The prognostic value of NT-proBNP in chronic heart failure

Chronic heart failure (HF) is generally accompanied by a progressive activation of compensatory neurohormonal systems that contribute to the worsening of the symptoms. Cardiac natriuretic peptides are known to be increased in patients with HF. To determine the prognostic value of such natriuretic peptides, assays were carried out in samples taken from almost 4000 patients with chronic heart failure who had participated in the large Valsartan Heart Failure Trial (Val-HeFT). It was found that a single measurement of the aminoterminal fragment of brain natriuretic peptide (NT-proBNP) provided the best independent predictor of clinical outcome.

by Dr S. Masson, Dr R. Latini and T. Vago

According to the neurohormonal model of the disease, the progression of heart failure (HF) is the result of several cardiac and extra-cardiac biohumoral systems that are activated by the initial injury to the heart having a deleterious effect on the circulation. The progressive reduction in cardiac stroke volume causes the release of endogenous vasoconstrictive substances such as noradrenaline, angiotensin II, endothelin peptides and vasopressin that in turn increase peripheral resistance and result in further direct damage to cardiac cells [1]. Clinical improvement has been shown in many patients with HF when they are treated with drugs that have an effect on these systems, such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-adrenergic blocking agents and aldosterone agents. Measurement of circulating biomarkers of cardiovascular disease has been proposed as a surrogate end-point of clinical outcome in trials of such drugs in patients with HF [2].

First isolated from rat atria and porcine brain, natriuretic peptides have been shown to reduce the vasoconstriction that is seen in patients with HF; in other words they may be considered as "beneficial cardiac hormones". Secreted mainly by ventricular and atrial myocytes in response to increased mechanical stress, they act on peripheral receptors and cause diuresis and vasodilatation. They also decrease renin, aldosterone and endothelin secretion, and have direct antifibrotic effects. The plasma concentration of various fragments of cardiac natriuretic peptides has been shown to be elevated in patients with HF in contrast to that in apparently healthy volunteers. The determination of such plasma concentrations of certain natriuretic peptides, or their precursors, can therefore be helpful in the diagnosis of HF. These biomarkers perform particularly well in excluding (ruling out) HF in patients presenting with symptoms of dyspnea. Measurement of the plasma concentration of cardiac natriuretic peptides has been included in the guidelines for the diagnosis and treatment of chronic HF as proposed by the European Society of Cardiology [3].

VISIO PLUS – Bringing Vision to Blood Collection

The VACUETTE VISIO PLUS Needle guarantees the best possible result during the blood collection process. Due to the visual blood flow control via the view window, you see immediately if the vein has been punctured correctly. The latest innovation to ensure a safe and comfortable blood collection technique.

www.gbo.com

VISIO PLUS NEEDLE

The Visualization of Safety

www.cli-online.com & enter 22661
Brain natriuretic peptides are powerful markers for risk stratification and prognosis in chronic HF [4], even when compared to established demographic or clinical criteria, such as age New Y ork Heart Association (NYHA) functional class.

Pro Brain Natriuretic protein (pro-BNP) is a molecule comprising 108 amino acids and is a common prohormone to both BNP itself (amino acids 77-108) and the amino-terminial fragment of BNP (NT-proBNP) (amino acids 1-76). Both BNP and NT-proBNP are secreted in equimolar amounts and can be reliably measured using approved automated assay systems.

Whereas BNP is a bioactive hormone, the biological role of NT-proBNP is not known at present. There are substantial differences between the two molecules, e.g. in their biological half-life, in vitro stability, as well as the mechanisms of elimination from the body.

Our knowledge on the prognostic value of brain natriuretic peptides in chronic HF derives from different clinical settings and from clinical trials. In the Valsartan Heart Failure (Val-HeFT) trial, 5010 patients with mild to moderate chronic HF were randomly assigned to receive an angiotensin II type 1 receptor blocker (Valsartan) or placebo, on top of standard recommended medical therapy [5]. The primary outcomes of the trial were all-cause mortality and the combined end-point of mortality and morbidity with a mean follow-up duration of 23 months. A significant reduction in the combined end-point (13%) was achieved in patients treated with Valsartan [5]. In the Val-HeFT trial, plasma samples were collected at enrolment and during follow-up in ~ 85% of the patients, resulting in one of the largest clinical plasma banks relating to HF. This valuable plasma bank has allowed the clinical utility and prognostic value of more than 10 circulating biomarkers to be evaluated [6]. It was considered that the measurement of both BNP and NT-proBNP in this plasma bank would enable a head-to-head comparison of these two markers of outcome in the largest sample of patients with chronic HF studied up till now.

Plasma NT-proBNP was assayed in two central laboratories using an automated electrochemoluminescent method (ECLIA Elecsys 2010 analyser, Roche Diagnostics). This assay system had satisfactory interassay reproducibility (CV 4.7%) [7]. The median baseline concentration of NT-proBNP for the 3916 patient samples assayed was 895 pg/mL (interquartile range 375-1985 pg/mL), i.e.

Figure 1. Analytical correlation between baseline concentration of BNP (immunoradiometric assay) and NT-proBNP (ECLIA) in patients participating in the Val-HeFT trial.

Figure 2. Kaplan-Meier curves for all-cause mortality and hospitalisation for HF. Data shown as a function of baseline NT-proBNP concentration measured in samples taken from patients participating in the large Val-HeFT clinical trial.
above the respective diagnostic cut-off values suggested for patients suspected of having HF that were younger than 75 years of age (125 pg/mL) or older than (450 pg/mL). Interestingly, there was a fairly good correlation between NT-proBNP concentration and that of BNP as measured with a manual immunoradiometric assay [Figure 1].

As suggested by the known physiopathological mechanisms regulating natriuretic peptides secretion and metabolism, it was found that in patients with reduced ejection fraction of the left ventricle or dilation, NT-proBNP values increased with the age. Patients with impaired renal function also had higher levels of NT pro-BNP.

The baseline concentration of NT-proBNP was a powerful biomarker of outcome in Val-HeFT. When patients were grouped into quartiles of NT-proBNP concentration, the risk of dying or being admitted in hospital for worsening of HF increased across quartiles [Figure 2]. An increment of 500 pg/mL in the concentration of NT-proBNP at study entry corresponded to a 3.8% increase in the risk of mortality and 3.0% increase in the need for hospitalisation for HF. Remarkably, NT-proBNP was clearly the best independent predictor of outcome, well before the other classical clinical variables collected in the trial, such as age, symptoms on physical activity, renal and ventricular functions.

The analysis of the samples from the Val-HeFT trial also confirmed that BNP and NT-proBNP had almost identical prognostic value in patients with chronic HF, there being only subtle differences of unexplored clinical value. Together with a many other scientific reports, the results from the analysis of the Val HeFT trial demonstrates that brain natriuretic peptides (BNP or NT-proBNP) are strong prognostic indicators for patients with HF at all stages of disease. They seem to be better predictors of survival than many traditional prognostic indicators, such as New York Heart Association class, serum creatinine, or left ventricular ejection fraction. The risk of death and cardiovascular events increases continuously with increase in the value of the biomarker, even at very low concentrations, thus casting some doubts on the concept of normal values. Perhaps more importantly, the measurement of changes as a function of time in the concentrations of circulating natriuretic peptide in individual patients [8] may help in guiding and monitoring their treatment for HF.

References

The authors
Serge Masson, PhD, Roberto Latini, MD, and Tarciro Vago*, BioID.

Department of Cardiovascular Research, Istituto di Ricerche Farmacologiche “Mario Negri” Milan, Italy.

* Laboratory of Endocrinology, Ospedale Luigi Sacco, Milan, Italy

Author for correspondence:
Serge Masson, PhD, Department of Cardiovascular Research, Istituto di Ricerche Farmacologiche “Mario Negri”, via Eritrea 62, 20157 Milan, Italy.
e-mail: masson@marionegri.it

www.cli-online.com & enter 23133

www.cli-online.com & enter 22730