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Coronary artery disease as the cause of incident heart failure in the population

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Aims New approaches in the treatment of ischaemic left ventricular dysfunction, including revascularization, make it increasingly important to identify heart failure cases resulting from coronary artery disease. Without angiography these cases may be missed. We investigated the frequency of coronary artery disease in incident cases of heart failure in the population.

Methods and Results We identified all incident cases of heart failure in a population of 292 000 in South London, U.K. by monitoring patients admitted to hospital and through a rapid access heart failure clinic. The presence and severity of coronary artery disease was identified by coronary angiography in patients under 75 years. Myocardial perfusion scanning was used to elucidate the aetiological significance of the coronary artery disease and identify hibernating myocardium. Three hundred and thirty-two cases of new heart failure were identified over 15 months. One hundred and thirty-six cases were under 75 years and angiography was undertaken in 99/136 (73%). Coronary artery disease was the aetiology in 71/136 (52%). In 18 of these 71 cases (25%), the aetiology was not recognised to be due to coronary artery disease prior to angiography, including eight cases with hibernating myocardium.

Conclusion Coronary artery disease is the cause of 52% (95% CI 43–61%) of incident heart failure in the general population under 75 years. Clinical assessment without angiography under-estimates the proportion of patients with coronary artery disease, and fails to identify those patients who may benefit from revascularization.
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Key Words: Heart failure, coronary disease, epidemiology, hibernation.

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Introduction

The epidemiology of heart failure has been extensively investigated[1] but the aetiology of heart failure in a contemporary population remains incompletely described[2]. The increase in the burden of heart failure, particularly in terms of hospitalization[3–6] may be associated with changing patterns in disease aetiology[1]. Changes in treatment, particularly the possibility of revascularization in those with hibernating myocardium[7–9], imply that physicians should establish the aetiology of heart failure in individual cases. The Framingham study emphasized the importance of hypertension in the aetiology of heart failure. However, the Framingham study did not undertake systematic coronary angiography and may have under-estimated the importance of coronary artery disease. Previous population studies from our group[2], and others[10,11], allocated aetiology mainly on the basis of clinical assessment without coronary angiography. It is often not possible to identify an aetiology in this way, and in particular the presence of coronary artery disease may be under-estimated[12]. There are no population studies involving systematic cardiac catheterization available to describe the modern aetiology of heart failure.

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The aims of this study were to identify all incident (new) heart failure cases in a defined population and in cases under 75 years to establish, through coronary angiography and myocardial perfusion imaging, the presence and importance of coronary artery disease, together with the prevalence of hibernating myocardium.

Methods

Case identification

Incident heart failure cases were identified from amongst a population of 292 000 individuals registered with the 151 General Practitioners (GPs) working in 59 practices within Bromley Health Authority, South London, U.K. Demographic data on the Bromley population were obtained from Bromley Health Authority. The methods of case ascertainment described below were closely related to those employed in a previous epidemiological study of heart failure from our group[2].

GPs were asked to refer all suspected new cases of heart failure to a dedicated daily rapid access heart failure clinic (RAHFC). Patients who required admission through the Accident and Emergency Department (Emergency Room) were identified by daily surveillance of all admissions by a research nurse. Surveillance of all hospitalized patients for the development of heart failure was maintained. This involved monitoring of echocardiogram requests, running a hospital consultation service for suspected heart failure, visits to wards, and educating colleagues about the study. Local GPs alerted the study team to cases of heart failure admitted to neighbouring hospitals by onward referral to the RAHFC after the patients had been discharged home.

Assessment

Possible new cases of heart failure were assessed either in the RAHFC or on the wards by one of the investigators (K.F.). A standardized history and physical examination, an electrocardiogram (ECG), chest radiograph, and transthoracic echocardiogram were performed. Blood samples were drawn for full blood count, electrolytes, lipids, liver function tests and thyroid function.

GP audit of case ascertainment

In order to confirm the accuracy of case ascertainment, an audit of 10 of the 59 GP practices included in the study was undertaken. In these practices patients newly prescribed diuretics or angiotension converting enzyme inhibitors during the study period were identified by computer search of patient records. The medical records were then reviewed. Cases who appeared likely to have fulfilled the definition of heart failure but were not identified by the study team were recorded. By adding up the small number of such 'missed' cases, an indicator of the completeness of case identification was obtained. The audit revealed 18% of cases overall (95% CI 14–22%) missed by the case finding-methods employed, with an estimate of 12% of cases missed (95% CI 8–18%) in those under 75 years.

Case definition

The definition of heart failure used in this study is based on the European Society of Cardiology guidelines[13] and is the same as that used in the Hillingdon Heart Failure Study[2]. To meet the case definition of heart failure, patients had to have appropriate symptoms (shortness of breath, fatigue, fluid retention or any combination of these symptoms) with clinical signs of fluid retention (pulmonary or peripheral) in the presence of abnormal cardiac function. If an element of doubt remained, a beneficial response to therapy for heart failure (e.g. a brisk diuresis accompanied by substantial improvement in breathlessness) was taken to confirm the diagnosis.

Panel

All data collected were presented to a panel of three cardiologists (A.C., G.C.S., D.A.W. — the case definition panel). The panel determined on the basis of a majority decision whether the case definition had been met. The reproducibility of panel decisions for case definition, checked by re-presentation of a random sample of 7·5% of cases, was excellent, Cohen's $\kappa = 1{\cdot}00$ (95% CI 0·68–1·00).

Assessment of aetiology

Coronary artery disease was identified as the primary aetiology, in the absence of angiographic data, if the patient had a documented history of an acute ischaemic syndrome (typical chest pain with ECG changes), or stable angina with evidence of reversible ischaemia on exercise testing or myocardial perfusion imaging. Hypertension was considered an aetiological factor if there was a documented history of hypertension and evidence of hypertensive cardiac disease (e.g. left ventricular hypertrophy either electrocardiographically or echocardiographically). Atrial fibrillation, while frequently present, was only assigned as the primary aetiology where there did not appear to be significant left ventricular dysfunction on echocardiography at the time of presentation, and there was no other demonstrable cardiac pathology, together with a temporal relationship between the arrhythmia and onset of heart failure. Assigning aetiology to valvular disease depended on clinical assessment including echocardiography. Alcohol was assigned as the primary aetiology where there was a history of

chronic excessive alcohol consumption associated with a dilated ventricle with systolic dysfunction. Additional aetiologies were assigned depending on the clinical circumstances. Where no aetiology could be assigned, cases were classified as being of undetermined aetiology. The reproducibility of panel decisions for assignment of aetiology was checked by re-presentation of a random sample of 7·5% of cases and showed good reproducibility with Cohen's κ=0·71 (95% CI 0·50–0·93).

Coronary angiography

Cases under 75 years, who had not previously undergone cardiac catheterization, underwent left ventriculography and coronary angiography. The age cut-off was determined by ethical considerations including the potential benefit to the patient of the information gained. The cut-off was close to the upper age at which revascularization would be considered in our institutions, while being as near to the median age of cases (76 years) as possible.

Patients undergoing angiography for research purposes underwent catheterization at the Royal Brompton Hospital after appropriate written consent. Angiograms were reported visually twice: at the time of angiography and on a separate occasion by a cardiologist specialising in interventional cardiology (S.D.), who was blinded to clinical information. Anatomically significant coronary artery disease was defined as a luminal stenosis greater than or equal to 50% in one or more epicardial arteries[14,15]. Functional significance was assessed by combining the anatomical data with information from the clinical assessment and non-invasive investigations, including myocardial perfusion imaging.

Myocardial perfusion scanning

Where the clinical situation allowed, cases with significant coronary artery disease underwent myocardial perfusion scintography. Single photon emission tomography (SPET) was performed using a dual-headed gamma camera (International General Electric, Optima), and conventional parameters for data acquisition and image reconstruction. Technetium labelled tracers (MIBI or Tetrafosmin) were used except in four patients where Thallium was used. When technically and clinically feasible, ECG gating of the resting Technetium tomograms was performed in order to assess myocardial viability and function simultaneously. Stress injections of tracer were given during adenosine infusion ($140\ \mu g\ .\ kg^{-1}\ .\ min^{-1}$) combined with bicycle exercise up to 75 W, if tolerated, over a 6 min protocol. Resting injections of tracer were given 5 min after two puffs of sublingual glyceryl trinitrate. A one day stress/rest protocol was used for the Technetium agents, and a one day stress/redistribution protocol was used for Thallium. Tracer uptake was graded visually using a semi-quantitative five-point scale in nine myocardial segments[14,16]. Segments were classified as hibernating if stress-induced ischaemia could be demonstrated, with uptake of greater than 50% of the maximum found in the resting images, and with severe hypokinesis or akinesis on gated SPET or other functional imaging technique. If two or more segments were classified as hibernating using these criteria, then the patient was considered to have clinically significant hibernation[14].

Final allocation of aetiology on the basis of all non-invasive and invasive data

A panel of three cardiologists (A.C., J.S.G., P.P-W.) re-evaluated the cases to allocate a 'final' aetiology. In particular, in order for cases with anatomically significant coronary artery disease to be assigned to coronary artery disease as the aetiology, further evidence that the anatomical disease was related to the left ventricular dysfunction in the form of regional wall motion abnormalities, myocardial perfusion abnormalities or ischaemic valvular dysfunction was needed.

Statistical analysis

Data were recorded on paper and then double entered into a computerized database designed for the study. Discrepancies were identified and resolved. Age-standardized incidence rate ratios and κ values with their confidence intervals (CI) were calculated using Stata™ software.

Ethical approval

Ethical approval was obtained from the Local Research Ethics Committees of the Royal Brompton NHS Trust and Bromley Hospitals NHS Trust.

Results

Over a 15-month study period, 332 incident cases of heart failure were identified. One hundred and seventy-eight (54%) cases were male and 154 cases (46%) female. Two hundred and eight cases (63%) presented as inpatients and 124 (37%) as outpatients.

The crude incidence rate was 0·9 cases per 1000 population per year, or 1·2 cases per 1000 population aged 25 or over per year. The incidence rate increased with age and at all ages the incidence rate was greater for men than women (Fig. 1). The age-standardized rate ratio for men compared to women was 1·80 (95% CI 1·45–2·24, P<0·001). The median age at presentation was 76 years (range 37–95). The median age for men was 75 years (range 37–91) and for women the median age was 79 years (range 51–95). Figure 2 shows the aetiology, as determined by the case definition panel, prior

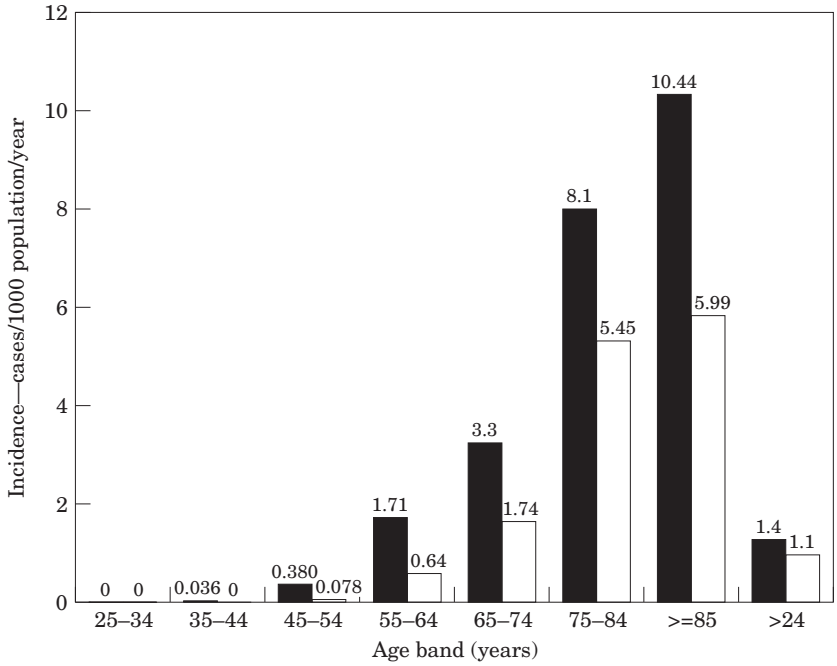

Figure 1 **Age- and sex-stratified incidence. ■=male; □=female.**

to study angiography and myocardial perfusion imaging. This is shown for all cases and separately for the cases aged under 75 years.

Angiographic data and perfusion imaging

One hundred and thirty-six cases were under 75 years. Angiographic data were available on 99 cases (73%). Sixteen cases died prior to possible catheterization, seven cases declined and 14 had other medical conditions, making catheterization inappropriate. One case without angiographic data had 'severe occlusive coronary artery disease' at post mortem, and two cases without angiographic data underwent stress perfusion imaging which was normal, making significant coronary artery disease unlikely.

Anatomically (but not necessarily aetiologically) significant coronary artery disease was detected at angiography in 66 (67%) of 99 cases under 75 years who underwent angiography. The presence of anatomically significant coronary artery disease for the different aetiologies assigned by the case definition panel prior to catheterization is shown in Table 1.

Twenty-seven (41%) out of 66 cases with significant coronary artery disease angiography underwent perfusion imaging, 10 using ECG gating. Perfusion imaging was generally not undertaken in cases who underwent urgent revascularization, or in patients with previous revascularization, or in those with primary valve disease where coronary artery disease, even where present, was not the aetiology of heart failure. In the 27 cases who underwent myocardial perfusion imaging, 10 (37%) demonstrated significant hibernating myocardium.

Final aetiology in cases under 75

The final aetiology in the 136 cases under 75 years was based on all the non-invasive and invasive data available and is shown in Fig. 3.

The information used to assign coronary artery disease as the aetiology in patients with single-vessel disease, in whom the assessment of coronary artery disease as the aetiology of heart failure might be most difficult, is shown in Table 2. A similar approach was used in cases with two- or three-vessel disease i.e. the panel required evidence of the impact of the coronary artery disease on left ventricular performance before allocating a case to coronary artery disease as the aetiology of heart failure.

Coronary artery disease was aetiological in 71 (52%) out of 136 cases. In three out of these 71 cases coronary artery disease was felt to be contributing to the aetiology, but was not the sole aetiology.

Twelve (17%) out of these 71 cases were assigned coronary artery disease as the aetiology in the absence of angiographic data. Either they died during the course of acute myocardial infarction associated with heart failure (10 cases) or declined angiography but developed heart failure during acute myocardial infarction as evidenced by chest pain, ECG changes and elevated creatine kinase (two cases).

Hypertension was the primary aetiology in six (4·4%) out of 136 cases. Valvular disease was the primary

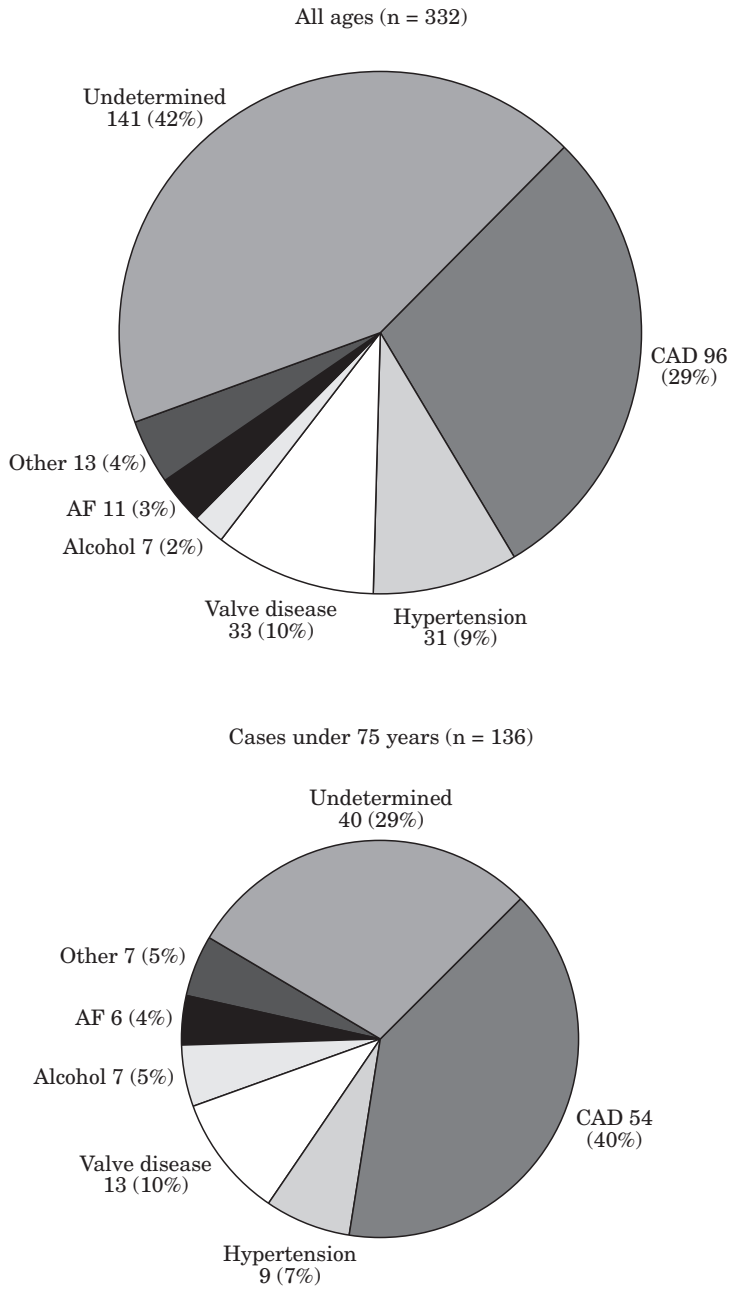

Figure 2 **Aetiology of 332 cases of heart failure (as assigned by case definition panel and prior to study angiography).**

aetiology in 13 (9·6%) out of 136 cases. In eight of these, anatomically significant coronary artery disease was present. Seventeen (13%) out of 136 cases presented with heart failure with no identifiable aetiology and normal or anatomically non-significant coronary artery disease at angiography.

In 13 (9·6%) of the 136 cases, angiographic data were not available (five died, one declined and seven had other medical conditions making angiography clinically inappropriate) and no aetiology could be identified on the available non-invasive data. These cases remained classified as undetermined.

Value of invasive investigation in altering aetiology

There were 21 cases, who had not previously undergone angiography, assigned by the case definition panel as due to hypertension, alcohol or atrial fibrillation. Fifteen (71%) underwent angiography and in seven (47%) out of 15 cases important coronary artery disease was present. This included three out of the five cases thought to be due to hypertension who underwent angiography. In the group of 40 out of 136 cases in whom the panel were unable to allocate an aetiology prior to angiography, 27

Table 1 Presence of coronary artery disease (in the 99/136 cases under 75 years with angiographic information available) in the groups of patients allocated by the case definition panel prior to study angiography to coronary artery disease, other aetiologies or in whom no aetiology could be determined

Aetiology allocated by panel prior to angiography	Normal or minor CAD	Significant CAD (≥50% stenosis in an epicardial artery)	Cases who underwent revascularization prior to study entry
Coronary artery disease (n=42)	2* (5%)	21 (50%)	19 (45%)
Other defined aetiologies (n=30)	14 (47%)	14 (47%)	2† (7%)
Aetiology undetermined by case definition panel (n=27)	17 (63%)	10 (37%)	0 (0%)
All cases (n=99)	33 (33%)	45 (45%)	21 (21%)

*One case who gave a history of myocardial infarction but no evidence of regional wall motion abnormalities on ventriculography and only minor coronary artery disease at catheterization, and one case with clinical evidence of a myocardial infarction but anatomically non-significant coronary artery disease.
†Heart failure due to valve disease, i.e. non-aetiological coronary artery disease.

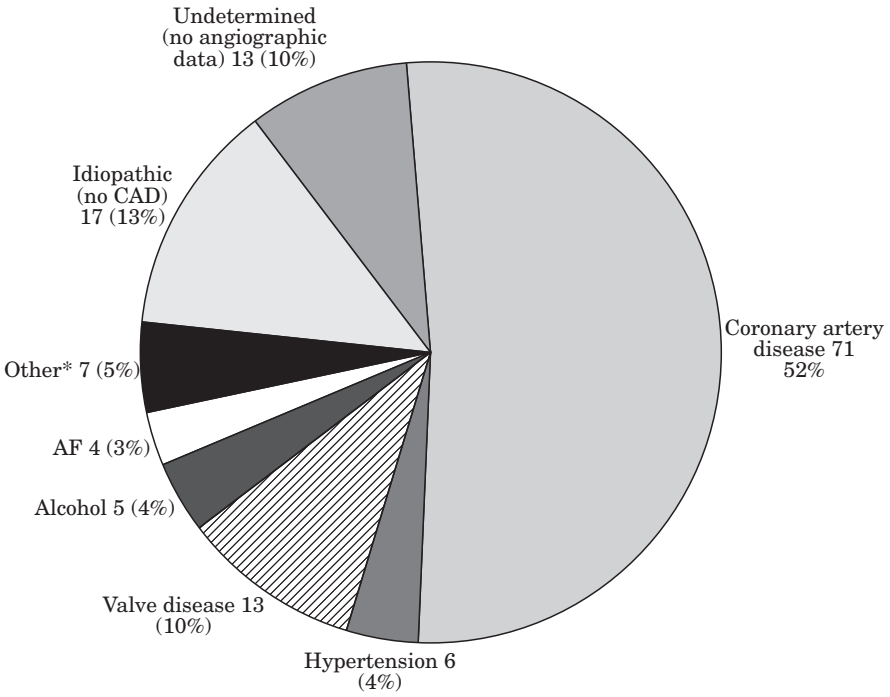

***Figure 3* 'Final' aetiology of heart failure in 136 cases aged less than 75 years using angiographic and myocardial perfusion data (where available).**
***Aortic root dilatation leading to aortic regurgitation (two cases) cor pulmonale (one case), complete heart block (one case), atrial tachycardia (one case), constrictive pericarditis (one case) heart failure associated with a proximal myopathy (one case).**

Table 2 Evidence implicating coronary artery disease in the aetiology of heart failure in cases with single vessel coronary artery disease

Case	Vessel	% luminal stenosis	RWMA on echocardiogram or ventriculogram	Abnormal segments on perfusion scan (total=9)	Comments
1	RCA	85	Yes	3	Inferior MI, underwent PTCA
2	RCA	50	No	N/A	90% large OMI, antero-lateral ST depression, ischaemic rupture PMVL, severe MR
3	RCA	90	Yes	N/A	Presented with ischaemic VT leading to HF. PTCA to RCA performed
4	RCA	50	Yes	2	Also 90% OMI
5	LAD	100	Yes	2	Large anterior MI
6	LAD	90	Yes	7	Large anterior MI, recannalized LAD
7	LAD	100	Yes	7	Large anterior MI
8	LAD	80	Yes	5	Anterior MI (CK 4000) Also 90% D1, 90% OMI

RWMA=regional wall motion analysis; RCA=right coronary artery; LAD=left anterior descending artery; OMI=first obtuse marginal artery; D1=first diagonal artery; MI=myocardial infarction; PTCA=percutaneous transluminal coronary angioplasty; CK=creatine kinase ($U.l^{-1}$); PMVL=posterior mitral valve leaflet; HF=heart failure; MR=mitral regurgitation; VT=ventricular tachycardia.

(68%) underwent catheterization. Angiography demonstrated important coronary disease in 10 (37%) of these 27 cases (Table 1). Overall, the further information from coronary angiography altered the allocated aetiology of 18 cases (26% of the 70 cases who underwent angiography for the first time subsequent to study entry).

Prevalence of hibernating myocardium

Ten out of 27 (37%) patients with aetiological coronary artery disease undergoing myocardial perfusion imaging had significant amounts of hibernating myocardium. This includes five cases from the group with an undetermined aetiology prior to angiography and three cases where the initial aetiology was not coronary artery disease.

Discussion

Incidence of heart failure

The definition of heart failure used in this study employs criteria which are both strict, highly reproducible and clinically recognisable. This was not a study of patients with left ventricular dysfunction, but those who have developed heart failure with fluid retention and symptoms of breathlessness and fatigue.

The incidence was very similar to that recorded in the Hillingdon Heart Failure Study from West London which, using similar methodology, found an incidence of 0·8 cases per 1000 population per year[2]. Under-ascertainment of cases was minimized by setting up the rapid access service and establishing awareness of the study by local GPs through individual practice visits, educational meetings and regular written feedback to the GPs informing them of the progress of the study. Patients living on the periphery of the study area or very frail patients may have been missed.

Case identification and attribution of aetiology

The establishment of coronary artery disease as aetiological in a patient's heart failure, requires not only the presence of coronary artery disease, but evidence that the coronary artery disease is responsible for the development of heart failure. Coronary angiography remains the definitive method of identifying coronary anatomy and therefore was considered essential rather than relying on indirect evidence from other forms of investigation. In this study, information from post mortem or myocardial perfusion imaging was noted but not used to include patients amongst the 99 cases with information on coronary anatomy. The functional importance of the coronary artery disease needs to be determined. No current investigation can, with absolute certainty, differentiate ischaemic myocardium from other forms of dysfunctional myocardium[15,17], but considerable information can be gained by combining clinical, echocardiographic and anatomical information with myocardial perfusion imaging. This study aimed to investigate the presence of hibernating myocardium and hence 99-Technetium radionuclide myocardial perfusion imaging, also validated for identifying hibernating myocardium[16,18–20], was used.

Previous epidemiological studies of heart failure have allocated aetiology without using invasive investigations such as angiography. The Framingham study[10] described hypertension as present in 70% and coronary artery disease in 59% of men and 48% of women. Other studies have not shown such a high proportion of hypertensives. A study in Eastern Finland found non-invasive evidence of coronary artery disease in 61% and

hypertension in 55%[11]. In this study, 128 (39%) out of 332 cases had a history of hypertension, including 60 (44%) of the 136 cases under 75 years. Work from Hillingdon, West London, ascribed 34% to coronary artery disease, but was unable to allocate an aetiology in 31% of cases. (i.e. coronary artery disease was present in 60% of those with an identifiable aetiology)[2].

In this study, using angiographic data, 71 of the 136 cases (52%) under 75 years had coronary artery disease causing heart failure (population 95% CI 43–61%). It is likely that some of the 23 cases with non-invasively assigned aetiologies other than coronary artery disease who did not undergo angiography had important coronary artery disease. Hence the proportion of all cases due to coronary artery disease may be higher than 52%. Assuming the proportion of important coronary artery disease in these cases was the same as in those who did undergo angiography would raise the overall proportion with aetiological coronary artery disease in the 136 cases of heart failure under 75 years to 59%.

Hibernation and its importance

Increasing evidence suggests that revascularization is a treatment option in patients with significant hibernating myocardium[7–9,21]. Until now there has been no data on the prevalence of hibernating myocardium amongst incident heart failure cases in a population setting. The only data have come from highly selected cohorts of patients awaiting revascularization. One study suggested improvement in left ventricular function in 18/84 (33%) of such patients, implying the presence of hibernating myocardium prior to revascularization[22]. This figure may have little relevance to incident heart failure cases in the general population, and in particular amongst cases of heart failure who would not normally be considered for revascularization on the basis of their angina status. The figure of 37% of myocardial perfusion scans indicating the presence of significant hibernating myocardium in this study represents the first such estimate from a population sample of incident heart failure cases.

Implications for clinical practice

The clinician is often faced with cases of incident heart failure who survive the initial presentation, do not have cardiac catheter data, who lack clear non-invasive evidence of coronary artery disease, or whose suspected aetiology is hypertension, alcohol, arrhythmia or undetermined. The data from this study provide information on the likely results of angiography in such cases and the potential for revascularization of cases who are found to have significant coronary artery disease. Within the 136 incident cases under 75 years, 44 out of the 99 with angiographic data fall within these aetiological categories. The outcome of angiography and myocardial perfusion imaging revealed 17 (39%) out of these 44 cases to have significant coronary artery disease. Eleven (65%) of the 17 cases had either significant hibernation to justify consideration of revascularization (eight cases) or underwent revascularization prior to myocardial perfusion imaging (three cases).

The finding of coronary artery disease has additional treatment implications beyond revascularization. Coronary secondary prevention measures such as aspirin and in particular lipid lowering therapy to prevent coronary events[23], and also possibly prevent deterioration in left ventricular function[24] should be initiated.

In conclusion, this study demonstrates that coronary artery disease is the single most important aetiology in incident cases of heart failure. 52% of cases under 75 years in this study had aetiological coronary artery disease. Methods not including cardiac catheterization or myocardial perfusion imaging underestimate the presence of coronary artery disease. Significant hibernating myocardium may be present in patients with coronary artery disease whether this is suspected clinically or not.

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