Measurment of Ankle-Brachial Pressure Index, Homocystein Level, and Evaluation of Coronary Artery Disease Association with Other Macrovascular Diseases in Patients with Myocardial Infarction

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Abstract

We aimed to measure ankle-brachial pressure index (ABPI) and homocysteine levels, and to evaluate frequency of cerebrovascular disease (CVD) and/or peripheral arterial disease (PAD) combination of patients with myocardial infarction (MI). 39 patients (26 males, 13 females) with acute or subacute MI and 36 control cases (9 male, 27 female) were included in the study. ABPI and homocysteine levels were measured, and bilateral carotid-vertebral and bilateral lower extremity arterial Doppler ultrasonography, and coronary angiography were examined. Homocysteine was significantly higher in patient group than control group (p=0.0001). The ABPI was not significantly different in two groups (p=0.428). However the frequency of patients with lower ABPI (≤0.9) was significantly higher compared to the frequency of control patients with lower ABPI (25.6% and 3%, respectively; p=0.02). The combination of the atherosclerotic findings in the carotid artery and coronary artery disease (CAD) were found significantly higher compared to that of the bilateral lower extremity (59%, 25.6%). Screening of CVD should be done in patients with MI history. Determining carotid arterial lesions may be useful for the early diagnosis and treatment of any possible CVD in cases with CAD. Studies with larger numbers of cases are needed.

Key Words: Myocardial infarction, cerebrovascular disease, peripheral arterial disease, ankle-brachial pressure index, homocysteine, C reactive protein, fibrinogen

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Introduction

Atherosclerosis is a widespread pathology involving the entire body. The ankle-brachial pressure index (ABPI) is an easily accessible and inexpensive test that can be performed at the bedside to make the diagnosis of PAD in symptomatic patients and to determine the vascular risk in asymptomatic patients [1]. Having a low ABPI is an independent risk factor for the cardiovascular disease and its fatal or non-fatal complications [2].

Hyperhomocysteinemia causes endothelial dysfunction and atherosclerosis. It is a risk factor for many macrovascular diseases [3, 4]. High levels of homocysteine are more frequent in patients with coronary artery disease (CAD), cerebrovascular disease (CVD), and peripheral artery disease (PAD) [3]. Hyperhomocysteinemia develops as a result of the deficiencies of the enzymes. Furthermore, cofactor deficiencies (vitamin B12, vitamin B6, and folic acid), drugs, and conditions causing endothelial dysfunction (diabetes, hypertension, dyslipidemia, renal failure, inflammatory intestinal diseases, systemic lupus, hypothyroidism, smoking, drugs) can also cause hyperhomocysteinemia [5].

Modestly high concentrations of C-reactive protein (CRP), the classical acute phase protein, are associated with the long-term risk of coronary heart disease in general populations. The major acute phase response of CRP following myocardial infarction (MI) is associated with death and cardiac complications [6].

The purpose of our study was to measure ABPI and homocysteine levels and to investigate frequency of CAD and/or PAD combination in patients with MI.

Materials and Methods

39 patients hospitalized in the coronary intensive care unit with diagnosis acute or subacute MI (26 female, 13 male) and 36 control cases (27 female, 9 male) were included in the study. Inclusion criteria of patients were being without any known chronic diseases (PAD, diabetes mellitus, cardiac insufficiency, chronic renal insufficiency, CVD, hypertension) and younger than 75 years of age. Subjects without CAD history, with normal ECG, and without any known systemic disorder were included in the control group. Blood samples were collected from the patients and the controls at 8 AM after 12-hour fasting. Serum triglyceride (TG) and total

cholesterol levels were measured with enzymatic methods, and high density lipoprotein (HDL) was measured with immunoinhibition method using Olympus AU 5223 analyzer. Friedewald formula [Low density lipoprotein (LDL) (mg/dl) = {total cholesterol (mg/dl) – TG (mg/dl) / 5} – HDL (mg/dl)] was used to determine LDL levels. CRP was measured in Image analyzer (Beckman Coulter Inc, USA) with nephelometry. Normal range was 0-0.800 mg/dL for CRP. Fibrinogen levels were run with turbidimetry, and normal range was 200-400 mg/dL. Plasma homocysteine was studied with the High Performance Liquid Chromatography (HPLC) method using a Chromsystems kit (Germany) in an Agilent 1100 (USA) device. The reference range for homocysteine was 5.0-14.0 μmol/L. Folic acid (FA) and vitamin B12 levels were studied in an Immulite 2000 (Siemens Healthcare Diagnostics) device with the chemiluminescence immunoassay method. Reference values for FA were 3-17 ng/ml, and 180-900 pg/ml for vitamin B12.

Coronary angiography was performed in all patients after acute or subacute disease had become stable.

Body mass index (BMI) was calculated according to the formula body weight divided by the square of the height (kg/m2).

Bilateral lower extremity arterial color Doppler ultrasound examination (CDUSG) and bilateral carotid-vertebral arterial CDUSG were performed. A Toshiba Power Vision 6000 Doppler device and a 10 MHz-linear probe were used. Atherosclerotic changes in vessels, intimal/medial thickness and the presence of plaques, and stenosis were evaluated with Doppler USG. The presence of one or more of these findings was interpreted as the existence of an atherosclerotic lesion.

American Heart Association recommendations were taken into consideration for ABPI calculation. Blood pressure were measured the patients after they rested for 5 minutes in the supine position from the brachial arteries in both arms and from the one pedal artery on each of the lower extremities. The ABPI was found by dividing the highest systolic pressure of brachial artery by the highest systolic pressure of lower extremity. Reference value of the ABPI was taken as > 0.9 [7].

Statistical analyzes were performed by SPSS 16 program. The values were presented as mean±standart deviation. Mann Whitney U test was used to compare the means between the two groups. $p<0.05$ was accepted to be significant.

Written informed consent was taken by the participants. This study was approved by local ethics committee, and complied with the declaration of Helsinki.

Results

Thirty-nine patients diagnosed with acute or subacute MI, and 36 control cases were included in the study. There were no differences between the patient and control groups regarding mean age and gender distribution (59±7.9 and 56.8±9.7 years; respectively; p=0.632). There were no differences between the two groups in terms of BMI (26.42 ± 3.90 kg/m2; 24.29 ± 4.48 kg/m2; p=0.07). No statistically significant differences were found between the two groups with regard to smoking habits (48.1%, 45.3% p=0.741). Family history of CAD was significantly higher in the patient group (35.5%, 18.8% p=0.041). Demographic datas are shown in Table 1. While total cholesterol, HDL, and LDL levels were statistically different in two groups, triglycerid levels were not (188.2±42.8 mg/dL; 211.3±45.6 mg/dL; p=0.017, 43±26.9 mg/dL; 54.4±15.2 mg/dL; p=0.001, 110.1±31.9 mg/dL; 123±27.7 mg/dL; p=0.047, 175.8±95.7 mg/dL; 158.81±38.5 mg/dL; p=0.256; Table 2). Angiographically, single coronary vessel ± branch involvement was present in 48% of patients, two coronary vessels ± branch involvement was present in 35.8%, and 3 coronary vessels ± branch involvement was present in 15.5% of patients.

Table 1. Demographic datas

	Patient	**Control**	**p**
Age (years)	59±7.9	56.8±9.7	p=0.632
Sex (n) (male/female)	26/13	9/27	
BMI (kg/m2)	28.42 ± 3.90	24.29 ± 4.48	p=0.07
Smoking (%)	66.7	60.3	p=0.641
Family history of CAD (%)	35.9	18.8	**p=0.041**

Homocysteine, CRP, and fibrinogen were significantly higher in patient group than control group (18.0±6.6 µmol/L; 11.9±4.3 µmol/L; p=0.0001, 5±5.1 mg/dL; 0.5±0.5 mg/dL; p=0.0001, 502.5±256.6 mg/dL; 306.7±76.7 mg/dL; p=0.003) (Figure 1). However, there were no statistically significant differences between the groups in terms of vitamin B12 and FA (326.7±204.6 pg/ml; 312.1±183.5 pg/ml; p=0.7 and 9.1±4.0 ng/ml; 9.5±2.4 ng/ml; p=0.394, Table 2). No significant correlation was found between the number of affected coronary vessels and the level of homocysteine (p>0.05).

Table 2. Biochemical and ABPI data

							Mann-Whitney U		
	Group	**Mean**	**Median**	**Min**	**Max**	**SD**	**Sequential Average**	**z**	**p**
T.Chol. (mg/dL)	**Patient**	188.2	183.0	116.0	345.0	42.8	29.2	-2.390	**0.017**
	Control	211.3	209.5	158.0	361.0	45.6	40.7		
TG (mg/dL)	**Patient**	175.8	155.0	50.0	438.0	95.7	35.7	-1.135	0.256
	Control	158.8	129.0	66.0	777.0	138.5	30.3		
HDL (mg/dL)	**Patient**	43.0	44.0	18.0	80.0	11.1	26.9	-3.177	**0.001**
	Control	54.4	53.0	19.0	82.0	15.2	42.1		
LDL (mg/dL)	**Patient**	110.1	102.0	70.0	234.0	31.9	28.8	-1.989	**0.047**
	Control	123.0	117.0	81.0	193.0	27.7	38.3		
CRP (mg/dL)	**Patient**	5.0	2.8	0.2	23.7	5.1	44.2	-5.873	**0.000**
	Control	0.5	0.2	0.1	2.3	0.5	16.1		
Fibrinogen (mg/dL)	**Patient**	502.5	433.0	150.0	1083.0	256.6	38.7	-2.974	**0.003**
	Control	306.7	297.0	200.0	482.0	76.7	24.5		
ABPI	**Patient**	1.06	1.09	0.7	1.7	0.22	34.71	-0.793	0.428
	Control	1.12	1.06	0.73	1.81	0.18	38.62		
Homocysteine (µmol/L)	**Patient**	18.0	17.2	7.5	43.1	6.6	47.4	-4.815	**0.000**
	Control	11.9	10.5	8.0	30.0	4.3	23.6		
Vitamin B12 (pg/ml)	**Patient**	326.7	263.0	100.0	1081.0	204.6	34.3	-0.385	0.700
	Control	312.1	255.4	140.0	971.6	183.5	32.4		
Folic acid (ng/ml)	**Patient**	9.1	9.1	2.3	24.0	4.0	32.3	-0.852	0.394
	Control	9.5	8.8	5.9	14.7	2.4	36.4		

The mean ABPI was 1.06±0.22 in the control group and 1.12±0.18 in the patient group. It was not significantly different in two groups (p=0.428, Table 2, Figure 1). However the frequency of patients with lower ABPI (≤0.9) was significantly higher compared to the frequency of control patients with lower ABPI (25.6% and 3.0%, respectively; p=0.02, Table 3). There was no statistically significant relationship between ABPI with the number of affected coronary arteries (p>0.05).

Table 3. Distribution of ABPI groups within patient and control groups

		Patient		Control		Total	
		n	%	n	%	n	%
ABPI	≤0.9	10	25.6	1	3.0	11	15.3
	>0.9	29	74.4	35	97.0	64	84.7
	Total	39	100.0	36	100.0	75	100.0
Chi-Square=5.421 ; p=0.020							

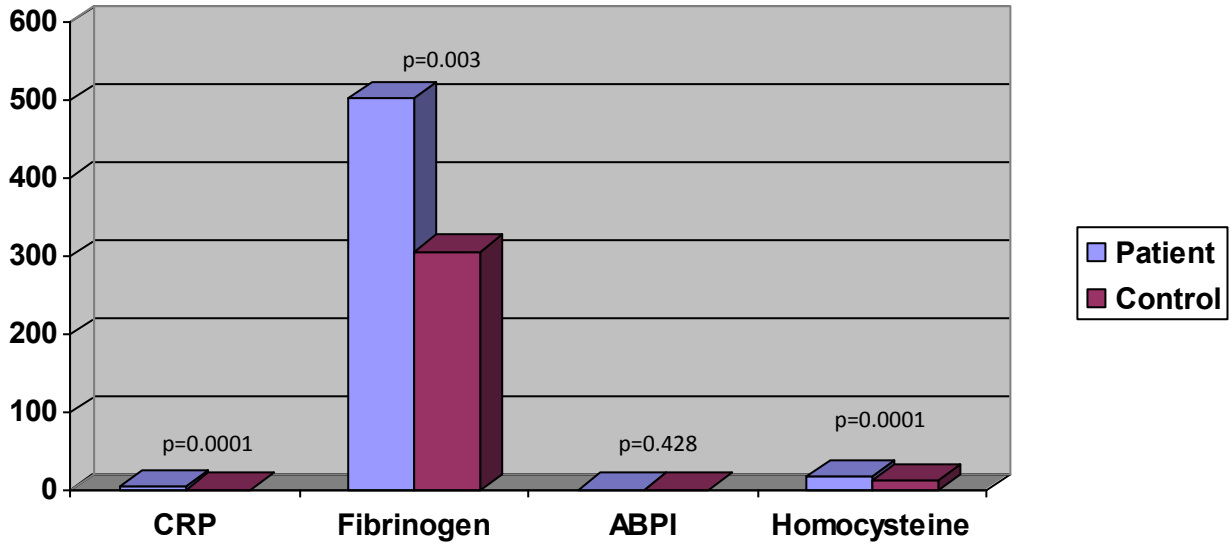

Figure 1. Mean C-reactive protein (CRP), Fibrinogen, Ankle-brachial pressure index (ABPI) and Homocysteine levels in patient and control groups

The number of patients with atherosclerotic findings in the bilateral carotid-vertebral artery CDUSG was greater compared to the number of patients with atherosclerotic findings in the bilateral lower extremity arterial CDUSG (59.0%, 25.6%). The percentage of patients with atherosclerotic findings in both arterial system CDUSG was 20.5%. These rates in the control group were 3%, 6.1%, and 0%, respectively (Figure 2). One patient with ABPI=0.5 had peripheral arterial stenosis, two patients with ABPI=0.7 and 0.8 had vertebro-basillary insufficiency.

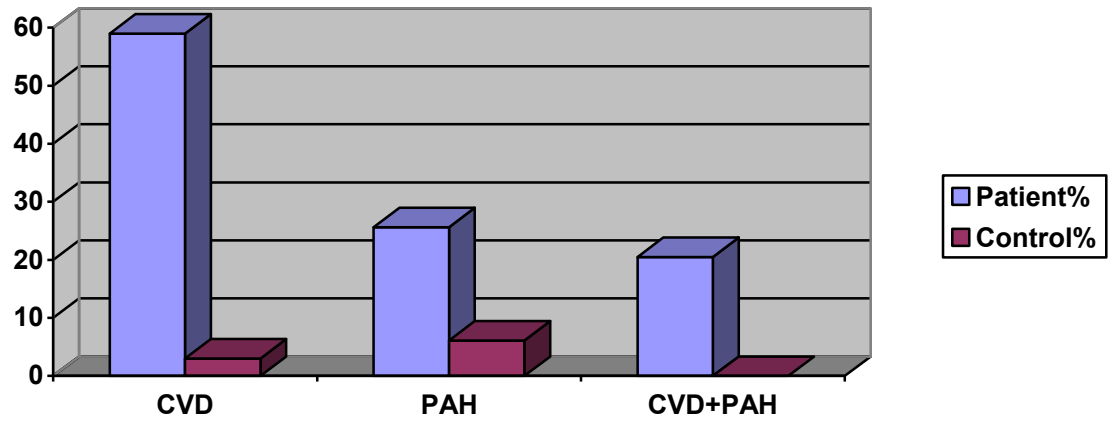

Figure 2. Distribution of cerebrovascular disease (CVD) and peripheral artery disease (PAH) in patients and control groups

Discussion

Atherosclerosis and its complications are the leading causes of mortality and morbidity worldwide. Many risk factors have been defined for atherosclerosis and CAD. ABPI value is implemented as an easy and noninvasive method for early determination of atherosclerotic lesions in the lower extremity arteries. Many studies have shown that PAD incidence increases in cases with ABPI ≤0.9. Low ABPI values in patients with CAD were related the existence of PAD and the number of affected coronary arteries [8, 9]. In our study, the mean ABPI was 1.06±0.22 in the patient group and 1.12±0.18 in the control group. No statistically significant differences between the patient and control groups were observed in terms of ABPI (Table 2, Figure 1). No significant correlation was found between the ABPI values and the number of coronary arteries involved in patients with ABPI ≤0.9. Relatively small number of cases may cause these different results. However the frequency of low ABPI (≤0.9) was significantly higher compared to the control patients (Table 3).

Since atherosclerosis plays a role in the pathogenesis of each, the possibility of co-occurrence of vascular diseases such as CAD, PAD, and CVD is high. Different ratios have been reported in the literature for the combination of CAD and CVD. In patients candidate coronary artery bypass operation, the accompaniment of carotid stenosis ≥50% has been reported with diverse rates between 3.8% and 22% [10- 12]. Merino et al found a strong relationship between PAD and the incidence of major cardiovascular events [13]. Uzun et al found the ABPI was significantly lower in patients with CAD compared to those without CAD. Again, a significant relationship was found between the severity of coronary disease and ABPI [14]. We found atherosclerotic changes in peripheral arteries in 25.6% of patients. This combination was lower compared to the accompaniment of CAD by carotid arterial lesions (59.0%). 20.5% of the patients had atherosclerotic changes both in the peripheral arteries and carotid-vertebral arteries (Figure 2).

CRP is a marker of inflammation that has been shown in multiple prospective epidemiological studies to predict incident MI, stroke, peripheral arterial disease, and sudden cardiac death. CRP levels have also been shown to predict risk of both recurrent ischemia and death among those with stable and unstable angina, those undergoing percutaneous angioplasty, and those presenting to emergency rooms with acute coronary syndromes [15]. Similar to CRP, fibrinogen levels also

increase following acute MI. It is related with the prognosis of the diseases and is an independent risk factor for the development of MI [16]. In our study, CRP and fibrinogen levels were significantly higher in the patients as compared to control cases as expected (Table 2, Figure 1). There was no relationship between the number of coronary arteries involved, CRP, and fibrinogen levels.

Homocysteine is an independent risk factor for atherosclerosis [17, 18]. High homocysteine level is seen in patients with intimal-medial wall thickening in the carotid artery. Robinson et al found a positive correlation between increased serum homocysteine levels and increasing CAD risk [19]. Ubbink et al found hyperhomocysteinemia in 41.9% of the patients with CAD, and observed that homocysteine levels were significantly higher in those with two or three occluded coronary arteries [20]. Tokgözoğlu et al showed that homocysteine levels exceeding 15 μmol/L were present in half of those with CAD and hyperhomocysteinemia increased coronary risk by 2.1-fold [21]. In our study, high homocysteine levels were likewise found in 74.4% of the cases with CAD while they were 18.2% in the control groups. Homocysteine was significantly higher compared to the control (Table 2, Figure 1). However, no significant correlation was found between the number of coronary vessels involved and the level of homocysteine ($p>0.05$).

The accompaniment of CAD by other major atherosclerotic vascular diseases such as PAD and CVD, and atherosclerotic risk factors such as the homocysteine level and ABPI was examined in this study. Homocysteine, CRP and fibrinogen levels were significantly higher in our patient group, as expected. Literature data that low ABPI values (≤ 0.9), which is used for the early diagnosis of peripheral arterial lesions, and particularly lower extremity arterial lesions, could also predict CAD was confirmed in our study.

On the other hand, we found that severe CAD was more significantly combined with CVD cases than PAD. Based on this finding, screening of CVD should be done in patients with MI history. In other words, determining carotid arterial lesions may be useful for the early diagnosis and treatment of any possible CVD in cases with CAD. Studies with larger numbers of cases are needed.

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