Isometric exercise in the denervated heart: a Doppler echocardiographic study

S C ROBSON, S S FURNISS, A HEADS, R J BOYS,* C MCGREGOR,† R S BEXTON

From the Departments of Cardiology and †Cardiothoracic Surgery, Freeman Hospital, and *University Department of Statistics, Newcastle upon Tyne

SUMMARY The haemodynamic responses to isometric exercise of eight recipients of orthotopic heart transplants and eight healthy controls were studied. Each performed sustained exercise at 30% of maximal voluntary contraction for three minutes on a handgrip dynamometer. Cardiac output was measured by combined Doppler and cross sectional echocardiography before exercise and every 30 seconds during and after exercise. In the controls cardiac output and blood pressure increased significantly owing to an increase in heart rate with no change in stroke volume. In the transplant group cardiac output, heart rate, and stroke volume remained unchanged throughout exercise.

In contrast with its response to dynamic exercise the denervated human heart is unable to increase cardiac output during isometric exercise. The pressor response that occurs is mediated via an increase in peripheral vascular resistance.

Although reinnervation of the transplanted heart has been well documented after orthotopic transplantation of the canine heart,¹ the transplanted human heart seems to remain both functionally and anatomically denervated indefinitely.² Studies in normally innervated human hearts have shown that isometric exercise results in significant increases in cardiac output, heart rate, and mean blood pressure without changes in stroke volume, ventricular dimensions, or myocardial contractility.³⁻⁵ Although the transplanted denervated heart is able to maintain a relatively normal cardiac output during dynamic exercise⁶⁻⁸ through the Frank-Starling mechanism, it is difficult to envisage how it can produce an appropriate increase in cardiac output during semi-supine static exercise.

Cardiac output can be calculated from blood velocity in the ascending aorta, measured by Doppler ultrasound, combined with aortic orifice area, measured by cross sectional echocardiography.^{9,10} The technique is reproducible^{11,12} and allows quick, non-invasive measurements of cardiac output both at rest and during supine and upright exercise.¹³⁻¹⁵ Left ventricular size and performance can be accurately

measured by M mode echocardiography.^{16,17} We used these techniques to investigate the haemodynamic changes during handgrip isometric exercise in recipients of orthotopic heart transplants and in controls.

Patients and methods

Eight recipients of orthotopic heart transplants (six men) were recruited. The details of the group were as follows: mean (SD) age 40 (10) years, mean (SD) height 1.71 (0.08) m, mean (SD) weight 64.8 (9.5) kg. All patients were clinically and functionally well with no clinically significant biochemical or haematological abnormality at the time of the study. Mean haemoglobin was 12.3 g/l and mean creatinine clearance was 58 ml/min. The mean length of survival after transplantation was 11 (range 5-21) months and all patients were receiving standard immunosuppressive treatment (prednisolone, azathioprine, and cyclosporin). In all cases a recent cardiac biopsy specimen had shown no evidence of rejection. We also studied eight normal healthy volunteers (seven men), who were age and sex matched to the heart donors (mean age 25 (6) years, mean height 1.76 (0.08) m, mean weight 68.0 (8.8) kg).

All those studied were known to be good echocardiographic subjects. The experimental protocol was approved by the ethical committee of Newcastle Health Authority. The procedure was explained to

Requests for reprints to Dr S S Furniss, Regional Cardiothoracic Centre, Freeman Hospital, Newcastle upon Tyne NE7 7DN.

Accepted for publication 29 November 1988

Isometric exercise in the denervated heart: a Doppler echocardiographic study

each person and their informed consent was obtained.

Investigations were performed in a warm quiet room with the subjects in the semisupine position after they had rested for 10 minutes. Basal measurements were recorded on two occasions, five minutes apart, and the mean value was taken as the baseline. They performed isometric exercise on a Harpenden handgrip dynamometer (British Indicators). Participants were asked to exert the maximal compressive force with their dominant hand on three occasions to determine maximal voluntary contraction. After a further 10 minutes' rest they were asked to perform isometric exercise at 30% of their maximal voluntary contraction for three minutes. Investigations were repeated after 30, 60, 90, 120, and 180 seconds of exercise and then 1, 3, 5, and 10 minutes after exercise. The participants were carefully observed to ensure that none of them performed the Valsalva manoeuvre during the exercise period.

The Doppler principle and the assumptions of the Doppler method for calculation of cardiac output have been described elsewhere.¹⁸ Aortic velocities were recorded by a 1.9 MHz independent continuous wave Doppler transducer (Hewlett-Packard 77020A). Cross sectional and M mode echocardiograms were recorded by a 3.5 MHz transducer (ATL Mark 4). Doppler velocities and M mode echocardiograms were recorded, along with an electrocardiogram, on a strip chart at a paper speed of 100 mm/s. Blood pressure was measured from the non-exercising arm by an automatic sphygmomanometer (Dynamap).

Blood velocity in the ascending aorta was recorded from the suprasternal notch by continuous wave Doppler. The direction of the ultrasound beam was adjusted until the highest velocities with the "cleanest" envelope were obtained and then 10–15 cardiac cycles were recorded. These velocities were taken to represent velocities at the aortic orifice with the ultrasound beam parallel with flow. The area under the velocity curve or velocity integral (VI) was determined by tracing from the baseline around the maximum velocity curve with a digitising tablet linked to a microcomputer.¹⁹ Eight to 10 beats were averaged for each determination.

The aortic diameter was measured from cross sectional echocardiograms recorded on videotape. The orifice diameter was measured during systole from the parasternal long axis plane by the leading edge to leading edge method. The diameters from five consecutive beats were averaged and the cross sectional area (CSA) was calculated from the equation $\pi \times (D/2)^2$ where D = mean aortic diameter. Simultaneous cross sectional and Doppler echocar-

diographic recordings were made at each time point. Heart rate (HR) was determined directly from the RR interval of the simultaneously recorded electrocardiograph. Stroke volume (SV) and cardiac output (CO) were calculated as follows:

$$SV (ml) = VI (cm) \times CSA (cm^2)$$

$$CO (l/min) = SV (ml) \times HR (min^{-1}) \div 1000.$$

Standard left ventricular M mode echocardiograms were recorded from the parasternal long axis plane.²⁰ Left ventricular end diastolic dimension (EDD) and end systolic dimension (ESD) were obtained from the tracings according to the recommendations of the joint International Society and Federation of Cardiology/World Health Organisation task force.²¹ Four consecutive beats were averaged for each measurement. Two indices of left ventricular function were calculated from the mean left ventricular measurements. Ejection fraction (EF) was calculated by the following formula²²:

$$EF (\%) = [(EDD)^3 - (ESD)^3] \div (EDD)^3$$

The mean velocity of circumferential fibre shortening (mean Vcf) was calculated from the following formula²³:

$$\text{Mean Vcf (diameters/s)} = (EDD - ESD) \div (\text{ejection time} \times EDD)$$

The left ventricular ejection time was determined from the aortic velocity trace.

STATISTICAL ANALYSIS

A repeated measures analysis of variance was performed for each variable with the *Biomedical Programs Statistical Package* (BMDP). The total variance consists of a component to take account of differences between the subjects (σ_s^2) and a component for differences within subjects (σ_w^2). The within subject variance is made up of a component for differences between time points (σ_T^2) and a component representing the residual variability (σ_R^2).

To make allowance for the problem of multiple significance testing, the differences between time points within the transplant and control groups were compared by means of the studentised range at the 1% level²⁴ (studentised range = $q(v) \times [\sigma_R - \sqrt{n}]$, where $q(v)$ = critical value for comparing two time points, σ_R^2 = residual mean square with v degrees of freedom, and n = number of subjects). Thus any change greater than the studentised range was considered to be statistically significant. Comparisons between the transplant and control groups at each time were based on approximate 95% confidence intervals for each variable:

$$\text{Mean} \pm 2 \times \sqrt{[\sigma_s^2 + \sigma_R^2] \pm 8}.$$

Results

The mean (SD) value for 30% of the maximal voluntary contraction was 10.0 (1.6) kg in the transplant group and 14.2 (2.7) kg in the control group

($p < 0.002$). Two transplant recipients could only maintain 30% of their maximal voluntary contraction for approximately 150 s, so data after 180 s exercise was only available for six in this group. Satisfactory serial echocardiographic recordings

Fig 1 Changes in mean blood pressure (MBP), stroke volume (SV), heart rate (HR), and cardiac output (CO) during and after isometric exercise in heart transplant recipients (△) and controls (●). Values shown are means and 95% confidence intervals. The studentised ranges for the two groups are shown on the right (see text for explanation).

were obtained from all time points in the remainder. Figure 1 shows changes in mean blood pressure, heart rate, stroke volume, and cardiac output. Figure 2 shows changes in left ventricular end diastolic and end systolic dimensions, ejection fraction, and mean

rate of circumferential fibre shortening (mean Vcf).

CONTROL GROUP

Mean blood pressure increased from 94.8 mm Hg before exercise to 113.8 mm Hg at the end of

Fig 2 Changes in left ventricular end diastolic dimension (EDD), end systolic dimension (ESD), ejection fraction (EF), and mean rate of circumferential fibre shortening (mVcf) during and after isometric exercise in heart transplant recipients (Δ) and controls ($\bullet$). Values shown are means and 95% confidence intervals. The studentised ranges for the two groups are shown on the right (see text for explanation).

exercise, the increase being significant by 1.5 minutes of exercise. Blood pressure had returned to pre-exercise values within one minute of the end of exercise. Stroke volume before exercise was 87.0 ml and there was no change during exercise. One minute after the end of exercise, however, stroke volume increased to 98.4 ml and was still higher than pre-exercise values three minutes after the end of exercise. Mean heart rate before exercise was 70.0 beats/min and increased to 84.2 beats/min within 30 seconds of the start of exercise, reaching a maximum after three minutes' exercise (92.0 beats/min). Heart rate also returned to pre-exercise values within one minute of the end of exercise. Cardiac output increased from a mean of 6.05 l/min before exercise to a maximum of 8.07 l/min after three minutes' exercise, the increase being significant after one minute. Immediately after exercise stopped cardiac output fell to 6.80 l/min but this was still higher than before exercise, and basal values were not reached till three minutes after exercise.

The end diastolic left ventricular dimension was larger one minute after exercise (5.18 cm) than before exercise (4.93 cm) or after three minutes' exercise (5.02 cm). The end systolic dimension and ejection fraction did not change significantly during the study. Although mean velocity of circumferential fibre shortening increased during exercise from 1.23 diameters/second before exercise to 1.40 at three minutes, this primarily reflects the increase in heart rate. When mean velocity of circumferential fibre shortening was standardised for heart rate according to the formula of Mangiarotti *et al*²⁵ there was no longer a significant increase. Thus there was no evidence of a change in myocardial contractility, independent of heart rate, during isometric exercise in the control group.

TRANSPLANT GROUP

Mean blood pressure increased from 105.0 mm Hg before exercise to 120.6 mm Hg after three minutes of exercise, the increase being significant after one minute. Blood pressure returned to basal values within one minute of the end of exercise. As in the control group, stroke volume remained constant during exercise but increased one minute after it had stopped, from 69.3 ml at the end of exercise to 74.5 ml. Although stroke volume was consistently lower in the transplant group than in the controls this variable only reached significance at one and three minutes after exercise. The resting heart rate before exercise was 95.6 beats/min, which was significantly higher than the resting heart rate in the control group. There was no change in heart rate during or after exercise. The mean cardiac output before exercise (6.66 l/min) was not significantly different

from that found in the control group. In contrast with the controls, however, there was no change in cardiac output during exercise. One minute after the end of exercise cardiac output increased to 7.08 l/min but had returned to basal values by three minutes after the end of exercise.

The end diastolic dimension remained unchanged during the period of study. The end systolic dimension increased from 2.97 cm before exercise to 3.14 cm after 1.5 minutes of exercise. This increase was maintained until the end of exercise, returning to pre-exercise values by 1 minute after the end of exercise. The ejection phase indices showed a rather different pattern in the transplant recipients. Both ejection fraction and mean velocity of circumferential fibre shortening decreased during exercise. Analysis of the changes in individual subjects found four who showed a pronounced fall in both ejection phase indices; the remainder showed little change.

Discussion

The assessment of ventricular performance by Doppler echocardiography is now well established. It has been validated in both resting^{9,10} and exercising subjects.^{13,14} This study is the first to use this reliable, non-invasive, repeatable method to look at the response to isometric exercise of the denervated heart.

We showed that during sustained handgrip exercise in normal people there is a statistically significant increase in blood pressure, heart rate, and cardiac output. Left ventricular dimensions, stroke volume, and ejection fraction are unchanged and mean rate of circumferential fibre shortening when corrected for the increase in heart rate is also unchanged. The haemodynamic effects of isometric exercise in healthy adults by various techniques and our results accord with these studies.²⁶⁻²⁸

In controls the pronounced increase in blood pressure was primarily caused by an increase in cardiac output with no significant change in the calculated systemic vascular resistance. As we have shown, this increased cardiac output was predominantly the result of an increase in heart rate with no change in stroke volume. End diastolic volume and pressure, determinants of preload, and end systolic dimension (which is relatively preload independent) were unchanged. Despite the ventricular geometry remaining constant during the period of exercise, blood pressure increased.

In this study the transplant patients showed a normal pressor response but there were no significant changes in heart rate or cardiac output during exercise. End diastolic and end systolic dimensions and stroke volume were unchanged during the period

of exercise, as in the normal group. This is in marked contrast with the situation during dynamic exercise in such patients when, the initial response, at least, is caused by increased venous return and an increase in cardiac output via the Frank-Starling mechanism.⁷ The only other study to look at the response of denervated hearts to isometric exercise is by Savin *et al.*²⁹ They used an invasive technique and compared patients with denervated hearts with patients undergoing cardiac surgery rather than with healthy controls. Wire coils were implanted in the left ventricle at the operation and data were obtained by fluoroscopy only once before and once after sustained handgrip exercise. The responses of the innervated hearts in their study were at variance with most other studies and they concluded that in both innervated and denervated hearts the response to isometric exercise results from an increase in systemic vascular resistance.

During sustained handgrip exercise, if preload and heart rate are unchanged, the rapid near normal pressor response we have shown is likely to be the result of an increase in systemic vascular resistance. We suggest that during isometric exercise in transplant patients afferents from the exercising muscles are stimulated as in normal individuals and, although the heart is denervated and unable to respond directly, the efferent pathways to peripheral arterioles remain intact and respond to sympathetic stimulation. This leads to vasoconstriction and an increase in systemic vascular resistance and an increase in blood pressure.

The tendency of the mean velocity of circumferential fibre shortening and ejection fraction to fall during the period of exercise in the transplant patients was the result of a considerable reduction in four of the eight patients. This reduction in these four patients may reflect impaired left ventricular reserve and increasing difficulty in pumping against an increasing afterload. This reduction is also seen in normal people during very strenuous exercise and in patients with coronary artery disease.³⁰ This tendency of the rate of circumferential fibre shortening to fall in some patients requires further investigation.

References

- 1 Thames MD, Kontos HA, Lower RR. Sinus arrhythmia in dogs after cardiac transplantation. *Am J Cardiol* 1969;24:54-8.
- 2 Stinson EB, Griep RB, Schroeder JS, Dong E Jr, Shumway NE. Hemodynamic observations one and two years after cardiac transplantation in man. *Circulation* 1972;45:1183-94.
- 3 Stefadouros MA, Grossman W, El Shahawy M, Witham AC. The effect of isometric exercise on the left ventricular volume in normal man. *Circulation* 1974;49:1185-9.
- 4 Stefadouros MA, Grossman W, El Shahawy M, Stefadouros F, Witham AC. Noninvasive study of effect of isometric exercise on left ventricular performance in normal man. *Br Heart J* 1974;36:988-95.
- 5 Laird WP, Fixler DE, Huffines FD. Cardiovascular response to isometric exercise in normal adolescents. *Circulation* 1979;59:651-4.
- 6 Leacham RD, Leatherman LL, Rochelle DG, *et al.* Physiologic behavior of the transplanted heart in six human recipients. *Am J Cardiol* 1969;23:393-400.
- 7 Pope SE, Stinson EB, Daughters GT, Schroeder JS, Ingels NB Jr, Alderman EL. Exercise response of the denervated heart in long-term cardiac transplant recipients. *Am J Cardiol* 1980;46:213-8.
- 8 Bexton RS, Milne JR, Cory-Pearce R, English TAH, Camm AJ. Effect of beta blockade on exercise response after cardiac transplantation. *Br Heart J* 1983; 49:584-8.
- 9 Rose JS, Nanna M, Rahimtoola SH, Elkayam U, McKay C, Chandraratna PAN. Accuracy of determination of changes in cardiac output by transcutaneous continuous wave Doppler computer. *Am J Cardiol* 1984;54:1099-101.
- 10 Robson SC, Dunlop W, Moore M, Hunter S. Combined Doppler and echocardiographic measurement of cardiac output: theory and application in pregnancy. *Br J Obstet Gynaecol* 1987;94:1014-27.
- 11 Ihlen H, Endresen K, Myreng Y, Myhre E. Reproducibility of cardiac stroke volume estimated by Doppler echocardiography. *Am J Cardiol* 1987; 59:975-8.
- 12 Robson SC, Boys R, Hunter S. Doppler echocardiographic estimation of cardiac output: analysis of temporal variability. *Eur Heart J* 1988;9:313-8.
- 13 Daley PJ, Sagar KB, Collier BD, Kalbfleisch J, Wann LS. Detection of exercise induced changes in left ventricular performance by Doppler echocardiography. *Br Heart J* 1987;58:447-54.
- 14 Ihlen H, Endresen K, Golf S, Nitter-Hauge S. Cardiac stroke volume during exercise measured by Doppler echocardiography: comparison with the thermodilution technique and evaluation of reproducibility. *Br Heart J* 1987;58:455-9.
- 15 Daley PJ, Sagar KB, Wann LS. Doppler echocardiographic measurement of flow velocity in the ascending aorta during supine and upright exercise. *Br Heart J* 1985;54:562-7.
- 16 Murray JA, Johnston W, Reid JM. Echocardiographic determination of left ventricular dimensions, volumes and performances. *Am J Cardiol* 1972;30:252-7.
- 17 Feigenbaum H. Echocardiographic evaluation of the cardiac chambers. In: *Echocardiography*. 3rd ed. Philadelphia: Lea & Fabiger, 1981: 119-87.
- 18 Ascah KJ, Stewart WJ, Levine RA, Weyman AE. Doppler echocardiographic assessment of cardiac output. *Radiol Clin North Am* 1985;23:659-70.
- 19 Goldberg SJ, Allen HD, Marx GR, Flinn CJ. *Doppler echocardiography*. Philadelphia: Lea & Fabiger, 1985: 80.

- 20 Roelandt J. Instrumentation and examination techniques of M-mode and two-dimensional echocardiography. In: Roelandt J, ed. *The practice of M-mode and two-dimensional echocardiography*. The Hague: Martinus Nijhoff, 1983:17-50.
- 21 O'Rourke RA, Hanrath P, Henry WN, et al. Report of the Joint International Society and Federation of Cardiology/World Health Organization Task Force on recommendations for standardization of measurements from M-mode echocardiograms. *Circulation* 1984;**69**:854A-7A.
- 22 Pombo JF, Troy BL, Russell RO. Left ventricular volumes and ejection fraction by echocardiography. *Circulation* 1971;**43**:480-90.
- 23 Karliner JS, Gault JH, Eckberg D, Mullins CB, Ross J. Mean velocity of fibre shortening. A simplified measure of left ventricular myocardial contractility. *Circulation* 1971;**44**:323-33.
- 24 Pearson ES, Hartley HO. *Biometrika tables for statisticians, vol 1*. London: Cambridge University Press, 1966:52-5.
- 25 Mangiarotti R, Martinotti R, Monzani V, et al. Robson, Furniss, Heads, Boys, McGregor, Bexton. Influence of the heart rate on mean circumferential shortening velocity: echocardiographic study of 163 normal subjects. *Cardiology* 1986;**73**:347-53.
- 26 Martin CE, Shaver JA, Leon DF, Thompson MB, Reddy PS, Leonard JJ. Autonomic mechanisms in haemodynamic responses to isometric exercise. *J Clin Invest* 1974;**54**:104-15.
- 27 Helfant RH, deVilla MA, Meister SG. Effect of sustained isometric handgrip exercise on left ventricular performance. *Circulation* 1971;**44**:982-93.
- 28 Ehsani AA, Heath GW, Hagberg JA, Schschman K. Noninvasive assessment of changes in left ventricular function induced by graded isometric exercise in healthy subjects. *Chest* 1981;**80**:51-5.
- 29 Savin WM, Alderman EL, Haskell WL, et al. Left ventricular responses to isometric exercise in patients with denervated and innervated hearts. *Circulation* 1980;**61**:897-901.
- 30 Grossman W, McLaurin LP, Saltz SB, Paraskos JA, Dalen JE, Dexter L. Changes in the inotropic state of the left ventricle during isometric exercise. *Br Heart J* 1973;**35**:697-704.