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New methods in laboratory diagnostics of dilated cardiomyopathy

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Abstract

Dilated cardiomyopathy (DCM) is a multifactorial heart disease in which there is enlargement and systolic dysfunction of one or both ventricles. The exhaustion of compensatory mechanisms leads to symptoms of congestive heart failure, which is a significant problem in contemporary cardiology. DCM is still diagnosed using clinical assessment; echocardiography is necessary, and in some clinical situations we need hemodynamic assessment in order to identify the etiology and progression of heart disease. These tests are necessary for choice of treatment and qualification for heart transplant. Investigators are looking for new, valuable, additional parameters which could be of use in screening and heart disease progression assessment, and which may be helpful in the management and risk stratification of patients with DCM. These monitoring and prognostic tools in patients with chronic heart failure can be biomarkers, such as natriuretic peptides: BNP and NT-proBNP, cardiac troponins or inflammatory cytokines and their receptors. Moreover, there are ongoing research projects concerning persistently elevated uric acid, Ca-125 and osteopontin concentrations for the identification of patients with DCM, as well as adverse prognoses. (Cardiol J 2008; 15: 388–395)

Key words: dilated cardiomyopathy, natriuretic peptides, cardiac troponins, inflammatory cytokines

Dilated cardiomyopathy

Dilated cardiomyopathy (DCM) is a heart muscle disease in which one or both heart ventricles become enlarged and their pumping function is decreased.

The most frequent causes of dilating heart ventricles include coronary thrombosis, particularly after a heart attack, a dilated form of hypertensive cardiomyopathy, infectious factors, inflammatory immunology diseases, storage diseases, and, finally, a hereditary or idiomatic form of DCM. Dilated heart ventricles may also be a consequence of acquired cardiac valve defects, especially when they have not been corrected by surgery or when the surgery has not improved the function of the heart muscle as expected [1]. Table 1 shows the collated etiopathogenesis of dilated cardiomyopathy [2].

Table 1. Etiopathogenesis of dilated cardiomyopathy [2].

Genetic — family cardiomyopathy
Idiopathic
Specific — ischemic:
— hypertensive
— inflammatory
— autoimmunology
— puerperal
— alcoholic
— metabolic (diabetic, in beriberi disease, in obesity, in malabsorption syndrome)
— tachyarrhythmic
— catecholamine (in pheochromocytoma and hyperthyroidism)
— postradiation
— iatrogenic (drug-induced)

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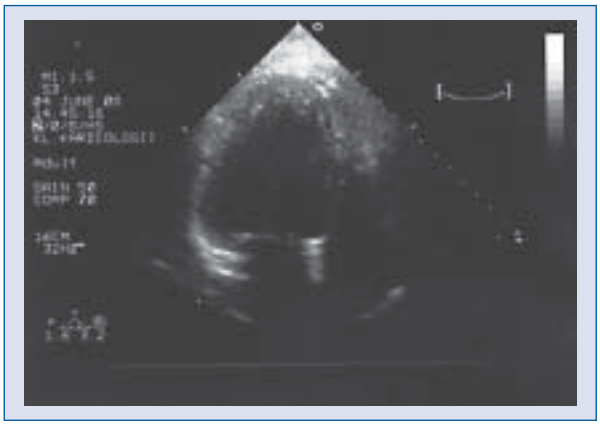

Figure 1. Apical four-chamber projection in patient showing dilated cardiomyopathy and incorrect shape of the left ventricle.

Hereditary DCM constitutes 30–50% of DCM cases; it often co-exists with bradycardia, the slowing of atrial-ventricular and intraventricular transmission, dystrophy of skeletal muscles, myopathy, deafness and mental disability. Most frequently, it is inherited as an autosomal dominant. This form of the disease includes the following mutations of protein-coding genes [3]:

— cytoskeleton: desmin, tapasin, beta-sarcoglycan, 8-sarcoglycan, dystrophin, metavinculin;
— intercellular connections: vinculin;
— nucleus: laminin, emerin;
— sarcomer: troponin T, heavy chain in beta-myosin, actin, telotonin;
— ionic channels: phospholamban (calcium pump), a subunit of the heart potassium channel sensitive to triphosphate;
— mitochondrion DNA.

The exhaustion of compensation mechanisms results in the occurrence of congestive heart failure symptoms, which is a significant problem in modern cardiology. According to the estimates of the European Society of Cardiology, this pathology may occur in 0.4–2% of the European population [4]. The annual death rate in the group of people suffering from heart failure, independent of etiology, amounts to an average of 10%, but depending on hemodynamic condition it amounts to 12% of patients in the 2nd class according to NYHA and even 56% of those in the 4th class according to NYHA [5, 6].

Early diagnosis of DCM is of great prognostic importance because an effective treatment started at the beginning of the disease may stop its progress and delay the development of symptomatic heart failure. The basis of diagnosing DCM, especially in its latent phase, is a thorough clinical assessment. Echocardiography is essential and, in some clinical cases, a hemodynamic assessment may also be essential to determine the etiology as well as to evaluate how advanced the heart failure is, and this information is then used in the therapy and for qualifying patients to heart transplant [7]. Valuable additional biochemical parameters are currently being searched for, which, together with clinical and echocardiographic assessment, will bring new useful information at various phases of the disease.

Table 2. Anatomical changes occurring in dilated cardiomyopathy

Dilation of the left ventricle
Changes in the shape of the left ventricle (from ellipsoidal to spherical)
Changes in spatial configuration of the mitral valve subvalvular apparatus
Enlargement of the left atrium, the right ventricle and the right atrium

The role of echocardiography in dilated cardiomyopathy

Echocardiography of a patient with DCM includes anatomical and functional assessment with the use of all available techniques. In most cases, the left ventricle is spherical in shape and global hypokinesis of its walls can be observed (Fig. 1) Anatomical changes occurring in DCM are presented in Table 2.

Global function of the left ventricle depends on the joint assessment of left ventricular filling volume (diastolic function) as well as on left ventricular ejection fraction (systolic function).

Echocardiographic and Doppler indicators of an unfavourable prognosis in DCM are presented in Table 3 [8].

Natriuretic peptides: BNP and NT-proBNP in diagnosing dilated cardiomyopathy

Early diagnosis of DCM in its initial phase enables the start of effective treatment with the purpose of stopping the progress of the disease and delaying the development of symptomatic heart failure. Regarding this fact, scientists are searching for routine and widely accessible diagnostic methods which could be used in assessing the state of advancement of the disease and in controlling the results of treatment and the prognosis. Such a role

Table 3. Echocardiographic and Doppler indicators of an unfavourable prognosis in dilated cardiomyopathy [8]

Size and function of the left ventricle:
— left ventricular internal diameter in systole > 55 mm and in diastole > 64 mm
— left ventricular end-diastolic volume > 5 mL/m^2
— left ventricular end-systolic volume > 55 mL/m^2
— left ventricular ejection fraction < 40%
— sphericity index < 1.5
— the maximal first derivative of left ventricular pressure — dP/dt < 600 mm Hg/s
— TEI index (myocardial performance index) > 0.4
Diastolic function of the left ventricle:
— restrictive mitral inflow pattern
— pseudonormalization of mitral inflow

may be played by natriuretic peptides, especially brain natriuretic peptide (BNP) and N-terminal prohormone brain natriuretic peptide (NT-proBNP). Concentrations of BNP and NT-proBNP in blood serum are similar in healthy people, but in people with heart failure the concentration of NT-proBNP is 2–10 times higher than that of BNP. BNP is secreted into blood as a biologically active and shorter peptide, and NT-proBNP is secreted as a biologically inactive NH2 — the final part. They are secreted in equal amounts but BNP has a shorter half-life in blood serum and, as a consequence, its concentration is lower. A factor stimulating the secretion of BNP is the stretching of myocytes rather than the pressure load itself [9, 10]. BNP causes a dose dependent decrease of arterial pressure resulting in direct vasodilatation and movement of intravascular volume into extravascular space (which is a result of vascular endothelium increased permeability and of increased hydrostatic pressure in the capillary bed). Other mechanisms decreasing initial load are diuresis and natriuresis, which also inhibit the activity of the renin–angiotensin–aldosterone system. Natriuretic peptides inhibit adrenergic stimulation through central suppression of sympathetic discharge and through suppressing secretion of catecholamines from nerve endings in a synapses. Through enlargement of afferent arterioles and contraction of efferent arterioles, they increase intraglomerular pressure and glomerular filtration; relaxation of mesangial cells increases the filtering surface. Moreover, natriuretic peptides inhibit the transport of sodium and water in proximal tubules dependent on angiotensin II and, being antagonists of vasopressin, they inhibit the transport of water in collecting tubules and block reabsorption of sodium [11].

BNP as a screening test in the diagnosis of left heart ventricle dysfunction

Testing the concentration of BNP in blood serum enables the identification of the disease in its early phase, which allows the commencement of effective treatment and slows the changes in heart construction [12]. An example of research that confirms that BNP assessment may be useful as a screening test in the general population is the study by Nakamura et al. [13]. The authors confirmed that BNP assessment is a useful test which efficiently identifies patients with heart failure of origins connected with heart function disorder documented by clinical, electrocardiographic, radiological and echocardiographic assessment, regardless of etiology and degree of left ventricular dysfunction. In this test, even a threshold value of BNP concentration of 50 ng/L (14.4 pmol/L) managed to differentiate unhealthy subjects from healthy ones (with an area below AUC curve for ROC curve 0.97, sensitivity 87.7% and specifity 95.7%). Apart from echocardiography, determining the concentration of NT-proBNP is of great importance, giving significant possibilities for its use in differentiating diagnostics of dyspnoea. In the research carried out by Januzzi et al. [14], it was determined that a concentration of NT-proBNP < 300 pg/mL virtually excludes structural heart disease which threatens life. In the research by Miller et al. [15], levels of BNP in patients with ischemic DCM and those in patients with DCM of other than ischemic origin were compared. Concentrations of BNP were statistically significantly higher in patients with ischemic cardiomyopathy and amounted to 776 ± 91 pg/mL compared to 532 ± ± 85 pg/mL in patients with cardiomyopathy of non-ischemic origin ($p < 0.05$). The death rate of cardiovascular causes in 10 ± 1 months of observation amounted to 48% in patients with heart failure of ischemic origin and 23% in patients with primary cardiomyopathy ($p < 0.05$). As can be seen, BNP levels and death rates were significantly higher in patients with cardiomyopathy of ischemic origin. In research carried out by Ishikawa et al. [16], it was determined that in patients with primary DCM the survival rate studied within 42 months was significantly higher in patients with high-sensitivity C-reactive protein (hsCRP) level < 1 mg/L and BNP level < 110 pg/mL. The relative risk of the occurrence of cardiac death in patients with hsCRP level

Table 4. Diagnostic age-dependent values of brain natriuretic peptide (BNP) and N-terminal prohormone brain natriuretic peptide (NT-proBNP) levels in patients with dyspnea.

Heart failure	Natriuretic peptide	In general age < 75 [pg/mL]	Age ranges [pg/mL]	
			< 50	50–75
Diagnostic value	BNP	> 100	> 500	> 900
	NT-proBNP	> 300	> 450	> 900
Negative predictive value	BNP	< 70		
	NT-proBNP	< 125		

> 1 mg/L and BNP level > 110 pg/mL amounted to 15.8 (95% confidence interval 1.9–127.2) compared to the group with BNP < 110 pg/mL and hsCRP < 1 mg/L.

BNP is also assessed by heart ventricle filling index. Pathophysiological premises suggest that this non-invasive substitute marker is useful to assess the pressure of filling the left ventricle. The results of early research are not explicit. Part of the research confirms the importance of the correlation between BNP and hemodynamic parameters, as well as of the decrease in BNP value proportional to the decrease of pulmonary capillary wedge pressure as a response to treatment [17, 18]. However, results obtained by other researchers question the usefulness of BNP assessment as a non-invasive equivalent of pulmonary capillary wedge pressure in the assessment of heart failure in various clinical situations [19, 20]. At present, for the purposes of clinical diagnosis, the following exclusive values are proposed in patients over the age of 75: BNP < < 70 pg/mL; NT-proBNP < 125 pg/mL. In addition, in the case of acute dyspnoea, values of BNP < 100 pg/mL or NT-proBNP < 300 pg/mL weigh against diagnosing a cardiological cause. According to Moe [21], in patients over the age of 50, the proposed values confirming the diagnosis of heart failure, with high probability, amount to the following: BNP > 500 pg/mL and NT-proBNP > 450 pg/mL; in patients in the age range 50–75, the confirming values are the same both for BNP and NT-proBNP and exceed 900 pg/mL. Values useful in clinic diagnostics are compared in Table 4.

Reports from June 2007 from the European Congress of Heart Failure in Hamburg confirm the role of NT-proBNP as a more useful marker of the clinical course of heart failure than BNP. Furthermore, increased concentration of NT-proBNP seems to be an unfavourable prognostic factor because intensifying pharmacological treatment in patients with increased concentration of NT-proBNP did not improve the prognosis further. In the assessment of heart failure, it is difficult to base decisions only on values of natriuretic peptides because of the variety of factors which can influence their concentration in blood serum, such as demographic differences in studied populations and the treatment used, which at the given moment influences hemodynamic conditions, including the pressure of heart ventricle filling. The treatment used influences the concentration of natriuretic peptides to various degrees; pharmaceutics used in heart failure decrease their concentration by as much as 60% [22]. A significant element decreasing the credibility (especially the diagnostic credibility) of natriuretic peptides is the fact that many factors exist which influence their concentration in blood serum. Factors independent of the degree of heart defect include age (levels increase in direct proportion to age), sex (levels are higher in women), glomerular filtration (levels increase in kidney dysfunction) and obesity (levels decrease in direct proportion to body mass index; they reach lower values in obese patients and higher values in slimmer patients, not only in cachectic patients) [23–26]. Ischemia as a result of local hypoxia, changes in local pH, activation of local paracrine substances, occurrence of arrhythmia, pulmonary artery thrombosis and other factors resulting in right ventricle dysfunction increase the concentration of natriuretic peptides [27–29].

Lately, there have also been reports about changes in the concentration of natriuretic peptides in patients with stable heart failure; the differences between consecutive tests of the same patient may even amount to 40–60% in the case of tests for BNP and 33% in the case of those for NT-proBNP [30].

The usefulness of assessing the concentration of BNP or NT-proBNP during the choice of pharmacotherapy intensity is the subject matter of the following multicentre clinical research projects which is being carried out at present: BATTLE--SCARRED (BNP-Assisted Treatment to Lessen Serial Cardiac Readmissions and Death), RABBIT

Table 5. The causes of increase in serum troponin concentration.

Myocardial infarction
Pulmonary embolism and right ventricle overload
Pericarditis
Myocarditis
Acute and serious chronic congestive heart failure
Septicemia and shock
Cardiotoxic drugs like adriamycin, doxorubicin, 5-fluorouracyl
Heart injury
Chronic renal failure
Hypothyroidism

(Rapid Assessment utilizing Bedside BNP In Treatment trial) and IMPROVE-CHF (Improved Management of Patients with Congestive Heart Failure in Canada using NT-proBNP study). They are aimed at assessing the concentration of BNP as an indicator of treatment effects in heart failure.

The role of cardiac troponins in diagnostics of dilated cardiomyopathy

At present, research is being carried out to assess the role of cardiac troponin (cTn) concentration in blood serum for diagnostics and risk assessment in patients with DCM. The cardiac troponins are part of the troponin/tropomyosin complex in thin filaments of heart muscle myofibrils. This complex consists of troponin C (TnC), troponin I (TnI), troponin T (TnT) and tropomyosin. Troponins do not occur outside cells; therefore, their occurrence in blood is a sensitive and peculiar indicator of heart muscle cell defects.

During the necrosis of cardiomyocytes and proteolytic degradation of contractile proteins, liberation of the following substances occurs: free cTnT, cTnT-cTnI-TnC (TIC) complex, fragments of cTnT, cTnI-TnC (1C) complex and free cTnI. The total concentration of cTnI amounts to 5–12 times more than the concentration of free cTnI. The liberated TIC complex quickly disintegrates to cTnT and IC complex. Therefore, free cTnT, IC complex and a certain amount of free cTnI occur in blood [31]. Table 5 presents the causes of increased concentrations of cTn in blood serum.

Nellessen et al. [32] assessed the usefulness of tests for TnI as prognostic indicators in patients with chronic heart failure. The mean concentration of cTnI in blood serum of patients with congestive heart failure amounted to 0.66 ± 1.8 ng/mL compared to 0.11 ± 0.48 ng/mL in healthy volunteers ($p < 0.001$). No significant differences were observed between patients with primary dilated cardiomyopathy and those with cardiomyopathy of ischemic origin. It was also observed that liberation of TnI was significantly higher in patients who died afterwards (0.84 ng/mL *vs*. 0.56 ng/mL, $p < 0.05$). The results confirm that the loss of cardiomyocytes in progressing heart failure is connected with the liberation of TnI, which can be an indicator of an unfavourable prognosis. Miller et al. [33] determined that an increase of TnT concentration and BNP concentration in patients with chronic heart failure above the determined constant level is connected with an increased risk of negative events, such as death, heart transplant or hospitalization. The group at highest risk include patients in which an increase of TnT as well as BNP was observed. The authors emphasized how important it is to monitor those indicators during risk assessment in patients with heart failure. Research carried out by Sato et al. [34] confirmed that persistent increased values of TnT in patients with dilated cardiomyopathy indicate that degeneration of myocytes is in progress, which is connected with the deterioration of the patients' clinical condition.

Pro-inflammatory cytokines in dilated cardiomyopathy

During the last few years, more and more evidence has emerged that cellular as well as humoral autoimmune processes are involved in the pathogenesis of DCM. Many patients display persistent or chronic heart muscle inflammation described as inflammatory cardiomyopathy according to World Health Organization classification. The breaking down of control mechanisms protecting against autoimmune reactions leads to the creation of antibodies reacting directly with the tissue, and of T cells which are harmful in the two following ways: indirectly through cytotoxic cytokines, and directly as cytotoxic cells [35]. An increased concentration of inflammatory markers was observed not only in inflammatory cardiomyopathy but also in heart muscle damage of another etiology. In the research carried out by Mandi et al. [36], it was determined that 85% of patients with DCM and ischemic cardiomyopathy had increased levels of tumour necrosis factor alfa (TNF-α) and of interleukin-6 (IL-6) in blood serum, while patients with hypertrophic cardiomyopathy had increased levels of IL-6 only. The mechanisms responsible for the development

of DCM are still unknown. The high production of pro-inflammatory cytokines in leukocytes of patients with DCM and the presence of TNF-α and IL-6 in their heart tissue suggest the presence of a strong immunology component in the pathogenesis of this disease. Interest in the role of pro-inflammatory cytokines in heart failure comes from the observation that many symptoms of this disease may be explained by the biological effects of these molecules. If the expression of cytokines is high enough, they can imitate certain properties of heart failure phenotype, including progressing left ventricular function defect, pulmonary oedema, restructuring of the left ventricle, expression of foetal genes and cardiomyopathy. Cytokine hypothesis proves that their excessive expression participates in the progress of heart failure as a consequence of left ventricular function defect. The accumulation of cytokines, just like the accumulation of neurohormones, may constitute a biological mechanism responsible for the progress of heart disease in patients with heart failure [6]. TNF-α also has a potential cardiotoxic effect, mainly by influencing the development of left ventricular dysfunction, including pulmonary oedema and cardiomyopathy, as a result of restructuring the left heart ventricle (proved in experimental conditions), metabolic disorders of heart muscle, uncoupling of receptor P and adenyl cyclase, disorders of mitochondrion energetic processes and activation of foetal genes programme, as well as a decrease of blood flow in lower limbs [37, 38]. Tentolouris et al. [39] assessed a relationship between concentrations of IL-6, TNF-α and functions of vascular endothelium in patients with ischemic heart failure, DCM, and correct function of the left heart ventricle as well as in a control group. The ability to dilate blood vessels in response to congestion (RH% reactive hiperemia) or nitrates was recognized as an indicator of blood vessel dilation ability dependent on, or independent of, vascular endothelium. Blood flow in the forearm was measured with plethysmography. Concentrations of IL-6 and TNF-α were statistically higher in patients with ischemic cardiomyopathy than in patients with cardiac ischemia without left ventricular dysfunction ($p < 0.05$), and higher than in subjects from the control group ($p < 0.05$). Concentration of IL-6 was significantly higher in patients with DCM compared to the control group ($p < 0.05$). Concentration of TNF-α was statistically higher in patients with DCM than in patients with cardiac ischemia ($p < 0.05$) or in those from the control group ($p < 0.05$). Reactive hyperemia (RH%) was significantly lower in patients with ischemic cardiomyopathy and DCM compared to patients with coronary thrombosis without left ventricular dysfunction ($p < 0.05$) and the control group ($p < 0.001$). The research proved that endothelium dysfunction and inflammatory process expressed with higher concentration of pro-inflammatory cytokines occurred in ischemic heart failure as well as in DCM. In patients with ischemic heart failure, the observed endothelium dysfunction was greater than in those with DCM, which may be a result of atherosclerosis. In patients with DCM (33 of them had coronary thrombosis as well), a significant relationship between the levels of receptor for IL-2 (IL-2R) and left ventricular end-diastolic volume was observed. After 24 months of observation, a negative clinical course of the disease (death, necessary heart transplant, deterioration of clinical condition) was observed in 17 of 76 assessed patients. In 75% of patients with a negative course of the disease, concentrations of the receptor for IL-2 soluble in blood serum were increased ($\leq$ 800 pg/mL) compared to 6% of patients with a stable clinical course of the disease. Increased concentration of sIL-2R in patients with DCM turned out to be an independent factor of a negative clinical course of the disease [40]. Brooksbank et al. [41] noticed that hyperproduction of TNF-α in patients with ischemic cardiomyopathy remains the same despite the hemodynamic improvement obtained as a result of standard therapy with diuretics, angiotensin converting enzyme inhibitors and beta-adrenolytics. It was observed that modification of cytokine levels leads to the improvement of heart function as a pump and to the control of clinical symptoms of overt heart failure. For instance, in the research carried out by Gürgün et al. [42], 12-weeks of therapy with fluvastatin decreased levels of TNF-α and IL-6 in patients with DCM and ischemic cardiomyopathy, which was accompanied by clinical and hemodynamic improvement. Significant changes in levels of C-reactive protein (CRP) and BNP were not observed. Further research assessing the prognostic value of inflammatory markers in patients with cardiomyopathy and the influence of their pharmacological modification on levels of these substances and the clinical condition of patients is necessary. Using statin in patients with DCM without coronary thrombosis was an independent factor of reducing the general death rate (HR = = 0.38; CI = 0.18 $\pm$ $\pm$ 0.82; $p = 0.0134$) as well as the death rate from cardiovascular origins (HR = 0.42; CI = 0.18 $\pm$ 0.95; $p = 0.037$) [43]. In the research carried out by Sampietro et al. [44], the authors assessed whether or not low levels of HDL cholesterol and inflammation

are related to idiomatic DCM. Coronary microcirculation in idiopathic DCM is impaired, probably because of vascular endothelial dysfunction. High-density lipoproteins (HDL) potentially regulate functions of endothelium by modulating inflammatory reactions and immunological response. In patients with idiomatic DCM, lower levels of HDL, apolipoprotein A-I and apolipoprotein A-II, as well as higher levels of triglycerides, were observed. The levels of all studied inflammatory markers (CRP, soluble intercellular adhesion molecule, soluble endothelial leukocyte adhesion molecules) were significantly higher in patients with idiomatic DCM than in the control group, and they were negatively correlated with HDL. These results also weigh in favour of the potential role of HDL in microvascular dysfunction of vascular endothelium in patients with idiomatic DCM.

In diagnostics of heart failure, which is also of DCM origin, researchers try to use other new biochemical markers like osteopontin, which is a protein involved in the restructurizing of the extracellular matrix. The increased levels of this protein turned out to be an unfavourable prognostic factor in heart failure [45].

Osteopontin plays an important role in myocardial remodelling, by promoting collagen synthesis and accumulation in experimental animal models.

In Satoh at al. research [46] osteopontin and collagenase I mRNA levels were highly expressed in the DCM group with large left ventricular end-systolic diameter (LVESD ≥ 54.5 mm) or low left ventricular ejection fraction (LVEF < 29.5%), compared to the control group ($p < 0.01$), which means that osteopontin may play a pivotal role in the development of collagenase-I-induced cardiac fibrosis and dysfunction in DCM.

Increased serum levels of carbohydrate antigen 125 (CA125), a tumour marker associated with ovarian cancer, are associated with the severity of congestive heart disease and are also independent predictive markers for re-hospitalization [47].

In the research by Núñez et al. [48], serum levels of CA125 > 35 U/mL (established cut-off point value) obtained in patients admitted with a diagnosis of acute heart failure were shown to be an independent predictor of mortality up to the 6-month follow-up.

In the research carried out by Filipiak et al. [49], it was found that the simultaneous determination of NT-proBNP and tumour antigen CA-125 gives the highest predictive accuracy of death risk in heart failure. Subsequent observations, confirming the negative influence of increased uric acid concentration on prognostics in patients with heart failure, point to the necessity of carrying out randomized clinical research on the influence of pharmaceuticals which decrease its concentration (e.g. allopurinol) on the clinical course of heart failure and eventual improvement in prognostics [50].

Summary

More efficient, simple, cheap and quick methods for diagnostics and risk assessment in patients with heart failure are being sought. Creating a panel of useful laboratory tests performed in this group of patients will enable the start of early pharmacological therapy, the implementation (depending on the results) of mechanical circulation support or resynchronizing therapy, and the selection of patients who should be qualified to heart transplant first. Because of numerous limitations and the influence of extracardial factors, the determination of the levels of one biochemical marker cannot be relied upon as a universal and infallible criterion of recognition. Perhaps researchers will manage to select a set of laboratory tests which will enable the recognition of cardiomyopathy at an early stage and which will be used to monitor treatment efficiency and to prognosticate. Nowadays it is recommended that BNP and troponin measurements be taken; perhaps future research will confirm the usefulness of other potential prognostic markers like osteopontin, Ca-125 and cytokines.

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