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Echocardiographic subtypes of heart failure in consecutive hospitalised patients with dyspnoea

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ABSTRACT

Heart failure with preserved ejection fraction (HFpEF) involves half of hospitalised patients with heart failure (HF), but estimates vary due to unclear diagnostic criteria. We performed a prospective observational study of hospitalised patients admitted with dyspnoea. The aim was to apply contemporary guidelines to diagnose HF due to valvular disease (HFvhd), HF due to reduced ejection fraction (HFrEF), HF due to midrange EF (HFmrEF) and HFpEF in relation to presumed cardiac or non-cardiac dyspnoea.

Methods We included consecutive hospitalised patients with presumed HF or dyspnoea and excluded patients with acute coronary syndrome, estimated glomerular filtration rate <30 mL/min/1.73 m² or low NT-proBNP (<296 ng/L). Higher age-adjusted NT-proBNP values excluded patients with presumptive non-cardiac dyspnoea. Contemporary criteria for HFpEF and diastolic dysfunction were assessed, and we adjudicated whether acute decompensated HF (ADHF) had been the primary diagnosis.

Results Of 707 eligible patients, we included 370 patients of whom 75 had non-cardiac dyspnoea. Of these, 10% (38/370) had no cardiac dysfunction. Cardiac dysfunction consisted of 18.4%, HFvhd, 30.1% HFrEF, 10.2% HFmrEF and 41.3% HFpEF. HFpEF was twice as common in presumptive non-cardiac dyspnoea versus cardiac dyspnoea (71% vs 34%, p<0.0001). However, adjudicated ADHF was the primary diagnosis in 80% of HFrEF, 62% of HFmrEF and just 28% of HFpEF.

Conclusion HF according to contemporary criteria applied to 90% of patients admitted with dyspnoea and elevated NT-proBNP irrespective of the presumptive cause of dyspnoea, of whom 10% had HFmrEF and 41% HFpEF. However, significant non-cardiac diagnoses related to 9 out of 10 with HFpEF with pulmonary disease as the predominant adjudicated problem.

Key questions

What is already known about this subject?

- Heart failure with preserved ejection fraction (HFpEF) involves 50% of hospitalised patients with heart failure (HF).
- Dyspnoea is *the* cardinal symptom of HF, but dyspnoea is frequently caused by non-cardiac comorbidity.

What does this study add?

- The majority of previous studies did not examine consecutive patients with dyspnoea and did not base their HF diagnosis on natriuretic peptides and a comprehensive echocardiogram with evaluation of diastolic function.
- In our prospective observational study, we asked, 'what is the diagnostic outcome of applying European Society of Cardiology (ESC) criteria including natriuretic peptide and a comprehensive echocardiogram to consecutive patients admitted with dyspnea?'.
- The echocardiogram showed cardiac dysfunction, and therefore HF, in 90% of patients admitted with dyspnoea and elevated NT-proBNP, where 41% had HFpEF, and 10% HF with EF 40%–49%. However, pulmonary disease was the predominant adjudicated clinical diagnosis in patients who fulfilled contemporary echocardiographic criteria for HFpEF.

How might this impact on clinical practice?

- This study supports that HF is a frequent complication in pulmonary disease, and we show the outcome of using the 2016 ESC guideline strategy to identify HF in consecutive patients admitted with dyspnoea.
- Although HFmrEF and HFpEF subtypes accounts for half of all HF, 9 out of 10 have significant non-cardiac disease as the predominant adjudicated problem, which calls for a multidisciplinary management plan and more research addressing this particular problem.

INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) involves 50% of hospitalised patients with heart failure (HF),[1] but evaluation of the scale of the problem varies due to unclear diagnostic criteria,[2] comorbidity and various types of hospitals.[1] Previous registry studies of HF epidemiology were not based on comprehensive echocardiograms, and they rarely describe the underlying subtype of HF. Knowing the subtype of HF is essential for selecting evidence-based treatment, but there seems to be a mismatch between

patients entering randomised clinical trials and patients seen in clinical practice.[3]

Recent guidelines authorise the use of natriuretic peptide to rule out HF[4]; they acknowledge left ventricular (LV) hypertrophy and enlarged left atrium (LA) as a reason for HFpEF and give clear criteria for diastolic dysfunction.[4 5] The doorway to finding patients with HF is to examine patients with dyspnoea, and therefore, we asked, 'what is the diagnostic outcome of applying novel guideline criteria including a comprehensive echocardiogram to consecutive patients admitted with dyspnea?'.

We used a prospective observational study to describe the subtype of cardiac dysfunction, if any, among all comers admitted with dyspnoea. Although data were collected in 2010,[6] the recent 2016 guidelines were used to diagnose HFpEF and 'HFmrEF'[4] (midrange LV EF from 40% to 49%). The aim was to describe the frequency of subtypes of cardiac dysfunction in patients hospitalised with dyspnoea and elevated NT-proBNP, in relation to HFpEF, HFmrEF and HF due to reduced EF (HFrEF) and to examine the impact of non-cardiac comorbidity.

METHODS

Study design and population

The Copenhagen Heart Failure with Preserved Ejection Fraction study was designed as a prospective observational study to evaluate all patients ≥40 years of age admitted with acute dyspnoea to the acute medical unit, general medicine ward and department of cardiology at Bispebjerg University Hospital, a non-tertiary hospital serving about 250 000 people in 2010. Patients from the accidents and emergency department were examined only if they were subsequently hospitalised. Screening was performed at 180 predefined randomly selected study days between 16 November 2009 and 31 July 2011, covering all days of the week.

The Danish regional ethical committee waived requirement for informed consent because NT-proBNP measurement and echocardiography were considered appropriate examinations and the study was classified as a prospective registry.

Patients were identified by a research fellow in cardiology (CMC) who screened all medical records within the first 24 hours after non-elective admission. The research fellow verified data from the clinically working physicians and collected supplementary baseline data including previous and presumptive diagnoses (see figure 1).

Inclusion criteria and presumptive cause of dyspnoea

Patients were eligible if dyspnoea (any sensation of shortness of breath, resting dyspnoea, orthopnoea or paroxysmal nocturnal dyspnoea) or suspected HF was the dominant or codominant reason for admission. The initial presumptive causes of dyspnoea, as made by the staff physicians within 24 hours, were systematically reviewed by the research fellow and categorised into: (1) non-cardiac dyspnoea or (2) presumptive cardiac dyspnoea based on the following criteria.

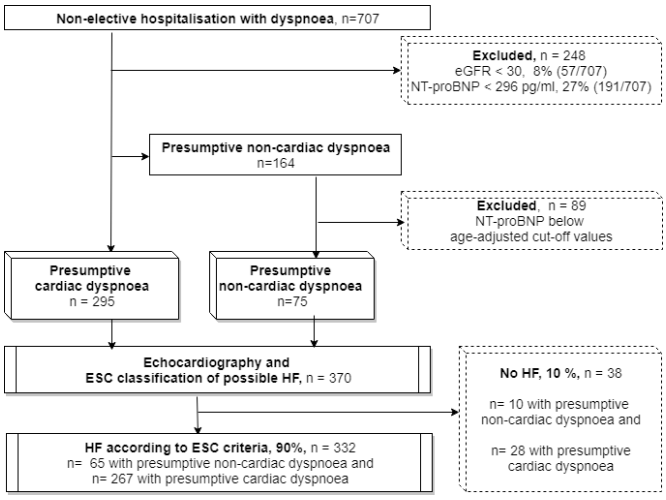

Figure 1 Consort diagram of patients. eGFR, estimated glomerular filtration rate; HF, heart failure.

Non-cardiac dyspnoea

- Patients presenting with obvious non-cardiac conditions: known irreversible intractable chest malignancy, previous admissions with documented severe chronic obstructive pulmonary disease (COPD) and forced expiratory volume <50% of expected value in an outpatient setting, previous COPD admission with need of home oxygen prior to admission, acute pneumonia documented on X-ray, or acute pulmonary embolism, severe anaemia (haemoglobin <5 mmol/L) or severe obesity (body mass index >40).

Presumptive cardiac dyspnoea

- Remaining patients were classified as presumptive cardiac dyspnoea, also including dyspnoea of unknown aetiology (figure 1).

Exclusion criteria

Patients were excluded if they had chronic kidney disease stage 4 and 5 with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m² using the Modification of Diet in Renal Disease formula, or if they had predominantly chest pain with acute coronary syndrome and scheduled for an acute coronary angiogram. Patients with presumptive non-cardiac dyspnoea were excluded if NT-proBNP was under the below mentioned age-adjusted rule-in values.

NT-proBNP analysis

NT-proBNP was analysed at time of admission using a commercially available immunoassay (Elecsys NT-proBNP, Roche Diagnostics, pmol/L) on the Cobas e 411 platform. Our laboratory reports an inter-run coefficient of variation <2.0%. The rule out threshold was NT-proBNP concentration <35 pmol/L, equal to 296 ng/L (to convert ng/L to pmol/L, multiply by 0.118).[7] Patients with presumptive non-cardiac dyspnoea were excluded if

NT-proBNP <50 pmol/L (423 ng/L) for age 40–49 years; <100 pmol/L (846 ng/L) for age 50–74 years; and <200 pmol/L (1691 ng/L) for age 75 years or more. These values are slightly lower than the age adjusted rule-in values of 450 ng/L, 900 ng/L and 1800 ng/L that were previously recommended for the respective age groups.[7 8]

Echocardiogram

A comprehensive echocardiogram was performed by the cardiology fellow in all included patients (figure 1) within 48 hours of admission, unless an echocardiogram within the last 3 months existed and documented an left ventricular ejection fraction (LVEF) <40% or severe valvular heart disease (VHD). The echocardiogram included systematic evaluation of cardiac structure and function,[9] and all patients with LVEF of 40% or above were examined for diastolic dysfunction.[10 11] Measurements equalled the median over 3–5 cardiac cycles when patients had sinus rhythm and median over 5–10 cycles for patients in atrial fibrillation (AF).

LVEF and severe valve disease were reported to the clinical staff promptly, but remaining parameters were analysed later on stored images (Xcelera system by Philips). Validation of the individual echocardiographic parameters was performed by a second reviewer (OWN and/or LK). LA maximum volume was calculated in four-chamber and two-chamber view using the area length formula.[12] Key structural alterations were defined as: LA maximum volume index >34 mL/m^2 and LV hypertrophy, defined as LV mass index ≥115 g/m^2 for males and ≥95 g/m^2 for females.[4] For the present analyses, we defined 'definite diastolic dysfunction' according to a recent consensus paper[5] as the presence of 3 or 4 of the following four parameters: velocity of septal e′ <7 cm/s or lateral e′ <10 cm/s; average E/e′ ratio >14; LA maximum volume index >34 mL/m^2; peak TR velocity >2.8 m/s. e′ was calculated as the mean from anterior, posterior, septal and lateral walls.

ESC classification of HF subtypes

Evidence for abnormal cardiac function or structure were classified according to 2016 ESC criteria,[4] where severe VHD was classified first to avoid interference of VHD with subsequent grouping. Hence, cardiac dysfunction was classified in the ranked order:

1. First, in case of severe VHD, patients were classified as 'HFvhd'.
2. The remaining with LVEF <40% were denoted HF with reduced EF, that is, 'HFrEF'.
3. The remaining with LVEF from 40% to 49% were classified as 'HFmrEF'.
4. The remaining with LVEF ≥50% who had 'definite diastolic dysfunction', LA enlargement or LV hypertrophy were denoted as 'HFpEF'.
5. The rest with LVEF ≥50% and 'indeterminate or no definite LV diastolic dysfunction' were denoted as 'not HF'.

Clinical scores of HF signs and comorbidity

The research fellow documented all subjective and objective signs and symptoms needed for the Framingham and Boston heart failure score.[13 14] The Boston HF score adds signs and symptoms into a score from 0 to 12 where 0–4 denote 'unlikely HF', 5–7 denote 'possible HF' and 8–12 denote 'definite HF'. The Charlson Comorbidity Index was calculated as the total of the patient's comorbid conditions, which had been weighted without giving weight to age.[15 16]

Adjudicated primary diagnosis

Acute decompensated HF (ADHF) was adjudicated as the primary diagnosis if ADHF had been the most significant problem during admission based on review of medical records, staff diagnoses and echocardiography. The adjudicated diagnosis required consensus among the clinical working cardiologists and the research fellow in cardiology. In case of inconsistency or doubt, the final diagnosis was further adjudicated by additional two cardiologists (OWN and LK). To minimise the ambiguity of clinical judgement, the definition of ADHF relied on documentation of central or peripheral fluid retention as the most significant clinical problem, with an adequate response to diuretic therapy, accompanied by abnormal function or structure in the reviewed echocardiogram. Reversible reasons for acute decompensation such as arrhythmias or abnormal loading conditions were also considered valid reasons for ADHF.

Statistics

Values are expressed as means and SD, medians and quartiles or counts and percentages as appropriate in relation to normality.

Participants with missing values were minimised by adhering to the inclusion and exclusion criteria. No imputation was made for participants with missing values, but data validity was ensured by reporting variables for subgroups with a high rate of non-missing values (see online supplementary table for missing values). Sensitivity analyses were inherently performed for patients with and without cardiac dyspnoea and by comparing diastolic function to patients with 'No HF'. NT-proBNP was transformed with the natural logarithm before comparing mean values in trend analyses. Univariate analyses of variables between groups were performed with the Kruskall-Wallis test and non-parametric test for trend examined trends between groups. P<0.05 was taken to indicate significance and all statistical analyses were performed using Stata V.13 statistical software.

RESULTS

Population

Seven hundred and seven patients with dyspnoea were eligible during 180 days of screening, after excluding 57 patients due to chronic kidney disease and 191 with low NT-proBNP values (figure 1). The 191 patients excluded

Table 1 Characteristics of patients according to presumptive working diagnosis

		Presumptive cardiac dyspnoea	Presumptive non-cardiac dyspnoea	P value
N		295	75	
Age, mean (SD)		77.0 (11.9)	72.9 (10.9)	0.007
Female gender		145 (49.2%)	43 (57.3%)	0.21
Previous hosp for HF		98 (33.2%)	7 (9.3%)	<0.001
Known valve disease		36 (12.2%)	2 (2.7%)	0.015
Known HFrEF		56 (19.0%)	0 (0.0%)	<0.001
IHD		76 (25.8%)	12 (16.0%)	0.076
Diabetes		61 (20.7%)	16 (21.3%)	0.90
COPD		91 (30.8%)	51 (68.0%)	<0.001
Atrial fibrillation, history or new		150 (50.8%)	27 (36.0%)	0.022
Hypertension, history or ≥140/90 mm Hg		216 (73.2%)	47 (62.7%)	0.072
Anaemia (HgB <8.1 M or <7.4 F)		116 (39.3%)	39 (52.0%)	0.047
Chronic kidney disease	≥90	46 (15.7%)	13 (17.3%)	0.86
Groups from eGFR	60–89	127 (43.3%)	30 (40.0%)	
	30–59	120 (41.0%)	32 (42.7%)	
NT-proBNP, median (IQR), ng/L		3102 (1322, 8729)	2712 (1686, 9034)	0.74
Charlson Comorbidity Index, mean (SD)		2.5 (1.9)	3.1 (2.3)	0.023
Signs and symptoms of HF on examination				
Boston score	0–4 point	30 (10.2%)	3 (4.0%)	0.005
	5–7 point	83 (28.1%)	35 (46.7%)	
	8–12 point	182 (61.7%)	37 (49.3%)	
Framingham HF	Negative	100 (33.9%)	42 (56.0%)	<0.001
	Positive	195 (66.1%)	33 (44.0%)	

COPD, chronic obstructive pulmonary disease;HF, heart failure; HFrEF, heart failure due to reduced EF; IHD, ischaemic heart disease; eGFR, estimated glomerular filtration rate.

because of low NT-proBNP had a mean age of 62.7 (SD 12.6) years, eGFR of 80.9 (SD 14.5), NT-proBNP of 129 (SD 68) ng/L, 57% had COPD/asthma and 2.7% AF. Of 164 patients with presumptive non-cardiac dyspnoea, we excluded 89 who had NT-proBNP below the age-adjusted rule-in values. Hence, a total of 370 patients were included of whom 295 patients had presumptive cardiac dyspnoea and 75 had presumptive non-cardiac dyspnoea (figure 1). Significant signs or symptoms of HF related to more than 90% of patients, as indicated by a Boston score above 4 points. (table 1)

HF subtypes in examined patients

No cardiac dysfunction was found in 10% of included patients (figures 1and and 2) (38/370, 95% CI 7% to 13%), with similar rates for presumptive non-cardiac and cardiac dyspnoea (13.5% vs 9%, ns.). Among 332 patients with cardiac dysfunction, 10.2% had HFmrEF (34/332, 95% CI 7% to 14%) and 41% HFpEF (137/332, 95% CI 35% to 47%). HFpEF was twice as common in patients with presumptive non-cardiac dyspnoea as compared with presumptive cardiac dyspnoea (70.8% vs 34.1%, p<0.0001, figure 3). Of the 62 patients with severe valve disease, 42% (26/62, 95% CI 20% to 54%) also had LVEF <40%.

Patients characteristics in relation to HF subtype

Moving from HFrEF over HFmrEF to HFpEF there was a significant trend for higher age, more females, lower diastolic BP, higher pulse pressure and lower NT-proBNP (table 2). HFmrEF was comparable with HFrEF in most aspects, apart from less comorbidity and a higher age in HFmrEF patients. HFmrEF was associated with significantly more of AF and ischaemic heart disease as compared with HFpEF.

Acute decompensated HF was adjudicated as the primary clinical diagnosis in 80% of HFrEF, 62% of HFmrEF and 27.7% of HFpEF (figure 4 and table 3). Similarly, pulmonary disease was the most frequent adjudicated primary clinical diagnosis in patients classified as HFpEF (table 3).

HFpEF without a non-cardiac adjudicated primary diagnosis related to just 11% (38/332) of all patients fulfilling the ESC criteria for HF (n=38 with ADHF in table 3).

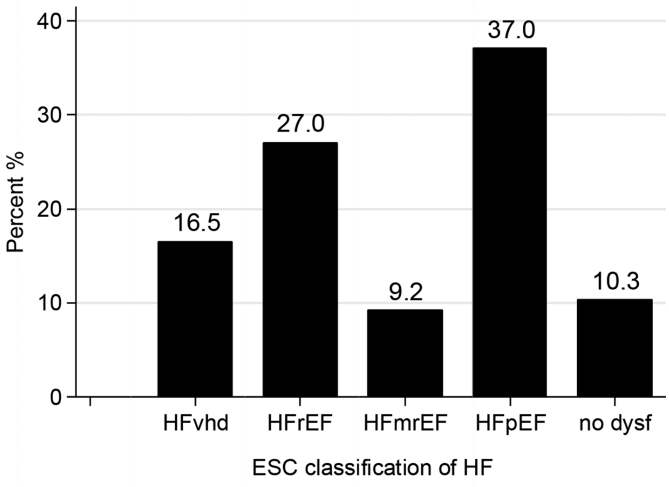

Figure 2 Percentage distribution of ESC HF subtypes and no cardiac dysfunction (no dysf, n=38) among all 370 included patients, where HFvhd is HF due to valvular heart disease (n=61), HFrEF is HF with reduced ejection fraction (n=100), HFprEF is HF with mid range ejection fraction (n=34) and HFpEF is HF with preserved ejection fraction (n=137). EF, ejection fraction; HF, heart failure; HFmrEF, HF due to midrange EF; HFpEF, HF with preserved EF; HFrEF, HF due to reduced EF.

Diastolic dysfunction in patients with LVEF of 40% or more

'Definite' diastolic dysfunction was observed in 62% of HFmrEF and 60% of HFpEF based on diastolic function parameters (table 4), while 'normal' diastolic function comprised less than 10% in HFmrEF and HFpEF. More than 95% of HFmrEF and HFpEF patients had enlarged LA. Indeterminate diastolic dysfunction was observed in about one-third of all subtypes including the 'no HF' group (table 4).

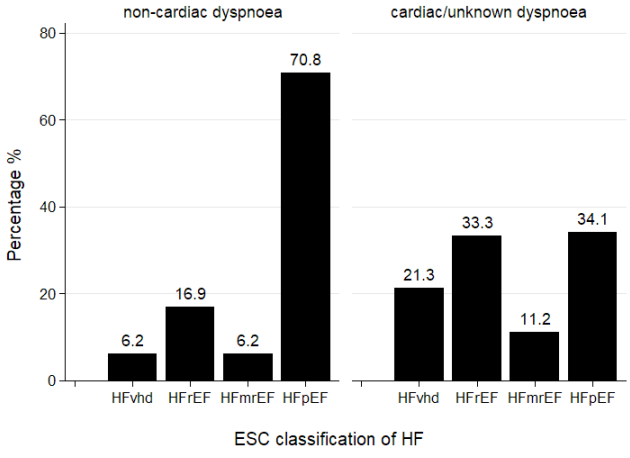

Figure 3 Percentage distribution of ESC types of cardiac dysfunction among 65 patients with presumptive non-cardiac dyspnoea: HFvhd (n=4); HFrEF (n=11), HFmrEF (n=4) and HFpEF (n=46), and 267 HF patients with presumptive cardiac dyspnoea: HFvhd (n=57); HFrEF (n=89), HFmrEF (n=30) and HFpEF (n=91). EF, ejection fraction; HF, heart failure; HFmrEF, HF due to midrange EF; HFpEF, HF with preserved ejection fraction; HFrEF, HF due to reduced EF; HFvhd, HF due to valvular disease.

DISCUSSION

Cardiac dysfunction according to contemporary ESC criteria for HF was demonstrated in 90% of consecutive hospitalised patients with dyspnoea and elevated NT-proBNP, where 41% could be ascribed to HFpEF and 10% to HFmrEF. Presumed non-cardiac dyspnoea and elevated NT-proBNP was associated with a 71% prevalence of HFpEF, and the diagnosis primarily grounded on structural rather than functional abnormalities since 40% of HFpEF patients lacked 'definite diastolic dysfunction'. HFpEF presenting as ADHF accounts for merely 11%, not 41%, since pulmonary disease was the predominant adjudicated problem in patients with HFpEF.

HF criteria in clinical studies

Our study differs from other studies by examining consecutive patients with undifferentiated dyspnoea, instead of just patients with presumptive cardiac dyspnoea. By use of the contemporary 2016 ESC criteria for HF and diastolic dysfunction, merely 10% did not have one of the ESC HF subtypes, which is unprecedented information.

The ESC criteria for cardiac dysfunction are objective and externally valid.[4 5] However, it may be questioned whether LA enlargement and/or LV hypertrophy alone may account for hospitalised HFpEF, because both findings are highly prevalent in elderly patients with hypertension and/or AF. In a recent community-based study, 49% of patients had one or two abnormal measures of diastolic dysfunction.[17] Although LA enlargement and LV hypertrophy do not cause HF per se, they predispose to the symptoms and signs of HF by reducing the patients ability to compensate when the cardiovascular system become challenged.[18]

A causal relationship between dyspnoea and HFpEF is more convincing if three or four out of four diastolic dysfunction criteria are abnormal.[5] However, diastolic dysfunction parameters are dynamic, and the E/e′ and tricuspid regurgitant velocity vary in relation to LV filling pressure, so timing of echocardiography becomes important. In this study, echocardiography was made within 48 hours of admission, and the Doppler signs of diastolic dysfunction probably diminished in some patients after appropriate treatment.

ESC subtypes of HF

HFmrEF occurred in 10%, which is lower than previous estimates of 10%–20%,[19] probably because we classified severe valve disease before all the other subtypes. HFmrEF patients had a higher burden than HFpEF with respect to AF, ischaemic heart disease and ADHF as the adjudicated primary clinical diagnosis. Just 5.9% of HFmrEF patients had a normal diastolic function, indicating that HFmrEF patients have a significant cardiac dysfunction.

Although one out of two patients had a LVEF above 40%, at most 1 in 10 could be considered for a clinical

Table 2 Characteristics of HFrEF, HFmrEF and HFpEF

Characteristic		HFrEF N=100	HFmrEF N=34	HFpEF N=137	P value trend
Age, mean (SD)	Mean (SD)	73.2 (11.6)	77.2 (12.0)	77.1 (11.3)*	0.021
Male, n (%)	Mean (SD)	71 (71.0%)	19 (55.9%)†	43 (31.4%)*	<0.001
Body mass index, mean (SD)	Mean (SD)	26.3 (4.9)	28.8 (7.8)	26.7 (6.2)	0.923 0
Heart rate per min	Mean (SD)	93.9 (26.8)	92.3 (26.8)	92.8 (22.2)	0.896
BP systolic, mm Hg	Mean (SD)	140.9 (31.2)	143.9 (28.0)	143.5 (29.3)	0.326
BP diastolic, mm Hg	Mean (SD)	83.1 (22.0)	80.6 (20.6)	75.1 (16.5)*	0.008
Pulse pressure, mm Hg	Mean (SD)	57.8 (22)	63.3 (21.2)	68.1 (21.4)*	<0.001
Respiratory rate, per min	Mean (SD)	23.4 (7.3)	21.8 (5.4)	23.4 (6.8)	0.656
NT-proBNP, ng/L	Mean (SD)	8700 (8701)	6151 (7598)†	2987 (3392)*	<0.001
NT-proBNP in intervals	0–422	1 (1.0%)	0 (0.0%)	9 (6.6%)*	<0.001
Groups ng/L	423–845	4 (4.0%)	4 (11.8%)	11 (8.0%)	
	846–1690	10 (10.0%)	8 (23.5%)	34 (24.8%)	
	1691+	85 (85.0%)	22 (64.7%)	83 (60.6%)	
Clinical signs of heart failure					
Dyspnoea at rest	Number (%)	42 (42.0)	12 (35.3)	74 (54.0)	0.057
Functional dyspnoea	Number (%)	86 (86.0)	30 (88.2)	126 (92.0)	0.140
Dyspnoea when walking stairs	Number (%)	99 (99.0)	33 (97.1)	133 (97.1)	0.331
Rales on auscultation	Number (%)	51 (51.0)	14 (41.2)	62 (45.3)	0.405
Rhonchi on auscultation	Number (%)	23 (23.0)	7 (20.6)†	60 (43.8)*	0.001
Congestion on chest X-ray	Number (%)	41 (41.0)‡	5 (14.7)	28 (20.4)*	0.001
Echocardiography					
LVEF %	Mean (SD)	27.4 (7.4)‡	44.0 (2.8)†	58.5 (5.7)*	<0.001
LV mass index,	Mean (SD)	117.7 (31.3)‡	97.4 (20.6)†	87.8 (23.0)*	<0.001
LA volume index, mL/m^2	Mean (SD)	59.6 (16.0)	58.7 (20.4)†	51.8 (15.9)*	0.001
IVSd (cm)	Mean (SD)	1.1 (0.2)	1.1 (0.2)†	1.0 (0.2)	0.206
LVDd (cm)	Mean (SD)	5.5 (0.7)‡	5.0 (0.7)†	4.6 (0.6)*	<0.001
PWTd (cm)	Mean (SD)	1.0 (0.2)	0.9 (0.2)	0.9 (0.2)*	0.003

*P<0.05 for individual comparison: HFrEF versus HFpEF.
†P<0.05 for individual comparison: HFmrEF versus HFpEF.
‡P<0.05 for individual comparison: HFrEF versus HFmrEF.
BP, blood pressure; EF, ejection fraction; HF, heart failure; HFmrEF, HF due to midrange EF; HFpEF, HF with preserved EF; HFrEF, HF due to reduced EF; IVSd, interventricular septum in diastole; LA, left atrium; LV, left ventricular; LVDd, left ventricular diameter in diastole; PWTd, posterior wall thickness in diastole.

trial evaluating new therapy for HFpEF, calculated as an overall 41.3% prevalence of HFpEF (figure 2) of whom 27% were adjudicated to have ADHF (see figure 4).

Use of natriuretic peptides to diagnose HF

Guidelines recommend NT-proBNP screening in patients presumed to have HF, where a value below 300 ng/L rules out HF. However, guidelines are indecisive regarding routine use of NT-proBNP testing in patients with presumptive non-cardiac dyspnoea and recent clinical trials of acute HF included patients based on much higher NT-proBNP values, above 2000 pg/mL.[20 21]

Our results support that an echocardiogram including evaluation of diastolic function is indicated if NT-proBNP is elevated above the here applied threshold values. A recent study of 80+ year old patients from Singapore and New Zealand showed that similar rule-in values had a sensitivity of 89% and negative predictive value of 94%.[22]

Problems with diagnosing HF

The high frequency of comorbidities in consecutive patients with dyspnoea precludes the idea of assigning an 'exclusive' HF diagnosis as the undisputed cause of dyspnoea, and there is an unmet need for guidelines and clinical trials of HF to address this problem. It is well known that comorbidity begets HF, and comorbidity is much more than an innocent bystander to HF. The mechanisms for pulmonary disease to interact with

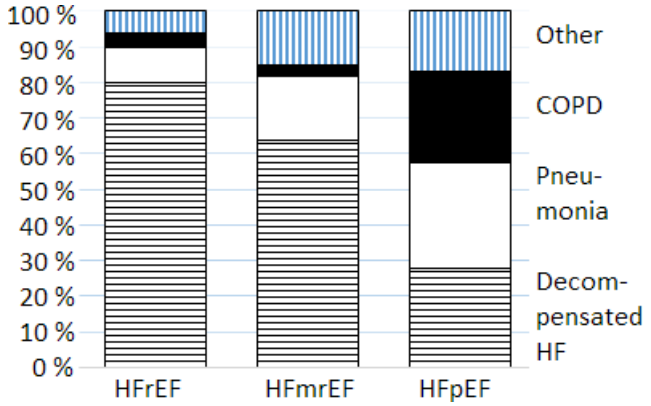

Figure 4 The adjudicated primary diagnosis (HF, pneumonia, COPD or other) that dominated during admission according to ESC HF type: HFrEF (n=100), HFmrEF (n=34) and HFpEF (n=137). EF, ejection fraction; HF, heart failure; HFmrEF, HF due to midrange EF; HFpEF, HF with preserved EF; HFrEF, HF due to reduced EF.

HFpEF could be through a decreased cardiorespiratory reserve[18] secondary to systemic inflammation, endothelial dysfunction, increasing load on the peripheral as well as the pulmonic vasculature which lead to higher LV filling pressure, abnormal diastolic function parameters[23] and pulmonary hypertension. However, there is also a risk that the contemporary diagnostic criteria will 'overdiagnose' HFpEF in patients with preexisting asymptomatic left atrial enlargement[24] or LV hypertrophy.

Strengths and limitations

The main advantage of the present study is that the HFpEF diagnosis was evaluated in a large population based on a comprehensive echocardiogram instead of the more widely used incomplete criterion 'lack of an echocardiogram showing a low EF'. Unlike most other studies, we examined consecutive patients and did a systematic prospective work-up in every patient with dyspnoea including a comprehensive echocardiogram and a careful validation in each patient in relation to competing comorbidities. Large registry studies of hospitalised patients with HF do not provide this type of information.

Clinical research in the emergency setting is challenging with a lot of pitfalls, but it is the only way to characterise acute real-world patients presenting with a plethora of presumptive diagnoses. We could not entirely avoid selection bias and excluded stage 4 and 5 kidney disease, because severe kidney disease is known to increase NT-proBNP and induce congestion, and this entity should be subject for a separate investigation.[25] Our data also do not reflect patients presenting with acute coronary syndrome, critically acute patients who died, were transferred or trivial cases with mild symptoms that were discharged immediately from the emergency room.

Generalisability of our results may not apply to other healthcare systems who have a different level of threshold

Table 3 Characteristicsof HFrEF, HFmrEF and HFpEF

Supplementary characteristics		HFrEF N=100	HFmrEF N=34	HFpEF N=137	P value trend
Adjudicated primary diagnosis					
Decompensated HF		80 (80.0%)	21 (61.8%)*	38 (27.7%)†	<0.001
Pneumonia		10 (10.0%)	6 (17.6%)	41 (29.9%)	
COPD		4 (4.0%)	2 (5.9%)	35 (25.5%)	
Other		6 (6.0%)	5 (14.7%)	23 (16.8%)	
NT-proBNP in intervals	0–422	1 (1.0%)	0 (0.0%)	9 (6.6%)†	<0.001
groups ng/L	423–845	4 (4.0%)	4 (11.8%)	11 (8.0%)	
	846–1690	10 (10.0%)	8 (23.5%)	34 (24.8%)	
	1691+	85 (85.0%)	22 (64.7%)	83 (60.6%)	
Chronic kidney disease					
Stage 1 with eGFR	80+	14 (14.1%)	4 (11.8%)	23 (16.8%)	0.423
Stage 2 with eGFR	60–79	38 (38.4%)	18 (52.9%)	56 (40.9%)	
Stage 3 with eGFR	30–59	47 (47.5%)	12 (35.3%)	58 (42.3%)	
Echocardiography					
IVSd (cm)	Mean (SD)	1.1 (0.2)	1.1 (0.2)*	1.0 (0.2)	0.206
PWTd (cm)	Mean (SD)	1.0 (0.2)	0.9 (0.2)	0.9 (0.2)†	0.003

*HFmrEF with HFpEF.
†HFrEF with HFpEF.
‡HFrEF with HFmrEF.
EF, ejection fraction; HF, heart failure; HFmrEF, HF due to midrange EF; HFpEF, HF with preserved EF; HFrEF, HF due to reduced EF ; IVSd, interventricular septum in diastole ; PWTd, posterior wall thickness in diastole.

Table 4 Characteristics of all patients with LVEF of 40% or more in relation to cardiac dysfunction type HFmrEF, HFpEF and no dysfunction (no HF)

	LVEF 40–49	LVEF ≥50%		
	HFmrEF	HFpEF	No HF	P value
Characteristics	N=34	N=137	N=38	trend
Age, mean (SD)	77.2 (12.0)	77.1 (11.3)	72.9 (11.6)	0.110
Male, n (%)	19 (55.9)	43 (31.4)	16 (42.1)	0.275
NT-proBNP ng/L, median (IQR)	3496 (1246–6797)	2008 (1161–3356)	996 (551–3729)	<0.001
Presumptive reason for dyspnoea				
Cardiac dyspnoea	30 (88.2%)	91 (66.4%)	28 (73.7%)	0.207
Non-cardiac dyspnoea	4 (11.8%)	46 (33.6%)	10 (26.3%)	
eGFR, mean (SD)	62.8 (23.6)	67.5 (25.4)	83.4 (31.4)	0.002
Charlson Comorbidity Index, mean (SD)	2.3 (1.8)	2.5 (2.1)	1.6 (1.3)	0.106
Boston score, median (IQR)	7.5 (5, 9)	7 (6, 9)	7.5 (7, 8)	0.737
Framingham HF positive	21 (61.8%)	65 (47.4%)	14 (36.8%)	0.036
Echocardiography, structural values				
IVSd (cm), mean (SD)	1.1 (0.2)	1.0 (0.2)	0.9 (0.2)	<0.001
LVDd (cm), mean (SD)	5.0 (0.7)	4.6 (0.6)	4.2 (0.5)	<0.001
LA vol index, mean (SD) mL/m^2	58.7 (20.4)	51.8 (15.9)	27.4 (4.4)	<0.001
LV mass index, mean (SD)	97.4 (20.6)	87.8 (23.0)	63.6 (11.5)	<0.001
LV hypertrophy	8 (25.0%)	32 (26.4%)	0 (0.0%)	0.001
Diastolic dysfunction, four criteria				
LA volume index ≥34 mL/m^2 BSA	31 (91.2%)	131 (95.6%)	0 (0.0%)	<0.001
TR velocity ≥2.8 m/s	15 (60%)	65 (68%)	14 (52%)	0.512
E/e'>14	18 (52.9%)	59 (43.1%)	5 (13.2%)	<0.001
e' reduced	32 (94.1%)	119 (86.9%)	31 (81.6%)	0.116
Diastolic function, grading				
Normal (0 or 1 criteria)	2 (5.9%)	12 (8.8%)	23 (60.5%)	<0.001
Indeterminate (exactly 2 criteria)	11 (32.4%)	43 (31.4%)	15 (39.5%)	
Definite abnormal (3 or 4 criteria)	21 (61.8%)	82 (59.9%)	0 (0.0%)	

BSA, body surface area;EF, ejection fraction; HF, heart failure; HFmrEF, HF due to midrange EF; HFpEF, HF with preserved EF; HFrEF, HF due to reduced EF; IVSd, interventricular septum in diastole;LA, left atrium; LVDd, left ventricular diameter in diastole; TR, Tricuspid regurgitation; eGFR, estimated glomerular filtration rate; LA vol index, left atrium volume index.

to admit patients. It is also a limitation that our data are obtained in a single centre, but transferability of our results may be ensured by using the same objective selection criteria based on NT-proBNP, acute coronary syndrome and renal dysfunction.

IMPLICATION

This study reflects what would be the outcome of making a comprehensive examination in consecutive hospitalised patients with dyspnoea and elevated NT-proBNP. Current guidelines already recommend natriuretic peptide testing and/or echocardiography in hospitalised patients with suspected acute HF.[4] However, the overwhelming problem is 'when to suspect heart failure' among the many hospitalised patients with unclear signs and symptoms. This study supports making a comprehensive echocardiogram in all patients presenting with dyspnoea and elevated NT-proBNP disregard of presumptive cause of dyspnoea although using differential NT-proBNP threshold values. Our study also indicates that a new hypothetical drug for 'essential' HFpEF may only be applicable to about 1 in 10 patients hospitalised for HF, meaning that a diagnostic and therapeutic dilemma still exists for the majority of patients who fulfil echocardiographic criteria for HFpEF. It is not known if such patients would benefit from a cardiologist advice, and there are ongoing trials to examine if prognosis of HFpEF can be improved by use of a multidisciplinary integrated care management.[26]

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provided clinical input to the project and made critical revisions to the manuscript. All authors gave final approval of the manuscript. OWN is the overall guarantor of the manuscript.

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