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ORIGINAL ARTICLE

Measurement of Natriuretic Peptides in Patients with Suspected Heart Failure to Prevent Overuse of Echocardiography - a Pilot Study

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SUMMARY

Background: **European Society of Cardiology (ESC) guidelines recommend measuring natriuretic peptides (BNP or NT-proBNP) in patients with suspected heart failure (HF) as a first-line tool. HF should be ruled-out if concentrations of NT-proBNP are below 300 ng/L and 125 ng/L for acute HF and chronic HF, respectively.**
Methods: **Patients with suspected HF referred for transthoracic echocardiography (TTE) were enrolled; NT-proBNP concentrations were obtained from medical charts (measurement < 48 hours) or prospectively measured on the day of TTE.**
Results: **Out of 109 patients, NT-proBNP was measured by the referring department before TTE in 40 patients (36.7%), and 37.5% of these patients had NT-proBNP concentration below the rule-out threshold. NT-proBNP was measured in additional 38 patients on the day of TTE. Overall, 38.5% of the patients had a NT-proBNP concentration below the threshold value.**
Conclusions: **Natriuretic peptides are not routinely measured in patients with suspected HF; systematic measurement would reduce unnecessary TTE by at least 38.5%.**
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INTRODUCTION

B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP), which are derived from a common precursor, are secreted by cardiomyocytes in response to heart wall stress, and increased levels are associated with severity of heart failure (HF) [1,2]. Since 2016, the European Society of Cardiology (ESC) guidelines have recommended measuring NT-proBNP in patients with suspected HF as a first-line tool [3,4]. In patients with increased/grey zone natriuretic peptide concentrations, additional tests, such as transthoracic echocardiography (TTE) examinations, are warranted, because HF is a possibility, whereas TTE examinations are not recom-

mended in patients with suspected acute HF (AHF) and suspected chronic HF (CHF) if the NT-proBNP concentration is < 300 ng/L and < 125 ng/L, respectively [4]. Given high rates of HF hospitalization and diagnostic uncertainty in patients with dyspnoea, many patients with HF are cared for by non-cardiologist clinicians [5, 6]. This prospective study aimed to assess the compliance with the ESC guidelines and to determine the proportion of the TTE examinations that should not have been performed in patients from non-cardiology departments based on their NT-proBNP concentrations.

MATERIALS AND METHODS

Patients with suspected HF, referred to the echocardiography laboratory at the Department of Cardiology, Avicenne University Hospital (Bobigny, France), were enrolled in the study between October 2018 and March 2019. Patients without any signs or symptoms (i.e., those referred for detection of left ventricular [LV] dysfunction, pulmonary hypertension, valvular disease in the course of systemic disease and/or during cardiotoxic pharmacotherapy) were excluded. Informed consent was obtained from each patient, and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in an a priori approval by the institution's human research committee (Comite Local d'Ethique pour la recherche Clinique, Avicenne). All TTE examinations were performed < 48 hours after the request by senior cardiologists using an IE-33 system (Phillips, Bothell, WA, USA) and after the patients had rested for 15 minutes. All echocardiographic images were analyzed offline (ComPACS, Version 10.8.3; MediMatic, Genova, Italy) by two independent cardiologists that were bound to NT-proBNP measurements. TTE measurements included LV cavity dimensions, volume, and wall thickness; LV ejection fraction (Simson method); left atrial volume; detailed valvular evaluation; pulsed Doppler transmitral flow; tissue Doppler echocardiography; and pulmonary arterial pressure.

NT-proBNP concentrations were obtained from medical charts (measurement < 48 hours) and, if not performed before, measured from blood samples on the day of TTE. All NT-proBNP concentrations were centrally measured by using the Roche NT-proBNP electrochemiluminescence assay on the cobas® 6000 analyzer (both Roche Diagnostics International Ltd., Rotkreuz, Switzerland).

Continuous variables and qualitative data were compared by using Student's *t*-test and chi-squared test/Fisher's exact test, respectively. Statistical analyses were performed by using STATA software (StataCorp., LP, version 13.0; College Station, TX, USA).

RESULTS

Overall, 109 patients were included in the analysis (mean age: 65.2 years; male: 53.2%; Table 1). The overall TTE results are presented in Table 2. NT-proBNP was measured by the referring department before TTE in 40 (36.7%) patients, and more often in patients with suspected AHF than CHF (58.8% vs. 26.7%, respectively; p = 0.001; Table 1). Out of these 40 patients, 15 (37.5%) patients had NT-proBNP measurements below the rule-out threshold.

NT-proBNP was measured in additional 38 patients on the day of TTE, resulting in 78 available measurements. Of these 78 patients with available measurements, 30 (38.5%) patients had NT-proBNP measurements below the rule-out threshold, more often in patients with suspected CHF than AHF (41.3% vs. 34.3%, respectively; p = 0.191; Table 1).

None of the patients with NT-proBNP measurements below the rule-out threshold had TTE abnormalities, except for a single patient with LV ejection fraction (LVEF) between 40 - 45% (Table 2).

DISCUSSION

The 2016 ESC guidelines recommended measuring NT-proBNP in patients with suspected HF as a first-line tool; these recommendations were also encompassed into the 2021 guidelines [3,4]. In patients with natriuretic peptide concentrations below the rule-out threshold, an alternative diagnosis should be considered, and TTE is deemed unnecessary [3,4]. Conversely, in patients with increased/grey zone natriuretic peptide concentrations, additional tests, such as TTE examinations, are warranted, because HF is a possibility.

Adherence to clinical guidelines for the management of HF has been extensively studied; however, information around adherence to diagnostic guidelines is limited. Hayhoe et al. investigated 16,597 patients with suspected HF in the primary care setting and reported that only 39% of the patients underwent natriuretic peptide or TTE examination at a median of 292 days after onset of the symptoms [7]. Moreover, there is limited literature around adherence to the appropriate use criteria for TTE [8]. The estimated percentage of inappropriately ordered TTEs for any indication is up to 32%, with the lowest rate observed for HF [9,10]; this study supports these findings in the specific context of patients with suspected HF. Notably, even some patients with low NT-proBNP concentrations were referred for TTE, which is assumed to be due to a lack of knowledge among non-cardiologists when it comes to the interpretation of natriuretic peptide measurements, despite an around the clock availability of the test.

The negative predictive value of natriuretic peptides for ruling out AHF and CHF has been established [3,4]. Though this study was not designed to investigate the negative predictive value of NT-proBNP, there was a

Table 1. Baseline characteristics of the study group.

	Total population (n = 109)
Mean age, years ± SD	65.2 ± 21.1
Male gender n (%)	58 (53.2)
BMI, kg/m^2, median (IQR)	26.6 (22.7 - 30.2)
Patients with suspected AHF, n (%)	34 (31.2)
Patients with suspected CHF, n (%)	75 (68.8)
TTE requests by department:	
Respiratory medicine	53
Internal medicine	4
Surgery department	7
Geriatric unit	3
Emergency department	2
All other departments	< 5
ECG performed, n (%)	86 (78.9)
ECG normal, n (%)	54 (62.8)
Blood tests, median (IQR)	
Sodium, mmol/L	140 (138 - 142)
Potassium, mmol/L	4.3 (4.0 - 4.7)
Creatinine, μmol/L	76 (57 - 94)
Hemoglobin, g/dL	12.2 (10.6 - 13.6)
NT-proBNP measured before TTE, n (%)	40 (36.7)
In suspected AHF, n (%)	20 (58.8)
In suspected CHF, n (%) Below the rule-out threshold, n (%) Above the rule-out threshold, n (%)	20 (26.7) 15 (37.5) 25 (62.5)
NT-proBNP concentration, median (IQR) [a]	
Suspected AHF, ng/L	850 (323 - 2,733)
Suspected CHF, ng/L	131 (73 - 491)
NT-proBNP concentrations below the rule-out threshold, n (%) [a] Suspected AHF, n (%) Suspected CHF, n (%)	30 (38.5) 11 (34.3) 19 (41.3)

TTE examinations are not recommended if NT-proBNP concentration is < 300 ng/L in patients with suspected AHF and < 125 ng/L in patients with suspected CHF. [a] - out of the 78 patients with available NT-proBNP measurements. Abbreviations: AHF - acute heart failure, BMI - body mass index, CHF - chronic heart failure, ECG - electrocardiogram, IQR - interquartile range, NT-proBNP - N-terminal pro-BNP, TTE - transthoracic echocardiography.

single patient with a low NT-proBNP concentration and a reduced LVEF of < 50% (without associated increase in filling pressure or positive airway pressure).

In this study, only patients referred for TTE due to suspected HF were included, even though similar studies have included patients at high risk for HF for the screening of asymptomatic LV dysfunction [11]. Most patients hospitalized in cardiology departments have confirmed cardiac diseases; therefore, biomarkers for the diagnosis and prognostication of cardiac diseases are routinely implemented. Thus, this study assessed patients referred to non-cardiology departments. One limitation of this study is the small sample size, obtained at a single center (a university teaching hospital), which may have resulted in underestimated non-adherence to the ESC guidelines - a hypothesis that warrants confirmation in a larger, multi-center study.

In conclusion, our findings show that natriuretic peptides are not routinely measured in patients with suspected HF; systematic measurement would reduce the rate of unnecessary TTE examinations by at least 38.5%. These findings highlight an unmet need for education of non-cardiologist clinicians on the utility of natriuretic peptides measurement to prevent overuse of

Table 2. Overall transthoracic echocardiography results.

	Total population (n = 109)	Acute HF (n = 32) [b]		Chronic HF (n = 46) [b]	
		NT-proBNP < 300 ng/L (n = 11)	NT-proBNP ≥ 300 ng/L (n = 21)	NT-proBNP < 125 ng/L (n = 19)	NT-proBNP ≥ 125 ng/L (n = 27)
Mean LV end-diastolic diameter, mm	46 ± 6	46 ± 3	46 ± 7	45 ± 6	46 ± 8
Mean septum thickness, mm	10 ± 2	11 ± 1	12 ± 4	10 ± 2	10 ± 1
Mean posterior wall thickness, mm	10 ± 2	10 ± 1	10 ± 1	10 ± 1	10 ± 1
LVEF, %	61 ± 8	59 ± 7	59 ± 10	62 ± 7	61 ± 9
LVEF < 50%, n (%)	9 (8.3)	1 (9.1)	4 (19.1)	0 (0)	3 (11.1)
Mean doppler transmitral E/A ratio	0.8 ± 0.5	0.7 ± 0.1	1.1 ± 0.4	0.9 ± 0.3	1.0 ± 0.8
Mean E' lateral mitral annulus velocity, cm/s	9.7 ± 2.9	9.0 ± 1.7	10.3 ± 3.5	9.1 ± 2.5	9.4 ±2.9
Mean mitral E/E' ratio	8.1 ± 3.0	7.9 ± 2.8	9.5 ± 3.4	7.8 ±2.3	8.5 ±4.0
Mean indexed left atrial volume, cm^2/m^2	30.0 ± 17.0	22.7 ± 7.7	38.5 ± 17.3	23.9 ± 8.5	35.2 ± 22.4
Diastolic dysfunction, n (%)	7.0 (6.4)	0 (0.0)	2 (9.5)	0 (0)	2 (7.4)
Grade 2 or 3 diastolic dysfunction, n (%)	7.0 (6.4)	0 (0.0)	2 (9.5)	0 (0)	2 (7.4)
Moderate/severe valvular disease, n (%)	6 (5.5)	0 (0.0)	1 (4.8)	0 (0)	5 (18.4)
Mean TAPSE, mm	23 ± 5	25 ± 4	20 ± 5	23 ± 6	21 ± 4
Mean tricuspid regurgitation maximal velocity, m/s	2.7 ± 0.5	2.5 ± 0.2	2.8 ± 0.6	2.5 ± 0.3	3.0 ± 0.5
Mean systolic pulmonary arterial pressure, mmHg [a]	36 ± 11	31 ± 4	40 ± 12	32 ± 7	42 ± 13
Increased pulmonary arterial pressure, n (%)	5 (4.5)	0 (0.0)	3 (6.3)	0 (0)	1 (3.7)

[a] - Pulmonary arterial hypertension was defined as a systolic PAP of > 35 mmHg in patients aged < 70 years and > 45 mmHg in patients aged ≥ 70 years. All mean values are ± standard deviation.
[b] - NTproBNP concentrations obtained in 78 patients.
Abbreviations: E/A - the early (E) and late (A) diastolic filling velocities ratio, E' - early diastolic, E/E' - the ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity, LV - left ventricular, LVEF - left ventricular ejection fraction, NT-proBNP - N-terminal pro-BNP, PAP - positive airway pressure, TAPSE - tricuspid anteroposterior excursion.

echocardiography.

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Declaration of Interest:
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