

# The Relationship between Plasma Endothelin-1, Nitric Oxide Levels, and Heart Rate Variability in Patients with Coronary Slow Flow

Hasan Pekdemir, M.D., Dilek Cicek, M.D., Ahmet Camsari, M.D., M. Necdet Akkus, M.D., V. Gokhan Cin, M.D., Oben Doven, M.D., H. Tuncay Parmaksiz, M.D., M. Tuna Katircibasi, M.D., and I. Turkey Ozcan, M.D.

From the Department of Cardiology, Medical Faculty, Mersin University, Mersin, Turkey

**Background:** Coronary slow flow (CSF) is characterized by delayed opacification of coronary arteries in the absence of epicardial occlusive disease. In this study, we aimed to determine endothelin-1 (ET-1), nitric oxide (NO<sub>x</sub>) levels and time domain heart rate variability (HRV) parameters in patients with CSF and relationship among these parameters.

**Methods:** Thirty-three patients with CSF detected in the coronary angiography (17 females; mean age 55 ± 7) and 19 patients with normal coronary flow (10 females; mean age 54 ± 11) as a control group were enrolled in the study. Patients were divided into two groups according to exercise testing as if positive (group A, n = 8) or negative (group B, n = 25).

**Results:** Plasma ET-1 levels were higher in the group A patients (28.7 ± 17.4 pg/ml) than that of group B (15.9 ± 10.6 pg/ml) and control group (6.0 ± 5.7 pg/ml); and higher in group B patients than that of control group (P < 0.05). Although groups A and B did not differ according to plasma NO<sub>x</sub> levels (23.4 ± 13.5 μmol/L vs. 32.8 ± 22.7 μmol/L, P > 0.05), NO<sub>x</sub> levels in group A were lower than the control group (23.4 ± 13.5 μmol/L versus 42.5 ± 15.9 μmol/L, P < 0.05). Time domain HRV parameters were decreased in all patient groups. This was more prominent in group A. Additionally, HRV parameters were negatively correlated with ET-1 and TIMI frame counts. TIMI frame count was also significantly correlated with ET-1 and NO<sub>x</sub> levels (r = 0.61, P < 0.0001, r = -0.30, P < 0.05). Upon intravascular ultrasonography investigation, the common finding was longitudinally extended massive calcification throughout the epicardial arteries. Mean intimal thickness was 0.50 ± 0.13 mm (group A; 0.58 ± 0.11 mm, group B 0.47 ± 0.12 mm, P = 0.029).

**Conclusions:** The present study demonstrated that in patients with CSF, both increased plasma ET-1, decreased plasma NO<sub>x</sub> and diffuse atherosclerosis may cause the decrease in HRV by effecting myocardial blood flow.

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coronary slow flow; endothelin-1; nitric oxide; atherosclerosis; heart rate variability

Coronary slow flow (CSF) is a phenomenon characterized by delayed opacification of coronary arteries in the absence of epicardial occlusive disease.<sup>1</sup> Many etiological factors such as endothelial dysfunction, coronary vasospasm, and small vessel disease have been implicated in CSF.<sup>1-5</sup> It is well known that endothelin-1 (ET-1) and nitric oxide (NO<sub>x</sub>) are key molecules in normal autoregulatory mechanisms such as modulating coronary circulation.<sup>6,7</sup> The endothelial dysfunction in the small coronary arteries (increased ET-1 levels) in patients with angina pectoris and normal coronary

angiography may increase coronary resistance and may cause myocardial ischemia.<sup>8,9</sup>

Time domain heart rate variability (HRV) is a reliable method, which can be used as an index of cardiac autonomic balance.<sup>8,9</sup> It is a noninvasive technique, based on electrocardiogram (ECG) sampling of RR interval variation, thus providing a dynamic assessment of sympathetic and parasympathetic components of the autonomic nervous system.<sup>10</sup> In clinical practice, indices of HRV have been proved to be good predictors of arrhythmic events, sudden death, acute ischemic syndromes,

suggesting that low HRV parameters are associated with increased risk of cardiovascular morbidity and mortality.<sup>11</sup> Moreover, low HRV predicts progression of coronary artery disease, providing information beyond that obtained by traditional risk markers of atherosclerosis.<sup>12</sup> Rosano et al.<sup>13</sup> using the analysis of HRV, showed a sympathetic predominance in syndrome X. Autonomic imbalance may influence vasomotor control of the coronary circulation. In the same way, autonomic imbalance would contribute to the pathogenesis of the CSF. In the present study, we investigated relationship between ET-1, NO<sub>x</sub> plasma levels and measures of cardiac autonomic function, obtained by time domain HRV analysis, an accepted clinical indicator of cardiac autonomic activity.<sup>10</sup> Additionally, we investigated diffuse atherosclerotic changes in these patients by using intravascular ultrasonography (IVUS).

## MATERIAL AND METHODS

The study population consisted of 33 patients with slow coronary flow (17 females; mean age =  $55 \pm 7$  years), who underwent coronary angiography to determine whether or not obstructive coronary artery disease existed because of typical and quasi-typical symptoms of angina and ECG changes between January 2001 and June 2002 at Cardiology Clinic of Mersin University. The patients with CSF had angiographically normal coronary arteries without luminal irregularities. The patients who suffered from one of the following diseases or associated disorders were excluded from this study; myocardial and/or valvular heart disease, tortuous coronary vessels, myocardial bridge, coronary ectasia, a proximal lumen diameter less than 3 mm, and left ventricular hypertrophy. The intravascular ultrasonography was performed on all patients with coronary angiography, then, all medications were stopped and at the end of a week, 24-hour ECG Holter monitorization was performed. Patients were divided into two groups according to exercise testing as if positive (group A,  $n = 8$ ) or negative (group B,  $n = 25$ ). Nineteen patients with normal coronary flow in the coronary angiography and normal exercise testing (10 females; mean age  $54 \pm 11$ ) as a control group were enrolled in the study. The study was carried out according to the principles of the Declaration of Helsinki and approved by Mersin University, School of Medicine, investigational review board.

## Coronary Angiography and TIMI Frame Count

Coronary angiography was applied by femoral approach using standard Judkins technique. Coronary arteries in left and right oblique planes, and cranial and caudal angles were demonstrated. Left ventricular and aortic pressures were obtained. During the coronary angiography, loprovide (Ultravist-370, Schering AG) was used as contrast agent and was manually injected (6–8 ml contrast agent at each position). Proximal coronary lumen diameter was measured by quantitative computer-assisted (QCA) facility and those with a caliber of 3 mm or more were enrolled for further CSF measurements. For the quantitative measurement of coronary blood flow, the time elapsed from the appearance till the contrast agent reached the distal end of coronary artery in terms of cineframe count was considered to be the TIMI frame count.<sup>4,14</sup> Thereafter, the final count was subtracted from the initial and the exact TIMI frame was calculated for the given artery. However, it was divided by 1.7 when left anterior descending coronary artery was the case, for adjusted correction. TIMI frame counting was undertaken by two different cardiologists. In case of conflict, the frames were referred to a third one. The corrected cut-off values due to the length, for normal visualization of coronary arteries were  $36.2 \pm 2.6$  frames for left anterior descending coronary artery,  $22.2 \pm 4.1$  frames for left circumflex coronary artery, and  $20.4 \pm 3$  frames for right coronary artery.<sup>14</sup> Any values obtained above these thresholds were considered to be CSF. All TIMI frame counts were measured in matched projections with use of Medcon Telemedicine Technology (version 1.900, Israel).

## Intravascular Ultrasound

All patients enrolled in the study underwent IVUS investigation; 7Fr guiding catheter was positioned in the given coronary artery. Two micrograms of nitroglycerine was administered via intracoronary injection. "Endosonics in Visions Imaging System" was utilized during IVUS. The imaging catheter (The Endosonic Visions Five-64 F/X catheter) had a 30 frames/second maximum frame rate and 20-MHz single-piezoelectric crystal transducer mechanically rotating at 1,800 rpm within a 3.5-F monorail catheter, was advanced

over the 0.014-inch guide wire into the coronary artery as distally as possible and was then carefully pulled back to continuously image the wall morphology. The size of Judkins catheter was used to calibrate the length of the coronary segment. Images were analyzed frame-by-frame having the external elastic lamina border manually traced, maximal and minimal intimal thicknesses were measured within the same segment. The following criteria<sup>15</sup> were chosen for lesion characteristics and severity; Atherosclerotic plaque; in any segment intimal thickness  $\geq 5$  mm, eccentric lesion; if maximal thickening exceeded two-fold minimal thickening, calcified lesion; focal or diffuse calcification leading to acoustic shadowing. All images were recorded on recordable compact disk for subsequent data analysis. Each IVUS image was analyzed off-line by two independent experienced IVUS analysts.

### Exercise Testing

All patients performed the modified Bruce protocol. Electrocardiograms were recorded using an exercise system (T2000 Treadmill, Marquette Electronics Systems Inc., Millwaukee, WI, USA). The treadmill exercise end point was defined as: (1) reaching the maximum heart rate ( $220 - \text{age}$ ), (2) typical angina pectoris, (3) ST segment depression in the sequential two derivation with or without angina pectoris ( $> 1.0$  mm after J point, 60 ms horizontal or downsloping ST segment depression), (4) severe dyspnea or syncope, (5) repeated ventricular arrhythmia, (6)  $> 10$  mmHg fall in systolic blood pressure at any stage.

### Holter ECG Monitoring

Patients and controls were monitored for 24 hours using version 1.04 Flash Card digital Holter recorder. Recordings were evaluated on Holter for Windows version 3.6F computer (North East Monitoring Inc., USA) and time domain analyses of HRV are derived from statistical calculations performed on the set of normal-to-normal (NN) interbeat intervals: the average heart rate in beats per minute, standard deviation of all NN intervals (SDNN, ms), standard deviations of all NN intervals for all 5-minute segments of the entire recording (SDNN index, ms), percentage of the differences of adjacent NN intervals greater 50 ms normalized to all differences within the interval (pNN50,%), the root mean square of adjacent differences of NN intervals (RMSSD, ms), total number of NN intervals

divided by the height of the histogram of all NN intervals measured on discrete scale with bins of 7.8125 ms (1/128 s) (triangular index) and standard deviation of averages of NN intervals in all 5-minute segments of the entire recording (SDANN, ms) were calculated. RMSSD and pNN50 primarily reflect parasympathetically mediated changes in heart rate.<sup>16</sup> The other time domain variables reflect a mixture of parasympathetic, sympathetic, and other physiologic influences.<sup>16</sup> Subjects with less than 22-hour recordings or normal sinus beats less than 80% of total beats were excluded.

### Analysis of Endothelin-1

Plasma samples were drawn into chilled EDTA tubes (1 mg/ml blood) containing aprotinin (500 KIU/ml of blood). The whole blood samples were centrifuged at 1600 xg for 15 minutes at 0°C. The plasma fractions were transferred to a plastic tube and stored at -70°C for long term storage. After a short incubation period, the excess sample was washed out and a polyclonal antibody to ET-1 was labeled and the enzyme horseradish peroxidase was added. This labeled antibody was bound to the ET-1 and was captured on the plate. After a short incubation period, the excess labeled antibody was washed out and substrate was added. The substrate, which reacted with the labeled antibody was bound to the ET-1 and was captured on the plate. The color generated with the substrate was read at 450 nm, and was directly proportional to the concentration of ET-1 in the sample (Human Endothelin-1, catalog no EIA-3111, DRG International Inc., USA).

### Analysis of Serum Nitrite and Nitrate

The levels of nitrite and nitrate were determined using a procedure based on the Griess reaction. Blood samples were centrifuged at 4000 rpm for 10 minutes. Serum samples were then separated and stored at -70°C until used for assay. Equal volumes of serum and potassium phosphate buffer were placed in an ultrafilter and centrifuged at 4000 rpm for 45 minutes. The ultrafiltrate was collected and used in the test. Nitrates were quantitatively converted to nitrites for analysis. Enzymatic reduction of nitrate to nitrite was carried out using coenzymes (NADPH, FAD) in the presence of nitrate reductase in step of incubation assay. N-1-(naphthyl) ethylenediamine dihydrochloride,

sulfanilamide and incubation solutions were mixed at a ratio of 1:1:2 (v/v). These mixtures were incubated for 5 minutes at room temperature and measured at 540 nm. Sodium nitrite of 1.00 mM was used as standard for determination of nitrite and potassium nitrate of 80 mM was used as standard for determination.

### Statistical Analysis

Statistical analysis was performed using SPSS software package (version 10.0, SPSS Inc., Chicago, Illinois, USA). Categorical variables were expressed as counts and percentages. Comparison of categorical variables was made by Pearson Chi-square test. Continuous variables were defined as means  $\pm$ SD. The time domain HRV parameters and other continuous variables of the patient groups and control group were compared with one-way ANOVA test. The posthoc analysis was done by Bonferroni's test. Correlations were examined by Pearson's correlation. All hypothesis testing was 2-tailed. The P values  $<0.05$  were considered to be significant.

### RESULTS

The clinical characteristics of study groups were given in Table 1. Groups were similar according to age, gender, systolic and diastolic blood pressures, total cholesterol level, current smoking, and family history of coronary heart disease. Two patients in group A had left bundle branch block. During con-

trast agent injection in the coronary angiography, ECG of seven patients (six patients in group A, one patient in group B) have showed 2–3 mm ST segment depression and five of them (all in group A) have developed angina pectoris. The exercise testings were stopped in eight patients (involving all patients in group A) because of ST segment depression over 2 mm and angina pectoris. In the control subjects, angina pectoris and ST segment depression were not observed during the coronary angiography and exercise testing.

Plasma ET-1 levels were higher in the group A patients than that of group B and control group and higher in group B patients than that of control group. Although NO<sub>x</sub> levels in group A were lower than control group, the difference of NO<sub>x</sub> levels in the other groups was statistically insignificant (Table 1).

Time domain HRV parameters were decreased in all patient groups. This was more prominent in group A (Table 1). All time domain HRV parameters of patient groups and control group and their analysis with Bonferroni's test are shown in the Table 2. Additionally, HRV parameters were negatively correlated with ET-1 levels and TIMI frame counts (Figs. 1 and 2, respectively). However, any correlation between HRV parameters and NO<sub>x</sub> levels was not detected. While, a positive correlation was observed between TIMI frame count and plasma ET-1 levels, correlation between TIMI frame count and NO<sub>x</sub> levels was negative ( $r = 0.61$ ,  $P = 0.0001$ ,  $r = -0.31$ ,  $P = 0.028$ , respectively).

**Table 1.** Baseline clinical and laboratory characteristics of patients with coronary slow flow and controls

	Group A (n = 8)	Group B (n = 25)	Control group (n = 19)
Age (year)	50 $\pm$ 6	56 $\pm$ 9	54 $\pm$ 11
Gender (female) n(%)	3(37.5)	14(56.0)	10(52.6)
Total cholesterol (mg/dl)	214.4 $\pm$ 39.0	228.4 $\pm$ 37.8	212.7 $\pm$ 32.1
Diabetes mellitus n (%)	1(12.5)	2(8)	–
Smoking n (%)	5(62.5)	8(32)	7(36.8)
Family history n (%)	2(25)	4(16)	9(47.4)
Systolic blood pressure (mmHg)	140 $\pm$ 16	142 $\pm$ 14	132 $\pm$ 13
Diastolic blood pressure (mmHg)	81 $\pm$ 16	77 $\pm$ 20	75 $\pm$ 18
End-diastolic pressure (mmHg)	11 $\pm$ 3	10 $\pm$ 5	10 $\pm$ 4
TIMI frame count <sup>a</sup> (frame)	55.3 $\pm$ 10.9	52.6 $\pm$ 11.8	26.2 $\pm$ 4.6
Left ventricle ejection fraction (%)	63.6 $\pm$ 6.5	66.8 $\pm$ 4.3	65.8 $\pm$ 6.4
Endothelin 1 (pg/ml) <sup>b,c,d</sup>	28.7 $\pm$ 17.4	15.9 $\pm$ 10.6	6.0 $\pm$ 5.7
Nitric oxide ( $\mu$ mol/L) <sup>e</sup>	23.4 $\pm$ 13.5	32.8 $\pm$ 22.7	42.5 $\pm$ 15.9

<sup>a</sup>P  $< 0.0001$  (group A vs. control and group B vs. control); <sup>b</sup>P  $< 0.05$  (group A vs. group B), <sup>c</sup>P  $< 0.0001$  (group A vs. control), <sup>d</sup>P  $< 0.05$  (group B and control), <sup>e</sup>P  $< 0.05$  (group A vs. control).

**Table 2.** Time domain heart rate variability (HRV) parameters of patients with coronary slow flow and controls

HRV parameters	Group A (n = 8)	Group B (n = 25)	Control (n = 19)
Heart rate (beat/min)	72 ± 13	71 ± 12	74 ± 15
SDNN (ms) <sup>a,b</sup>	103.0 ± 19.5	136.3 ± 44.7	170.4 ± 38.9
SDANN (ms) <sup>c,d,e</sup>	92.4 ± 12.8	121.3 ± 29.6	143.7 ± 24.4
RMSSD (ms) <sup>f</sup>	21.9 ± 9.5	28.3 ± 8.6	34.8 ± 12.1
SDNN index (ms) <sup>c,d,e</sup>	40.8 ± 13.8	70.1 ± 29.2	90.3 ± 18.0
PNN 50 (%) <sup>d,g</sup>	13.3 ± 5.7	18.4 ± 6.9	27.1 ± 8.9
Triangular index <sup>a,b</sup>	18.5 ± 9.6	24.8 ± 8.3	33.7 ± 9.3

<sup>a</sup>P < 0.001 (group A vs. control); <sup>b</sup>P < 0.05 (group B vs. control); <sup>c</sup>P < 0.05 (group A vs. group B); <sup>d</sup>P < 0.0001 (group A vs. control), <sup>e</sup>P < 0.05 (group B vs. control), <sup>f</sup>P < 0.05 (group A vs. control), <sup>g</sup>P < 0.001 (group B vs. control).

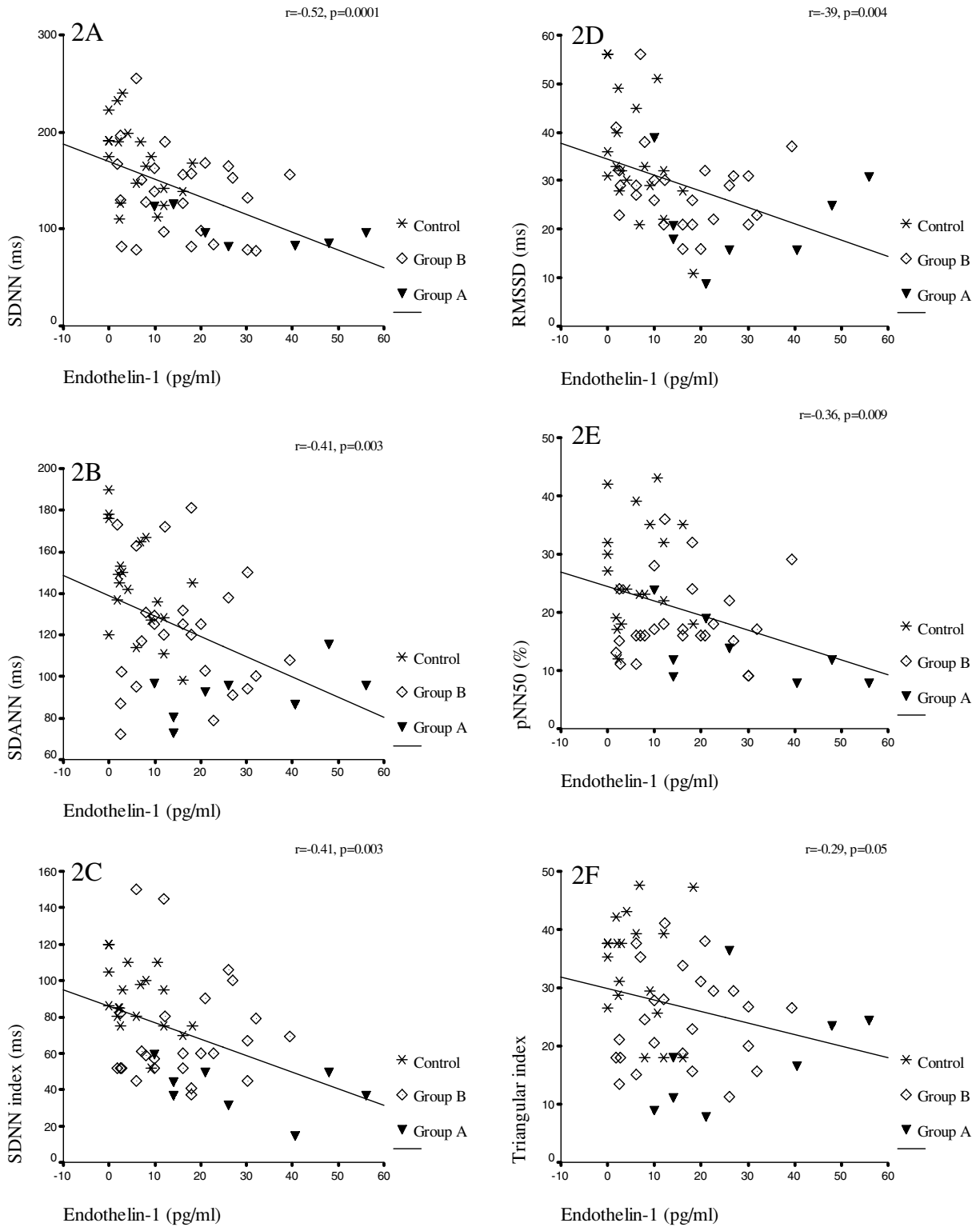
Upon IVUS investigation, the common finding was longitudinally extended massive calcification throughout the epicardial arteries in 15 patients and regional calcification in eight patients. Mean intimal thickness was 0.50 ± 0.13 mm (group A; 0.58 ± 0.11 mm, group B 0.47 ± 0.12 mm P = 0.029) and in 14 patients eccentric lesions were observed (Fig. 3). All patients in group A had eccentric lesions and diffuse calcification.

## DISCUSSION

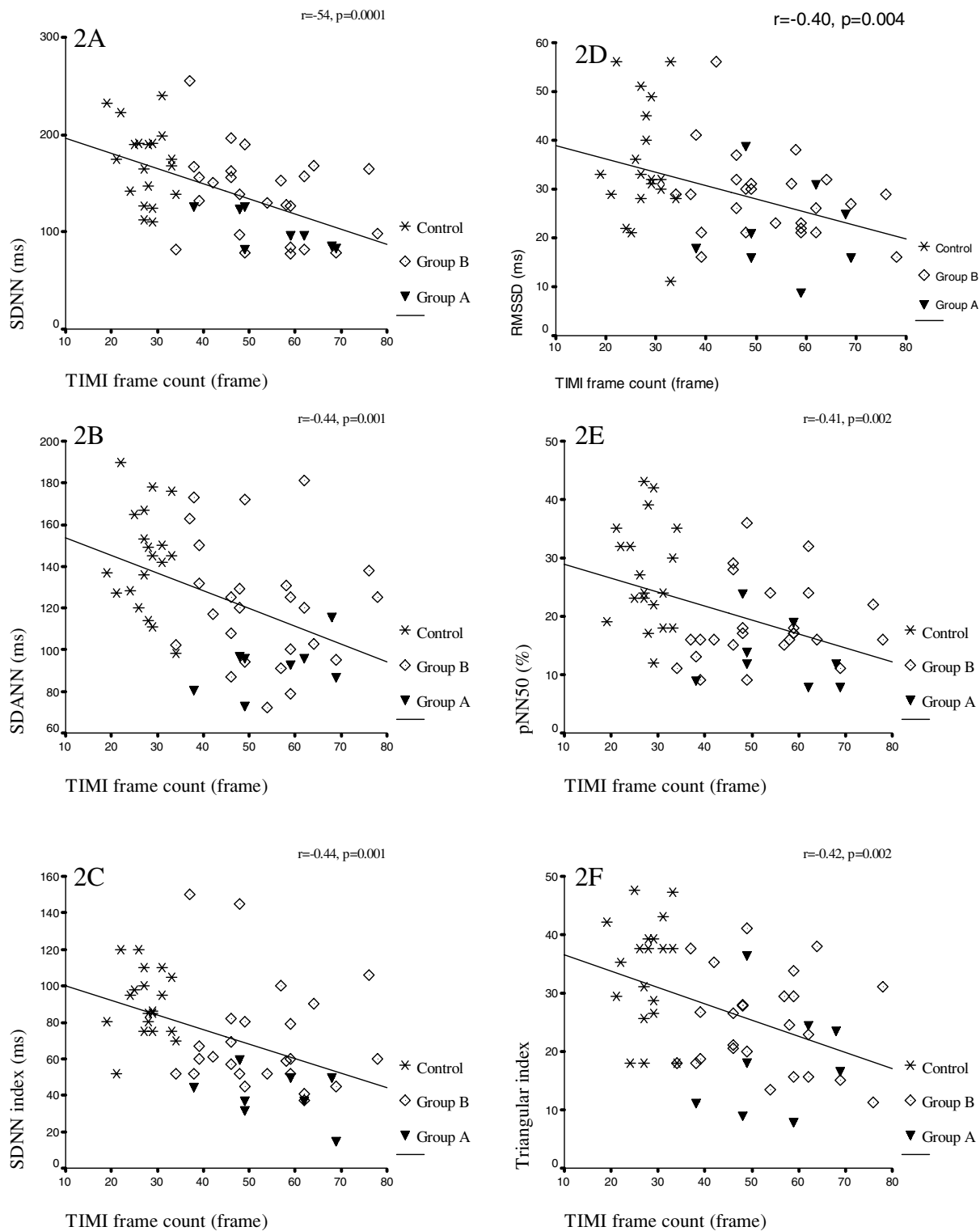
In many studies,<sup>1-4</sup> pathophysiology of CSF phenomenon is especially focused on microvascular disease. Furthermore, it is discussed as if it is a subgroup of syndrome X. However, in the present study, we found diffuse calcification and intimal thickening in all segments of the vessels by using IVUS despite the absence of focal stenosis or plaques in coronary angiography of CSF patients. According to these findings, we speculate that CSF may be a form or preliminary phase of diffuse atherosclerotic process that involve both small vessels and epicardial coronary arteries. Accordingly, some postmortem studies<sup>17,18</sup> revealed a coincidence of epicardial and small vessels disease, which supports our opinion. According to preliminary data, in the early phase of atherosclerosis or with intensive coronary artery disease risk factors, vasodilation capacity of coronary resistive arterioles by pharmacologic and physical stress was disturbed before development of angiographic atherosclerotic disease.<sup>19,20</sup> Besides, IVUS imaging can detect intimal thickening and is suitable for detection of early atherosclerosis, which cannot be detected by conventional angiography.<sup>15,21,22</sup>

Experimental studies on monkeys that fed with an atherogenic diet have demonstrated a relationship between resting heart rate and progression of coronary atherosclerosis,<sup>23,24</sup> and there was also a strong relationship between heart rate and arterial stiffness.<sup>25</sup> Reduced HRV and elevated heart rate result from altered cardiac autonomic regulation with sympathetic predominance and/or reduced vagal tone. Increased sympathetic tone with elevated catecholamine levels may have direct effects on vascular smooth muscle cells,<sup>26</sup> or it may affect other factors promoting the progression of atherosclerosis.<sup>27</sup>

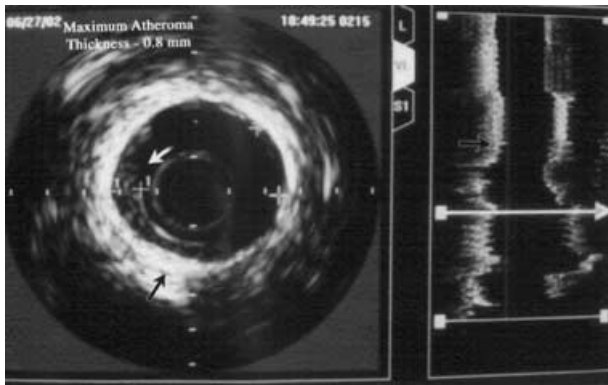
Endothelin-1 and NO<sub>x</sub> play an important role in cardiovascular regulation and pathophysiology.<sup>6,7</sup> Endothelin-1 has been shown to aggravate ischemia-induced ventricular arrhythmias. Proposed mechanisms for the arrhythmogenic effects of ET-1 are prolongation or increased dispersion of monophasic action potential duration, QT prolongation, development of early afterdepolarizations, acidosis, and augmentation of cellular injury.<sup>28</sup> Endothelin contributes to the progression of atherosclerosis and increased ET-1 may substantially contribute to cell growth and the regulation of vascular tone in the very early stages of plaque evolution, when a plaque is clinically still imperceptible.<sup>29</sup> All these data support the hypothesis that elevated ET levels may have pathophysiologic significance in angiographically normal coronary arteries. Considering the autonomic regulation of coronary flow, a report using positron emission tomography demonstrated a correlation between time domain HRV and myocardial perfusion.<sup>30</sup> These data suggest that a low HRV, indicative of deficient autonomic function, may be related to coronary endothelial dysfunction and/or



**Figure 1.** Correlation among HRV parameters and endothelin-1 (ET-1) in patients' coronary slow flow. (A) between SDNN and ET-1, (B) between SDANN and ET-1, (C) between SDNN index and ET-1 (D) between RMSSD and ET-1, (E) between pNN50 and ET-1, (F) between triangular index and ET-1.



**Figure 2.** Correlation among HRV parameters and TIMI frame count in patients with coronary slow flow. (A) between SDNN and TIMI frame count, (B) between SDANN and TIMI frame count, (C) between SDNN index and TIMI frame count (D) between RMSSD and TIMI frame count, (E) between pNN50 and TIMI frame count, (F) between triangular index and TIMI frame count.



**Figure 3.** Intravascular ultrasound image in a patient with coronary slow flow showing longitudinally extended diffuse calcification throughout the epicardial artery and increased intimal thickness.

vasomotor disorders. Thus, impaired HRV levels could be the result of a deficient coronary perfusion. The results of this study show that baseline ET-1 plasma levels were higher in patients with CSF than in control subjects. Additionally, we found that the time domain HRV parameters reduction is correlated to the increase in plasma ET-1 levels. Thus, the autonomic impairment was significantly correlated to the degree of endothelial dysfunction and diffuse atherosclerosis in our study.

Angiographic evaluation of CSF was made visually since first defined by Temb et al.<sup>1</sup> Gibson et al.<sup>14</sup> found TIMI frame count system and especially used it to evaluate coronary artery patency and flow velocity after thrombolytic treatment in patients with acute myocardial infarction. Later, this system was used to evaluate flow velocity quantitatively in patients with CSF.<sup>4,31</sup> TIMI frame count system is an important method to detect a numeric value of anterograde blood flow objectively in patients with SCF.

In this study, HRV parameters were negatively correlated with ET-1 and TIMI frame counts. While a positive correlation was observed between TIMI frame count and plasma ET-1 levels, correlation between TIMI frame count and NO<sub>x</sub> was negative. This finding could indicate that TIMI frame count system is a valuable parameter showing correlation between increase in diffuse coronary arterial resistance and anterograde blood flow.

There is a dynamic interaction between sympathetic and parasympathetic effects on heart rate

regulation.<sup>32</sup> However, time domain HRV parameters RMSSD and pNN50 primarily reflect vagal modulation.<sup>16</sup> In our study, RMSSD levels were lower in group A compared to control group. Also pNN50 levels were lower in both group A and group B compared to the control group. These findings may reflect that autonomic control of the cardiovascular system in patients with CSF is shifted toward a sympathetic predominance. Several previous studies reported indirect evidence of an increased adrenergic activity in patients with syndrome X,<sup>13,30,33,34</sup> abnormalities in HRV and baroreflex sensitivity<sup>13,30,34</sup>, and prolonged QT and QTc interval.<sup>33,35</sup>

The effects of adrenergic stimulation on coronary microvascular tone complex are controversial. Sympathetic activation increases coronary flow indirectly through metabolic vasodilation secondary to an increase in heart rate and myocardial contractility<sup>36</sup> and, in part, to endothelium-mediated vasodilation.<sup>37</sup> On the other hand, it may have both direct vasodilator and vasoconstrictor effects through alpha-receptor and beta-receptor stimulation, respectively,<sup>36</sup> the net effect likely depending on the pathophysiologic state of small coronary arteries. Indeed, an increased sympathetic stimulation may cause of abnormal microvascular constriction in endothelial dysfunction.<sup>38</sup> Additionally, ET-1 can modulate central and peripheral sympathetic outflow.<sup>39</sup> Aronson et al. have observed ET-1 may play an important role in the autonomic dysfunction characteristic of congestive heart failure.<sup>39</sup> In the present study, we found the correlation between ET-1 levels and time domain HRV parameters. These HRV parameters may show markers of neurohormonal activation in CSF. Autonomic imbalance may influence vasomotor control of the coronary circulation. This, in turn, may cause transient reductions in regional myocardial perfusion responsible for ischemia at rest but also may reduce coronary flow reserve and cause angina during effort<sup>40</sup>. Gould et al.<sup>41</sup> have observed a graded, longitudinal, base-to-apex myocardial perfusion gradient, indicating diffuse coronary arterial narrowing by noninvasive positron emission tomography in patients with diffuse atherosclerosis without dipyridamole-induced segmental myocardial perfusion defects caused by flow-limiting stenoses.

In conclusion, the present study demonstrated that increased plasma ET-1 levels, decreased



plasma NO<sub>x</sub> levels and diffuse atherosclerosis may decrease HRV parameters by decreasing myocardial blood flow in patients with CSF.

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