

Evaluation of thrombinogenesis *in vivo* in acute myocardial infarction in relation to concentrations of thrombin–antithrombin III complexes and antithrombin III activity

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Abstract

Background: *Thrombotic processes play an essential role in the progression of the atheromatosis and pathogenesis of acute coronary syndromes. The role of haemostatic factors in the development of circulatory system diseases, ischaemic heart disease in particular, has met with great research interest. The purpose of the present research is to define the role of haemostatic factors in the pathogenesis of atheromatosis and ischaemic heart disease and also to deal with their impact on diagnosis and prognosis. The aim of the present study was to evaluate thrombin generation in vivo and to define the role of the main inhibitor of coagulation in patients with acute myocardial infarction.*

Methods: *The study was performed using a group of 70 patients with acute myocardial infarction with ST segment elevation (STEMI). The control group comprised 25 healthy subjects matched for age and gender. Concentrations of thrombin-antithrombin III complexes (TAT complexes) and antithrombin III (AT III) activity were measured; the sample was taken before essential treatment was administered.*

Results: *In a group of patients with myocardial infarction, significantly higher average concentrations of TAT complexes ($p < 0.0001$) and AT III activity ($p < 0.001$) were found. An inverse correlation between AT III activity and kinase phosphocreatine concentration ($p < 0.02$) was shown as well as a positive correlation between AT III activity and the time elapsing from the onset of infarction symptoms to admission ($p < 0.05$). The increase in TAT complex concentration and AT III activity did not depend on sex, age and risk factors for ischaemic heart disease, nor did it predict late complications.*

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Conclusions: *The results provide evidence of an intensification of thrombinogenesis processes in patients with acute myocardial infarction. The increase of AT III activity may reflect a compensatory mechanism of the haemostatic system with regard to intensified thrombinogenesis.* (Folia Cardiol. 2006; 13: 465–472)

Key words: myocardial infarction, antithrombin III (AT III), thrombin–antithrombin III complexes (TAT complexes)

Introduction

The formation of a thrombus in coronary vessels is the most common cause of acute coronary syndromes. The role of the haemostatic system in the pathogenesis of ischaemic heart disease, acute coronary syndromes in particular, has been the focus of great research interest. In the diagnostics of intravascular activation of coagulation tests can be applied to monitor thrombus formation and its effects.

The strongest natural anticoagulant is antithrombin III (AT III), a single-chain glycoprotein consisting of 432 amino acids. This is produced in the liver, in the endothelial cells, and probably in the megacariocytes. In laboratory conditions it is possible to evaluate either AT III concentration or AT III activity, an evaluation that is much needed for clinical purposes. AT III inactivates thrombin, forming a stable and inactive thrombin-antithrombin (TAT) complex. The endogenous co-factor, which accelerates the reaction through a change in the spatial structure of AT III, is heparan sulphate.

TAT complexes are amongst the most sensitive and specific markers of thrombosis; an increase in their concentration reflects the intensity of thrombinogenesis *in vivo* [1–3]. Together with AT III, the haemostatic factors which are natural coagulants are less known with regard to their role in the development of diseases of the cardiovascular system. The relation between the risk and intensity of coronary disease symptoms and AT III activity has been shown in a small number of studies, but the results remain ambiguous. At first it was thought that only decreased values in the concentration or activity of AT III were of importance and predisposed to acute thrombotic events. However, subsequent reports showed the relationship between a rise in the activity of AT III and an increased risk of intravascular clotting, particularly when coexisting with hyperfibrinogenaemia or increased thromboplastic activity [4, 5].

The purpose of the study was to evaluate thrombinogenesis intensity *in vivo* by assessment of TAT complex concentration and to define the role

of the main coagulation inhibitor, AT III, in patients at an early stage of acute myocardial infarction before the administration of the relevant treatment which, it is assumed, modifies the haemostatic parameters.

Method

The study comprised 70 patients (54 men and 16 women with an average age of 54.1 ± 8.7 years) with acute myocardial infarction with ST segment elevation (STEMI). Myocardial infarction was diagnosed by anamnesis, ECG findings and laboratory results which confirmed necrosis of the myocardial cells: troponin I, kinase phosphocreatine (CPK) and its CK-MB fraction). In the group examined the mean time elapsing between the onset of chest pain and hospitalisation was 6 hours.

The exclusion criteria were as follows: age above 70, resuscitation on admission to hospital, cardiogenic shock at admission, pharmacologically treated hyperlipidaemia, diabetes, neoplastic disease, other chronic disease (renal or hepatic insufficiency) and oral anticoagulant therapy. The control group comprised 25 healthy subjects selected by age and sex.

TAT complex concentrations and AT III activity were measured in all the patients under examination and in the subjects of the control group. TAT complex concentrations were measured by means of a commercial ELISA method kit (an Enzygnost TAT kit by Behring-Marburg, standard: $1.0\text{--}4.1 \mu\text{g/L}$). The plasma activity of AT III was measured using chromogenic substrate and spectrophotometry (the Berichrom Antithrombin III test by Behringer Mannheim with a normal value range of 80–120%). Blood for the above-mentioned tests was taken, together with the blood sample for other routine diagnostic measurements, directly after admission to hospital, after the informed consent of the patients had been obtained and before administration of the relevant treatment.

All the results were analysed statistically. For various samples basic statistics were calculated

(mean value: x , standard deviation: SD). Additionally, in view of the clear asymmetry in some samples, the values of the median, lower and upper quartiles were calculated. The significance level was set at $p \leq 0.05$. Where all the values had a normal distribution, the standard Student's t -test was applied to compare the groups. However, when a given value was not derived from a population with normal distribution, the Mann-Whitney test (the rank sum test) was used to compare two samples. To investigate the relationships between individual features a correlation matrix was defined and the Pearson correlation coefficient calculated. In the case of a pair of non-parametric values, the Spearman rank correlation coefficient was computed. The results were worked out using Microsoft® Access 2.0 for Windows and StatSoft® Statistica 5.0 for Windows.

Informed consent was obtained from each patient. The protocol for the study was approved by the Local Ethics Committee.

Results

The results obtained in the group of patients with myocardial infarction ($n = 70$) were compared to the results for the healthy subjects who had formed a control group ($n = 25$). The groups did not differ statistically with respect to age, sex, weight and height (BMI) or other basic biochemical parameters (Table 1).

Significant discrepancies in additional tests resulted from the definition of the group investigated and concerned parameters directly linked to myocardial infarction (risk factors of myocardial ischaemia and biochemical markers of myocardial infarction).

In the group of patients studied with myocardial infarction the TAT complex concentration was increased in comparison with standard values and significantly higher than in the control group ($p < 0.0001$). The mean activity of AT III in the group of patients with myocardial infarction was significantly higher compared to the control group ($p < 0.002$) (Table 2).

Table 1. General characteristic and essential laboratory parameters in the group with myocardial infarction and the control group.

	Myocardial infarction	Control group	p
Age (years)	54.1 ± 7.7	50.8 ± 7.2	NS
Body mass index	26.7 ± 3.5	27.6 ± 4.3	NS
Hb [g/dl]	14.5 ± 1.1	15.0 ± 1.0	NS
Ht (%)	44 ± 3.8	44 ± 2.7	NS
Creatinine [mg/dl]	0.91 ± 0.19	0.89 ± 0.13	NS
BUN [mg/dl]	15.3 ± 4.7	14.6 ± 3.8	NS
SGPT [U/L]	35.5 ± 19.7	28.6 ± 17.5	NS
Glucose [mg/dl]	123 ± 32	105 ± 18	0.02
Total cholesterol [mg/dl]	238 ± 46	209 ± 43	0.01
LDL cholesterol [mg/dl]	159 ± 40	137 ± 36	0.05
HDL cholesterol [mg/dl]	49 ± 14	52 ± 11	NS
Triglycerides [mg/dl]	159 ± 105	107 ± 46	0.01
CPK [U/L]	1681 ± 1630	118 ± 47	0.0001
CK-MB [U/L]	212 ± 374	11 ± 5	0.0001

Table 2. The comparison between TAT complex concentration and AT III activity in patients with myocardial infarction and in the control group.

	Myocardial infarction				Control group				p
	X ± SD	Mediana	Lower quartile	Upper quartile	X ± SD	Mediana	Lower quartile	Upper quartile	
TAT [μ g/L]	26.3 ± 36.7	6.8	3.9	33.9	2.9 ± 1.2	2.9	1.9	3.7	0.0001
AT III (%)	115.5 ± 17.2	116.1	103.4	126.0	102.5 ± 13.7	100.1	95.3	110.2	0.001

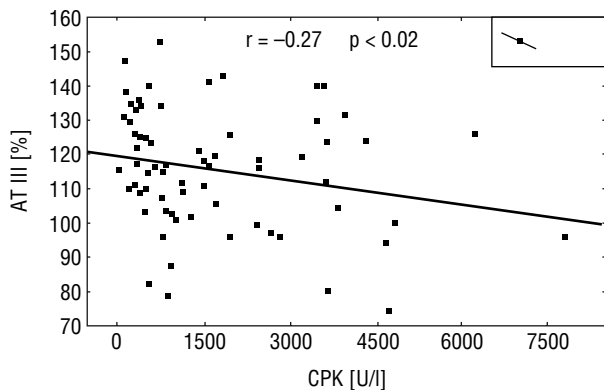


Figure 1. The correlation between AT III activity and maximum CPK levels in patients with myocardial infarction.

Additionally, an inverse correlation was shown between AT III activity and maximal CPK concentration in the patients studied (correlation coefficient $r = -0.27$ and level of relevance $p < 0.02$) (Fig. 1).

A positive correlation was found ($r = 0.24$, $p < 0.05$) between the activity of AT III and the time elapsing between the onset of infarction symptoms and hospital admission, the so called “pre-hospital period” (Fig. 2).

No significant differences between the sexes were found in TAT complex concentration and AT III activity.

Selected parameters of haemostasis were also compared between the age groups (≤ 55 years *vs.* > 55 years). In the subgroup of older patients the mean values of TAT complex concentration were higher albeit statistically insignificant. No substantial differences were found in TAT complex concentration and AT III activity in patients with early diagnosis of coronary disease or patients with

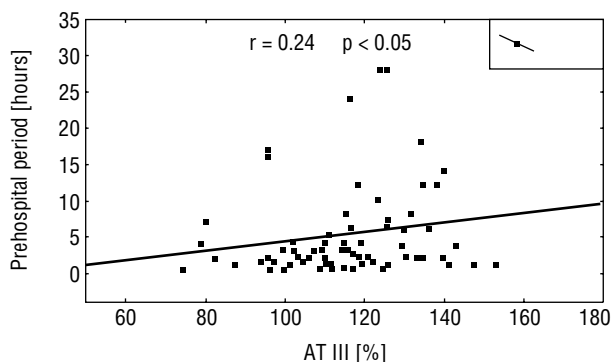


Figure 2. The correlation between AT III activity and the duration of the pre-hospital period in patients with myocardial infarction.

myocardial infarction as the first symptom of ischaemic heart disease.

To analyse the role of obesity with reference to the examined parameters of homeostasis, the group of patients with BMI above 30 was selected. No significant differences in TAT complex concentrations or AT III activity were found in these patients as compared to other patients ($BMI \leq 30$), although the mean concentration of TAT complexes was lower and AT III activity higher in the group with $BMI > 30$.

Concentrations of TAT complexes and AT III activity were evaluated in the group of patients with complications in the course of myocardial infarction (recurrent infarction during hospitalisation or death) and those without complications. No significant differences in the studied parameters were found in either group of patients. No relationship was demonstrated between TAT complex concentration and AT III activity and the values of total cholesterol, LDL-cholesterol, HDL-cholesterol or triglycerides. No substantial differences were found in TAT complex concentration and AT III activity in relation to previous smoking or a history of hypertension.

Discussion

The study evaluated selected parameters of coagulation in acute myocardial infarction determined as soon as possible after the onset of symptoms. The method applied allowed the impact of pharmacological treatment on the parameters of haemostasis in acute myocardial infarction to be excluded. Similarly, the material was selected so that all factors which could distort the results, other than myocardial infarction itself, were marginalised.

Thrombin-antithrombin complexes

A clear rise in TAT complexes within the first 24 hours of infarction appeared to be consistent with the results of several studies and reports and showed distinct activation of the coagulation system cascade during acute myocardial infarction [6–9].

In the TIMI-5 study (Thrombolysis in Myocardial Infarction) the baseline values of TAT complex concentration estimated before the onset of relevant therapy were higher alongside higher concentrations of fibrinogen A and prothrombin fragments F1+2 [10]. The results of Lopez et al. [11] showed a significant increase in TAT complex concentration in acute myocardial infarction as compared to the control group ($p < 0.0001$). Furthermore, a significant rise was found in prothrombin fragments F1+2, fibrinopeptide A, PAP complexes and D-dimers,

as well as positive correlations between: TAT complex concentration and D-dimers, TAT complexes and PAP, PAP complexes and D-dimers. This would appear to support both coagulation and fibrinolysis activation in the acute phase of the disease. Szczeklik et al. observed significantly higher values of TAT complexes in a group of 100 patients with acute myocardial infarction as compared to the control group ($35.7 \pm 4.7 \mu\text{g/L}$ vs. $2.1 \pm 0.8 \mu\text{g/L}$) [12].

An attempt was made by Italian investigators to define the time relations between ischaemic events and activation of the coagulation system in unstable angina pectoris [13]. The results demonstrated a higher production of thrombin in unstable angina pectoris; nevertheless, they also showed that such activation was not always related time-wise to the clinical manifestation of angina. No activation of the coagulation system was found in about 25% of ischaemic events, and more than half of all periods of intensified coagulation did not result in clinical symptoms of ischaemia. According to the authors [13], such results are not surprising and can be explained by the short half-life of the TAT complex in serum or by the role of vascular contraction in the pathogenesis of coronary events. The possible coexistence of an increased production of thrombin outside the coronary vessels may explain the false positive results. The results obtained demonstrate that coronary instability results from numerous processes. A certain "critical mass" of local thrombus may be necessary for increased TAT levels to be found in the peripheral circulation [14, 15].

In our research material a concentration of TAT complexes above the upper limit was found in 47 (71%) of cases. An analogous index given by Seitz et al. [14] accounted for 50% of cases, while in the group of patients with myocardial infarction reported by Szczeklik et al. [12] the percentage of "positive" results was highest and reached 90%.

We found no significant differences in TAT complex concentration between men and women. The comparison of age groups (those below and those above 55 years) showed higher mean values of the parameter in older patients ($6.2 \mu\text{g/L}$ vs. $7.7 \mu\text{g/L}$) but these differences were statistically insignificant.

The results are consistent with the Giansante report, which did not find any relation between TAT complex concentration and age, while the concentration in women was significantly higher ($p < 0.05$) compared to that in men in the groups studied [23]. In the material of Musiał et al. [16] mean concentrations of the TAT complexes in patients with coronary disease were higher in women than in men.

These authors also showed a positive correlation of TAT complexes in relation to age in women, while no such relationship was found in the male group. The absence of differences in concentration of TAT complexes between women and men in our research material could result from the relatively small number of women (16 patients or 23% of the group as a whole). The population of the study mentioned above comprised 417 patients, including 222 women (53%). Presumably sex-dependant differences found in a stable clinical phase may become blurred or may alter during intensified thrombinogenesis as a result of an individual rise in marker concentration.

No correlation was found in our material between the baseline concentration of TAT complexes and late complications of infarction during hospitalisation. The values for TAT complexes determined by Szczeklik before the start of a relevant treatment in patients did not enable infarction complications to be predicted, while the dynamics of the parameter showed a later distinct rise accompanying complications (heart failure, recurrent infarction, death) [12, 17]. In the TIMI-5 study increased mortality was associated with an increased concentration of TAT complexes determined one hour after admission [10].

To sum up, in patients with acute myocardial infarction a highly significant rise in TAT complexes was found, which was unrelated to any of the factors analysed and which is in congruence with reports by other authors. The rise in TAT complexes accompanying complications of infarction found in some reports and in our research material was observed at the moment of occurrence, while previous values were of no prognostic importance [12].

Antithrombin III

With regard to AT III, it is known that a deficiency of coagulation inhibitors, including AT III, increases the risk of venous thrombosis. However, the results of studies on the relationships between this protein and arterial thrombosis are ambiguous. The increased activity of AT III in acute myocardial infarction found in the group of patients studied is confirmed by reports by other authors. However, any attempt to interpret the results requires analysis of AT III values in healthy subjects and in various clinical phases of ischaemic heart disease.

The first significant study of the role of the coagulation system in ischaemic heart disease was a prospective Northwick Park Heart Study (NPHS), in which 1511 subjects without ischaemic heart

disease were enrolled [18]. Later the summary of baseline results of the NPHS study was extended by the observation of the group in question until the end of 1990 as performed by Meade et al. [19]. This showed that the highest number of deaths resulting from cardiovascular diseases (and ischaemic heart disease) occurred in subjects in whom previous determinations of antithrombin were in the marginal range (at the lower or upper limit). These observations allowed the researchers to conclude that a risk of death resulting from cardiovascular system diseases was related to either low or high values of AT III activity.

The ARIC and PLAT studies ascertained that low values of AT III activity were related to an increased risk of thrombosis and ischaemic events [20, 21]. Among patients who participated in the ECAT Study the AT III antigen level was lower ($p = 0.008$) in patients after myocardial infarction compared to other patients [22, 23].

In another significant population study, the Rotterdam Study ($n = 7983$), AT III activity and the degree of atheromatosis intensity were analysed. The activity of AT III in men was highest in the group of patients with moderate atheromatosis. A greater intensity of atheromatosis was not associated with a rise in the parameter in question but rather with a decrease to the levels found in a healthy population [5]. The combined results of the NPHS, PLAT and Rotterdam Study allow researchers to assume that in patients with an active atheromatic process an increased level of AT III activity can result from activation of a defensive mechanism against a pro-thrombotic impact. The efficiency of defensive mechanisms is limited and we do not observe a further rise in antithrombin activity in cases of advanced atheromatosis. In sub-clinical thrombotic processes increased consumption of AT III results in lower levels of this anticoagulant, despite its increased production. As a result, either a rise or a drop in AT III activity can signal vessel damage and an increased risk [5]. The results of the Rotterdam Study showed that the increased risk of cardiovascular diseases was related to increased AT activity, whereas a drop in AT activity, accompanying thrombotic vascular events, reflected intensified consumption of AT.

The TIMI II (Thrombolysis in Myocardial Infarction Phase II Trial) study was designed to verify the hypothesis that myocardial infarction was related to the deficiency of coagulation inhibitors AT III and proteins C and S. However, it appeared that only the level of protein S was decreased, while protein C and AT III were significantly higher in

patients with myocardial infarction as compared to the control group [24]. These observations are congruent with the results of the present study; in the acute phase of myocardial infarction, significantly higher values of AT III activity were found.

A deficiency of coagulation inhibitors, particularly of AT III, both congenital and acquired, can cause thrombophilia. In prospective observations of a vast material a relationship was found between low AT III activity and a higher risk of ischaemic heart disease or exacerbation of existing disease [5, 19, 20, 25]. The explanation of the increased risk in patients with higher AT III activity, found also in NPHS, ARIC and Rotterdam Study, was more difficult to explain. It could be caused by a compensatory reaction related to the intensity of the thrombotic processes in the arteries with atheromatic lesions [19, 26]. It seems that the higher activity of AT III found in our study and in other reports [19, 24] is a response to intensified thrombinogenesis and increased consumption of antithrombin in acute myocardial infarction.

In our own research material no relationship was found in patients with acute myocardial infarction between AT III and sex, age, BMI, lipids, history of hypertension and smoking. In the reports evaluating the activity of AT III in patients with exacerbation of ischaemic heart disease or myocardial infarction no relationships were found between this parameter and particular factors differentiating the group evaluated [24, 27].

In the group of patients examined a negative correlation was demonstrated between AT III activity and a maximal concentration of CPK and a positive correlation between AT III activity and the time measured between the onset of infarction symptoms to admission to hospital. The authors did not find any reports in the literature which put forward these relationships. We can justify the correlations observed by assuming that the increased activity of AT III demonstrated results from a defensive reaction compensating for activation of the coagulation processes. The longer pre-hospital period corresponds to an increased activity of AT III; this may support the idea of the gradual activation of compensative mechanisms, the effect of which increases with time. One may try to explain the negative correlation of AT III and the maximal concentration of CPK as follows: the more intensified reaction, which compensates for activation of coagulation (higher AT III activity), is related to a lower level of the marker of myocardial cell lesion.

In the relationship discussed between AT III and ischaemic heart disease two qualitatively

different scenarios are possible. On the one hand, decreased levels of AT III found in a stable clinical period of coronary artery disease are the cause of an increased thrombotic threat and predispose to thrombotic events. This is supported by Thompson's et al. study [28], which shows a low level of activity of AT III without simultaneous activation of coagulation, which can be detrimental in ischaemic heart disease. On the other hand, an increased level of activity of AT III can result from overcoagulation, because activation of coagulation is a stimulus which triggers compensative mechanisms, manifesting themselves in the mobilisation of the main coagulation inhibitor, namely an increase in AT III activity [24].

Conclusions

1. In the group of patients examined with acute myocardial infarction, higher concentrations of TAT complexes are found in comparison with healthy subjects in the control group.
2. Higher concentrations of TAT complexes provide evidence of the intensity of thrombinogenesis in patients with acute myocardial infarction, while the higher level of activity of AT III could express the compensative mechanism of thrombinogenesis.
3. Increased concentrations of TAT complexes and AT III activity seem to be unrelated to patient age and sex or the presence and intensity of risk factors of ischaemic heart disease.
4. Higher concentrations of TAT complexes and AT III activity probably have no prognostic importance for the observed complications of myocardial infarction.
5. The negative correlation between AT III and maximal concentrations of CPK can point to a possible protective role of this anticoagulant in the process of the cardiomyocyte lesion during acute myocardial infarction.

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