Coronary occlusive disease and late graft failure after cardiac transplantation

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Abstract

Objective—Coronary occlusive disease is the main cause of late mortality after cardiac transplantation. It has both similarities and differences compared with conventional atherosclerotic coronary disease. The pathophysiology of late graft failure from coronary occlusive disease is unclear at present. We reviewed the experience of this disorder in our cardiac transplant programme.

Design—A retrospective analysis of angiographic and pathological data.

Setting—A regional cardiothoracic centre and transplant unit.

Patients—Of a population of 383 orthotopic cardiac transplant recipients operated upon between January 1979 and June 1990, 447 coronary angiograms were available for review in 193 patients. Thirteen of a possible 18 results of post mortem examinations from patients dying from coronary occlusive disease were available.

Main outcome measure—Coronary occlusive disease was defined as any evidence of disease on coronary angiography. Post mortem examinations were performed with standard techniques.

Results The angiographic prevalence of coronary occlusive disease was 3% (1/32 patients) and 40% (19/47 patients)

at one and five years respectively. Twenty six grafts failed due to coronary occlusive disease compared with 132 graft failures from all causes during this period. Acute thrombosis was present in a large vessel in seven of 13 fatal cases undergoing necropsy (54%). Noticeable large vessel involvement with disease in smaller distal vessels was present in four patients (31%). The remaining two patients (15%) had small vessel disease alone. Twelve of the 13 patients had significant cardiomegaly (cardiac weight ≥ 400 g) with a mean weight of 510 (range 370–740) g.

Conclusion—Coronary occlusive disease is the main late complication after cardiac transplantation. A combination of coronary thrombosis, ischaemia from stenoses of large and small coronary vessels, and cardiomegaly contribute to the graft failure of these patients.

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Coronary occlusive disease is the main cause of death in orthotopic cardiac transplant recipients more than one year after cardiac transplantation.¹ This disease differs from conventional atherosclerosis in that it is tubular, concentric, diffuse, and often affects smaller coronary vessels.^{2,3} It may not only develop proximally in larger coronary arteries as in conventional atherosclerosis, but may be distal and obliterative (fig 1). Often it appears as a combination of these types of lesion and characteristically progresses rapidly.⁴ As patients are denervated at the time of operation, cardiac ischaemia can develop without symptoms until severe cardiac dysfunction and death occurs.⁵

Serial coronary angiography has been the main method of assessing coronary occlusive disease after operation. It is performed to detect coronary disease and left ventricular dysfunction, and to plan appropriate treatment. Also it is used as a research tool for studying a form of accelerated coronary disease in humans. What remains unclear is the prognostic importance of the various coronary angiographic lesions found in patients with coronary occlusive disease, and what is the mechanism of graft failure and death.

We documented the incidence and time to occurrence of any form of coronary occlusive disease as apparent from coronary angiography at our hospital. We reviewed the available data from post mortem examination

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Figure 1 Left anterior oblique view showing diffuse irregularity and terminal occlusion of left anterior descending and left circumflex coronary artery.

of patients who died during the study, and examined some of the processes which led to graft failure.

Patients and methods

A total of 383 patients received their first cardiac transplant at Papworth Hospital between January 1979 and June 1990. Most (88%) of the recipients were male (n = 338). The mean age of these patients was 44 (range 6–63) years at the time of operation. Ischaemic heart disease (53%) and dilated cardiomyopathy (43%) were the main indications for transplantation.

IMMUNOSUPPRESSIVE TREATMENT

The first 29 patients in the cardiac transplant programme received azathioprine and prednisolone only. Cyclosporin was introduced at Papworth Hospital in March 1982 and was used in 121 patients in conjunction with either azathioprine or prednisolone for the next four years (double treatment). Triple treatment, combining cyclosporin with azathioprine and prednisolone, was started in April 1986. Oral steroids are gradually withdrawn, if possible, in the triple treatment group starting three months after operation.

ANGIOGRAPHY PROTOCOL

Up to March 1983, patients underwent annual coronary angiography. After this time, a different protocol was devised. The first coronary angiogram is now performed two years after operation. If coronary occlusive disease is detected, annual angiography is performed and if not, the next angiogram is performed at four years. After four years, all patients undergo annual angiography.

Angiograms were assessed serially for each patient by two observers blinded to the clinical history. Coronary occlusive disease was defined as any sign of disease on angiography. Coronary disease was graded according to the diameter of the stenosis of the most severe lesion compared with an adjacent healthy artery. The primary coronary arteries were defined as the left anterior descending coronary artery, left circumflex coronary artery, and right

coronary artery. Their main branches were classified as secondary coronary arteries (first and second diagonal, first and second obtuse marginal, and posterolateral or posterior descending branch of the right coronary artery). Initially, attempts to assess disease angiographically in smaller (tertiary) branches of these arteries were made. Without annual serial films, the consistent ability to detect disease affecting these vessels in all patients was not possible.⁴ Therefore this approach was abandoned. Significant coronary disease was defined as a lesion producing a greater than 50% reduction in intraluminal arterial diameter.

PATHOLOGY

Efforts to procure the heart for pathological examination were made in all patients who died. After fixation in buffered formalin solution, the coronary arteries were examined throughout their lengths. Serial transverse sections were taken at regular intervals and paraffin sections were stained with haematoxylin and eosin. Both large (primary and secondary) and small (tertiary) vessels were examined by light microscopy. Cardiomegaly was defined as a post mortem heart weight of ≥ 400 g.⁶ The diagnosis of death due to coronary occlusive disease was made in several patients at post mortem examinations performed at other hospitals. Unless the heart was released for examination here, this data is not included in our study.

STATISTICAL METHODS

Statistical analysis was performed with the *BMDP* statistics package. Results are expressed as mean (ranges) for continuous measurements. Actuarial survival was calculated by the life table method. The risk of death associated with improved immunosuppressive treatment was assessed by Cox regression analysis and tested with the likelihood ratio test.

Results

The overall survival figures have improved with changes in immunosuppressive treatment (fig 2). Most patients undergoing coronary angiography received cyclosporin treatment. No documented change in the incidence of coronary occlusive disease has occurred, however, with the various developments in immunosuppressive treatment here or elsewhere as yet.⁴ This is shown by the similarity in slope of the decline in survival curves after the first year in each immunosuppressive treatment group (fig 2).

CORONARY ANGIOGRAPHY

We reviewed 447 coronary angiograms in 193 patients. Ninety nine patients had two or more coronary angiograms. Coronary occlusive disease was present in 3% (1/32) of patients undergoing coronary angiography by the first year, and 40% (19/47) at five years after operation. Figure 3 shows freedom from coronary occlusive disease as assessed on coronary angiography over seven years from transplantation. Coronary collateral vessels were seen to

Figure 2 Actuarial survival after orthotopic cardiac transplantation according to type of immunosuppressive treatment. RR, relative risk; numbers in parentheses are ranges.

Figure 3 Freedom from coronary occlusive disease as indicated by coronary angiography.

supply 12% (3/26) of the occluded coronary arteries in our study.

The severity of coronary stenosis produced by coronary occlusive disease was usually modest. For example, of the angiograms showing coronary occlusive disease in the left anterior descending coronary artery, 55% (61/110) showed lesions that decrease the diameter of affected vessels by <25% of the diameter of the adjacent arteries. Only 12% of the cine films (13/110) showed lesions of >50% stenosis in the left anterior descending coronary artery. Therefore, the degree of luminal obstruction was usually not severe. The disease, however, often affects different portions of the same artery as well as other vessels. This pattern of distribution of the disease makes accurate anatomical description difficult.

GRAFT FAILURE

Coronary occlusive disease caused failure of 26 grafts (20%) compared with 132 graft losses from all causes during this period. Most of these patients died later than one year after operation (table 1). Thirteen patients who had undergone coronary angiography died and the heart was available for full examination. Seven patients underwent eight cardiac retransplantation operations. The remaining five patients died and had necropsies, but the heart was not examined at this hospital.

The mean age of all patients at the time of graft failure was 39 (range 23–57) years. The median time from the identification of coronary occlusive disease angiographically to death in the group dying of coronary occlusive disease was 2.3 (range 0.1–5.6) years. Twelve of the 13 patients who died and had post mortem

examinations had considerable cardiomegaly (weight ≥400 g) with a mean overall weight of 507 (range 370–740) g.

Coronary angiograms were performed before graft failure in 18 of the patients who had pathology data available (table 2). Coronary angiography tended to underestimate the severity of the stenosis in coronary occlusive disease found at post mortem examination. It is, however, difficult to assess accurately the severity of stenosis in post mortem samples that have not been pressure perfused. This structural comparison is therefore limited in value.

MORTALITY

Thirteen patients died and underwent detailed post mortem examination. The mode of death was acute thrombosis on a significant lesion affecting a primary or secondary vessel in seven cases (table 2). In two of these patients there was evidence of old thrombus in different vessels to the ones affected by the acute thrombus. There was post mortem evidence of previous non-transmural myocardial infarction in two cases, and a recent infarction in one patient who died.

In four of the 13 patients undergoing post mortem examination there was histological evidence of coronary disease in small tertiary branches, as well as the large primary and secondary coronary vessels. Three patients died with diffuse involvement of small tertiary vessels alone. When disease in small coronary vessels was the only cause of death, coronary angiography did not detect coronary disease. It was performed in two of these cases before death, and appeared normal, and was not done in the remaining patient as death occurred before the first routine coronary angiogram was performed.

The time from the first sign of coronary disease to death progressively decreased as more primary coronary arteries were diseased, but the differences were not statistically significant (fig 4). Longer follow up in more patients is required to clarify this. Coronary occlusive disease was not detected on coronary angiography in 107 (55%) patients at any stage during the study period. Eight of these patients have died: two of coronary occlusive disease, two of malignancy, two of sudden death, and two of other causes.

Table 1 Causes of death in cardiac transplant patients between January 1979 and June 1990

Causes of death	Time from transplantation		
	0–90 days	90 days–1 year	> 1 year
Rejection	23	9	1
Infection	21	8	3
Coronary occlusive disease	0	2	26
Sudden cardiac death	1	1	3
Donor heart failure	6	0	0
Stroke	4	1	0
High pulmonary resistance	4	0	0
Multifactorial	4	0	0
Lymphoma	1	0	2
Malignancy	0	1	5
Abdominal complications	2	0	0
Operative bleeding	1	0	0
Unknown	1	1	1
Total	68	23	41

RETRANSPLANTATION

Seven patients were retransplanted for coronary occlusive disease. One patient required a further retransplant for recurrent coronary disease. The median time from transplantation to reoperation was 3.6 (range 0.3–8.8) years. These patients had progressive coronary disease that allowed elective reassessment for reoperation. Only three of these patients had coronary angiography performed on their second graft during the study period. Therefore there is insufficient data to assess angiographic recurrence of coronary disease in retransplanted patients.

Table 2 Post mortem data

Patient No	Age (y)	TTF (y)	An	PM	Event	Wt of heart (g)
1	29	3	NCA	2VD T	death	440
2	49	3.5	MINLVD	1VD T	death	400
3	50	1.7	NCA	1VD	death	600
4	52	5.9	3VD	LMain T 3VD MI(old)	death	510
5	23	8	MINLVD	2VD T	death	580
6	30	2.5	MINLVD	1VD Told	death	480
7	46	0.7	NCA	SVD	death	480
8	44	4	Cx	3VD	death	500
9	45	4	LVD-OM	1VD-T	death	480
10	52	4.5	NAD	SVD	death	740
11	26	2.8	3VD	3VD Told old and new MIs	death	390
12	36	1.9	3VD	1VD-T MI	death	610
13	28	1	NCA	1VD	death	670
14	25	3	NCA	SVD	RETX	440
15	35	8.8	2VD SVD	3VD	RETX	600
16	34	3.1	2VD	3VD	RETX	370
		1.2	2VD	3VD	RETX	370
17	21	4.4	NCA	2VD	RETX	480
18	36	5.2	3VD	3VD	RETX	545
19	26	4.1	3VD	3VD	RETX	510
20	57	0.3	NCA	SVD	RETX	470

TTF, time to graft failure; An, angiographic lesion or stenosis; PM, post mortem lesion or stenosis; NCA, no coronary arteriogram available; VD, vessel disease; T, fresh thrombus; MINLVD, minor disease in large epicardial coronary artery; SVD, disease in tertiary vessels on histology; LMain, left main coronary artery; T old, old thrombus; CX, left circumflex artery; LVD-OM, large vessel disease obtuse marginals; RETX, retransplanted; MI, myocardial infarction.

Discussion

Coronary occlusive disease probably occurs as a result of responses to immunologically mediated vascular injury.⁷ It may be related to the arteriopathy seen in other transplanted solid organ grafts.⁸ Higher incidences of myocardial cellular rejection^{9 10} and vascular (humoral) rejection¹¹ have been reported in patients developing coronary occlusive disease. Hyperlipidaemia, often exacerbated by steroid¹² and cyclosporin treatment,¹³ is probably an important cofactor in the development of coronary occlusive disease. High total cholesterol, high LDL cholesterol,¹³ and low HDL cholesterol concentrates,¹⁴ and hypertriglyceridaemia¹⁵ have been implicated in some studies. Cytomegalovirus infection has been suggested as a potential cause of the disorder.¹⁶ The relation between virus infection and coronary occlusive disease has not been found at other centres.¹⁴ There is no evidence, as yet, of cytomegalovirus causing direct coronary artery damage. Other factors have been reported as being associated with development of disease (table 3). The aetiology is unclear at present. No single factor appears to be so important that it stands out, because of the few patients studied. It is probable that coronary occlusive disease is a manifestation of chronic vascular rejection in combination with other cofactors.²² Until the pathogenesis

becomes clearer, appropriate preventive and therapeutic strategies are difficult to design.

Serial coronary angiography has been the main method of assessing coronary occlusive disease after cardiac transplantation. As a result of the previously described differences from conventional coronary artery disease, it underestimates the presence and severity of lesions. The reported prevalence of angiographic coronary occlusive disease after cardiac transplantation in other centres varies from between 2% and 18% at one year and 40% and 44% at five years.^{4 23 24} The differences may partly represent variations in reporting criteria.⁷

It is clear from our study that angiographic evidence of coronary disease does not always accurately predict the prognosis in an individual patient. The low number of graft failures from coronary occlusive disease in transplant patients limits the comparisons with the large trials undertaken in conventional coronary artery disease.²⁵ The apparently increased risk of death in cardiac transplant patients with coronary disease may be due to the disturbed relation between coronary arterial structure, as defined by angiography, with coronary vascular and myocardial function. The concentric luminal narrowing, sequential stenoses, the diffuse nature of the disease, and the involvement of small vessels are responsible for the functional impairment. The few patients who have died from coronary occlusive disease precludes identification of potential associated risk factors for death.

Coronary disease with acute coronary thrombosis in primary and secondary vessels caused death in seven of 13 available cases as shown at post mortem examination. Most of these atheromatous plaques (six of seven) had considerable severity of stenosis. Again, reservations must occur regarding the accuracy of measurements of stenosis with these post mortem findings. This experience of plaque rupture as a cause of sudden death, however, is similar to that seen in coronary atherosclerotic

Figure 4 Survival from first angiographic evidence of coronary occlusive disease according to number of vessels affected.

Table 3 Risk factors associated with coronary occlusive disease

Factor	Reference
Hypertension	Becker <i>et al</i> ¹⁷
Increased donor and recipient age	Sharples <i>et al</i> ¹⁸
Ischaemic heart disease as indication for transplant	Sharples <i>et al</i> ¹⁴
HLA mismatch and	Pennock <i>et al</i> ¹⁸
Anti-HLA antibodies	Reemtsma <i>et al</i> ¹⁹
Cytotoxic B cell antibodies	Hess <i>et al</i> ²⁰
Haemostatic factors (fibrinogen, VIIc, VIIIc)	Hunt <i>et al</i> ²¹

disease in non-transplant patients. For example, in a series of 100 consecutive sudden coronary deaths, 44% had a >50% coronary arterial stenosis with a thrombosis.²⁶ It is also evident that most of the patients had considerable cardiomegaly. The cause of this is unclear, as the patients did not have untreated hypertension (two had treated hypertension). Presumably graft failure, at least in some patients, was a result of coronary occlusive disease in large and small vessels producing symptom free cardiac ischaemia in a denervated, hypertrophied heart. This resulted in myocardial infarction in some cases, and presumably, fatal arrhythmias in all cases.

Coronary occlusive disease can produce several outcomes. Sudden plaque rupture is unpredictable and leads to infarction or death in both conventional and transplant coronary disease.⁵ In progressive coronary occlusive disease leading to left ventricular dysfunction, full assessment for further treatment can be made. At present, cardiac retransplantation is the only established treatment. Unfortunately, survival outcome is poorer than for first time transplant patients,¹ and the recurrence rates of coronary occlusive disease are higher.²⁷ Justifying such treatment in the face of acute donor shortage is difficult.²⁸ Percutaneous transluminal coronary angioplasty can be used to dilate discrete lesions in the proximal coronary arteries in cardiac transplant patients. The short-term results are comparable with the effectiveness in conventional atherosclerosis.²⁹ Its long-term impact on cardiac function and prognosis is unclear. The use of coronary artery bypass grafting has been limited, as distal coronary vessels suitable for surgery are rare.³⁰

The lack of suitable treatment for coronary occlusive disease calls into question the clinical value of routine coronary angiography in the follow up of symptom free cardiac transplant patients after operation. This contrasts with its research role, where it is clear that although more patients are required, risk factor analysis may eventually provide insights into associated cofactors in development of disease. The presence of severe lesions in larger coronary arteries is likely to be associated with a poor prognosis as suggested by our study. The mortality data, however, suggests that moderate epicardial coronary disease and disease in smaller vessels are also important in the increased mortality in long-term heart transplant patients. Ventricular hypertrophy may also be an important risk factor.

Non-invasive methods of detection of coronary occlusive disease have been disappointing.³¹ We should therefore attempt to use newer

methods of measuring impairment of myocardial perfusion and function produced by coronary occlusive disease.³² With this information, improved preventive and therapeutic strategies for long-term cardiac transplant patients with coronary occlusive disease could be made.

In conclusion coronary occlusive disease is the main cause of late mortality and morbidity in cardiac transplant patients. Coronary disease affecting primary and secondary coronary arteries is the main factor in late mortality after cardiac transplantation, although disease in smaller distal vessels and ventricular hypertrophy are also implicated. Improved methods of measuring impairment of myocardial perfusion and function produced by coronary occlusive disease should be developed.

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