Thrombin activatable fibrinolysis inhibitor (TAFI) in stable angina pectoris patients undergoing coronary artery bypass grafting (CABG)

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Abstract

Purpose: Thrombin activatable fibrinolysis inhibitor (TAFI) seems to be a potential haemostatic risk factor of coronary artery disease (CAD). Taking into account interactions between TAFI and haemostasis, especially during cardiopulmonary bypass, we decided to determine concentration of TAFI and activated TAFI (TAFIa) and other haemostasis markers in CABG patients.

Material and methods: 45 CAD patients (11 women, 34 men) undergoing elective CABG were included in the study. Blood samples were taken before the operation, on the 3rd, 7th day and 3 months after CABG. A value of $p<0.05$ was considered statistically significant.

Results: We found a significant decrease in TAFIa concentration on 3rd postoperative day: 6 μg/ml (0.3-43.2) vs 8.9 μg/ml (0.5-37) before CABG ($p<0.05$), a significant increase in TAFI concentration on the 7th postoperative day: 127.7%±36.8 vs 112.18%±30.34 of standard plasma concentration before CABG ($p<0.05$), significant increase in plasmin-antyplasmin (PAP) complexes concentration on 3rd and 7th day, respectively: 645 μg/l (323-1237) vs 406 μg/l (197-1840) before CABG ($p<0.001$); and 1030 μg/l (640-2149) vs 406 μg/l (197-1840) before CABG ($p<0.0001$). Before operation we found a significant negative correlation between PAP complexes concentration before CABG and EuroSCORE risk scale value ($p<0.01$).

Conclusions: In CABG patients, there is a significant increase in fibrinolytic activity due to decrease in TAFIa concentration, with simultaneous increase in PAP complexes. A significant negative correlation between PAP complexes concentration before CABG and EuroSCORE risk scale value stressed a potentially higher operation risk in patients with lower fibrinolytic activity.

Key words: thrombin activatable fibrinolysis inhibitor (TAFI), coronary artery bypass grafting (CABG), coronary artery disease (CAD), haemostasis.

Intoduction

Coronary artery disease (CAD) is a leading cause of mortality in well developed societies. This occurs in spite of growing knowledge of atherosclerosis pathogenesis. Atherosclerosis begins as a functional or/and structural changes in endothelium, which in turn causes its injury and impairs humoral and secreting function. Haemostasis plays an important role in the progression of atherosclerosis, development of cardiac complications (acute coronary syndromes) – especially after cardiac surgery with cardiopulmonary bypass. Increased risk of cardiovascular diseases is combined with high activity of coagulation system and lower activity of fibrinolytic system, enhanced platelets activation, and dysfunction of the endothelium. In spite of that, research still continues to determine the precise role of each of haemostatic factors in increased risk of coronary artery disease and its complications.

Decrease of fibrinolytic activity is considered to be a risk factor for arterial thrombosis. Thrombin activatable fibrinolysis inhibitor (TAFI), a glikoprotein identified by Bajzar [1] in 1995, seems to play special role as a potential risk factor of CAD. Mosnier et al. [2] proved that plasma TAFI concentration in normal individuals correlates with clot lysis time. Activated TAFI (TAFIa) inhibits the conversion of Glu-plasminogen to Lys-plasminogen [3]. Thrombin-thrombomodulin complex is a physiological activator not only for TAFI, but also for

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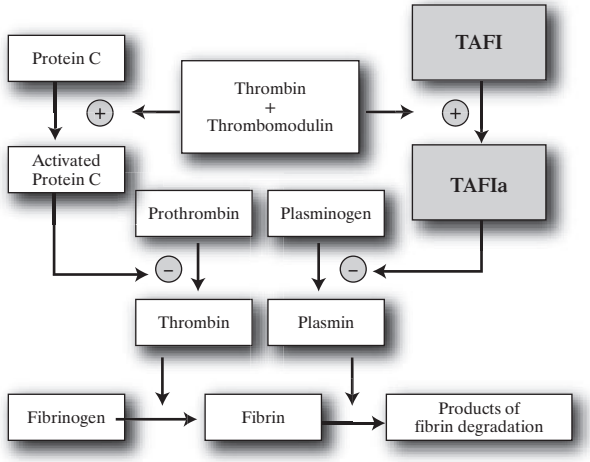
Figure 1. **Physiological role of TAFI in haemostasis**



TAFI – thrombin activatable fibrinolysis inhibitor
TAFIa – activated thrombin activatable fibrinolysis inhibitor

Table 1. **Clinical characteristics of the study group**

Number of patients (n)	45
Females	11
Males	34
CCS class (n)	
II	25
III	20
Age (years)	60.4±9.38 (35-75)
Body mass index (kg/m^2)	29±3.5
Ejection fraction of the left ventricle (%)	48.18±9.85
Ejection fraction between 50% and 30% (n)	13
Ejection fraction <30% (n)	3
EuroSCORE (points)	2.2±1.5
Aspirin withdraw before CABG (days)	12.24±7.81 (5-30); median – 9
MI (n)	
Q-wave	18
Non-Q	10
Segmental wall motion abnormalities of the left ventricle (n)	36
Previous coronary angioplasty (n)	4
Hypertension (n)	32
Cigarette smoking (n)	17
Obesity (n)	17
Peripheral atherosclerosis (n)	4
Obstructive lung disease (n)	1
Mild renal failure (n)	1

MI – myocardial infarction; EuroSCORE – cardiac surgery operative risk scale; CCS class – Canadian Cardiovascular Society Grading Scale for Angina Pectoris

protein C – that is why TAFI could be a kind of link between coagulation and fibrinolysis. Activation of TAFI is mediated by thrombin – generated by the coagulation cascade [4]. TAFIa is a substrate for transglutaminases – e.g. factor XIIIa builds TAFIa into fibrin net – it ensures localisation activity and may protect against its inhibitors [4]. The physiological role of TAFI in haemostasis is shown on *Fig. 1*.

In an animal arterial and vein thrombolysis models inhibition of TAFI by specific inhibitors enhanced tPA induced lysis of a thrombus [5]. Van Tilburg et al. [6] showed that TAFI plasma concentration above the 90th percentile of the controls increased the risk for thrombosis nearly 2-fold compared with TAFI plasma concentration below the 90th percentile. Schroeder et al. [7] revealed in intracoronary plasma samples of CAD patients a significant increase of TAFI concentration compared to the control group. They showed also a positive correlation between TAFI concentration and fibrinogen and total cholesterol concentration, but they showed no correlation neither between TAFI and others cardiovascular risk factors nor between TAFI and extent of coronary atherosclerosis. They suggested that TAFI might be a risk factor for development of CAD. Silveira et al. [8] found a significant increase in TAFI plasma concentration in pre-CABG patients with stable angina pectoris (110 men) compared to the control group. In a subset of 31 men, they observed a decrease in TAFI concentration on 3rd postoperative day and its increase on 6th postoperative day compared with preoperative concentration. Silveira et al. [9] suggested that increased TAFI concentration could enhance early occlusion of venous bypass grafts as well as acceleration of thrombosis in native atherosclerotic coronary arteries by fibrinolysis inhibition. Lau et al. [9] have proposed a novel potential predictor of angiographic coronary restenosis after percutaneous transluminal coronary angioplasty (PTCA) – increased concentration of TAFI together with decreased concentration of PAI-1.

However, the final role of plasma TAFI concentration in arterial thrombotic events is not clear yet. Brouwers et al. [10] investigated 209 unstable angina pectoris (UAP) patients of which 76 were refractory to medical treatment. Patients with more severe form of UAP had significantly lower plasma TAFI concentration. Moreover, Juhan-Vague et al. [11] observed that low plasma TAFI concentration was associated with significantly higher risk of myocardial infarction (MI).

Taking all these data into consideration, we designed a prospective study to determine the effects of CABG on TAFI concentration and activated TAFI (TAFIa) concentration, as well as on markers of coagulation: prothrombin fragments F 1+2, thrombin-antythrombin (TAT) complexes, fibrinolysis: plasmin-antyplasmin (PAP) complexes and endothelial dysfunction: von Willebrand factor (vWF), thrombomodulin (TM). We assessed also correlations between TAFI, other biochemical and perioperative parameters and clinical outcome of CABG patients.

Material and methods

Patients

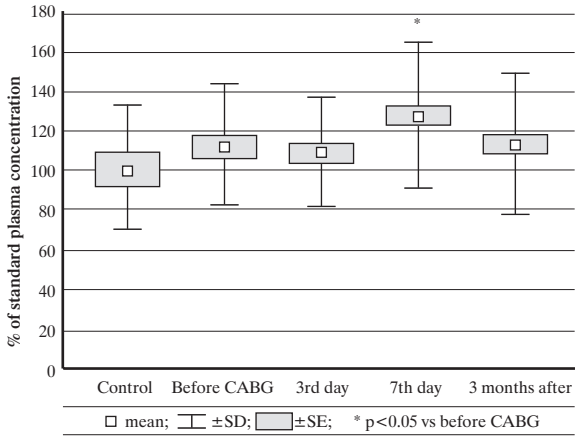
Forty-five stabile angina pectoris patients (11 women, 34 men) with CAD confirmed by angiography, udergoing elective CABG were included in the study. Patients were qualified for the operation according to ACC/AHA Guidelines for CABG – class I and IIa. *Tab. 1* shows characteristics of the study group. Exclusion criteria were: diabetes mellitus, liver dysfunction, treating with oral anticoagulants, unstable angina pectoris, and

Table 2. **Procedural data and clinical perioperative parameters**

Procedural data		
Duration of procedure (hours)	6.19±1.16	
Duration of cardiopulmonary bypass (min)		106.02±36
Cross-clamping time (min)		59.8±28.03
Number of grafts (n)		2.73±0.81
Postoperative course		
Myocardial ischaemia events (n)		12
Perioperative MI (n)	Non-Q	3
	Q-Wave	1
Intra-aortic balloon pump (n)		2
Blood transfusion (n)		34
Haemofiltration (n)		4

MI – myocardial infarction

Figure 2. **Plasma TAFI concentration**



absence of lipid disorders. Aspirin therapy was withdrawn to all the patients about two weeks before the operation (average 12 days, minimum 5 days) and restarted in the evening of the day of CABG. There were no significant differences in pharmacology treatment in the study after the surgery. That way its potential disturbing influence on investigated parameters was minimized. The Ethics Committee of the Medical University of Białystok approved the study protocol.

Methods

CABG was performed typically – via median sternotomy. Standard anesthetic and cardiopulmonary bypass (CPB) techniques with normotermia were used. *Tab. 2* shows procedural data and clinical perioperative parameters. Blood samples were taken the day before the operation, on the 3rd, 7th day and 3 months after CABG. The first post-CABG measurements were performed three days after the procedure to minimize the effects of surgical stress, blood transfusion or agents used perioperatively on the concentration of examined haemostatic parameters.

Blood samples were taken from antecubital vein without the stasis, in the morning and were collected on citrate (3,8% trisodium citrate – 1 ml of citrate, 9 ml of blood). Blood samples were centrifuged within one hour at 3000 rpm for 10 minutes. Half of the supernatant was taken from the middle layer of plasma. Plasma samples were stored at -70°C until assayed.

The control group consisted of 33 age- and sex-matched healthy volunteers to obtain the normal ranges of the haemostatic parameters studied.

TAFI antigen concentration (TAFI Ag) was determined by commercially available immunoassay (TAFI-EIA, Affinity Biologicals Inc, Canada). TAFI concentration was expressed as percentage of standard plasma concentration. TAFIa concentration was determined by commercial chromogenic assay (ACTICHROME® Plasma TAFI Activity Kit, American Diagnostica, USA). Other haemostatic markers were also determined by using commercial immunoassays: prothrombin fragments 1 +2 (F 1+2) – Enzygost® F 1+2 micro, Dade – Behring, Germany; thrombin-antythrombin (TAT) complexes – Enzygost® TAT micro, Dade – Behring, Germany; plasmin-antyplasmin (PAP) complexes – Enzygost® PAP micro Dade – Behring; Germany; thrombomodulin (TM) – IMUBIND® Thrombomodulin ELISA Kit, American Diagnostica, USA; von Willebrand factor (vWF) – IMUBIND® vWF ACTIVITY Elisa, American Diagnostica Stago USA. All assays were performed according to manufacturer's instructions by the same person.

Other coagulation and biochemical parameters were determined using standard laboratory methods: prothrombin time (PT), INR, activated partial thromboplastin time (APTT), fibrinogen, complete blood count, platelets, creatinine, urea, bilirubin, sodium, potassium, total protein, alanine aminotransferase (AlAT), aspartate aminotransferase (AspAT), creatinine kinase (CK) and its cardiac isoenzyme (CK-MB), glucose, total cholesterol and its fractions.

We estimated the operative risk for each patient from the study group, according to EuroSCORE (cardiac surgery operative risk scale). The higher EuroSCORE value indicated higher operative risk.

Statistical analysis

Statistical analyses were performed using Statistica 6.0 PL software for Windows (Tulsa, OK, USA). Shapiro-Wilk test was used to check the data distribution. Whenever possible in skewed distribution, logarithmic transformation was performed before the analysis. In normally distributed variables statistical analysis was performed using one way ANOVA test with following post hoc Tukey's test. In a case on non-normal distribution, Kruskall-Wallis analysis of variance with post hoc Mann-Whitney test was used. All the normally distributed parameters were presented as means ±SD. Others are given as medians and minimal-maximal values. A value of $p<0.05$ was considered statistically significant. Correlations between parameters were analyzed with Pearson's or Spearman's correlation coefficient, as appropriate.

Results

We found a significant increase in TAFI concentration on the 7th day after CABG: 127.7%±36.8 vs 112.18%±30.34 of standard plasma concentration before CABG, $p<0.05$ (*Fig. 2*).

Figure 3. **Plasma TAFIa concentration**

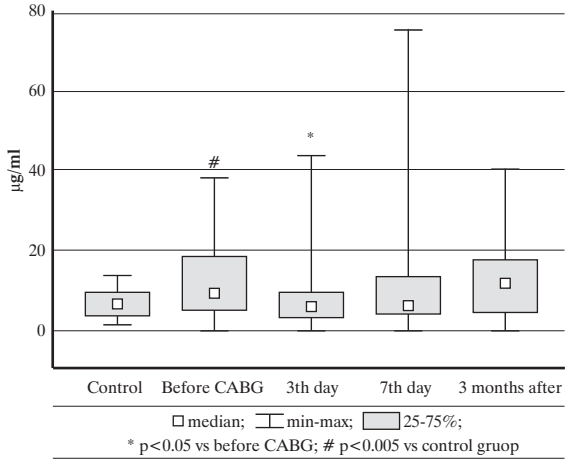


Figure 4. **Plasma plasmin-antiplasmin (PAP) complexes concentration**

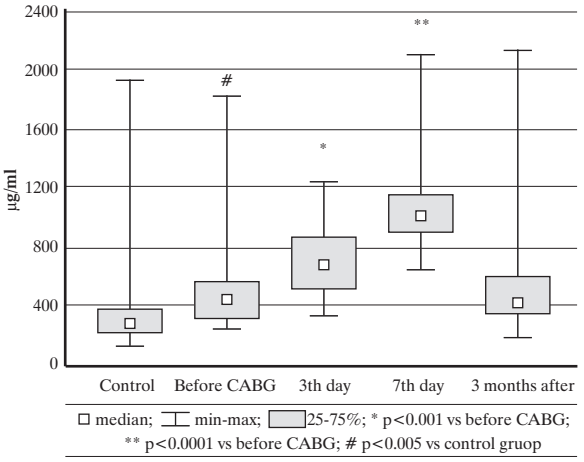


Figure 5. **Plasma von Willebrand factor (vWF) activity**

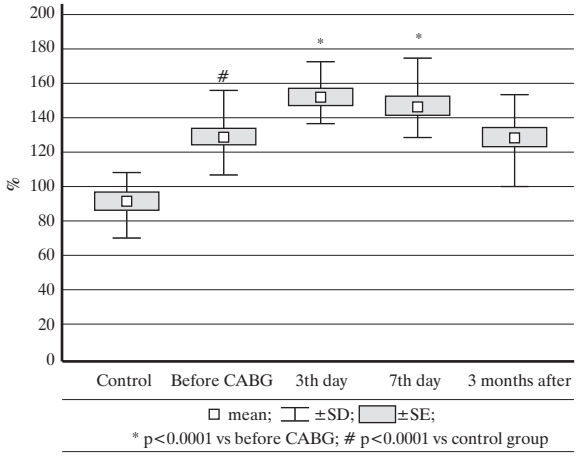
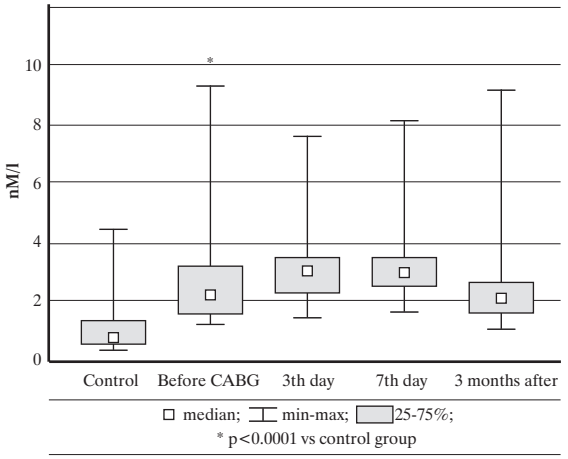


Figure 6. **Plasma prothrombin fragments 1+2 (F 1+2) concentration**



There was a significant decrease in TAFIa concentration on the 3rd postoperative day: 6 µg/ml (0.3-43.2) vs 8,9 µg/ml (0.5-37) before CABG, p<0.05 (*Fig.* 3).

Significant increase in PAP complexes on the 3rd and 7th day was found, respectively: 645 µg/l (323-1237) vs 406 µg/l (197-1840) before CABG, p<0.001; and 1030 µg/l (640--2149) vs 406 µg/l (197-1840) before CABG, p<0.0001 (*Fig. 4*). Significant increase in vWF activity on the 3rd and 7th day, respectively: 154.3%±17.8 vs 129.6%±24.4 before CABG, p<0.0001 and 150.95%±21.1 vs 129.6%±24.4 before CABG, p<0.0001 (*Fig. 5*). No significant F 1+2 fragments (*Fig. 6*) and TAT complexes (*Fig. 7*) concentration alteration, before vs after CABG were found. On the 3rd postoperative day a tendency to decrease in TAT complexes was observed when compared to the pretreatment values. However, it did not reach statistical significance (p=0.06) (*Fig. 7*). There was no significant TM concentration alteration, before vs after CABG. However on the 3rd postoperative day we found statistical margin increase in TM concentration compared to the values from before the procedure: 4 ng/ml (0.64-15,88) vs 2.52 ng/ml (0.12-25,8) before CABG, p=0.059) (*Fig. 8*).

TAFIa concentration, PAP complexes concentration, F 1+2 fragments concentration, TAT complexes concentration, vWF activity were significant higher in studied patients before an operation then in control group. There were respectively: TAFIa concentration 8.9 µg/ml (0.5-37) vs 4.4 µg/ml (1.1-10.6) p<0.005 (*Fig. 3*); PAP complexes 406 µg/l (197-1840) vs 285 µg/ml (126-1917) p<0.005 – *Fig. 4*; F 1+2 fragments 2.07 nM/l (1.11--9.28) vs 0.63 nM/l (0.26-4.52) p<0.0001 (*Fig. 6*); TAT complexes 7.95 µg/l (0.4-124.4) vs 1 µg/l (1-4) p<0.0001 (*Fig. 7*); vWF 129.6%±24.4 vs 88.2%±15.2 p<0.0001 (*Fig. 5*). TAFI (*Fig. 2*) and TM (*Fig. 8*) concentrations did not differ significantly between control group and patients before the CABG.

In the study group we also found significant decrease in total cholesterol, LDL-cholesterol and triglycerides concentrations 3 months after CABG compared to before an operation, respectively: 4.77 mmol/l±1.38 vs 5.71 mmol/l±1.11 p<0.05; 2.91 mmol/l±1.15 vs 3.59 mmol/l±1.14 p<0.05; 1.43 mmol/l±0.59 vs 1.9 mmol/l±0.79 p<0.05. A significant decrease in haemoglobin, erythrocytes concentrations and haematocrit value on 7-th postoperative day compared to before an operation was found, respectively: 7.01 mmol/l±1.09 vs 8.53 mmol/l±0.72

Figure 7. **Plasma thrombin-antithrombin (TAT) complexes concentration**

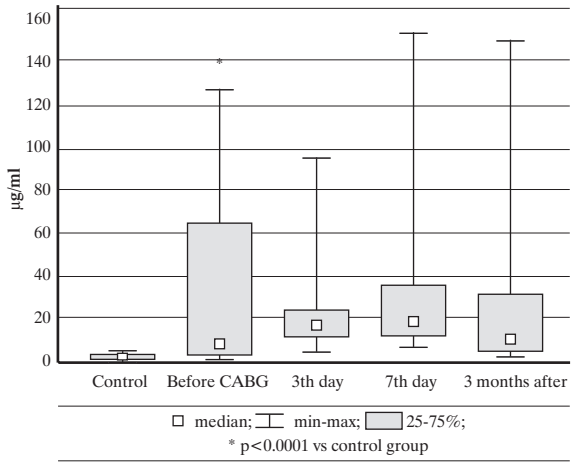
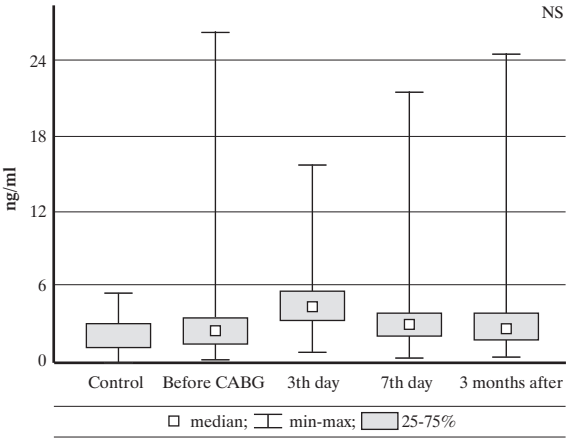


Figure 8. **Plasma thrombomodulin (TM) concentration**



p<0.05; 3.86 x10^9/mm^3±0.78 vs 4.52 x10^9/mm^3±0.34 p<0.05; 34.98%±6.03 vs 41.18%±3.42 p<0.05. On 7th postoperative day compared to before an operation a significant increase in platelets concentration was found: 331.33 x10^3/mm^3±108.32 vs 215.84 x10^3/mm^3±45.52.

Correlations

– significant positive correlation between TAFIa concentration before CABG and total cholesterol concentration (p<0.05; r=0.41);

– significant positive correlation between TAFIa concentration on the 3rd postoperative day and concentration of fibrinogen (p<0.05; r=0.49);

– significant negative correlation between PAP complexes concentration before CABG and EuroSCORE risk scale value (p<0.01; r=-0.44);

– significant positive correlation between F 1+2 fragments concentration on the 3rd postoperative and aorta clamping time (p<0.05; r=0.31);

– significant positive correlation between vWF activity on the 7th postoperative day and duration time of the procedure (p<0.05; r=0.33).

Discussion

Since TAFI has been identified and its role in haemostasis and thrombosis has been confirmed, a possibility of important role of TAFI in CAD, has been considering. There was few data on TAFI concentration, and/or TAFIa concentration and their correlations with independent risk factors for CAD and other haemostasis parameters in CAD patients [7,9-11].

In the studied group, there was significant increase of TAFI concentration on the 7th postoperative day compared to the values before the procedure. Taking into account simultaneous increase of the markers of plasmin formation (PAP-complexes), increase of TAFI concentration could be a response to increased fibrinolytic activity. That is even more prominent because increase of TAFI concentration took place despite hemodilution after CABG.

Silveira et al. [8] also revealed increase of TAFI concentration on the 6th day after CABG in CAD patients, compared to the values obtained before the procedure and to the control group. Simultaneously in a subset of 31 men, they observed decrease of TAFI concentration on the 3rd postoperative day and its increase on the 6th postoperative day compared with preoperative values [8]. In our study on the 3rd postoperative day we observed statistical decrease of TAFIa concentration, however we did not observe statistical decrease in TAFI concentration. In our study TAFIa concentration before CABG was higher than in healthy volunteers. So, decreased TAFIa concentration on the 3rd postoperative day could rather reflect an increased fibrinolytic activity in our studied group. Moreover, PAP complexes concentration statistically increased on the 3rd and 7th postoperative day when compared to the pretreatment values. Concentrations of thrombin generation markers – (F 1+2 fragments and TAT complexes) were no statistically different before and after CABG. These preliminary results on the effects of CABG on markers of ongoing coagulation and vWF were reported previously [12]. On the other hand, TAFIa concentration as well as F 1+2 and TAT complexes were significanlty higher in patients undergoing CABG when compared to the healthy volunteers. All haemostatic parameters studied returned to baseline values after 3 months following CABG. An observed decrease of TAFIa concentration after CABG could be a result of used CPB. There was a hypercoagulability state before the operation followed by hyperfibrinolysis in early postoperative period (3rd to 7th day). CPB could decrease TAFIa concentration by reduction of TAFI activator-thrombin concentration [13]. The significant negative correlation between TAFIa concentration on the 3rd postoperative day and cross clamping time of aorta during the operation may speak in favour that CPB could reduce TAFIa concentration.

Silveira et al. [8] reported also a significant decrease in PAI-1 concentration on the 3rd postoperative day and a little higher, but still lower than before the CABG on the 6th post-

operative day. It may suggest an increased plasma fibrinolytic activity. In our study we found an increase in PAP complexes on the 3rd and 7th day after CABG, which reflected an increased plasma fibrinolytic activity. We did not find an increase in TAFIa concentration on the 7th day after CABG, but a tendency to a decrease in TAFIa concentration. Silveira et al. [8] suggested that a mechanism of impaired fibrinolysis resulted in more stable fibrin deposits and increased the risk of precocious CAD as well as early occlusion of venous bypass grafts. They proposed that high plasma TAFI concentration might be a potential risk factor for CAD and for early vein graft occlusion [8].

In our study we found that TAFIa concentration was higher in stable CAD patients before CABG when compared to the healthy volunteers, therefore our data might support the results reported by Silveira et al. [8]. In fact, Juhan-Vague et al. [11] observed that TAFI concentration above the 90th percentile significantly correlated with lower risk of MI experienced between 3 to 6 months before the study. They even suggested that TAFI increase could protect against MI. It was a multicentre study, which comprised of patients both from the North and South Europe. However, non-prosepctive design and wide TAFI polymorphism are the main limitations of this study [11]. We should also stress that in Juhan-Vague et al. [11] study the healthy volunteers were on Mediterranean diet. Moreover, secondary prevention of CAD in post MI patients was different in countries studied. Brouwers et al. [10] investigated UAP patients with refractory and non-refractory form to medical treatment. Plasma TAFI concentration was significantly higher in non-refractory patients compared to refractory patients. They determined also the association between plasma TAFI concentration, TAFI gene polymorphism, other biochemical parameters and clinical outcome of UAP patients. Patients with more severe form of UAP had significantly lower plasma TAFI concentration [10]. But as showed in our study – increase of TAFI concentration might have been a consequence of the increase of fibrinolytic activity. However, the Brouwers et al. [10] did not study fibrinolytic activity or markers of ongoing fibrinolysis in their patients. On the other hand, according to Lau et al. [9] reported that patients with serious restenosis (>50%) after PTCA exhibited a significantly higher concentration of TAFI and lower concentration of PAI-1. Therefore, it seems that the role of TAFI in arterial thrombotic events remains unclear.

In the literature TAFI was also considered as an acute phase protein. In our study we found a positive correlation between TAFIa concentration and fibrinogen on the 3rd postoperative day. Similar data were reported previously [7,8], however, other did not agree with this suggestion [14]. In patients undergoing CABG, it is very difficult to assess whether TAFI is an acute phase protein, because CPB always caused huge general inflammatory response [15-17], and we did not observe a significant increase in TAFI concentration on the 3rd postoperative day. A negative correlation between TAFI concentration and fibrinogen after 3 months following CABG did not support this suggestion.

We observed a positive significant correlation between TAFIa concentration and total cholesterol concentration only on the 7th postoperative day. A significant positive correlation between TAFI concentration and total cholesterol, LDL-cholesterol and VLDL-cholesterol concentrations were observed by Silveira et al. [8] only in the study group, but not in the control group. Schroeder et al. [7] showed a similar correlation between TAFI concentration and total cholesterol concentration. However, Juhan-Vague et al. [11] did not observe such a correlation it in nearly 600 CAD patients after MI. These discrepances may be due to the fact that all patients studied were taking statins before and 3 months after CABG. Statins were withdrawn at least one week before the CABG because of temporary increase in aminotransferases activity caused by CPB. All the patients studied obligatory continued statin therapy since 7-14th postoperative day. Therefore, a significant decrease in total cholesterol, LDL-cholesterol and triglycerides, was found 3 months after CABG. According to accepted standards, all patients should receive statins after CABG, as a secondary prevention, unless contraindicated.

We found a significant negative correlation between PAP complexes concentration before CABG and EuroSCORE value. EuroSCORE is universally administered scale which estimates risk of cardiac surgery operation in European population [18]. Patients which have more points in EuroSCORE (have higher operative risk) had lower PAP complexes concentration. It means that they had lower plasma fibrinolytic activity. These patients could have higher risk of acute coronary syndrome occurrence during/after CABG, especially because they also revealed a hypercoagulable state [19] before the procedure.

In studied group, on the 3rd and 7th postoperative day there was significant increase of vWF activity (a marker of disturbed endothelium function), compared to the baseline values. After 3 months – vWF activity returned to the baseline values. Simultaneously vWF activity in studied group before CABG was significantly higher than in healthy volunteers as described by others [20,21]. A rise in vWF may suggest a further endothelium injury after operations with CPB. In our study we found a statistically positive correlation between vWF activity on the 7th postoperative day and duration time of the procedure.

We found a significant increase in platelet count occurring 7 days after CABG. Several morphotic blood elements, including platelets, undergo destruction during CPB [22]. An increase in the number of platelets 7 days after CABG may be a compensatory reaction to peri-operative injury. In studied group we also found a significant decrease in haematocrit value, erythrocyte count and haemoglobin concentration on 7th day after CABG. These findings may be due to haemodilution – a process caused by CPB, or due to both peri- and postoperative blood loss. All these parameters returned to the baseline values 3 months after CABG.

Due to the fact that haemostatic disturbances after CPB are still not fully understood, further studies are needed to recognize the pathogenetic mechanisms of haemostatic abnormalities in coronary heart diease and the effect of CABG, as well as the role of TAFI in these processes.

Conclusions

1. In patients with stable angina pectoris undergoing CABG, an increase in fibrinolytic activity may be due to the

fall in TAFIa concentration with simultaneous rise in PAP complexes.

2. Positive significant correlation between TAFIa concentration and total cholesterol concentration before CABG may suggest the role for TAFI as a potential risk factor for CAD.

3. Significantly negative correlation between PAP complexes and EuroSCORE value stressed a potentially higher operation risk in patients with lower fibrinolytic activity.

4. Positive significant correlation between F 1+2 fragments concentration on the 3rd postoperative day and aorta clamping time could prove that F 1+2 fragments may contribute to postoperative acute coronary syndromes.

5. Postoperative rise in vWF may suggest an endothelium injury after operations with CPB.

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