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The association of ventricular tachycardia and endothelial dysfunction in the setting of acute myocardial infarction with ST elevation

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Background: Ventricular tachycardia (VT) is frequently seen in ischemic settings like acute myocardial infarction with ST segment elevation (STEMI). Endothelial dysfunction (ED) represents inflammation and the loss of all protective features of the endothelium. We aimed to examine the association between VT and ED in patients with STEMI.

Material/Methods: The study included 90 subjects (30 with VT and acute STEMI, 30 with STEMI without VT, and 30 controls). Sera of all subjects were tested on ED markers by enzyme immunoassay: sICAM-1 (intracellular adhesive molecule-1), sVCAM-1 (vascular adhesive molecule-1), P- and E-selectins, and VEGF (vascular endothelial growth factor). In addition, CRP (C-reactive protein) was detected.

Results: Significantly increased values of low-density lipoprotein, triglycerides, leukocytes, creatinine, and the number of cigarettes smoked were observed among patients with VT+STEMI in comparison to controls. The levels of E-selectin were significantly lower in the VT+STEMI group than in the other groups, while the levels of VCAM-1 were significantly higher in the groups with STEMI and VT+STEMI compared to the controls. Lower levels of VEGF were recorded in STEMI and VT+STEMI groups compared to the control group. A significant correlation between CRP and VCAM-1 in patients with VT +STEMI was demonstrated.

Conclusions: We showed that ED may have a role in the immunopathogenesis of VT in patients with STEMI. The role of sE-selectin and correlation of sVCAM-1 with CRP as possible ED predictive markers in patients with VT+STEMI should be further investigated in a large cohort of patients.

Key words: ventricular tachycardia • acute myocardial infarction with ST segment elevation • endothelial dysfunction • adhesion molecules

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Background

Ventricular tachycardia (VT) is characterized by wide QRS complexes of at least 3 consecutive ventricular beats and frequencies faster than or equal to 100 beats per minute. It is most common in men of middle age, and it is commonly caused by ischemic heart disease. Other causes include: other structural cardiac defects, medications, metabolic imbalance, inflammation (infectious/noninfectious), and genotype, but in about 10% of patients it is idiopathic. Pathophysiology and etiology of VT are not unique. The most common mechanism is the so-called reentry mechanism, in which the scarred myocardium is an electrically insufficient locus and pro-arrhythmogenic seat [1–4].

Acute myocardial infarction with ST elevation (STEMI) is the most severe form of the 3 clinical entities in acute coronary syndrome group: STEMI, unstable angina (UA), and myocardial infarction without ST elevation (NSTEMI) [5–8]. It is widely believed that coronary heart disease begins due to atherosclerosis, and that atherosclerosis is basically inflammation. Atherosclerotic arteries, before the development of constriction, show reduced vasodilatation ability, which is mediated by endothelial dysfunction (ED). ED represents inflammation and the loss of all protective features of the endothelium, which may be particularly important in the pathogenesis of STEMI. Atherosclerotic plaque causes narrowing of coronary arteries, and the properties and features on this plaque play a role in clinical coronary disease. ED is in turn a factor that determines whether the plaque will be unstable. During acute coronary syndrome (ACS), especially STEMI, significantly increased flow of cytokines and mediators of ED is registered.

Endothelial dysfunction (ED) is, simply put, the loss of endothelial protective factors – antiplatelet, anti-aggregation, and anti-inflammatory – acting on the proliferation, migration, invasion, survival, and permeability of endothelial cells. ED is thus the common name for all those changes that cause damage to the wall of blood vessels. There is a very important role of ED at the microvascular level, in different organic systems in numerous acute infectious, but also noninfectious and chronic, diseases [9–18].

The objectives of our study were to investigate a possible association of individual markers of ED with VT that appeared as a result of STEMI, and to analyze possible differences in ED markers in patients with VT + STEMI in comparison to patients with STEMI only.

Material and Methods

The study was conducted from April 2010 to June 2011 at the Institute of Cardiovascular Diseases, Department of Internal Medicine, Clinical Hospital Center "Sisters of Charity" in Zagreb, and Department for Research at the Clinic for Infectious Diseases "Dr. Fran Mihaljević", Zagreb.

Subjects

The study included a total of 90 subjects who were divided into 3 groups: 1) 30 patients with documented VT as a result of proven STEMI (VT + STEMI); 2) 30 patients who have had a myocardial infarction with ST segment elevation and no documented VT (STEMI); 3) a control group of 30 patients who did not have acute myocardial infarction or VT, but were under medical control due to hypertension or nonspecific stenocardia, but with no STEMI or STEMI+VT.

In this study, the term STEMI refers to patients within the first 48 h after onset of ischemia. VT refers to periprocedural VT and VT that occurred 6 h after PCI until 48 h of the beginning of ischemia. VT here does not include the reperfusion arrhythmias.

The study was approved by the Hospital "Sisters of Mercy" Ethics Committee's and the Ethics Committee of the Medical Faculty in Zagreb. Croatian and international ethics norms were respected. By signing the informed consent, the subjects gave permission to perform all required tests, as well as the anonymous use of the results.

Assessment of study groups

Before the enrolment in the study, subjects had to meet a set of inclusion and exclusion criteria. Inclusion criteria were: 1) electrocardiographically (ECG) documented STEMI and VT in the first group of patients; 2) ECG-documented STEMI in patients in the second group; 3) urgent therapeutic percutaneous coronary intervention (PCI) and stent insertion into the coronary artery "culprit" lesion for the first 2 groups of patients; 4) negative results of treadmill testing among patients in the control group; 5) men and women below 76 years of age; 6) normal levels of serum potassium (K) and creatinine; 7) normal levels of magnesium (Mg) for the first group of patients; 8) metildigoxsin levels within therapeutic values for the patients of the first group, if the patient uses it; 9) fasting blood glucose levels 5.0–7.0 mmol/L (for the first 2 groups of patients, the first measured fasting plasma glucose in the Coronary Care Unit (CCU), and for patients in the control group it was a random fasting plasma glucose reading); 10) patients without or with well-controlled arterial hypertension (HA) in terms of measured values of pressure on both arms below or equal to 140/90 mmHg (for patients in the first 2 groups it was first measured blood pressure on arrival in the CCU, and for the control group of patients it was first measured blood pressure before the treadmill testing); 11) left ventricular ejection fraction (EFLV) ≥35% (in this study only due to ischemic or hypertensive cardiomyopathy); 12) for the first group of patients,

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they did not take treatment within 14 days before blood sampling or the appearance of VT, which has an adverse effect of QT interval prolongation (except for amiodarone, sotalol, and propafenone) and; 13) patients were included regardless of their smoking status. Exclusion criteria were: 1) diabetes; 2) congenital disorders such as arrhythmogenic right ventricular dysplasia, Brugada syndrome, long QT syndrome, or patients with idiopathic ventricular tachycardia or familial hypertrophic cardiomyopathy; 3) malignant and infectious diseases, as well as any other acute and/or chronic non-communicable diseases (e.g., renal insufficiency of any kind) other than atherosclerosis, hypertension, and hyperlipidemia.

Assessment of other risk factors

From all patients, medical history was taken and physical examination was done by trained medical staff. In addition, the collection of blood samples and the assessment of cigarette smoking, blood biochemistry, body mass index (BMI), and blood pressure (systolic and diastolic) were performed. Smoking status was presented in units of "pack per year" and the number of years of smoking at a given number of cigarettes consumed per day. Known treated or untreated hypertension and hyperlipidemia were recorded as well.

Laboratory tests

From all patients, 5 mL of venous blood was taken for laboratory tests, and blood was tested in the hematology and biochemistry laboratories of the University Hospital "Sisters of Charity", and ED markers were tested at the Department for Research, The University Hospital for Infectious Diseases "Dr. Fran Mihaljević".

For all subjects, several blood tests were performed: total number of leukocytes (L), C-reactive protein (CRP), creatinine, potassium, fasting plasma glucose, cholesterol, triglycerides, low-density lipoprotein (LDL), and high-density lipoprotein (HDL). In patients with VT + STEMI and STEMI only, a few additional blood tests were performed at admission: the first measured value of troponin T (cTnT) and the maximal value of creatinine phosphokinase (CPK). In patients with VT+STEMI, serum level of magnesium (Mg) was determined. None of the patients involved used derivatives of digoxin; therefor, digoxin serum levels were not determined. None of the included patients had been using other anti-arrhythmics, besides low doses of non-selective beta-blockers, which used by some of our patients for treatment of hypertension.

Sera samples of all patients were tested for the soluble markers of endothelial dysfunction: 1) adhesion molecules – intracellular adhesive molecule-1 (sICAM-1) and vascular adhesive molecule-1 (sVCAM-1); 2) selectins – sP-selectin and sE-selectin; and 3) vascular endothelial growth factor (VEGF). ELISA was performed according to the manufacturer's instructions (Quantikine TM, R & D Systems, Oxon, UK).

Forty-two serum samples from the first and second groups of patients were taken before primary PCI, or prior to the systemic and intracoronary application of heparin (which is proven to have a calming effect on ED markers). The remaining of 18 serum samples in this study were taken during the acute phase of STEMI, the first 24 h after performed PCI, and 6 h after coronary reperfusion.

Statistical analysis

Distributions of quantitative characteristics were tested for normality with the Kolmogorov-Smirnov test. To test the difference between the groups, nonparametric tests, Kruskal-Wallis, Mann-Whitney, and Fisher Exact tests were used. The possible correlation among tested variables was calculated by Spearman correlation coefficient.

Results

Age and sex characteristics

In total, this study included 77 (86%) males and 13 (14%) females. The same percentages of males (83%) and females (17%) were analyzed in the group of patients with STEMI and the control group. In the group of patients with STEMI+VT, the percentage of females was lower (10%), but the difference was not statistically significant (Fisher Exact test, χ^2=0.57, p=0.353) (Table 1). Age structure analysis showed that STEMI or STEMI+VT in men occurred at the age of about 60 years, while women with STEMI or STEMI+VT were 10 years older (in their 70s). By contrast, in the control group (in which patients had hypertension or nonspecific stenocardia, but without STEMI, or STEMI+VT), women were slightly younger than men (Table 1).

Risk factors

Analyzing multiple parameters that represent risk factors for developing cardiovascular disease, we found statistically significant differences between the study groups in levels of several possible indicators: the levels of LDL (p<0.001) and triglycerides (p<0.001) were significantly higher in patients with STEMI or STEMI+VT in comparison to the control group. It was also clearly demonstrated that patients with STEMI or STEMI+VT smoked twice as much as subjects in the control group (p<0.001) (Table 2).

CPK and troponin T levels

Table 3 shows the results of maximum CPK values and the value of cardiac troponin T in patients with STEMI and STEMI+VT.

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Table 1. Age and sex distribution of study groups.

Group	Sex	N	Average age	S.D.	Min.	Max.
Control	Males	25	57.92	7.094	43	70
	Females	5	49.20	11.345	38	62
	Total	30	56.47	8.386	38	70
STEMI	Males	25	61.16	10.566	39	76
	Females	5	70.60	7.829	59	77
	Total	30	62.73	10.661	39	77
STEMI+VT	Males	27	59.44	11.564	37	76
	Females	3	70.33	5.132	66	76
	Total	30	60.53	11.521	37	76
Total	Males	77	59.51	9.931	37	76
	Females	13	62.31	13.567	38	77
	Total	90	59.91	10.489	37	77

Table 2. Risk factors for cardiovascular disease were analyzed in patients with STEMI, STEMI +VT and control groups.

Risk factors		N	Median	Q1	Q2	Mini.	Max.	Kruskal-Wallis Test
HDL	Control	30	1.200	1.000	1.400	.600	2.000	χ^2=3.702 df=2 P=0.157
	STEMI	30	1.000	0.900	1.225	.900	1.600	
	VT+STEMI	30	1.100	0.900	1.300	.600	1.500	
LDL	Control	30	2.400	1.900	3.000	1.100	5.700	**χ^2=13.421 df=2 P<0.001**
	STEMI	30	3.500	2.450	4.350	1.600	7.200	
	VT+STEMI	30	3.650	2.700	4.800	1.800	5.700	
Smoking	Control	20	20.00	15.00	20.00	5.000	30.000	**χ^2=29.046 df=2 P<0.001**
	STEMI	13	40.00	30.00	49.00	20.000	63.000	
	VT+STEMI	16	40.00	30.00	43.75	15	70	
Cholesterole	Control	30	5.000	4.100	5.700	3.500	8.900	χ^2=2.952 df=2 P=0.229
	STEMI	30	5.250	4.175	6.450	3.000	9.200	
	VT+STEMI	30	5.400	4.800	6.875	2.800	19.100	
Trigiceride	Control	30	1.000	0.700	1.200	0.400	1.900	**χ^2=16.066 df=2 P<0.001**
	STEMI	30	1.500	1.100	2.550	0.600	6.000	
	VT+STEMI	30	1.450	0.875	2.700	0.500	17.600	

Table 3. The values of creatinine phosphokinase, and cardiac troponins in patients with STEMI and STEMI+VT.

		N	Median	Q1	Q3	Min.	Max.	Mann-Whitney Test
Max. CPK	STEMI	30	3143	1442	4450	307	7096	Z=0.510 P=0.612
	VT+STEMI	30	2642.5	1041	4586	114	9412	
cTnT	STEMI	30	0.077	0.032	1.686	0.007	8.100	Z=0.237 P=0.813
	VT+STEMI	30	0.074	0.028	1.313	0.007	8.100	

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Table 4. Clinical and laboratory parameters in patients with STEMI or STEMI+VT compared to the control group.

Parameter	Group	N	Median	Q1	Q3	Min.	Max.	Kruskal-Wallis Test
BMI (kg/m^2)	Control	30	30.2	27.9	32.2	21.3	37.1	**χ^2=19.259 df=2 P<0.001**
	STEMI	30	26.0	24.5	28.4	19.1	33.9	
	VT+STEMI	30	26.9	25.0	28.5	23.1	35.3	
RR sistolic	Control	30	130.0	120.0	135.0	100	140	**χ^2=9.591 df=2 P=0.008**
	STEMI	30	120.0	110.0	140.0	80	170	
	VT+STEMI	30	107.5	80.0	128.8	70	180	
RR diastolic	Control	30	80.0	75.0	90.0	60	90	**χ^2=6.123 df=2 P=0.047**
	STEMI	30	80.0	60.0	80.0	50	100	
	VT+STEMI	30	75.0	60.0	80.0	40	100	
Potassium (mmol/L)	Control	30	3.9	3.6	4.1	3.1	4.7	χ^2=1.003 df=2 P=0.606
	STEMI	30	3.8	3.6	4.2	3.2	4.9	
	VT+STEMI	30	3.8	3.6	4.0	2.9	4.7	
Creatinine (µmol/L)	Control	30	90.0	84.0	97.0	66	105	**χ^2=8.192 df=2 P=0.017**
	STEMI	30	93.5	80.8	102.0	72	120	
	VT+STEMI	30	101.5	86.8	108.3	71	120	
Glucose (mmol/L)	Control	30	6.0	5.2	6.4	4.6	7.1	χ^2=5.677 df=2 P=0.058
	STEMI	30	6.3	5.7	6.9	4.2	8.0	
	VT+STEMI	30	6.7	5.8	7.0	1.2	7.0	
Leukocytes ($10^9/L$)	Control	30	6.0	5.4	7.1	4	10	**χ^2=42.308 df=2 P<0.001**
	STEMI	30	9.5	8.0	13.0	6	15	
	VT+STEMI	30	10.0	9.0	13.3	6	20	
Years	Control	30	58.0	51.0	63.0	38	70	χ^2=5.769 df=2 P=0.056
	STEMI	30	64.0	57.5	73.0	39	77	
	VT+STEMI	30	58.5	53.8	70.0	37	76	
Mg (mmol/L)	Control	0				.	.	n.t.
	STEMI	30	0.86	0.81	0.95	.80	.97	
	VT+STEMI	30	0.83	0.79	0.89	.67	.97	
cQT	Control	0				.	.	n.t.
	STEMI	30	0.319	0.266	0.352	.251	.360	
	VT+STEMI	30	0.312	0.278	0.341	.251	.367	
ECHO (EFLV)	Control	0				.	.	n.t.
	STEMI	30	50.00%	45.00%	55.00%	35.00%	65.00%	
	VT+STEMI	30	50.00%	41.50%	55.00%	35.00%	65.00%	

n.t. – not tested.

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No significant differences in these parameters were found between the 2 analyzed groups, although patients with STEMI had slightly higher levels of CPK. However, the maximum CPK value was in the VT+STEMI group.

Clinical and other laboratory parameters

Table 4 shows differences between the groups in several clinical and laboratory parameters. There are significant differences in BMI between the control group and the STEMI group (Mann-Whitney test, p<0.001), as well as compared to STEMI+VT (Mann-Whitney test, p<0.001). Systolic blood pressure was significantly lower in patients with STEMI+VT compared to the control group (Mann-Whitney test, p=0.003), as well as in patients with STEMI only (Mann-Whitney test, p=0.040). Significantly lower diastolic blood pressure was observed in patients with STEMI+VT compared to the control group (Mann-Whitney test, p=0.038) and patients with STEMI only (Mann-Whitney test, p=0.037). Creatinine values were significantly higher in patients with STEMI+VT compared to the control group (Mann-Whitney test, p=0.004), while the number of leukocytes was significantly higher in the STEMI group (Mann-Whitney test, p<0.001), as well as in the group with STEMI+ VT (Mann-Whitney test, p <0.001), compared to the control group.

Echocardiography

One of the inclusion criteria was left ventricular ejection fraction (EFLV) ≥35% (in this study, only due to ischemic or hypertensive cardiomyopathy).

The lowest value of EFLV among the patients with STEMI+ peracute VT was 35%, and the median value was 42%.

The lowest value of EFLV among the patients with STEMI+ VT (non-peracute and non-reperfusion, starting from 6 hours post-PCI during the acute phase of STEMI) was 35%, and the median value was 53%.

The lowest value of EFLV among the patients with STEMI only was 45% and the median value was 50%.

Ventricular tachycardia

VT discussed here refers to periprocedural VT and VT that occurred 6 h after PCI until 48 h of the beginning of ischemia.

None of the patients used derivatives of digoxin; therefor, digoxin serum levels were not determined. None of the patients had previously used other anti-arrhythmics other than low-dose nonselective beta-blockers, which were used by some of our patients for treatment of hypertension.

There were 12 periprocedural VTs: 3 self-limited in a non-sustained form, 2 sustained that were then converted by amiodarone i.v., 1 hemodynamically unstable VT that was then converted by a direct current cardioversion during short-term general anesthesia, and 6 patients presented in cardiorespiratory arrest.

There were 18 postprocedural VTs: 10 in a self-limited non-sustained form and 8 in a sustained form (7 of those 8 were then treated with amiodarone, and 1 patient's sinus rythm was restored by direct current cardioversion during short-term general anesthesia).

Altogether, 5 VTs later became ventricular fibrillation. The culprit lesion was in 16 cases in the left anterior descending (LAD) artery and 2 were in the left „main" coronary artery.

Markers of endothelial dysfunction

Analyzing 6 markers of endothelial dysfunction, using the Kruskal-Wallis test, we found significant differences in the levels of 4 tested markers: sE-selectin (p=0.0107), sVCAM-1 (p=0.028), VEGF (p=0.099), and CRP (p=0.030) (Figure 1).

Looking at the selectins, we found that the serum levels of sE-selectin were significantly lower in patients with STEMI +VT than in the STEMI group (p=0.033) or the control group (p=0.005) (Figure 1A). The median levels of sP-selectin in the STEMI+VT group were also lower than in the other 2 groups, but without statistical significance (Figure 1B). Serum levels of sVCAM-1 were significantly higher in patients with STEMI compared to the control group (p=0.006), and some elevation was recorded in the STEMi+VT group (Figure 1C). However, there were no differences in the levels of sICAM-1 among all 3 groups (Figure 1D). A significant decrease of VEGF levels in sera of patients with STEMI only (p=0.025) were recorded in comparison to health controls (Figure 1E). The values of CRP (Figure 1F) were significantly higher in the control group (p=0.0297). Patients with VT were found to have higher CRP values than patients with STEMI, but no significant difference was observed.

Interestingly, a significant correlation (r=0.7046, p<0.001) between CRP and VCAM-1 in patients with STEMI+VT was found (data not shown).

Discussion

Our study was focused on endothelial dysfunction in 2 distinct cardiovascular disease (CVD) clinical entities and the possibility of translation and application of additional diagnostic/prognostic factors in clinical practice. The correlation between cardiovascular disease and mechanisms of endothelial dysfunction has been intensely explored in the past 20 years, but there are

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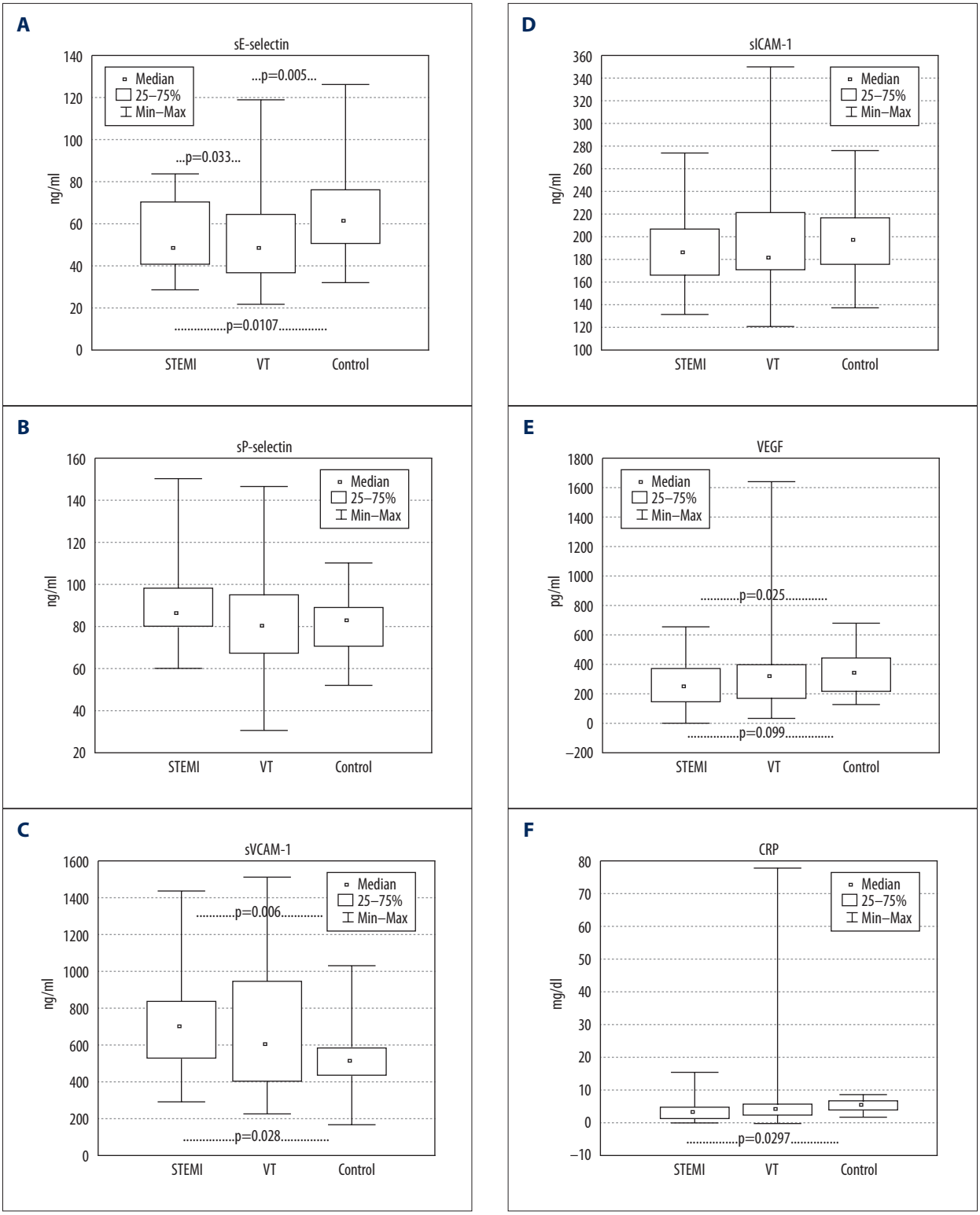

Figure 1. Endothelial dysfunction markers in patients with STEMI+VT, STEMI and control.

still few clinical studies with relevant data in this area. In this study, we investigated the link between ventricular tachycardia and endothelial dysfunction in patients with acute STEMI in comparison to patients with STEMI only or a control group of patients (hypertension and/or non-specific stenocardia). We reasoned that VT leads to disturbed blood flow, and associated

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reciprocating low shear stress generally upregulates the EC genes and proteins that promote atherogenesis [19].

We did not include patients with diabetes or very old patients, which are the only 2 clearly proven factors that encourage and reinforce ED. Cardiovascular patients included in this study, as we expected, had traditional risk factors for the development of cardiovascular disease: arterial hypertension, hyperlipidemia, and atherosclerosis [1]. We excluded patients with other chronic (e.g., chronic renal insufficiency or autoimmune diseases) or infectious diseases because these diseases may stimulate, prolong, and enhance endothelial dysfunction [7,11,18].

A large number of people in the general population have atherosclerosis, but ED is the type that seems to affect the existence of some of the atherosclerotic plaque, along with other factors leading to acute coronary syndrome. All previous studies on ED and STEMI have searched for predictors to enable professionals to detect life-threatening incidents earlier [16–18].

All parameters studied are proven mediators of ED; they are mutually intertwined and often act synergistically. Studies have shown that not all mediators of ED are constantly present in the sera or that the presences of certain ED factors necessarily induces CVD [13–20].

Elevated VCAM-1 is a proven predictor of future acute coronary syndrome in patients with stable coronary artery disease. Studies have demonstrated higher values of this marker in the ED in STEMI than in the other 2 forms of ACS. According to available data bases, there have been no studies on correlation of VCAM-1 with VT/VF [22–24]. The sex of patients may also have some influence on tested ED mediators. For example, the baseline value of P-selectin may be elevated in men, but no clinical predictive value for CVD has been found; whereas in women it is considered as a predictor of future cardiovascular events [27,28]. However, E-selectin is a marker of cigarette smoking and is also a serum marker of myocardial infarction in both sexes [27,28]. Of the tested ED markers, only ICAM-1 is a proven independent risk factor for CVD, which is apparently the best-studied mediator and marker of ED [29,30]. ICAM-1 is a marker of myocardial infarction, an indicator of smoldering ED [31], and a predictor of reperfusion arrhythmias [32]. Some authors consider CRP value higher than 3 mg/L as a relevant predictor of CV incidents only in combination with other elevated ED mediators [29,30]. On admission due to ACS, VCAM-1values higher than 780 ng/mL, in combination with CRP higher than 3 mg/L, are associated with risk of repeated ACS, either in terms of fatal or nonfatal MI or UA with a positive predictive value higher than 90% [33]. VCAM-1 is recognized as an independent predictor of future CV incidents in patients with a history of STEMI. Some researchers have demonstrated that lower values of VCAM-1, ICAM-1, and E-selectin, in relation to initial values, could be indicators of successful coronary reperfusion [34–37].

Previous publications on the connection between VT and acute coronary syndromes with ED have not separated hemodynamically unstable VT from VF [38–42]. Some authors have investigated the association of individual ED markers and intrahospital incidence of VT/VF after successful reperfusion due to STEMI. Others identified and recognized the value of CRP higher than or equal to 10 mg/L as an ED marker, on admission because of STEMI. They suggested this value as a predictor of hemodynamically deteriorating VT/VF during the first 48 h after onset of symptoms of coronary hypoperfusion [39].

The association of CRP, as an ED marker, and activation of internal cardioverter defibrillator (ICD), was also investigated. Certain studies have attempted to demonstrate a possible predictive role of CRP. Multivariate analysis revealed that prior infarction, absence of preinfarction angina, and peak CRP ≥10 mg/dL were independent determinants of VT/VF [39].

In our study, the statistical analysis of ED markers in patients with STEMI and STEMI +VT in comparison to the control group showed statistically significant differences in the level of 4 tested markers: sE-selectin, sVCAM-1, VEGF, and CRP. Surprisingly, CRP values were significantly higher in the control group compared to patients with STEMI and STEMI+VT. In the control group, patients had hyperlipidemia, although treated with statins, and treated hypertension in a larger proportion of patients than in the VT + STEMI and STEMI groups. However, this result is somewhat unexpected and we cannot fully explain it. It is in accordance with the opinion of some authors about the relative unreliability of CRP as an ED marker. In fact, in more recent publications, CRP is considered to be predictive for CVD in combination with other markers of ED [33,34,43], but there are publications that discuss the role of CRP as the only ED marker in CVD [27,44]. Thus, knowing that CRP is not highly selective and that is linked to smoking and atherosclerosis, not only of the coronary arteries, might partly help to explain the results. Also, CRP has been shown to be associated with CRP genetic variants and incident hypertension. In the study of Kong H et al. [45], the minor alleles of rs1130864 and rs3093059 were significantly associated with elevated CRP levels, and the minor alleles of rs1205, rs1800947, and rs2246469 were associated with decreased CRP levels. It was shown that plasma CRP levels were substantially associated with common genetic variants in the CRP gene and could predict the development of hypertension. Whether some genetic variants are responsible for higher CRP levels in our control group than in the STEMI or VT+STEMI groups remains to be answered in future studies.

The values of E-selectin were significantly lower in patients with STEMI+VT than in patients with STEMI only or in the control

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group. E-selectin is a marker of cigarette smoking [27], but it is also an indicator of successful reperfusion [28]. It is known from the literature that heparin lowers its serum values [35]. All sera from patients with STEMI only were taken before the systemic and intracoronary application of heparin, while 18 serum samples from STEMI +VT group were taken 6 h after reperfusion and systemic application of heparin, thus explaining the lower value of this selectin in our study.

In our study, sICAM-1 values were equal in all tested groups of patients. However, we found significantly higher values of sVCAM-1 in STEMI patients in comparison to the control group. VCAM-1 levels were elevated in patients with STEMI+VT as well, but with no significant difference compared to the control group. According to the available databases, there are no publications that have linked elevated levels of this mediator in patients with STEMI+VT. A significant correlation between CRP and VCAM-1 in patients with STEMI VT + was recorded in our study as well.

Patients with STEMI had in our study had significantly lower VEGF levels than in the control group. VEGF is a marker of hypoxic tissue revascularization, and is expected to show lower values in patients with STEMI and/or VT. VEGF is, however, an indicator of prothrombotic activity and size of thrombus in acute STEMI [34]. In patients with STEMI+VT, maximum CPK values were higher than in the STEMI group. Ischemia was stronger and greater IM scope was detected, which explains the difference, although it was statistically insignificant, between the value of VEGF in STEMI+VT and STEMI groups.

Results of this study do not provide strong evidence that changes in some ED markers during STEMI+VT are the results of VT. However, we presume that changes in blood flow during VT may induce some elements of ED that followed atherosclerosis development and further influence on VT deterioration leading to some kind of *circulus vitiosus*.

Limitations and strengths of the study

We showed here for the first time the possible involvement of several different ED markers in the pathogenesis of STEMI+VT in comparison to patients with STEMI only or individuals with some other CVD like hypertension or non-specific stenocardia. It is clear that certain differences among ED markers could be found in patients with VT in comparison to other CVD patients. Future studies with higher numbers of patients should be undertaken to identify possible specific ED markers as predictors for VT development. Such markers may also be useful in VT prevention.

This study has several limitations. The number of patients was quite low and it is hard to expect that differences between individual ED markers will be clearly visible between all 3 tested groups, although some significant differences are detected. We believe that future studies with more patients with VT will show more precise differences in ED markers. Also, if highly sensitive ELISA tests were used, some more differences would be expected.

Conclusions

We indirectly may consider from our results that ED may have a certain role in the immunopathogenesis of VT in patients with STEMI, although its role in immunopathogenesis was not directly proven here. The role of sE-selectin and correlation of sVCAM-1 with CRP as possible ED predictive markers in patients with VT+STEMI should be further investigated in a larger cohort of patients.

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