EDITORIAL

# Brain-derived neurotrophic factor and heart failure: a promising new road to explore?

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by Pytka et al

Heart failure (HF) is a complex clinical syndrome resulting from structural and / or functional abnormalities of the heart leading to an inadequate cardiac output at rest and / or during exercise and, consequently, insufficient tissue and organ perfusion. Natriuretic peptides (NPs), especially the N-terminal prohormone of brain natriuretic peptide (NT-proBNP), are the most commonly evaluated biomarkers in patients with suspected HF, allowing both to rule out the diagnosis of HF (cutoff level for NT-proBNP <125 pg/ml) and to provide the prognosis for these patients.[1] However, there are some limitations to the use of NPs, as their levels increase with age, are higher in patients with chronic kidney disease (CKD) due to slower clearance and, of interest, they do not provide information on the presence and grade of structural and / or functional impairment of the heart. Therefore, validation of new circulating biomarkers for identification of HF patients with more advanced cardiac remodelling and dysfunction could be extremely helpful for clinicians.[2]

In this issue of *Polish Archives of Internal Medicine*, Pytka et al[3] compared cardiac structure and function using echocardiography in ambulatory and clinically stable patients with HF and left ventricular (LV) ejection fraction (LVEF) below 50%, with lower and higher brain-derived neurotrophic factor (BDNF) serum concentrations. Among the 361 patients included in the study, those with lower serum concentrations of BDNF (<23.5 ng/dl) had more dilated right and left atria, larger right ventricular end-diastolic area and LV end-systolic diameter, higher mitral E/A and E/e' waves ratio, lower tricuspid annulus plane systolic excursion (TAPSE), shorter pulmonary acceleration time, and higher concentration of NT-proBNP. Notably, these findings were independent of the patient age, sex, body mass index, systolic blood pressure, and heart rate. Although the influence of other comorbidities, such as diabetes, hypertension, coronary artery disease, or atrial fibrillation could not be excluded, the authors concluded that lower levels of BDNF in patients with advanced systolic HF might reflect the disease that lasts longer or has induced more serious chronic adaptation of the heart and, therefore, the measurement of serum levels of BDNF could be used as a biomarker for identification of more advanced systolic HF patients.[3]

Neurotrophins are a class of growth factors that promote neuronal proliferation, differentiation, and survival. BDNF is the most important neurotrophin and is implicated to modulate the functions of both the central and peripheral nervous systems.[4] Of interest, recent studies demonstrated that BDNF can be synthesized in many non-neuronal tissues and cells (including the myocardium, endothelial cells, and platelets), and may play a critical role in the development of the cardiovascular system as well as in maintaining the integrity of cardiac structure and function through binding to its receptor tropomyosin-related kinase receptor B (TrkB) actively expressed in cardiomyocytes.[5,6] Indeed, experimental studies showed that alterations in the BDNF-TrkB pathway are associated with impaired cardiac contraction and relaxation, cardiomyocyte death, decreased cardiac function, increased cardiac inflammation, and oxidative stress, leading to early postnatal death and development of HF in the adult heart.[7-9] Furthermore, previous studies reported that serum concentrations of BDNF are reduced in patients with systolic HF, and its lower levels are associated with more impaired heart functional capacity (ie, advanced New York Heart Association class), higher levels of NT-proBNP, and higher incidence of death and rehospitalization, thus suggesting that BDNF can be a useful prognostic biomarker in patients with HF.[10,11] However, to date, data regarding the relationship between BDNF concentration and severity of HF using echocardiography are scarce. In this regard, a recent study showed

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that low BDNF levels are associated with adverse cardiac remodelling (higher LV mass, posterior wall thickness, and E/A ratio) and higher levels of NT-proBNP, even though patients with severe CKD, previous myocardial infarction (MI), and LVEF below 40% were excluded.[12] Expanding these findings, the study by Pytka et al[3] showed that even in patients with advanced HF (as reflected by a median LVEF of 31%) lower BDNF levels are associated with more advanced structural changes in the heart. Even though the underlying mechanisms are unknown and cannot be deducted from this study, these findings allow to speculate that the decrease in serum BDNF levels could be implicated in the pathogenesis and progression of HF. Of note, it has been suggested that BDNF release could increase during acute myocardial ischemia and might play a protective role against ischemic damage and the adverse cardiac remodelling following MI.[13] Given that several interventions (eg, physical activity, imipramine, S-citalopram) can be used to increase serum BDNF concentration, further investigations aimed at elucidating the underlying mechanisms of the association reported in this study and its role as a potential therapeutic target are strongly warranted.

Finally, increased levels of serum BDNF have been reported in patients with unstable angina as compared with patients with stable coronary artery disease (CAD) or controls without CAD, suggesting their possible role in the pathogenesis of acute coronary syndromes (ACS). Moreover, a recent study found higher BDNF levels in patients with ST-elevation MI than in those with non–ST-elevation ACS, and higher BDNF levels were associated with coronary macrophage infiltrates and lower prevalence of healed plaques, suggesting that BDNF could be involved in the thromboinflammatory activation occurring in patients with ACS.[14,15]

In conclusion, accumulating evidence suggests a role for BDNF in the pathogenesis of cardiovascular disease, and further studies are needed to confirm its potential diagnostic, prognostic, and therapeutic implications.

## ARTICLE INFORMATION

**DISCLAIMER** The opinions expressed by the author(s) are not necessarily those of the journal editors, Polish Society of Internal Medicine, or publisher.

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