) olan bireylerde girişimsel olmayan yöntemlerle epikardiyal koroner arterlerde mikro-vasküler dolaşımın ve endotel işlevlerinin değerlendirilmesiydi.

• **Materyal ve Metod:** PAH olan 27 hasta (ankle brachial index (ABI<0,9) ve klodikasyonu olmayan (ABI>1) 26 sağlıklı birey çalışmaya alındı. Bazal ve dipridamol sonrası koroner diyastolik zirve akım velositeleri ölçüldü. Hiperemik diyastolik zirve velositelerinin bazale oranı (CFR), aortik strain ve distensibilite hesaplandı. Karotis arterlerinde intima media kalınlığı (IMK) da ölçüldü.

• **Bulgular:** Hasta ve kontrol gruplarında demografik parametreler, koroner kalp hastalığı risk faktörleri benzerdi. PAH olan hasta ve sağlıklı kontrol gruplarında bazal diyastolik zirve ve ortalama akım velositeleri benzerdi (sırasıyla p=0,56 ve p=0,69). Hiperemik diyastolik zirve ve ortalama akım velositeleri hasta grubunda kontrol grubuna oranla belirgin olarak düşük bulundu (sırasıyla 45,64±14,21 cm/s vs 73,08±29,61 cm/s p<0,01 ve 35,68±10,83 cm/s vs 54,31±22,28 cm/s p<0,01). CFR, hasta grubunda 1,49±0,36 iken kontrol grubunda 2,51±0,74'tü (p<0,01). PAH olan grupta IMK belirgin olarak artmıştı (p<0,01). Aortik strain ve distensibilitenin PAH olanlarda bozulmuş olduğu saptandı (p<0,01).

• **Sonuç:** Bu çalışma koroner mikrovasküler ve endotelyal işlevleri girişimsel olmayan yolla gösteren CFR'nin PAH olan bireylerde belirgin olarak bozulduğunu göstermiştir. Bozulmuş CFR, artmış karotis IMK'sı, azalmış aortik strain ve distensibilite, erken aterosklerotik değişiklikler olarak, ateroskleroz riski olan hastalarda koroner arter hastalığının öngörülmesinde değerli olabilir.

• **Anahtar Kelimeler:** Periferik arter hastalığı; koroner akım velositesi rezervi; aortik strain; aortik distensibilite; karotid arter intima media kalınlığı. **Nobel Med 2009; 5(3): 58-64**

INTRODUCTION

Peripheral artery disease (PAD), a manifestation of atherosclerosis, frequently accompanies comorbid medical conditions, such as coronary artery disease (CAD), systemic hypertension, and diabetes mellitus.[1] The increased risk of CAD has been previously established in patients with atherosclerotic PAD.[2-5] Patients with PAD incur a 3.1-fold increase in all-cause mortality over patients without PAD and a 6.6-fold increased risk of death from CAD.[6] A recent study showed that only 10% of patients with lower extremity ischaemia had normal coronary arteries by cardiac catheterization. Of these patients 28% had severe CAD.[7] Furthermore, the presence of PAD, even in the absence of a history of CAD, confers the same relative risk of death from a cardiovascular cause as in patients with a previous cardiovascular event.[8, 9]

Current guidelines accept patients with PAD as patients at high risk.[10] Recent studies revealed that patients with PAD have more prevalent silent coronary ischemia and endothelial dysfunction. 44 patients with PAD who were asymptomatic for CAD underwent flow mediated dilatation (FMD) evaluation by brachial artery ultrasound and dipyridamole myocardial perfusion imaging (MPI). Silent ischemia was present in 39% of the patients by MPI. FMD was also significantly decreased in patients with abnormal MPI results (p=0.04).[11] Multivariate analyses supported that FMD was the only significant predictor of abnormal MPI results in patients with PAD. Exercise stress test is not the test of choice in the detection of CAD in patients with PAD due to intermittant claudication. Nuclear cardiologic investigations are expensive and could not be used widely. In such patients there is need for an easy, fast and cheap ischemia detection method. Our aim was to evaluate myocardial micro-vascular circulation and endothelial function of epicardial coronary arteries by the measurement of coronary flow velocity reserve via a non-invasive technique, transthoracic Doppler echocardiography, in PAD. We also aimed to measure aortic elastic properties which are accepted as cardiovascular risk predictors.[12]

MATERIAL and METHOD

The study was approved by the local institutional ethics committee and all participants gave written informed consent. Twenty-seven patients with peripheral artery disease (55±9 years old, ankle-brachial index <0.9) and as a control group, 26 healthy subjects without claudication (52±4 years old, ankle-brachial index>1) have been recruited in the study. All the patients and control subjects were former or current smokers. Systolic and diastolic blood pressures were measured on

the right arm of subjects in an upright sitting position after at least 5 minutes of rest using a sphygmomanometer with appropriate cuff size. Two readings were recorded for each individual. The average of 2 readings was defined as the subject's blood pressure. Echocardiographic measurements: Before the echocardiographic studies, all the subjects' blood pressures were measured in the supine position with a mercury sphygmomanometer. A Vivid 7 Doppler echocardiographic unit (General Electrics, Horten, Norway) with 2.5 MHz probe was used. All the subjects were placed in a mild recumbent position and ascending aorta was recorded in the two-dimensional guided M-mode tracings. Aortic diam eters were recorded 3 cm above the aortic valve by M-mode echocardiography. The reproducibility of the method has previously been described.[13]

Aortic strain and distensibility were calculated as the following

Aortic strain= (AoS-AoD)/ AoD
Aortic distensibility=2x(AoS-AoD)/(AoDxPP)
(AoS: Systolic aortic diameter, AoD: Diastolic aortic diameter, PP: pulse pressure.)

Measurement of carotid intima media tickness

The carotid arteries were evaluated with a Vivid 7 (General Electrics, Horten, Norway) echocardiograph by using a 10 MHz linear probe. The acquired images were recorded on a hard disk drive and compact disks. The common carotid artery, the carotid bulb, internal and external carotid arteries on both sides were visualized. The intima media tickness (IMT) of the carotid arteries were measured in the distal common carotid artery at a level 15-20 mm proximal to the carotid bulb. The two bright echogenic lines in the arterial wall were identified in the far wall from the ultrasound probe as the intima and the media. Three measurements were made for each side of the body; separate means were calculated and recorded as the right and left IMT. None of the patients had stenosis, atheroma plaque or local thickening in excess of 2 mm in the carotid arteries. The intraobserver coefficient of variation for carotid IMT measurements was 2.8%.

Coronary flow measurements

The coronary flow velocity recordings were performed by a single investigator (H.O.), experienced in this data acquisition. Coronary flow velocity (CFV) recordings were performed with the Vivid 7 echocardiography device using a middle range frequency (3-8 MHz) broadband transducer. CFV recordings were performed in the left anterior descending coronary artery (LAD) by transthorasic Doppler echocardiography (TTDE),

as previously described.[14] The acoustic window was around the midclavicular line in the fourth and fifth intercostal spaces in the left lateral decubitus position. The LV was imaged in the long-axis cross section and the ultrasound beam was inclined laterally. The coronary blood in the mid-to-distal LAD was searched by color Doppler flow mapping guidance with the optimal velocity range (+12 to+15 cm/sec). Then, the sample volume (1.5 or 2.0 mm wide) was positioned on the color signal in the LAD artery. We measured variables of LAD artery velocity using fast Fourier transformation analysis. After baseline recordings of flows, dipyridamole (Persantin, Boehringer Ingelheim, 0.56 mg/kg) was infused over a 4 minutes period. An additional infusion of dipyridamole (0.28 mg/kg over a 2-min period) was used if the heart rate did not exceed a %10 increase from the baseline. Two minutes after the end of the infusion, hyperemic spectral profiles in the LAD artery were recorded. All images were recorded for playback analysis and were later measured off-line. Averaged diastolic peak velocity (ADPV) was measured at baseline and under hyperemic conditions. Coronary flow velocity reserve (CFVR) was defined as the ratio of ADPV at hyperemia: ADPV at baseline. The intraobserver variability of CFVR measurement was %4.9 in the current study. All of the measurements were performed between 8 and 9 AM and all of the subjects abstained from smoking and caffeine-containing drinks for at least 12 hours before testing.

Statistical analysis

Quantitative variables were expressed as mean value (SD), and qualitative variables were expressed as percent (%). Comparisons of parametric values between the two groups were performed by means of t test. Categorical variables were compared by the chi-squared test. Spearman rho's and Pearson tests were used for correlation analysis. A p value<0.05 was considered statistically significant.

RESULTS

Twenty-seven patients with peripheral artery disease (55±9 years old, ankle-brachial index<0.9) and as a control group, 26 healthy subjects without claudication (52±4 years old, ankle-brachial index>1) have been recruited in the study. The ankle-brachial index was 0.60±0.10 in the patients group. All the patients and control subjects were former or current smokers (at least 1 packet/per day) and the mean tobacco using time were 19.2±3.7 years and 10.2±5.6 years in patient and control groups respectively (patients with PAD were longer cigarette smokers, p<0.001). Eleven patient and 10 control subject were former smokers at the enrollment. Of the patients 4 have experienced ampu-

tation of low extremities due to ischemia. Hypertension and diabetes mellitus were present in 12 and 2 subjects in patients with peripheral artery disease. In the control group 10 and 1 of the subjects were hypertensive and diabetic respectively. Patients and control subjects were on a similar anti-hypertensive regimen including angiotensin-converting enzyme inhibitors, statins and calcium channel blockers (11, 14, 12 and 12, 13, 11 in patients with PAD and control subjects respectively).

Demographic parameters, risk factors of CAD and hematological parameters were similar between the patient and control groups. Patients with PAD had higher fasting glucose levels (p=0.02) but diabetes mellitus prevalence was similar in both groups. Patient characteristics, biochemical and hematological parameters are shown in Table 1.

Baseline diastolic peak flow velocity of LAD artery was similar between patients with PAD and healthy control subjects (p=0.56). Diastolic mean flow velocity of LAD artery was also similar between the two groups (p=0.69). Hyperemic diastolic peak flow velocity was significantly lower in the patient group compared to those in the controls (45,64±14,21 cm/s versus 73,08±29,61 cm/s, p<0.01). Patients with PAD had also significantly lower hyperemic diastolic mean flow velocity of LAD artery compared to healthy control subjects (35,68±10,83 cm/s versus 54,31±22,28 cm/s, p<0.01). CFR was 1,49±0,36 and 2,51±0,74 in patients and healthy control subjects respectively (p<0.01). Baseline and hyperemic peak and mean flow velocities of the LAD artery and CFR are shown in Table 2 and Figure 1.

Patients with PAD had significantly increased carotid IMT (1,16±0,31 mm) compared with healthy subjects (0,62±0,17 mm) (p<0.01). Both, aortic strain and distensibility were impaired in patients with PAD compared to healthy control subjects. Aortic strain was 4,38±3,43% in patients with PAD and 10,29±5,95% in control subjects (p<0.01). Aortic distensibility was also decreased in patients with PAD compared to healthy subjects (3,67±2,95 cm^2 dyn-1 10-6 versus 6,96±3,38 cm^2 dyn-1 10-6) (p<0.01). Carotid IMT, aortic strain and distensibility values are shown in table 3.

DISCUSSION

In our study we determined that patients with PAD had significantly lower CFR by TTDE. The presence of an impaired aortic strain, aortic distensibility and increased carotid IMT which reflects atherosclerotic changes, were also determined in patients with PAD compared to healthy control subjects. Studies showed that an approximately 2 to 4 fold increased risk of CAD and cerebrovascular disease in patients with

PAD.[3-5] The prognosis of patients with lower extremity PAD is characterized by an increased risk for cardiovascular ischemic events due to concomitant CAD and cerebrovascular disease.[3,4] Approximately one third to one half of the patients with lower extremity PAD have evidence of CAD based on clinical history and electrocardiogram. Abnormal stress test results have been determined in two thirds of these subjects. Significant CAD of at least 1 coronary artery has been reported in up to 60% to 80% of those with lower extremity PAD.[8,15-28] Recent studies have also shown that the presence of hemodynamically significant carotid artery stenoses in 12% to 25% of patients with lower extremity PAD by duplex ultrasound.[19-21] As a consequence of coexisting

Table 1: Baseline characteristics of the patient and control groups.

	Patient group (n=27)	Control group (n=23)	p value
Age (years)	55±9	52± 4	0.15
Height (cm)	161±33	166±7	0.55
Weight (kg)	67±11	73±11	0.06
Cigarette smoking (n, %)	22 (81)	18 (78)	0.77
Diabetes Mellitus (n, %)	10 (37)	4 (17)	0.12
Hypertension (n, %)	7 (26)	5 (22)	0.73
Glucose (mg/dl)	100±36	81±9	0.02
Creatinin (mg/dl)	0.80±0.13	0.79±0.13	0.74
Hemoglobin (g/dl)	13.2±1.9	13.9±1.5	0.19
Total cholesterol (mg/dl)	198±39	192±32	0.61
HDL cholesterol (mg/dl)	43±5	44±6	0.51
LDL cholesterol (mg/dl)	132±37	127±31	0.64
Triglycerides (mg/dl)	132±38	127±36	0.67

Values are mean ± standard deviation. HDL: high density lipoprotein, LDL: low density lipoprotein.

Table 2: Transthorasic Doppler Echocardiographic Measurements in Patients with PAD and Healthy Control Subjects.

	Patient group (n=27)	Control group (n=23)	p value
Baseline DPFV (cm/s)	33.11±21.43	30.34±9.16	0.56
Hyperemic DPFV (cm/s)	45.64±14.21	73.08±29.61	<0.01
Baseline DMFV (cm/s)	26.55±16.15	25.13±7.50	0.69
Hyperemic DMFV (cm/s)	35.68±10.83	54.31±22.28	<0.01
CFR	1.49±0.36	2.51±0.74	<0.01

Baseline and hyperemic measurements. DPFV; diastolic peak flow velocity, DMFV; diastolic mean flow velocity, CFR; coronary flow velocity reserve.

Table 3: Carotid intima-media thickness, aortic strain and distensibility

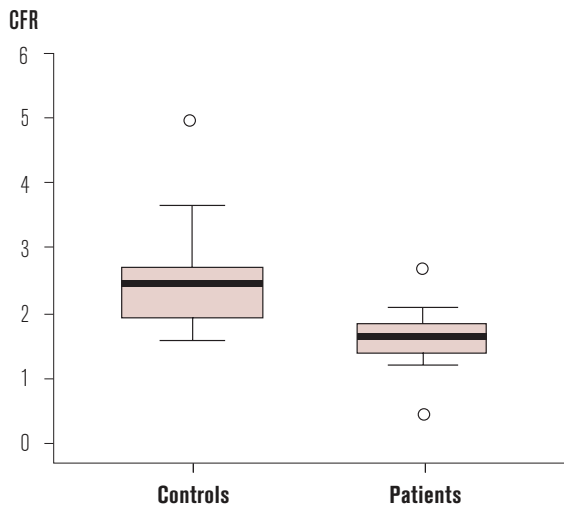|	Patients with PAD	Healthy controls	p value
Total IMT (mm)	1.16±0.31	0.62±0.17	<0.01
Aortic strain (%)	4.38±3.43	10.29±5.95	<0.01
Aortic distensibility (cm^{2}dyn^{-1}10^{-6})	3.67±2.95	6.96±3.38	<0.01

Figure 1. Coronary flow velocity reserve in patients and healthy controls
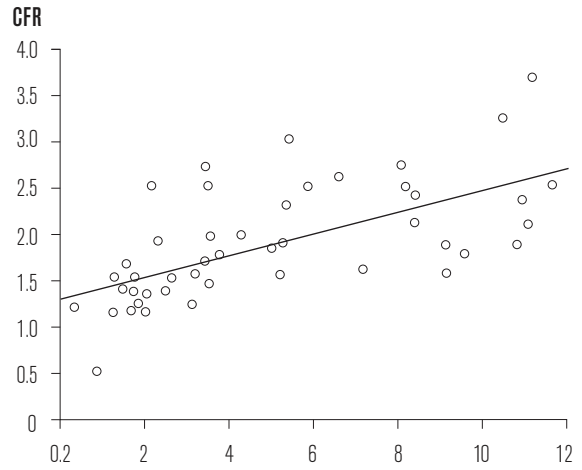(**CFR:** coronary flow velocity reserve)

Figure 2-B. Coronary flow velocity reserve and aortic distensibility
(**CFR:** Coronary flow velocity reserve, Ao distensibility (cm^{2}dyn^{-1}10^{-6}); aortic distensibility.)
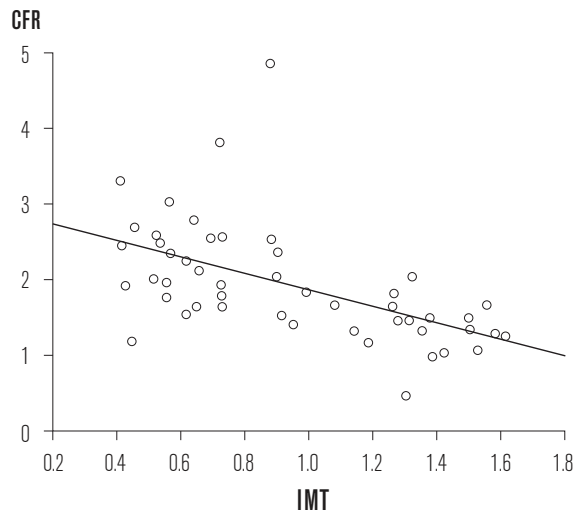

Figure 2-A. Coronary flow velocity reserve and carotid intima-media thickness
(**CFR:** Coronary flow velocity reserve, IMT (mm); carotid intima-media thickness)
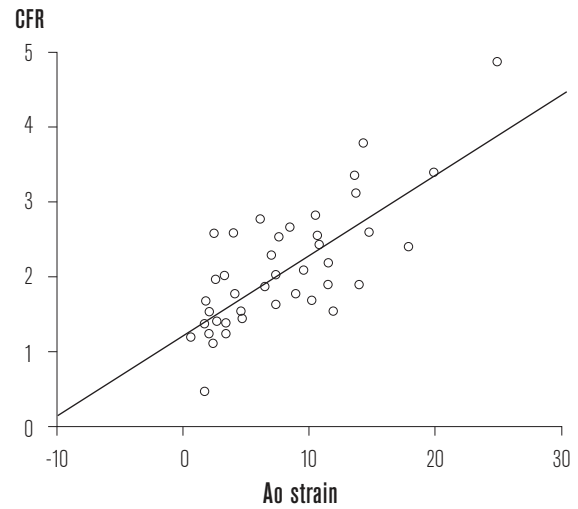

Figure 2-C. Coronary flow velocity reserve and aortic strain
(**CFR:** Coronary flow velocity reserve, Ao strain (%); aortic strain)

coronary and cerebrovascular disease, there is an increased risk of MI, stroke, and cardiovascular death in patients with lower extremity PAD. There is a 20% to 60% increased risk for MI and a 2- to 6 fold increased risk of death due to coronary heart disease events.[6, 22-26] Approximately one third of men and one fourth of women with known coronary or cerebrovascular disease also have lower extremity PAD.[3] The high prevalence of diabetes, cigarette smoking, hypertension, and hypercholesterolemia cause markedly increased risk of atherosclerotic ischemic events in patients with lower extremity PAD.[27,28] Thus, current guidelines include all patients with lower extremity PAD as a high-risk category or as an equivalent of CAD. Patients with PAD are frequently diabetics and asymptomatic or silent ischemia is a common clinical presentation of CAD in these patients. Therefore in asymptomatic subjects there is need for additional techniques to determine CAD. Especially in patients who are candidates for major surgical procedures, the detection of coronary ischemia becomes more important.

The conventional coronary ischemia detection method, exercise stress testing, may not be eligible in patients with PAD due to lower extremity claudication. In the detection of coronary ischemia, positron emission tomography (PET) and pharmacological stress tests (diprydamole myocardial perfusion SPECT) could be used in such patients but these tests are expensive and could not be found in most of health centers. The CFR measurement by TTDE which reflects coronary microvascular function and endothelial funciton of epicardial coronary arteries, as a cheaper and easy screning test, may be used as a detection method in the assessment of major epicardial coronary arteries. A CFR of <2 may be evidence of severe CAD. Recent studies revealed that CFR measurement could be safely and accurately used in the detection of CAD and a significant correlation has been previously determined between lower CFR values and coronary angiography.[29] More aggressive risk modification and anti-ischemic therapies may be necessary in PAD patients with lower CFR. The relationship between the severity of atherosclerotic→

CAD and increased carotid IMT has previously been established.[30, 31] Our results showed that a contrary relation between the CFR and carotid IMT (r:-0.53, p<0.01, Figure 2A).

In the prediction of cardiovascular risk, measurement of aortic elastic properties has also diagnostic value. Especially in patients with hypertension and atherosclerotic vascular disease, decreased aortic stiffness and strain have been reported.[12, 32-34] In our study we determined that aortic stiffness and strain has been significantly decreased in patients with PAD. This decrease was correlated with decreased CFR measurements (r: 0.62, p<0.01 and r: 0.78, p<0.01 for aortic distensibility and aortic strain respectively, Figure 2-B and 2-C). We think that carotid IMT, aortic compliance and CFR measurements; together could be used in the early prediction of atherosclerosis or in estimation of the severity of atherosclerotic disease.The risk profile in the present study; a decrease in CFR and aortic compliance with an increase in carotid IMT,

indicates that a more severe CAD may be present in patients with PAD.

In our study patients were asymptomatic regarding coronary ischemia. Therefore we did not perform coronary angiography or myocardial perfusion SPECT to investigate CAD in patients with lower CFR results. Comparison of coronary angiographic results with CFR values might increase the safety of CFR results in the estimation of atherosclerotic CAD.

CONCLUSION

We conclude that CFR, which establishes coronary microvascular function and epicardial coronary arterial endothelial function non-invasively, is significantly impaired in patients with PAD. The impaired CFR, increased carotid IMT, decreased aortic distensibility and aortic strain as early atherosclerotic changes, may have value in the prediction of CAD in patients under increased risk.

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