CHRONIC PANCREATITIS WITH ISCHEMIC HEART DISEASE — THE ROLE OF THE FIBRINOLYTIC SYSTEM AND ENDOTHELIAL DYSFUNCTION IN COMORBID COURSE

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Key words: chronic pancreatitis, coronary heart disease, fibrinolytic potential, endothelial dysfunction, comorbidity

The clinical course of chronic pancreatitis with Peculiarity of ischemic heart disease (IHD) in the presence of chronic cardiac insufficiency syndrome (ChCI) is the blood reology disturbances. Enchancement of the non-stable processes in the hemostasis system is the result of proteolytic aggression hypoxia, excessive activation of free-radical processes which are observed in patients with chronic pancreatitis, IHD in the presence of ChCI, as well as their comorbid course. Biological membranes of the blood uniform elements and endotheliocytes experience corresponding changes that determines activation of intravascular blood coagulation, accompanying with hemoreological disturbances and development of microcirculatory hypoxia [7, 8]. In spite of all this, hemocoagulating blood potential increaseas. Besides, circulation restriction in large vessels of the abdominal cavity, retroperitoneal area may be considered as a specific characteristic [5]. Changes arise mainly due to atherosclerotic damages of pancreatic vessels, deterioration of the blood reology, congestion in the vessels due to ChCI development. It should be noted, that vessels damages are connected with sclerotic, atrophyc or lipid processes in the gland and reduction of its outersecretory function [2, 13], carbohydrate metabolism derangements.

Hyperglycemia is proatherogenic factor promoting atherosclerosis progression owing to the mechanism of glucose effect on the structure of vessels' wall due to peroxide action. For all this basic membrane of the capillaries becomes thicker, territorial matrix volume increases as a result of increased production of fibronectin, collagen type IV and VI and a decrease of proteoglycans content [1, 3]. Consequence

of hyperglycemia effect is also intensification of gene expression of inducible NO-synthase (iNOS) in mesangial cells contributing to an increased production of nitrogen oxide, and later on to the development of endothelial dysfunction (ED) not only owing to endothelial NOS decrease, an increase of endothelin-1 indices, but activation of peroxidase enzymes and cyclooxygenase (COG) with the production of eicosanoids and free radicals [26]. It's impossible to exclude a close relation of endothelial dysfunction with sensitivity of cells to insulin, since endothelium of vessels, for all this, prevents normal insulin transition into interstitial space even at adequate response to hyperglycemia [22]. Soluble adhesion molecules are of regulatory significance, particularly — sVCAM-1 (soluble Vascular cellular adhesion molecules 1).

Oversecretion of cytokines results in activation of the systemic inflammatory reaction including local vascular level. Activation and/or endothelium injury have fundamental significance in the development of spectrum of pathological processes [6, 10]. It is obvious that estimation of the endothelial state may be of great significance for broadening of comprehension pathogenesis of many human diseases [12, 17], the more so, as endothelial dysfunction is one of the significant links between inflammation and increase of the risk origin of the vascular complications. Under the influence of proinflammatory mediators endotheliocytes from the state of rest pass to the activated one, lose antiadhesive properties, contribute to the formation of prothrombogenic surface of the vascular wall, produce adhesion molecules, interleukine-1 (IL-1), IL-6, that is, stipulate local inflammation progression. It has been determined that atherosclerosis, IHD, as a rule, are accompanied by the sings of chronic inflammatory reaction, which at the very early stages of lipid precipitation in the inner membrane of the arteries, is manifested by "adherence" of leukocytes to endothelium surface and their penetration into the vessel wall, that occurs with participation of vascular and intercellular adhesion molecules [19, 20, 21], influencing on ED development. In the process of myocardial regeneration in case of acute clinical course of myocardial infarction, VCAM-1 contribute to adhesion of mesenchymal stem cells in the place of vascular endothelial damage. They increase

their concentration at IHD, including ChCI, making favourable conditions for ED development, namely — hypoxia, derangements of metabolic function of the coronary endothelium, an increase and imbalance of the content of different biologically active substances (cytokines, leukotrienes and others). Besides, in case of chronic pancreatitis exacerbation, activation of immune inflammation, penetrance of the vascular wall increases at the action of anti-inflammatory mediators, excreting by neutrofiles and macrophages and forming a local swelling process. Activation of endothelial cells (in its turn) results in transendothelial migration of neutrofiles, monocytes and lymphocytes to parenchyma of the pancreas and excretion of mediators (for example, neutrofile elastase) by other cells, which may lead to larger injury than pancreatic enzymes. In spite of all this, there occurs activation of proteolysis, reduction of fibrinolysis, activation of coagulative processes, microcirculatory injuries due to microthrombosis, intensifying derangements of hemostasiologic (hemostatic) processes. Such processes may overburden the clinical course of chronic pancreatitis in combination with IHD at ChCI, since they may be the reason of thromboses in the myocardium and pancreas.

The aim of the research is the investigation of indices of fibrinolytic blood activity, state of endothelial functioning (endothelium dependent vasodilatation — EDVD), as well as the content of metabolites of nitrogen monoxide in the patients suffering from the combined pathology.

Materials and methods

52 patients were examined, among them there were 21 (group I) patients with chronic pancreatitis, 12 patients (group II) suffering from IHD at ChCI, 19 patients (group III) at comorbid course of chronic pancreatitis with IHD in case of ChCI and 10 apparently healthy persons (AHP). The age of the patients under study was equal to 49,7±1,2 years on average, prescription of the disease constituted from 7 to 11 years, 58,8% men and 41,2% women.

Diagnosis of chronic pancreatitis was made up according to the clinical protocol of MPH order of Ukraine from 13.06.2005, №271 “Clinical protocol of giving medical aid to the patients suffering from chronic pancreatitis”. IHD was

diagnosed according to the Order of MPH of Ukraine №436 from 03.07.2006 "On Confirmation of Protocols of Giving medical Aid in Speciality "Cardiology".

Criteria of inclusion for ChP were abdominal pain syndrome, intermittent dispepcic disorders; confirmation of the structural changes P (due to USD indices), as well as derangements of outersecretory function of P, signs of slight, moderate exacerbation of ChP, long-term smoking, alcohol abuse, presence of well-informed agreement of a patient for participation in the research. Criteria of inclusion into research of the patients with IHD, stable angina of tensity I-II FC, ChCI IIA-B, FC II-III (NYNA) were: ChCI II or III FC; absence of angina attack during 3 months; regular intake of inhibitors of angiotensin — converting enzyme or blockers of angiotensin II receptors, β-blocker, statins and antithrombocytic preparatious during 3 months; well-informed angreement of the patient.

There were the following criteria for exclusion: oncological diseases, cancer of the pancreas; persons who underwent acute pancreatitis, or exacerbation of chronic recurrent pancreatitis, surgical intervention during the last 4 weeks; angina of the tensity requiring nitrate intake; acute myocardial infarction underwent during the last 3 months; other severe concomitent diseases of the cardio-vascular system under condition of decompensation; chronic kidney disease, insulin dependent diabetes mellitus, dysfunction of the thyroid gland.

Endothelial functional state was evaluated as to the content in the blood plasma of stable metabolites of nitrogen monooxide — NO (nitrates, nitrits) according to the method of A. S. Green et al. (1982). Instrumental — functional methods of investigation (plan radiographs, electrocardiograms, investigation of echostructure of cardiac muscle, carotic artery, ultrasonic examination of organs of the abdominal cavity, dopplergraphy of the brachial artery (for the purpose of determination of endothelial dependent vasodilatation) were carried out. Fibrinolytic potential was evaluated by the total fibrinolytic activity (TFA), enzymatic fibrinolytic activity (EFA) of the blood plasma by meaus of reagents set of "Simko Ltd" firm, (Ukraine).

Mathematical prossessing of the results was carried out using variative — statistical analysis on IBM PC Pentium II by means of Statistica® 5.1 programmes

(Statsoft, Inc.). Average arithmatical (M), average quadrate deviation (q), error of average arithmetical (m), coefficients of the direct (r) and indirect (η) correlation. Difference profability was determined by t-criteria Student and F-criteria Fisher for parametric data.

Results of research and their discussion

Analysis of the compaints testified that mostly pain in the abdomen localized in the left hypochondrium in 7 patients (17,5%) and epigastrium in 14 patients (35.0%), rarely in both hypochondria-6 (15% of patients), and in the rest of patients — in pyloroduodenal area. Intensity of the pain syndrome in the majority of patients was moderate (intermittent pain of a moderate strength, revealed in 12 patients (57,1%) of the I-st group and in 6 patients (31,5% — group III) was accompanied by meteorism, that exhausted psychophysiological condition of the patients. More than two thirds of the patients pointed out the presence of pain "equivalents" in the form of abdominal discomfort, heavyness, bloating and distention into epigastrial region. Complaints of irradiation of pain into the left arm, neck are typical for comorbid course and were often connected by the patients with excessive (as to the volume) food taking, but not suffocation and other cardiological symptoms. To the specific characteristics of comorbid course of ChP with IHD we attributed the presence of coronary atherosclerosis in 87,5%, according to atherosclerotic changes of carotic arteries from local to diffuse with significant and insignificant hemodynamic disturbances. Combined disruptions of some vessels: aorta + abdominal trunk — 25,0%, aorta + upper mesenteric artery — 7,5%, abdominal trunk + upper mesenteric artery — 12,5%, aorta + abdominal trunk + upper mesenteric artery — 17,5% (USD of the abdominal cavity vessels) were observed in the most of cases of group III patients.

Due to hemostasiologic (hemostatic) processes damaging in case of chronic inflammation of small intensity (that is one of the main links for progression of chronic pancreatitis, IND and ChCI), for the object of comparison and determination of peculiarities of their reaction at comorbidity of the given diseases, the state of fibrinolytic potential was investigated in all patients under study. Decrease of the TFA index 14,6% in group I and 27% in group II mostly due to decrease of

enzymatic fibrinolytic activity 34,4% and 54,0% correspondingly (table 1) was revealed in the groups under study. Detected changes were accompanied by nonenzymatic fibrinolytic activity increase in patients with ChP 8,8%, in persons with IHD at chronic CI — 10,3%, and at comorbid damage of the pancreas with IHD according to chronic cardiac insufficiency — 19,1% ($p<0.05$) in comparison with the group of apparently healthy persons.

Table 1

Indices of Fibrinolytic Activity of the Blood Plasma in Patients with ChP and Comorbid Course at IHD due to ChCI (M±m)

Indices	Apparently Healthy Person n=10	ChP n=21	IHD+ChCI n=12	ChP+IHD+ChCI n=19
Total fibrinolytic activity, mcg azofibrin/ml for 1 hour	1,88±0,05	1,64±0,03*	1,44±0,27*	1,35±0,12*/**
Non-enzymatic fibrinolytic activity, mcg azofibrin/ml for 1 hour	0,68±0,02	0,74±0,01*	0,75±0,19	0,81±0,12*/**
Enzymatic fibrinolytic activity, mcg azofibrin/ml for 1 hour	1,21±0,03	0,90±0,02*	0,71±0,12*	0,62±0,011*/**

Note: ** — probable difference in comparison with index in apparently healthy persons (P<0,05); ** — probable difference in comparison with index in patients with ChP (P<0,05).

Thus, in ChP patients with IHD at chronic cardiac insufficiency TFA may be reduced at the expense of EFA inhibition, and derangement of the structure of total fibrinolysis may be connected with NFA increase (owing to hypoxia and acidosis).

Moderate TFA decrease, significant EFA reduction may contribute to formation of microscopic thrombocytic and fibrin clots in the system of the tissue hemocirculation, resulting in the development of intravascular blood microclot, that at the extent of pathological process progression in pancreas disturbs the local circulation with the following increase of the pancreas tissue hypoxia, penetration of the cellular membranes, destruction of acinar cells and release of pancreatic enzymes to systemic circulation, closing “defective” circuit, with subsequent fibrotization (fibrosis) of the gland parenchema and the development of outer — and intrasecretory insufficiency. Besides, TFA decrease, according to certain authors

[14], contributes to degradation of the cellular matrix, disturbance of the growth and cell division; tissue regeneration, development of sclerosis and fibrosis of the pancreas, myocardium, that aggravates the course of both diseases.

It is possible that EFA decrease in ChP patients with IHD at ChCI, connected with phospholipase A2 activation, the level of which increases both at exacerbation and during the period of ChP unstable remission, promotes concentration of thrombocsan A2 and leukotrien B4. They are the inducers of activation of thrombocytes, vasoconstrictors, which inhance tissue ischemia and inhibit EFA owing to discrease of plasminogen quantity, stipulating reduction of endothelial cells, exposure of their basal membrane, where adhesion of thrombocytes occurs, increasing vascular penetration [4], that contributes to endothelial dysfunction progression. So, it is necessary to take into consideration this mechanism, admitting medical rehabilitation means.

Determination of endothelial vasodilatation test is the earliest, unspecific test, indicative of the formation of pathologic processes on the level of cells, as the earliest hypoxia compensation and disorders of metabolism processes on the level of paracrine coexistence both the endothelial cells and cells of the loose connective tissue.

Dilatation increas of the brachial artery more than 10% was considered as normal endothelial dependent vasodilatation.

It has been detected that in patients under study the diameter of the brachial artery is probably wider in comparison with control ($P<0,05$) (table 2).

Reduction of initial blood circulation that may be connected with the development of hyperviscosity syndrome in this category of patients was observed in patients with IHD and patients suffering from chronic pancreatitis with concomitent IHD at chronic CI.

Table 2

Indices of Endothelium Functioning in Patients Suffering from ChP with IHD at ChCI (M±m)

Indices	Groups of observation			
	Apparently healthy persons n=7	**ChP n=11**	**IHD+ChCI n=9**	**ChP+IHD+ChCI n=10**
D0, см	0,35±0,004	0,39±0,008*	0,37±0,01 *	0,46±0,008*
V0, см/с	88,82±2,89	71,01±3,13*	73,65±5,81 *	70,49±2,88*
τ_0, дін/см^2	50,03±1,56	36,57±1,88	39,81±2,43	30,48±1,25*
D1, см	0,41±0,002	0,44±0,008*	0,44±0,008*	0,49±0,007*
V1, см/с	134,46±5,06	104,16±5,02	104,98±6,79	98,94±3,18
τ_1, дін/см^2	65,50±2,42	47,98±2,77	50,73±2,58	40,17±1,28*
Δd, см	0,055±0,003	0,046±0,004	0,044±0,006	0,034±0,005
Δτ, дін/см^2	15,47±0,98	11,41±1,29	10,92±1,67	9,68±0,45*
Приріст d,%	16,68±0,81	11,33±0,73*	9,76±0,87*	6,49±1,25*/**
Приріст V,%	51,28±2,51	46,8±4,45	29,2±1,17*	33,79±1,9*/**
K, ум. од.	0,51±0,029	0,41±0,048	0,39±0,018	0,24±0,037*

Note: τ_0 — initial level of shift intensity; τ_1 — shift intensity in response to reactive hyperemia, Δτ — change of intensity in response to reactive hyperemia; ΔD — change of brachial artery diameter in response to reactive hyperemia; K — sensitivity of the brachial artery to shift intensity; * — distinction of identical index ($p<0,001$) in respect to control group.

Thus, endothelial dependent vasodilatation in group I was lower by 1,47 times, in group II — by 1,71 times and in group III — by 2,57 times, in comparison with AHP group ($p<0,05$) with the presence of difference ($p< 0,05$) between groups.

Coefficient K, namely the artery sensitivity to the tensity shift in our patients reduced 24,3%, 30,8% and 112,5% as compared with AHP, with probable difference in group III, that testifies to sensitivity decrease of the brachial artery to the tensity shift and deterioration of regulation of the artery tone in the patients with combined diseases. Index K, amounting to 0, that is the evidence of complete regulation loss of the brachial artery diameter was obtained in 15% of persons of group III.

Derangements of the shift reaction in case of reduction of blood velocity in the arteries are the valid factors initiating synthesis by endothelium of proinflammatory cytokines [11].

In some patients the blood velocity increase in the brachial artery following its temporary occlusion resulted in paradoxic vasoconstrictory reaction instead of the

expected normal vasodilatation, which may be explained by significant disorders of endothelial vasoregulating function.

It shouldn't reject the fact, that vascular oxidative stress is the key mechanism in the decrease of endothelial dependent vasodilatation [6].

Inadequate vasodilatation in case of test with reactive hyperemia, disturbance of endothelial dependent vasodilatation should be considered as the metabolism disorders of endothelial relaxing factor [15], that has been confirmed by our research of the content of metabolites NO in patients with combined pathology (table 3).

It has been determined that the content of metabolites NO in patients of group I decreased by 1,2 times, group II — by 1,4 times ($p<0,05$), and in the patients of group III there was the decrease of the same index by 1,8 times ($p<0,05$) in comparison with AHP (table 3).

Table 3

Content of Metabolites of Nitrogen Monooxide (NO_2/NO_3) (mcmol/l) in the Blood of the Patients Under Study (M±m)

Indices	Apparently healthy persons n=7	ChP n=11	IHD+ChCI n=9	ChP+IHD+ ChCI n=10
NO_2/NO_3, mcmol/l	21,36±1,16	18,27±1,18	15,14±0,74*	11,68±0,62*/**/***

Note: * — distinction of identical index ($p<0,001$) in ratio with index in the group of apparently healthy persons; ** — difference is probable in comparison with index in patients suffering from ChP ($p<0,05$); *** — difference is probable in comparison with index in patients suffering from IHD at ChCI.

Analyzing the data obtained, it is possible to confirm, that indices of metabolic products of nitrogen monooxide decrease but to the less extent than in case of the combined curse with ischemic disease at ChCI in the patients with chronic pancreatitis, testifying to exhaustion of this mechanism of endothelial function regulation. Correlative dependence between indices of nitrogen monooxide at TFA has been studied by us in the patients of group III. It has certified a direct connection (correlation coefficient — 0,54) between indices decrease of nitrogen oxide and fibrinolysis disorders, that activates chronic DIS syndrome. Thus, the obtained data give reasons to confirm that due to the presence of fibrinolytic potential disorders

proteolysis activation occurs, promoting microthromboses, and together with decrease of endothelial function of the vessels and the prevalence of vasoconstrictive mechanisms this situation results in the development of cardiovascular events according to comorbidity data of the diseases.

So, according to the data obtained it is possible to consider that patients suffering from chronic pancreatitis with IHD at ChCI have more intensive manifestations of ED owing to increase of LPO products [9, 16], synthesis ET-1 increase [18], synthesis NO decrease, derangements of endothelium dependent vasodilatation, that may cause the development of fibrose changes in pancreas [24, 25] and myocardium with further remodeling [23]. Moderate TFA decrease, significant EFA decrease, NEA increase is the risk development of chronic DIS-syndrome since it contributes to the formation of microscopic thrombocytic and fibrin clots in hemomicrocirculation system, that may give right to make conclusion as to aggravating course of these diseases, and requires a careful observation and administration of adequate medicinal treatment. The more so, as with the progression of chronic pancreatitis against a background of atherosclerosis such process disturbs the local blood stream with a subsequent increase of sclerozing and fibrosis (fibrotization) and development of outer- and intrasecretory pancreatic insufficiency.

Conclusions

1. Thus, disorders of overall fibrinolysis at the expense of inhibition of enzymatic and increase of non-enzymatic constituent are observed in the patients suffering from ChP with IHD.
2. Pronounced dysfunctions of endothelial state in the form of the absence increase of the brachial artery diameter and paradoxic vasoconstriction in the response to reactive hyperemia mostly occur in the persons due to combination of diseases that may be considered as a bad prognostic sing of the clinical course of the disease.

Perspective of further investigation is a quest of medicinal correction of the revealed signs of endothelial dysfunction with the object of raising efficacy of holiatry of the patients with a combined pancreatocardial pathology.

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Chronic pancreatitis with ischemic heart disease — the role of the fibrinolytic system and endothelial dysfunction in comorbid course

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Article presents the original data indicating changes of fibrinolytic potential and endothelial function in patients with comorbid course of chronic pancreatitis and coronary heart disease. The results indicate that due to the increased proteolytic potential (due to the reduction of fibrinolysis) and vasoconstriction (due to the endothelial dysfunction) chronic DIC-syndrome is activated. It is possible to assume that these processes (mechanisms) are aggravating as they contribute to the risk of cardiovascular events and ischemic pancreatitis.