

Exercise response after cardiac transplantation: correlation with sympathetic reinnervation

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Abstract

Objective—To investigate the relation between sympathetic efferent reinnervation and chronotropic competence during exercise testing after cardiac transplantation.

Patients—Twenty five long-term cardiac transplant recipients and 11 normal controls.

Setting—Regional cardiothoracic centre.

Methods—Intracoronary tyramine was given to the transplant recipients and the per cent heart rate change measured. Exercise tests were performed in patients and controls according to the chronotropic assessment exercise protocol, and the per cent heart rate reserve measured at peak exercise and 6 min afterwards to estimate the recovery rate.

Results—The mean (SD) percentage heart rate change after intracoronary tyramine was 15.7 (15.4). Heart rate reserve achieved at peak exercise was 68.3 (20.6)% compared with 102.7 (9.3)% in the controls ($P < 0.001$). Heart rate recovery at 6 min was 41.7 (20.1)% compared with 79.5 (9.0)% in the controls ($P < 0.001$). Total workload was 69.0 (33.0) METS.min compared with 117.2 (41.9) METS.min in the controls ($P < 0.01$). There was a positive correlation between heart rate reserve achieved at peak exercise and response to tyramine ($r = 0.66$, $P < 0.01$), between heart rate recovery and response to tyramine ($r = 0.69$, $P < 0.001$), and between total workload and response to tyramine ($r = 0.63$, $P = 0.04$).

Conclusion—Functional sympathetic efferent reinnervation of the sinus node occurred in some patients after transplantation, and was associated with improved heart rate response during and recovery after exercise, as well as with increased total workload.

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Keywords: sinus node reinnervation; exercise response; cardiac transplantation; tyramine

A combination of abnormal haemodynamic responses results from cardiac transplantation.¹ Cardiac denervation occurs during surgery and thus reflexes dependent on nerves will be absent after transplantation. If reinnervation occurs, then any return to normality

depends on its extent and pattern as well as its timescale. In addition, transplant recipients are recovering from moderate to severe cardiac failure, and some of the associated chronic cardiovascular abnormalities may recover independently of reinnervation.²

Chronotropic response to exercise is abnormal after transplantation and may return towards normal with time.^{3,4} We and others have suggested recently that an improved chronotropic response may be related to sympathetic efferent reinnervation.^{5,6} Exercise capacity is an important component of quality of life, and may be related to sinus node reinnervation and improved cardiac sensory innervation in transplant recipients. This study investigated the correlation of heart rate increase during exercise with sinus node efferent reinnervation measured by heart rate response to intracoronary tyramine.

Patients and methods

PATIENTS

Twenty five orthotopic cardiac transplant recipients (23 male; mean age 45.6 years) were recruited at the time of routine surveillance coronary angiography at more than 22 months after transplantation (mean (range) 40 (22-96) months). All were in sinus rhythm and none had a permanent pacemaker or overt sinus node dysfunction. Eleven normal controls (nine male; mean age 46.3 years) not taking medication were also recruited. They did not undergo angiography.

Approval was obtained from the Newcastle Health Authority Ethical Committee and prior informed consent was obtained from all participants. All cardioactive drugs including calcium channel blockers were stopped at least 36 h before the study started. Immunosuppression including cyclosporin, azathioprine, and prednisolone was continued throughout. Patients with rejection graded histologically greater than ISHLT-II (International Society for Heart and Lung Transplantation), known impairment of cardiac function, peripheral vascular disease or limiting arthropathy, or diseases potentially causing autonomic neuropathy, including diabetes and significant renal impairment, were excluded.

SINUS NODE FUNCTION

At cardiac catheterisation an electrode was positioned in the donor right atrium in 16 of the transplant recipients under fluoroscopic

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control and corrected sinus node recovery time was measured using standard pacing techniques.⁷

TYRAMINE TESTING

Tyramine was injected into the artery supplying the sinus node following the protocol of Wilson *et al.*⁸ Some 4 µg/kg of tyramine were injected into the right coronary artery and 8 µg/kg into the left when that artery supplied the sinus node, and the catheter immediately flushed. Donor electrocardiograms (ECGs) were recorded from the surface ECG at a paper speed of 100 mm/s for at least 2 min after injection. Consecutive RR intervals were measured manually in milliseconds.

Resting cycle length was averaged over the 10 beats before injection. Maximum and minimum cycle lengths were measured during the 2 min after injection and expressed as a percentage of resting cycle length. As the effect of tyramine may be observed for up to 7 min after initial injection,⁸ the initial decline in cycle length was modelled using a negative exponential function to predict minimum cycle length. These predictions did not differ significantly from observed minimum cycle length, and thus minimum cycle length was used in the subsequent analysis.

EXERCISE TESTING

Exercise tests were performed on a treadmill on a separate day according to the chronotropic assessment exercise protocol.⁹ Heart rate was derived from ECG traces recorded at 50 mm/s at the end of each stage of the protocol and for 10 min after peak exercise. Data were analysed using the concept of heart rate reserve,⁹ which takes into account resting heart rate as well as age predicted maximum heart rate.

Heart rate reserve (HRR) was calculated using the formula:

$$\text{HRR} = \frac{(\text{Heart rate at peak exercise} - \text{resting heart rate})}{(\text{Age predicted maximum heart rate} - \text{resting heart rate})}$$

Recovery after peak exercise was calculated using the formula:

$$6 \text{ min recovery} = \frac{(\text{Heart rate at peak exercise} - \text{heart rate 6 min later})}{(\text{Age predicted maximum heart rate} - \text{resting heart rate})}$$

where age predicted maximum heart rate is 220—recipient age in years.

STATISTICAL ANALYSIS

Mean chronotropic response to exercise

workload, and response to tyramine were compared using Student *t* test. Relation between response to tyramine and exercise variables were quantified using linear regression analysis.

Results

No transplant recipient had significant angiographic coronary artery disease and none had impairment of left ventricular function.

SINUS NODE FUNCTION

Sinus node function was normal in the 16 transplant recipients in whom it was tested (corrected sinus node recovery time < 525 ms).

RESPONSE TO INTRACORONARY TYRAMINE

Heart rate increased after intracoronary injection of tyramine by 15.7% (range 1–55%). In all but one patient heart rate reached a maximum and decreased 2 min after injection. Heart rate increased by more than 25% in only eight patients.

RESPONSE TO EXERCISE TESTING

The table summarises the results of exercise testing. Four transplant recipients said that the main reason for stopping was leg pain, and they were excluded from the analyses because their limitation was not fatigue. All others were limited by fatigue or dyspnoea. None experienced chest pain. Exercise time and total workload were reduced in transplant recipients compared with that in the controls. Mean (range) peak HRR achieved was 68.3% (27–115%) in the transplant recipients and 102.7% (86–113%) in the controls. Heart rate recovery at 6 min was reduced in the transplant recipients (mean (SD) 41.7 (20.1)%) compared with that in the controls (mean (SD) 79.5 (9.0)%) (*P* < 0.001). There was no relation between time after transplantation and exercise workload, heart rate at peak exercise, or heart rate recovery. HRR achieved at peak exercise was above 70% in 10 transplant recipients and in all controls.

RELATION BETWEEN CHRONOTROPIC RESPONSE TO EXERCISE AND TO TYRAMINE

Heart rate change after tyramine was related to HRR achieved at peak exercise (*r* = 0.66, *P* < 0.01, fig 1) and HRR recovered at 6 min (*r* = 0.69, *P* < 0.001, fig 1). It was also related to total workload (*r* = 0.63,

Exercise variables of controls, all transplant recipients, and those with a heart rate (HR) increase of > 25% in response to intracoronary tyramine.

	No	Recipient age (years)	Donor age (years)	Time after transplantation (months)	Exercise at peak time (min)	HRR at peak exercise (%)	HRR recovered at 6 min (%)	Total workload (METs.min)
Normal controls	11	46.3			17.2 (2.7)	102.7 (9.3)	79.5 (9.0)	117.2 (41.9)
All transplant recipients	25	45.6	31.1	40	13.1 (3.4)†	68.3 (20.6)†	41.7 (20.1)†	69.0 (33.0)†
Transplant recipients with > 25% increase in HR after tyramine	8	44	29	48	14.7 (3.2)†	85.6*	62.2*† (19.5)	85.4 (40.2)

Results are means (SD). **P* < 0.01 compared with all transplant recipients. †*P* < 0.01 compared with controls. HRR, heart rate reserve; METS, metabolic equivalents.

Figure 1 Relation between (A) response to tyramine and peak heart rate reserve and between (B) response to tyramine and heart rate reserve recovered at 6 min after peak exercise. Patients who stopped exercise because of leg pain are represented as open squares and are omitted from the analysis.

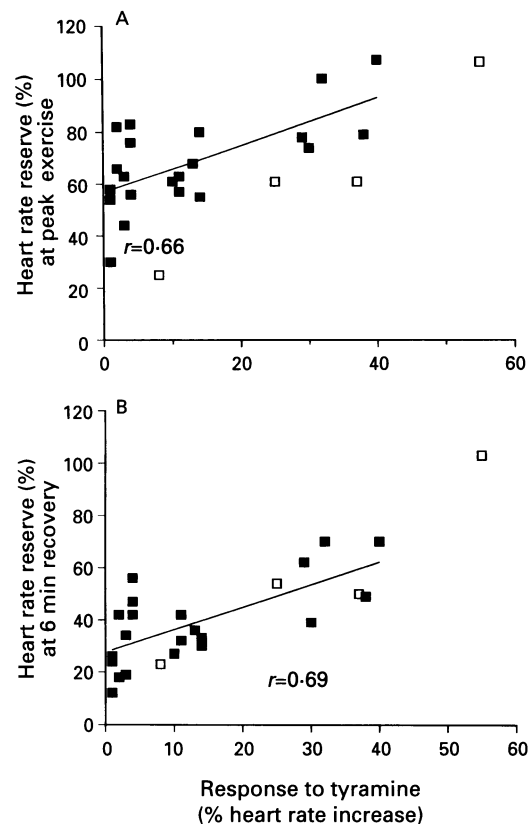
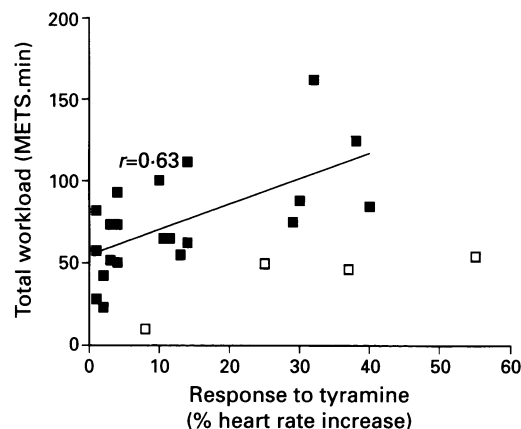


Figure 2 Relation between response to tyramine and total workload during exercise. Patients who stopped exercise because of leg pain are represented as open squares and are omitted from the analysis.



$P = 0.04$, fig 2). Peak heart rate and heart rate recovery at 6 min were significantly greater in the eight patients in whom heart rate response to tyramine was more than 25%, but were still reduced compared with that in controls.

Discussion

This study demonstrates that the improved chronotropic response to exercise observed in some cardiac transplant recipients is associated with sympathetic efferent reinnervation to the sinus node.

IMPAIRED EXERCISE TOLERANCE AFTER TRANSPLANTATION

Chronotropic response to exercise is impaired during the first year after transplantation.¹⁰ This may be the result of cardiac denervation, but also to the effects of a major operation, to rejection, or continuing cardiac functional

impairment of other cause. Sinus node function may also be impaired independently of denervation, and such dysfunction could affect chronotropic competence. We minimised this possibility by selecting patients without overt sinus node dysfunction and by demonstrating normal sinus node function in the first 16 patients. In a previous study¹¹ 33 cardiac transplant recipients without overt sinus node dysfunction had normal sinus node function tests, suggesting that covert sinus node dysfunction is rare, and we therefore decided to omit further sinus node function testing to minimise procedure time and patient discomfort.

We have previously studied the return of chronotropic competence in transplant recipients during the first 6 months after transplantation⁵ and demonstrated recovery of chronotropic competence in five of 31 patients. Some of this improvement occurred between 3 and 6 months after transplantation and was not explained by recovery of sinus node function, rejection, or changes in cardiac function. This further study demonstrates that this observation is likely to be due to sympathetic reinnervation.

In recipients studied 6 weeks after transplantation, peak heart rate is reduced and delayed until after peak exercise, and recovery is slower. This phenomenon has been ascribed to dependence on circulating catecholamines,¹⁰ and so improvements in heart rate response to exercise and recovery after exercise can be seen as measurements of sinus node reinnervation. Several studies^{3 6 10} have demonstrated increased heart rate at maximum exercise in patients late after cardiac transplantation compared with that in different groups studied during the first post-transplant year.

Absolute heart rate rise during exercise could be reduced in cardiac transplant recipients because of higher resting heart rate. HRR takes this difference into account, and therefore the reduction in HRR achieved in transplant recipients during exercise must have another cause. As circulating catecholamine concentrations increase normally or supranormally during exercise in transplant recipients,¹⁰ and β adrenergic receptor sensitivity is increased,¹² the shortfall in HRR achieved may be ascribed to efferent sympathetic denervation, and its subsequent improvement could therefore be due to reinnervation.

REINNERVATION

Cardiac reinnervation has been conclusively demonstrated in dogs and other animals during the first year after transplantation.^{13 14} While there are considerable differences in cardiac innervation between dogs and humans, there is no reason to suppose that reinnervation cannot occur in humans. Regrowth of nerves across the aortic anastomosis in humans has been demonstrated within the first year after transplantation using microscopy.¹⁵ Myocardial catecholamine content has been assessed at cardiac biopsy and found to be low soon after transplantation,

and subsequently to increase, although the levels remain subnormal.¹⁶ Uptake of metaiodobenzylguanidine by sympathetic nerve terminals is low soon after transplantation, but increases from the base of the heart with time.¹⁷ Kaye *et al*⁴ have demonstrated that resting cardiac noradrenaline spillover is reduced early after transplantation, but is comparable with that in normal controls more than 2 years after transplantation. However, noradrenaline spillover in response to exercise was reduced in both early and late transplant recipients. They concluded that sympathetic efferent reinnervation occurs and is incomplete even at several years after transplantation.

RESPONSE TO TYRAMINE

Because of uptake by other nerve terminals only 10–20% of noradrenaline released at sympathetic terminals is measurable in the bloodstream,¹⁸ and so the measurement of noradrenaline gradients alone is of uncertain value. Thus the chronotropic response to tyramine may be regarded as a more reliable measure of sympathetic reinnervation, if only of the sinus node. Wilson *et al*¹⁹ demonstrated cardiac acceleration of more than five beats/min in 32 of 45 patients in response to intracoronary tyramine and that tyramine given to the artery not supplying the sinus node does not cause cardiac acceleration. Thus, if tyramine measures *functional* reinnervation then a correlation with peak heart rate and with rate of recovery after exercise would be expected. The fact that we have demonstrated a similar relation between total workload and response to tyramine suggests that intact sinus node innervation is important in determining exercise capacity by improved chronotropic competence.

CONCLUSIONS

This study has demonstrated that chronotropic competence and response to intracoronary tyramine vary widely among transplant recipients at more than 2 years after transplantation. While both techniques measure the changing physiological responses after transplantation, the fact that there is a significant correlation between them suggests that they are both related to sympathetic efferent sinus node reinnervation. Further-

more, in those patients in whom sinus node reinnervation was demonstrated using tyramine, exercise time and total workload were increased. This is the first demonstration that sympathetic reinnervation has clinical consequences.

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