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Coronary flow reserve is impaired early after cardiac transplantation

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Abstract. The highest mortality rate after cardiac transplantation, at present, occurs within the first year after cardiac transplantation. The state of the coronary microcirculation soon after cardiac transplantation has not been previously assessed. We investigated the hypothesis that coronary flow reserve (CFR) is impaired in the early postoperative period after cardiac transplantation. A 3F intracoronary Doppler flow probe was inserted into the left anterior descending coronary artery and maximal coronary flow was assessed using the non-endothelial-dependent vasodilator papaverine. We compared two groups of patients: group A – 13 patients studied 3 months after operation; and group B – 25 patients studied at a median of 4 years after operation (range 2–8 years) without coronary occlusive disease (COD). CFR was defined as the quotient of maximum hyperaemic to resting velocity (vel). CFR was markedly impaired in group A patients compared with group B (3.3 SEM 0.3 versus 4.2 SEM 0.2, $P < 0.01$). No significant differences between mean resting or peak velocities, original diagnosis, age, active rejection, blood pressure, lipid levels, ischaemic time, cyclosporin levels or cytomegalovirus (CMV) status were noted. Responses to papaverine in resistance coronary vessels are impaired in the early postoperative period after cardiac transplantation. This is caused by a combination of higher resting flow and lower peak flow in the early group. This impairment of function in the coronary microcirculation may contribute to early graft dysfunction and reflect changes in vascular smooth muscle function leading to the development of COD.

Key words: Cardiac transplant – Coronary microcirculation – Impairment of endothelial vasodilation

Cardiac transplantation is established as standard therapy for end-stage heart failure [11]. The main causes of death within the first year are infection and rejection [11]. These conditions may be accompanied by deterioration in cardiac graft function by mechanisms which are poorly understood. The main cause of late graft failure is COD [11]. This disease is diffuse and often affects smaller coronary vessels in contrast to conventional atherosclerosis [6]. The pathophysiology of COD is still unclear [19].

The coronary microcirculation is an important determinant of the ability of the heart to respond appropriately to physiological stimuli such as exercise, and ischaemia [3, 8]. In the absence of significant epicardial coronary arterial stenoses the ability of the coronary microcirculation to conduct hyperaemic blood flow can be assessed [7]. Experimentally, the ability of the coronary vascular bed to vasodilate in response to pharmacological stimuli, such as papaverine, at a constant perfusion pressure can be measured in humans. The use of small-diameter (3 French) intracoronary Doppler flow catheters allows subselective estimations of coronary blood velocity in individual coronary vessels [8, 24]. This is a simple, reproducible method for evaluating coronary flow reserve [23]. This method has been more extensively evaluated than any other technique currently employed [10].

Perioperative factors may damage the coronary arterial system and damage vascular smooth muscle in patients after cardiac transplantation. We investigated the hypothesis that coronary flow reserve using the non-endothelial-dependent vasodilator papaverine is impaired in patients soon after cardiac transplantation.

Methods

Patients

Studies were performed in a total of 38 cardiac transplant recipients; 33 males and 5 females (Table 1). The mean age of all patients was 46 years (range 21–60 years). Of the 38 patients, 20 had originally undergone transplantation for ischaemic heart disease, and the remainder for dilated cardiomyopathy. Group A (13 patients) was

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Table 1. Patient details

	Group A (n = 13)	Group B (n = 25)
Age	52 (range 43–60 years)	45 (range 21–59 years)
Sex	All Male	Male – 20; female – 5
Original diagnosis	IHD – 7; DCM – 6	IHD – 13; DCM – 12
Heart rate	90 (19)	84 (17)
BP	95 (6)	96 (3)
LVEDP	8 (4)	7 (2)
Ischaemic time	160 (50)	154 (43)
Cyclosporin level	504 (351)	259 (150)
HDL cholesterol	1.1 (0.6)	1.0 (0.3)
LDL cholesterol	4.8 (1.2)	4.4 (0.2)
Triglycerides	2.5 (1.3)	1.9 (0.9)
CMV + or mismatch	10	19

All values + standard deviation where appropriate
IHD, ischaemic heart disease; DCM, dilated cardiomyopathy; LVEDP, left ventricular end-diastolic pressure; BP, mean systemic pressure; CMV, cytomegalovirus

assessed 3 months after transplantation. Group B (the remaining patients) consisted of cardiac transplant recipients without evidence of coronary occlusive disease on coronary angiography at a median of 4 years postoperatively (range 2–8 years).

Immunosuppressive regime and drug therapy

In group B, 14 patients were receiving double therapy, i.e. cyclosporin and azathioprine or steroids. The remaining group B patients and all group A transplant recipients received triple immunosuppressive therapy (cyclosporin, azathioprine and steroid therapy). None of the patients received β-antagonist therapy or premedication. All vasoactive medication (e.g. calcium antagonists) was omitted 24 h prior to the procedure.

Biopsy protocol

All 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 cellular rejection [1] and evidence of vascular rejection.

Blood analysis

Routine analysis was performed for full blood count, urea and electrolytes, liver function tests, fasting lipids (total cholesterol, HDL and LDL cholesterol) and trough whole-blood cyclosporin level on the day of study.

Catheterization protocol

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 radio-opaque 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 least 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). A temporary pacing wire was inserted into the apex of the right ventricle, and the pacing rate set at five beats per minute below the resting value for each patient.

Baseline resting and phasic coronary blood flow velocity were taken in each patient. After an initial intracoronary 2 mg test dose of papaverine hydrochloride administerd via the guiding catheter, further injections of up to 14 mg 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 the various drugs. CFR was defined as the ratio of the peak flow velocity (PFV) achieved with papaverine compared to the resting blood flow velocity (RVF).

Coronary angiography

Each coronary angiogram was assessed by two independent observers blinded to the clinical history. 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). This method has previously been used in studies examining both coronary occlusive disease progression [17] and coronary flow reserve [9]. Two views were taken and projected onto a sheet of paper using a Tagarno system. The arterial diameter was measured in the left anterior descending coronary artery from tracings of the projected image, at a distance of 2–3 mm from the tip of the Doppler flow probe. The diameters were calculated using the mean of the measurements of these two views. Left ventricular angiography was performed at the end of the study.

Statistical analysis

Results are expressed as means with standard deviations for continuous measurements, and frequencies for categorical variables. The means of the two groups were compared pairwise using the Student's t-test. Statistical validity was accepted for P values < 0.05.

Ethical committee approval

This study was approved by the Huntingdon District Health Authority Ethical Committee.

Results

CFR was impaired in group A patients compared with group B (Table 2) – 3.3 SEM 0.3 versus 4.2 SEM 0.2 ($P = 0.01$). There was an overall increase in both groups in the percentage of LAD diameter compared with baseline (group A – + 20% SD 8%; group B – + 14% SD 4%). The heart rate in group A was higher than group B, but this did not reach statistical significance (Table 1). There was no important difference in mean systemic pressure between the two groups for each drug or drug combination. Other clinical variables did not differ between the two groups either (Table 1). Acute cellular rejection was present in two patients in group A and three Group B patients dur-

Table 2. Coronary blood flow

	CFR	Resting velocity (cm/s)	Peak velocity (cm/s)
Group A $n = 13$	3.3 (0.3)	8.0 (1.0)	25.3 (3.7)
Group B $n = 25$	4.2 (0.2)	6.6 (0.7)	28.3 (3.6)

Values (SEM)
CFR, coronary flow reserve

ing the study. The coronary flow reserve of these patients was 3.2 (SD 1.7) similar to the group A mean value (3.3 SD 1.0). There was no evidence of vascular rejection in any of the patients in either group.

Discussion

This study demonstrates that impairment of coronary flow response to papaverine occurs in patients soon after cardiac transplantation. Since there were no significant differences in proximal coronary arterial diameter between groups after papaverine, these responses must be mediated by differences in coronary microvascular function. Cardiac mortality occurs, at present, predominantly within the first 90 days after cardiac transplantation from infection and rejection [11, 20]. It is possible that this high attrition rate is related in part to coronary vascular dysfunction during this period.

Papaverine is a non-specific vasodilator which acts principally on resistance rather than proximal coronary vessels [25]. This is confirmed by the fact that there were no significant differences in LAD diameter after the drug in the two groups studied here. The causes of abnormal vasodilator response may include donor-related sympathetic endothelial coronary arterial damage [18] followed by smooth muscle responses, cold perfusion injury [21], vascular rejection [2], conventional atherosclerosis risk factors [26] or a combination of these. Experimentally, vascular endothelial damage initially leads to platelet deposition and vasoconstriction [5]. Vascular smooth muscle migration, proliferation and hypertrophy occur within days and persist for several weeks [22]. If the endothelial injury is severe, smooth muscle proliferation continues. Abnormal vasodilatory response to intracoronary nitroglycerine has previously been reported in proximal coronary vessels early after cardiac transplantation [12]. We have demonstrated that the coronary microcirculation non-endothelial function is abnormal soon after cardiac transplantation. Any change in coronary flow reserve in the early group of patients at increasing times from operation are unclear at present.

It is notable that the patients with angiographically normal coronary arteries at least 2 years after operation had a CFR consistent with previously published results in conventional and transplant patients [13]. In these patients, it is likely that any early vascular vasodilatory dysfunction initially improves, except in those patients who subsequently develop coronary occlusive disease [14]. Longitudinal studies are underway at present to evaluate this. The only established treatment of for end-stage coronary occlusive disease at present is cardiac retransplantation [15]. Unfortunately the mortality rates are higher than in first-time cardiac transplant recipients, and there may be a higher recurrence rate of coronary disease. The use of angioplasty for treatment of proximal coronary stenoses in patients with coronary occlusive disease is of some benefit in the short term [16], but longer-term results are not available. Coronary artery bypass grafting has been attempted in a limited number of cases [4]. The diffuse and distal disease limits widespread application of this method of revascularization. This lack of effective treatment for coronary occlusive disease indicates that a better understanding of the pathophysiology of the disease is important. These results suggest that efforts to reduce coronary artery damage at the time of cardiac implantation, and to prevent vascular smooth muscle dysfunction could reduce the high early mortality in cardiac transplant recipients and retard or prevent the development of coronary occlusive disease.

Conclusion

Coronary flow reserve is impaired in patients soon after cardiac transplantation. Non-endothelial-dependent vasodilatory dysfunction occurs in the coronary microcirculation soon after cardiac transplantation. This may contribute to the early mortality in cardiac transplant recipients and be related to the development of coronary occlusive disease.

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