

NT-proBNP for heart failure diagnosis in primary care

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Diagnosing heart failure (HF) in patients presenting in primary care is difficult. Clinical assessment of symptoms and signs has limited sensitivity and specificity.

NT-proBNP determination has been proven to be useful and accurate for ruling out the diagnosis of systolic HF, and some have even proposed different cut-offs depending on the age of the patient.

Incorporation of natriuretic peptide tests in primary care improves the diagnostic algorithm of HF by selecting the patients who need an echocardiographic study. In addition, it results in an optimization of healthcare resources in a setting where a high percentage of the initially suspected cases of HF are not confirmed due to difficulties in early stages of the diagnostic process.

Introduction

The accurate diagnosis of heart failure (HF) presenting in primary care is difficult. Clinical assessment of symptoms and signs has limited sensitivity and specificity. Patients are often elderly with comorbidity, symptoms may be mild, and echocardiography may not be universally available [1, 2, 3].

Overdiagnosis of HF in the community is a well-documented phenomenon, with only a quarter to a third of patients with suspected HF, by general practitioners [4].

Thus, it is evident that other elements are needed to optimize the diagnostic algorithm of HF. Currently, fast and simple tests are available to facilitate the clinical evaluation: determination of natriuretic peptides (B-type natriuretic peptide [BNP] and N-terminal pro-B-type natriuretic peptide [NT-proBNP]) in venous blood or urine.

These biomarkers enable selection of patients who should undergo a confirmatory echocardiography study and allow reasonable exclusion of the initial suspected HF diagnosis in others.

Natriuretic peptides

Natriuretic peptides are hormones with diuretic and vasodilator effects, mainly secreted in the left ventricle as a mechanism to compensate for pressure overload. Concentrations of this biomarker are increased in patients with HF and in other structural heart diseases such as valve disease and atrial fibrillation.

Gender (women), age and deteriorated renal function are other causes of elevated natriuretic peptide concentrations. In contrast, obesity, treatment with diuretics, betablockers and inhibitors of the renin-angiotensin-aldosterone axis decrease the plasma concentrations of these substances [5, 6].

The cut-offs used to rule out HF have been clearly established in emergency rooms and specialized centers, where natriuretic peptides have shown proven value for screening and diagnosing patients with suspected HF because of their high sensitivity and excellent negative predictive value [7].

Nonetheless, there is little available data on the usefulness of natriuretic peptides in primary care. Only few studies [1, 3, 8, 9, 10, 11, 12, 13] have assessed the added value of natriuretic peptides in diagnosing patients with HF or preserved left ventricular ejection fraction (LVEF) in this setting, despite the fact that the test can be carried out in the physician's consulting room and the results obtained in less than 15 minutes when a point-of-care (POC) instrument is used. In addition to being advantageous from the diagnostic viewpoint, this biomarker would be cost-effective: unnecessary echocardiography requests could be avoided, thus reducing cost and delays.

When appropriate cut-offs are used, the very high sensitivity of NT-proBNP implies a very low risk of failing to exclude HF, an essential feature for a good initial test strategy. The use of natriuretic peptides is an aid in the standard evaluation and management of patients in this context. The use of NT-proBNP as a preliminary test in

the primary care setting has been demonstrated to be cost-effective [10, 11].

One of the more common problems in the use of the natriuretic peptides for ruling out heart failure is that increasing values occur with age [6]. This affects both BNP and NT-proBNP. The age-associated increase in natriuretic peptide values, thought mainly to be due to parallel increases in subclinical heart disease with age, may lead to an increased risk of a false attribution of a diagnosis of heart failure in an elderly patient if the decision limits optimized for younger patients for either marker are used. In addition, a higher decision limit could result in too many false negatives in the younger age group. The meta-analysis performed by Hildebrandt *et al.* [14] shows age-dependent cut-offs to rule out systolic dysfunction (Table I).

On the other hand, NT-proBNP can help confirm the suspicion of HF. Previous reports on the diagnostic power of the physical examination of suspected heart failure are scarce. Warnings have even been given for the serious limitations of physical examination and very low positive predictive values [2, 15, 16].

Knowledge of the plasma level of NT-proBNP (>400 pg/mL) results in a large gain in diagnostic accuracy. The diagnostic rule including NT-proBNP as an additional test adds considerable diagnostic power [17]. Furthermore, blood can be drawn in the patient's home, and the measurement can be performed in most laboratories. In addition, POC tests for NT-proBNP are available, further facilitating the application of the diagnostic rule.

Cut-off	Sensitivity,(%)	Specificity,(%)	Negative predictive value (%)
< 50 years (50 ng/L)	99.2	57.2	99.7
50-75 years (75 ng/L)	94.9	51.0	96.8
>75 years (250 ng/L)	87.9	53.7	92.4

TABLE I: Age-dependent values of NT-proBNP [14]

Study	N	Cut-off	Negative predictive value, %	Positive predictive value, %
Zaphiriou (2005)	306	125 ng/L	97	44
Nielsen (2004)	345	93 and 144 ng/L	97	57 and 48
Gustafsson (2005)	367	125 ng/L	99	15
Fuat (2006)	279	150 ng/L	92	48
Al-Barjas (2004)	220	125 ng/L	97	76
Verdú (2012)	220	280 ng/L	100	72

TABLE II: Cut-offs for rule out heart failure in primary care [5, 7, 11, 12, 13, 18]

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Studies

Major studies in primary care and their cut-offs to rule out the need for other explorations like echocardiography are shown in Table II.

In a recent study [18], consecutive patients referred by their general practitioners to echocardiography due to suspected heart failure were included. Clinical history and physical examination based on Framingham criteria, electrocardiogram, chest X-ray, NT-proBNP measurement and echocardiogram were performed. Heart failure diagnosis was made by a cardiologist blinded to NT-proBNP value, using the European Society of Cardiology diagnosis criteria (clinical and echocardiographic data).

220 patients (65.5 % women; median 74 years) were evaluated (and heart failure diagnosis was confirmed in 52 patients (23.6 %)). Median values of NT-proBNP were 715 pg/mL (interquartile range 511-1575 pg/mL) and 78 pg/mL (interquartile range 58-180 pg/mL) for patients with and without heart failure, respectively. The best cut-off was 280 pg/mL with an area under receiver operating characteristic (ROC) curve of 0.94. Six patients with heart failure diagnosis (11.5 %) had NT-proBNP values <400 pg/mL. In this study population measurement of natriuretic peptides would have avoided 67 % of requested echocardiograms.

In this study, carried out in an ambulatory population seen in primary care, the best NT-proBNP cut-off value to rule out HF was 280 pg/mL (sensitivity 100 %, specificity 88 %; positive predictive value 72 % and negative predictive value 100 %), with an area under the ROC curve of 0.94. The study used the consensus echocardiographic criteria of diastolic dysfunction published in 2007 [16], which were not applied in previous studies. If the 2007 consensus criteria had not been used, the area under the ROC curve would have been only 0.79 and the optimal cut-off would have been lower, ~100 pg/mL, and very similar to that reported in the primary care studies.

None of the patients diagnosed with HF presented values below 280 pg/mL, independently of age. If other NT-proBNP cut-offs had been applied to the population, such as the 400 pg/mL recommended in the latest NICE consensus guidelines [17], 11.5 % of final HF diagnoses

would have been excluded (false negatives); hence, the NT-proBNP value to rule out HF should have been lower. If, however, the most widely agreed upon cut-off for ambulatory patients (125 pg/mL) had been used, there would have been 57 false-positive results instead of the 20 false positives in the study; i.e., the false-positive rate would have almost tripled and the negative predictive value would not have changed.

Usefulness of employing a POC method

It is beyond question that a rapid method for NT-proBNP determination to exclude the diagnosis of HF in the physician's consulting room, when the patient is still there, is highly useful.

NT-proBNP determination has been proven to be useful and accurate for ruling out the diagnosis of systolic HF, and some have even proposed different cut-offs depending on the age of the patient [12]. It was not the aim of the described study to seek cut-offs according to age, but instead to find a rapid POC determination that would reasonably exclude the need for additional tests, regardless of the patient's characteristics.

Lastly, the use of natriuretic peptide analysis as a screening element prior to echocardiography in patients with suspected HF presenting in primary care can support the initial suspected diagnosis. By measuring NT-proBNP the post-test probability of HF can be several times higher compared to the pre-test probability. This will optimize the decision-making process, by improving accessibility to electrocardiography and reducing health costs.

In the described case, use of the NT-proBNP rule-out cut-off of 280 pg/mL would have avoided 67 % of echocardiographic studies. Taking into consideration that the average cost of an NT-proBNP test is less than half the cost of an echocardiogram, it would be a cost-effective measure, which would establish the diagnosis faster.

A hypothesis is proposed; further studies designed for this purpose are needed to confirm this idea.

Incorporation of natriuretic peptide tests in primary care improves the diagnostic algorithm of HF by selecting the patients who need an echocardiographic study. In addition, it results in an optimization of healthcare resources in a setting where a high percentage of the initially suspected cases of HF are not confirmed due to difficulties in early stages of the diagnostic process.

In the study described based on a community population attended in primary care, the best cut-off for NT-proBNP to rule out heart failure was 280 pg/mL. NT-proBNP measurement improves work-out diagnosis and could be cost-effective.

References

1. Cowie MR, Struthers AD, Wood DA *et al.* Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. *Lancet* 1997; 350: 1349-53.
2. Fonseca C, Morais H, Mota T *et al.* The diagnosis of heart failure in primary care: value of symptoms and signs. *Eur J Heart Fail* 2004; 6: 795-802.
3. Dahlstrom U, Hakansson J, Swedberg K *et al.* Adequacy of diagnosis and treatment of chronic heart failure in primary health care in Sweden. *Eur J Heart Fail* 2009; 11: 92-98.
4. Hobbs F, Doust J, Mant J *et al.* Diagnosis of heart failure in primary care. *Heart* 2010; 96: 1773-77.
5. Fuat A, Murphy JJ, Hungin AP *et al.* The diagnostic accuracy and utility of a B-type natriuretic peptide test in a community population of patients with suspected heart failure. *Br J Gen Pract* 2006; 56: 327-33.
6. Raymond I, Groenning BA, Hildebrandt PR *et al.* The influence of age, sex and other variables on the plasma level of N-terminal pro brain natriuretic peptide in a large sample of the general population. *Heart* 2003; 89: 745-51.
7. Nielsen LS, Svanegaard J, Klitgaard NA *et al.* N-terminal pro-brain natriuretic peptide for discriminating between cardiac and non-cardiac dyspnoea. *Eur J Heart Fail* 2004; 6: 63-70.
8. Remes J, Miettinen H, Reunamen A *et al.* Validity of clinical diagnosis of heart failure in primary care. *Euro Heart J* 1991; 12: 315-21.
9. Cowie MR, Struthers AD, Wood DA *et al.* Value of natriuretic peptide in assessment of patients with possible new heart failure in primary care. *Lancet* 1997; 350: 1349-53.
10. Hildebrandt P, Collinson P. Amino-terminal pro-B-type natriuretic peptide testing to assist the diagnostic evaluation of heart failure in symptomatic primary care patients. *Am J Cardiol* 2008; 101 (suppl): 25A-28A.
11. Zaphiriou A, Robb S, Murray-Thomas T *et al.* The diagnostic accuracy of plasma BNP and NT-proBNP in patients referred from primary care with suspected heart failure: results of the UK natriuretic peptide study. *Eur J Heart Fail* 2005; 7: 537-41.
12. Gustafsson F, Steensgaard-Hansen F, Badskjaer J *et al.* Diagnostic and prognostic performance of N-terminal proBNP in primary care patients with suspected heart failure. *J Card Fail* 2005; 11 (suppl): S15-S20.
13. Al-Barjas M, Nair D, Ayrton P *et al.* How can the role of N-terminal pro B natriuretic peptide (NT-proBNP) be optimised in heart failure screening? A prospective observational comparative study [abstract]. *Eur J Heart Fail* 2004; 3 (suppl 1): 223.
14. Hildebrandt P, Collinson P, Doughty R *et al.* Age-dependent values of N-terminal pro-B-type natriuretic peptide are superior to a single cutpoint for ruling out suspected systolic dysfunction in primary care. *European Heart Journal* 2010; 31: 1881-89.
15. Leier C, Chatterjee K. The physical examination in heart failure—Part I. *Congest Heart Fail* 2007; 13: 41-47.
16. Leier C, Chatterjee K. The physical examination in heart failure—Part II. *Congest Heart Fail* 2007; 13: 99-104.
17. Hobbs FD, Doust J, Mant J *et al.* Heart failure: diagnosis of heart failure in primary care. *Heart* 2010; 96: 1773e[1].
18. Verdú JM, Comin-Colet J, Domingo M *et al.* Rapid point-of-care NT-proBNP optimal cut-off point for heart failure diagnosis in primary care. *Rev Esp Cardiol.* 2012; 65: 613-19.
19. Paulus WJ, Tschöpe C, Sanderson JE *et al.* How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J* 2007; 28(20): 2539-50.
20. National Clinical Guideline Centre. Chronic heart failure: the management of chronic heart failure in adults in primary and secondary care. London: National Clinical Guideline Centre; 2010. Available at: <http://guidance.nice.org.uk/CG108/Guidance/pdf/English>