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Coronary flow reserve and coronary occlusive disease

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Abstract. The functional effects of coronary occlusive disease (COD) in cardiac transplant patients on small-resistance coronary vessels are unclear. We investigated the changes in coronary flow reserve (CFR) in response to the non-specific smooth muscle vasodilator papaverine. A 3F Doppler probe was inserted into the left anterior descending (LAD) coronary artery in 61 patients following orthotopic heart transplantation. Studies were performed in 57 males and 4 females with a mean age of 46 years (range 20–61 years). The median time from operation was 4 years (range 3 months to 10 years). Coronary blood velocity was measured at rest (RFV) and maximum hyperaemia (PFV) produced by intracoronary papaverine. Coronary flow reserve (CFR) was defined as the ratio of PFV to RFV. Minor lesions in epicardial vessels were found in 23 transplant patients. The mean percentage diameter of the most severe lesion in the coronary tree was 23% SD 3% including 12 lesions in the LAD coronary artery itself (mean 24% SD 4%). Patients with COD had an impaired CFR (2.6 SEM 0.2) compared with normals (3.9 SEM 0.2, $P = 0.0003$), adjusting for year after operation. Mean resting flow velocity was similar in both groups (minor COD, 6.8 cm/s SEM 1.2; normals, 7.1 cm/s SEM 0.6), but mean peak flow velocity response to papverine was reduced (16.5 cm/s SEM 2.5 versus 27.3 cm/s SEM 2.6; $P = 0.007$). In the presence of minor epicardial disease, coronary flow reserve in resistance vessels was reduced due to impairment of peak flow. This demonstrates that non-endothelial-dependent coronary resistance vessel vasodilatation is abnormal and may be caused by a defect in vascular smooth muscle function.

Key words: Cardiac transplant – Coronary microcirculation – Coronary occlusive disease

Coronary occlusive disease is the major long-term problem facing cardiac transplantation [8]. Clinical monitoring of the disease is usually dependent on serial coronary angiography. This is insensitive for detecting coronary occlusive disease in heart transplant patients [4, 10] and underestimates its presence compared with post-mortem data [13]. It also affects small- and medium-sized coronary vessels. It is not possible to assess these vessels angiographically. The relationship between coronary structure defined by angiography and prognosis in cardiac transplant patients is therefore not clear.

Coronary angiographic assessment of conventional and transplant-related coronary occlusive disease has other limitations. For example, it is possibility that narrowings of intermediate 'severity' are significant [9]. Coronary flow reserve measurements are increasingly being used as potential methods for estimating the physiological impact of coronary pathology [3], including coronary disease which may affect smaller vessels [11].

Coronary flow reserve is defined as the ratio of the maximum to the resting coronary flow at a given perfusion pressure, when coronary vessels are maximally vasodilated. In the normal coronary circulation, coronary flow reserve is reduced by lesions producing approximately 35–50% stenosis or more in primary coronary arteries [6, 7, 9]. To maintain myocardial blood flow, coronary resistance vessels vasodilate to compensate for the resistance offered by proximal stenoses [7]. The maximal flow at a given coronary perfusion pressure is predominantly determined by the total cross-sectional area of the resistance vessels. A reduction in the number, calibre or impaired function of these coronary resistance vessels could have a marked impact on coronary flow reserve. This may limit their ability to respond to reductions in myocardial flow produced by proximal coronary lesions [5].

The relationship between 'minor' angiographic abnormalities and myocardial perfusion has not previously been assessed in a large number of cardiac transplant patients.

Patients and methods

Patients

This study was approved by the Huntingdon District Health Authority Ethical Committee. A group of 61 patients was investigated after cardiac transplantation; 55 males and 6 females. Of these, 56

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Table 1. Patient variables

	Heart rate	MAP (mm Hg)	LVEDP (mm Hg)	Age (years)	Sex	Hct (%)
'Minor' COD	87 (11)	96 (2)	9 (1)	47 (12)	22 M 1 F	40 (3)
Normal	83 (12)	94 (3)	8 (2)	47 (9)	33 M 5 F	38 (2)

All values + standard deviation where appropriate
COD, coronary occlusive disease; MAP, mean arterial pressure; LVEDP, left ventricular end-diastolic pressure; Hct, haematocrit

Table 2.

	Group 1	Group 2
Original diagnosis	IHD 12 DCM 11	IHD 20 DCM 18
Median time post-operation (years)	5 (0.3–10)	4 (0.3–8)
Ischaemic time (min)	160 (45)	157 (40)
CyA level	282 (252)	326 (220)
Cholesterol	6.2 (1.0)	5.65 (1.9)
HDL cholesterol	0.95 (0.5)	1.0 (0.7)
LDL cholesterol	5.3 (1.4)	4.6 (1.2)
Triglyceride	2.2 (1.3)	1.9 (0.6)

All values + standard deviation where appropriate
COD, coronary occlusive disease; CyA, cyclosporin; DCM, dilated cardiomyopathy; IHD, ischaemic heart disease

were receiving cyclosporin and azathioprine immunosuppression with or without steroid therapy. No patients were taking β-antagonist therapy. All vasoactive medication (e.g. calcium antagonists) was omitted 24 h prior to the procedure. None of the patients received premedication. Patients underwent right ventricular endomyocardial biopsy on the day of coronary angiography. These samples were examined by conventional light microscopy and graded according to standard histological criteria for the presence of acute rejection [1].

The patients were fasted prior to cardiac catheterization. Coronary angiography was performed via the right femoral artery in all patients using the Judkins technique. Coronary injections were performed manually using up to 8 ml of intracoronary radiopaque contrast (Niopam) and ciné film recordings made in multiple projections. After routine angiography the proximal left anterior descending coronary artery was centred for optimal viewing. A period of at lest 10 min was allowed to elapse before the study continued to eliminate vasoactive effects from the contrast medium.

Heparin 10000 units was given intravenously. A size 8F angioplasty guiding catheter was advanced into the left coronary ostium. A 0.014-inch guidewire was advanced into the distal part of the left anterior descending coronary artery. Using a monorail technique, a size 3F 20 MHz intracoronary Doppler flow probe (Schneider, UK) was advanced over the guidewire into the proximal segment of the left anterior descending coronary artery. The Doppler flow probe and the range gate of the velocimeter were adjusted to obtain good quality phasic and mean coronary blood flow velocity signals. These signals were recorded with the surface electrocardiogram on a Mingograf recorder (Siemens-Elema, Sweden).

Baseline resting and phasic coronary blood flow velocity were taken in each patient. After an initial intracoronary 2-mg test dose of papaverine hydrochloride via the guiding catheter, further injections of up to 14 mg of papaverine (2 mg/ml in 0.9% saline) were given until maximum flow was achieved. The hyperaemic response was recorded in the form of maximum blood flow velocity in centimetres per second (cm/s). Velocity profiles were allowed to return to baseline levels between doses of papaverine.

Each coronary angiogram was assessed by two independent observers blinded to the clinical history. Coronary occlusive disease was defined as any evidence of disease in primary or secondary coronary arteries on angiography. The primary coronary arteries were defined as the left anterior descending coronary artery, left circumflex coronary artery and right coronary artery (primary vessels). Their main branches were classified as secondary coronary arteries (diagonal, obtuse marginal, and posterolateral or posterior descending branch of the right coronary).

Coronary disease was graded according to the stenosis diameter of the most severe lesion in primary or secondary coronary vessels compared with an adjacent 'healthy' artery. The coronary lumen was defined as the effective perfusion channel and measurement was performed in diastolic frames. Quantitative measurements of arterial diameter in coronary vessels were performed using digital electronic calipers (Sandhill Scientific). Coronary angiography was performed at rest, at peak hyperaemia and changes in coronary diameter measured. Left ventricular angiography was performed at the end of the study.

Coronary flow reserve and coronary vascular resistance index

Coronary flow reserve, was defined as the ratio of the peak flow velocity (PFV) achieved to the resting blood flow velocity (RFV). To offset any changes in blood pressure during the study, a coronary vascular resistance index (CVRI) was calculated from the following expression:

$$\text{CVRI} = \frac{\text{Mean BP at peak flow\PFV}}{\text{Mean BP at rest\RFV}}$$

where BP = aortic blood pressure.

Statistical analysis

Results are expressed as means with standard errors for continuous measurements, and frequencies for categorical variables. Linear regression analysis was performed to adjust coronary flow reserve measurements for the year after operation. Unpaired Student's *t*-tests were used to assess differences between group means. Statistical significance was assumed for P values < 0.05.

Results

The median time from operation for all cardiac transplant patients was 4.5 years (range 3 months to 10 years). Of the transplant recipients, 32 had originally undergone transplantation for ischaemic heart disease, and the remaining 29 patients for dilated cardiomyopathy. For the groups investigated, relevant patient information, haemodynamic measurements and other variables are shown in Tables 1 and 2. Patients with 'minor COD' were significantly further out from operation compared with normal transplant patients ($P = 0.007$). Several variables which could potentially be related to the development of coronary occlusive disease (Table 2), did not show any association with impaired coronary flow reserve. The mean age of the donor hearts was 26.5 years (SEM 1.5 years). The mean cold ischaemic time was 159 min (range 77–260 min). The donors for 16 (26%) patients were female and for the remaining 45 were male.

Normal coronary angiograms were found for 38 cardiac transplant patients, and 23 transplant patients had minor lesions in epicardial vessels. The mean percentage diameter of the most severe lesion in the coronary tree was 23% SD 3% including 12 lesions in the left anterior descending coronary artery itself (mean 24% SD 4%). Nine of these patients had minor coronary disease in one

Table 3. Coronary flow measurements

	CFR	CVRI	RFV	PFV
'Minor' COD	2.5 (0.2)	0.42 (0.04)	6.8 (1.1)	16.5 (2.5)
COD	3.9 (0.2)	0.26 (0.02)	7.1 (0.6)	27.3 (2.6)

Values in parentheses are SEM
CFR, coronary flow reserve; RFV, resting flow velocity (cm/s); PFV, peak flow velocity (cm/s); SEM, standard error of the mean; CVRI, coronary vascular resistance index; COD, coronary occlusive disease

primary or secondary vessel, four patients had disease in two vessels, while the remainder had disease in three or more coronary arteries.

Coronary flow reserve measurements

Adjusting for year from operation, patients with minor COD had a significantly impaired coronary flow reserve and a higher coronary vascular resistance index ($P < 0.0001$) (Table 3). The mean resting coronary blood flow was similar in both groups. Mean peak flow velocity was also impaired compared with normals ($P = 0.007$). There was overall dilation by + 18% (SD 6%) of the left anterior descending coronary artery in both groups in response to papaverine. Reproducibility of the arterial diameter measurements was acceptable with minimal inter-observer ($r = 0.91$) and intra-observer variation ($r = 0.95$).

Discussion

This study demonstrates a reduction in coronary flow reserve and maximum hyperaemic coronary blood flow in cardiac transplant patients with minor proximal coronary occlusive disease. The degree of stenosis in the left anterior descending coronary artery was relatively minor, and affected this vessel in only 52% (12/23) of cases. In addition there were no differences between the groups in the degree of vasodilation produced by papaverine in the proximal left anterior descending coronary artery. This suggests that the dilatory dysfunction occurs in the coronary resistance vessels in these patients.

This reduction in coronary flow reserve and maximum hyperaemic coronary flow could be explained by progressive occlusion of resistance vessels [12]. Occlusion of small tertiary (branches of primary and secondary coronary vessels) coronary branches is commonly seen at postmortem [2], but would have to be extremely widespread to have such a large effect on its own. Aspects of the function of resistance vessel vascular smooth muscle may also be damaged during the development of coronary occlusive disease. Both these factors may operate.

Other alternative explanations for impairment of coronary flow reserve and peak coronary flow in the group with coronary occlusive disease need to be excluded. There were no obvious significant differences in heart rate, myocardial contractility or ventricular dilatation, elevated left ventricular end-diastolic pressure or in haematocrit levels between the three groups. It is known that left ventricular hypertrophy, ventricular wall motion abnormalities and collateral vessels can produce abnormal flow reserve measurements [6]. None of the patients had these features.

Functional assessment of the coronary vasculature in patients with coronary occlusive disease is attractive. However, the clinical importance of these reductions in coronary flow reserve and peak hyperaemic response in individual cardiac transplant patients is unknown. Longitudinal studies are underway to evaluate the relevance of these findings.

Conclusion

Coronary flow reserve and hyperaemic response to the non-endothelial-dependent vasodilator papaverine is significantly impaired in heart transplant recipients when 'minor' coronary occlusive disease is present on coronary angiography. Dysfunction of the coronary microcirculation may contribute to the significant late morbidity and mortality produced by the disease. This may probe an important method of evaluating coronary occlusive disease in patients following cardiac transplantation.

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