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LUNG VESSELS THROMBOSIS IN HOSPITALIZED PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA: ROLE OF ENDOTHELIAL FUNCTION, HEMOSTASIS, FIBRINOLYSIS AND INFLAMMATION ON DIFFERENT PHASES OF TREATMENT

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ABSTRACT

Introduction: There are limited data on the relationship between the severity of community-acquired pneumonia (CAP), biomarkers of inflammation and coagulation as well.

The aim was to evaluate the association between the severity of CAP and risk of thrombosis in patients with moderate and severe CAP. To estimate the role of parameters of systemic inflammation, endothelial dysfunction, hemostasis, coagulation on different phases of treatment.

Materials and methods: The main group was 75 patients CAP. We divided the main group according severity: subgroup 1 – 41 patients with moderate CAP, subgroup 2 – 34 patients with severe CAP. Blood coagulation test, determination of biomarkers was performed at admission before starting of antibacterial treatment and after clinical stability on 7–10 day after hospitalization.

Results: We found that in both subgroup 1 and subgroup 2 the mean levels of CRP and fibrinogen were higher than in control group. Moreover, the mean level of D-dimer was significantly higher and protein C (PC) was significantly lower in both subgroups in comparison with control group.

Normalization of PC is coming after 7–10 days of antibacterial treatment, vice versa ET-1, which reflects prolong endothelial dysfunction in patients with severe CAP.

Conclusions: patients with severe CAP have the high risk of thrombosis which can be associated with endothelial dysfunction; definition of such parameters as ET-1 and PC can be useful for establishment of different coagulant disorders in patient with mild and moderate CAP, and their dynamic changes could be the initial point of prescribing or cancelling of anticoagulant treatment.

KEY WORDS: CAP, thrombosis, endothelial dysfunction, inflammation, markers

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INTRODUCTION

The endothelium is a functional barrier between vessel wall and blood stream that for a long time has been regarded as a relatively inert container for blood [1]. However, the last 20 years, researchers have found an extraordinary variety of important endothelial functions, including control of coagulation, fibrinolysis, vascular tone, growth, and immune response. It is now clear that dysfunction of the endothelium disturbs the physiological protective regulatory balance and could be associated with increased mortality in patient with different diseases including community-acquired pneumonia (CAP) [2, 3].

CAP is one of the most common causes of mortality among other infectious diseases all over the world. The mortality rate of patients with CAP depends on the severity of the disease and comorbidity [4]. Therefore, the early identification of patients at risk of serious complications is critical to the management of CAP. To improve the outcomes in the management of CAP, there has recently been a significant attention paid to evidence-based scoring systems and biological markers. They can objectively help to predict the severity, to justify hospital or ICU admission [5]. The role of inflammatory markers has been already established rather good. Researchers believe that some coagulation and thrombotic disorders during severe CAP could lead to some intravascular disorders and even be the reason of lethal end in hospitalized patients with CAP [6]. The perfect severity score and biomarker does not yet exist. There are limited data on the relationship between the severity of community-acquired pneumonia (CAP) and biomarkers of inflammation and coagulation as well [7, 8]. At present, the combination of biomarkers and clinical scores has shown promising results in predicting mortality and severe outcomes in CAP.

THE AIM

The aim was to evaluate the association between the severity of CAP (according to SMRT-CO score) and risk of thrombosis (according to Padui score) in patients with moderate and severe CAP. And furthermore, to estimate the role of parameters of systemic inflammation (C-reactive

Table I. Levels of systemic inflammation parameters in patients with moderate to severe CAP, Me [25-75%]

Parameter	Main group	Control group	p
CRP, mg/l	168.6 [102.6–277.3]	4.5 [3.4–5.5]	0.002
Fibrinogen, mcg/ml	6.8 [4.7–12.2]	2.7 [2.4–3.0]	0.000

Table II. Levels of parameters of endothelial dysfunction, hemostasis and fibrinolysis in patients with moderate to severe CAP, Me [25-75%]

Parameter	Main group	Control group	p
ET-1, ng/ml	0.64 [0.4–1.86]	0.77 [0.45–1.03]	0.778
PC, %	75.0 [64.0–95.0]	95.0 [83.0–105.0]	0.008
DD, ng/ml	1561.2 [989.4–5325.3]	267.0 [254.0–1298.0]	0.000

Table III. Levels of systemic inflammation and coagulation parameters in patients with moderate to severe CAP, Me [25-75%]

Parameter	Visit 1		Visit 2		Control group
	subgroup 1	*subgroup 2*	*subgroup 1*	*subgroup 2*	
CRP, mg/l	126,7 [68,7–192,0]*#^	197,6 [147,8–311,7]*#^	10,6 [5,0–19,2]*#^	49,0 [6,6–93,0]*#^	4,5 [3,4–5,5]
ET-1, ng/ml	0,5 [0,36–0,81]*^	1,4 [0,41–2,5]*#^	0,6 [0,4–0,7]*^	1,1 [0,7–2,4]*#^	0,77 [0,45–1,03]
PC, %	80,0 [68,0–95,0] #^	70,0 [63,0–95,0]#^	101,5 [88,5–115,0]^	106,5 [80,0–135,0]^	95,0 [83,0–105,0]

Notes: * – $p < 0.05$ between subgroups on Mann-Witney;
– $p < 0.05$ with control group on Mann-Witney;
^ – $p < 0.05$ between visits on Wilkoxon.

protein (CRP), fibrinogen), endothelial dysfunction (endothelin 1 (ET-1)), hemostasis (protein C (PC)), fibrinolysis (D-dimer (DD) on different phases of treatment.

MATERIALS AND METHODS

The main group was 75 patients with moderate to severe CAP. Depending on the severity all patients of the main group were divided into 2 subgroups: subgroup 1 – 41 patients with moderate CAP (the mean age was 48.0 [33.0–61.0] years old, men – 33 (80.0%)), subgroup 2 – 34 patients with severe CAP (the mean age was 56.0 [46.0–60.0] years old, men – 22 (65.0%). Subgroups had no significant difference according to age (p=0.178) and sex (p=0.166).

The formulation of diagnosis CAP and assessment of its severity were determined according to the international guidelines [4] and SMRT-CO scale [9].

General clinical analysis, blood coagulation test, determination of biomarkers was performed at admission before starting of antibacterial treatment (visit 1) and after clinical stability on 7–10 day after hospitalization (visit 2).

DD and CRP levels were estimated by immunoturbodimetric method [10, 11], ET-1 was estimated by immuassay test, activity of PC was established with optic method [12, 13].

The study was conducted according to Helsinki declaration with the permission of the Bioethical commission Dnipropetrovsk medical academy of the ministry of Health of Ukraine.

Received results were compared with values in control group. The control group was 16 healthy people (the mean age was 56.0 [52.0–69.0] years old, men – 13 (81.0%)).

The risk of thrombosis was estimated with the help of Padua Prediction Score for risk of lung thrombosis [14].

At died patients we observed autopsy data including electronic microscope investigations.

Statistical processing of the results in research was carried out using the methods of biometric analysis, implemented in software packages EXCEL-2003 (№ 74017-641-9475201-57075) and STATISTICA 6.0 (№ 31415926535897) [15].

RESULTS AND DISCUSSION

Analyzing the data of main group patients, we detect that during hospitalization everybody has clinical symptoms of CAP combining with mono- or bilateral lung infiltration on chest X-ray.

The severity according to the SMRT-CO scale of patients in subgroup 1 was 0.0 [0.0–1.0] scores, in subgroup 2 was 3.0 [3.0–5.0] scores (p=0.000), which proved the right distribution of patient among subgroups.

During investigation of systemic inflammatory markers on visit 1, we found that in both subgroup 1 and subgroup 2 the mean levels of CRP and fibrinogen were higher than in control group (table I). Detailed analysis showed that patients with severe CAP had significantly higher levels of CRP (197.6 [147.8–311.7] mg/l in subgroup 2 comparing with 126.7 [68.7–192.0] mg/l in subgroup 1, p=0,000), which reflects the severity of inflammation in patients with CAP. The level of fibrinogen did not differ between subgroups and was 7.3 [3.7–13.3] mcg/ml in subgroup 1 and 7.8 [5.5–12.2] mcg/ml in subgroup 2 (p=0.483).

During investigation of parameters of endothelial function (ET-1), hemostasis (PC) and fibrinolysis (DD) we found that in both subgroup 1 and subgroup 2 the mean level of DD was significantly higher and PC was significantly lower in comparing with the mean levels of these parameters in control group, but the result of ET-1 depended on the severity of the CAP. Detailed

analysis showed that patients with severe CAP had significantly higher levels of ET-1 and the lowest level of PC (table II, table III). This fact shows the highest risk of thrombosis in patients with severe CAP.

Additionally, the mean level of scores by Padua scale in patients with severe CAP was 5.0 [5.0–6.0] scores, which was significantly higher than in patients with moderate CAP, who had 1.0 [1.0–2.0] scores (p=0.000).

All patients received guided-based antibacterial treatment and mucolytic. On the visit 2 which was on 7–10 day after hospitalization most of them had signs of clinical stability: normalization of the temperature, decreasing of cough and dyspnea.

The proving of general positive effect of treatment is demonstrated by great decreasing of mean level of CRP in both patients with severe and mild CAP (table III). However, it was still differing from normal value in control group, which shows that stabilization of this marker is rather long process.

Regarding ET-1, the mean level of which was increased only in severe patients on visit 1, also significantly decreased on visit 2, but nevertheless it was still differing from the corresponding parameter in control group. This fact demonstrates that endothelial dysfunction which is one of the pathogenetical mechanisms of severe pneumonia presents its role during rather prolonged time (more than 7–10 days' period).

Opposite situation was with nature anticoagulant PC. The mean level of this parameter not only significantly increased till the visit 2 but also normalized and didn't differ from the mean level of PC in healthy persons on the 7–10 day.

CONCLUSIONS

1. In-patient cases of CAP are characterized by systemic inflammation, which comes out in intensive increasing of CRP and hypercoagulation which comes out in decreasing of PC, increasing of DD and fibrinogen.
2. Patients with severe CAP have the high risk of thrombosis which can be associated with endothelial dysfunction and manifested in maximal scores by Padua scale, the highest levels of ET-1 and the lowest level of PC.
3. Normalization of PC is coming after 7–10 days of antibacterial treatment of CAP, vice versa ET-1, which reflects prolong endothelial dysfunction in patients with severe CAP.
4. Definition of such parameters as ET-1 and PC can be useful for establishment of different coagulant disorders in patient with mild and moderate CAP, and their dynamic changes could be the initial point of prescribing or cancelling of anticoagulant treatment.

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Authors' contributions:
According to the order of the Authorship.

Conflict of interest:
The Authors declare no conflict of interest.

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