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.

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 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.3 As patients are denervated at the time of operation, cardiac ischaemia can develop without symptoms until severe cardiac dysfunction and death occurs.4 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

Figure 1 Left anterior oblique view showing diffuse irregularity and terminal occlusion of left anterior descending and left circumflex coronary artery.
Coronary occlusive disease and late graft failure after cardiac transplantation

Coronary occlusive disease and
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 be-
tween 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 indica-
tions for transplantation.

IMMUNOSUPPRESSIVE TREATMENT
The first 29 patients in the cardiac transplant
programme received azathioprine and pred-
nisolone 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 dif-
ferent 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. Coron-
ary 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. 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 solu-
tion, the coronary arteries were examined
throughout their lengths. Serial transverse sec-
tions were taken at regular intervals and paraffin
sections were stained with haematoxylin and
cosin. Both large (primary and secondary) and
small (tertiary) vessels were examined by light
microscopy. Cardiomegaly was defined as a post
mortem heart weight of $\geq 400$ g. The diag-
nosis of death due to coronary occlusive disease
was made in several patients at post mortem
examinations performed at other hospitals. Un-
less 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 expres-
sed 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 else-
where as yet. 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 dis-
ease was present in 3% (1/32) of patients
undergoing coronary angiography by the first
year, and 40% (19/47) at five years after opera-
tion. Figure 3 shows freedom from coronary
occlusive disease as assessed on coronary
angiography over seven years from transplan-
tation. 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.](http://heart.bmj.com/BrHeartJ-1st-published-as-10.1136/hrt.68.9.260-on-1-September-1992. Downloaded from http://heart.bmj.com on September 17, 2023 by guest. Protected by copyright.)
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>
<thead>
<tr>
<th>Causes of death</th>
<th>Time from transplantation</th>
<th>0–90 days</th>
<th>90 days–1 year</th>
<th>&gt;1 year</th>
</tr>
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<tbody>
<tr>
<td>Rejection</td>
<td>23</td>
<td>9</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>21</td>
<td>8</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Coronary occlusive disease</td>
<td>0</td>
<td>2</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Donor heart failure</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td></td>
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<tr>
<td>High pulmonary resistance</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Multifactorial</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Lymphomas</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>0</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Abdominal complications</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Operative bleeding</td>
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<td>0</td>
<td>0</td>
<td></td>
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<tr>
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<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>68</td>
<td>23</td>
<td>41</td>
<td></td>
</tr>
</tbody>
</table>

**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

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Age (y)</th>
<th>TTF (y)</th>
<th>An</th>
<th>PM</th>
<th>Event</th>
<th>Ws of heart (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29</td>
<td>3</td>
<td>NCA</td>
<td>2VD-T</td>
<td>death</td>
<td>440</td>
</tr>
<tr>
<td>2</td>
<td>49</td>
<td>3-5</td>
<td>MINLVD, VD</td>
<td>1VD</td>
<td>death</td>
<td>400</td>
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<tr>
<td>3</td>
<td>50</td>
<td>1-7</td>
<td>NCA</td>
<td>1VD</td>
<td>death</td>
<td>600</td>
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<tr>
<td>4</td>
<td>52</td>
<td>5-9</td>
<td>3VD</td>
<td>1VD</td>
<td>death</td>
<td>510</td>
</tr>
<tr>
<td>5</td>
<td>23</td>
<td>8</td>
<td>MINLVD</td>
<td>2VD T</td>
<td>death</td>
<td>580</td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td>2-5</td>
<td>MINLVD</td>
<td>1VD Told</td>
<td>death</td>
<td>480</td>
</tr>
<tr>
<td>7</td>
<td>46</td>
<td>0-7</td>
<td>NCA</td>
<td>3VD</td>
<td>death</td>
<td>480</td>
</tr>
<tr>
<td>8</td>
<td>44</td>
<td>4</td>
<td>Cx</td>
<td>3VD</td>
<td>death</td>
<td>500</td>
</tr>
<tr>
<td>9</td>
<td>45</td>
<td>4</td>
<td>LV-OM</td>
<td>1VD T</td>
<td>death</td>
<td>480</td>
</tr>
<tr>
<td>10</td>
<td>52</td>
<td>4-5</td>
<td>NAD</td>
<td>3VD</td>
<td>death</td>
<td>740</td>
</tr>
<tr>
<td>11</td>
<td>26</td>
<td>2-8</td>
<td>3VD</td>
<td>3VD</td>
<td>death</td>
<td>390</td>
</tr>
<tr>
<td>12</td>
<td>36</td>
<td>1-9</td>
<td>3VD</td>
<td>1VD T MI</td>
<td>death</td>
<td>610</td>
</tr>
<tr>
<td>13</td>
<td>28</td>
<td>1</td>
<td>NCA</td>
<td>1VD</td>
<td>death</td>
<td>670</td>
</tr>
<tr>
<td>14</td>
<td>25</td>
<td>3</td>
<td>NCA</td>
<td>3VD</td>
<td>RETX</td>
<td>440</td>
</tr>
<tr>
<td>15</td>
<td>35</td>
<td>8-8</td>
<td>2VD SVD</td>
<td>3VD</td>
<td>RETX</td>
<td>600</td>
</tr>
<tr>
<td>16</td>
<td>34</td>
<td>3-1</td>
<td>2VD</td>
<td>3VD</td>
<td>RETX</td>
<td>370</td>
</tr>
<tr>
<td>17</td>
<td>21</td>
<td>4-4</td>
<td>NCA</td>
<td>2VD</td>
<td>RETX</td>
<td>480</td>
</tr>
<tr>
<td>18</td>
<td>36</td>
<td>5-2</td>
<td>3VD</td>
<td>3VD</td>
<td>RETX</td>
<td>545</td>
</tr>
<tr>
<td>19</td>
<td>26</td>
<td>4-1</td>
<td>3VD</td>
<td>3VD</td>
<td>RETX</td>
<td>510</td>
</tr>
<tr>
<td>20</td>
<td>57</td>
<td>0-3</td>
<td>NCA</td>
<td>SVD</td>
<td>RETX</td>
<td>470</td>
</tr>
</tbody>
</table>

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; L.Main, left main coronary artery; T old, old thrombus; Cx, left circumflex artery; LV-OM, large vessel disease obtrude marginals; RETX, retransplanted; MI, myocardial infarction.

Discussion

Coronary occlusive disease probably occurs as a result of responses to immunologically mediated vascular injury. It may be related to the arteriopathy seen in other transplanted solid organ grafts. Higher incidences of myocardial cellular rejection and vascular (humoral) rejection have been reported in patients developing coronary occlusive disease. Hyperlipidaemia, often exacerbated by steroid and cyclosporin treatment, is probably an important cofactor in the development of coronary occlusive disease. High total cholesterol, high LDL cholesterol, and low HDL cholesterol concentrations, and hypertryglyceridaemia have been implicated in some studies. Cytomegalovirus infection has been suggested as a potential cause of the disorder. The relation between virus infection and coronary occlusive disease has not been found at other centres. 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. 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. The differences may partly represent variations in reporting criteria.

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. 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
Table 3 Risk factors associated with coronary occlusive disease

<table>
<thead>
<tr>
<th>Factor</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Becker et al. (1)</td>
</tr>
<tr>
<td>Increased donor and recipient age</td>
<td>Sharples et al. (2)</td>
</tr>
<tr>
<td>Ischaemic heart disease as indication for transplant</td>
<td>Sharples et al. (3)</td>
</tr>
<tr>
<td>HLA mismatch</td>
<td>Pennock et al. (4)</td>
</tr>
<tr>
<td>Anti-HLA antibodies</td>
<td>Reemtsma et al. (5)</td>
</tr>
<tr>
<td>Cytotoxic B cell antibodies</td>
<td>Hess et al. (6)</td>
</tr>
<tr>
<td>Haemostatic factors (fibrinogen, VIIc, VIIIc)</td>
<td>Hunt et al. (7)</td>
</tr>
</tbody>
</table>

Methods of measuring impairment of myocardial perfusion and function produced by coronary occlusive disease. 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.


21 Hunt B, Segal H, Yacoub M. Haemostatic changes after...
Coronary occlusive disease and late graft failure after cardiac transplantation


