

THE CHANGES OF PLASMA THROMBIN-ANTITHROMBIN COMPLEX IN THE PATIENTS WITH PERIPHERAL ARTERIAL DISEASE UNDERGOING SURGICAL REVASCULARIZATION

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In patients with severe lower limb ischemia the coagulation and fibrinolytic systems have been found to be activated preoperatively.

The aim of the study was to evaluate the changes of TAT level as a selected coagulation factor, before, during and after surgical revascularization and the analysis of the impact of coexisting diseases on the coagulation during the procedure.

Material and methods. 50 patients with PAOD, in Fontaine stages IIb to IV (29 men and 21 women; median age 65.8 years, ASA II/III) undergoing elective surgical revascularization were studied. Two groups of patients were compared: 20 undergoing reconstruction on aorto-femoral and 30 on femoro-popliteal level. Blood samples were collected 5 times: 24 hours before the operation; intraoperatively after artery exposure; after heparin administration and clamping; after reperfusion and -24 hours postoperatively.

Results. Elevated values of TAT ($10.5 \text{ g/l} \pm 7.1$) were found before the operation. The elevated value of TAT increased intraoperatively ($25.1 \text{ g/l} \pm 44.58$; $p < 0.001$) (norm $1\text{--}4.1 \text{ g/l}$) and maintaining higher levels after the surgery. The significant correlations between plasma level of TAT and ischemia degree were found. Also the correlation between intraoperative increase of TAT and the duration of surgery was noticed. No significant differences between two analysed groups were observed.

Conclusions. The results indicate the activation of coagulation and prothrombotic state in the patients with advanced arteriosclerosis. During the surgical revascularisation permanent increase of activation of blood coagulation was observed. This activation depends on duration of the procedure and maintains increased one-day after the operation. Our findings may explain the unexpected occurrence of early thrombotic complications after technically successful vascular reconstructions.

Key words: thrombin-antithrombin complex (TAT), revascularization, coagulation, limb ischemia

Vascular reconstructions in arteriosclerotic arterial disease are performed for limb salvage. Early graft thrombosis (in the first 30 days) with resulting worsening of ischemia and risk of limb lost is observed after the operation. The reasons of early graft thrombosis have been attributed to technical mistakes and as a result of inadequate arterial outflow, embolization and coagulation disorders including deficiencies of coagulation and fibrinolysis factors (1).

Arteriosclerosis is usually associated with changes in activation of blood coagulation and fibrinolysis system resulting in pro-thrombot-

ic state. This is probably due to continuous thrombus formation on arterial vessel wall defects and reactive fibrinolysis (2).

The number of studies (2, 3, 4) has indicated that in patients with severe lower limb ischemia the coagulation and fibrinolytic systems have been found to be activated preoperatively. A surgical procedure, additionally induce a procoagulant response, which further promotes a severity of pro-thrombotic state.

The aim of the study was to evaluate the changes of plasma level of thrombin-antithrombin complex (TAT) as a selected coagula-

tion factor before, during and after surgical revascularization. Additionally the analysis of the impact of coexisting diseases such as diabetes, dyslipidemia and severity of ischemia (Fontaine score) on the coagulation during the procedure was studied.

Also the changing level of TAT in plasma in two groups of patients: aorto-femoral and infrainguinal reconstructions was compared. The impact of time of the procedure on the changes of TAT was evaluated.

MATERIAL AND METHODS

The study group consisted of 50 consecutive patients (29 men and 21 women; median age 65.8 years, ASA II/III) with PAOD, in Fontaine stages: IIb (n=19), III (n=21) and IV (n=10) undergoing elective surgical revascularization in the Department of Vascular Surgery and Angiology in Lublin. Two groups of patients were compared: 20 undergoing reconstruction on aorto-femoral and 30 on infrainguinal level.

The patients presented with the following co-morbidities: hypertension (n=32), ischemic heart disease (n=21), respiratory failure (n=10) and diabetes mellitus (n=16). All the patients had been informed about the procedure and the aim of the study. All of them had agreed to have their blood examined for this research. The agreement of the Ethics Committee of the Medical University in Lublin was obtained.

Blood samples for analysis were drawn from the antecubital vein without venous stasis into plastic centrifugation tubes containing trisodium citrate in proportion 9:1. The samples were centrifuged for 10 min. at the speed of 3000 rpm.

Blood samples were collected 5 times: 24 hours before the operation, intraoperatively after artery exposure, after heparin administration and clamping, after reperfusion and -24 hours postoperatively.

The TAT concentration was determined by the immunoenzymatic method (ELISA) with Enzygnost® TAT micro set (Dade Behring, Germany).

The obtained results of the extinctions were processed using the curves given by the producer. For each sample the mean and standard deviation were set using Microsoft Excel® 6.0 i Statsoft Statistica® 4.0. Statistical significance was calculated using t-Student test in Fischer modification. To evaluate statistical

significance changes between perioperative measurements of TAT the variance analysis using HSD Tukey test were performed.

RESULTS

Before the operation, in the studied group of patients the average concentration of TAT was elevated: $10.5 \text{ g/l} \pm 7.1$. In 7 cases (14%) the normal TAT level was observed ($1\text{--}4.1 \text{ g/l}$). In 43 cases (86%) TAT level was more than 4.1 g/l . In none of the cases the concentration lower than 1 g/l was observed. There was the correlation between plasma level of TAT and ischemia degree (20.59 g/l in patients with IV° vs 6.49 g/l in patients with IIa° Fontaine's score)

Changes between perioperative measurements of TAT: (a) 24 hours before the operation: $10.5 \text{ g/l} \pm 7.1$; (b) intraoperatively after artery exposure $18.35 \text{ g/l} \pm 10.84$; (c) after heparin administration and clamping $25.1 \text{ g/l} \pm 44.58$; (d) after reperfusion $21.81 \text{ g/l} \pm 14.8$ and (e) 24 hours postoperatively $25.25 \text{ g/l} \pm 12.82$ (fig. 1).

There is no significant correlations between changes of TAT level and coexisting diabetes, ischemic degree and LDL level ($p=0.05$). The correlation between higher intraoperative increase of TAT and the duration of surgery was noted (fig. 2).

No significant differences between two analysed groups (aorto-femoral and infrainguinal level) were observed (fig. 3).

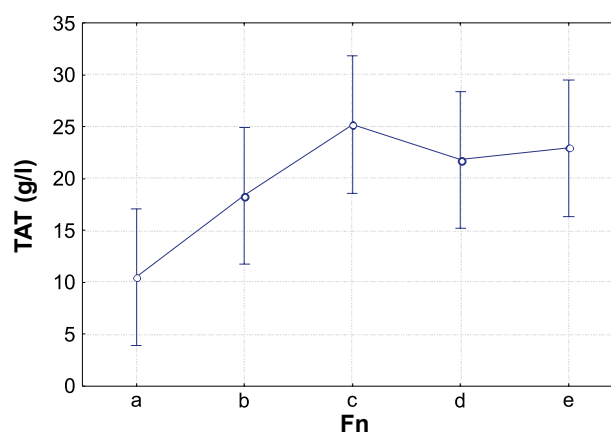


Fig. 1. Variability of TAT level

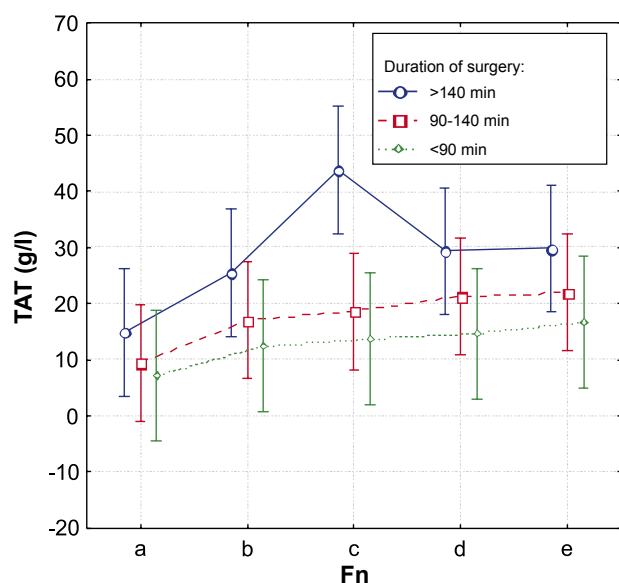


Fig. 2. Correlation between TAT level and duration of surgery

DISCUSSION

Hyperagulability in vascular diseases is still the important challenge for science. Hemostatic abnormalities have prognostic significance in natural history of ischemic disease. Searching for the causes of the early graft thrombosis after technically successful vascular reconstructions is still not satisfactory.

The thrombin-antithrombin complex is a factor which plasma level may assess the level of coagulation activation and directly assesses the quantity of inactivated thrombin in following stages of surgical revascularization.

The results show pro-thrombotic state in patients with lower limb ischemia IIb to IV degree of Fontaine's score, especially in cases with critical limb ischemia. Before surgery high TAT concentration was observed in 86% of the examined cases. During the preoperative period no significant correlations between the TAT level and coexisting diabetes, LDL level and the occlusion level were observed.

The vascular reconstruction caused further creation of trombin which can be judged by significant increase in TAT during surgery (with the highest level after heparin administration and clamping) and maintaining higher levels after the surgery.

There is no significant correlations in the next intra- and postoperative measurements between TAT level and coexisting diabetes and

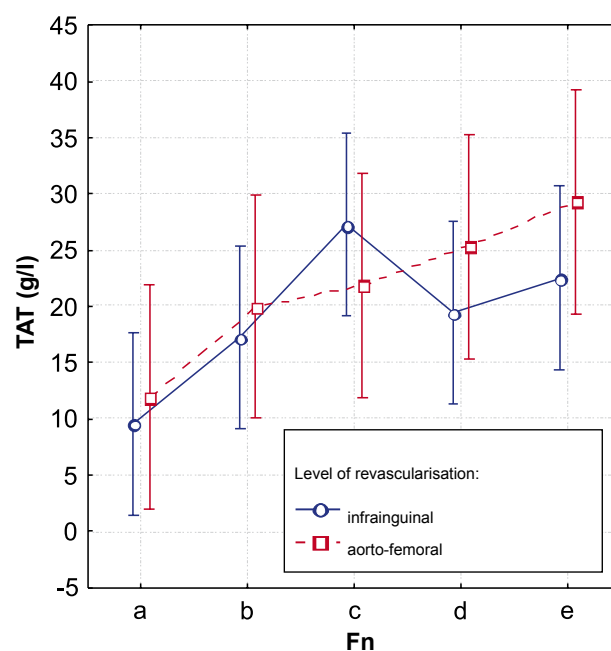


Fig. 3. Variability of TAT level in two groups

LDL level. The correlation between plasma level of TAT and ischemia grade observed before surgery maintain in next measurements.

During surgery the differences between TAT level in aorto-femoral and infrainguinal groups were random, but in the measurement 24 hours postoperatively the higher TAT level in aorto-femoral group was observed (26.6 vs 20.5 g/l). This difference was not statistically significant ($p=0.99$).

In the group with duration of surgery longer than 140 minutes the significantly higher TAT level after heparin administration and clamping was observed in comparison to the group whose surgery lasted shorter.

High TAT concentration in the patients with peripheral atherosclerotic occlusive disease were observed by numerous authors (fig. 4).

In Strano study (4) high TAT levels in the patients with PAD clinically stable Leriche stage II degree: 10.2 ± 8.9 g/l; $p<0.001$.

The TAT level were significantly higher in patients with critical limb ischemia (3.14 g/l range 2.09-58.11), compared to controls (2.36 g/l range 1.49-7.38, $p = 0.004$) (3).

Higher level of TAT was observed in other artery disease causing ischemia (fig. 5).

The TAT concentration is significantly elevated in Buerger disease (33.69 ± 23.9 g/l) (5).

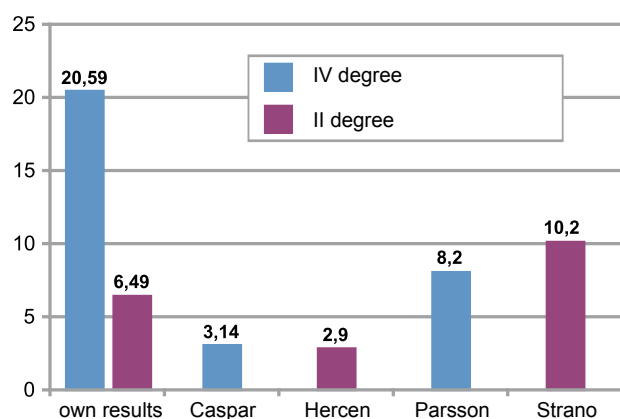


Fig. 4. TAT level in PAOD depending on ischemia degree (according to Fontaine's score)

In the patients with acute limb ischemia the TAT level is 5 times higher (11 to 21 g/l, range 16 g/l) than TAT level in the patients with PAOD (2 to 4 g/l, range 3 g/l), $p < 0.003$ (6).

In Giannitsis study the TAT level in the patients with angiographically verified graded coronary artery disease (CAD) free of concomitant peripheral atherosclerosis, cerebrovascular disease or diabetes mellitus is significantly higher (15.6 ± 2.7 g/l) compared to controls (2.96 ± 0.32 g/l) $p < 0.001$ (7), but other papers describe the lack of the increase of TAT level (3.34 g/l) in the patients with coronary artery disease (CAD) (8).

Resulting from other studies values for TAT in patients with acute myocardial infarction (AMI) at 10 days increased significantly, and three months later it decreased to normal (9).

The plasma level of a TAT was evaluated in the patients with advanced chronic heart failure – New York Heart Association class IV (3.8 g/l) compared to control (2.4 g/l) (10).

In evaluating research the role of coagulation and fibrinolysis abnormalities in stroke significant elevation of TAT level in 1st (5.96 ± 0.67 g/l), 3rd (7.68 ± 0.93 g/l) and 7th day ($6.98 \pm$) was proved (11). These results are confirmed by other authors (12, 13).

Variability of TAT concentration in perioperative period was determined during examining of activity of coagulation and fibrinolysis in the patients with various vascular procedures.

In the patients undergoing PTA the level of TAT before the procedure were 5.3 ± 6.3 g/l, 1 hour after significantly increased to 12.1 ± 15.8 g/l and 48 hours after the PTA the level of TAT were 10.3 ± 18.5 g/l (14).

Cassar confirms significant rise in TAT levels at 1 hour after angioplasty in PAOD (15).

Activation of coagulation and fibrinolysis during infrainguinal surgical revascularisation in patients with critical limb ischemia were studied by Pärson. Preoperative value of TAT were significantly elevated compared to control, increased 60 minutes after the reperfusion and were on the same level 24 hours after (2).

Englberger compared the changes of TAT level in the patients with abdominal aortic aneurysm underwent endovascular and open surgical repair. During the procedure TAT values were significantly elevated in both groups and returned to values near baseline 5

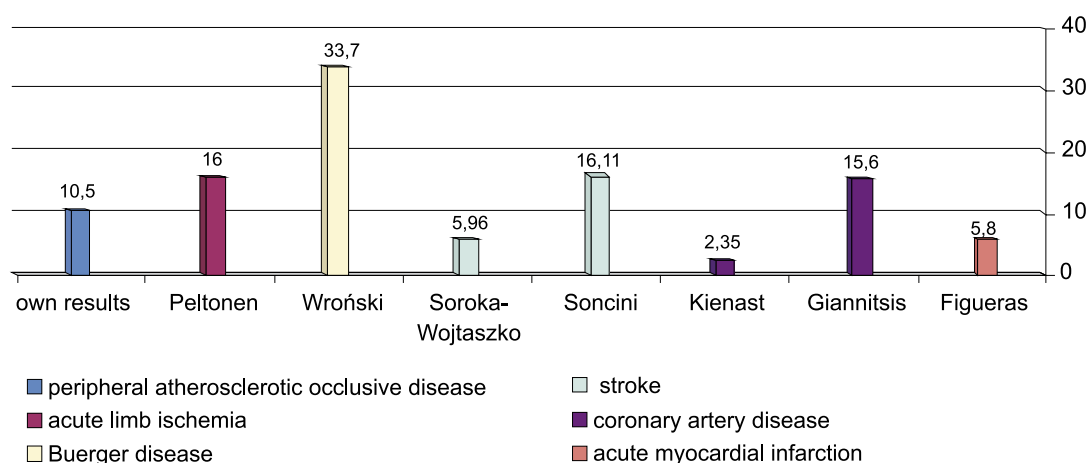


Fig. 5. TAT level in artery disease causing ischemia

days after the operation (16). In another study, Bailey demonstrated significantly higher levels of TAT in patients after EVAR versus patients after open aorta repair at 5 months after intervention (17).

Parolari studied the coagulation-fibrinolytic profile during a 2-month follow-up period after coronary artery surgery. TAT level were significantly increased during the first week after the intervention compared with preoperative value and normalized at 45 days (18).

The TAT level were examined in experimental study on porcine model assessed coagulopathy during aortic cross-clamping. One group of animal underwent supraceliac aortic cross-clamping (SC AXC) for 30 and 60 minutes and compared to group underwent infrarenal aortic cross-clamping (IR AXC). No heparin was used. TAT level in-

creased in both SC AXC groups, but were not significantly greater than in the IR AXC group (19).

CONCLUSIONS

The results indicate the activation of coagulation and prothrombotic state in the patients with advanced arteriosclerosis. During the surgical revascularization permanent increase of activation of blood coagulation was observed. This activation depends on duration of the procedure and maintains increased 24 hour after the operation. Our findings may explain the unexpected occurrence of thrombotic complications in early period after technically successful vascular reconstructions.

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