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CLINICAL STUDY

Coagulation profile after esophagectomy in SIRS and sepsis evaluated by thromboelastography and relationship with organ dysfunction development

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ABSTRACT

OBJECTIVES: Assessment of organ dysfunction development and relationship to coagulation changes measured by standard coagulation tests and thromboelastography in patients after major surgery.

BACKGROUND: Some authors reported that hypercoagulation present in systemic inflammatory response syndrome (SIRS) is caused by infection, while others reported hypocoagulation. We hypothesize that hemocoagulation status depends on severity and time course of sepsis/SIRS and that coagulation profile influences organ dysfunction.

METHODS: Hemocoagulation profile was evaluated in patients undergoing surgical esophagectomy on the morning of surgery and then at 24-hour intervals for the following six days. Results: From 34 analyzed patients, 26 went through postoperative SIRS and eight patients developed sepsis complication. Hypercoagulation trend was found in both nonseptic and septic patients early after operation represented by short R and K. We also found significant correlation ($p < 0.05$) between antithrombin level and organ dysfunction score in both groups, for nonseptic group ($r = –0.78$, $r^2 = 0.60$) and for septic group ($r = –0.94$, $r^2 = 0.88$).

CONCLUSION: Hemocoagulation in both SIRS and sepsis is initially accompanied by a hypercoagulation trend and low level of antithrombin is connected to organ dysfunction development. Therefore, normal antithrombin level might prevent organ dysfunction in postoperative period *(Fig. 1, Ref. 14)*. Text in PDF *www.elis.sk.*

KEY WORDS: esophagectomy, coagulation, sepsis, thromboelastography, antithrombin, organ dysfunction.

Introduction

The relationship between inflammation and coagulation is a well- known phenomenon. The primary aim of inflammation is to localise infection by forming fibrin. This protective role becomes out of control when inflammation reaction and fibrin formation dissipates to the whole body and thus presents itself as systemic inflammatory response syndrome (SIRS). This overreaction of the body response is connected with a higher organ dysfunction score (1–3), because of formed fibrin deposits in microvasculature preventing organ perfusion. Lissauer has shown that coagulation profile differs between patients with SIRS and sepsis using standard coagulation tests such as PT, aPTT, fibrinogen, platelets, D-dimers (4) and new studies in this area are still missing. Compared to standard tests, a more sophisticated method such as thromboelastography (TEG) might be better for describing coagulation changes as it provides information about all coagulation phases (initiation, propagation, fibrinolysis) using whole blood as well as functional status of fibrinogen. Recently, TEG has been described as a tool for assessment of coagulation abnormalities in sepsis (5). However, even by using TEG, some authors say that sepsis is accompanied by hypercoagulation (6) while others demonstrate hypocoagulation (5, 7). Müller in her systematic review emphasizes that coagulopathy in sepsis is a dynamic process and encourages studies where coagulation profile is measured sequentially (8).

We hypothesized that coagulation status depends on the severity of sepsis/SIRS and on the time course and that coagulation profile influences organ dysfunction development. The aim of this study was to describe coagulation changes accompanying systemic inflammatory response by standard coagulation tests and TEG and to look for relationship to organ dysfunction development. In order to reach this objective, patients undergoing big surgery such as two-cavity esophagectomy were recruited to the study and divided postoperatively into those, who only presented with SIRS and those, who also developed sepsis. We also looked for relationships between sequential organ failure assessment score (SOFA score) and inflammation/coagulation parameters changes.

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Although treatment for infection is antibiotics, organ dysfunction could be prevented also by intervention in coagulation.

Materials and methods

This study was approved by the Ethics Committee for Multi-Centric Clinical Trials of the University Hospital Motol, Prague, Czech Republic. All patients undergoing elective esophagectomy provided a written informed consent before inclusion in the study. Following surgery, all patients were extubated in the operating theatre and then transferred to the surgical intensive care unit (ICU). Postsurgical medications for all patients included antibiotics (for the first 48 hours), thoracic epidural analgesia, Diclofenac 1 x 75 mg/24 h and Enoxaparin 1 x 0.4 ml (40 mg) at evening hours. Blood samples were obtained from the cubital vein using the syringe needle method (venepuncture) on the morning before surgery and then at 24-hour intervals for the following 6 days.

Thromboelastography method

Thromboelastography analysis was conducted with a computer-controlled thrombelastography haemostasis system (TEG Haemoscope, Niles, IL) using native cuvettes (without heparinase) and the native method (non-activated, without kaolin) for following parameters: R (reaction time, time from beginning of test to detectable clot formation represented by 2 mm amplitude), K (kinetics parameter, time from R to amplitude of 20 mm), α angle, MA (maximal amplitude-maximum strength of clot in mm), TPI (thrombodynamic potential index; TPI = EMX/K, relative shear modulus divided by kinetics of clot development, where EMX is E at maximum amplitude-MA /E is an elasticity constant, which is a normalised G parameter; G parameter is actual measure of clot firmness/, EMX = (100 x MA)/(100-MA); K is measured in mm.), CI (coagulation index), LY30 (percentage of lysis 30 minutes from MA), LY60 (percentage of lysis 60 minutes from MA). Functional fibrinogen (FF, reagent contains IIb/IIIa blocker of platelets) was examined and FFMA was evaluated. We also measured the difference between MA and FFMA, representing platelets function (MA-Pl).

Hypercoagulation trend was defined as shortening of initiation phase of coagulation represented by short R and K parameter, then by faster propagation phase represented by increased α angle, then by increased strength of coagulum represented by higher value of MA and finally by higher TPI. The hypocoagulation status was defined as prolongation of R, K, decrease of α angle, MA and TPI.

Laboratory methods

Blood samples were also analysed for lactate level (Cobas Integra 400+; Roche, Switzerland), platelets count (Coulter LH 750 HematologyAnalyzer; Beckman-Coulter, Miami, FL), antithrombin (AT) activity, D-dimers concentration, international normalized ratio for prothrombin time (PT-INR) and activated partial thromboplastin time (aPTT; all CA-7000 automated coagulation analyzer; Sysmex; Kobe, Japan).

The septic group was formed by patients, who fulfilled the criteria of sepsis defined by ACCP-SCCM conference (9) during postoperative period and the nonseptic group was formed by patients with no proven infection. The ICU doctors in charge of the definition and assignment of patients into the groups were blinded to the results of the study tests. The laboratory results of all inves-

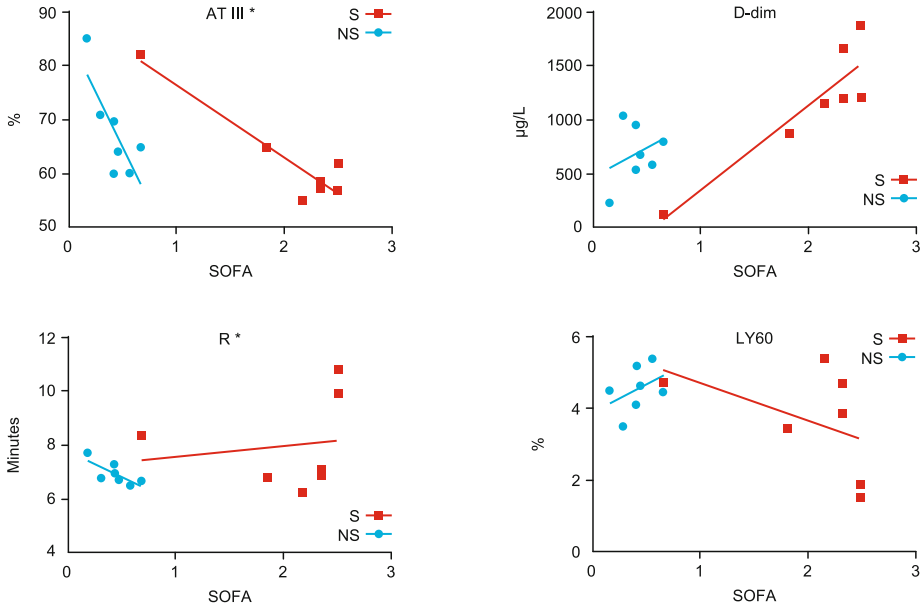

Fig. 1. Relationship between SOFA score and TEG/laboratory parameters from day of surgery (D0) to Day 6 after surgery (D6) in nonseptic (NS, blue colour) and septic (S, red colour) groups.
SOFA, Sequential Organ Failure Assessment score. In NS group for AT (antithrombin) r = –0.78, r^2 = 0.60, p < 0.05; for D-dim (D-dimers) r = +0.3, r^2 = 0.09, p > 0.05; for R parameter (reaction time) r = –0.76, r^2 = 0.58, p < 0.05; for LY60 (% of fibrinolysis) r = +0.4, r^2 = 0.16, p > 0.05. In S group for AT r = –0.94, r^2 = 0.88, p < 0.05; for D-dim (D-dimers) r = +0.90, r^2 = 0.81, p < 0.05; for R parameter (reaction time) r = +0.16, r^2 = 0.03, p > 0.05; for LY60 (% of fibrinolysis) r = –0.5, r^2 = 0.22, p > 0.05; * indicates p < 0.05.

tigated parameters mentioned above were compared between the two groups for every day.

Statistical analysis

Statistical analysis was performed using Prism 6.0 statistical software (Graph Pad Software, Inc.). Values were tested for normality using D´Agostino–Pearson omnibus normality test.

Two-way ANOVA multiple unpaired t-test was used to compare nonseptic group data with septic group data for each day and statistical significance was corrected using the Holm–Sidak method, $p < 0.05$ was considered significant. The data were expressed as the mean values ± SD. For correlation statistics, Pearson r correlation coefficients were calculated and $p < 0.05$ was considered significant.

Results

Thirty-nine patients undergoing surgical esophagectomy with a thoracoabdominal approach were included in the original study. However, completed TEG data were available from 34 patients (27 men, 7 women, mean age 59 years, minimum 40 years, maximum 73 years). Exclusion criteria were hepatic insufficiency, renal insufficiency and coagulation disorders. The length of the surgery was 240–300 minutes (for both groups). From 34 analysed patients, 26 went through postoperative SIRS (20 men and 6 women; mean age for men 58 years, minimum 40 years, maximum 70; mean age for women 58 years, minimum 48 years, maximum 70 years) and eight patients developed sepsis complication (six men and two women; mean age for men 64 years, minimum 53 years, maximum 73; age of the women 68 years; 5 x pneumonia diagnosed on the second postoperative day (four men and one woman) and 3 dehiscence of gastroesophageal anastomosis diagnosed on the fifth postoperative day (two men and one woman).

Similar coagulation changes early after surgery in both groups

In TEG parameters, we found similar hypercoagulation trend in both nonseptic (SIRS) and septic patients early after operation represented by short R and K-faster initiation and propagation phase of coagulation until day five when R and K value restored to normal values, although R and K were significantly higher and TPI with LY60 were significantly lower in septic patients ($p < 0.05$) (Fig. 1). We found similar trends in laboratory coagulation parameters in both groups with no significant differences in most of the parameters (with exception of D-dimers) until day four when significantly higher values of PT-INR were present in septic patients ($p < 0.05$) and day five when lower AT level and higher values of aPTT and PT-INR were also found in septic patients ($p < 0.05$). Interestingly, D-dimers were significantly higher in septic patients already from the second postoperative day ($p < 0.05$).

Coagulation differences between SIRS and sepsis

In the septic patients, statistically significant differences were found in the initiation phase represented by longer R parameter meaning a slower initiation of coagulation in day five ($p < 0.05$) and in day six ($p < 0.001$), in propagation phase represented by longer K parameter in day five ($p < 0.001$) and day six ($p < 0.01$) decreased α angle parameter meaning a weaker propagation of coagulation in day six ($p < 0.05$) (Tab. 1). Global coagulation status represented by TPI was weaker in day five and six (both $p < 0.05$) in the same group, and also CI in day six ($p < 0.05$). Later phase of fibrinolysis represented by parameter LY60 was decreased significantly ($p < 0.05$) in day five. No significant differences between both groups were found in maximal strength of coagulum-MA, in early fibrinolysis-LY30 ($p > 0.05$) (Tab.1), in values of functional fibrinogen level-FFMA and in platelets function-MA-Pl (Tab. 1). In laboratory, coagulation parameters in the septic group were significantly higher, value of D-dimers on the second and third postoperative day ($p < 0.01$) and on day four and six ($p < 0.001$), higher value of PT-INR on day four and five ($p < 0.05$), higher value of aPTT on day five ($p < 0.05$). Significantly lower level of antithrombin was found in septic patients on day five ($p < 0.05$) and no differences between both groups were indentified in platelets count and fibrinogen level for the whole study ($p > 0.05$). In the evaluated SOFA score, we found that it was higher in the septic group ($p < 0.05$) since the first postoperative day. There were no significant differences in the lactate level between groups ($p > 0.05$).

Relationship between coagulation, inflammation and SOFA

When looked for relationships between SOFA and inflammation/coagulation parameters in nonseptic (SIRS) patients, we found a significant negative correlation of SOFA with AT level ($r = –0.78$) and R parameter ($r = –0.76$) ($p < 0.05$) (Fig. 1). There was also positive correlation with D-dimers and LY60 although it was not statistically significant. In the septic patients, the correlation of SOFA with AT was even more significant in the same direction ($r = –0.94$) ($p < 0.01$) and positive significant correlation was found for D-dimers ($r = +0.90$) (Fig. 1). Negative correlation for LY 60 and positive correlation for R parameter were also observed,but those were not statistically significant.

Discussion

Hypercoagulation trend was found in both nonseptic and septic patients early after operation represented by short R and K until day five when R and K restored to normal values, although R and K were significantly higher and TPI with LY60 were significantly lower in the septic patients and low antithrombin level was connected with the higher SOFA score. In the SIRS patients, we found a significant correlation of SOFA AT and R parameter. In the septic patients, the correlation of SOFA with AT and D-dimers was found. Inflammation upregulates microvascular expression of the tissue factor and plasminogen activator inhibitor 1 and down regulates natural anticoagulant proteins such as protein C, protein S and antithrombin; these changes trigger activation of coagulation (10). Subsequent disseminated intravascular coagulation (DIC) is associated with activated coagulation, including fibrin formation, partly because of the interaction with microvasculature fibrin meshwork(3). This microvasculature damage may contribute to the development of hypoperfusion and multiorgan dysfunction syndrome (MODS) (11). Systemic inflammatory response syndrome (SIRS) represents a host response to various insults and sepsis is the body inflamma-

tory response to infection. According to Lissauer et al, inflammation response in SIRS differs from that in sepsis (4).Thromboelastography as viscoelastic test using whole blood is better for coagulation assessment than standard tests and although it has been used by many authors also in sepsis, the conclusion is not clear. Authors showed both hyper and hypocoagulable state in sepsis (12, 5–7). Our results brought two main contributions: the coagulation profile of the inflammatory response, as assessed by TEG and clotting study, goes through dynamic changes over time course and there are differences regarding to coagulation profiles between patients with SIRS and those with SIRS + infection-sepsis. Early phase of inflammatory response syndrome in both SIRS and sepsis is accompanied by hypercoagulation, which is represented by short R, K values, which are out of normal range until day five and this is accompanied by consumption of AT. This finding is similar to Myung SP and co-authors, who moreover found a higher incidence of pulmonary embolism in the patients after injury (13). When we look to D-dimers, we could see that significantly higher level was found in the sepsis group already from the second postoperative day. This means that stronger hypercoagulation is presented in microcirculation of septic patients, which is accompanied by significantly higher SOFA score. The fact that fibrinolysis is not detected on TEG can be explained by the theory that TEG can only detect fibrinolysis present in macrocirculation (venous blood). From the day five, significant hypocoagulation changes are seen in septic patients while nonseptic patients become hypercoagulable. This is demonstrated on parameters R, K, α angle, CI and TPI (Tab. 1). Antithrombin level was low in both groups all the time, but was significantly lower in septic group from the day 5, which says that hypocoagulation may be the result of the consumption of coagulation factors consumed during DIC. We found very good negative correlation between SOFA and ATin both SIRS and septic patients as well as positive correlation with D-dimers especially in sepsis (Fig. 1).

Our findings are in accordance with results of Ostrowski et al. who found a higher SOFA and DIC score in hypocoagulable patients and lower in hyper or normocoagulable patients (14). Adamzik et al found also hypocoagulation status presented in non-survivor patients, while patients who were hypercoagualable survived sepsis better (12). This is interesting, because both authors measured coagulation profile in the patients after admission to ICU with diagnosis of sepsis, but the time elapsed from beginning of sepsis was not known. In our results, we could demonstrate that if patient was at the beginning of sepsis, he was hypercoagulable and he became hypocoagulable with time elapsing from onset of sepsis and with its progression. This was accompanied with higher SOFA score.

The limitation of our study is a relatively low number of patients, but it was done as a pilot study and the results were able to reach statistical significance.

In conclusion, our findings suggested that the hemocoagulation changes after big operation depended on time elapsed from SIRS/sepsis onset. However, early postoperative SIRS/sepsis period was accompanied by hypercoagulation trend with low AT level and there was significantly positive correlation between SOFA and AT level. Therefore, normal antithrombin level might prevent organ dysfunction in postoperative period.

Learning points

1. Hemocoagulation in both SIRS and sepsis is initially accompanied by a hypercoagulation trend.
2. In SIRS/sepsis, low level of antithrombin is connected to organ dysfunction development.
3. The character of coagulation status depends on time elapsed from SIRS/sepsis onset.
4. Hypocoagulation profile of sepsis is accompanied by increased SOFA score.

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