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B-type natriuretic peptide (BNP) and isolated diastolic heart failure: an opportunity for more precise diagnosis?

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Diastolic heart failure with preserved left ventricular (LV) function has been intensively investigated and clinically analysed in recent years. It is now regarded as the cause of 50–55% of all heart failure hospital admissions. When compared with systolic heart failure it prevails in women and the elderly and coincides with hypertension, atrial fibrillation and chronic obturatory lung disease. However, bearing in mind that diastolic heart failure is diagnosed in 90% of patients suffering from ischaemic heart disease (IHD), we may state that ischaemia should be identified as a main cause of impaired LV diastolic function. Studies and clinical observations have documented the association between the impairment of LV diastolic function that can precede systolic disorders and all types of IHD. Evaluation of LV systolic function among patients with a history of myocardial infarction still remains the main diagnostic concern during echocardiographic examination; LV diastolic function analysis often recedes into the background. The difficulties arise from the method's limitations, the unsettled criteria and insufficient appreciation of diastolic function impairment as a prognostic factor in myocardial infarction survivors.

A cohort of patients with preserved LV systolic function after acute myocardial infarction catheter-based coronary interventions was regarded as a special population because no substantial segmental contractility disturbances had been diagnosed in this group. The study results demonstrate that 51 out of 83 patients presented LV diastolic dysfunction, which in 15 cases coincided with high NT-proBNP values that identified patients with the most evident diastolic function abnormalities. It may be assumed, although the study lacks such data, that some of these patients demonstrated heart failure symptoms or would develop them in the future despite their preserved LV systolic function and the absence of features of traditionally defined LV remodelling.

The mechanisms that trigger diastolic abnormalities in IHD are quite complex. The impairment of active relaxation, the deterioration of myocardial compliance and heterogenic LV diastole are among the most important contributors [1]. Active myocardial relaxation is a very hypoxia-sensitive process. Disturbances of this relaxation phase are the earliest manifestations of ischaemia in echocardiographic examination, preceding impairment of systolic function. Chronic myocardial ischaemia and post-infarction damage promote maladaptive processes that lead to cardiomyocyte hypertrophy and dilatation, followed by fibrosis and deposition of extra-cellular matrix and ending with myocyte necrosis that significantly limits LV diastolic function. IHD is usually associated with heterogenic LV myocardial damage that causes heterogenic inactivation and burden. During this ongoing remodelling process changes in LV electrical activation frequently lead to asynchrony of myocardial contraction, which is aggravated by heterogenic myocardial structure, loss of myocardial contractility and segmental hypertrophy [2]. It has been demonstrated in many studies that LV diastolic dysfunction is the dominant IHD abnormality and that it is present both in patients with and without impaired LV systolic function. Irrespective of systolic impairment, diastolic dysfunction significantly contributes to the elevation of LV end diastolic pressure and pulmonary wedge pressure [3, 4]. Elevated filling pressure

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during ischaemia is commonly regarded as one of the most important causes of effort dyspnoea in patients with angina pectoris and those who have had a myocardial infarction. Diastolic impairment is present in 95% of myocardial infarction survivors. It is always present in the case of systolic dysfunction and manifests itself in a pseudonormal or restrictive transmitral inflow pattern [5]. Both in the population of infarction survivors without systolic dysfunction and in the cohort analysed by the authors relaxation abnormalities are dominant, probably as a result of existing ischaemia or impaired coronary reserve.

There is increasing research to indicate that the degree of LV diastolic impairment in the population of patients who have experienced myocardial infarction is a powerful prognostic factor, irrespective of LV systolic dysfunction. Diastolic disturbances of the LV relaxation type are identified as an especially powerful negative predictor. Among patients suffering from post-infarction heart failure there is an evident negative correlation between early mitral inflow deceleration time and pulmonary wedge pressure. Patients with a pulmonary wedge pressure higher than 12 mm Hg were very distinctly identified by an E-wave time shorter than 153 ms [6]. Poulsen et al. [7] reported that among post-infarction patients early inflow E-wave deceleration time is an important and independent predictor of heart failure symptoms. Many studies demonstrate that early mitral inflow deceleration time is the most powerful independent predictor of morbidity and mortality among myocardial infarction survivors. It has been reported that the restrictive profile of diastolic inflow with shortening of the early filling phase is the most negative predictor both in cardiomyopathy and post-infarction patients. Two significant meta-analyses, American and Canadian, covering almost 7400 patients have recently been published in the NEJM. These compare the clinical course and prognosis in patients with heart failure and in those preserved or impaired LV systolic function. Comparison was made between the two groups in terms of clinical presentation, course of hospitalisation, co-morbidity, re-hospitalisation and one-year mortality and its predictors. A similar clinical course and hospitalisation rate were observed in both groups, the only difference being a slightly lower mortality rate in the cohort of patients with preserved LV systolic function (one-year mortality 29% *vs.* 32% and five-year mortality 65% *vs.* 68%). During the three five-year periods analysed the survival rate in low ejection fraction heart failure increased (HR 0.98 per year, CI 95%, $p = 0.005$) with mortality in the population of patients with preserved LV ejection fraction remaining at the same level. It seems that a systematic increase in the incidence of preserved LV systolic function heart failure may be attributed to the increasing prevalence of atrial fibrillation, hypertension and diabetes mellitus that are the main contributors to the development of heart failure with preserved LV systolic function. In the above-mentioned meta-analyses the only trend toward increased survival in the heart failure population as a whole was a statistically significant increase in the cohort of patients with low ejection fraction. This may be explained by the fact that there have been several spectacular breakthroughs in the diagnostics and treatment of patients with low ejection fraction, whereas heart failure with preserved LV systolic function remains a challenging diagnostic and therapeutic issue [8, 9]. The precise diagnostics of diastolic dysfunction is still highly demanding and far from perfect. Doppler echocardiography, despite its limitations, remains the most common method of identifying LV diastolic dysfunction [10]. These limitations, as highlighted by Wita et al. [11], result from the fact that, apart from the so-called "internal factors" determining diastole (myocardial dependent), venous and transmitral inflow parameters reflect a number of external factors such as preload and afterload of the left ventricle, left atrial systolic function, right ventricle function, characteristics of the pericardium, valvular (especially mitral) function and heart rhythm and rate [12, 13]. Incorporating all these issues into the analysis of LV diastole appears to be of vital importance. E-wave mitral inflow velocity measurement in correlation with mitral ring early diastolic speed movement in tissue Doppler examination may contribute to a more accurate identification of isolated diastolic heart failure.

There has been an increasing number of studies in recent years suggesting the importance of natiuretic peptides, especially BNP and NT-proBNP, in the diagnostics of diastolic heart failure. BNP, a very sensitive indicator of the functional condition of the heart, shows good correlation with heart failure NYHA stage and with the haemodynamic measurements such as pulmonary wedge pressure, LV late diastolic pressure, ejection fraction and pulmonary artery pressure. It is a strong predictor of LV heart failure and mortality in the cohort of myocardial infarction survivors [14–17]. The relevance of BNP measurement in the analysis of LV diastolic disorders was reported by Lubien et al. [18], who observed a significant discrepancy in the average peptide concentration between the following groups of patients: those with relaxation disorders — 203 pg/ml, those with pseudonormal mitral

inflow — 294 pg/ml, those with restrictive disorders — 402 pg/ml as against 33 pg/ml in the control group.

Subanalysis of the PRIDE trial has revealed that among patients treated for paroxysmal dyspnoea BNP and NT-proBNP concentration levels turned out to be twice as high among patients with systolic heart failure as in those with diastolic heart failure. The same analysis also demonstrated a more accurate correlation between NT-pro BNP concentration and progression of the disease in the cohort of patients with diastolic heart failure than in patients with systolic dysfunction [19]. The PRIDE trial results made it possible to create the paroxysmal dyspnoea diagnostic algorithm for emergency departments. The work of Wita et al. [11] is a valuable contribution that supports the thesis of NT-proBNP utility in heart diastolic function analysis. It is worth emphasising, however, that BNP and NT-proBNP concentration levels are influenced by a number of factors such as left and right ventricular systolic function, valvular function, LV mass, heart rhythm, age, sex, weight, blood pressure, renal function and respiratory state [20, 21]. Natiuretic peptides may prove useful in diastolic heart failure diagnostics, provided that the results are carefully analysed in correlation with clinical and echocardiographic data.

The present work indicates that, even after modern management of myocardial infarction, the majority of patients with preserved LV function suffer from diastolic disorders that may evolve into more advanced stages of heart failure. Proper and accurate identification of these abnormalities is of vital practical importance in tailoring optimal diagnostics and treatment in this group of patients.

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