Hemodynamic Performance of a Transplanted Human Heart

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SUMMARY
Cardiac catheterization studies, performed 3 weeks after cardiac homotransplantation, re-auded nearly normal cardiac performance. Alteration in heart rate by right atrial pacing, passive elevation of the legs, and exercise modified cardiac performance predominantly by variation in ventricular filling. Isoproterenol infusion increased stroke volume above the level predicted from the ventricular end-diastolic pressure.

The heart was hypersensitive to beta-adrenergic stimulation with isoproterenol, as judged by a greater responsiveness of the donor sinus node than the recipient sinus node, by prolongation of ventricular filling time, and by shortening the P-R interval for any given paced heart rate. These measures permitted tests for endogenous catecholamine effects during passive leg elevation and during exercise. Only after the 3 minutes of exercise was a small beta-adrenergic effect detectable.

These data demonstrate the dependence of the denervated human heart upon variation in ventricular filling as the predominant mode of regulation of cardiac performance.

Additional Indexing Words:
- Ventricular function
- Denervation
- Exercise
- Isoproterenol
- Starling's law of the heart
- Preoperative electrocardiograms

Sarnoff and Mitchell demonstrated that regulation of cardiac performance occurs predominantly by variation in end-diastolic ventricular filling (heterometric regulation) and by variation in myocardial contractility (homeometric regulation). Subsequently, studies by Sarnoff and his associates have shown that both mechanisms interact in the control of human cardiac performance. Cardiac homotransplantation in a 50-year-old man provided an opportunity to assess the relative roles of variation in ventricular filling and of response to circulating catecholamines in regulating the performance of a denervated human heart.

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Methods
The patient, a 50-year-old man, had experienced 3 years of intractable progressive dyspnea and edema. His status progressed to a point of complete invalidism despite maximal use of digitalis, diuretics, and salt restriction.

Physical examination revealed a wasted dyspneic man with a blood pressure of 90/70, a pulse of 100/min, and a respiratory rate of 24/min. Massive cardiomegaly and an murmur of mitral regurgitation were found, with evidence of severe pulmonary and systemic congestion.

Preoperative electrocardiograms revealed left ventricular hypertrophy and an intraventricular conduction defect. Chest x-rays documented gross cardiomegaly. Preoperative cardiac catheterization and coronary angiography failed to clarify the etiology of the heart disease.

On December 27, 1968, the patient received the heart of a 24-year-old man who had received irradiation brain trauma. At surgery, the recipient's ventricles were removed, leaving the posterior wall of the left atrium and the posterior lateral wall of the right atrium, including the sinus node. The donor heart was transposed in its entirety, including its sinus node, and was sewn in by using slight modifications of the technique described by...
Cooley and his co-workers. The postoperative convalescence was essentially uneventful. Early during the recovery period, repeated bedside observations were made of pulse rate and blood pressure in the supine, sitting, and standing positions, and after light exercise. On no occasion did the pulse rate change quickly as a result of change in posture or activity. However, approximately 3 min after standing or after the onset of light exercise there was commonly an increase of 3 or 4 beats/min in the pulse rate. For the first 48 hours after operation, isoproterenol was utilized to maintain an adequate blood pressure with a central venous pressure of less than 20 cm of water. The amount of isoproterenol required to perform this was extraordinarily small, ranging between 0.1 and 0.8 μg/min.

The patient was discharged from the hospital on the 24th hospital day. He gradually increased his physical activity to a level of light labor about his home over the subsequent 2 months. He was free of symptoms until February 10, 1969, when an irregular pulse was noted; atrial flutter was confirmed. This was treated with increased levels of immunosuppressive agents and with elective cardioversion, using 12 mg of diazepam intravenously for sedation amnesia. Heart size, electrocardiographic QRS complexes, and myocardial enzymes had not changed. Atrial flutter recurred twice during the next 2 weeks and was successfully converted. Atrial flutter with 4:1 A-V block recurred 1 week later and was not converted. The patient's state of well-being, chest x-rays, electrocardiogram, enzymes, immunoglobulins, and serum complement levels remained stable through March 20, 1969. On March 22, mild exertional dyspnea developed and he was readmitted to the hospital. Over the succeeding 24 hours, his venous pressure rose, arterial pressure fell, peripheral perfusion decreased dramatically, and renal shutdown occurred. All efforts to reverse the cardiogenic shock failed, including isoproterenol, glucagon, diverse vasopressors, and large doses of immunosuppressive agents. The patient died on March 28, 1969.

Cardiac catheterization had been performed 3 weeks postoperatively in an effort to study the relative roles of left ventricular filling and response to circulating catecholamines in the regulation of cardiac performance. Cardiac catheterization was performed without sedation, in the supine position, and 4 hours after the most recent meal. No medication was given on the morning of catheterization. Medication which had been given the day before and which was continued subsequently consisted of azathioprine, 200 mg daily, prednisone, 40 mg daily, antilymphocytic globulin, 5 ml intramuscularly twice weekly, and digoxin, 0.375 mg daily. One catheter was placed in the pulmonary arterial wedge position. A pacing catheter, advanced from the left arm to the right atrium, was connected to a battery-powered external pacemaker unit with variable rate control. A catheter was passed retrograde across the aortic valve into the left ventricle from an incision in the left brachial artery.

Intracardiac pressures were measured with equisensitive strain gauges using an optical galvanometer system. Intracardiac shunts were excluded by sodium ascorbate indicator-dilution curves. Pressures and electrocardiographic lead II were recorded on photographic paper at a recording speed of 75 mm/sec. Cardiac outputs were determined by use of the Fick principle with blood samples obtained from the left ventricle and the pulmonary artery and with 2-min collections of expired air. Details of technics used in this laboratory have been reported previously. Left ventricular and other intracardiac pressures were measured directly.

Five measurements of cardiac output were made. The initial study was performed at rest in the supine position, with right atrial pacing at a rate of 96/min. Isoproterenol was then administered intravenously at two dose levels of 0.4 and 0.8 μg/min while pacing was continued. Cardiac output was measured during the higher of the two dose levels, at a paced rate of 130/min. Ten minutes was allowed for the effect of isoproterenol to disappear. Pacing was continued at 128/min during the third measurement of cardiac output. The patient's legs were then elevated on a stationary bicycle; 4 min later the cardiac output and pressure measurements were repeated. Exercise was then begun. Pressure measurements were recorded 1.5 and 3 min after the start of exercise. Cardiac output was measured during the fourth minute of exercise.

Before and during the administration of isoproterenol, right atrial pacing at multiple heart rates was performed. Left ventricular diastolic filling times were measured at each of the multiple heart rates in the absence of isoproterenol and during the administration of 0.4 μg/min and 0.8 μg/min of isoproterenol. In this way the effect of beta-adrenergic stimulation of the heart could be assessed directly. Measurements obtained subsequently with the legs elevated and during exercise were compared with these values to provide an estimate of endogenous beta-adrenergic stimulation.

Both donor and recipient sinus P waves were identifiable. The rates of the two sinus nodes before isoproterenol and during the two infusion levels were recorded as an estimate of the effect of beta-adrenergic stimulation on the innervated recipient sinus node and the denervated donor sinus node. The P-R intervals obtained during
Table 1

Hemodynamic Data from Patient after Cardiac Homotransplantation

<table>
<thead>
<tr>
<th>Heart rate*</th>
<th>Status</th>
<th>Oxygen consumption (ml/min/m²)</th>
<th>Cardiac output (l/min/m²)</th>
<th>Stroke volume (ml/bl/m²)</th>
<th>Left vent. pressure (mm Hg)†</th>
<th>Pulmonary arterial pressure (mm Hg)</th>
<th>Right vent. pressure (mm Hg)</th>
<th>Left vent. dp/dt (mm Hg/sec)</th>
<th>a wave in left ventricle (mm Hg)</th>
<th>Recipient Donor</th>
</tr>
</thead>
<tbody>
<tr>
<td>P96</td>
<td>Rest</td>
<td>117</td>
<td>4.49</td>
<td>47</td>
<td>131/3/10</td>
<td>29/11</td>
<td>32/5</td>
<td>2020</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>P130</td>
<td>Isoproterenol (0.8 µg/min)</td>
<td>128</td>
<td>6.12</td>
<td>47</td>
<td>135/0/8</td>
<td>25/11</td>
<td>—</td>
<td>2940</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>P128</td>
<td>Rest</td>
<td>120</td>
<td>5.18</td>
<td>40</td>
<td>132/1/7</td>
<td>29/14</td>
<td>—</td>
<td>2130</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>P98</td>
<td>Legs up</td>
<td>126</td>
<td>5.05</td>
<td>52</td>
<td>139/4/13</td>
<td>32/15</td>
<td>—</td>
<td>1900</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>N103</td>
<td>Exercise</td>
<td>280</td>
<td>6.10</td>
<td>59</td>
<td>144/8/18</td>
<td>44/18</td>
<td>45/7</td>
<td>2380</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>

* N = normal sinus rhythm; P = right atrial pacing.
† Systolic/early diastolic/end diastolic.

right atrial pacing at multiple rates have been used in previous studies to estimate modifications of A-V conduction time produced by various drug interventions. This technic was used during the present study as a second means of testing for hypersensitivity to circulating catecholamines. P-R intervals were measured at multiple paced rates before isoproterenol infusion and during the infusion of 0.8 µg/min. The effect of this level of isoproterenol was compared with results obtained in five other patients with diverse cardiac lesions but without evidence of A-V nodal disease. These five patients had also had atrial pacing at multiple rates before and during isoproterenol infusion. However, as noted by others, larger doses are required to alter A-V conduction time in innervated hearts. The dose rate used was 5 µg/min.

Results

The basic hemodynamic data obtained during this catheterization are presented in table 1. The general levels of pressures and of output were remarkably close to normal. The mean right atrial pressures at rest and during exercise were 5 mm Hg and 6 mm Hg, respectively. The mean pulmonary arterial wedge pressure, measured at rest only, was 12 mm Hg. The left ventricular pressure contour was normal both in systole and diastole. No diastolic dip and plateau of restrictive heart disease was seen. Both donor and recipient a waves could be identified in the right atrium and in the left ventricle. The heights of the respective a waves in the left ventricle are presented in table 1. The first derivative of left ventricular pressure was normal, and it increased both during isoproterenol infusion and during exercise.

Stroke volume is plotted against end-diastolic pressure. Right atrial pacing at two rates, passive leg elevation, and supine exercise altered left ventricular end-diastolic pressure and stroke volume concordantly. Isoproterenol infusion increased stroke volume above the level predicted from the other four data points.

Stroke volume is plotted against end-diastolic pressure in figure 1. As shown, an increase in heart rate produced a decrease in end-diastolic pressure and a corresponding decrease in stroke volume. Elevation of the legs increased ventricular filling and produced an appropriate increase in stroke volume. Exercise further increased ventricular filling and stroke volume. These four data points suggest that stroke volume varied predominantly as a function of ventricular filling. The data obtained during isoproterenol infusion at 0.8 µg/min are also shown; this infusion produced a higher stroke volume at an end-diastolic pressure similar to that obtained at a comparable heart rate in the absence of isoproterenol. This suggests that the performance of the heart can be significantly modified by circulating cate-
The administration of 0.4 \( \mu \text{g/min} \) of isoproterenol increased filling time by 35 msec at a heart rate of 100/min. Isoproterenol, at a dose rate of 0.8 \( \mu \text{g/min} \), increased diastolic filling time by 60 msec at slower heart rates and by 30 msec at faster heart rates. The diastolic filling time did not shift above the predicted value for the corresponding heart rate when the legs were passively elevated for 1.5 or 3 min. By 1.5 min of exercise, diastolic filling time had increased very slightly, but probably significantly. By 3 min of exercise diastolic filling time, at a heart rate of 103, had increased by 30 msec. This change is equivalent to approximately 0.4 \( \mu \text{g/min} \) of isoproterenol effect.

These data suggest that there is a minor but measurable effect on cardiac performance from circulating catecholamine appearing relatively late after the onset of exercise.

The question of hyperresponsiveness of this denervated heart to circulating catecholamines was tested in two ways. As shown in figure 2, the recipient sinus nodal rate increased from 72 to 83 impulses/min with the infusion of isoproterenol. At the same time the donor sinus nodal rate increased from 88 to 112 impulses/min. This suggested a greater responsiveness of the donor sinus node compared to that of the recipient sinus node to infusion of isoproterenol. The P-R interval values obtained during pacing at multiple rates are plotted against the corresponding heart rate in figure 4. As shown, the P-R interval progressively lengthened as paced heart rate was increased. The infusion of 0.8 \( \mu \text{g/min} \) of isoproterenol shortened the P-R interval at any comparable heart rate by approximately 60 msec. Data from a
interval at any comparable heart rate by approximately 17 msec. This individual, however, received 5 \( \mu \text{g}/\text{min} \), more than six times the dose administered to the denervated heart. The P-R interval of the donor heart thus shortened by approximately 74 msec/\( \mu \text{g} \) of isoproterenol; the corresponding figures for the other five subjects ranged from 4 to 14 msec/\( \mu \text{g}/\text{min} \).

The P-R intervals obtained at other times during the entire study of this patient and the corresponding heart rates were as follows: during the infusion of 0.4 \( \mu \text{g}/\text{min} \), a P-R of 148 msec; with the legs up for 1.5 min, the P-R interval was 170 msec at a heart rate of 98; after 3 min of leg elevation the P-R interval was 168 msec at a heart rate of 92/min; at 1.5 min of exercise the P-R interval was 160 msec at a heart rate of 98/min; after 3 min of exercise the P-R interval was 140 msec at a heart rate of 103/min. These observations on P-R interval also demonstrate the absence of beta-adrenergic stimulation except after the third minute of exercise.

**Discussion**

The patient described in this study had an intact autonomic system as judged by clinical observation of perspiration, pilo-erection, gastrointestinal tract function, ocular reactions, and orthostatic control of blood pressure. Complete cardiac denervation in this individual is supported by the lack of heart rate response to carotid sinus massage, to the Valsalva maneuver, to acute changes in bodily position, by the studies reported in this paper, and by similarity to studies obtained after cardiac denervation.\(^7\), \(^8\)

The data obtained in the present study demonstrate that cardiac performance can vary with demand in the absence of cardiac innervation, relying almost exclusively upon variations in left ventricular filling to provide control of cardiac performance. Responsiveness to circulating catecholamines was demonstrable with levels of response far exceeding those observed at comparable dose levels with innervated hearts.

**Figure 4**

The electrocardiographic P-R interval is plotted against heart rate. Isoproterenol infusion shortened the P-R interval by approximately 60 msec. Exercise shortened the P-R interval by an amount approximately equivalent to that attained during the infusion of 0.4 \( \mu \text{g}/\text{min} \) of isoproterenol. Symbols as in figure 3.

**Figure 5**

P-R intervals are plotted against heart rate. These data, obtained in an individual with moderate constrictive pericarditis, reflect the ordinary change in P-R interval with isoproterenol infusion. In this individual, a change of approximately 17 msec was achieved with an infusion rate of 5 \( \mu \text{g}/\text{min} \). Solid circles represent data obtained before isoproterenol infusion. Open circles represent the values obtained during infusion of 5 \( \mu \text{g}/\text{min} \) of isoproterenol.

similar study conducted in one of the five other subjects are presented in figure 5. In this individual isoproterenol shortened the P-R
With moderate supine exercise, cardiac performance changed predominantly by augmenting left ventricular filling. No hemodynamic effect of circulating catecholamines could be demonstrated. However, the donor sinus rate, left ventricular diastolic filling time, and the P-R interval all indicated the appearance of definite but small degrees of catecholamine effect approximately 3 min after the onset of exercise. It is presumed that this reflects circulating catecholamine released at other sites in the body.

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