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The coagulation system changes in patients with chronic heart failure

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Key words: *chronic heart failure; coagulation system; fibrinogen; platelets; endothelium.*

Summary. *Though heart failure can mainly be caused by systolic or diastolic dysfunction, the impairments of the neurohormonal, immune, and hemostatic systems are observed too. Therefore, it is not easy to determine etiology of the syndrome. Parameters that can be helpful to predict chronic heart failure, to evaluate its course and the risk of complications are still being searched. The aim of this article is to review the recent studies in order to find the links between the coagulation system and the development of chronic heart failure.*

Stress is a key factor for the development of most diseases including chronic heart failure too. Signals of emotional and physical stress via particular structures trigger an increase in concentrations of the following hormones: noradrenaline, renin, angiotensin II, aldosterone, vasopressin. It is proved that it causes the disorders of the coagulation system: an increase in the following factors of plasma coagulation (fibrinogen, VII, VIII, fibrinopeptide A, thrombin-antithrombin complex), fibrinolysis (D-dimer), endothelium (interleukin 1, endothelin 1, vascular cell adhesion molecules, endothelial growth factor), platelet activity (von Willebrand factor, intercellular adhesion molecules, platelet factor 4, P-selectin, thromboxane A_2, thromboglobulin, CD63P) and cytokines (tumor necrosis factor, interleukin 6) and decrease in E-selectin.

The role of particular coagulation factors for the development of chronic heart failure has not been understood yet. Thus, it is necessary to carry out further studies.

Introduction

In the general European population, the prevalence of symptomatic heart failure ranges from 0.4% to 2%. More frequently, it afflicts older subjects (1). Heart failure (HF) carries a poor prognosis if the cause of disease cannot be removed. Around half of patients with chronic HF (CHF) die within 4 years (2). A growing number of risk factors (non–insulin-dependent diabetes mellitus, overweight, aging population, and others) may contribute to new incidences of heart failure (3).

Accurate diagnostics of CHF and its etiological factors is more complicated among older patients because of comorbidity. Diagnosis based only on clinical presentation may be not correct. An accurate diagnosis is required to apply an optimal treatment aimed at removal the cause of the disease.

A key factor for the development of CHF is heart dysfunction, accompanied by impairments of the peripheral circulation, particularly, in kidney and skeletal muscles. Activation of the neuroendocrine system is common in CHF. It is proved that activation of different inflammatory markers has an effect on cardiac dysfunction and the progression of CHF clinical syndrome (4–6).

Although the importance of neuroendocrine mechanisms in the pathogenesis of CHF is recognized, still their role in diagnostics is unclear. Cohort studies have proved that concentrations of circulating hormones (noradrenalin, renin, angiotensin II, aldosterone, vasopressin) and hemostasis markers (endothelin 1, fibrinogen, and others) are linked to severity and prognosis of CHF; however, it is difficult to interpret these predictors in every case. Diuretics, vasodilatators, ACE inhibitors, and β-adrenoblockers alter the concentrations of blood neuroendocrine substances making difficult interpretation of concentrations of these compounds when diagnosing the disease.

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Moreover, plasma noradrenaline concentration increases with aging, and it can exceed the limit determining heart failure in healthy subjects older than 75 years (5).

Therefore, parameters that can be helpful to predict CHF, to evaluate its course and the risk of complications are still being searched. The aim of this article is to review the scientific literature on the changes of the coagulation system in patients with CHF, their relationships, and links to inflammatory parameters as well as CHF etiology and severity.

The changes of hemostatic system in patients with chronic heart failure

Investigation of hemostatic system markers in patients with CHF was conducted by authors from different aspects. Some authors tried to relate coagulation markers to HF etiology, the severity degree; the others made a comparison of concentration of these markers between healthy subjects and patients, between women and men with the disease. However, most authors found the changes of one or another type in coagulation system that proved the presence of hypercoagulable state in subjects with CHF.

Different authors investigated plasma hemostatic markers and related concentrations of cytokines, hormones, compounds secreted from platelets, markers of endothelial damage, and others. It was found that significantly higher levels of the following parameters were present in subjects with CHF: hemostatic markers, von Willebrand factor (vWF) and fibrinogen; intercellular adhesion molecules (ICAM); platelet and endothelial adhesion molecules (PECAM); platelet factor 4 (PF4), P-selectin; tissue-type plasminogen activator (t-PA), D-dimer; fibrinopeptide A; selectin; vascular cell adhesion molecules (VCAM) (Table); cytokines, tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6); enzyme urokinase, thromboxane reductase, other compounds (thioredoxin, serotonin); and lysosome and platelet dense granule transmembrane protein (16).

One of the factors influencing CHF – stress – increases the concentrations of vWF and plasma coagulation factors VII and VIII via mediators (Fig.). It is stressed that there is an increase in vWF and fibrinogen levels in subjects with CHF (4, 14, 19, 20). Fibrinogen and vWF concentration is higher in women than men, though men more frequently are afflicted by CHF. The cause of this difference is unclear (4). vWF and t-PA levels were significantly higher in subjects with CHF and left ventricular aneurysm than in patients without aneurysm. Therefore, according to authors, such patients are indicated for antithrombotic therapy (21). Based on significant differences in plasma vWF levels between subjects with functional class II and III CHF (plasma vWF levels were higher in functional class III than class II), it was determined that endothelial function was poorer in functional class III patients as compared with class II patients (22). The higher level of fibrinogen and its synthesis rate were found in subjects with lower body mass index (23). In authors' opinion, these parameters change due to response to cytokine hyperproduction. Since acute-phase protein synthesis becomes more intensive in the liver due to the high level of cytokines, there is insufficiency of amino acids required for protein synthesis in striated muscle (23).

Table. Changes in hemostasis parameters in patients with chronic heart failure

Parameter	Change in parameter	Literature source
Plasma coagulation factors		
Fibrinogen	↑	2, 4, 7, 8
Fibrinopeptide A	↑	9
TAT	↑	4, 9
Thrombin	↑	9
Marker of fibrinolysis		
D-dimer	↑	4, 10
Markers of endothelial damage		
Thrombomodulin	↑	4, 11
E-selectin	↓	4
	without changes	12
	↑	11
VCAM (CD106)	↑	4, 9, 13
Endothelial growth factor	↑	2, 14
Markers of platelet activity		
β-thromboglobulin	↑	9, 15
Osteonectin	↑	9
vWF	↑	4, 7, 11
	without changes	12
ICAM	↑	4, 9, 13
PF4	↑	9, 14
P-selectin	↑	2, 9, 13, 14, 16, 17, 18
Thromboxane	↑	13
Platelet aggregation	↑	9,13

TAT, thrombin-antithrombin complex; VCAM, vascular cell adhesion molecules; vWF, von Willebrand factor; ICAM, intercellular adhesion molecules; PF4, platelet factor 4.

Scientific studies give much attention to the markers of fibrinolysis and endothelial damage. It was found that patients with CHF had significantly higher levels of thrombomodulin, t-PA, thrombin-antithrombin III complex (TAT-III), D-dimer (4, 9, 10, 13, 24), endothelial growth factor, but lower levels of E-selectin (2) than healthy patients.

Thromboembolism is the most frequent complication of CHF (25). Thus, the levels of β-thrombo-

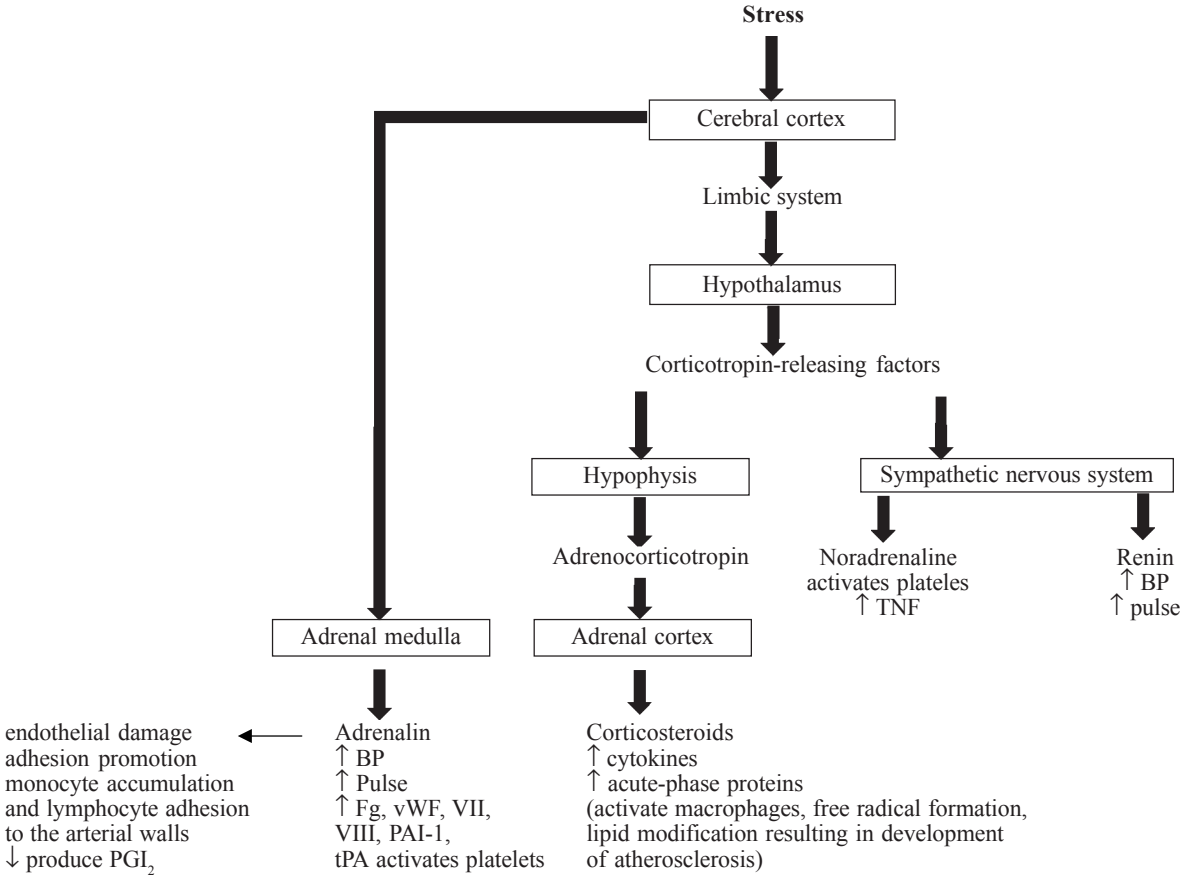

Fig. Effect of stress on changes in the activity of different compounds and cells, and other processes
TNF-α, tumor necrosis factor α; BP, blood pressure; Fg, fibrinogen; PGI_2, prostacyclin I_2;
tPA, tissue plasminogen activator; PAI-1, plasminogen activator inhibitor 1.

globulin (β-TG), fibrinopeptide A, circulating platelet aggregates, PF4, and cell adhesion molecules (P-selectin, platelet/adhesion molecules) were measured in patients with CHF.

β-TG is one of α-granule components of platelets. It is a very sensitive but insufficiently specific marker of platelet activity since the levels of plasma β-TG and PF4 increase in subjects with ischemic and idiopathic cardiomyopathy. Moreover, endothelium produces, accumulates, and secretes PF4. Heparin releases accumulated PF4 that causes elevated plasma PF4 concentration, though platelet activity is not increased. The levels of PF4 and thromboglobulin may increase if chronic kidney failure is present (26).

Osteonectin, which is present at the internal face of α-granules within platelets, along with α-granule content migrates outside of platelets after platelet activation. The levels of this compound are found to be significantly higher in subjects with CHF than healthy people (27).

The following markers that showed platelet activity were more frequently investigated: vWF, PF4, P-selectin, adhesion molecules ICAM, PECAM-1, VCAM, and platelet aggregation. The level of PECAM-1 was found almost twice higher in blood of subjects with CHF than healthy people (9). The levels of ICAM, VCAM, P-selectin, osteonectin, and PF4 were also significantly higher in the CHF group than healthy group (Table). Moreover, ADP-induced platelet aggregation (5 μmol) and thromboxane level were higher in those with CHF if compared with healthy individuals (13) suggesting the relationship among endothelium, leukocytes, and platelets via adhesion proteins due to inflammatory response. This contributes to the progression of CHF (9). In addition, it was found that platelets in healthy persons secrete sialic acid, which is one of the compounds maintaining platelets in an inactive state. Lower platelet sialic acid levels were reported in CHF patients, and it was concluded that this can be a contributing factor for the higher aggregability of the platelets (28).

vWF concentration in subjects with CHF is considered as the parameter that reflects both endothelial damage (10) and thrombogenicity (4).

It is known that CHF is associated with the impaired endothelium-dependent vasodilatation (shortage of nitric oxide, NO). An increased vWF level reflects endothelial dysfunction in patients with CHF. With an increase in vWF level, prothrombic state is developing because platelet adhesion to endothelium is activated. Due to sympathoadrenergic and catecholamine effect, activation of platelets occurs. When blood stream through the liver and kidneys reduces, clearance of platelet-activating substances decreases. This is one of the causes of thrombotic complications (9).

Patients with higher levels of platelets are found to have an increased risk of cardiovascular diseases. PAI-1 is directly proportional to platelet mass. Since PAI-1 is an inhibitor of fibrinolysis, the high platelet count may indirectly reflect the tendency for thromboresistance. Thrombopoietin regulates platelet mass and count. Its high levels are found during the first days after acute myocardial infarction. Thrombopoietin is activated by cytokines (particularly IL-6) triggering reactive thrombocytosis (29).

While analyzing the significance of inflammatory processes in CHF pathogenesis, significantly higher levels of cytokine TNF (4, 5) and IL-6 (4, 5, 10) are being found in subjects with the disease. These compounds are thought to be important in maintenance and progression of prothrombic state, since they promote inflammation and angiogenesis (IL-6 and vascular endothelial growth factor); they also enhance procoagulant properties of blood by activation of tissue factor (10).

Interestingly, some authors did not find any difference in hemostasis parameters, such as fibrinogen, plasminogen, PAI-1, t-PA, and vWF, comparing subjects with CHF and healthy individuals. According to their results, neither the activity of coagulation system nor inflammation affects HF pathogenesis (30).

An intercorrelation between the parameters reflecting coagulation, fibrinolysis, platelet, and endothelial function was also analyzed. Coagulation and fibrinolysis markers correlated with the markers of endothelial damage: vWF concentration showed a moderately strong correlation with fibrinogen, TAT, t-PA, IL-6 concentrations and E-selectin concentration correlated with D-dimer concentration (4, 7). The concentration of the markers of endothelial damage correlated with concentration of cytokine and adhesion molecules: vWF correlated with IL-6 and ICAM, and thrombomodulin with ICAM. Tumor necrosis factor receptor 2 (TNFR-2) correlated with IL-6, ICAM, VCAM, and ICAM – with IL-6. Fibrinogen concentration correlated with t-PA antigen and vWF, IL-6 (4). An elevated P-selectin level in subjects with CHF correlated with the other markers of platelet function and increased platelet aggregation. P-selectin and β-thromboglobulin concentrations demonstrated a moderately strong significant correlation with platelet count (15). Additionally, P-selectin concentration significantly correlated with thioredoxin concentration and did not correlate with TNF and IL-6 concentrations (31).

A moderately strong or strong significant relationship between cytokines (IL-6) and fibrinogen and C-reactive protein (CRP) involved in inflammatory process was found (7, 23). Some authors searched for hemostasis parameters that correlated with left ventricular ejection fraction (LVEF). The latter was not found to be correlated either with vWF or E-selectin concentrations. E-selectin concentration showed a weak correlation with systolic and diastolic blood pressure (12). Correlation between the other markers of hemostasis and LVEF has not been searched yet.

The progression of CHF is linked to the changes in heart muscle, since an increased expression of metalloproteinase 2 and 9, tissue inhibitors of metalloproteinases 1 and 2 was found. In addition, subjects with CHF were found to have elevated levels of plasma prometalloproteinase 9, active metalloproteinase 9, prometalloproteinase 2, and tissue inhibitor of metalloproteinase 1 (32). Plasma concentration of metalloproteinase did not depend on CHF functional class according to the NYHA (New York Heart Association). Metalloproteinase 2 concentration correlates with the volume of the left ventricle. Metalloproteinase 9 concentration correlates with lactate dehydrogenase, fibrinogen concentration, and aspartate aminotransferase (33). Since it was proven that the concentration of metalloproteinase 9 is associated with changes in the heart muscle and concentration of this enzyme correlates with fibrinogen level, it suggests that fibrinogen level reflects the changes in the heart muscle indirectly.

Expression of the immune modulator CD154 on platelets statistically significantly correlated with NYHA functional class (17).

The relationship between coagulation parameters and CHF etiology, severity, and gender was also searched. The levels of vWF, thrombomodulin, t-PA, E-selectin did not depend on CHF etiology (4, 10), and fibrinogen and TNF-α concentrations showed a significant correlation with NYHA functional class (8).

The relationship between CHF etiology or severity and platelet activity was not detected. NYHA functional class also did not have any influence on the markers of platelet activity. It was found that in the presence of active platelets, the levels of platelet/leukocyte adhesion molecules were increased (13).

Authors point out that the level of P-selectin increases in case of decompensated CHF, and β-TG – both in ischemic and nonischemic CHF (13). There were no differences in the levels of thrombomodulin, t-PA, and E-selectin comparing subjects with ischemic or idiopathic CHF, while in patients with decompensated CHF, an increase in IL-6 level was documented (5). It suggests that in the presence of high degree of CHF severity, not only impairments of other systems occur but also the coagulation system is affected and inflammatory processes develop; meanwhile, these changes did not depend on the cause of CHF.

Concluding remarks

Despite etiology and severity of chronic heart failure, according to the data from most authors, impairments of the coagulation system and endothelial function occur in patients with chronic heart failure. The levels of the parameters of plasma coagulation (fibrinogen, fibrinopeptide A, thrombin-antithrombin complex, thrombin), endothelial damage (thrombomodulin, vascular cell adhesion molecules, endothelial growth factor), platelet activity (β-thromboglobulin, intercellular adhesion molecules, P-selectin, thromboxane) were significantly higher in patients with CHF than healthy individuals. However, different relationships are found by different authors. Moreover, levels of the parameter of endothelial damage, E-selectin, and parameter of platelet activity, von Willebrand factor, were also found to be not similar in diseased patients and healthy individuals. It was determined that the higher functional class of chronic heart failure, the greater levels of fibrinogen and tumor necrosis factor α concentrations were. No associations between other parameters of the coagulation system and functional class of chronic heart failure were found as well as between parameters of the coagulation system and etiology of chronic heart failure. Obviously, the influence of hemostasis parameters on the development of heart failure, their relationships with the markers of inflammation and endocrine system should be further investigated.

Krešėjimo sistemos pokyčiai sergant lėtiniu širdies nepakankamumu

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Raktažodžiai: lėtinis širdies nepakankamumas, krešėjimo sistema, fibrinogenas, trombocitai, endotelis.

Santrauka. Širdies nepakankamumui didžiausią įtaką turi širdies funkcijos sutrikimas, kartu būna sutrikusios neuroendokrininė, imuninė bei hemostazės sistemos. Todėl nustatyti etiologinius sindromą sukeliančius veiksnius gana sudėtinga. Vis ieškoma rodmenų, padėsiančių prognozuoti lėtinį širdies nepakankamumą, įvertinti jo eigą ir komplikacijų riziką. Šio straipsnio tikslas – apžvelgti naujausius mokslininkų darbus siekiant atrasti, kaip susiję krešėjimo sistemos rodmenų pokyčiai su lėtiniu širdies nepakankamumu.

Svarbi priežastis, lemianti daugelio ligų, tarp jų ir širdies nepakankamumą, yra stresas. Emocinio ir fizinio streso signalai per tam tikras struktūras sukelia hormonų noradrenalino, renino, angiotenzino II, aldosterono, vazopresino kiekio padidėjimą kraujyje. Įrodyta, kad tai sąlygoja sutrikimus krešėjimo sistemoje: padaugėja plazmos krešėjimo (fibrinogeno, VII, VIII faktorių, fibrinopeptido A, trombino antitrombino komplekso), fibrinolizės (D-dimerų), endotelio pažeidimo (interleukino-1, endotelino-1, kraujagyslių ląstelių adhezijos molekulių, endotelio augimo faktoriaus), trombocitų aktyvumo (Vilebrando faktoriaus, viduląstelinės adhezijos molekulių, 4-trombocitų faktoriaus, P-selektino, tromboksano, β-tromboglobulino, granulozifino) žymenų bei citokinų (tumoro nekrozės faktoriaus, interleukino-6), sumažėja E-selektino. Koks konkrečių krešėjimo sistemos rodmenų indėlis vystantis lėtiniam širdies nepakankamumui, kol kas nepakankamai ištirta. Tam išsiaiškinti reikalingi tolesni tyrinėjimai.

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