



Heart failure with a normal ejection fraction

John E Sanderson

Heart published online 30 Dec 2005;
doi:10.1136/hrt.2005.074187

Updated information and services can be found at:

<http://heart.bmjjournals.com/cgi/content/abstract/hrt.2005.074187v1>

These include:

Rapid responses

You can respond to this article at:

<http://heart.bmjjournals.com/cgi/eletter-submit/hrt.2005.074187v1>

Email alerting service

Receive free email alerts when new articles cite this article - sign up in the box at the top right corner of the article

Notes

Online First contains unedited articles in manuscript form that have been peer reviewed and accepted for publication but have not yet appeared in the paper journal (edited, typeset versions may be posted when available prior to final publication). Online First articles are citable and establish publication priority; they are indexed by PubMed from initial publication. Citations to Online First articles must include the digital object identifier (DOIs) and date of initial publication.

To order reprints of this article go to:

<http://www.bmjjournals.com/cgi/reprintform>

To subscribe to *Heart* go to:

<http://www.bmjjournals.com/subscriptions/>

Review: Heart failure with a normal ejection fraction.

John E Sanderson MD FRCP FACC

Department of Cardiology,
Keele University Medical School
University Hospital of North Staffordshire NHS Trust
Stoke-on-Trent. UK

Running title: HFNEF

Address for correspondence:

Professor John Sanderson
Department of Cardiology
University Hospital of North Staffordshire NHS Trust
City General Hospital
Stoke-on-Trent
ST4 6QG
Email: John.Sanderson@uhns.nhs.uk
Tel: 01782 553036

Key words : diastolic heart failure ; ejection fraction ; remodeling.

"The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non-exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd and its Licensees to permit this article to be published in Heart editions and any other BMJ PGL products to exploit all subsidiary rights, as set out in our licence (<http://heart.bmjournals.com/misc/ifora/licenceform.shtml>) . "

Abstract.

Nearly half of patients with symptoms of heart failure are found to have an LV ejection fraction which is within normal limits. These patients have variously been labeled as having diastolic heart failure, heart failure with preserved LV function or heart failure with normal ejection fraction (HFNEF). Since recent studies have shown that systolic function is not entirely normal in these patients, HFNEF is the preferred term. The epidemiology, aetiology and possible pathophysiology of this contentious condition are reviewed. The importance of the remodeling process in determining whether a patient presents with systolic heart failure or HFNEF is emphasized and this can be used to classify patients in a more rational manner.

It has been realised for some time that many patients presenting with symptoms of what is apparently heart failure are found on further investigation to have a left ventricular ejection fraction within normal limits. These patients have been variously labelled as having diastolic heart failure, heart failure with preserved systolic function or heart failure with a normal ejection fraction (HFNEF). The preferred term should be HFNEF because accumulative evidence suggests that the physiological abnormalities in these patients are not restricted to diastole only and systolic function is not entirely “preserved” when measures other than the ejection fraction are used. There are epidemiological, clinical, pathological and physiological similarities and differences between patients that have reduced left ventricular ejection fraction with ventricular dilatation, what is commonly called systolic heart failure (SHF), and those with HFNEF.

Epidemiology

Population based epidemiology prevalence studies suggests that nearly half the patients with heart failure have HFNEF although in hospital cohorts the percentage appears to be less. The proportion of patients with HFNEF in the various studies ranges from 40% to 71% (with a mean of 56%).¹ However, all these studies are compromised by variable definitions of heart failure and the precise threshold for what is considered to be a normal left ventricular ejection fraction. In the cardiovascular health study 80% of patients had a LVF >0.45 but only 55% had a LVF >0.55.² In hospital based cohort studies the proportion of patients with HFNEF are slightly lower ranging from 24-55% (mean 41%).¹ A possible explanation is that patients with HFNEF have less severe symptoms or are less frequently admitted. The average age of patients with HFNEF tends to be older than those with SHF and in most studies the majority have been women. This appears to be a consistent feature. HFNEF appears to be common in China and India perhaps due to the high prevalence of hypertension in these communities.³ The aging of the populations in Asia combined with hypertension which is often poorly treated presage a substantial increase in the number of patients with HFNEF in these areas.⁴ The morbidity, hospitalisation rates and health care costs per patient however are very similar between those with HFNEF and SHF.¹ Reported mortality rates vary widely. In the Framingham Heart Study, for patients with HFNEF the annual mortality rate was 8.7% compared to 3% in matched controls and for SHF was 18.9% compared to a 4.1% in age

and gender managed controls over 6.2 years.⁵ In contrast, in the Cardiovascular Health Study the population attributable mortality risk was greater for those with HFNEF than those with SHF⁶ but this is partly explained by the higher prevalence of HFNEF in the elderly population.

Many of these epidemiology studies may be unreliable because at the moment HFNEF is a diagnosis of exclusion, since the criteria for diastolic dysfunction independent of age related changes have not been clearly delineated (see below). Many patients with obesity, chronic obstructive airways disease, or with ankle oedema are often labelled as having heart failure. There is a need for studies which carefully assess whether there is indeed true heart failure in these patients or not through metabolic exercise testing. In a revealing study Caruana et al⁷ found that a third of their patients labelled with HFNEF were either obese or very obese, half had considerable reductions in respiratory function (FEV1 70% or less) and many had evidence of a myocardial infarction or ischaemia. Only 7 out of 109 patients diagnosed as having HFNEF did not have another explanation for their symptoms. However, in this study only simple mitral inflow E/A ratios were used to establish diastolic dysfunction. Many of these elderly patients do have several co-morbidities that often contribute to their symptoms.

Aetiology and Pathophysiology

A history of hypertension with LV hypertrophy is commonly associated with HFNEF.¹ Also, new onset atrial fibrillation (AF) is frequent and the loss of the atrial contribution and reduced filling time may combine to precipitate pulmonary oedema.¹ Hypertension predisposes towards the development of atrial fibrillation especially if LV filling pressures are high and left atrial size is increased. Thus the onset of AF in a hypertensive may be the precipitating factor for the symptoms of heart failure to develop and the subsequent hospital admission. Ischemia and diabetes are also important. In a study from Hong Kong it was clear that hypertension, ischaemic heart disease and diabetes overlapped and all were common in HFNEF patients.³ All of these aetiological factors can impair both systolic and diastolic function particularly ventricular long axis function even in the presence of a normal LV ejection fraction.^{8,9}

The development of newer echocardiographic techniques such as tissue Doppler imaging has enabled a more accurate assessment of ventricular function. In an early study Yip et al showed that both peak annular systolic and peak early diastolic velocities and the respective excursions which are measures of ventricular long axis function were reduced in HFNEF compared to age-matched controls.¹⁰ These findings have now been confirmed in 6 other studies.¹¹⁻¹⁶ Thus, despite a normal ejection fraction, systolic function in the long axis is not normal in HFNEF. This should come as no surprise as systole clearly will be affected as much as diastole by both left ventricular hypertrophy and fibrosis. Shan et al showed that both peak annular systolic velocity and the early diastolic velocity are equally affected by interstitial fibrosis within the myocardium.¹⁷ Physiologically, systole and diastole are closely intertwined. We found a close relationship between annular systolic and diastolic velocities across a wide range of LV ejection fractions¹⁸ which has been confirmed by others.^{13, 16} In reality systole and diastole constitute one cycle and the major determinant of early diastolic filling is the strength and coordination

of the previous systole which is the driver for ventricular suction. In addition, incoordinate systolic contraction will prolong isovolumic relaxation and further impair diastolic function.¹⁹ Interestingly the peak early diastolic velocity has emerged as a powerful predictor of prognosis in a variety of cardiac diseases including heart failure.²⁰ This may be because this measurement of motion of the ventricular base during early diastole is reflecting both systolic and diastolic function of the ventricle, because early diastolic filling is so dependent on LV suction. Moreover, the subendocardial fibres which are mainly responsible for long axis contraction may be more susceptible to the effects of fibrosis, hypertrophy and ischemia because of their position, and thus explain why this measurement is a good early marker of disease. In addition, hypertension, left ventricular hypertrophy, aging and diabetes all alter global myocardial architecture and fibre orientation which will probably have important effects on ventricular torsion and recoil during relaxation. Reduced ventricular twist and long axis motion during systole will also impact on ventricular suction.²¹

It is thus artificial to separate the two phases of the cardiac cycle. Despite this some have argued that in HFNEF systolic function is completely normal and the clinical condition is due entirely to diastolic dysfunction alone, and SHF and HFNEF are distinctly different.²² These studies are based on global measurements derived from pressure-volume relationships which take no account of regional dysfunction or abnormalities of long axis function which are compensated for initially by increased radial function.¹³ Even measures such as tau and LV end-diastolic pressure volume relationships have considerable theoretical and practical drawbacks and neither accurately measure “relaxation” or “stiffness” as popularly supposed.²³ Global pressure-volume loops can be remain normal despite significant changes in myocardial architecture and shape which perhaps are reflected better by the long axis measurements.

Titin, a giant sarcomere protein that acts like a molecular spring, may also have a role as titin isoform shifting may have an impact on diastolic function. In idiopathic dilated cardiomyopathy Nagueh et al have recently shown an increase in the N2BA/N2B isoform ratio compared to controls.²⁴ This shift to a larger isoform would predict a substantial decrease in passive myocardial stiffness which was found in myocardial strips but also will affect the restoring forces and elastic recoil of the cardiac myocyte and hence ventricular suction.

Remodeling: The main physiological difference between systolic heart failure and HFNEF is the increase in ventricular volume and change in shape due to ventricular remodeling. A myocardial infarction (or rarely viral myocarditis) appears to be potent stimulants for the remodeling process which leads to increased ventricular volumes and reduced ejection fraction.²⁵ In hypertensive heart disease remodeling is a slower process. Initially left ventricular hypertrophy by itself will lead to reduced systolic and diastolic function particularly in the long axis.⁸ Compensatory increased radial contraction normalises the ejection fraction. However, at later stages further remodelling will occur and the left ventricular volumes will increase and the patient will slip from HEFNEF to more obvious systolic heart failure (figure). Thus, from a physiological point it is more sensible to categorise patients with heart failure according to whether remodeling has taken place or not. Remodeling is a very important therapeutic target and reversing remodeling is probably a powerful predictor of improvement. Nearly all therapies which

are proven to reduce mortality and improve symptoms in heart failure has also induced reverse remodeling, for example beta blockers and cardiac resynchronisation therapy.^{26,27}

Peripheral factors: In a recent experimental study of HEFNEF the time to complete relaxation was significantly prolonged compared to controls which worsened with increased arterial pressure.²⁸ Also, end-systolic elastance was increased in this experimental heart failure model and was closely linked to collagen volume fraction. Afterload affects both systolic and diastolic LV performance prolonging contraction and relaxation. This effect is seen early in the progression of systolic dysfunction and will lead to a shortening of the diastolic filling period. This action of an increased afterload would be particularly troublesome with faster heart rates such as with exercise or AF. Kawaguchi et al found in humans that end-systolic elastance (stiffness) was higher in patients with HFNEF as was effective arterial elastance due to reduced total arterial compliance, and these were higher than that associated with ageing and/or hypertension.²⁹ This ventricular-arterial stiffening, presumably due to abnormal myocardial and arterial collagen, will amplify stress-induced hypertension thus worsening diastolic dysfunction. Impaired renal function and renal arterial atherosclerosis in the elderly may also be involved in causing rapid rises in blood pressure and excessive fluid retention.

Clinical features and diagnosis

Although there are clinical differences between the typical patient presenting with HFNEF and systolic heart failure these relate more to aetiology and whether remodelling has taken place or not (table). The typical patient with HFNEF is an elderly lady with a history of hypertension often with diabetes whose heart failure is episodic often precipitated by an episode of AF, ischaemia or infection.³⁰ In fact these simple criteria based on aetiology and the presence or absence of ventricular remodelling point to a more useful classification. HFNEF patients usually have hypertensive heart failure with left ventricular hypertrophy whereas the typical SHF patient has usually had a previous myocardial infarction with significant left ventricular remodeling, myocarditis or idiopathic dilated cardiomyopathy. It would appear to be more useful to approach the diagnosis of all types of heart failure along the following lines:

- a. Establish the presence of heart failure: symptoms with BNP levels (and exercise testing if unsure).
- b. Determine the main aetiology and mechanisms: hypertension and/or ischaemia, infarction etc.
- c. Has remodeling taken place (are LV volumes increased)?
- d. Are additional factors deleterious factors present: dyssynchrony, arrhythmias, metabolic/electrolyte abnormalities etc?

This process focuses on the two major stages of the clinical process: firstly deciding is this heart failure and secondly are there treatable factors such as ischemia, remodeling, dyssynchrony etc. Echocardiography has a vital role in all these processes. Measurement of the LVEF is not relevant. It is clear that the theoretical underpinning of the concept that SHF and HFNEF are physiologically fundamentally different has been undermined by recent research as outlined above. Both conditions have a mixture of systolic and diastolic abnormalities and it would appear to be more useful to classify according to the

aetiology and the mechanisms involved in the individual patient which may be different. Measurements of long axis function are sensitive and can be used to confirm the presence of impaired systolic and diastolic dysfunction and the peak early diastolic velocity is a powerful predictor of future prognosis.²⁰ However, all measurements of long axis function and mitral inflow velocities need to be corrected for age. Aging has a powerful deleterious effect on ventricular function and on these diastolic indices. Criteria for diagnosis of HFNEF based on diastolic measurements of mitral inflow velocities are not usually corrected for age. Indeed the whole definition of diastolic dysfunction, using echocardiography, is difficult and there is no “gold standard”. Extreme mitral filling patterns such as the restrictive filling pattern are obvious indicators of severe diastolic dysfunction but usually only occur in the presence of severe systolic dysfunction as well. Indeed, Simm et al found there was no difference in the left ventricular filling patterns seen on echocardiography between an appropriate reference population and patients with breathlessness³¹. The previous guidelines on diagnosis of “diastolic heart failure” are now less relevant in view of these recent findings and new guidelines are clearly required.

Treatment

There is little evidence to guide treatment as previously patients with HFNEF have been excluded from clinical trials on the basis of a normal LV ejection fraction. The CHARM – Preserved Trial assessed the additional effect of treatment with Candesartan on cardiovascular death or admissions to hospital.³² Candesartan had a modest impact in preventing hospital admissions but no effect on cardiovascular death. In one study diuretic withdrawal was associated with more frequent but non-significant recurrence of heart failure in patients with HFNEF and Digoxin reduced hospitalisations in another although it had no effect on mortality.^{33,34} A number of studies are ongoing which may provide more data for a more evidence-based approach. At the moment diuretics can be recommended to reduce symptoms of breathlessness. On the basis that many of these patients have left ventricular hypertrophy ACE inhibitors or ARB's may be of value. Clinical trials in this group of patients are often difficult because patients with HFNEF are frequently elderly and have much other co-morbidity, in particular renal failure.

Conclusion.

HFNEF is a relatively common cause of heart failure symptoms. As in all forms of heart failure there is a mixture of abnormalities of systolic and diastolic function and the LV ejection fraction is not a good measurement on which to base a classification that dichotomises heart failure patients into two groups. Aetiology and the presence of remodelling (increased ventricular volumes) are clinically more useful parameters to use for a classification. It is still unclear how often HFNEF evolves into SHF due to ventricular remodeling but it is probable that this does occur. However, it is likely that there is over-diagnosis of HFNEF because of the absence of good age-independent measurements of diastolic dysfunction, and many labelled as having HFNEF may not have heart failure but merely mild fluid overload.

References:

1. Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function: epidemiology, clinical characteristics, and prognosis. *J Am Coll Cardiol*, 2004; 43:317-327.
2. Kitzman DW, Gardin JM, Gottdiener JS et al. Importance of heart failure with preserved systolic function in patients >or+65 years of age. CHS Research Group. Cardiovascular Health Study. *Am J Cardiol* 2001;87:413-9.
3. Yip GWK, Ho PPY, Woo KS, Sanderson JE. Comparison of frequencies of left ventricular systolic and diastolic heart failure in Chinese living in Hong Kong. *Am J Cardiol* 1999;84:563-567.
4. Sanderson JE, Tse TF. Heart failure: a global disease requiring a global response. *Heart*. 2003;89:585-6.
5. Vasan RS, Larson MG, Benjamin EJ et al. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. *J Am Coll Cardiol* 1999;33:1948-55.
6. Gottdiener JS, McClelland RL, Marshall R et al. Outcome of congestive heart failure in elderly persons: influence of left ventricular systolic function. The Cardiovascular Health Study. *Ann Intern Med* 2002;137:631-9.
7. Caruana L, Petrie MC, Davie AP, McMurray JJV. 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;321:215-9.
8. Wang M, Yip GWK, Wang A, Zhang Y, Ho PY, Tse D, Yu CM, Sanderson JE. Tissue Doppler Imaging provides incremental prognostic value in patients with hypertension and left ventricular hypertrophy. *J Hypertension* 2005;23:183-91.
9. Fang ZY, Leano R, Marwick TH. Relationship between longitudinal and radial contractility in subclinical diabetic heart disease. *Clin Sci (Lond)* 2004;106:53-60.
10. Yip G, Wang M, Zhang Y, Fung JWH, Ho P, Sanderson JE. Left ventricular long axis function in diastolic heart failure is reduced in both diastole and systole: time for a redefinition? *Heart* 2002;87:121-125.
11. Petrie MC, Caruana L, Berry C, McMurray JJ. “Diastolic heart failure” or heart failure caused by subtle left ventricular systolic dysfunction. *Heart* 2002;87:29-31.
12. Nikitin NP, Witte KK, Clark AL, Cleland JG. Color tissue Doppler-derived long-axis left ventricular function in heart failure with preserved global systolic function. *Am J Cardiol* 2002;90:1174-7.
13. Vinereanu D, Nicolaidis E, Tweddel AC, Fraser AG. “Pure” diastolic dysfunction is associated with long-axis systolic dysfunction. Implications for the diagnosis and classification of heart failure. *Eur J Heart Fail* 2005;7:820-828.
14. Garcia EH, Perna FR, Farias EF, Obregon RO, Macin SM, Parras JI, Agüero MA, Moratorio DA, Pitzus AE, Tassano EA, Rodriguez L. Reduced systolic performance by tissue Doppler in patients with preserved and abnormal ejection fraction: new insights into chronic heart failure. *Int J Cardiol* 2005;Epub.
15. Yu CM, Lin H, Yang H, Kong SL, Zhang Q, Lee SW. Progression of systolic abnormalities in patients with “isolated” diastolic heart failure and diastolic dysfunction. *Circulation* 2002;105:1195-201.

16. Bruch C, Gradaus R, Gunia S, Breithardt G, Wichter T. Doppler tissue analysis of mitral annular velocities: evidence for systolic abnormalities in patients with diastolic heart failure. *J Am Soc Echocardiogr* 2003;16:1031-6.
17. Shan K, Bick RJ, Poindexter BJ et al. Relation of tissue Doppler derived myocardial velocities to myocardial structure and beta-adrenergic receptor density in humans. *J Am Coll Cardiol* 2000;36:891-6.
18. Yip GW, Zhang Y, Tan PYH, Wang M, Ho PY, Brodin L-A, Sanderson JE. Left ventricular long-axis changes in early diastole and systole: impact of systolic function on diastole. *Clin Sci (London)* 2002; 102:515-522.
19. Gibson DG, Brown DJ. Relation between diastolic left ventricular wall stress and strain in man. *Br Heart J* 1974;36:1066-77.
20. Wang M, Yip GWK, Yu CM, Zhang Y, Zhang Q, Tse MK, Kong SL, Sanderson JE. Independent and incremental prognostic value of early diastolic annular velocity in patients with impaired left ventricular systolic function. *J Am Coll Cardiol* 2005;45:272-7.
21. Ashikaga H, Criscione JC, Omens JH, Covell JW, Ingels NB. Transmural left ventricular mechanics underlying torsional recoil during relaxation. *Am J Physiol Heart Circ Physiol*, 2004;286:H640-H647.
22. Baicu CF, Zile MR, Aurigemma GP, Gaasch WH. Left ventricular systolic performance, function, and contractility in patients with diastolic heart failure. *Circulation* 2005;111;2306-12.
23. Gibson DG, Francis DP. Clinical assessment of left ventricular diastolic function. *Heart* 2003;89:231-8.
24. LeWinter MM. Titin isoforms in heart failure: are there benefits to supersizing? *Circulation* 2004;110:109-11.
25. Mann DL, Bristow MR. Mechanisms and models in heart failure: the biomechanical model and beyond. *Circulation* 2005;111:2837-49.
26. Groenning BA, Nilsson JC, Sondergaard L, Fritz-Hansen T, Larsson HB, Hildebrandt PR. Antiremodeling effects on the left ventricle during beta-blockade with metoprolol in the treatment of chronic heart failure. *J Am Coll Cardiol* 2000;36:2072-80.
27. Yu CM, Chau E, Sanderson JE, Fan K, Tang MO, Fung WH, Lin H, Kong SL, Lam YM, Hill MRS, Lau CP. Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. *Circulation* 2002; 105:438-445.
28. Munagala VK, Hart CYT, Burnett JC, Meyer DM, Redfield MM. Ventricular structure and function in aged dogs with renal hypertension. A model of experimental diastolic heart failure. *Circulation* 2005;111:1128-1135.
29. Kawaguchi M, Hay I, Fetis B, Kass DA. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. *Circulation* 2003;107:714-20.
30. Banerjee P, Clark AL, Nikitin N, Cleland JGF. Diastolic heart failure: Paroxysmal or Chronic? *Eur J Heart Fail* 2004;6:427-431.

31. Sim MF, Ho SF, O'Mahoney MS, Steward JA, Buchalter M, Burr M. European reference values for Doppler indices of left ventricular diastolic filling. *Eur J Heart Fail*. 2004;6:433-8.
32. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJV, Michelson EL, Olofsson B, Ostergren J, for the CHARM investigators and Committees. Effects of candesartan in patients with chronic heart failure and preserved left ventricular ejection fraction: the CHARM-Preserved trial. *Lancet* 2003;362:777-81.
33. van Kraaij DJ, Jansen RW, Sweep FC, Hoefnagels WH. Neurohormonal effects of furosemide withdrawal in elderly heart failure patients with normal systolic function. *Eur J Heart Fail* 2003;5:47-53.
34. Digitalis Intervention Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997;336:525-33.

Acknowledgements:

I thank Drs Gabriel Yip, Alan Fraser, Derek Gibson, Michael Frenneaux, Mei Wang, and Cheuk-Man Yu for their helpful discussions and thoughts over the past few years. There are no competing interests.

Legend to the Figure.

Time course of and pattern of development of heart failure primarily due to myocardial infarction with marked remodeling and shape change leading to systolic heart failure (SHF) and that due to hypertension leading to heart failure with a normal ejection fraction (HFNEF) are illustrated. Lower normal limits of LVEF and peak annular systolic velocity are indicated on axes. Both patients with a myocardial infarction and hypertension may pass through a HFNEF and SHF period.

Table: comparison of clinical features of SHF and HFNEF

	<u>HF with reduced EF (SHF)</u>	<u>HF with normal EF (HFNEF)</u>
Gender	M>F	F>M
Age	50-60 years	60-70 years
Aetiology	Myocardial infarction; idiopathic DCM	Hypertension ± diabetes; Atrial fibrillation Transient ischaemia
Clinical progress	Persistent HF	Often episodic HF
Ventricular remodeling (increased LV volumes)	+++	0
LVH	+/-	+++
Dyssynchrony	common	? less common
Mitral inflow pattern	RFP or ARP	ARP
Peak mitral annular systolic velocity	Markedly reduced	Moderately reduced
Peak mitral annular early diastolic velocity	Markedly reduced	Moderately reduced
LA pressure	raised	raised
LA volume	increased	increased

DCM= dilated cardiomyopathy; HF= heart failure; RFP= restrictive filling pattern; ARP= abnormal relaxation pattern.

Figure 1

