Cardiomyopathic syndrome caused by coronary artery disease

III: Prospective clinicopathological study of its prevalence among patients with clinically unexplained chronic heart failure¹

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SUMMARY Each day, for one year, the medical records of adult patients who died in hospital were reviewed before seeing the necropsy findings. For those patients who had had chronic left or left and right heart failure, a presumptive cause was assigned on the basis of antemortem clinical data. Of 740 consecutive patients who were studied at necropsy, 90 had had chronic heart failure. In 15 patients the cause of heart failure was not apparent by clinical criteria; of these, 7 were found at necropsy to have cardiomyopathic syndrome caused by coronary artery disease. In retrospect, the presence of overt diabetes mellitus was a clue that cardiomyopathy caused by coronary artery disease was the cause of clinically unexplained heart failure; 5 of 7 patients with unexplained heart failure who were found to have this at necropsy were diabetic, whereas only 1 of the other 8 patients with clinically unexplained heart failure was diabetic ($P < 0.05$). Patients in whom clinically unexplained heart failure was found to be the result of cardiomyopathy caused by coronary artery disease had multiple myocardial infarctions on pathological examination, which, with one exception, were nontransmural. By contrast, myocardial infarctions were transmural on pathological examination in each of 7 matched 'controls' with heart failure, in whom the diagnosis of coronary artery disease had been clinically apparent ($P < 0.01$).

Cardiomyopathic syndrome caused by coronary artery disease is far more common than are the other clinicophysiological syndromes caused by coronary artery disease that are associated with chronic heart failure (ventricular aneurysm; relatively isolated mitral regurgitation; ventricular septal rupture; and transient recurrent ischaemia) (Brody and Criley, 1970; Baxley *et al.*, 1971; Yatteau *et al.*, 1974; Dash *et al.*, 1977b; Lee *et al.*, 1977). Furthermore, the other syndromes of coronary artery disease that cause heart failure, when they occur, are almost always considered as diagnostic possibilities in an individual patient with heart failure because of an accompanying history of chest pain, because of the

detection of a cardiac murmur, or because of electrocardiographic evidence of myocardial infarction. By contrast, cardiomyopathy caused by coronary artery disease is known to occur, at least occasionally, without accompanying clinical clues to the presence of coronary artery disease (Raftery *et al.*, 1969).

Why the diagnosis of cardiomyopathy caused by coronary artery disease should not ever be inapparent on clinical grounds is unclear, since the mechanism of heart failure in such patients is a substantial reduction in left ventricular ejection fraction brought about by multiple myocardial infarctions (Yatteau *et al.*, 1974; Dash *et al.*, 1977b). In addition, the frequency with which cardiomyopathic syndrome caused by coronary artery disease is an unsuspected cause of heart failure is not established. The results of catheterisation studies suggest that cardiomyopathy caused by coronary artery disease is only

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rarely an unsuspected diagnosis (Yatteau *et al.*, 1974; Dash *et al.*, 1977b). Patients undergoing catheterisation, however, represent a selected population. The possibility remains that among elderly patients who would often not be candidates for catheterisation because of age considerations, cardiomyopathy caused by coronary artery disease may often not be accompanied by clinical stigmata of underlying coronary artery disease.

The present study is a prospective clinicopathological analysis of the prevalence of cardiomyopathy caused by coronary artery disease among patients whose heart failure is unexplained on clinical grounds, but who are not considered to be candidates for cardiac catheterisation by the physicians caring for them. In addition, we examine whether a pathological explanation exists for the absence of clinical stigmata of coronary artery disease in patients in whom cardiomyopathy caused by coronary artery disease is found to be the cause of clinically unexplained heart failure. Finally, because we have found cardiomyopathy caused by coronary artery disease to be particularly common among diabetic patients with coronary artery disease (Dash *et al.*, 1977a), we ask whether the presence of diabetes mellitus is a clinical clue that cardiomyopathy caused by coronary artery disease is the cause of heart failure when other clues suggesting the presence of coronary artery disease are absent.

Methods

CLINICAL CLASSIFICATION

The medical records of all patients more than 20 years of age who died in hospital and who came to necropsy were reviewed each day, during a 1-year period (1 October 1974 to 30 September 1975). Based on antemortem clinical data, patients who had had chronic heart failure were identified, and a presumptive cause of heart failure was specified, either before necropsy or before knowledge of the cardiac findings at necropsy.

Patients were identified as having had chronic left heart failure if all of the following had been present some time in their course (not necessarily concurrently): (1) dyspnoea; (2) digitalis and diuretic therapy; (3) apical third heart sound; (4) basilar râles; and (5) pulmonary venous hypertension (upper zone flow redistribution, with or without interstitial or alveolar pulmonary oedema) on a chest x-ray film report. Clinical evidence of right heart failure was not required. Only patients who had had chronic heart failure before the terminal hospital admission were included. Patients who had had only a single episode of heart failure in the setting of an acute event, such as acute myocardial infarction, were

excluded.

Patients identified as having had chronic left heart failure were assigned a presumptive diagnosis of coronary artery disease, valvular heart disease, congenital heart disease, cardiomyopathy (unrelated to coronary artery disease), heart failure resulting from hypertension, or unexplained heart failure. Coronary artery disease was assigned when either a history of typical angina pectoris, a history of myocardial infarction, or a transmural myocardial infarction pattern on the electrocardiogram had been present. Valvular or congenital heart disease was assigned when catheterisation evidence was available or if the clinical diagnosis had been made by an experienced clinical cardiologist. Cardiomyopathy (unrelated to coronary artery disease) was assigned when normal or insignificantly diseased coronary arteries and the absence of important valvular disease had been proved by catheterisation. All other patients were classified as having unexplained heart failure. For purposes of this study, hypertension was not considered to be a cause of chronic heart failure unless severe uncontrolled hypertension was present at the time that heart failure was present.

Documentation in the medical record of blood glucose levels was erratic, so diabetes mellitus was defined when the diagnosis had been made during life by the patient's doctor and this had required dietary or drug treatment, or both. A history of hypertension was defined as a blood pressure recording of greater than 140/90 mmHg on 2 separate occasions.

NECROPSY ANALYSIS

In addition to routine necropsy examination, post-mortem coronary angiography (Schlesinger, 1938) was performed in 12 of 15 patients in whom heart failure had been unexplained. In each of these cases, the extramural coronary arteries were removed from the heart. After complete formalin fixation and decalcification, each artery was cross-sectioned at 2 mm intervals, and the degree of stenosis in each segment was recorded. Coronary artery disease was judged to be present when 70 per cent or greater reduction in cross-sectional luminal area was present.

In all patients classified as having had unexplained heart failure, the ventricular myocardium was examined by gross inspection of transverse ventricular sections and by histological evaluation of samples from both randomly selected and pathological areas. Transmural infarction was defined as the presence of dense, contiguous fibrosis extending from the endocardium to the epicardium. Non-transmural infarction was defined as being present when either confluent fibrosis or dense patches of

fibrosis occupied at least one-half of a low-power microscopical field, but did not extend contiguously from the endocardium to the epicardium. Stains for amyloid were not routinely performed.

CASE CONTROL COMPARISON

Patients who had been classified as having unexplained heart failure and who were discovered at necropsy to have coronary artery disease as its cause ('case') were randomly and individually matched for sex and, as closely as possible, for age to patients who had been classified before necropsy as having coronary artery disease as the cause of chronic left heart failure (control). The pathological findings in the coronary circulation and in the myocardium were compared in the two groups. The pathologist (JTF) who examined each heart and coronary circulation did not know whether the case being examined was a 'case' or a control.

STATISTICAL ANALYSIS

Proportions of groups having the same event were compared by Fisher's exact test.

Results

During the 1-year period, necropsy was performed in 740 patients who died in hospital. Of these patients, 90 had had, by our criteria, chronic left heart failure. Their age distribution is shown in the Fig. Thirty-six patients (40%) were 75 or older, and only 4 patients (4%) were less than 50 years old. The clinical classification of the presumptive causes of left heart failure is shown in Table 1. Heart failure was not attributed to hypertension in any of the patients. Of the 75 patients who had been assigned coronary artery disease, valvular heart disease, congenital heart disease, or cardiomyopathy (unrelated to coronary artery disease) as the presumptive cause of heart failure, the diagnosis was confirmed as

Fig. Histogram of the age distribution of the 90 study patients who had had clinical evidence for chronic heart failure. Within each decade, the subgroup of patients with clinically unexplained heart failure is shown by the shaded portion of the bar.

correct at necropsy in 69. Of the 6 patients in whom the clinical diagnosis was unconfirmed, none had undergone cardiac catheterisation. Thus, the clinical diagnosis was correct in 86 per cent (36 of 42) of patients not catheterised in whom the cause of heart failure had been thought to be diagnosable on clinical grounds. Of the 6 patients in whom the clinical cardiac diagnosis was mistaken, 2 had insufficient findings at necropsy to account for heart failure.

Necropsy findings and clinical features of the 15 patients classified clinically as having unexplained heart failure are shown in Table 2: 7 were found to have coronary artery disease as the cause of their heart failure, which occurred in the form of cardiomyopathy caused by coronary artery disease (multiple areas of infarction) in all 7; 5 had cardiomyopathy unrelated to coronary artery disease; and

Table 1 Presumptive clinical diagnosis of causes of left heart failure

Presumptive clinical diagnosis	Total no. of patients	No. of patients in whom diagnosis not documented by cardiac catheterisation during life	No. of patients in whom clinical diagnosis not confirmed by necropsy findings
Coronary artery disease	23	21	3
Valvular heart disease	48 (15)*	21	3
Congenital heart disease	1	0	0
Cardiomyopathy (unrelated to coronary artery disease)	3	0	0
	—	—	—
Total	75	42	6
Unexplained	15	15	—

*The number in parentheses refers to patients in whom the clinical events suggested that coronary artery disease was present in addition to valvular heart disease.

Table 2 Patients who on clinical grounds were assigned 'unexplained' as cause of chronic left heart failure

Case no.	Age, sex	Electrocardiogram	Diabetes	Hypertension	Heart weight (g)	CAD†	LV chamber dilatation‡	LV wall§ thickness (cm)	Cause of heart failure at necropsy
1*	60, F	Complete heart block	Yes	Yes	369	3	3+	1.5	CM-CAD**
2*	87, M	Intraventricular conduction defect	No	No	536	3	4+	1.5	CM-CAD
3*	55, F	Poor praecordial R wave progression	Yes	No	405	3	2+	1.3	CM-CAD
4*	86, M	Non-specific ST-T abnormalities	Yes	No	456	2	1+	1.6	CM-CAD¶
5*	65, M	Left ventricular hypertrophy	Yes	No	354	3	3+	1.0	CM-CAD
6*	74, M	Left ventricular hypertrophy	No	Yes	553	3	2+	2.0	CM-CAD
7	81, M	Non-specific ST-T abnormalities	Yes	No	340	2	1+	1.7	CM-CAD
8*	58, M	Poor praecordial R wave progression	No	No	663	0	3+	1.4	Cardiomyopathy
9	64, M	Intraventricular conduction defect	No	Yes	660	0	4+	2.3	Cardiomyopathy
10*	62, F	Complete heart block	No	Yes	483	0	2+	1.8	Cardiomyopathy
11*	84, F	Intraventricular conduction defect	Yes	Yes	548	0	2+	1.6	Cardiomyopathy
12*	66, F	Intraventricular conduction defect	No	No	568	0	3+	1.3	Cardiomyopathy
13*	62, M	Poor praecordial R wave progression	No	No	498	1	3+	2.1	Calcific aortic stenosis
14	82, F	Left ventricular hypertrophy	No	Yes	500	1	1+	1.7	Calcific aortic stenosis
15*	60, M	Left ventricular hypertrophy	No	No	619	2	3+	1.2	Rheumatic valvular disease, aortic, mitral, and tricuspid

*Postmortem selective coronary angiography performed.

†Coronary artery disease (number of vessels with 70% or greater stenosis).

‡Left ventricular chamber dimensions, judged subjectively, 0-4+.

§Measured in mid anterior wall.

¶Rheumatic valvular disease, aortic and mitral, was also present.

**CM-CAD, cardiomyopathic syndrome caused by coronary artery disease.

3 had significant valvular heart disease, the importance of which had been unappreciated during life. A history of hypertension was present in 6 patients, but heart failure was not attributed to hypertension in these patients (see Methods section). The data in Table 2 imply that only a single cause of heart failure was found in each patient. In fact, multiple cardiac abnormalities (excluding a history of hypertension as an abnormality) were present in 4 patients. But only in 1 patient—a patient with cardiomyopathy caused by coronary artery disease and rheumatic valvular disease—did more than one abnormality appear potentially related to heart failure (and the valvular abnormalities were relatively minor in this patient). All 3 patients with severe valvular disease also had coronary artery disease, but the heart failure was judged to be unrelated to coronary artery disease (only 1 of the 3 had myocardial infarction, and in that patient the infarct was small). We have assumed that abnormalities of the heart valves or myocardium that are present on a microscopical basis only, that is that do not cause an abnormality apparent on gross examination of the valves or myocardium (such as post-inflammatory or

degenerative changes or microscopic amyloid), are not severe enough to cause chronic heart failure.

Six of the patients classified clinically as having had unexplained heart failure had been diabetic (4 on oral antidiabetic agents, 2 on insulin; adult onset in 5). Of these, 5 were in the group of 7 patients who had coronary artery disease discovered at necropsy to be the cause of heart failure, and only 1 was in the group of 8 patients who were found to have a cause of heart failure other than coronary artery disease ($P < 0.05$) (Table 2). Hypertension, however, was not a marker of whether coronary artery disease was found at necropsy in patients who had been classified as unexplained heart failure. Of 6 patients who had been hypertensive, 2 were found at necropsy to have coronary artery disease and 4 were not.

A comparison is shown in Table 3 of the extent of coronary artery disease and of the type and distribution of myocardial infarction in patients who had been classified as having unexplained heart failure, but in whom coronary artery disease was found at necropsy to have been the cause of heart failure ('cases'), and 'control' patients who had been given a

Table 3 Comparison of extent of coronary artery disease and of type and distribution of myocardial infarctions found at necropsy in patients with clinically unexplained heart failure found to have cardiomyopathy caused by coronary artery disease ('cases') and in 'control' patients (matched for age and sex) who had been classified as having coronary artery disease as presumptive cause of heart failure on clinical grounds

	Age	LCA† stenosis	No. of diseased vessels‡	No. of sites of remote infarction (fibrosis)§		Number of sites of recent infarction§	Syndrome of coronary artery disease that caused heart failure
				Non-transmural	Transmural		
‘Cases’							
1	60	Yes	3	2	0	1	CM-CAD*
2	87	No	3	2	0	0	CM-CAD
3	55	Yes	3	3	0	1	CM-CAD
4	86	No	2	2	0	1	CM-CAD
5	65	No	3	3	0	1	CM-CAD
6	74	Yes	3	2	0	1	CM-CAD
7	81	No	2	1	1	1	CM-CAD
‘Controls’							
1	61	Yes	3	1	1	0	CM-CAD
2	87	No	3	2	1	0	CM-CAD
3	55	No	3	1	1	0	CM-CAD
4	81	No	2	2	2	0	CM-CAD
5	50	Yes	3	2	1	1	CM-CAD
6	74	No	1	0	1	0	LV¶ aneurysm
7	75	No	3	1	2	0	CM-CAD

*CM-CAD, cardiomyopathy caused by coronary artery disease.

†LCA, main left coronary artery.

‡Other than LCA.

§Number of 4 left ventricular sites (free anterior wall, septum, posterior wall, lateral wall) showing infarction.

¶LV, left ventricular.

presumptive clinical diagnosis of coronary artery disease. The 2 groups differed in the frequency with which remote infarction was transmural as compared with non-transmural. Of the 7 'cases', only 1 had a transmural infarction, which was posterolateral in location, whereas each of the 7 'controls' had transmural infarctions ($P < 0.01$), which involved the anterior left ventricular wall in all.

Discussion

The present study was carried out prospectively so that our judgement as to the probable cause of heart failure would be made, as it is in everyday clinical practice, on the basis of clinical information alone and so that postmortem coronary angiography could be performed in cases where the cause of heart failure was not apparent. Our experience, similar to that of others (Crawford, 1977), is that routine examination of the coronary arteries at necropsy, as compared with postmortem coronary injection studies, results in an appreciable underdiagnosis of coronary artery disease. Our study has the disadvantages of necessarily limited numbers of patients and of sharing with all necropsy studies the fact that it is not necessarily applicable to living populations.

Even with these reservations, however, one conclusion of our study seems clear: cardiomyopathic syndrome resulting from coronary artery

disease which is not apparent from the patient's history and the electrocardiogram is a more frequent cause of clinically unexplained chronic heart failure than the results of cardiac catheterisation studies suggest (Yatteau *et al.*, 1974; Dash *et al.*, 1977b). In 17 per cent of our necropsied patients, chronic left heart failure could not be explained clinically. In approximately one-half of such patients, necropsy showed that there was cardiomyopathy caused by coronary artery disease. Looking at the issue from another standpoint, of a total of 25 patients in whom coronary artery disease was the cause of chronic heart failure (excluding 2 patients who had undergone cardiac catheterisation during life), the diagnosis of coronary artery disease had not been apparent in 7 (28%). Twenty-eight per cent may be considered the frequency with which a *false negative* diagnosis of coronary artery disease as the cause of chronic heart failure was made in our study. By comparison, the diagnosis of coronary artery disease was *false positive* in 14 per cent of cases; of 21 patients who had not undergone cardiac catheterisation and in whom heart failure was attributed on clinical grounds to coronary artery disease, the diagnosis was found to be incorrect in 3.

The relatively high prevalence of false negatives in the diagnosis of cardiomyopathy caused by coronary artery disease does not imply that a more extensive diagnostic evaluation is required in caring for the individual patient with unexplained heart failure.

No convincing data exist to suggest that the management of patients with cardiomyopathy caused by coronary artery disease should differ from the management of patients with dilated cardiomyopathy of the idiopathic type (Yatteau *et al.*, 1974; Wexler *et al.*, 1976; Dash *et al.*, 1977b).

Rose and Wilson (1959) found a lower prevalence of coronary artery disease in their study of necropsied patients with clinically unexplained heart failure than we have, but they utilised standard necropsy techniques for the identification of coronary artery disease, which probably underestimate its prevalence. Furthermore, several of their patients appear to have been misidentified as having had heart failure, since 36 per cent were found not to have specifiable heart disease at necropsy. It is important to use criteria for heart failure that, in combination and including radiological signs, are highly specific (Harlan *et al.*, 1977), though undersensitive, in its detection. Consequently, we failed to find cardiac findings sufficient to explain the occurrence of heart failure in only 2 of 90 patients in our study.

Pomerance has found that 65 per cent of patients with heart failure who are over 75 years of age have multiple cardiac abnormalities (Pomerance, 1965a). In the present study, we seldom found it necessary to assume more than one cause of heart failure in an individual patient, either on clinical grounds or after necropsy, perhaps because 60 per cent of our patients were less than 75 years of age. Hypertension was not assumed in our study to be a cause of heart failure unless sustained severe hypertension was present at the time that heart failure was present (see below), whereas past hypertension was included as a causal factor for heart failure in the Pomerance study. Moreover, we have, by design, specified as the cause of heart failure the predominant cardiac abnormality present, and have reported more than one cause only if a second abnormality appeared likely to have been of haemodynamic significance. Hence, our study possibly underestimates the number of patients in whom heart failure is the result of a combination of abnormalities, perhaps, in some cases, no one of which would have caused heart failure in itself. For the same reasons, we may have also underestimated the contribution of mitral annular calcification as a cause of heart failure (Pomerance, 1970). We found mitral annular calcification to be the predominant cause of heart failure in only one patient. Even so, we believe that chronic heart failure is most often the result of a single factor, and this is seldom mitral annular calcification, even though multiple cardiac abnormalities, including mitral annular calcification, are frequently present in the most elderly. In those patients who are of principal interest in the present

study, namely, those in whom a cause of heart failure was not apparent clinically, a single cause was found at necropsy in 14 of 15.

One-third of the patients in our study in whom heart failure was unexplained clinically were found at necropsy to have cardiomyopathy. The hearts of such patients were strikingly increased in weight, and showed left ventricular chamber dilatation that was of at least moderate degree in each and was of extreme degree in 3; no important valvular abnormalities or coronary artery lesions were present. The gross pathological findings correspond to those of idiopathic congestive cardiomyopathy (Roberts and Ferrans, 1975), at least in the 3 cases in which the most striking degree of left ventricular chamber dilatation was present. We have assumed that hypertension is not the predominant cause of chronic heart failure unless hypertension is not treated or cannot be controlled with medical treatment. This is because effective antihypertensive therapy greatly reduces the number of patients with recurrent episodes of heart failure as well as the number in whom heart failure is the cause of death among patients with hypertension (Wolff and Lindeman, 1966; Hodge and Smirk, 1967; Veterans Administration Cooperative Study Group on Anti-hypertensive Agents, 1970), at least during the first few years of follow-up. Therefore, heart failure was not attributed to hypertension in a single patient in our study, because in no patient was sustained, uncontrolled, severe hypertension present at the time that heart failure was present. Nevertheless, the possibility exists that an occasional patient with hypertension suffers the development of a 'hypertrophic cardiomyopathy' that, once present, persists to cause heart failure even after hypertension is controlled. If so, 3 of the 5 patients in whom clinically unexplained heart failure was ascribed after necropsy to cardiomyopathy should be considered candidates for the diagnosis of hypertension-induced cardiomyopathy, because they had a history of treated hypertension.

We found no instances in which chronic heart failure was attributable to senile cardiac amyloidosis, probably because most of our patients were less than 80 years of age, and senile cardiac amyloidosis only becomes common over the age of 80 (Pomerance, 1965b). Though we performed no special stains for amyloid, we believe that we were unlikely to have overlooked cases in which senile cardiac amyloid was responsible for heart failure, because amyloid deposition is severe and apparent on gross examination in cases in which it causes heart failure (Pomerance, 1965b).

Studies of patients undergoing cardiac catheterisation have shown that cardiomyopathy caused by

coronary artery disease is the result of multiple myocardial infarctions, and, furthermore, that the infarctions are distributed in the territory of more than one coronary artery (Yatteau *et al.*, 1974; Dash *et al.*, 1977b). The patients with cardiomyopathy caused by coronary artery disease in the present study in whom heart failure had been unexplained during life had similar findings, by necropsy criteria, to patients who have been identified in catheterisation studies: multiple infarctions and multivessel coronary artery disease. But an explanation as to why the diagnosis of cardiomyopathy caused by coronary artery disease had not been apparent, at least on the electrocardiogram, was forthcoming: the remote infarctions found at necropsy were either nontransmural in location, and hence not diagnosable by electrocardiographic Q waves (Georas *et al.*, 1963), or were transmural but located in areas where transmural infarctions are unassociated with Q waves in the standard 12-lead electrocardiogram. Why typical ischaemic cardiac pain was absent in these patients is unclear. Approximately 25 per cent of patients who suffer a transmural myocardial infarction do not experience typical chest pain (Kannel *et al.*, 1970). The present study shows that nontransmural myocardial infarctions also, even when multiple, may occur without typical chest pain.

This study also suggests that the presence of clinically overt diabetes mellitus appears to be a useful clue to the diagnosis of cardiomyopathy caused by coronary artery disease in patients whose chronic heart failure would otherwise be unexplained. Unexplained heart failure was caused by cardiomyopathy resulting from coronary artery disease in 83 per cent of patients who were being treated for diabetes, but the same was true of only 22 per cent of patients who were not being treated for diabetes. Though the number of patients studied is small, the difference is significant. This simple observation is interesting and somewhat surprising in view of the uncertainty that is extant with regard to the definition of diabetes, at least on the basis of the glucose tolerance test, in this age group (Andres, 1971). The increased prevalence of undiagnosed cardiomyopathy caused by coronary artery disease in diabetics is almost certainly the explanation for the excessive prevalence of heart failure, compared with the prevalence of overt coronary events, in the diabetic population of the Framingham study (Kannel *et al.*, 1974). Perhaps cardiomyopathy caused by coronary artery disease is a more frequent cause of otherwise unexplained heart failure in diabetics because diabetics are more prone to myocardial infarctions that are painless. To our knowledge, however, a definite relation between diabetes mellitus and 'silent' myocardial infarction

has never been conclusively shown (Kannel *et al.*, 1970).

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