Evaluation of serum platelet-derived growth factor receptor-ß and brain-derived neurotrophic factor levels in microvascular angina

Gamze Aslan, Veli Polat[1], Evin Bozcalı, Mustafa Hakan Şahin[1], Nurcan Çetin[2], Dilek Ural

Department of Cardiology, Faculty of Medicine, Koç University Hospital; İstanbul-*Turkey*
[1]Department of Cardiology, Bakırköy Dr. Sadi Konuk Training and Research Hospital; İstanbul-*Turkey*
[2]Düzen Laboratory; İstanbul-*Turkey*

ABSTRACT

Objective: Microvascular angina (MVA) is a coronary microcirculation disease. Research on microcirculatory dysfunction has revealed several biomarkers involved in the etiopathogenesis of MVA. Platelet-derived growth factor receptor β (PDGFR-β) and brain-derived neurotrophic factor (BDNF) are 2 biomarkers associated with microcirculation, particularly pericytes function. The aim of this study was to investigate the role of PDGFR-β and BDNF in MVA.

Methods: Ninety-one patients (median age, 56 y; age range, 40–79 y; 36 men) with MVA and 61 control group subjects (median age, 52 y; age range, 38–76 y; 29 men) were included in the study. Serum concentrations of PDGFR-β and BDNF were measured with commercially available enzyme-linked immunosorbent assay kits.

Results: PDGFR-β [2.82 ng/ml; interquartile range (IQR), 0.57–7.79 ng/ml vs. 2.27 ng/ml; IQR, 0.41–7.16 ng/ml; p<0.0005] and BDNF (2.41 ng/ml; IQR, 0.97–7.97 ng/ml vs. 1.92 ng/ml; IQR, 1.07–6.67 ng/ml; p=0.023) concentrations were significantly higher in patients with MVA compared with the controls. PDGFR-β correlated positively with age (r=0.26, p=0.001), low-density lipoprotein (r=0.18; p=0.02), and BDNF (r=0.47; p<0.001), and BDNF showed a significant positive correlation with age (r=0.20; p=0.01). In binary logistic regression analysis, high-sensitivity C-reactive protein, uric acid, and PDGFR-β values were found to be independent predictors of MVA.

Conclusion: MVA is associated with higher PDGFR-β and BDNF levels. This association may indicate an abnormality in microvascular function. Future studies are required to determine the role of these biomarkers in the pathogenesis of MVA. *(Anatol J Cardiol 2020; 24: 397-404)*

Keywords: brain-derived neurotrophic factor, microvascular angina, pericytes, platelet-derived growth factor receptor beta

Introduction

Microvascular angina (MVA) is described as anginal chest pain with evident myocardial ischemia despite angiographically normal epicardial coronary arteries. Its prevalence varies between 10% and 30% among patients undergoing diagnostic coronary angiography, and it is more frequently observed in women compared with men (1-3). Despite controversial reports, patients with primary MVA appear to have a good prognosis, but symptoms may recur over time (4, 5).

Although there are still many mysteries regarding its pathogenesis, coronary microvascular dysfunction (CMVD) is the most widely accepted mechanism of MVA (6). Various structural alterations such as microvascular rarefaction, decreased microvascular density, and perivascular fibrosis and functional abnormalities, including impairment of endothelial vasodilation and decreased microvascular reactivity, have been reported to contribute to the pathogenesis of MVA.

Many studies have examined the role of 2 components, namely endothelial cells and smooth muscle cells, in the development of CMVD. Another important component of microcirculation is pericytes. Pericytes, mostly known as the perivascular cells, have many physiopathological roles in organs such as retina, kidney, and brain (7). They are key mediators in multiple microvascular processes, such as endothelial cell proliferation and differentiation (8), contractility and tone (9), stabilization and permeability (10), and morphogenesis (11). Despite their high number in cardiac capillaries, the role of pericytes in coronary physiology has not been thoroughly examined. Current data indicate that cardiac pericytes play important roles in the adjustment of local blood flow, regulation of angiogenic processes, and vascular permeability, as well as triggering procoagu-

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lant incidents (Fig. 1) (7-12). Previous studies have shown that pericapillary pericytes express α-smooth muscle actin (SMA), β-SMA, γ-SMA, skeletal muscle actin, desmin, and non-smooth muscle myosin variants (13). They constrict or dilate in response to chemical or electrical stimuli and can thus regulate capillary blood flow.

Pericyte abnormalities cannot directly be visualized with current imaging techniques. Nevertheless, biomarkers expressed by pericytes may indirectly reflect their dysfunction (14). Platelet-derived growth factor receptor-β (PDGFR-β), a transmembrane receptor with tyrosine kinase activity, is the most widely used pericyte marker. PDGF-BB, a growth factor secreted from endothelial cells, binds to the PDGFR-β on pericytes and plays an important role in angiogenesis, fibroblast migration, proliferation, and activation (15). Although PDGF-BB is expressed by endothelial cells, smooth muscle cells and pericytes express PDGFR-β (16). In addition, PDGF-BB and PDGFR-β interactions influence the recruitment of pericytes, proliferation of vascular smooth muscle cells, and induce differentiation of mesenchymal cells (17).

Brain-derived neurotrophic factor (BDNF), a well-established neurotrophic factor, is expressed from endothelial cells, activated platelets, and pericytes. BDNF and its receptor tyrosine receptor kinase B (TrkB) play significant roles in angiogenesis, tissue repair, and regeneration (18, 19). Pericytes increase BNDF production under stress and hypoxia conditions (14). Previous studies have shown increased BNDF expression in coronary atherosclerotic plaques of patients with angina pectoris (20), but circulatory BDNF levels of the patients with coronary artery diseases have shown conflicting results depending on the characteristics of the study groups (21, 22).

The relationship of these biomarkers to MVA is unknown. Considering the presented data, the aim of this study was to evaluate serum PDGF-β and BDNF levels in patients with MVA and to assess their possible associations with other atherosclerotic risk factors.

Methods

Study population

This study was a retrospective analysis of a previous trial on circulatory biomarkers in MVA patients (23). Consecutive patients who presented to the Cardiology Department of Bakırköy Dr. Sadi Konuk Education and Research Hospital between December 2015 and September 2017 with chest pain were included in this study. According to a power analysis based on these data (alpha, 0.05; power, 95%), a minimum total of 134 patients were planned to be included in the study. MVA was diagnosed according to the following criteria: (1) presence of a typical exertional angina; (2) positive exercise electrocardiogram stress test response, which was defined as 0.1 mV or greater horizontal or downsloping ST-segment depression or reversible myocardial

perfusion defects during stress imaging evaluated by single-photon emission computed tomography; and (3) angiographically normal coronary arteries without coronary luminal irregularity (24). In patients with MVA, epicardial coronary artery spasm was excluded by prolonged hyperventilation or ergonovine administration during coronary angiography. Patients were excluded if they had documented congenital heart disease, congestive heart failure, valvular heart disease, myocardial infarction, unstable angina, arrhythmia, conduction disturbances, left bundle branch block, neoplasm, systemic inflammatory disease, acute or chronic kidney, or liver diseases. The control group consisted of subjects with normal coronary arteries. This group was comprised of individuals who had applied to the cardiology outpatient clinic with ongoing chest pain (i.e., angina-like symptoms), had inconclusive findings in stress tests or functional imaging, and underwent diagnostic coronary angiography to rule out obstructive coronary artery disease (CAD).

Age; sex; family history of CAD; body mass index; smoking status; and history of hypertension, hyperlipidemia, or diabetes mellitus were recorded for each study subject. All participants gave written informed consent, and the Institutional Ethics Committee approved the study protocol.

The main objective of the study was to evaluate the circulatory level of PDGFR-β and BDNF in MVA patients. The secondary objective was to determine their possible associations with other cardiovascular risk factors.

Laboratory analysis

Fasting (10–12 h) cubital venous blood specimens were obtained in the morning. Serum glucose, lipid profile, high-sensitivity C-reactive protein, and uric acid concentrations were measured by standard laboratory methods. Blood samples were immediately centrifuged at 1000 rpm for 15 minutes, and sera were extracted. Collected serum samples were frozen at −80°C and stored at this temperature until the time of analysis. Serum PDGFR-β and BDNF were measured with a commercially available enzyme-linked immunosorbent assay kit according to the manufacturer's instructions (Hangzhou Eastbiopharm Co., Ltd., Hangzhou, China). Values were normalized to the standard curve. The intra- and inter-assay variances for PDGFR-β and BDNF were less than 10% and less than 12%, respectively.

Statistical analysis

SPSS software (Statistical Package for the Social Sciences, version 23; SSPS Inc., Chicago, IL, USA) was used to evaluate all analyses. The normality of distribution was found by using the Kolmogorov-Smirnov test. Continuous variables were expressed as mean±standard deviation or median (interquartile range), and categorical variables were expressed as percentages. The Student t test was used to compare the variables that showed a normal distribution. Variables with a nonhomogeneous distribution were compared using the Mann–Whitney U test. The chi-square test was used to compare the categorical variables. Correlations

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were determined using Pearson's correlation test. The Hosmer and Lemeshow test was used to assess the overall fitting of the regression model. A backward stepwise binary logistic regression analysis adjusted for variables with a p value less than 0.05 in univariable analysis was performed to determine independent parameters associated with MVA. Receiver operating curve analysis was used to determine the cutoff values of the 2 biomarkers. All 2-tailed p values less than 0.05 were accepted as statistically significant.

Results

The study group consisted of 91 patients with MVA (median age, 56 y; age range, 40–79 y; 36 men) and 61 controls (median age, 52 y; age range, 38–76 y; 29 men). Age, sex, smoking, bosy mass index, presence of hypertension, diabetes mellitus, family history of CAD, diastolic blood pressure, fasting glucose, HDL cholesterol, and triglyceride concentrations were similar between the 2 groups (Table 1). Systolic blood pressure, total and low-density lipoprotein (LDL) cholesterol, hs-CRP, uric acid, and serum concentrations of PDGFR-β and BDNF were significantly higher in patients with MVA compared with controls (Table 1, Fig. 2).

In Pearson correlation analysis, PDGFR-β and BDNF levels were significantly correlated with each other (r=0.471; p<0.001). In subanalysis, the significant positive correlation between the 2 biomarkers persisted within each group (MVA: p=0.455, p<0.001 and controls: p=0.440, p<0.001) (Fig. 3a). Other correlates of PDGFR- β were age (r=0.257; p=0.001), systolic blood pressure (r=0.159; p=0.051), and LDL cholesterol (r=0.186; p=0.022). However, in subgroup analysis, the significant correlation to age disappeared in patients with MVA but persisted in controls (r=0.315; p=0.013), whereas the correlation to systolic blood pressure continued in MVA patients (r=0.249; p=0.017) and disappeared in controls (Fig. 3b). BDNF levels showed significant positive correlations with age (r=0.202; p=0.012) and mild correlations with borderline statistical significance with systolic blood pressure (r=0.159; p=0.051) and hs-CRP (r=0.155; p=0.057). Like PDGFR-β, the correlation with age originated from controls (r=0.340l; p=0.007) and the correlation with systolic blood pressure from MVA patients (r=0.228; p=0.030). Sex, smoking, history of hypertension, diabetes, and drug usage did not affect PDGFR-β and BDNF levels.

The Hosmer and Lemeshow test was used to assess the overall fitting of the regression model. In binary logistic regression analysis adjusted for age, systolic blood pressure, LDL cholesterol, and total cholesterol (R^2, 0.40; odds ratio, 0.016; p<0.001 for the model with backward stepwise methodology), MVA was significantly associated with hs-CRP (p<0.0001), uric acid (p=0.004), and PDGFR-β (p=0.011) (Table 2).

According to receiver operating characteristic curve analysis, the optimal cutoff value of PDGFR-β for MVA patients in this study was greater than 2.71 ng/ml, with 59% sensitivity, 41%

Table 1. Baseline and laboratory characteristics of the study population

Clinical characteristics	MVA group (n=91)	Control group (n=61)	*P* value
Age (years)	56 (40-79)	52 (38-76)	0.078*
Sex (female/male)	55/36	29/32	0.330¶
Hypertension (%)	46.1	47.5	0.867¶
Diabetes mellitus (%)	26.3	24.5	0.805¶
Family history of CAD (%)	32	23	0.215¶
Smoking (%)	24	34	0.169¶
Body mass index (kg/m^2)	28 (16.9-43)	28.3 (18.7-43.7)	0.688*
Systolic blood pressure (mm Hg)	120 (95-150)	110 (90-135)	**0.008***
Diastolic blood pressure (mm Hg)	70 (55-100)	70 (50-85)	0.297*
Fasting glucose (mg/dL)	101 (77-284)	101 (71-186)	0.930*
Total cholesterol (mg/dL)	199 (125-285)	182 (94-275)	**0.019***
High-density lipoprotein (mg/dL)	43 (25-67)	45 (30-69)	0.682*
Low-density lipoprotein (mg/dL)	127 (41.6-221.4)	108 (31-195)	**0.010***
Triglycerides (mg/dL)	138 (45-307)	125 (59-395)	0.099*
Creatinine (mg/dL)	0.77±0.21	0.78±0.17	0.742≠
Uric acid (mg/dL)	4.6 (1.9-8.4)	3.8 (2.2-7.6)	**<0.0005***
High-sensitivity C-reactive protein (mg/L)	2.6 (0.4-8.8)	1.3 (0.2-3.1)	**<0.0005***
Brain-derived neurotrophic factor (ng/mL)	2.41 (0.97-7.94)	1.92 (1.07-6.64)	**0.023***
Platelet-derived growth factor receptor B (ng/mL)	2.82 (0.57-7.79)	2.27 (0.41-7.16)	**<0.0005***

Data is reported as median (interquartile range) or frequency counts (percentages) as appropriate. ≠t test. *Mann–Whitney U test. ¶Chi-square test.
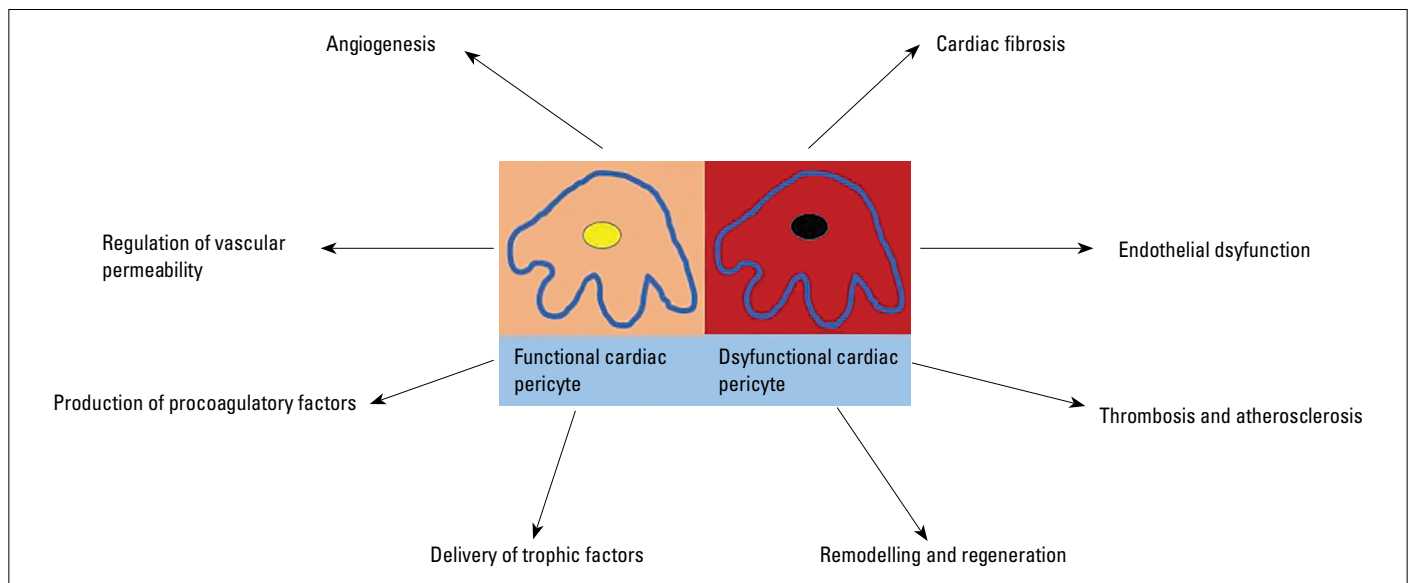CAD - coronary artery disease; MVA - microvascular angina; NS - nonsignificant

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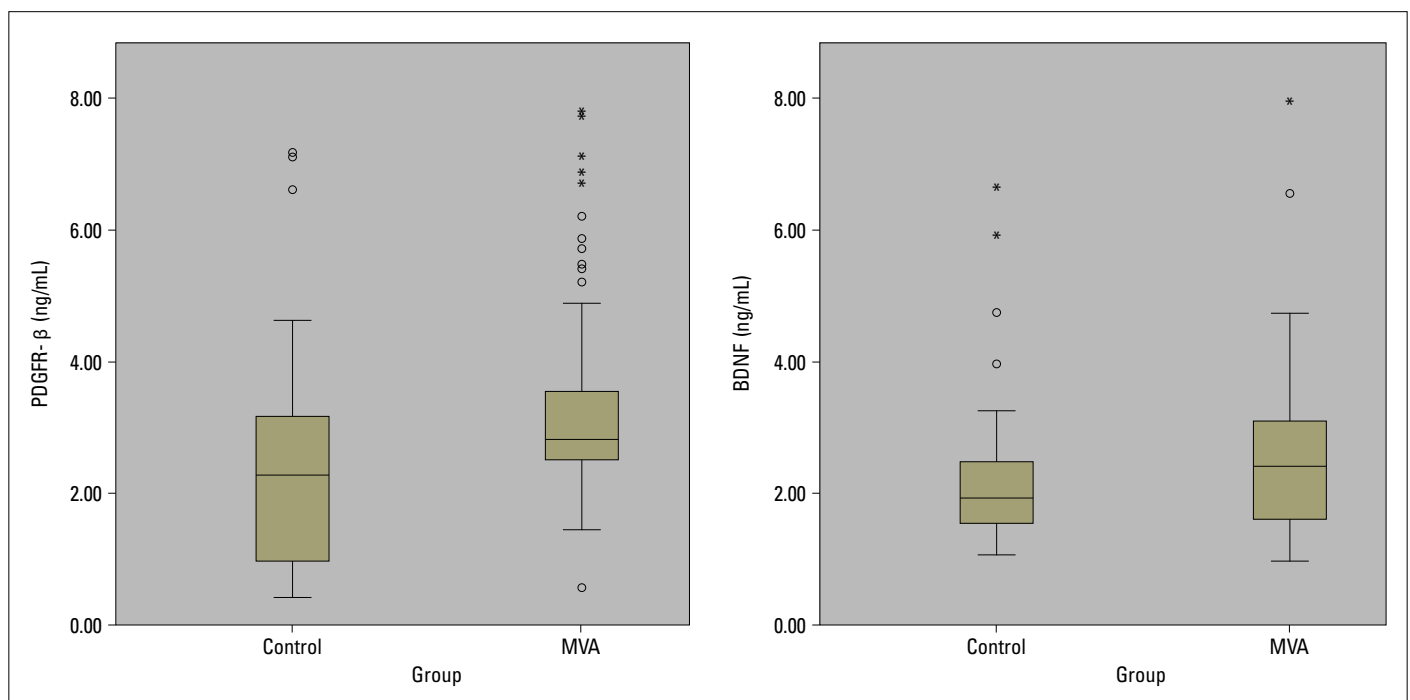**Figure 1.** The role of cardiac pericytes in the cardiovascular system

Figure 2. Serum PDGFR-β and BDNF concentration in patients with MVA and controls

specificity [area under the curve (AUC), 0.68; 95% confidence interval, 0.58–0.77; p<0.001). The optimal cutoff value of BDNF was greater than 2.18 ng/ml, with 60% sensitivity, 41% specificity (AUC, 0.60; 95% confidence interval, 0.51–0.69; p=0.023) (Fig. 4).

Discussion

The findings of this study demonstrated the following: (1) patients with MVA displayed higher PDGFR-β and BDNF levels

than the controls; (2) PDGFR-β in patients with MVA and control subjects was significantly correlated with BDNF; (3) age was a significant contributor of higher PDGFR-β and BDNF levels in controls, but this finding was not detected in MVA patients; and (4) the presence of MVA was associated with high levels of inflammation along with higher PDGFR-β.

Circulating levels of PDGFR-β have been studied in a few studies about cancer and stroke, but not in patients with CADs (25, 26). In a study on nonalcoholic fatty liver disease, higher levels of PDGFR-β were associated with increased hepatic fi-
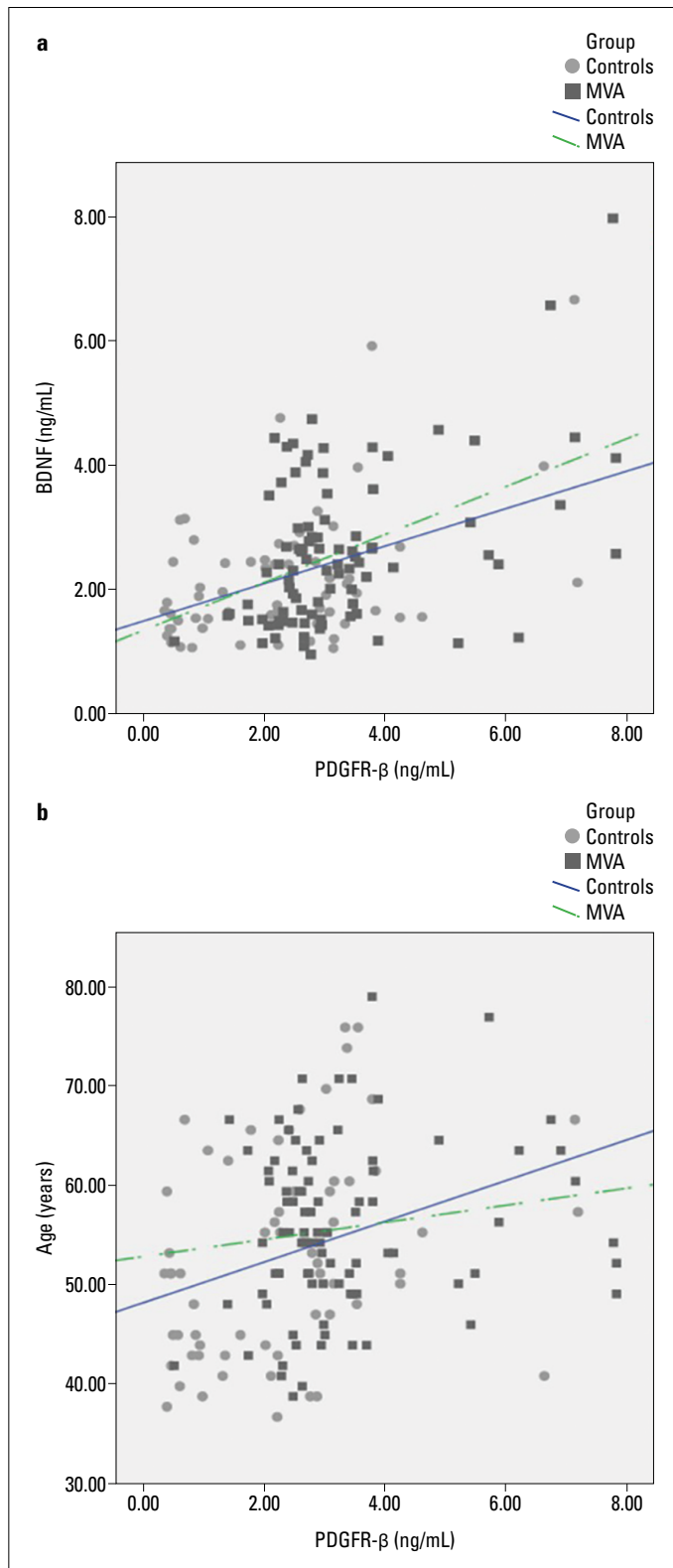
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Figure 3. Correlations between PDGFR-β and BDNF (a) and age (b) in MVA and controls

Figure 4. Receiver operating characteristic curve analysis for values of BDNF (2.18 ng/ml, with 60% sensitivity, 41% specificity [area under the curve (AUC), 0.60; 95% confidence interval (CI), 0.51–0.69; *P*=0.023]) and PDGR-B [2.71 ng/ml, with 59% sensitivity, 41% specificity (AUC, 0.68; 95% CI, 0.58–0.77; *P*<0.001)]

brosis (27). Studies on the association of PDGFR-β and atherosclerosis have shown increased expression of platelet-derived gr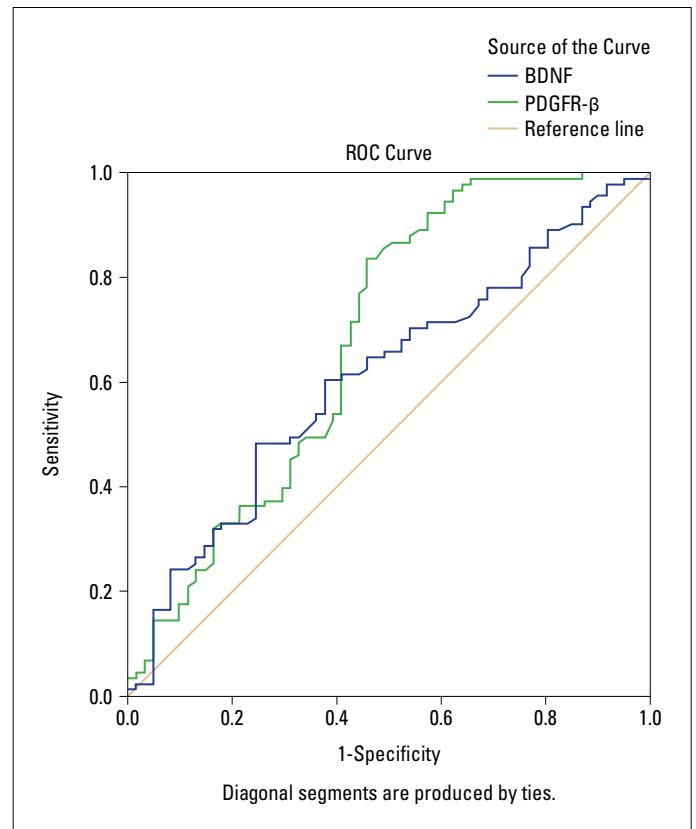owth factor and PDGFR-β in atherosclerotic plaques with sig-nificant stenosis (28) and a direct effect of increased PDGFR-β signaling on chemokine secretion, leukocyte accumulation, and advanced plaque formation in the coronary arteries (29). Increased PDGF receptor activity appears to affect mainly 2 cells, namely smooth muscle cells and fibroblasts, by inducing their proliferation, differentiation, apoptosis, migration, and invasion, thus resulting in tissue fibrosis (30). The finding of the higher PDGFR-β in elderly controls in the current study is compatible with increased fibrosis associated with aging. The blunted association with age and PDGFR-β in MVA patients despite presence of higher levels than the controls suggests accelerated vascular aging and a tendency to atherosclerotic plaque formation in those patients.

Previous studies on the relation of circulating BDNF to CAD have revealed conflicting results. In patients with acute myocardial infarction, serum BDNF showed a significant positive correlation with Killip class and predicted the onset of acute heart failure (21). However, most other studies demonstrated that low, rather than high, levels of BDNF were associated with coronary artery disease, formation of larger fibrin thrombi, and unfavorable outcome (31). In this study, BDNF levels in MVA patients were significantly correlated with PDGFR-β and systolic blood pressure (32). Considering the results of the previous studies, these

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Table 2. The microvascular angina associated with variables according to binary logistic regression

| Variables | Binary logistic regression analysis, method: backward stepwise | | | | | |
| | Univariate analysis | | | Multiple analysis (R², .40; odds ratio, 0.016; *P*<0.001) | | |
	Exp (B)	95% CI	*P* value	Exp (B)	95% CI	*P* value
Age	1.03	0.99-1.07	0.080	1.01	0.96-1.06	0.610
Total cholesterol	1.01	1.00-1.02	0.022	1.00	0.98-1.02	0.901
Low-density lipoprotein	1.01	1.00-1.02	0.034	1.00	0.98-1.02	0.734
Systolic blood pressure	1.03	1.00-1.05	0.007	1.02	0.99-1.06	0.074
Brain-derived neurotrophic factor	1.39	1.01-1.91	0.040	1.05	0.68-1.64	0.804
Uric acid	2.14	1.47-3.11	<0.0005	1.90	1.23-2.93	0.004
High-sensitivity C-reactive protein	4.65	2.64-8.19	<0.0005	4.09	2.29-7.31	<0.0005
Platelet-derived growth factor receptor B	1.64	1.23-2.17	0.001	1.48	1.09-2.02	0.011

CI - confidence interval

associations may suggest a protective secretion of BDNF from pericytes in response to PDGF-BB after inflammatory stress like high blood pressure. Another explanation of this association may be endothelial dysfunction. The TrkB expressed by pericytes plays a major role in the maturation of vessels. Endothelial cells produce BDNF that is the ligand for TrkB. BDNF and TrkB signaling is critical for the development of the endothelial-pericyte barrier. Anastasia et al have shown that reduced pericyte coverage of the cardiac microvasculature causes abnormal endothelium and increased vascular permeability in TrkB-deficient mice (33). In the present study, deteriorated BDNF levels could cause endothelial dysfunction owing to the affected pericytes' function in MVA patients.

Current reports show that the pericytes are regulators of coronary microvascular function, yet the precise mechanism of pericytes' function remains undefined. They provide structural support of microvascular endothelial tubes, secrete specific growth factors, and modulate extracellular matrix (34). The interaction between the pericytes and the endothelial cells is regulated by the crosstalk between some ligands and receptors, such as PDGF-BB and PDGFR-β (7). Preclinical studies show that pericytes require PDGFR-β signal transduction for vascular smooth muscle cell development in embryos (35). Mellgren et al. (36) have emphasized in mice that PDGFR-β signaling is required for efficient cell migration and development of coronary vascular smooth cells. Chintalgattu et al. (37) have reported that sunitinib, an inhibitor of PDGFR-β signaling, induced cardiotoxicity is associated with the depletion of coronary microvascular pericytes, resulting in changes of the coronary microvasculature. Zymek et al. (38) have shown that impairment of PDGFR-β signaling results in a defective infarct vasculature, impaired maturation of the scar, prolonged inflammation, and decreased collagen ingredient in the wound. Nevertheless, the role of pericytes in myocardial and perivascular

fibrosis has not yet been adequately elucidated (39). Despite the existence of data for fibrosis in microvascular dysfunction, an association between MVA and the biomarker PDGFR-β has not been reported in previous studies. In this study, the independent association between MVA and serum PDGFR-β, along with hs-CRP, suggests induction of pericyte-led fibrotic pathways by inflammation in CMVD.

Another finding of this study was the independent association between uric acid and MVA, which has been demonstrated by other studies previously (40). Eroglu et al. (41) have shown that hs-CRP and uric acid, which could be associated with inflammation and endothelial dysfunction, were higher in MVA patients. In primary cultured vascular smooth muscle cells from rat aorta, uric acid stimulated proliferative pathways by PDGFR-β phosphorylation and appeared to play an important role in the development of cardiovascular diseases (42).

These findings may be signs of inflammation-induced endothelial dysfunction and myocardial fibrosis associated with the dysfunction of pericytes in MVA. Future studies are required to show the pathogenesis and the role of pericytes function biomarkers and MVA.

Study limitations

There are several limitations in the present study. First, this study had a small sample size, so our hypothesis needs to be explored in large, multicenter studies. Second, our study did not include imaging and follow-up data to show the development of fibrosis in MVA patients with higher PDGFR-β levels.

Conclusion

In this study, patients with MVA had higher PDGFR-β and BDNF levels than the control group. PDGFR-β, uric acid, and hs-

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CRP levels were significantly associated with MVA. These findings suggest an underlying pericyte dysfunction associated with inflammation, endothelial dysfunction, and myocardial fibrosis in MVA.

Conflict of interest: None declared.

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