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NT-proBNP, THE GUARDIAN ANGEL OF HEART FAILURE

NT-proBNP is currently the most powerful biological marker in the diagnosis and follow-up of heart failure

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Abstract

BNP and NT-proBNP are effective biomarkers of heart failure in the emergency setting. Many other causes are associated with a rise in BNP, particularly in elderly patients with multiple comorbidities. Nevertheless, taking into account the empirical pre-test probability of heart failure improves the diagnostic contribution of these 2 biomarkers. A single value must not on its own decide a treatment (diuretics or vasodilators), given the risk of deleterious iatrogenic complications. NT-proBNP is more stable than BNP: it degrades only after 4 days at room temperature, a definite asset whenever tubes have to be transported.

The case of Mr Jolicoeur

Mr Jolicoeur, a happy 70-year-old retiree, whom you have been following for a long time. Mr Jolicoeur consults you today for progressive dyspnoea that has been developing over several weeks. In his history, he is known for atherosclerotic heart disease with stable angina II/IV, and he smokes a pack of cigarettes a day. Nothing in the history or in the physical examination points you towards an infectious cause. He has bilateral lower-limb oedema that worsens at the end of the day. After a complete evaluation, two diagnoses remain in your mind to explain this dyspnoea: heart failure (HF) of ischaemic origin, or chronic obstructive pulmonary disease (COPD). Can NT-proBNP help you decide the origin of the dyspnoea?

A little pathophysiology

The term NT-proBNP is the acronym for "N-terminal portion of the B-type natriuretic propeptide". Natriuretic peptides are secreted by the cardiac myocytes in response to increased tension in the atria or the ventricles. Type A natriuretic peptide (for atrial) is mainly secreted by the atria and is less useful clinically, whereas type B (for brain), although initially identified in the pig brain, is mainly secreted by the cardiac ventricles. There are four natriuretic peptide factors (A, B, C, D or urodilatin), all of which play a more or less important role in sodium homeostasis and the regulation of blood volume. Schematically, pre-proBNP is secreted by the ventricular myocytes of the left ventricle (LV), because the LV is much more voluminous than the right ventricle. The role of BNP is to counterbalance the activation of pro-vasoconstrictor hormones (endothelin) and cytokines and the activation of the renin–angiotensin–aldosterone system when there is increased wall tension (parietal stress, or stretching of the myocytes) of the LV. BNP allows systemic and pulmonary arterial vascular relaxation, lowers angiotensin, aldosterone and endothelin-1 levels, increases glomerular filtration and the renal excretion of sodium, and is thought to reduce the proliferation of vascular smooth muscle. It therefore has a natriuretic, diuretic and vasodilator action. NT-proBNP, secreted at the same time as BNP, is a 76-amino-acid peptide resulting from the cleavage of proBNP in the blood. Unlike BNP (20 minutes), NT-proBNP has a longer half-life (90 minutes) and has no physiological activity. In the blood, its concentrations are five to ten times higher than those of BNP. NT-proBNP and BNP rise with age, probably secondary to the physiological LV hypertrophy of elderly subjects. Obesity is thought to lower its blood concentrations. Levels are increased in women. Diabetes, on the other hand, is not thought to modify its values. Nevertheless, apart from advanced age (> 75 years), neither weight, nor sex, nor moderate renal impairment (creatinine clearance ≥ 60 ml/min) would significantly modify the cut-off values of NT-proBNP or BNP. However, as for BNP, severe renal impairment (creatinine clearance < 50 ml/min) raises the cut-off value of NT-proBNP and lowers the diagnostic performance of this biomarker.

NT-proBNP in the diagnosis of heart failure

Since NT-proBNP is secreted in response to increased tension on the walls of the cardiac ventricles, its concentration is increased in ventricular dysfunction, allowing its diagnosis. The NT-proBNP value does not differentiate right from left heart failure, but the latter is in any case far more frequent. The main usefulness of NT-proBNP is to RULE OUT heart failure as a cause of dyspnoea in a symptomatic patient. At a level below 300 pg/mL, NT-proBNP has a sensitivity of 90 %, a specificity of 84 % and a negative predictive value (NPV) of 98 %. Thus, if a dyspnoeic patient has an NT-proBNP value below 300 pg/mL, you are 98 % certain that HF is NOT the cause of the dyspnoea. Conversely, a high NT-proBNP value can help in the diagnosis of HF, but its specificity is less good.

Diagnosing heart failure early in type 2 diabetics

Like most chronic diseases, heart failure remains asymptomatic for a long time and, in congestive forms, the ejection fraction deteriorates progressively before the first signs appear. Can this slow deterioration be diagnosed early in type 2 diabetic patients?

Several studies appear to indicate that it can. Thus, in the ADVANCE study, measurement of NT-proBNP and troponin assessed the risk of death and the occurrence of cardiovascular events in 3,500 type 2 diabetic patients. In a Danish study, an NT-proBNP level > 125 ng/L proved to be a factor of poor prognosis in 350 type 2 diabetic subjects, independently of microalbuminuria. In the PONTIAC study, 300 type 2 diabetic patients with no history of heart disease and with an NT-proBNP > 125 ng/L were followed either in endocrinology (control group) or in cardiology, where treatment doses (beta-blockers, ACE inhibitors, ARBs, etc.) were adjusted more intensively, with in particular the objective of halving NT-proBNP levels. This strategy reduced all-cause and cardiovascular hospitalisations and mortality. the events Although these elements need to be confirmed by larger studies, the early identification of high-risk diabetic patients thanks to the NT-proBNP level could allow their management to be intensified.

Follow-up of heart failure

From this point of view, knowledge has progressed considerably, and the first indication for NT-proBNP measurement is now the optimisation of the treatment of chronic HF, which has been validated by several studies showing a reduction in morbidity and mortality thanks to this strategy. The assay identifies patients who are not stable even though they appear so on clinical examination. Each time NT-proBNP levels rise, the treatment must be optimised and, in particular, drug doses must be increased to the recommended doses. In practice, the therapeutic objective is to reach a validated NT-proBNP threshold ≤ 1,000 ng/L or, failing that, the lowest possible level. Ideally, an assay should be available before each consultation to judge the course of HF against the previous one.

Back to the case of Mr Jolicoeur

An NT-proBNP assay, performed the same day, comes back at 200 pg/mL. You are therefore comfortable ruling out HF in your differential diagnosis. You prescribe outpatient spirometry for your patient and start treatment for COPD.

NT-proBNP preferred over BNP

Assayed in our laboratory, BNP has been replaced by NT-proBNP. Various pre-analytical, analytical and biological reasons motivated our choice:

- In patients suffering from moderate heart failure (NYHA I and II), the sensitivity (87 %) and the specificity (94 %) of NT-proBNP are better than those of BNP (sensitivity: 78 %; specificity: 87 %)
- NT-proBNP is assayed on a sample collected on lithium heparinate, which is the same sample as the one used for troponin measurement
- NT-proBNP shows a longer stability in the sample (3 days at room temperature)
- As the half-life of NT-proBNP (1 to 2 h) is longer than that of BNP (20 min), its blood concentration will be higher
- The NT-proBNP concentration is not influenced in a patient treated with a recombinant BNP
- The indication for NT-proBNP measurement is the same as that for BNP

Other factors that increase NT-proBNP

In addition, several factors can increase the serum concentration of NT-proBNP, such as age and renal impairment.

As regards renal impairment, since NT-proBNP is excreted by the kidneys, a glomerular filtration rate below 60 mL/min/1.73 m² does not allow high NT-proBNP values to be interpreted. Conversely, a normal value in the presence of renal impairment or of advanced age is all the more reassuring.

Table 1 – Clinical circumstances with variation of BNP (non-exhaustive list)

Category	Concentration
Cardiac disorders:	
• Heart failure	Marked increase
• Acute coronary syndrome	Increase
• Supraventricular tachycardia AF)	Increase
Pulmonary disorders:	
• Pulmonary embolism	Normal or increase
• COPD	Normal or increase
• Primary pulmonary arterial hypertension	Normal or increase
• ARDS	Normal or increase
Other disorders:	
• Hepatic failure with ascites	Increase
• Renal failure (acute or chronic)	Moderate or marked increase
• Septic shock	Increase
• Meningeal haemorrhage/stroke	Normal or increase
• Anaemia	Normal or increase
• Obesity	Normal or decrease

Other indications and prospects

- **NT-proBNP and acute coronary syndrome (ACS)**

In a patient presenting with an ACS with or without ST-segment depression, NT-proBNP measurement is indicated for prognostic purposes: high levels are associated with an increased risk of death, and this independently of other factors (age, troponin levels, LVEF, etc.). Thus, in the GUSTO IV study, which included 7,800 patients, NT-proBNP levels made it possible to stratify the risk of the patients and to identify those who obtain the greatest benefit from immediate revascularisation.

Ventricular remodelling is an active process after myocardial infarction which may promote a sometimes severe left ventricular dysfunction. It may appear in the weeks or the months that follow. Cardiac ultrasound remains the reference examination for assessing this remodelling, but it does not deliver all the information. In post-MI (myocardial infarction) patients, a British team showed that the most powerful parameter for predicting the wall motion index at 4.5 days (median) and 50 days (median) was NT-proBNP measurement. The NT-proBNP level correlated well with ventricular dysfunction: high in particular in the patients who had the most severe alterations or who had died. Conversely, a level < 2029 ng/L was predictive of a favourable outcome.

- **Monitoring of cardiac function in patients undergoing chemotherapy**

Some anticancer chemotherapies have a cardiotoxic effect, in particular the anthracyclines, whose doses are cumulative with a risk of cardiac disorders appearing (in particular heart failure, but also supraventricular rhythm disturbance and myocardial ischaemia) from 450 mg/m² onwards. To identify subjects at risk of cardiac events (in particular the occurrence of HF), NT-proBNP is more informative than troponin or CK-MB. In one study, 34 % of patients had, after chemotherapy, a rise or a transient rise in NT-proBNP. Some of them had a persistent rise in NT-proBNP linked to an increased risk of developing HF in the medium term. NT-proBNP assays performed before treatment and then during treatment therefore make it possible to identify subjects at risk, to assess the cardiac effects of these therapies and potentially to help in decision-making: introduction of a treatment blocking the RAAS to prevent the onset of the disease. Finally, in women with breast cancer receiving doxorubicin, whose cardiotoxic effects are known, NT-proBNP levels were significantly higher in those whose left ventricular ejection fraction was going to decrease. The reduction in the left ventricular shortening fraction correlated with high NT-proBNP levels.

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