Hemodynamic Observations One and Two Years after Cardiac Transplantation in Man

By Edward B. Stinson, M.D., Randall B. Griep, M.D., John S. Schroeder, M.D., Eugene Dong, Jr., M.D., and Norman E. Shumway, M.D.

SUMMARY
Cardiac catheterization studies were performed in eight patients 1 year after cardiac transplantation and in two of these again at 2 years. Intracardiac pressures at rest were normal in all patients, both 1 and 2 years postoperatively. Average cardiac index at rest at 1 year was 2.3 liters/min/m² and average heart rate was 90 beats/min. Responses to amyl nitrite, atropine, and tyramine failed to demonstrate efferent autonomic reinervation of the donor hearts. Findings associated with a 10-min period of submaximal supine bicycle exercise 1 year after transplantation included: (1) a gradual rise in heart rate throughout most of the exercise period; (2) prompt elevation of left ventricular end-diastolic pressure by an average increment of 10 mm Hg, followed by a decrease during late exercise in some patients; (3) a progressive increase in LV systolic pressure throughout the first half of the exercise period; (4) a continuously positive change in LV rate of pressure change (dp/dt) throughout exercise; (5) an average 44% increase in stroke volume; and (6) an average 92% increase in cardiac output. The slope of the regression of cardiac output on oxygen uptake during exercise was within the range of normal. Cardiac output, however, was lower than normal both at rest and during exercise, and the arteriovenous oxygen difference was accordingly widened.

In one patient studied 1 and 2 years after transplantation, hemodynamic findings were comparable on both occasions. In the other, however, the cardiac output response to exercise was distinctly diminished at 2 years as compared to 1 year, due almost entirely to failure of the stroke volume to increase. Coronary arteriography in this recipient revealed evidence of occlusive coronary disease compatible with graft atherosclerosis.

These studies demonstrate the sustained capacity of the transplanted human heart to support normal physical activity late in the postoperative period. Although utilizing atypical adaptive mechanisms characteristic of the denervated heart, the transplanted heart responds in a directionally appropriate manner to the metabolic demands of exercise.

Additional Indexing Words:
Immunosuppression Cardiac denervation Exercise
Myocardial contractility Stroke volume

The evaluation of graft function following clinical cardiac transplantation is an important feature in assessment of the therapeutic potential of this procedure. Moreover, definition of the physiologic responses of the transplanted heart provides an opportunity for additional insight into normal cardiovascular mechanisms. Previous experimental observations following cardiac allotransplantation, autotransplantation, and regional cardiac denervation in dogs, as well as long-term

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clinical observations after cardiac transplantation in man, attest to the functional capacity of the denervated, transplanted heart. Late postoperative hemodynamic studies of human cardiac allograft function, however, have not been described in detail.

Eight of the first 20 patients undergoing cardiac transplantation at this center have survived for 1 year or longer after operation, and four of these have lived more than 2 years after transplantation. The results of hemodynamic evaluation in these cases, at 1 and 2 years after transplantation, are presented in this report.

Patients and Methods

The details of recipient selection, surgical technics, and methods of immunosuppressive management have previously been described. Seven of the eight patients had the operative diagnosis of end-stage coronary heart disease (all male); one (case 10) underwent transplantation 18 days following acute myocardial infarction complicated by intractable cardiogenic shock. The remaining patient (case 17, female) presented with idiopathic nonobstructive cardiomyopathy with severe congestive heart failure. Pertinent clinical details are summarized in table 1.

Cardiac catheterization was performed approximately 1 year postoperatively in all eight patients and again at 2 years in cases 7 and 10. At the time of study all patients were clinically well and the results of cardiovascular examination were normal, except for the absence of sinus arrhythmia. No patient had received digitalis since the first postoperative month, but all required diuretics to remain free of edema. Studies were done in the fasting state after premedication with meperidine 50-75 mg intramuscularly or chloral hydrate 0.5-1.0 g by mouth.

Right heart catheterization was performed in a standard fashion with patients in the supine position. Electrical activity of the residual recipient atria was monitored with an intracardiac bipolar or unipolar electrode. Left ventricular and central aortic pressures (referred to midchest level) were measured through a RPX (id 0.109 cm) catheter advanced through the right brachial artery, and left brachial artery pressure with an indwelling needle (Statham P23db pressure transducers). Electrocardiograms and pressures were recorded on magnetic tape for further analysis. The rate of change of left ventricular pressure (dp/dt) was calculated off-line with an IBM 360/50 computer after filtering the pressure signal at 15 Hz (cases 4, 7, and 13), or with an active differentiating circuit showing linear response up to 80 Hz. Left ventricular ejection time was measured from a computer-averaged waveform of the brachial artery pulse over 70-140 cycles. In those cases failing to show a clearly defined incisura, the end of ejection was taken as the point at which the descending limb of the arterial pulse changed slope.

Cardiac output was estimated by the Fick technic with sampling from the pulmonary and brachial arteries; expired air was collected over 5 min at rest and over 2 min during exercise. Stroke volume was obtained by dividing the cardiac output by heart rate, and mean systolic ejection rate (ml/sec) was calculated by dividing stroke volume by left ventricular ejection time.

Table 1

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr)</th>
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<th>Survival (months)</th>
<th>Time of cathet (months postop)</th>
<th>Drugs at time of cathet (mg/day)</th>
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<tr>
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<tr>
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<td>49</td>
<td>CHD</td>
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</table>

*Deceased.

Abbreviations: CHD = coronary heart disease; MI = myocardial infarction.
Supine exercise was performed for 10 min with a bicycle ergometer set at predetermined workloads (20–60 watts). Measurements of cardiac output during exercise were obtained during the middle (4–6 min) and late (8–10 min) portions of the exercise period. Drugs administered during catheterization included amyl nitrite (cases 7 and 17), atropine 1.0 intravenously (cases 4, 7, 10, 14, and 17), and tyramine 0.035 mg/kg intravenously (case 4).

**Results**

**Hemodynamics at Rest**

Hemodynamic findings at rest 1 year after transplantation are summarized in table 2. Sinus rhythm, without respiratory variation, was present in all patients, and heart rates ranged from 72 to 110 beats/min (average 90 beats/min).

Intracardiac pressures, including left ventricular end-diastolic pressure (LVEDP), were normal or nearly normal in all cases. Cardiac index was within the range of normal (> 2.5 liters/min/m²) in four patients and slightly below in four; average cardiac index was 2.3 liters/min/m². Because of high heart rates at rest, stroke-volume index was lower than normal (average 25.5 ml/m²). Mildly increased arteriovenous oxygen (A-VO₂) difference at rest was found in six cases, and the average value for all patients was 5.42 vol %.

The average pulmonary vascular resistance was 2.1 units (compared to an average value of 5.8 units in seven of the eight patients studied preoperatively).

With elevation of the feet to the bicycle pedals in preparation for exercise, LVEDP increased by an average increment of 3.8 mm Hg in those cases in which it was measured. In association with the rise in LVEDP, the cardiac index increased by 6 to 26% (average 12.6%) to 2.51 liters/min/m² (P < 0.01), due to augmentation of stroke volume, with proportional diminution of the average A-VO₂ difference.

**Response to Exercise**

Findings during the middle and late portions of the 10-min period of supine bicycle exercise 1 year after operation are shown in table 3. Additional interval data are illustrated in figures 1–5.

In most patients heart rate increased gradually and almost linearly after the start of exercise, to reach relatively steady levels only after 5–6 min (fig 1). In one patient heart rate rose only by 3 beats/min during the 10-min interval (case 13). After exercise, heart rates fell slowly, and remained above control values for 20 or more minutes in all patients.

LVEDP increased promptly with the initiation of exercise, and then rose more slowly to plateau levels approximately halfway through the exercise period (fig 2). The average maximum increment in LVEDP was 9.8 mm Hg (range 7–16 mm Hg). In four patients LVEDP decreased during late exercise, as compared to maximum values during the midportion of exercise (fig 2).

Cardiac index increased during exercise to an average value of 4.3 liters/min/m² at 5 min, and to a slightly higher measured level of 4.8 liters/min/m² late in exercise (average 92% increase above values at rest with legs elevated). The cardiac index response of each patient, in relation to oxygen consumption, is illustrated in figure 3. The average increase in cardiac output per 100 ml/min increase in oxygen uptake ("exercise factors") was 657 ml/min (range 388–863 ml/min). All except one patient showed higher cardiac outputs late in exercise as compared to the midportion of exercise, and the mean difference between these two points was significant (P < 0.05). In three patients this late additional augmentation of cardiac output was associated with rises in both heart rate and stroke volume, while in two patients it appeared with continuing elevation of heart rate alone, and in one patient was manifested solely by further increase in stroke volume.

Stroke volume increased markedly during exercise in all cases. At 5 min the average stroke volume was 36% above control values, and at 9 min was slightly higher at 44% above control (range 12–72%).

Both systemic arterial and peak left ventricular systolic pressures rose with exertion, and in all studies the increases in pressure were progressive throughout the first half of the exercise period. During the latter half of
Table 2

**Hemodynamic Findings at Rest**

<table>
<thead>
<tr>
<th>Case</th>
<th>HR (beats/min)</th>
<th>SV (ml)</th>
<th>CO (liters/min)</th>
<th>RA (s/v/m)</th>
<th>RV (s/v/m)</th>
<th>PA (s/d/m)</th>
<th>PAW (m)</th>
<th>LV (s/v/m)</th>
<th>BA (s/d)</th>
<th>A-V O₂ diff (vol %)</th>
<th>O₂ cons (ml/min)</th>
<th>BSA (m²)</th>
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<td>4.4</td>
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<td>46*</td>
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<td>24/ 9/12</td>
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*Obtained after elevation of legs.

Abbreviations: HR = heart rate; SV = stroke volume; CO = cardiac output; RA = right atrium; RV = right ventricle; PA = pulmonary artery; PAW = pulmonary artery wedge; LV = left ventricle; BA = brachial artery; A-V = arteriovenous; BSA = body surface area.
### Table 3

**Hemodynamics during Supine Exercise**

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<th>Case</th>
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<th>SV (ml)</th>
<th>CO (liters/min)</th>
<th>Pressures (mm Hg)</th>
<th>A-V O₂ diff (vols %)</th>
<th>O₂ cons (ml/min)</th>
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<td>a</td>
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<tr>
<td>a</td>
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<td>11.62</td>
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Abbreviations: a = 4–6 min of exercise; b = 8–10 min of exercise; others as in table 2.

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Figure 1

*Donor heart rates during exercise. In this and subsequent figures control refers to measurements made after elevation of the feet to the bicycle pedals.*

*Circulation, Volume XLV, June 1972*
during exercise in all patients (fig 5), and, in general, rises in dp/dt paralleled changes in heart rate and systolic pressure. In case 13, however, left ventricular dp/dt increased progressively by a maximum 54% during late exercise without a significant change in heart rate and without further appreciable elevation of systolic pressure during the latter half of exercise; left ventricular end-diastolic pressure in this patient rose to a maximum during the fifth minute of exercise and then decreased slightly. Because of the recognized difficulties inherent in the recording of left ventricular pressures via conventional catheters, the calculated rates of pressure change in these patients should be taken to indicate directional changes only.

Mean systolic ejection rate (MSER) increased with exercise from an average control value of 200 (range 184–232) to 311 ml/sec (range 219–453 ml/sec) at 9 min (56% increase). In three patients MSER late in exercise was significantly higher than values calculated in the midportion of exercise ($P < 0.05$). Increases in MSER were due predominantly to augmentation of stroke volume since left ventricular ejection time...
CARCIC TRANSPLANTATION FOLLOW-UP

Figure 5

Left ventricular dp/dt during exercise. In most recipients dp/dt continued to increase throughout the exercise period.

changed relatively little (average 17% decrease) as compared to control (legs elevated) levels.

Comparison of Findings 1 and 2 Years After Transplantation

The results of serial catheterization studies 1 and 2 years after transplantation in cases 7 and 10 are included in tables 2 and 3. In case 7 intracardiac pressures and flows at rest were closely similar on both occasions. Cardiac output at rest was below normal at both studies and was associated with normal LVEDP. In response to exercise, increases in O\textsubscript{2} consumption and measured cardiac output and stroke volume were slightly less at 2 years despite similar workloads and elevation of heart rate and left ventricular filling pressure to comparable ranges (table 3).

In case 10, hemodynamic findings at rest were likewise similar 1 and 2 years after operation. The response of cardiac output to exercise at identical workloads, however, was distinctly diminished at 2 years in comparison to the 1-year study (table 3). This was due almost entirely to failure of the calculated stroke volume to rise significantly despite an increase in left ventricular end-diastolic pressure to 28 mm Hg. At 1 year the stroke volume rose by 72% above control, whereas at 2 years the increase in stroke volume was limited to 7%. Peak O\textsubscript{2} consumption during exercise at 2 years was lower than that observed at 1 year (227% increase above control versus 443%) and was associated with greater widening of A-VO\textsubscript{2} difference to a maximum extraction of 13.93 vol %.

Response to Drugs

In response to amyl nitrite inhalation mean arterial pressure decreased an average of 32 mm Hg in the three studies performed. Heart rate showed only slight changes, increasing by 3-6 beats/min at the time of peak hypotensive effect. No significant difference in response was observed 1 and 2 years after transplantation in case 7. In contrast, recipient atrial rates in these patients showed prompt acceleration after amyl nitrite, with an average rate increase of 18 beats/min.

The bolus injection of 1.0 mg atropine caused no significant change in resting heart rates in the five patients studied. Recipient atrial rates, however, increased by an average of 19 beats/min above control levels.

Tyramine caused elevation of mean arterial pressure by 13 mm Hg in case 4 without significant changes in heart rate. During the phase of rising arterial pressure, the recipient atrial rate slowed by 10 beats/min, but then rose to a level 11 beats/min above control despite persistence of increased arterial pressure.

Discussion

All of the patients included in this study were clinically stable and were receiving average maintenance doses of immunosuppressive drugs at the time of postoperative hemodynamic evaluation. None had sustained an episode of acute graft rejection within 6 months prior to catheterization. Following these studies, all except two patients have remained clinically well until the present time (16-34 months posttransplantation). In one of these cases sudden death was caused by myocardial infarction 21 months postoperatively, and in the other death resulted from gram-negative sepsis 24 months after operation. For these reasons the hemodynamic
findings in our patients at the time of cardiac catheterization can probably be considered representative of the functional capacity of the transplanted human heart late in the postoperative period.

At rest donor heart rates were faster than normal and were closely similar to "intrinsic" heart rates which are achieved by combined vagal and beta-adrenergic blockage (corrected for donor age). Respiratory variation in heart rate was absent.

Right and left ventricular filling pressures at rest were normal in all patients. Cardiac outputs, however, were consistently in the low normal range or slightly below normal. There was no correlation of donor heart size with output in these studies, although such an association may exist in the immediate postoperative period. At the present time it is not known whether the tendency to low normal output of the transplanted heart at normal filling pressures is the result of residual myocardial damage due to previous injury related to rejection or operation, or simply reflects the intrinsic pumping characteristics of the denervated heart. Although it has generally been considered that sympathetic stimulation of the normal human heart under basal conditions is minimal, many investigators have observed that acute beta-adrenergic blockade may be associated with mild depression of cardiac output at rest, ranging up to 20%. Thus, cardiac performance at rest late in the postoperative period may be influenced by multiple factors, but probably reflects mostly the denervated state. Of the primary determinants of cardiac output, i.e., heart rate, preload, afterload, and contractile state, it is the latter which, although not quantitatively defined in our patients, would appear to be limiting.

The adaptive mechanisms of the transplanted heart during exercise illustrate significant alterations from normal. Heart rates, which began to increase after the start of exercise, rose gradually over several minutes of a steady workload. Deceleration was likewise gradual, and heart rates returned to control levels only after 20 min or more following exercise.

LVEDP, which was normal at rest, increased markedly with exercise. That the elevation of LVEDP was not related simply to the delayed rise in heart rate is indicated by persistence of abnormal LVEDP despite a gradual increase in heart rate to levels comparable to normal. Similar findings have been noted in other transplant patients studied much earlier postoperatively. It would seem reasonable to assume that the rise in LVEDP during exercise in these patients was accompanied by increases in end-diastolic volume. Neither catecholamine stimulation nor heart rate changes in the range observed acutely affect this relationship. Some of the histopathologic findings observed in the grafts of other late-surviving patients, however, suggest that altered ventricular compliance may be present in some cases, and thus conceivably could contribute to the steep rise in LVEDP with the onset of exercise. Such lesions include widespread interstitial fibrosis as well as focal areas of myocardial scarring, features which might be expected to lead to increased stiffness of the ventricular walls.

Coronary artery narrowing due to chronic graft rejection is another factor which potentially could contribute to elevation of LVEDP during exercise. This would seem unlikely as a major single explanation in our cases, since other patients studied in the early postoperative period (at a time when significant coronary artery obstruction would not be expected to be present), as well as cardiac-denervated and allotransplanted dogs (Stinson EB: Unpublished data), have shown similar increases in LVEDP with exercise. In addition, the results of coronary arteriography 1 year postoperatively in cases 19 and 20 were normal. The hemodynamic findings at catheterization 1 and 2 years postoperatively in case 10, however, are of particular interest in this regard. At 2 years, stroke volume failed to rise significantly during exertion despite elevation of left ventricular end-diastolic pressure to 28 mm Hg. Selective coronary arteriography at this time revealed diffuse narrowing of all major coronary arteries with complete obstruction of the proximal left circumflex artery. These
arteriographic findings are compatible with the postoperative development of severe coronary atherosclerosis in the graft, as observed previously in other cardiac grafts examined more than a year postoperatively.\textsuperscript{22, 23} The pathogenesis of this complication and its relationship to arterial injury produced by immunologic rejection are unclear at present. It is apparent, however, that graft atherosclerosis may be associated with hemodynamic abnormalities similar to those found in spontaneous artherosclerosis, and will probably constitute an important factor in long-term survival.

In association with the elevation of LVEDP during exercise at 1 year in our patients, stroke volume increased up to 72\% above resting values (average 44\% increase), and contributed predominantly to the augmentation of cardiac output. Clearly, increases in stroke volume of this magnitude, even in the presence of a low ejection fraction at rest, suggest expansion of end-diastolic heart size. Thus, these observations illustrate a major role for the Frank-Starling mechanism in the response of the transplanted heart to exercise. This dependence of the transplanted heart on the Frank-Starling mechanism as a means of increasing output in response to relatively low workloads differs substantially from the normal state with intact neural control. In the latter situation the cardiac output response to submaximal supine exercise is accompanied by prompt increases in heart rate, while stroke volume remains constant or increases slightly in association with unchanged or diminished end-diastolic volume.\textsuperscript{24, 25} Even in the intact state, however, intense effort may be associated with augmentation of end-diastolic heart size, thus providing an additional increment to stroke output.\textsuperscript{26, 27}

The marked changes in stroke volume which accompanied elevation of LVEDP in our patients during exercise differentiate this response from the usual hemodynamic findings induced by stress in patients with depressed left ventricular function. In the latter situation, increases in left ventricular filling pressure with submaximal exertion have been found to be associated with either no change or a decrease in stroke volume.\textsuperscript{24, 29} It is recognized that the delayed responses in heart rate in our patients may affect this relationship, but in all cases a greatly increased stroke volume persisted throughout the exercise period even though heart rates gradually rose in most patients to levels consonant with a normal response in relation to the augmentation of oxygen consumption. In addition, the large increases in stroke volume were not accompanied by proportionate increases in ejection time, thus resulting in considerable enhancement of MSER. The failing ventricle, in contrast, tends to exhibit no change or even deterioration of MSER under stress.\textsuperscript{28} Thus, it would not appear appropriate to characterize the adaptive cardiac response seen in our patients during exercise as indicative of myocardial failure, although the elevation of LVEDP suggests this conclusion. Indeed, the response of the transplanted heart shortly after the onset of exercise resembles the upward movement of a normal ventricle along its function curve, similar to that shown by Braunwald and associates in normal persons subjected to rapid blood infusion under autonomic blockade with trimethaphan.\textsuperscript{30} Considerable increases in left ventricular minute work index (cardiac index × [LV systolic pressure–LVEDP] × 1.36), averaging 127\% above control occurred during exercise in our patients, and confirm the ability of the transplanted heart to generate an increased contractile effort without deterioration of the mean rate of left ventricular ejection due to excessive wall tension.

The participation of peripheral regulatory factors, though incompletely defined, have in addition been shown to be important determinants of the cardiac output response to exercise.\textsuperscript{31–33} Thus, the onset of muscular activity is associated with a rapid decrease in aortic outflow impedance due to metabolic vasodilatation within exercising muscles, and translocation of blood volume from the periphery to the central circulation. The prompt acceleration of heart rate under these
conditions is associated with an acute elevation of the cardiac output, regardless of increments in myocardial contractile state.\textsuperscript{24} In our patients, similar peripheral mechanisms would be expected to be operative, and probably account for the early rise in cardiac output in conformance with the Starling principle. However, the combination of low cardiac output and normal to elevated systemic arterial blood pressure, both at rest and during exercise, suggests that peripheral vascular resistance remained inordinately high in relation to work performed.\textsuperscript{24} Inhibition of the normal reduction in peripheral resistance during exercise may in turn limit left ventricular output.\textsuperscript{31} Similar inhibition of systemic resistance changes during exercise has been noted after pharmacologic beta-adrenergic blockade in normal persons,\textsuperscript{35} although under these circumstances blockade of vasodilator beta-receptors could be contributory. It may be that these findings represent reflex activation of peripheral alpha receptors in response to an insufficient rise in cardiac output, but such a relationship will require further study.

In view of the above considerations, it would seem justifiable at the present time to describe the response of the transplanted heart to exercise as "atypical" rather than "abnormal," since the latter usually implies intrinsic depression of myocardial function. This characterization is analogous to, but not identical with, the interpretations applied to the exercise response of patients with fixed heart rates due to complete heart block, in whom elevation of cardiac output is the result exclusively of increased stroke volume in association with raised filling pressures.\textsuperscript{36}

It is of interest to note that, although average cardiac output at rest in these patients was approximately at the lower limit of normal, the average increase in output in relation to increase in oxygen uptake during exercise was normal. Indeed, the slope of the regression of cardiac index on oxygen uptake for the eight independent exercise observations at 1 year postoperatively (cardiac index [liters/min/m²] = 1.84 + 0.00596 VO₂ [ml/min/m²]) is almost identical to that found by others in normal subjects.\textsuperscript{24} The theoretical value of cardiac index at zero oxygen uptake (Y intercept), however, is approximately 1.87 liters/min/m² below the average normal value.\textsuperscript{24} Thus, the downward displacement of cardiac output from normal at rest and during exercise is compensated by proportionately greater peripheral oxygen extraction (widened A-V oxygen difference). These considerations suggest that maximal oxygen uptake during exercise after transplantation may be restricted to subnormal levels. Indeed, in several patients, arterial blood analysis during submaximal exercise has shown evidence of anaerobic metabolism at relatively low workloads and levels of oxygen uptake. These preliminary results would tend to support the conclusion that maximal oxygen transport by the transplanted heart is limited, or that the increase in cardiac output during stress is insufficient to satisfy metabolic demands despite the exercise factors calculated.

The data obtained in our patients do not permit definite conclusions regarding changes in myocardial contractility which may occur in the transplanted heart during the stress of muscular exercise. The observed increases in stroke work, MSER, and left ventricular dp/dt may reflect changes in preload or afterload, or both, independently of any alteration in inotropic state. However, the augmentation of stroke volume, MSER, and left ventricular dp/dt late in the exercise period, as compared to the midportion of exercise, at a time when ventricular filling pressures were constant or even decreased and additional changes in heart rate were minimal, does suggest improvement in the rate of myocardial fiber shortening. Full elucidation of such relationships awaits detailed studies of ventricular dimensions during exercise.

The time course of these events, including the gradual and prolonged increase in heart rate, suggests the operation of a humoral mechanism, most likely circulating catecholamines. Previous investigations in man have demonstrated rises in levels of circulating catecholamines during exercise, roughly proportional to the degree of work...
performed. In addition, studies in the cardiac-denervated dog have shown that pharmacologic blockade of the effects of blood-borne catecholamines considerably attenuates the cardiac response to exercise and prevents the performance of more severe grades of work.

In conclusion, the hemodynamic findings described in this report demonstrate the sustained functional capacity of the transplanted human heart late in the postoperative period. It is also pertinent to note the apparent failure of all recipients to establish efferent autonomic innervation of the cardiac graft. This is somewhat surprising in view of the demonstration by Lower and associates of apparent efferent autonomic reinnervation in a significant proportion of canine cardiac allografts within several months postoperatively. The absence of evident reinnervation of the cardiac allograft in man at present remains unexplained. Despite persistence of the denervated state, however, the transplanted human heart is capable of supporting normal activity, and, although it utilizes atypical adaptive mechanisms, responds in a directionally appropriate manner to the metabolic demands of exercise.

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