

Diagnosis of heart failure

J G F Cleland

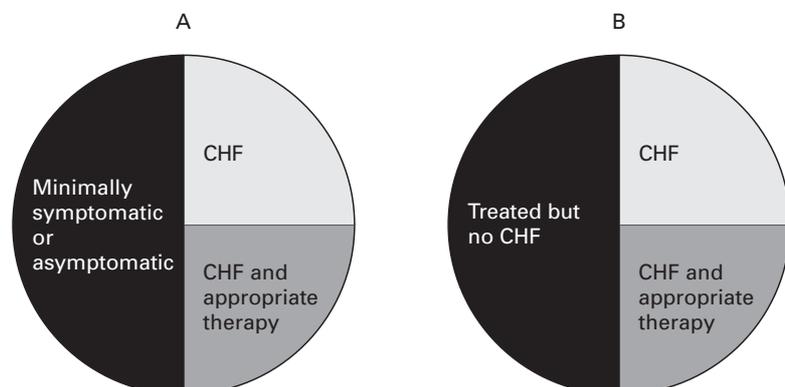
There is no doubt that many patients with clinically important ventricular dysfunction and symptoms suggestive of heart failure, such as exertional breathlessness, are not treated until overt signs of fluid retention are apparent. There is growing evidence that such patients benefit from a variety of treatments. However, a large proportion of patients who have developed signs of fluid retention or become breathless are treated with diuretics without real consideration of the underlying cause.^{1–4} More detailed diagnosis is required to establish that heart failure is the cause of symptoms and to ascertain the cause of heart failure itself.

The most commonly abused treatment for heart failure in the UK are the loop diuretics (4% of the population), while in Germany it is digoxin (3% of the population). It is a matter for debate which of these two treatments is most toxic when used inappropriately. The fact remains that many patients who have heart failure and who would benefit from treatment with an ACE inhibitor do not receive the most beneficial treatment.³ It is likely that inadequate diagnosis is a major factor in undertreatment.

The above considerations result in two “heart failure rules of halves” (fig 1). Rule 1 is that while about half of the patients with left ventricular systolic dysfunction (3–8% of the adult population)^{5,6} are receiving treatment for heart failure, half of them are receiving inappropriate treatment. Rule 2 is that only about half of the patients being treated for heart failure (about 3–4% of the population using prescription data) have confirmed left ventricular dysfunction, and among these patients half or less are being treated appropriately. These data highlight the ample scope for improving the diagnosis and management of heart failure.

Medical Research
Council Clinical
Research Initiative in
Heart Failure, West
Medical Building,
University of Glasgow,
Glasgow G12 8QQ, UK
J G F Cleland

Correspondence to:
Dr Cleland.
email: J.Cleland@
bio.gla.ac.uk



(A) Ventricular dysfunction—the first rule of halves. (B) Heart failure therapy—the second rule of halves.

Diagnostic process

The diagnostic process in heart failure has five components (table 1), each of which is important in determining the optimum treatment for that individual. These five components are not exhaustive; there is an added aim of predicting which patients are going to develop heart failure, which serves two purposes. First, if a patient is in a high risk group for developing heart failure then the onset of typical symptoms make a diagnosis of heart failure likely. Second, anticipating the occurrence of heart failure would allow the introduction of interventions that may help to prevent the onset of heart failure. ACE inhibitors,⁷ antihypertensive treatment,⁸ and lipid lowering agents⁹ have all been shown to reduce the risk of developing heart failure in at risk populations, and it is likely that β blockers will confer similar benefit.

Definition of heart failure

Classic definitions of heart failure based on cardiac output and filling pressures are derived from the physiology laboratory. While contributing to the understanding of heart failure they have limited practical use as, currently, only a few patients undergo haemodynamic evaluation. Furthermore, treatment to improve the haemodynamic markers of heart failure has not, so far, been shown to alter outcome. Consequently, there has been a move towards a more practical and clinically useful definition of heart failure.

A definition such as that adopted by the European Society of Cardiology (table 2) is more appropriate to clinical practice, although inevitably the clinician must still decide whether exertional breathlessness is more severe than might be expected in health, on the importance of any underlying cardiac dysfunction as a cause of symptoms, and if any response to treatment is genuine or just a placebo effect.¹⁰

Ascertaining that the patient has heart failure

Table 3 summarises the studies showing the inaccuracy of a clinical diagnosis of heart failure. Diagnosis of heart failure by a non-specialist appears to be wrong in up to 50% of cases when made by clinical means alone. It is likely that the specialist would not fare much better without resort to further tests. A survey of US cardiologists¹¹ indicated that they felt that they could diagnose only advanced heart

Table 1 Diagnostic aims in heart failure

| |
|--|
| To ascertain that the patient has heart failure |
| To ascertain the aetiology of heart failure (coronary disease, valve disease) |
| To determine the pathophysiological pattern of the disease (systolic, diastolic dysfunction) that is important for deciding the therapeutic strategy |
| To determine the presenting features (oedema, exertional breathlessness) |
| To identify features that predict morbidity and mortality |
| (To predict patients at risk of developing heart failure) |

Table 2 Definition of heart failure (based on the ESC guidelines)¹⁰

| | |
|---------------|---|
| Subjective | Symptoms of heart failure |
| Objective | Evidence of important cardiac dysfunction |
| Retrospective | Response to appropriate treatment for heart failure |

failure with certainty by clinical means alone (fig 1). For this reason additional clinical tests are usually required to confirm a suspected diagnosis of heart failure.

The ideal test for heart failure would fulfil several criteria: it should have high specificity and sensitivity; it should be objective; results should be recordable; and the test should be practical.¹² Furthermore, the results should be gradable, give prognostic information and provide clues to aetiology.¹² To date no single ideal test exists. Echocardiography comes the closest to fulfilling the criteria, but it is not without significant shortcomings.

SYMPTOMS

Tables 4 and 5 show the sensitivity and specificity of common symptoms and signs of heart failure.¹³ It is clear that no symptom or sign is both sensitive and specific for heart failure, indicating that diagnosis solely by clinical means is of limited value for the long term management of patients.

Symptoms, by definition, are a sensitive marker of the possibility of heart failure but have low specificity. It is difficult to make a reliable, direct record of a patient's symptoms and it can be equally difficult to judge whether breathlessness is caused by factors such as a low level of fitness, obesity, pulmonary or joint disease. Also, while the presence of a productive cough and wheezing on exertion suggests pulmonary disease, both cough and wheeze may be caused by heart failure. The scarce data that do exist on interobserver reproducibility of eliciting symptoms of heart failure is far from reassuring.¹⁴ Moreover, many patients with left ventricular dysfunction do not have symptoms.⁶ There is a grey area between clearly symptomatic and asymptomatic heart failure. For example, reduced exercise capacity is a frequent finding in patients with apparently asymptomatic left ventricular dysfunction.

Table 3 Accuracy of clinical diagnosis of heart failure

| Reference | Confirmatory tests | Diagnosis unlikely (%) | | Diagnosis probable (%) | |
|-----------|--|------------------------|------|------------------------|-------|
| 1 | Echocardiography and 6 months' follow up | Men | 16.2 | Men | 56.8* |
| | | Women | 47.1 | Women | 13.7* |
| 2 | Echocardiography | Men | 37 | Men | 63 |
| | | Women | 73 | Women | 27 |
| 3 | Objective signs or chest radiography or echocardiography | | 44.4 | | 55.6† |
| 4 | Echocardiography | | 84.5 | | 15.5 |

*Numbers do not make 100% as some patients were classified as possible heart failure.
 †Only 67% had left ventricular dysfunction on echocardiography, 20% had mitral valve disease, 8% had aortic valve disease, 2% had congenital heart disease. Only 1.3% had coronary arteriography.

Table 4 Sensitivity and specificity of symptoms in diagnosis of CHF¹³

| | Sensitivity (%) | Specificity (%) |
|-------------------------------|-----------------|-----------------|
| Dyspnoea | 66 | 52 |
| Orthopnoea | 21 | 81 |
| Paroxysmal nocturnal dyspnoea | 33 | 76 |
| Oedema | 23 | 80 |

Table 5 Sensitivity and specificity of signs in diagnosis of CHF¹³

| | Sensitivity (%) | Specificity (%) |
|--------------------------------|-----------------|-----------------|
| Tachycardia | 7 | 99 |
| Rales | 13 | 91 |
| Third heart sound | 31 | 95 |
| Raised jugular venous pressure | 10 | 97 |
| Oedema | 10 | 93 |

SIGNS

Although cardiologists can attain a high degree of agreement on the presence of raised jugular venous pressure, displaced apex beat, pulmonary crepitations or the presence of a third heart sound under study conditions, it is likely that interobserver agreement is lower among non-specialists and in the routine clinic setting (table 6).¹⁵⁻¹⁸ Peripheral oedema, pulmonary crepitations, and tachycardia are usually absent and jugular venous pressure is often normal in well treated heart failure, even if severe.¹⁹ Pulmonary crepitations and ankle oedema, although common signs, are not specific to heart failure.¹⁷

When several signs are present, a clinical diagnosis of heart failure may be made with some confidence. Although a clinical diagnosis reached in this way may be specific, it is likely to be insensitive, especially for patients with milder degrees of heart failure who might obtain greater benefit from treatment. The subjective component of the examination and the inability to make a permanent direct record with which to convince others who have not seen the patient, are further major weaknesses of relying on clinical features alone.

Although symptoms and signs are important, as they alert the observer to the possibility that heart failure exists, the clinical suspicion of heart failure must be confirmed by more objective tests.

HOSPITAL DIAGNOSIS

In the UK, approximately 30% of patients with heart failure are admitted to hospital within each 12 month period, and about 74% of patients with heart failure in the community at any time will have been seen by a hospital

Table 6 Interobserver reproducibility of physical signs in heart failure¹⁵⁻¹⁸

| Sign | % |
|------------------------------|----------|
| Peripheral oedema | 10 to 80 |
| Raised jugular vein pressure | 20 to 85 |
| Displaced apex | 35 to 72 |
| Murmur | No data |
| Third heart sound | 51 to 81 |
| Pulmonary crepitations | 10 to 88 |

Results depend on whether cardiologists or non-cardiologists are studied. Reproducibility of all signs is < 50% when three or more observers are studied.

physician.³ About half of all patients will have been seen because of referral by their general practitioner and half as a result of an emergency admission.³ The role of hospital diagnosis of heart failure, and the potential for improving this role should not be underestimated. If patients with heart failure are frequently in contact with the hospital, the investigative capacity must exist for making a proper, echocardiographically based diagnosis. However, the adequacy of diagnosis by hospital doctors also appears to be poor, and studies show that fewer than 50% of patients who have a hospital consultation are referred for echocardiography.^{3 20}

ELECTROCARDIOGRAPHY

A normal ECG is uncommon in patients with heart failure and, if present, it suggests that a diagnosis of heart failure should be reviewed carefully (table 7).²¹⁻²³ Left and, to a lesser extent, right bundle branch block are also markers for an increased risk of ventricular dysfunction, at least in a population with coronary artery disease.²⁴ ST segment elevation on treadmill exercise is also a marker of poor ventricular function.²³ However, a recent report suggests that 8% or more of patients with heart failure may have a normal ECG.²⁵ This area clearly requires further research before a normal ECG can be used confidently as a substitute for lack of evidence of important cardiac dysfunction on echocardiography.²³

CHEST RADIOGRAPHY

There is a poor relation between heart size on x ray and left ventricular function.²⁶⁻²⁹ The presence of cardiomegaly undoubtedly supports a diagnosis of heart failure, especially if it is associated with upper lobe venous dilatation, although the latter is a poor guide to the simultaneous pulmonary capillary wedge pressure.³⁰⁻³² A normal sized heart associated with clinical evidence suggesting chronic heart failure indicates that the diagnosis should be reviewed. Interobserver agreement in the

interpretation of pulmonary congestion on x rays is only modest.^{33 34} In patients who have suffered a myocardial infarction, prediction of left ventricular ejection fraction using clinical information has so far proved to be inaccurate even when combined with ECG and chest x ray results.^{31 35-37} However, chest radiography is useful in helping to exclude pulmonary disease as a cause for symptoms.

PULMONARY FUNCTION

Measurements of lung function are used to exclude respiratory causes of breathlessness, although the presence of pulmonary disease does not exclude co-existent heart failure. Epidemiological studies suggest that there is a strong association between chronic obstructive airways disease and ischaemic heart disease, which is one of the principal causes of heart failure.³⁸ Pulmonary function tests may predict those at greater risk of heart failure.³⁹

Peak expiratory flow rate and forced expiratory volume in one second are reduced in heart failure, but not to the same extent as in symptomatic obstructive airways disease. In patients presenting with severe breathlessness and wheeze, a peak expiratory flow rate < 200 l/min suggests a diagnosis of asthma rather than acute pulmonary oedema.⁴⁰

ECHOCARDIOGRAPHY

Echocardiography should be used routinely for the optimal diagnosis of heart failure.¹⁰ The test is widely available, simple, and safe. The interpretation of echocardiographic measures of diastolic ventricular function is complex, and although no practically useful Doppler echocardiographic guidelines are yet available for diagnosing diastolic heart failure, this is an active area of research.^{41 42} Atrial fibrillation reduces the reliability of these measurements and, in approximately 10% of patients, adequate transthoracic echocardiographic images cannot be obtained. It is also pertinent to mention that ejection fraction is based on two rather inaccurate measurements of volume, which are prone to calculation errors. This makes the accuracy and reproducibility of this variable poor.

NUCLEAR CARDIOLOGY

Nuclear angiography provides a simple assessment of global left and right ventricular systolic function, and of myocardial perfusion.¹⁴ Images may be obtained in patients in whom echocardiography is not possible. Myocardial perfusion imaging, at rest and during or after exercise, allows the presence and extent of ischaemia to be evaluated. The disadvantages

Table 7 Relation between ECG findings and congestive heart failure

| Reference | Patient population | ECG findings | No CHF (%) | CHF/LVD (%) |
|-----------|--|--------------------|-------------|--------------|
| 21 | CASS registry | Normal (n = 4034) | 92 | 0.6* |
| 22 | Open access | Normal (n = 275) | 98 | 2 |
| | Echocardiography | Abnormal (n = 259) | 65 | 35 |
| 23 | Referrals with CHF from community practice | Normal (n = 34) | 47 (n = 16) | 53 (n = 18) |
| | | Abnormal (n = 166) | 11 (n = 19) | 89 (n = 147) |

*Ejection fraction < 35%.

CHF, congestive heart failure; LVD, left ventricular dysfunction.

of nuclear angiography are that it is of minimal use for the assessment of valve function, it does not measure ventricular hypertrophy, and its availability is more restricted than for echocardiography. Reproducibility of ventricular volumes is only moderate and the patient is exposed to radiation. The latter limits the frequency with which studies can be performed. Nuclear angiography is also relatively expensive. Despite these limitations, radionuclide but not echocardiography derived ejection fraction has been shown to predict prognosis in multivariate analysis in heart failure populations.⁴³

EXERCISE TESTING

Reduced exercise performance, when the limiting symptoms are breathlessness or fatigue, is characteristic of but not specific to heart failure. Therefore, exercise testing is of limited value in the diagnosis of heart failure in clinical practice. Accurate assessment of functional capacity requires that the patient is familiar with what is required and that the observer has the required expertise. A normal exercise test in a patient not receiving treatment for heart failure excludes heart failure as a diagnosis. Pharmacological treatment and exercise training may improve exercise performance in patients with a definite diagnosis of heart failure, but rarely restore it to normal. In patients with an established diagnosis, exercise performance is a useful way of assessing the severity of the condition and possibly of monitoring its progress.

A pronounced fall in arterial oxygen saturation during exercise usually suggests the presence of pulmonary disease,⁴⁴ although small falls in arterial oxygen tension during exercise in patients with heart failure without evidence of pulmonary disease have been noted.^{44,45}

Measurement of oxygen consumption during exercise as well as being a research tool, is a potentially useful guide to prognosis and the need for transplantation. In clinical terms it can help determine whether exercise is limited by cardiorespiratory or by other factors. However, data relating the severity of heart failure to peak exercise oxygen consumption are inadequate, especially for women. Correcting oxygen uptake for age, sex, and weight may enhance the prognostic value of the exercise test.⁴⁶

CARDIAC CATHETERISATION

Invasive investigation is generally not required to establish the diagnosis of chronic heart failure but may be important in elucidating the cause. Heart failure may exist in the presence of a normal cardiac output and filling pressures at rest, at least in treated patients.^{14,15} Conversely, resting cardiac output may be depressed and filling pressure raised in patients with cardiac dysfunction who do not have symptoms of heart failure. Reduced cardiac output and raised pulmonary capillary wedge pressure during exercise may be caused by reversible myocardial ischaemia and are not specific to heart failure, whereas a normal haemodynamic response to maximum exercise excludes heart

failure as the cause of symptoms.

Exclusion of diastolic dysfunction by non-invasive means may be difficult. Diastolic heart failure in the absence of major systolic dysfunction should generally be confirmed by invasive haemodynamic study. Invasive measurement of cardiac output and filling pressures may also be helpful in supporting or excluding heart failure in the presence of pulmonary or hepatic disease.

NEUROENDOCRINE EVALUATION

The best candidates for neuroendocrine markers for diagnostic evaluation of heart failure in individual patients are the natriuretic peptides. Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) increase early in the course of cardiac dysfunction before the onset of symptoms. N-terminal ANP is an inactive byproduct of the ANP prohormone and its presence may reflect the presence and severity of ventricular dysfunction more accurately than ANP itself.^{47,48} It has the added advantages of stability, being relatively slow (several hours) to respond to physiological stimuli *in vivo*, and of being chemically stable *in vitro*.⁴⁹

There is growing evidence that BNP may be an even better marker of left ventricular dysfunction than N-terminal ANP. BNP changes more rapidly than N-terminal ANP *in vivo* but is of similar stability *in vitro*.

There may be a role for natriuretic peptides not only for diagnosis but also for therapeutic monitoring as natriuretic peptides have been shown to reflect cardiac filling pressure.⁵⁰ However, potential new treatments such as the neutral endopeptidase inhibitors increase plasma concentrations of ANP and BNP, which could invalidate their use for therapeutic monitoring. N-terminal ANP is not similarly affected.⁵¹

A raised plasma concentration of one of the natriuretic peptides associated with appropriate symptoms, in the absence of renal failure, strongly suggests a diagnosis of heart failure. A normal plasma concentration of natriuretic peptides in a patient receiving treatment does not necessarily refute a diagnosis of heart failure, as normal concentrations may reflect the effects of treatment.⁵² Plasma concentrations of natriuretic peptides increase to a modest extent with age and increase significantly in patients with renal failure. Thus natriuretic peptide concentrations should always be interpreted in conjunction with serum creatinine.

Determining the cause of heart failure

In many cases of heart failure, further investigations to disclose or confirm the underlying cause are warranted. However, many patients with heart failure are frail and elderly and this may limit therapeutic options such as surgery. If surgery or angioplasty are not options then there is little profit in undertaking coronary angiography. While investigations to determine whether heart failure is present should be a clinical routine, the investigation of the underlying cause of heart failure should be tailored to answering important questions that

will determine optimal management of individual patients.

Some diagnoses require sophisticated investigations. For example, coronary angiography is required to exclude coronary artery disease in patients with suspected dilated cardiomyopathy. Such complicated investigations are not indicated in all patients. In many cases, the optimum approach is to record the diagnosis as uncertain and then highlight the diagnostic suspicion rather than attribute the diagnosis to an aetiology without adequate evidence that may lull subsequent carers into a false sense of security.

Heart failure is the final common pathway of many diseases. Correctable causes of heart failure are rare individually but as a group contribute to a population that, considering the malignant prognosis of heart failure, is worthwhile identifying and treating. Determining the cause of heart failure is important for the selection of appropriate drug treatment. Most recent therapeutic developments, including ACE inhibitors, β blockers, and digoxin, have shown efficacy only in patients with concomitant left ventricular systolic dysfunction, the presence of which needs to be established by investigation.

HISTORY AND EXAMINATION

The patient's history of disease, such as myocardial infarction, alcohol intake, and drug treatment, is of paramount importance in determining the cause of heart failure. Symptoms also establish the presence of common concomitant disease, for instance a history of intermittent claudication is probably the best available symptomatic marker for renal artery stenosis.⁵³ While examination is not sensitive to determining whether the patient has heart failure, it can give valuable clues to its cause, especially valve disease, and important associated diseases.

Most patients with heart failure are over the age of 65 years and multiple co-existing degenerative diseases are commonly present that have implications for how heart failure should be managed. For example, loop diuretics may precipitate urinary retention in patients with prostatic hypertrophy. Fifty per cent of patients with intermittent claudication have renal artery stenosis⁵⁴; ACE inhibitors should be used with caution in such patients. Anaemia may exacerbate pre-existing heart failure. While a raised haematocrit suggests that breathlessness may be caused by pulmonary disease or cyanotic (congenital) heart disease. Measurement of serum urea or creatinine is essential for the differential diagnosis from renal failure, which may induce all the features of heart failure secondary to volume overload, and for subsequent management of heart failure.

Urine analysis is useful in detecting proteinuria and glycosuria, thereby alerting the clinician to the possibility of underlying renal problems or diabetes mellitus, conditions that may contribute to or complicate heart failure.

Heart failure due to thyrotoxicosis is fre-

quently associated with rapid atrial fibrillation and may be the presenting feature of thyrotoxicosis in the elderly. Hypothyroidism may also present as heart failure.

CARDIAC FUNCTION TESTS

The ECG is crucial in confirming heart rhythm; however, ECG abnormalities in patients with heart failure often do not point to any specific underlying cause. The presence of Q waves suggest myocardial infarction but in the absence of an appropriate history this needs to be confirmed by other investigations, such as echocardiography.

The shape of the cardiac silhouette may suggest a specific diagnosis as may calcification in valves, myocardium or pericardium. However, echocardiography is required to differentiate reliably between dilatation of cardiac chambers, hypertrophy, and pericardial effusion. This technique is invaluable in assessing the integrity of the cardiac valves and gives important insights into the nature and severity of ventricular and atrial dysfunction.

Myocardial perfusion imaging at rest and during or after exercise, allows the presence and extent of ischaemia to be evaluated. Rest redistribution myocardial imaging with thallium⁵⁴ or newer isotopes⁵⁵ has a valuable role to play in the detection and management of a non-contracting but viable myocardium (hibernating or stunned myocardium). The full importance of detecting hibernating myocardium awaits proper documentation of its prevalence and management. No controlled trials exist to support observational experience and current opinion that such patients should be re-vascularised.

Provocation of angina during exercise testing is not conclusive evidence of epicardial coronary disease, but in a patient with known coronary disease it does suggest reversible ischaemia. ST segment changes are frequently difficult to interpret in patients with heart failure as the resting ECG is usually abnormal. ST segment elevation is associated with poor ventricular function.²⁴ Imaging studies, most commonly and reliably by radionuclide techniques, currently offer the best method for defining ischaemia in this setting.

Haemodynamic studies are sometimes required to assess the importance of valve lesions or to assess formally systolic and diastolic function. However, their role in both settings has diminished with the development of echocardiography. Coronary angiography is required to exclude coronary disease when a diagnosis of dilated cardiomyopathy is being considered. Angiography will also be required in patients with heart failure and evidence of myocardial ischaemia if coronary revascularisation is considered a treatment option.

Endomyocardial biopsy, although a useful research tool, is of limited clinical use.^{56 57} In experienced hands, patients with unexplained myocardial dysfunction should be considered for biopsy to exclude infiltrative or inflammatory disease, such as amyloidosis, haemochromatosis or myocarditis.

Table 8 A simplified plan for the diagnosis of heart failure (adapted from ESC guidelines)

| Necessary | Opposes | Supports | Excludes alternatives and/or helps determine cause |
|--|-------------------|---|--|
| Symptoms of heart failure | Normal ECG | Improvement of symptoms in response to treatment | Medical history (past and current) and examination |
| Abnormal cardiac function (usually determined by echocardiography) | | Cardiomegaly on chest radiography | Biochemistry Urine analysis Haematology Chest radiography |
| | | Reduced exercise test duration (Lung disease) Raised plasma natriuretic peptide* | Pulmonary function tests (Lung disease) |

Tests in bold are considered to be the minimum necessary for the confirmation of a diagnosis of heart failure, for an initial attempt at determining its principal cause, and for excluding additional or alternative conditions as a cause of symptoms.

*Full diagnostic potential still under review, may be normalised by treatment and is increased in old age and by renal dysfunction.

Conclusions

The tests summarised in table 8 are the minimum requirements expected for a hospital diagnosis of heart failure. Ideally there should be no lower standard for diagnosis in the community. The ability to achieve such standards has been shown repeatedly.

- Remes J, Miettinen H, Reunanen A, *et al.* Validity of clinical diagnosis of heart failure in primary health care. *Eur Heart J* 1991;12:315–21.
- Wheeldon NM, MacDonald TM, Flucker CJ, *et al.* Echocardiography in chronic heart failure in the community. *Q J Med* 1993;86:17–23.
- Clarke KW, Gray D, Hampton JR. Evidence of inadequate investigation and treatment of patients with heart failure. *Br Heart J* 1994;71:584–7.
- Hobbs FDR, Davis RC, Wosornu D, *et al.* Screening the heart of England: heart failure epidemiology in the English West Midlands. *Proceedings of the 3rd European Congress on Family Medicine, Stockholm.* [abstract] 1996:41.
- Brockell U, Hense HW, Muscholl M, *et al.* Prevalence of left ventricular dysfunction in the general population [abstract]. *J Am Coll Cardiol* 1996;27(suppl):25A.
- McDonagh TA, Morrison CE, McMurray JJ, *et al.* The prevalence of left ventricular dysfunction in north Glasgow [abstract]. *Circulation* 1994;90(suppl):I-282.
- Yusuf S, Nicklas JM, Timmis G, *et al.* Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 1992;327:685–91.
- Moser M, Hebert PR. Prevention of disease progression, left ventricular hypertrophy and congestive heart failure in hypertension treatment trials. *J Am Coll Cardiol* 1996;27:1214–18.
- Kjekshus J, Pedersen T. Lowering of cholesterol with simvastatin may prevent development of heart failure in patients with coronary heart disease [abstract]. *J Am Coll Cardiol* 1995;25(suppl):282A.
- Cleland JGF, Erdmann E, Ferrari R, *et al.* Guidelines for the diagnosis of heart failure. *Eur Heart J* 1995;16:741–51.
- Hlatky MA, Fleg JL, Hinton PC. Physician practice in the management of congestive heart failure. *J Am Coll Cardiol* 1986;8:966–70.
- Cleland JGF, Habib F. Assessment and diagnosis of heart failure. *J Intern Med* 1996;239:317–25.
- Harlan WR, Oberman A, Grimm R, *et al.* Chronic congestive heart failure in coronary artery disease: clinical criteria. *Ann Intern Med* 1977;86:133–8.
- Marantz PR, Tobin JN, Wassertheil-Smolter S. The relationship between left ventricular systolic function and congestive heart failure diagnosed by clinical criteria. *Circulation* 1988;77:607–12.
- Butman SM, Ewy GA, Sranden JR, *et al.* Bedside cardiovascular examination in patients with severe chronic heart failure: importance of rest or inducible jugular venous distension. *J Am Coll Cardiol* 1993;22:968–74.
- Spiteri MA, Cook DG, Clarke SW. Reliability of eliciting physical signs in examination of the chest. *Lancet* 1988;i:873–5.
- Ishmail AA, Wing S, Ferguson J, *et al.* Interobserver agreement by auscultation in the presence of a third heart sound in patients with congestive heart failure. *Chest* 1987;91:870–3.
- O'Neill TW, Barry M, Smith M, *et al.* Diagnostic value of the apex beat. *Lancet* 1989;ii:410–1.
- Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemodynamics heart failure. *J Am Med Assoc* 1989;261:884–8.
- Hillis G, Trent R, Winton P, *et al.* Angiotensin-converting enzyme inhibitors: are we ignoring the evidence? *Q J Med* 1996;89:145–50.
- Rihal CS, Davis KB, Kennedy JW, *et al.* The utility of clinical, electrocardiographic, and roentgenographic variables in the prediction of left ventricular function. *Am J Cardiol* 1995;75:220–3.
- Davie AP, McMurray J. Open-access echocardiography. *Lancet* 1996;348:1387–88.
- Bruce RA, Fisher LD, Pettinger M, *et al.* ST segment elevation with exercise: a marker for poor ventricular function and poor prognosis. Coronary artery surgery study (CASS) confirmation of Seattle heart watch results. *Circulation* 1988;77:897–905.
- Freedman RA, Alderman EL, Sheffield LT, *et al.* Bundle branch block in patients with chronic coronary artery disease: angiographic correlates and prognostic significance. *J Am Coll Cardiol* 1987;10:73–80.
- Houghton AR, Staniforth AD, Sparrow NJ, *et al.* Using the electrocardiogram to select patients with suspected heart failure for echocardiography [abstract]. *Proceedings of Heart Failure Update '96* 1996:P-34.
- Cohn JN, Johnson GR, Shabetai R, *et al.* Ejection fraction, peak exercise oxygen consumption, cardiothoracic ratio, ventricular arrhythmias, and plasma norepinephrine as determinants of prognosis in heart failure. *Circulation* 1993;87:VI5–16.
- Alam M, Rosehamer G, Hoglund C. Comparability of echocardiography and chest X-ray following myocardial infarction. *Intern Med* 1989;226:171–3.
- Madsen EB, Gilpin E, Slutsky RA, *et al.* Usefulness of the chest X-ray for predicting abnormal left ventricular function after acute myocardial infarction. *Am Heart J* 1984;108:1431–6.
- McNamara RF, Carleen E, Moss AJ, and the Multicentre Post-Infarction Research Group. Estimating left ventricular ejection fraction after myocardial infarction by various clinical parameters. *Am J Cardiol* 1988;62:192–6.
- McHugh TJ, Forrester JS, Adler L, *et al.* Pulmonary vascular congestion in acute myocardial infarction: hemodynamic and radiologic correlations. *Ann Intern Med* 1972;76:29–33.
- Kostuk W, Barr JW, Simon AL, *et al.* Correlations between the chest film and hemodynamics in acute myocardial infarction. *Circulation* 1973;48:624–32.
- Chakko S, Woska D, Martinez H, *et al.* Clinical, radiographic, and hemodynamic correlations in chronic congestive heart failure: conflicting results may lead to inappropriate care. *Am J Med* 1991;90:353–9.
- Kundel RL, Revesz G. Digital analysis of chest radiographs in pulmonary vascular congestion. *Radiology* 1982;143:407–10.
- Rocker GM, Rose DH, Manhire AR, *et al.* The radiographic differentiation of pulmonary oedema. *Radiol* 1989;62:582–6.
- Gjorup T, Kelbaek H, Vestergaard B, *et al.* Prospective, randomised, double-blind study of radionuclide determination of left-ventricular ejection fraction in acute myocardial infarction. *Lancet* 1986;ii:583–5.
- Choy AM, Darbar D, Lang CC, *et al.* Detection of left ventricular dysfunction after acute myocardial infarction: comparison of clinical, echocardiographic, and neurohormonal methods. *Br Heart J* 1994;72:16–22.
- Gadssboll N, Hoiland-Carlson PF, Nielsen GG. Symptoms and signs of heart failure in patients with myocardial infarction: reproducibility and relationship to chest X-ray, radionuclide ventriculography and right heart catheterisation. *Eur Heart J* 1989;10:1017–28.
- Cook DG, Shaper AG. Breathlessness, lung function and the risk of heart attack. *Eur Heart J* 1988;9:1215–22.
- Kannel WB, D'Agostino RB, Silbershatz H. Use of vital capacity for cardiac failure risk estimation in persons with coronary disease and left ventricular hypertrophy. *Am J Cardiol* 1996;77:1155–8.
- McNamara RM, Cionni DJ. Utility of the peak expiratory flow rate in the differentiation of acute dyspnea; cardiac vs pulmonary origin. *Chest* 1992;101:129–32.
- Aguirre FV, Pearson AC, Lewen MK, *et al.* Usefulness of Doppler echocardiography in the diagnosis of congestive heart failure. *Cardiol* 1989;63:1098–102.
- Davie AP, Francis CM, Caruana L, *et al.* The prevalence of left ventricular diastolic filing abnormalities in patients with suspected heart failure. *Eur Heart J* 1997;18:981–4.
- Cleland JGF, McMurray JJJ, Cowburn PJ. *Heart failure: a systematic approach for clinical practice.* London: Science Press, 1997:1–123.
- Clark AL, Coats AJS. Usefulness of arterial blood gas estimations during exercise in patients with chronic heart failure. *Br Heart J* 1994;71:528–30.
- Moore DP, Weston AR, Hughes JMB, *et al.* Effects of increased inspired oxygen concentrations on exercise per-

- formance in chronic heart failure. *Lancet* 1992;**339**: 950–3.
- 46 Stelken AM, Younis LT, Jennison SH, *et al.* Prognostic value of cardiopulmonary exercise testing using percent achieved of predicted peak oxygen uptake for patients with ischaemic and dilated cardiomyopathy. *J Am Coll Cardiol* 1996;**27**:345–52.
- 47 Lerman A, Gibbons A, Rodeheffer RJ. Circulating N-terminal atrial natriuretic peptide as a marker for symptomless left ventricular dysfunction. *Lancet* 1993;**341**: 1105–9.
- 48 Wallen T, Landahl S, Hedner T, *et al.* Atrial peptides, ANP(1–98) and ANP (99–126) in health and disease in an elderly population. *Eur Heart J* 1993;**14**:1508–13.
- 49 Cleland JGF, Ward S, Dutka D, *et al.* Stability of plasma concentrations of N and C terminal atrial natriuretic peptides at room temperature. *Heart* 1996;**75**:410–13.
- 50 Richards AM, Cleland JGF, Tonolo G, *et al.* Plasma alpha natriuretic peptide in cardiac impairment. *Br Med J Clin Res Ed* 1986;**293**:409–12.
- 51 Cleland JGF, Struthers A. Neutral endopeptidase inhibitors: effects on peptide metabolism and potential therapeutic use in the treatment of heart failure. *Heart Failure* 1996;1273–92.
- 52 Anderson JV, Woodruff PWRB. The effect of treatment of congestive heart failure on plasma atrial natriuretic peptide concentration: longitudinal study. *Br Heart J* 1987; **57**:578–9.
- 53 Choudhri AH, Cleland JGF, Rowlands PC, *et al.* Unsuspected renal artery stenosis in peripheral vascular disease. *BMJ* 1990;**301**:1197–8.
- 54 Dilsizian V, Bonow RO. Current diagnostic techniques of assessing myocardial viability in patients with hibernating and stunned myocardium. *Circulation* 1993;**87**:1–20.
- 55 Udelson JE, Coleman PS, Metherall J, *et al.* Predicting recovery of severe regional ventricular dysfunction. Comparison of resting scintigraphy 201 TL and 99mTc-Sestamibi. *Circulation* 1994;**89**:2552–61.
- 56 Camerini F, Salvi A, Sinagra G. Endomyocardial biopsy in dilated cardiomyopathy and myocarditis: which role? *Cardiol* 1991;**31**:1–8.
- 57 Becker AE, Heijmans CD, Essed CE. Chronic non-ischaemic congestive heart disease and endomyocardial biopsies. Worth the extra? *Eur Heart J* 1991;**12**:218–23.