

# Global longitudinal strain in patients with suspected heart failure and a normal ejection fraction: does it improve diagnosis and risk stratification?

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**Abstract** Many patients have clinical, structural or biomarker evidence of heart failure (HF) but a normal left ventricular ejection fraction (LVEF; HeFNEF). Measurement of global longitudinal strain (GLS) may add diagnostic and prognostic information. Patients with symptoms suggesting heart failure and LVEF  $\geq 50$  % were studied: 76 had no substantial cardiac dysfunction (left atrial diameter (LAD)  $< 40$  mm and amino-terminal pro-brain natriuretic peptide (NTproBNP)  $< 400$  ng/l); 99 had “possible HeFNEF” (LAD  $\geq 40$  mm or NTproBNP  $\geq 400$  ng/l); and 138 had “definite HeFNEF” (LAD  $\geq 40$  mm and NTproBNP  $\geq 400$  ng/l). Mean LVEF was 58 % in each subgroup. Patients with definite HeFNEF were older, more likely to have atrial fibrillation, had more symptoms and signs of fluid retention, were more likely to have right ventricular dysfunction and had higher pulmonary pressures than other groups. Mean GLS (SD) was less negative in patients with definite HeFNEF ( $-13.6$  (3.0) % vs. possible HeFNEF:  $-15.2$  (3.1) % vs. no substantial cardiac dysfunction:  $-15.9$  (2.4) %;  $p < 0.001$ ). GLS was  $-19.1$  (2.1) % in 20 controls. During a median follow up of 647 days, cardiovascular death or an unplanned hospitalisation for heart failure occurred in 62 patients. In univariable analysis, GLS but not LVEF predicted events. However, in a multivariable analysis, only urea, NTproBNP, left atrial volume, inferior vena cava diameter and atrial fibrillation independently predicted adverse outcome. GLS is abnormal in

patients who have other evidence of HeFNEF, is associated with a worse prognosis in this population but is not a powerful independent predictor of outcome.

**Keywords** Heart failure with normal ejection fraction · Global longitudinal strain · Left atrial diameter · NTproBNP

## Introduction

Nearly half of patients thought to have heart failure (HF) have a normal left ventricular (LV) ejection fraction (EF). The term “heart failure with normal ejection fraction” (HeFNEF) is often used as a diagnostic label in these patients [1, 2]. In some studies [3, 4], morbidity and mortality of patients with HeFNEF are similar to those who have left ventricular (LV) systolic dysfunction. The mechanisms underlying HeFNEF are certainly heterogeneous and remain incompletely understood [5].

Recent studies suggest that abnormalities of both systolic and diastolic function co-exist and contribute to the pathophysiology of HeFNEF [6]. The commonest way of assessing LV systolic function is to measure LVEF, which often has a substantial subjective component, is highly dependent on image quality and may not identify small reductions in systolic function. Tissue Doppler is an alternative method for quantifying LV systolic and diastolic function [7] but is limited by angle dependency. Speckle tracking is a recent development based on frame-to-frame tracking of myocardial tissue movements in any direction that allows a more detailed and sophisticated analysis of LV function, including global longitudinal strain (GLS), which may be more useful for the detection

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of subtle impairment of LV systolic function than LVEF [8–10].

We investigated whether measuring GLS added clinical or prognostic information in patients referred to an outpatient clinic with symptoms suspicious of heart failure who were found to have a normal LVEF.

### Study population

Out-patients with chronic heart failure (CHF) attending a clinic serving a local population of approximately 550,000 between October 2008 and May 2010 were screened. Patients were included in the analysis if their LVEF was  $\geq 50\%$  and they had symptoms or signs suspicious of CHF.

Patients provided a detailed clinical history and blood tests (including haematology, biochemistry profile and amino-terminal pro-brain natriuretic peptide (NT-proBNP)). Electro- and echo-cardiograms were obtained on the same day. Ischaemic heart disease (IHD) was defined as a past history of myocardial infarction or angiographic evidence of significant ( $>70\%$ ) coronary artery disease. Patients were classified as diabetic if receiving treatment for diabetes. A diagnosis of hypertension was based on prior medical history or systolic blood pressure  $>140$  mmHg. A medical history of chronic obstructive pulmonary disease and smoking habits were also recorded. Patients in atrial fibrillation or atrial flutter were grouped as “AF”.

Informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution’s human research committee.

Three different subgroups were defined:

- Group A: Patients with no substantial cardiac dysfunction (LVEF  $\geq 50\%$ , left atrial diameter (LAD)  $< 4$  cm in parasternal long axis, NTproBNP  $< 400$  ng/l): N = 76;
- Group B: Patients with LVEF  $\geq 50\%$ , but LAD  $\geq 4$  cm or NTproBNP  $\geq 400$  ng/l, defined as “possible HeFNEF”: N = 99;
- Group C: Patients with LVEF  $\geq 50\%$ , LAD  $\geq 4$  cm and NTproBNP  $\geq 400$  ng/L, defined as “definite HeFNEF”: N = 138.

We created a congestion score, based on lung auscultation (normal, presence of basal, mid zone or diffuse crepitations), jugular venous pressure (JVP; not visible, raised 1–4 cm, raised to earlobe), peripheral oedema (none, ankles, below or above knees) and liver examination (not palpable, palpable) with one point attributed for each degree of severity. Patients with a score of three or more out of a possible nine were defined as being congested.

We also invited some subjects aged  $>50$  years who were identified from family doctor registers not to have a history of cardiovascular disease to act as a control group.

Patients with HeFNEF were managed with diuretics for symptom relief, and otherwise at their clinician’s discretion. Data regarding hospitalizations and death were collected from the hospital’s electronic systems supplemented by information from patients and their family doctors.

The primary outcome of interest was a composite of admission for worsening heart failure or cardiovascular death (due to terminal heart failure or sudden death out of hospital not explained by cancer or other non-cardiovascular disease). Admission for heart failure was defined as admission for symptoms of worsening heart failure requiring a substantial intensification of treatment (intravenous diuretic, inotropic or vasodilator therapy, or an increase in oral furosemide dose by  $\geq 40$  mg/day). If there was an in-hospital death attributed to worsening or terminal heart failure or acute myocardial infarction during an admission, the end point of CV death was used in preference to the date of hospitalisation as most deaths occurred within 48 h of admission. Patients who died out of hospital who had no other obvious cause of death were considered to have died a sudden cardiac death. To avoid errors due to the mis-attribution of cause of death, a second end point of all-cause mortality was also considered.

### Echocardiographic measurements

Echocardiograms were performed by experienced operators in accordance with the recommendations of the British Society of Echocardiography [11] using a Vivid-5 or -7 (GE Health care, UK) system operating at 3.4 MHz. Doppler tracings and two-dimensional images were obtained from parasternal long- and short-axis, apical and subcostal views. Echocardiograms were stored and retrospectively reviewed by a single operator (PP) blinded to other patient details using an EchoPAC station (GE Health care, UK). LVEF was measured using Simpson’s biplane method. LA volume was measured in the four chamber view and indexed to body surface area (LAVI). Tricuspid annular plane systolic excursion (TAPSE) was used to assess right ventricular (RV) systolic function. Pulmonary artery systolic pressure was estimated from the velocity of tricuspid regurgitation based on the modified Bernoulli equation,  $\Delta P = TR \text{ velocity}^2 \times 4$ . With the patient in the supine position, the maximum inferior vena cava (IVC) diameter during the respiratory cycle was measured approximately 3 cm before it merged with the right atrium.

A digital loop was acquired from apical 4-chamber, 2-chamber and 3-chamber views at frame rates between 40 and 80 frames/s for longitudinal strain analysis. Images were analyzed off-line. The strain curve was extracted

using dedicated software (GE). Peak systolic strain was defined as the peak negative value on the strain curve during the entire cardiac cycle. Values obtained from a model based on all 18 LV segments were then averaged. GLS was calculated if more than 12 LV segments could be analyzed. GLS was estimated from a single cardiac cycle. However, because speckle tracking analysis is influenced by AF, a sub-analysis was also conducted for patients who were in sinus rhythm (SR) only.

#### Statistical methods

16 GLS measurements and 276 individual segments were randomly selected and measured separately on two different occasions by an experienced operator (PP). The reproducibility of the GLS measurements, as well as of each segment, was tested using Bland–Altman plots.

Categorical data are presented as percentages; normally distributed continuous data as mean  $\pm$  SD; and non-normally distributed variables as median and interquartile range. One-way ANOVA and Kruskal–Wallis tests were used to compare continuous variables between groups depending on the normality of the distribution, and the Chi squared test was used for categorical variables.

Associations amongst demographic, clinical, echocardiographic and biochemical variables with prognosis were assessed using the Cox proportional hazards models. Because there were relatively few primary outcome events, two different multivariable models were tested to prevent over-fitting. In Model A, we chose, prospectively, eight candidate variables of interest in addition to GLS and diagnostic category; and for Model B, we selected the eight variables most strongly associated with prognosis in univariable analysis. Forward and backward procedures were used to determine which variables independently predicted the primary composite outcome. Treatment variables were not included in the model as these might be confounded by indication, might vary overtime and are not known to influence prognosis in HeFNEF. We did not include mitral and tricuspid regurgitation in the model, because their estimation was based on a semi-quantitative approach and because we included patients with AF, which might make the interpretation of valvular regurgitation difficult. For the second model, given the high correlation between IVC diameter and TR systolic gradient ( $R = 0.529$ ,  $p < 0.001$ ), we selected the IVC diameter, a strong predictor of an adverse outcome [12].

Kaplan–Meier curves with the log-rank statistic were used to illustrate outcome. Assumptions of the models were tested, such as multicollinearity and proportional hazards. All the analyses were performed using SPSS and Stata software. A 2-sided  $p$  value  $< 0.05$  was considered statistically significant.

## Results

### Patient characteristics

In the 20 control subjects, the mean age (SD) was  $65 \pm 11$  years, 55 % were women and their echocardiograms were normal (Table 1). Mean ( $\pm$ standard deviation) LVEF was  $60 \pm 5$  %, mean GLS by speckle tracking was  $-19.1 \pm 2.1$  % and median plasma NTproBNP was 107 pg/ml (IQR: 46–147).

Of the 780 consecutive patients assessed in clinic, 313 (40 %) had symptoms or signs suspicious of heart failure and an LVEF  $\geq 50$  %, thus fulfilling the study criteria (Table 1), the rest (467) had LVEF  $< 50$  %. Of the 313 patients with LVEF  $\geq 50$  %, 76 were considered not to have HeFNEF, 99 to have possible HeFNEF and 138 to have definite HeFNEF. Compared to the control group, patients with definite HeFNEF were older, were more likely to have AF, had more symptoms and more signs of fluid retention, and were more likely to be treated with diuretics. The proportion of patients with a history of IHD, diabetes, hypertension and COPD were similar in all three groups of patients, but fewer patients in Group A (no substantial cardiac dysfunction) had AF. When the analysis was restricted to patients in sinus rhythm (Table 2), patients with definite HeFNEF still were older, had more symptoms, worse renal function and higher systolic blood pressure and NTproBNP levels than the other two subgroups.

### Echocardiographic findings

LVEF was similar in all three sub-groups of patients and in control subjects. GLS was impaired in each group of patients compared to control subjects but most severely impaired in patients who fulfilled our criteria for definite HeFNEF. Patients with definite HeFNEF had greater LV volumes, more RV dysfunction (as estimated by TAPSE) and more substantial mitral and tricuspid regurgitation than the other two groups. They also had higher pulmonary pressure and IVC diameter. Similar results were seen when the analysis was restricted to patients in sinus rhythm (Table 2).

For 14 patients (3 with no heart disease, 4 with possible HeFNEF and 7 with definite HeFNEF) analysis of GLS was not possible due to poor quality images. For other patients, 85 % of LV segments could be analyzed. Internal consistency and reproducibility of measurements of GLS (mean difference = 0.12 %; 95 % Limits of agreement:  $-0.75$ , 0.99) and individual segments (mean difference = 0.12 %; 95 % Limits of agreement:  $-4.16$ , 4.40) were good.

Amongst the patient group as a whole, GLS was more negative (better function) in women v men [ $-15.8$  (3.0) % vs.  $-13.8$  (2.8) %,  $p < 0.001$ ] and in those with no history

**Table 1** Characteristics of patients

	Normal group (20)	All patients (313)	<i>p</i> value	Group A (76)	Group B (99)	Group C (138)	<i>p</i> value (between groups)
<b>Clinical and demographic</b>							
Age—years	65 (11)	74 (13)	0.005	67 (15)	73 (13)	78 (10)	<0.001
Men—no. (%)	9 (45)	181 (58)	0.261	37 (49)	57 (58)	87 (63)	0.126
<b>NYHA class</b>							
I	20 (100)	60 (19)	<0.001	21 (28)	20 (20)	19 (14)	0.014
II	0 (0)	151 (48)		28 (37)	56 (57)	67 (49)	
III	0 (0)	102 (32)		27 (35)	23 (23)	52 (37)	
IHD—no. (%)	0 (0)	136 (44)	<0.001	30 (40)	41 (41)	65 (47)	0.495
DM—no. (%)	0 (0)	85 (27)	0.007	20 (26)	27 (27)	38 (27)	0.981
Hypertension or SBP > 140 mmHg—no. (%)	0 (0)	219 (70)	<0.001	51 (67)	69 (70)	99 (72)	0.777
Smoker—no. (%)	1 (5)	40 (13)	0.305	13 (17)	14 (14)	13 (9)	0.242
Atrial fibrillation—no. (%)	0 (0)	126 (40)	<0.001	1 (1)	25 (25)	100 (73)	<0.001
COPD—no. (%)	0 (0)	47 (15)	0.061	13 (17)	20 (20)	14 (10)	0.086
BMI—kg/m <sup>2</sup>	27.0 (4)	29.9 (6)	0.054	29.8 (6)	31.1 (8)	29.1 (6)	0.058
SBP—mmHg	136 (13)	136 (24)	0.941	134 (22)	136 (23)	138 (26)	0.581
Heart rate—bpm	64 (8)	72 (14)	0.007	72 (13)	74 (14)	71 (15)	0.235
Congestion score ≥ 3 (%)	0 (0)	49 (16)	0.055	9 (12)	9 (9)	31 (23)	0.012
<b>Blood</b>							
Creatinine—μmol/l	73 (62–79)	98 (80–130)	<0.001	86 (84–109)	97 (77–127)	107 (82–141)	<0.001
Urea—mmol/l	4.9 (4.3–6.1)	7.0 (4.8–10.0)	<0.001	5.3 (3.9–7.3)	7.1 (4.8–9.1)	7.9 (5.6–11.8)	<0.001
eGFR—ml/min/1.73 m <sup>2</sup>	98 (23)	68 (30)	<0.001	78 (29)	71 (33)	61 (26)	<0.001
Haemoglobin—g/dl	14.4 (1.0)	13.1 (1.9)	<0.001	13.4 (1.5)	13.4 (1.8)	12.8 (2.0)	0.016
Albumin—g/l	39.9 (2.1)	37.8 (3.4)	<0.001	38.6 (3.8)	38.1 (2.9)	37.3 (3.5)	0.022
Bilirubin—μmol/l	13.2 (3.8)	15.0 (5.9)	0.196	13.2 (4.8)	14.4 (4.6)	16.4 (6.9)	<0.001
NT-proBNP—ng/l	107 (46–147)	591 (202–1,636)	<0.001	164 (59–268)	414 (143–887)	1,627 (868–2,837)	**
hsCRP—u/l	1.5 (0.77–2.4)	4.0 (1.7–7.8)	<0.001	3.6 (1.1–6.8)	3.6 (1.6–6.3)	4.8 (2.2–9.8)	0.104
<b>Medications—no. (%)</b>							
Beta-blocker	0 (0)	188 (60)	<0.001	37 (48)	57 (58)	94 (68)	0.018
ACE inhibitor or ARB	0 (0)	230 (74)	<0.001	56 (74)	72 (73)	102 (74)	0.944
Aldosterone antagonist	0 (0)	67 (21)	0.021	14 (18)	19 (19)	34 (25)	0.461
Loop diuretic	0 (0)	221 (71)	<0.001	43 (56)	73 (74)	105 (76)	0.008
*Dose of Furosemide	0 (0)	40 (40)	<0.001	24 (32)	33 (33)	48 (48)	<0.001
Statin	2 (10)	180 (58)	0.001	45 (59)	59 (59)	76 (55)	0.740
Antiplatelets	0 (0)	135 (43)	0.001	40 (53)	48 (49)	47 (34)	0.014

Table 1 continued

	Normal group (20)	All patients (313)	<i>p</i> value	Group A (76)	Group B (99)	Group C (138)	<i>p</i> value (between groups)
Digoxin	0 (0)	69 (22)	0.018	0 (0)	16 (16)	53 (38)	<0.001
Warfarin	0 (0)	90 (29)	0.005	5 (6)	20 (20)	65 (47)	<0.001
CRT	0 (0)	10 (3)	0.417	1 (1)	3 (3)	6 (4)	0.480
ICD	0 (0)	10 (3)	0.417	2 (3)	3(3)	5 (4)	0.228
Echocardiographic data							
LVEDD—mm	46 (6)	49 (7)	0.026	47 (6)	48 (7)	51 (6)	<0.001
LVEDV—ml	89 (28)	105 (37)	0.056	95 (29)	100 (38)	115 (38)	<0.001
LVEF—%	60 (5)	58 (6)	0.236	59 (6)	59 (6)	58 (6)	0.213
GLS—%	-19.1 (2.1)	-14.7 (3.1)	<0.001	-15.9 (2.4)	-15.2 (3.1)	-13.6 (3.0)	<0.001
LA Diameter—mm	31.5 (3.6)	42.5 (7.6)	<0.001	35.1 (4.6)	40.3 (5.5)	48.1 (5.7)	**
LAVI—ml/m <sup>2</sup>	20 (6)	40 (23)	<0.001	25 (10)	33 (13)	55 (25)	**
TAPSE—mm	23 (3)	20 (5)	0.001	21 (4)	21 (5)	18 (4)	<0.001
TR gradient—mmHg	20 (4)	27 (12)	<0.001	19 (5)	25 (12)	33 (12)	<0.001
IVC—mm	15 (2)	18 (5)	<0.001	15 (2)	17 (3)	22 (5)	<0.001
Mitral regurgitation							
None/trivial	15 (75)	209 (67)	0.231	67 (88)	79 (80)	63 (46)	<0.001
Mild	5 (25)	64 (20)		7(9)	16 (16)	41 (30)	
Moderate	0	40 (13)		2 (3)	4 (4)	34 (24)	
Tricuspid regurgitation							
None/trivial	20 (100)	233 (74)	0.035	74 (97)	80 (81)	79 (57)	<0.001
Mild	0	48 (15)		2 (3)	12 (12)	34 (25)	
Moderate	0	32 (10)		0 (0)	7 (7)	25 (18)	

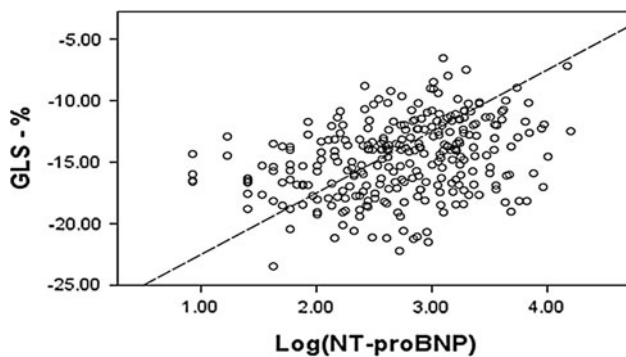
Data are mean and standard deviation if normally distributed and median and inter-quartile range if not. The statistical difference between patients with suspected heart failure and controls, and the difference between Groups A, B and C is shown. List of abbreviation used: *NYHA* New York Heart Association, *IHD* ischemic heart disease, *DM* diabetes mellitus, *COPD* chronic obstructive pulmonary disease, *SBP* systolic blood pressure, *BMI* body mass index, *eGFR* estimated Glomerular Filtration Rate, *NTproBNP* N-terminal B-type natriuretic peptide, *hsCRP* high sensitivity C-reactive protein, *CRT* cardiac resynchronization therapy, *ICD* implantable cardioverter defibrillator, *LVEDD* left ventricle end-diastolic diameter, *LVEDV* left ventricle end diastolic volume, *LVEF* left ventricular ejection fraction, *GLS* global longitudinal strain, *LA* Left atrium, *LAVI* left atrial volume index, *TAPSE* Tricuspid Annular Plane Systolic Excursion, *TR gradient* Trans-Tricuspid systolic gradient, *IVC* inferior vena cava diameter

\* Daily dose of furosemide or equivalent (bumetanide 1 mg = furosemide 40 mg). \*\* The difference between the 3 groups in LA size and NT-proBNP was significant by definition

**Table 2** Characteristics of patients in sinus rhythm

Variable	Group A (75)	Group B (74)	Group C (38)	<i>p</i> value (between groups)
Clinical and demographic				
Age	68 (15)	72 (13)	79 (9)	<0.001
Men—no. (%)	36 (48)	42 (57)	22 (58)	0.467
NYHA Class				
I	20 (27)	17 (23)	2 (5)	0.027
II	28 (37)	39 (53)	23 (60)	
III	27 (36)	18 (24)	13 (35)	
Congestion score $\geq 3$ (%)	9 (12)	8 (11)	5 (13)	0.932
IHD—no. (%)	30 (40)	31 (42)	25 (66)	0.023
DM—no. (%)	20 (27)	21 (28)	11 (29)	0.958
Hypertension or SBP > 140 mmHg- no. (%)	50 (67)	53 (72)	24 (63)	0.633
COPD—no. (%)	13 (17)	19 (26)	3 (8)	0.068
BMI—kg/m <sup>2</sup>	29.8 (5.7)	32.2 (8.2)	29.1 (5.4)	0.024
SBP—mmHg	134 (21)	139 (23)	146 (30)	0.012
Heart rate—bpm	72 (13)	73 (14)	63 (9)	0.001
Congestion score $\geq 3$ (%)	9 (12)	8 (11)	5 (13)	0.932
Blood				
NT-proBNP—ng/l	169 (59–270)	279 (133–533)	1,183 (682–2,532)	**
Creatinine— $\mu$ mol/l	86 (73–108)	91 (76–126)	119 (87–152)	<0.001
Urea—mmol/l	5.2 (3.9–7.2)	6.0 (4.6–8.9)	8.6 (6.2–14.5)	<0.001
eGFR—ml/min/1.73 m <sup>2</sup>	79 (29)	73 (34)	55 (25)	<0.001
Medications—no. (%)				
Beta-blocker	36 (48)	41 (55)	29 (76)	0.016
ACE inhibitor or ARB	55 (73)	51 (69)	28 (74)	0.797
Aldosterone antagonist	13 (17)	11 (15)	8 (21)	0.711
Loop diuretic	43 (57)	54 (73)	27 (71)	0.102
Echocardiographic data				
LVEDD—mm	47 (6)	48 (7)	51 (7)	0.003
LVEDV—ml	95 (30)	104 (40)	122 (39)	0.001
LVEF— %	59 (6)	58 (6)	57 (6)	0.102
GLS— %	-15.9 (2.4)	-15.4 (2.9)	-13.4 (2.8)	<0.001
LA Diameter—mm	35.1 (4.6)	40.6 (6.1)	45.4 (3.8)	**
LAVI—ml/m <sup>2</sup>	25 (10)	31 (11)	45 (15)	**
TAPSE—mm	21 (4)	22 (4)	18 (4)	<0.001
TR gradient—mmHg	19 (5)	24 (12)	29 (10)	<0.001
IVC—mm	15 (2)	16 (3)	19 (4)	<0.001
Mitral regurgitation				
None/trivial	66 (88)	62 (84)	18 (47)	<0.001
Mild	7(9)	9 (12)	14 (37)	
Moderate	2 (3)	3 (4)	6 (16)	
Tricuspid regurgitation				
None/trivial	73 (97)	65 (88)	25 (66)	<0.001
Mild	2 (3)	5 (7)	9 (24)	
Moderate	0 (0)	4 (5)	4 (10)	

Data are mean and standard deviation if normally distributed and median and inter-quartile range if not. \*\* The difference between the 3 groups in LA size and NT-proBNP was significant by definition. List of abbreviation used: *NYHA* New York Heart Association, *IHD* ischemic heart disease, *DM* diabetes mellitus, *COPD* chronic obstructive pulmonary disease, *SBP* systolic blood pressure, *BMI* body mass index, *eGFR* estimated Glomerular Filtration Rate, *NTproBNP* N-terminal B-type natriuretic peptide, *LVEDD* left ventricle end-diastolic diameter, *LVEDV* left ventricle end diastolic volume, *LVEF* left ventricular ejection fraction, *GLS* global longitudinal strain, *LA* Left atrium, *LAVI* left atrial volume index, *TAPSE* Tricuspid annular plane systolic excursion, *TR gradient* Trans-Tricuspid systolic gradient, *IVC* inferior vena cava diameter



**Fig. 1** Relation between GLS and log (NT-proBNP): LV long axis function worsens with higher plasma concentrations of NT-proBNP

of IHD [−15.2 (3.0) % vs. −14.0 (2.9) %,  $p = 0.001$ ]. GLS was higher (more impaired) in patients who were taking loop diuretics (−14.4 (3.0) % vs. −15.4 (3.0) %,  $p = 0.007$ ). There was no relation between GLS and either NYHA class or congestion score. There was no relation between GLS and age ( $r: -0.06$ ,  $p = 0.31$ ) but there was a relation between GLS and log (NT-proBNP) (worsening long axis function associated with increasing NT-proBNP,  $r: 0.32$ ,  $p < 0.001$ : see Fig. 1) and renal function (creatinine:  $r: 0.20$ ,  $p = 0.001$ , urea:  $r: 0.16$ ,  $p = 0.009$ ).

#### Outcome

All patients were followed for at least one year. There were 62 primary outcome events during the median follow up of 572 (IQ range: 440–736) days. The first qualifying event was hospitalisation due to worsening HF in 30 patients and CV death in 32 patients. In univariable Cox regression analysis (Table 3), GLS, but not LVEF, predicted events. Left atrial diameter, TAPSE, TR systolic gradient as well as moderate mitral regurgitation or tricuspid regurgitation were also associated with a worse outcome.

In multivariable analysis, increasing urea and log [NTproBNP] were the only variables independently related to an adverse outcome in Model A (Table 4). In Model B (Table 5), increasing urea and logNTproBNP, as well as increasing LAVI, IVC diameter and the presence of AF were independently related to outcome. Patients with a definite diagnosis of HeFNEF had the highest rate of adverse events; 25 % at 1 year (Fig. 2).

There were 48 deaths during the median follow of 598 (IQ range 471–756) days for all patients: AF, a greater LAVI and higher plasma NTproBNP were independent predictors of all-cause mortality (Table 5). Thus, a definite diagnosis of HeFNEF was associated with increased all-cause mortality.

**Table 3** Univariable Cox regression models for the composite endpoint CV death or HF hospitalization (313 patients, 62 events)

Variables	Univariable analysis		
	HR (95 % CI)	$\chi^2$	$p$ value
Age—years	1.06 (1.03–1.09)	15.60	<0.001
Men	1.03 (0.62–1.71)	0.02	0.902
NYHA class			
II	3.52 (1.06–11.61)	4.53	0.039
III	6.70 (2.05–21.90)	10.89	0.002
Definite HeFNEF	4.32 (2.44–7.64)	25.32	<0.001
IHD	1.14 (0.69–1.89)	0.26	0.611
DM	0.75 (0.44–1.27)	1.13	0.287
Atrial fibrillation	2.55 (1.52–4.26)	12.74	<0.001
COPD	2.35 (0.94–5.88)	3.34	0.068
SBP—mmHg	0.99 (0.98–1.01)	0.70	0.401
Heart rate—bpm	0.99 (0.98–1.01)	0.06	0.809
BMI—kg/m <sup>2</sup>	0.99 (0.96–1.04)	0.04	0.846
Congestion score $\geq 3$	3.88 (2.31–6.51)	26.38	<0.001
Creatinine—umol/l	1.01 (1.01–1.01)	20.26	<0.001
Urea—mmol/l	1.10 (1.07–1.14)	36.86	<0.001
eGFR—ml/min/1.73 m <sup>2</sup>	0.98 (0.97–0.99)	8.79	0.003
Haemoglobin—g/dl	0.67 (0.58–0.77)	32.59	<0.001
Albumin—g/l	0.87 (0.82–0.93)	16.82	<0.001
Bilirubin—umol/l	1.02 (0.98–1.06)	0.69	0.405
Log (NT-proBNP)	6.09 (3.73–9.96)	51.93	<0.001
Log (hsCRP)	2.13 (1.38–3.28)	11.72	0.001
Echocardiographic data			
LVEDV—ml	1.00 (0.99–1.01)	1.36	0.243
LVEF— %	1.00 (0.96–1.04)	0.00	0.991
GLS— %	1.09 (1.00–1.19)	3.98	0.046
LA Diameter—mm	1.07 (1.04–1.09)	22.46	<0.001
LAVI—ml/m <sup>2</sup>	1.02 (1.01–1.03)	30.23	<0.001
TAPSE—mm	0.87 (0.82–0.93)	19.65	<0.001
TR gradient—mmHg	1.04 (1.03–1.06)	33.55	<0.001
IVC—mm	1.21 (1.15–1.26)	72.94	<0.001
Mitral regurgitation			
Mild	1.35 (0.69–2.65)	0.75	0.385
Moderate/severe	4.67 (2.66–8.21)	28.68	<0.001
Tricuspid regurgitation			
Mild	2.15 (1.17–3.95)	6.18	0.013
Moderate/severe	5.48 (2.89–10.38)	27.23	<0.001

List of abbreviation used: *IHD* ischemic heart disease, *DM* diabetes mellitus, *COPD* chronic obstructive pulmonary disease, *SBP* systolic blood pressure, *BMI* body mass index, *eGFR* estimated Glomerular Filtration Rate, *NTproBNP* N-terminal B-type natriuretic peptide; *hsCRP* high sensitivity C-reactive protein, *LVEDV* left ventricle end diastolic volume, *LVEF* left ventricular ejection fraction, *GLS* global longitudinal strain, *LA* Left atrium, *LAVI* left atrial volume index, *TAPSE* tricuspid annular plane systolic excursion

**Table 4** A multivariable cox regression for the primary endpoint of CV death and admission with heart failure

Variables	Multivariable analysis		
	HR (95 % CI)	$\chi^2$	<i>p</i> value
Age	1.01 (0.97,1.04)	0.16	0.68
Definite HeFNEF	1.74 (0.97- 3.67)	2.15	0.14
NYHA class III vs. II	1.49 (0.82,2.65)	1.69	0.19
SBP—mmHg	0.99 (0.98,1.00)	2.17	0.14
Urea—mmol/l	1.11 (1.05,1.17)	17.30	<0.01
Atrial fibrillation	1.33 (0.68,2.61)	0.69	0.40
Log (NT-proBNP)	3.57 (1.61,7.89)	9.91	<0.01
GLS— %	0.99 (0.90,1.11)	0.06	0.80
Congestion score $\geq 3$	1.63 (0.86,3.10)	2.21	0.14
TR gradient—mmHg	1.00 (0.98,1.02)	0.11	0.74

Model A: eight candidate variables of clinical interest in addition to Global longitudinal strain (GLS) and the diagnostic category (Definite HeFNEF vs. others) were chosen. List of abbreviation used: *SBP* systolic blood pressure, *NTproBNP* N-terminal B-type natriuretic peptide, *TR gradient* trans-tricuspid systolic gradient

## Discussion

We have found that in patients referred with a possible diagnosis of heart failure but with a normal LVEF, a subtle impairment of LV longitudinal systolic function can be detected with advanced echocardiographic techniques, even in the absence of structural (dilated left atrium) or biochemical (increased NTproBNP) abnormalities. Worsening LV longitudinal systolic dysfunction was related to other indices of abnormal function. However, GLS provided no additional prognostic information to biochemical measures of cardiac dysfunction.

HeFNEF remains a controversial entity. The recently updated ESC guidelines on heart failure [13] have lowered the threshold levels of natriuretic peptides for the exclusion of chronic heart failure to 125 ng/L, recognising that previous guidance may have been too stringent. However, this increases the likelihood of including patients with no substantial cardiac pathology under the umbrella of “HeFNEF”, particularly older people in whom HeFNEF is especially common [14]. Indeed, 5 control subjects and 263 (84 %) of patients with suspected HeFNEF in the present study had values  $\geq 125$  ng/L. Although values  $<125$  ng/L may exclude serious ventricular dysfunction or indicate that it is very well managed, higher thresholds are required when NT-proBNP is used to identify patients likely to have disease. It is unlikely that the single threshold of 400 ng/L used in our analysis will be optimal for clinical practice although it conformed to the guidelines contemporary to this study [5, 15].

We have previously shown that the velocity of long-axis systolic shortening may be reduced in patients with HeFNEF, indicating impairment of the longitudinal component of systolic contraction [16, 17]. Mild impairment of LV longitudinal function is present even in young patients with hypertension (GLS:  $-17.5 \pm 2.8$  %) compared with healthy subjects ( $-21.1 \pm 2.0$  %,  $p < 0.001$ ) or athletes ( $-22.2 \pm 2.7$  %) but global circumferential strain, global radial strain and torsion are similar in these three groups [10]. Recently, Morris and colleagues demonstrated that GLS was abnormal in patients with HeFNEF [18]. Worse overall myocardial performance was associated with worse symptoms. Furthermore, in animal models, it has been shown that impairment of LV longitudinal function occurs in the early phase of LV hypertrophy, and continues to worsen until development of congestive heart failure [19].

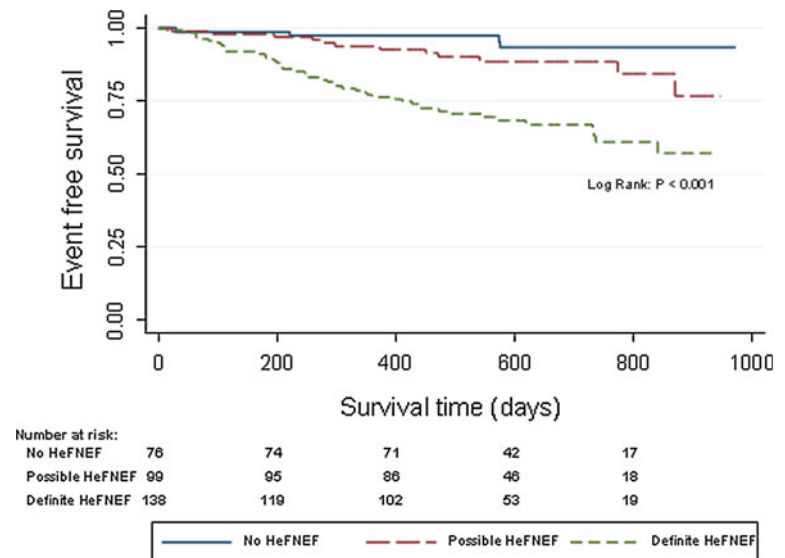
**Table 5** A multivariable cox regression for the primary endpoint of CV death and admission with heart failure (left) and for the secondary endpoint of death for all causes (right)

Variables	Multivariable analysis			Multivariable analysis		
	CV death and admission with heart failure			Death from all causes		
	HR (95% CI)	$\chi^2$	<i>p</i> value	HR (95% CI)	$\chi^2$	<i>p</i> value
Age	1.02 (0.97, 1.04)	0.14	0.91	1.02 (0.98, 1.06)	0.98	0.32
AF	2.51 (1.23, 5.12)	6.45	0.01	2.27 (1.03, 4.98)	4.17	0.04
Congestion score $>3$	1.64 (0.93, 2.98)	3.09	0.08	1.75 (0.91, 3.48)	2.85	0.09
Urea—mmol/l	1.10 (1.05,1.16)	16.19	<0.01	1.03 (0.98,1.09)	1.61	0.2
Log (NT-proBNP)	2.52 (1.25, 5.07)	6.72	<0.01	3.74 (1.71, 8.21)	10.83	<0.01
Definite HeFNEF	1.01 (0.47, 2.19)	0.01	0.98	2.41 (1.07, 5.43)	4.47	0.03
LAVI—ml/m <sup>2</sup>	1.01 (1.00, 1.02)	4.01	0.04	1.01 (1.00, 1.03)	4	0.04
IVC—mm	1.15 (1.09, 1.23)	21.71	<0.01	1.05 (0.97, 1.13)	1.49	0.22

Model B: The eight variables which were the strongest independent predictors of adverse outcome in the univariable analysis. List of abbreviation used: *AF* atrial fibrillation, *NTproBNP* N-terminal B-type natriuretic peptide, *IVC* inferior vena cava diameter, *LAVI* left atrial volume index



**Fig. 2** Kaplan-Meier (KM) curves for the composite endpoint (HF hospitalization or CV death) in patients considered to have no evidence of significant cardiac disease (*solid blue line*, Group A), in patients with “possible HeFNEF” (*red line*, Group B) and patients with definite HeFNEF (*green line*, Group C). For patients with definite HeFNEF, the hazard ratio for this outcome was 7.86 (95 % CI: 2.82–21.87;  $p < 0.001$ ) compared to those considered not to have evidence of significant cardiac disease



A common underlying factor may be myocardial fibrosis [6, 20] leading to reduced LV longitudinal function, altered torsion and delayed untwisting, loss of LV suction and thus impairment of early diastolic LV filling. Ventricular hypertrophy, delayed myocardial relaxation, atrial dysfunction and abnormal electrical conduction could also contribute to disturbed systolic and diastolic function.

Our results are also supported by a recent analysis of the I-PRESERVE trial [21]: up to 40 % of patients enrolled in that trial did not have structural or functional alterations of the cardiac chambers on echocardiography, such as LV hypertrophy, LA dilatation or evidence of diastolic dysfunction. However, in common with analyses of both the CHARM-Preserved and PEP-CHF trials, NT-proBNP was found to be a stronger predictor of outcome than any echocardiographic measure [22, 23]. We found that a combination of both a dilated LA and raised NTproBNP dramatically increased the risk of an adverse outcome.

Although deterioration in LV longitudinal function might be an early manifestation in the developing pathophysiology of HeFNEF, our finding also supports the notion that raised NTproBNP plasma levels and other echocardiographic measurements of pressure or fluid overload, such as increased LA size or IVC diameter, might be more useful in characterising and identifying those patients at higher risk of adverse outcome [24].

## Limitations

We chose to define cardiac dysfunction by LAD rather than LAVI but LAVI was well above the cut-off defined in guidelines as an indicator of HeFNEF [5]. Both LAD and

LAVI appear to identify patients with HeFNEF [25] and both measurements are strongly related to prognosis.

Standard echocardiographic measurements of diastolic function ( $E/E'$  and  $E/A$  ratio) were not routinely performed and were not available. Although  $E/E'$  ratio predicts cardiac events in patients with systolic HF [26], it may add little prognostic information to LAD. Large studies show that  $E/E'$  is not an independent predictor of adverse outcome in patients with HeFNEF [21, 27]. Moreover, we did not evaluate LV mass, which is also known to be associated with increasing cardiovascular risk in the general population [28].

Patients with symptoms but no conventional evidence of cardiac dysfunction may have had “latent” HeFNEF that might become overt on exercise, provoking symptoms [29, 30]. These patients had a similar prevalence of risk factors for cardiac dysfunction and heart failure, such as ischaemic heart disease, as patients with definite structural heart disease. It is also possible that some had symptoms reflecting reversible myocardial ischaemia. However, these patients had an excellent prognosis, in stark contrast to the patients we defined as definite HeFNEF.

Many patients had AF, which could cause problems in interpretation of echocardiographic data and might be a direct cause of atrial enlargement. AF could also cause a rise in natriuretic peptides [31]. Diagnosis of HeFNEF in patients with AF remains unsatisfactory.

## Conclusions

GLS is impaired in patients who present with symptoms or signs of heart failure, even when there is no other conventional evidence of this diagnosis. Impaired GLS is

associated with a worse prognosis but does not provide additional prognostic information to biochemical measures of cardiac dysfunction or LAVI.

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**Conflict of interest** None.

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