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

Full-text PDF: http://www.medscimonit.com/download/index/idArt/884026
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-arrhythmicogenic 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.
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 leucocytes (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 creatinase 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, χ²=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.
### 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   |

### 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          |    |        |     |     |       |      | χ²=3.702 df=2 P=0.157 |
| Control      | 30 | 1.200  | 1.000 | 1.400 | 9.500 | 2.000 |                      |
| STEMI        | 30 | 1.000  | 0.900 | 1.225 | 9.000 | 1.600 |                      |
| VT+STEMI     | 30 | 1.000  | 0.900 | 1.300 | 9.000 | 1.600 |                      |
| LDL          |    |        |     |     |       |      | χ²=13.421 df=2 P<0.001 |
| Control      | 30 | 2.400  | 1.900 | 3.000 | 1.100 | 5.700 |                      |
| 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      |    |        |     |     |       |      | χ²=29.046 df=2 P<0.001 |
| Control      | 20 | 20.00  | 15.00 | 20.00 | 5.000 | 30.000|                      |
| STEMI        | 20 | 40.00  | 30.00 | 49.00 | 20.000 | 63.000|                      |
| VT+STEMI     | 16 | 40.00  | 30.00 | 43.75 | 15    | 70   |                      |
| Cholesterol  |    |        |     |     |       |      | χ²=2.952 df=2 P=0.229 |
| Control      | 30 | 5.000  | 4.100 | 5.700 | 3.500 | 8.900 |                      |
| 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|                      |
| Triglyceride |    |        |     |     |       |      | χ²=16.066 df=2 P<0.001 |
| Control      | 30 | 1.000  | 0.700 | 1.200 | 0.400 | 1.900 |                      |
| 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.

| Risk factors | 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|                   |
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/m²)        | Control    | 30 | 30.2   | 27.9  | 32.2  | 21.3 | 37.1 | 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  | 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   | 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  | 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  | 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  | 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 (10⁹/L)| Control    | 30 | 6.0    | 5.4   | 7.1   | 4    | 10   | 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   | 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.   | n.t.  | n.t.  | n.t. | n.t. |                     |
|                    | STEMI      | 30 | 0.86   | 0.81  | 0.95  | 0.80 | 0.97 |                     |
|                    | VT+STEMI   | 30 | 0.83   | 0.79  | 0.89  | 0.67 | 0.97 |                     |
| cQT                | Control    | 0  | n.t.   | n.t.  | n.t.  | n.t. | n.t. |                     |
|                    | STEMI      | 30 | 0.319  | 0.266 | 0.352 | 0.251| 0.360|                     |
|                    | VT+STEMI   | 30 | 0.312  | 0.278 | 0.341 | 0.251| 0.367|                     |
| ECHO (EFLV)        | Control    | 0  | n.t.   | n.t.  | n.t.  | n.t. | 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.
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; therefore, 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 rhythm 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...
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
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 presence 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-1 values 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 hospital 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 it 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
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 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.

**References:**

1. Ellis K, Dressing T: Tachyarrhythmias. In: Griffin BP, Topol EJ (eds.). Manual of cardiovascular medicine. 2. izd. Lippincott, Williams & Wilkins, 2004; 283–314
2. Lerman BP: Ventricular arrhythmias. In: Goldman L, Ausiello D (eds.). Cecil medicine. 23. edit. Saunders Elsevier, 2008; 415–25
3. Olgin E, Zipes DP: Specific Arrhythmias: Diagnosis and Treatment. In: Libby P, Bonow RO, Mann DL et al, (eds.). Braunwald’s Heart Disease: A Textbook of Cardiovascular Medicine. 8. edit. Saunders Elsevier, 2007; 863–925
4. Ferencz M, Stix G, Kania M et al: Risk assessment of ventricular arrhythmia using new parameters based on high resolution body surface potential mapping. Med Sci Monit, 2011; 17(3): MT26–33
5. Killip T, Kimball JT: Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients. Am J Cardiol, 1967; 20: 457–64
6. Díez JL, Hernandez A, Cosín-Aguilar J, Aguilar A, Portolés M: Sum of effects of myocardial ischemia followed by electrically induced tachycardia on myocardial function. Med Sci Monit Basic Res, 2011; 19: 153–62
7. Škerk V, Markotić A, Pulinj I et al: Electrocardiographic changes in hospitalized patients with leptospirosis over a 10-year period. Med Sci Monit, 2011; 17(7): CR369–75
8. Lindahl B, Toss H, Siegbahn A et al: Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. FRISC Study Group. Fragmin during Instability in Coronary Artery Disease. N Engl J Med, 2000; 343: 1139–47
9. Kirma C, Akcakoyun M, Esen AM et al: Relationship between endothelial function and coronary risk factors in patients with stable coronary artery disease. Circ J, 2007; 71: 698–702
10. Holvoet P, Collen D: Thrombosis and atherosclerosis. Curr Opin Lipidol, 1997; 8: 320–28
11. Nieminen MS, Mattila K, Valtonen V: Infection and inflammation as risk factors for myocardial infarction. Eur Heart J, 1993; 4(Suppl.K): 12–16
12. Mizia-Steck K: Cytokines and adhesive molecules in detection of endothelial dysfunction. Pharmacol Rep, 2006; 58: 21–32
13. Bhagat K, Vallance P: Inflammatory cytokines impair endothelium-dependent dilatation in human veins in vivo. Circulation, 1997; 96: 3042–47
14. Martin J, Collot-Teixeira S, McGregor JL: The dialogue between endothelial cells and monocytes/macrophages in vascular syndromes. Curr Pharm Des, 2007; 13: 1751–59
15. Rupprecht Hl, Blankenberg S, Bickel C et al: Impact of viral and bacterial infectious burden on long-term prognosis in patients with coronary artery disease. Circulation, 2001; 104: 25–31

16. Sukhiya R, Fahdi I, Garza L et al: Inflammatory markers, angiographic severity of coronary artery disease, and patient outcome. Am J Cardiol, 2007; 99: 879–84

17. Ballantyne CM, Entman ML: Soluble adhesion molecules and the search for biomarkers for atherosclerosis. Circulation, 2002; 106: 766–67

18. Best PJ, Gersh BJ: Cell adhesion molecules and inflammation in acute coronary syndromes: markers and emerging risk factors. Eur Heart J, 2001; 22: 1155–59

19. Chiu J-J, Chien S: Effects of Disturbed Flow on Vascular Endothelium: Pathophysiological Basis and Clinical Perspectives. Physiol Rev, 2011; 91: 327–87

20. Efimov A, Sokolova L, Sokolov M: Diabetes mellitus and coronary heart disease. Diabetol Croat, 2001; 30–4: 115–20

21. Libby P, Geng Yi, Sukhova GK et al: Molecular determinants of atherosclerotic plaque vulnerability. Ann NY Acad Sci, 1997; 811: 134–42

22. Postadzhiyan AS, Tzontcheva AV, Kehayov I, Finkov B: Circulating soluble adhesion molecules ICAM-1 and VCAM-1 and their association with clinical outcome, troponin T and C-reactive protein in patients with acute coronary syndromes. Clin Biochem, 2008; 41: 126–33

23. Rallidis LS, Gika HI, Zolindaki MG et al: Usefulness of elevated levels of soluble vascular cell adhesion molecule-1 in predicting in-hospital prognosis in patients with unstable angina pectoris. Am J Cardiol, 2003; 92: 1195–97

24. Wallén NH, Held C, Rehnqvist N, Hjemdahl P: Elevated serum intercellular adhesion molecule-1 related to cardiovascular mortality? Eur J Clin Invest, 2002; 32: 1–8

25. Malik I, Danesh J, Whincup P et al: Soluble adhesion molecules and prediction of coronary heart disease: a prospective study and meta-analysis. Lancet, 2001; 358: 971–76

31. Siminiak T, Dye JF, Egdell RM et al: The release of soluble adhesion molecules ICAM-1 and E-selectin after acute myocardial infarction and following coronary angioplasty. Int J Cardiol, 1997; 61: 113–18

32. Murohara T, Kamijikkoku S, Honda T: Increased circulating soluble intercellular adhesion molecule-1 in acute myocardial infarction: a possible predictor of reperfusion ventricular arrhythmias. Crit Care Med, 2000; 28: 1861–64

33. Mulvihill NT, Foley JB, Murphy RT et al: Risk stratification in unstable angina and non-Q wave myocardial infarction using soluble cell adhesion molecules. Heart, 2001; 85: 623–27

34. Morrow DA, Rifai N, Antman EM et al: C-reactive protein is a potent predictor of mortality independently of and in combination with troponin T in acute coronary syndromes: a TIMI 11A substudy. Thrombosis in Myocardial Infarction. J Am Coll Cardiol, 1998; 31: 1460–65

35. Mulvihill NT, Foley JB, Murphy R et al: Evidence of prolonged inflammation in unstable angina and non-Q wave myocardial infarction. J Am Coll Cardiol, 2000; 36: 1210–16

36. Smith-Norowitz TA, Shani J, Weiser W et al: Lymphocyte activation in angiina pectoris. Clin Immunol, 1999; 93: 168–75

37. Mizia-Stec K, Zahorska-Markiewicz B, Mandecki T et al: Serum levels of selected adhesion molecules in patients with coronary artery disease. Int J Cardiol, 2002; 83: 143–50

38. Bellocci F, Biasucci LM, Gensini GF et al: Prognostic role of post-infarction C-reactive protein in patients undergoing implantation of cardioverter-defibrillators: design of the C-reactive protein Assessment after Myocardial Infarction to Guide Implantation of DEfibrillator (CAMI GUIDE) study. J Cardiovasc Med (Hagerstown), 2007; 8: 293–99

39. Kaneko H, Anzai T, Naito K et al: Role of ischemic preconditioning and inflammatory response in the development of malignant ventricular arrhythmias after reperfused ST-elevation myocardial infarction. J Card Fail, 2009; 15: 775–81

40. Piccini JP, Berger JS, Brown DL: Early sustained ventricular arrhythmias complicating acute myocardial infarction. Am J Med, 2008; 121: 797–804

41. Mehta RH, Starr AZ, Lopes RD et al: APEX AMI Investigators. Incidence of and outcomes associated with ventricular tachycardia or fibrillation in patients undergoing primary percutaneous coronary intervention. JAMA, 2009; 301: 1779–89

42. Mehta RH, Harjai KJ, Grines L et al: Primary Angioplasty in Myocardial Infarction (PAMI) Investigators. Sustained ventricular tachycardia or fibrillation in the cardiac catheterization laboratory among patients receiving primary percutaneous coronary intervention: incidence, predictors, and outcomes. J Am Coll Cardiol, 2004; 43: 1765–72

43. RebuZZi AG, Quaranta G, Liuzzo G et al: C-reactive protein in patients undergoing implantation of cardioverter-deßibrillators: design of the C-reactive protein Assessment after Myocardial Infarction to Guide Implantation of DEfibrillator (CAMI GUIDE) study. J Cardiovasc Med (Hagerstown), 2007; 8: 293–99

44. Berk BC, Weintraub WS, Alexander RW: Elevation of C-reactive protein in “active” coronary artery disease. Am J Cardiol, 1990; 65: 168–72

45. Kong H, Qian YS, Tang XF et al: C-reactive protein (CRP) gene polymorphisms, CRP levels and risk of incident essential hypertension: findings from an observational cohort of Han Chinese: Hypertens Res, 2012; 35: 1019–23