CARDIOVASCULAR MEDICINE

Excessive breathlessness in patients with diastolic heart failure

K K A Witte, N P Nikitin, J G F Cleland, A L Clark

Heart 2006;**92**:1425–1429. doi: 10.1136/hrt.2005.081521

See end of article for authors' affiliations

Correspondence to: Dr Klaus Witte, Academic Cardiology, Castle Hill Hospital, Castle Road, Cottingham, Hull HU16 5JQ, UK; klauswitte@hotmail.com

Accepted 24 March 2006
Published Online First 18 April 2006

Objectives: To establish the prevalence of preserved left ventricular (LV) systolic function (PSF) in 435 consecutive symptomatic patients referred to a heart failure clinic and to examine their ventilatory response to exercise when compared with 134 control volunteers.
Methods: 216 (50%) patients had systolic heart failure (SHF) (ejection fraction < 45%). 51 (11%) had an immediately apparent alternative causes of breathlessness and 168 (39%), with no obvious other cause of breathlessness, were divided into those with PSF and diastolic dysfunction (DD) (PSF_{DD}; n = 113 or 26% of referrals) and those without DD (PSF_N; n = 55 or 13% of referrals). The controls were divided into those with (C_{DD}; n = 32) and those without (C_N; n = 102) echocardiographic evidence of DD.
Results: Patients with SHF had lower peak oxygen consumption ($p\dot{V}O_2$), steeper slope of minute ventilation ($\dot{V}E$) to carbon dioxide production, lower exercise time and shorter 6 min walk test than PSF patients and controls. PSF_{DD} patients had lower $p\dot{V}O_2$, exercise time and 6 min walk test than C_{DD}, although their echocardiograms were not different. Exercise capacity did not differ between PSF_{DD} and PSF_N patients. The slope relating $\dot{V}E$ to symptoms (Borg/$\dot{V}E$ slope) was less steep in those with SHF than in PSF_{DD} (0.17 (0.04) *v* 0.20 (0.08), $p < 0.05$) and in PSF_N (0.19 (0.10), $p < 0.05$), implying greater symptoms of breathlessness for a given level of $\dot{V}E$. Both PSF groups had a steeper slope than C_{DD} (0.14 (0.09), $p < 0.05$ for both comparisons).
Conclusions: Patients with PSF have exercise tolerance intermediate between that of patients with SHF and controls. Exercise tolerance is similar in PSF_{DD} and PSF_N. Both groups have worse exercise tolerance than C_{DD}. PSF_{DD} and PSF_N patients seem to experience a greater awareness of $\dot{V}E$ than C_{DD} and patients with SHF.

Chronic heart failure is a syndrome characterised by exercise intolerance and symptoms of breathlessness and fatigue.[1] A diagnosis of chronic heart failure is usually associated with evidence of impaired left ventricular (LV) function, often on echocardiography. Depending on the population studied, up to one half of patients with symptoms of chronic heart failure do not have impaired LV systolic function and have been deemed to have diastolic heart failure (DHF) or heart failure with preserved systolic function (PSF).[2] Such patients are generally older and are more likely to be women, to have a history of hypertension and to have LV hypertrophy on echocardiography than those with systolic dysfunction.[2]

A positive diagnosis of DHF (rather than heart failure with PSF) usually depends on the presence of symptoms of chronic heart failure with PSF but also on objective evidence of impaired relaxation of the left ventricle. These include E:A wave reversal on transmitral Doppler, prolonged deceleration time of transmitral E wave or increased isovolumic relaxation time (IVRT).[3] However, these changes are also seen as a consequence of normal ageing. One or more of these variables is commonly abnormal in older patients to the extent that some authors have suggested that the diastolic variables may not be helpful in diagnosing DHF.[4]

Patients with DHF may therefore have symptoms of other causes of breathlessness, or even reduced fitness,[5] and have DHF diagnosed as a result of diastolic echocardiographic changes that are often seen in normal older people. Data are emerging that the diastolic impairment of normal ageing can be differentiated from diastolic impairment in patients presenting with breathlessness by using tissue Doppler imaging.[6] Nevertheless, the definition of what constitutes DHF remains controversial.[5]

The objective of the present study was to establish the prevalence of echocardiographically determined diastolic impairment (that is, DHF) in patients referred to a specialist heart failure clinic and to describe these patients' exercise capacity when measured objectively by exercise testing with metabolic gas exchange. We also looked at how peak oxygen consumption ($p\dot{V}O_2$) relates to symptoms as judged by the New York Heart Association (NYHA) classification in DHF and by the relationship of minute ventilation ($\dot{V}E$) to symptoms (Borg/$\dot{V}E$ slope).[7] This ratio is greater in patients with systolic heart failure (SHF) than in controls[7] and permits semiobjective assessment of symptoms during an exercise test.

METHODS

We studied 435 consecutive patients referred for assessment of breathlessness by their general practitioner to a heart failure clinic between July 2000 and July 2003. Each patient had a remote history of breathlessness thought to be caused by heart failure for which diuretic drugs had at some time in the past been started All patients were in a stable situation, were clinically not fluid overloaded and had no recent (< 4 weeks) change in heart failure drugs. We excluded patients in atrial fibrillation. We also investigated 134 controls of a similar age chosen at random from the patient lists of local

Abbreviations: C_{DD}, controls with diastolic dysfunction; C_N, controls with normal diastolic function; DD, diastolic dysfunction; DHF, diastolic heart failure; IVRT, isovolumic relaxation time; LV, left ventricular; NYHA, New York Heart Association; PSF, preserved systolic function; PSF_{DD}, preserved systolic function and diastolic dysfunction; PSF_N, preserved systolic function without diastolic dysfunction; $p\dot{V}O_2$, peak oxygen consumption; SHF, systolic heart failure; $\dot{V}CO_2$, carbon dioxide production; $\dot{V}E$, minute ventilation general practitioners with no history or symptoms of cardiovascular disease. All the control participants gave informed, written consent. The study was approved by the local ethics committee.

Echocardiography

Each participant underwent echocardiographic examination with a GE Vingmed Vivid FiVe scanner (Horten, Norway) equipped with 2.5 MHz phased array transducers. All Doppler echocardiographic recordings were obtained during normal respiration.

LV end diastolic diameter, LV end systolic diameter, and interventricular septum and LV posterior wall thickness at end diastole were measured from parasternal M mode echocardiography of the left ventricle. LV end diastolic and end systolic volumes were calculated with the modified Simpson's rule (biplane), and the standard formula was applied to give LV ejection fraction.

Doppler echocardiography

Pulsed wave Doppler studies were performed in apical views. Mitral flow velocities were recorded from an apical four-chamber view with the sample volume positioned adjacent to the tip of either the mitral or tricuspid leaflets in diastole. Care was taken to obtain the smallest possible angle between the direction of transvalvular flow and the ultrasound beam.

Peak velocity of early filling (E), peak velocity of atrial filling (A), and the E:A ratio were calculated for both transmitral and transtricuspid flow. Deceleration time of early filling and IVRT were measured from the transmitral Doppler spectrum. Deceleration time was calculated as the time between peak E wave and the upper deceleration slope extrapolated to the baseline. IVRT was measured by placing the sample volume between the anterior mitral leaflet and LV outflow tract.

All patients were stratified according to the presence or absence of significant LV systolic dysfunction (ejection fraction > 45%). Patients with PSF were then classified into those with (PSF_{DD}) and without (PSF_N) signs of diastolic dysfunction (DD) (ejection fraction > 45%, and at least one of E:A wave reversal on transmitral Doppler (< 0.5), a prolonged deceleration time of transmitral E wave (> 280 ms) or an increased IVRT (> 105 ms)).[3] We also assessed left atrial diameter in the parasternal long axis view. Controls were similarly divided into those with (C_{DD}) and without (C_N) evidence of DD.

Exercise testing

Participants described their own NYHA symptom class. Each person was then invited to perform a 6 min walk test[8] and incremental treadmill exercise testing with metabolic gas exchange according to a Bruce protocol modified by the addition of a stage 0 at onset consisting of 3 min of exercise at 1.61 km/h (1 mph) with a 5% gradient. Participants were encouraged to exercise to exhaustion. During the tests participants wore a tightly fitting facemask to which was connected a capnograph and a sample tube enabling online $\dot{V}E$ and metabolic gas exchange measurements (Jaeger Oxycon Delta, Würtzburg, Germany). A respiratory exchange ratio (carbon dioxide production ($\dot{V}CO_2$) to oxygen consumption ($\dot{V}O_2$) (RER)) > 1 was taken to indicate a maximal effort. Standard spirometry (forced expiratory volume in 1 s and forced vital capacity) was performed before the exercise test. The participants were asked to score their symptoms of breathlessness or fatigue between 0 and 10 (0 being no symptoms and 10 being the maximum) on a standard scale of perceived exertion[9] at the end of each stage during the test. The Borg/$\dot{V}E$ slope for each participant was plotted.[7] Exercise tests were reported by a single investigator blinded to the results of the echocardiograms.

We initially established three groups, consisting of the control group and two patient groups (patients with symptoms of breathlessness): those with SHF and those with PSF. To investigate further the influence of diastolic variables we then divided patients with PSF into PSF_{DD} (or DHF) and PSF_N. We divided the controls in the same way (C_{DD} and C_N).

Statistical analysis

To assess the difference between the NYHA classes and between the groups, we used analysis of variance (Statview; SAS Institute, Cary, North Carolina, USA). In assessing differences between categorical data we used the χ^2 test. A value of $p < 0.05$ was taken to be significant. We have presented unadjusted p values rather than correcting for multiple comparisons.[10 11]

RESULTS

Four hundred and thirty-five patients were referred for assessment. Each referred patient went through a standardised assessment as described above. The results presented here are assembled from a retrospective analysis of these systematically collected data. Fifty-one patients (11%) had a definite non-cardiac cause of breathlessness (significant airways disease with abnormal lung function (n = 31), severe arthritis (n = 7), anaemia (n = 7), pneumonia (n = 4) and lung cancer (n = 2)). This left a study group of 384. Of these patients, 216 (56%; 50% of referred patients) had an ejection fraction < 45% on echocardiography (SHF) and 168 (44%; 39% of referred patients) had PSF. Of those with PSF, 113 (26% of those referred) had symptoms of heart failure and echocardiographic evidence of DD (PSF_{DD} or DHF) and 55 (13% of referred patients) had symptoms but no signs of systolic or diastolic impairment (PSF_N) (fig 1).

In the study population (384 patients), 67 had concomitant conditions reducing the quality of their exercise test: 29 had arthritis, 32 had chronic airways disease, and 6 had a previous stroke. Thirty patients had a test unsuitable for analysis (not able to exercise past stage 1). These patients' test data were excluded from further analysis, leaving 287 patients: 186 in the SHF group, 61 in the PSF_{DD} group, and 40 in the PSF_N group. Diagnostic criteria for DD were E:A reversal in 37%, prolonged IVRT in 43% and prolonged deceleration time in 49% (table 1).

Patients excluded because of poor exercise test data did not differ in ejection fraction or NYHA class from those included, although older patients were more likely to refuse to walk on the treadmill or have a test unsuitable for analysis. Including the data from patients not achieving peak made no difference to the results, but we elected nevertheless to exclude these from the final analysis. Patients and controls were similar in age, height and weight. Although the patients with PSF_{DD} and PSF_N had non-dilated ventricles and a normal ejection fraction, their LV ejection fraction was lower than that of the controls. Left atrial diameter was greater in patients with PSF_{DD} and SHF than in patients with PSF_N and controls. Patients with PSF_{DD} and PSF_N were of a similar age to those with systolic dysfunction but more were women ($p < 0.05$). Table 1 shows the characteristics of the participants undergoing exercise testing. C_{DD} were older ($p < 0.05$) and more likely than C_N to be women. Indices of DD were not different between patients with PSF_{DD} and C_{DD}.

Table 2 and fig 2 show the exercise variables and symptom class for the five groups of participants. The NYHA class was better for patients with PSF than for those with reduced LV function (SHF group). Exercise capacity ($p\dot{V}O_2$ and exercise time) was lower and the $\dot{V}E/\dot{V}CO_2$ slope steeper in those with impaired systolic ventricular function than in patients with PSF. Exercise capacity and ventilatory response to exercise

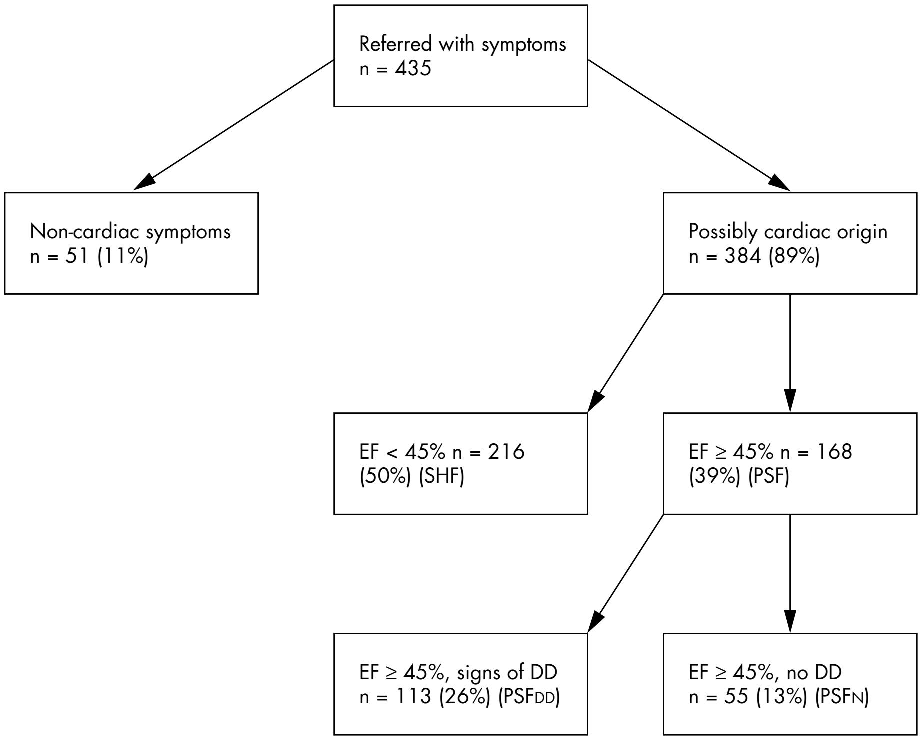

Figure 1 Breakdown of 435 patients referred to the heart failure clinic with systolic heart failure (SHF), preserved systolic function (PSF) with diastolic dysfunction (DD), and preserved systolic function without diastolic dysfunction (PSF_N). Non-cardiac breathlessness was caused by chronic airways disease (31), arthritis (7), anaemia (7), pneumonia (4) and lung cancer (2). EF, ejection fraction.

were similar in breathless patients with normal hearts (PSF_N) to patients in the PSF_{DD} (DHF) group. Patients in the PSF_{DD} group had significantly lower $p\dot{V}O_2$ ($p < 0.02$), exercise time ($p < 0.05$) and 6 min walk test distance than C_{DD} ($p < 0.02$) and a steeper $\dot{V}E/\dot{V}CO_2$ slope ($p < 0.05$), even though the diastolic variables were not different (table 2). The 6 min walk distance was greater in the PSF_{DD} and PSF_N groups than in SHF, although still lower than in the controls. The C_{DD} group performed less well than C_N on exercise testing. To compensate for the higher number of women in the PSF_{DD} group, we repeated the above analyses within the sexes. The patterns described above for the exercise variables remained significant for both men and women.

The mean inverse relationship between the $\dot{V}E/\dot{V}CO_2$ slope and $p\dot{V}O_2$ was greater in SHF than in PSF_{DD} (DHF) ($r = -0.51$ (0.25) *v* -0.46 (0.18), $p < 0.05$). The relationship in those with symptoms and normal hearts (PSF_N: $r = -0.44$ (0.26)) was the same as in the patients with DHF. There was no such relationship in controls.

Borg/$\dot{V}E$ slope was steeper in patients with PSF_{DD} and PSF_N than in those with SHF and both control groups, implying greater symptoms of breathlessness for a given level of $\dot{V}E$

Table 1 Characteristics of patients and controls stratified by presence or absence of significant left ventricular systolic dysfunction

	SHF (n = 186)	PSF_{DD} (n = 61)	PSF_N (n = 40)	C_{DD} (n = 32)	C_N (n = 102)	p Value (SHF *v* PSF_{DD})
Age (years)	69 (13)	69 (13)	64 (16)††	72 (15)	63 (12)**	NS
Men	56%	48%	58%†	35%	52**	<0.05
Height (cm)	174 (5.5)	175 (6.5)	175 (9.2)	175 (11.2)	177 (8.2)	0.74
Weight (kg)	80.6 (15.9)	84.6 (9.7)	83.5 (13.4)	85.2 (12.1)	82.5 (8.8)	0.65
FEV_1 (% expected)	90.0 (17.4)	87.2 (21.4)	88.3 (21.5)	102 (25.4)	116.0 (23.4)*	<0.02
FVC (% expected)	80.0 (22.9)	77.4 (19.6)	79.5 (21.6)	89 (24.3)	95.0 (22.6)	0.02
LVEDD (cm)	6.3 (1.0)	5.2 (0.9)	5.1 (0.8)	5.1 (0.8)	5.0 (0.7)	<0.0001
LVEF (%)	32.8 (8.2)	54.5 (7.6)	57.3 (8.9)	60.0 (9.6)	62.1 (11.6)	<0.0001
LA diameter (cm)	4.9 (1.2)	4.8 (1.3)	3.8 (1.2)†	4.4 (1.4)	3.9 (1.2)*	0.45
E:A ratio	1.5 (1.2)	0.8 (0.8)	1.0 (0.9)†	0.8 (0.8)	1.1 (0.3)**	<0.01
Deceleration time (ms)	185 (66)	236 (35)	215 (49)†	251 (65)	214 (44)*	<0.005
IVRT (ms)	93 (34)	118 (32)	96 (35)†	113 (28)	85 (20) *	<0.05
Drugs						
Furosemide‡	62 (37%)	56 (32%)	32 (46%)	0	0	
β blockers	154	46	0	1	3	
ACEI/AIIA	91/16	28/7	4/2	0/0	0/0	
Thiazide	20	14	8	3	1	
Spironolactone	36	8	0	0	0	

Values are mean (SD), number (%) or number.
*p<0.05, **p<0.02 for difference between C_N and C_{DD}; †p<0.05, ††p<0.02 for difference between PSF_{DD} and PSF_N; ‡mean daily dose of furosemide equivalent is given (1 mg bumetanide is equivalent to 40 mg furosemide).
ACEI, angiotensin-converting enzyme inhibitor; AIIA, angiotensin II inhibitor; C_{DD}, controls with diastolic dysfunction; C_N, controls with normal diastolic function; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; IVRT, isovolumic relaxation time; LA, left atrial; LVEDD, left ventricular end diastolic dimension from M mode echocardiography; LVEF, left ventricular ejection fraction; PSF_{DD}, preserved systolic function with diastolic dysfunction; PSF_N, preserved systolic function without diastolic dysfunction; SHF, systolic heart failure.

Table 2 Symptom scores and exercise results

	SHF (n = 186)	PSF_{DD} (n = 61)	PSF_N (n = 40)	C_{DD} (n = 32)	C_N (n = 102)	p Value (SHF *v* PSF_{DD})
NYHA class I	8%	18%	0%	100%	100%	
NYHA class II	65%	62%	34%	0	0	
NYHA class III	26%	20%	6%	0	0	
p$\dot{V}O_2$ (ml/kg/min)	20.0 (4.8)**	22.5 (5.5)‡‡	23.8 (6.4)	32.4 (10.2)†	36.2 (9.6)	<0.01
$\dot{V}E/\dot{V}CO_2$ slope	37.0 (8.6)**	33.0 (6.1)‡‡	32.8 (8.4)	29.8 (4.2)	28.5 (3.6)	<0.001
RER	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)	0.87
Exercise time (s)	455 (198)**	562 (261)‡‡	571 (281)	698 (292)†	846 (285)	<0.001
6 min walk (m)	221 (137)**	275 (147)‡‡	273 (164)	402 (168)†	472 (114)	<0.01
Borg/$\dot{V}E$ slope	0.17 (0.04)*	0.20 (0.08)‡	0.19 (0.10)	0.14 (0.09)	0.12 (0.07)	<0.05
Reason for stopping (B/F)	79/107*	28/33	12/28	21/11	42/60	<0.001

Values are mean (SD) or percentage.
*$p<0.02$, **$p<0.0001$ for difference between SHF and C_N; †$p<0.05$ for difference between C_{DD} and C_N; ‡$p<0.01$, ‡‡$p<0.001$ for difference between PSF_{DD} and C_N.
B/F, breathlessness or fatigue; Borg/$\dot{V}E$ slope, slope relating symptoms to minute ventilation; NYHA, New York Heart Association; p$\dot{V}O_2$, peak oxygen consumption; RER, peak respiratory exchange ratio; $\dot{V}E/\dot{V}CO_2$ slope, slope relating minute ventilation to carbon dioxide production.

(table 2, fig 3). C_{DD} had a lower Borg/$\dot{V}E$ ratio than PSF_{DD} patients ($p < 0.05$) and better exercise tolerance despite having similar echocardiographic variables of DD. Symptoms of breathlessness (Borg/$\dot{V}E$ slope) and LV ejection fraction were not related in any group.

Figure 4 shows the relationship between p$\dot{V}O_2$ and age in patients with SHF, all breathless patients with PSF and all of the controls. In the control group and patients with PSF, the p$\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ slope deteriorated gradually with age and the slopes are not statistically different. This relationship is not seen in patients with SHF.

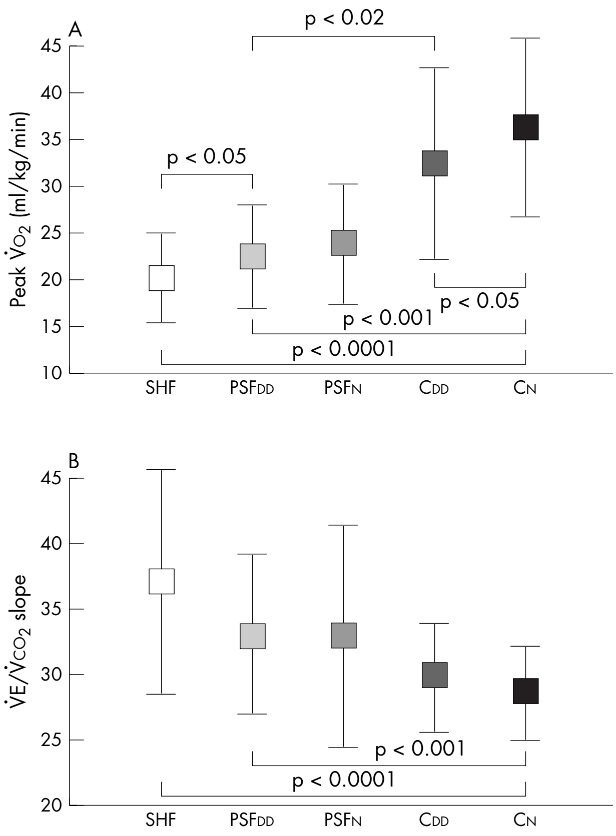

Figure 2 (A) Peak oxygen consumption (p$\dot{V}O_2$) and (B) slope relating minute ventilation to carbon dioxide output ($\dot{V}E/\dot{V}CO_2$ slope) in patients with systolic heart failure (SHF), preserved systolic function with diastolic dysfunction (PSF_{DD}) and preserved systolic function without diastolic dysfunction (PSF_N) and in controls with diastolic dysfunction (C_{DD}) and normal diastolic function (C_N).

DISCUSSION

The present study showed that 40% of patients referred to a heart failure clinic with symptoms of breathlessness had PSF on echocardiography. Many of these (67%) had signs of diastolic impairment, but one third had no cardiac problem identified. Patients with PSF had a better exercise tolerance (when measured by p$\dot{V}O_2$) and a lower ventilatory response to exercise ($\dot{V}E/\dot{V}CO_2$ slope) than patients with systolic dysfunction, but patients with and those without evidence of DD did not differ significantly. However, the exercise tolerance of those presenting with breathlessness was worse than that of controls of similar age. Patients presenting with breathlessness and PSF are also more symptomatic for a given $\dot{V}E$ than both those with systolic dysfunction and controls, including those controls with similar degrees of DD.

Exercise capacity (however assessed) is an important prognostic indicator in patients with heart failure caused by LV systolic dysfunction. Patients with SHF have reduced p$\dot{V}O_2$[12] and an increased $\dot{V}E/\dot{V}CO_2$ slope.[13 14] The $\dot{V}E/\dot{V}CO_2$ slope is abnormal throughout exercise[15] and correlates inversely with p$\dot{V}O_2$, so that the greater the ventilatory response, the lower the exercise capacity.[3 8] Peak $\dot{V}O_2$ and the $\dot{V}E/\dot{V}CO_2$ slope also relate independently to prognosis.[16]

Diastolic function is an important determinant of exercise capacity after myocardial infarction[17] and in the setting of chronic heart failure with LV systolic dysfunction.[18 19] One study that used a clinical diagnosis of DHF based on LV ejection fraction > 50% in 119 patients with breathlessness suggested

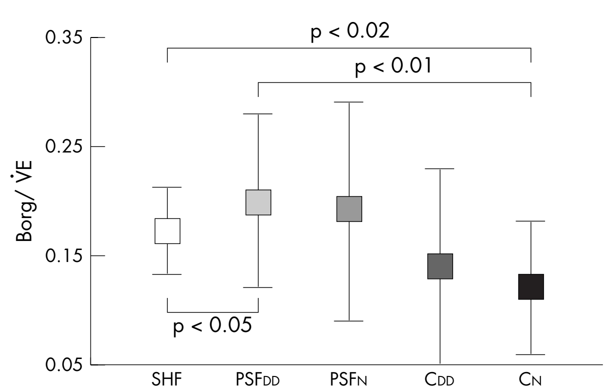

Figure 3 Slope relating symptoms to minute ventilation (Borg/$\dot{V}E$) in patients with systolic heart failure (SHF), preserved systolic function with diastolic dysfunction (PSF_{DD}) and preserved systolic function without diastolic dysfunction (PSF_N) and in controls with diastolic dysfunction (C_{DD}) and normal diastolic function (C_N).

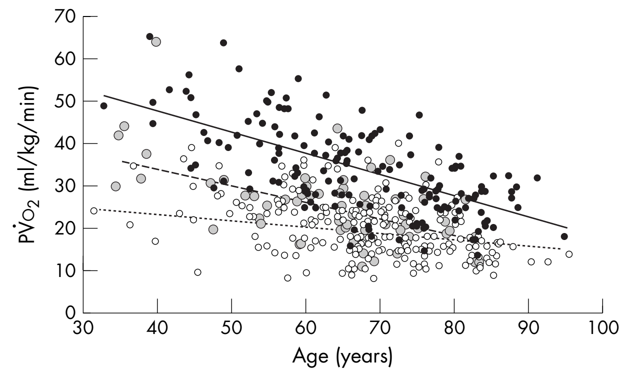

Figure 4 Peak oxygen consumption (pV̇O_2) against age for patients with systolic heart failure (SHF) (unfilled circles), patients with preserved systolic function with diastolic dysfunction (PSF_{DD}) (grey circles) and controls (solid circles). Regression lines for controls (solid line, r = 0.34), PSF_{DD} (long dashes, r = 0.37) and SHF (short dashes, r = 0.07).

that reductions of exercise capacity and abnormalities of the ventilatory response are similar in patients with DHF.[20]

The cause of impaired exercise tolerance in patients with heart failure is not clearly understood. Conventional measures of LV systolic function such as ejection fraction at rest have a poor correlation with pV̇O_2 and the V̇E/V̇CO_2 slope. A tissue Doppler-derived measure of systolic function has a closer relationship than ejection fraction,[21] and tissue Doppler indices can be useful to differentiate diastolic changes associated with normal ageing from pathological changes.[6] The correlation between tissue Doppler indices and exercise tolerance in patients with PSF_{DD} has not been established.

Patients with severe SHF often have diastolic abnormalities on tissue Doppler scanning. The two types of heart failure therefore may merely be a spectrum of the same condition. In our patients, the pathological inverse relationship between the V̇E/V̇CO_2 slope and pV̇O_2 seen in SHF[22] was also seen in those with DHF and in patients with PSF_N, although it was less steep. This has not been described before.

On the other hand, the age-related deterioration in pV̇O_2 seen in controls was also seen in breathless patients with PSF, unlike patients with SHF, where age is not closely related to pV̇O_2. Furthermore, by using the semiobjective Borg/V̇E slope, we showed that, for a given V̇E, patients with DHF and those with PSF_N are more symptomatic than those with SHF. We have also confirmed that there is no relation between symptoms of exercise intolerance as measured by the Borg/V̇E slope and LV ejection fraction. These data support the well-known concept that the degree of cardiac function does not relate to symptoms or the ventilatory abnormalities in either SHF or DHF.

Patients who have DD identified using basic indices might therefore merely be symptomatic individuals who have brought themselves to the attention of their general practitioner and subsequently their cardiologist with a combination of symptoms of breathlessness and fatigue. In these patients imaging investigations might reveal appropriate age-related cardiac function, combined with other non-cardiac causes of impaired exercise tolerance, or merely reduced fitness, that are not significantly different to their more tolerant peers. Indeed in our symptomatic patients with DD the diastolic variables were not significantly different to the controls with abnormal diastolic function, although the exercise capacity was significantly reduced.

Study limitations
The study was based on a retrospective analysis of systematically collected data. During the enrolment period, indices of DD that are less load dependent became accepted, but were not collected for all of our patients. Our conclusions should be viewed in the light of this limitation.

Conclusions
Our study showed that patients with DD and symptoms of breathlessness (DHF) have an intermediate reduction in exercise tolerance between those with SHF and controls. The reduced pV̇O_2 in patients with DHF does, however, correlate closely with age, unlike that in patients with SHF. We have also shown that patients with DHF and those with symptoms but no apparent signs of DHF are more symptomatic than those with SHF for a given V̇E.

....

Authors' affiliations
K K A Witte, N P Nikitin, J G F Cleland, A L Clark, Department of Academic Cardiology, Castle Hill Hospital, Kingston upon Hull, UK

Financial support: None declared.

Competing interests: None declared.

REFERENCES
1 **Clark AL**, Sparrow JL, Coats AJS. Muscle fatigue and dyspnoea in chronic heart failure: two sides of the same coin? *Eur Heart J* l995, **16**:49–52.
2 **Vasan RS**, Benjamin EJ, Levy D. Prevalence, clinical features and prognosis of diastolic heart failure: an epidemiologic perspective. *J Am Coll Cardiol* 1995;**26**:1565–74.
3 **Cleland JG**, Tendera M, Adamus J, *et al*. Perindopril for elderly people with chronic heart failure: the PEP-CHF study. The PEP investigators. *Eur J Heart Fail* 1999;**1**:211–7.
4 **Zile MR**, Gaasch WH, Carroll JD, *et al*. Heart failure with a normal ejection fraction: is measurement of diastolic function necessary to make the diagnosis of diastolic heart failure? *Circulation* 2001;**104**:779–82.
5 **Caruana L**, Petrie MC, Davie AP, *et al*. Do patients with suspected heart failure and preserved left ventricular systolic function suffer from ''diastolic heart failure'' or from misdiagnosis? A prospective descriptive study. *BMJ* 2000;**321**:215–8.
6 **Nikitin NP**, Witte KK, Clark AL, *et al*. Color tissue Doppler-derived long-axis left ventricular function in heart failure with preserved global systolic function. *Am J Cardiol* 2002;**90**:1174–7.
7 **Witte KKA**, Clark AL. The pattern of ventilation during exercise in chronic heart failure. *Heart* 2003;**89**:610–4.
8 **Guyatt GH**, Sullivan MJ, Thompson PJ, *et al*. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. *CMAJ* 1985;**132**:919–23.
9 **Borg G**. Subjective effort and physical activities. *Scand J Rehab* 1978;**6**:108–13.
10 **Rigby AS**. Statistical methods in epidemiology: I. Statistical errors in hypothesis testing. *Disabil Rehabil* 1998;**20**:121–6.
11 **Perneger TV**. What's wrong with Bonferroni adjustments. *BMJ* 1998;**316**:1236–8.
12 **Clark AL**, Poole-Wilson PA, Coats AJS. Exercise limitation in chronic heart failure: central role of the periphery. *J Am Coll Cardiol* 1996;**28**:1092–102.
13 **Buller NP**, Poole-Wilson PA. Mechanism of the increased ventilatory response to exercise in patients with chronic heart failure. *Br Heart J* 1990;**63**:281–3.
14 **Davies SW**, Emery TM, Watling MIL, *et al*. A critical threshold of exercise capacity in the ventilatory response to exercise in chronic heart failure. *Br Heart J* 1991;**65**:179–83.
15 **Witte KKA**, Clark AL. Is the elevated slope relating ventilation to carbon dioxide production in chronic heart failure a consequence of slow metabolic gas kinetics? *Eur J Heart Fail* 2001;**4**:469–72.
16 **Cohn JN**, Johnson GR, Shabetai R, *et al*. Ejection fraction, peak exercise oxygen consumption, cardiothoracic ratio, ventricular arrhythmias, and plasma norephinephrine as determinants of prognosis in heart failure. The V-HeFT VA Cooperative Studies Group. *Circulation* 1993;**87**(suppl 6):V15–6.
17 **Miyashita T**, Okano Y, Takaki H, *et al*. Relation between exercise capacity and left ventricular systolic versus diastolic function during exercise in patients after myocardial infarction. *Coron Artery Dis* 2001;**12**:217–25.
18 **Partenakis FI**, Kanoupakis EM, Kochaidakis GE, *et al*. Left ventricular diastolic filling pattern predicts cardiopulmonary determinants of function capacity in patients with congestive heart failure. *Am Heart J* 2000;**140**:338–44.
19 **Lapu-Bula R**, Robert A, De Kock M, *et al*. Relation of exercise capacity to left ventricular systolic function and diastolic filling in idiopathic or ischaemic dilated cardiomyopathy. *Am J Cardiol* 1999;**83**:728–34.
20 **Kitzman DW**, Little WC, Brubaker PH, *et al*. Pathophysiological characterisation of isolated diastolic heart failure in comparison to systolic heart failure. *J Am Med Assoc* 2002;**288**:2144–50.
21 **Witte KKA**, Nikitin NP, Cleland JGF, *et al*. Exercise tolerance and tissue Doppler imaging in chronic heart failure. *Heart* 2004;**90**:1144–50.
22 **Francis DP**, Shamim W, Davies LC, *et al*. Cardiopulmonary exercise testing for prognosis in chronic heart failure: continuous and independent prognostic value from VE/VCO(2) slope and peak VO(2). *Eur Heart J* 2000;**21**:154–61.