Heart Rate after Cardiac Transplantation

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SUMMARY

Two patients who have undergone heart transplantation 7 and 15 months previously were studied to determine basal heart rate, the effects of exercise, and acute changes in venous return and blood pressure as well as of vagal stimulation. In one case the effects of body temperature, isoprenaline (isoproterenol), beta blockade, and atropinization on heart rate were studied. Mean resting heart rates of 110 and 90, respectively, were observed in the two cases without any significant change with time since the surgical implantation. Sinus arrhythmia was not observed and heart rate was found to increase with exercise following isoprenaline infusion and following increase in body temperature. A decrease was observed after beta blockade, but no significant direct or baroreceptor reflex effects could be produced by changes in venous return, systemic blood pressure, vagal stimulation, and atropinization. Both patients are thus effectively denervated, and there is no evidence of reinnervation to date.

Additional Indexing Words:
- Atropinization
- Baroreceptor reflex
- Reinnervation
- Blood pressure
- Exercise
- Vagal stimulation
- Beta blockade
- Isoproterenol
- Venous pressure

CARDIAC TRANSPLANTATION results in complete denervation depriving the heart of one of its major rate-regulating mechanisms. It is the purpose of this paper to report on the resting heart rate, changes that occur after various circulatory manipulations in the denervated state, and on the search for evidence of reinnervation in two patients who have survived cardiac transplantation for 15 and 7 months, respectively.

Report of Cases and Methods

Case 1

The first subject of this study was a 58-year-old white male who underwent cardiac transplantation on January 2, 1968, for intractable cardiac failure due to ischemic heart disease.1 In addition he had generalized atherosclerosis with nonsymptomatic peripheral vascular disease. The donor heart was obtained from a 22-year-old Negro male who had had a fatal subarachnoid hemorrhage (table 1). Postoperatively the patient required digitalis and furosemide to assist his cardiac status. Maintenance immunosuppressive therapy consisted of prednisone and azathioprine. A course of antilymphocytic globulin was administered 6 months after surgery, during an episode of acute rejection. His clinical course has fluctuated between being reasonably well and active to being virtually moribund. The latter state has been attributed to an episode of acute rejection complicated by Listerella monocytogenes sepsis and severe jaundice presumably related to azathioprine toxicity. Prior to this he had had at least one episode of deterioration of cardiac function with signs of circulatory insufficiency diagnosed as a minor episode of rejection, requiring increased dosage of immunosuppressive drugs. For the past 6 months and up to the time of writing his condition has progressively deteriorated. His effort tolerance is obviously reduced mainly due to dyspnea and partly due to atrophy of the leg muscles (peripheral vascular disease plus steroid myopathy?).

Clinical signs of congestive heart failure were initially difficult to evaluate because of the effects of large doses of steroids but latterly persistently elevated jugular venous pressure, slight hepatomegaly, and edema of the legs have been
present. A persistent diastolic gallop sound has
developed, and an intermittent systolic murmur at
the apex is suggestive of mitral incompetence.
Radiological examination revealed an atrial
abnormally large and dilated in size. The electrocardiogram has shown a
persistent sinus tachycardia. Extensive T-wave
inversion has developed in the course of time.5
Partial catheterization during the second acute
postoperative period confirmed the presence of
an abnormally high central venous pressure and
an abnormally low cardiac output.

Resting heart rates have been recorded by
electrocardiograms performed daily or every
second day initially and latterly at twice weekly
intervals. The exercise test was undertaken when
the patient was at his best about 6 months after
his operation. He was exercised on a bicycle
ergometer in the sitting position, and was given
three consecutive periods of exercise for 5 min
each at work loads of 60, 80, and 120 kg/min.
Weakness of the leg muscles was the limiting factor.
During the exercise, heart rate was measured
from a continuously recorded electrocardiogram.
Ventilation, of consumption and respiratory
quotient were also measured. On the same day a
Valsalva maneuver was performed, heart rate, only
being recorded. The effect of body temperature
in heart rate was recorded by noting heart rate
during in a fabricile, illusory corresponding to
the first episode of rejection.

Mean values for heart rate and temperature were
plotted to determine the temperature coefficient
under these conditions. At a later time after about 3
months, a new episode of rejection occurred. The
patient was transferred in a bath of cold water, the
temperature of which was varied between 44 and 11°C. After
administration of propanolol in a dose of 0.2
mg/kg of body weight intravenously, the systolic
temperature was measured by means of a
thermistor probe and heart rate was recorded by
continuously recording electrocardiogram. The
temperature coefficient for heart rate under the
influence of beta blockade was then determined.

Table 1

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Changes in Venous Return

In April 1969, after a period of about 7
months, the patient was readmitted with a
short history of dyspnoea and angina.

Catheterization showed a marked increase in
right atrial pressure and a normal pulmonary
venous pressure. The right ventricular pressure
was not elevated, and the tricuspid valve was
able to be palpated. The pulmonary artery
pressure was raised to 48/13 mm Hg. A right
atrial catheter allowed a pressure reading to be
taken from the left atrium. The left atrial pressure
was found to be 24/14 mm Hg. The cardiac output
was 3.4 liters/min, and the systemic arterial
pressure was 100/60 mm Hg. The pulmonary
circulation was studied by the dye-dilution
method. Despite a high right atrial pressure,
the pulmonary transit time was normal. The
pulmonary vascular resistance was found to be
high, and the shunt was absent. The
hemoglobin was 11 g/dl. The Coombs test was
negative. The patient was treated with digitalis
and diuretics, and was discharged home in a
clinically satisfactory state.

In July 1970, the patient was readmitted with a
history of dyspnoea, syncope, and angina.

Catheterization showed an increase in right
atrial pressure and a normal pulmonary venous
pressure. The right ventricular pressure was
found to be normal, and the tricuspid valve was
able to be palpated. The pulmonary artery
pressure was raised to 50/14 mm Hg. A right
atrial catheter allowed a pressure reading to be
taken from the left atrium. The left atrial pressure
was found to be 26/14 mm Hg. The cardiac output
was 4.2 liters/min, and the systemic arterial
pressure was 110/60 mm Hg. The pulmonary
circulation was studied by the dye-dilution
method. Despite a high right atrial pressure,
the pulmonary transit time was normal. The
pulmonary vascular resistance was found to be
high, and the shunt was absent. The
hemoglobin was 11 g/dl. The Coombs test was
negative. The patient was treated with digitalis
and diuretics, and was discharged home in a
clinically satisfactory state.

Changes in Aortic Pressure

With the patient supine, intra-arterial pressure
measurement was performed on both legs and
heart rate were measured after amylnitrite
induced hypotension. Thereafter phenylephrine
was administered intravenously in increasing
doses, 1 ml:2 mg to raise the blood pressure
abruptly, the resultant heart rate change again
being monitored. The effect of vagal stimulation
by carotid sinus pressure and eyeball pressure
on heart rate were monitored. Finally, the effects
of drugs, such as atropine 0.04 mg/kg given
intravenously, propranolol 0.2 mg/kg intravenously
and isoproterenol (isoprenaline) on heart rate
were observed.

Case 2

An elderly woman was admitted to hospital
with a history of angina pectoris and syncope.

The patient was a 75-year-old woman who had
suffered from chronic rheumatic heart disease
during the previous 20 years. She had been treated
with digitalis and diuretics for heart failure and
mitral incompetence for many years. Mitral
valvotomy performed elsewhere had resulted in
some improvement for about 2 years, after which
her condition deteriorated and she was admitted
to hospital with angina pectoris and syncope.

Examination revealed chronic congestive heart
failure with a large heart and unimpressive mitral
murmurs. Cardiac catheterization confirmed the
presence of severe low output heart failure due
to
Left ventricular myocardial dysfunction with insignificant mitral and aortic insufficiency. Cardiac allograft transplantation was performed on September 7, 1968, the donor heart being obtained from a 36-year-old hypertensive female with a severely hypertrophied heart (table 1). The patient was given an initial course of antilymphocyte globulin and at present is being maintained on steroids and azathioprine but has not required digitalis or diuretic therapy since his discharge from hospital. His exercise tolerance is excellent; the heart size has remained normal and unchanged throughout. There has been no reduction in electrocardiographic voltage, and the ST-T wave changes of severe left ventricular hypertrophy have disappeared. He has had no frank episodes of rejection or serious complications of immunosuppressive therapy. Permission to perform full hemodynamic evaluation has been refused, and we have been able to observe only the resting rate and the effects of the Valsalva maneuver, posture, exercise, amyl nitrite inhalation, and vagal stimulation on one occasion 7 months after operation.

**Results**

The mean monthly heart rate at rest for the first two patients is shown in figure 1. In the first patient, the heart rate has varied between 85 and 120 beats/min at rest, and in the second patient between 75 and 105. There has been no significant change in mean monthly values since the operation in either case. During exercise in case 1, heart rate increased rather slowly from a resting level of 107 to 112, 115, and 120/min at each level of exercise, and after exercise declined slowly to control levels within about 8 minutes (fig. 2).

The second patient was capable of much more exercise and, greater exercise tachycardia was produced, the heart rate increasing from 95 to 134 beats/min, with an exercise load of 500 kgm/min. In the first patient, the temperature coefficient for heart rate during a febrile illness was 8 beats/°F increase in oral temperature (fig. 3) and during beta blockade 3.5 beats/°F change in esophageal temperature (fig. 4). Adequately performed Valsalva maneuvers produced no change in rate, and in case 1 in which we had a simultaneous pressure recording, the typical square wave or heart failure response was recorded. Changes in posture from the vertical to the 15° head-down position produced no changes in heart rate in either case. Changes in blood pressure induced by inhalation of amyl nitrite caused no change in rate in the first patient and a slight increase of 9 beats/min in a delayed and persistent fashion. Unlike the usual baroreceptor-induced tachycardia which occurs in normal patients. Administration of phenylephrine in the first patient elevated the blood pressure from 136 to 162 mm Hg without slowing the heart rate. Carotid sinus massage or eyelid pressure had no effect on heart rate in either case. Complete parasympathetic blockade by a full
Table 2

Summary of Results

<table>
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<tr>
<th>Date</th>
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<td>Esophageal temperature during beta blockade</td>
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blocking dose of atropine produced no change in heart rate (patient 1), while a full blocking dose of propranolol decreased the heart rate from the control level of 125 to 110/min. In the first patient an intravenous infusion of isoprenaline at the rate of 8 μg/min increased the heart rate from a control level of 110 to 130 beats/min. These results are recorded in table 2.

**Discussion**

In normal subjects resting heart rate is predominantly determined by vagal influences so that following atropinization, combined autonomic blockade or cardiac denervation resting heart rates are higher than normal. The heart rate following autonomic blockade has been termed the “intrinsic” heart rate and has been shown to be related to age, physical fitness, and possibly to the state of health of the myocardium. In the case of our first patient the heart rate under basal conditions is well over 100 beats/min. This tachycardia is probably not due to a high catecholamine drive or to catecholamine supersensitivity since a full blocking dose of propranolol under nonbasal conditions reduced the heart rate from 125 to 110 beats/min and even this degree of slowing may have been due to the nonspecific effect of the drug. A full blocking dose of atropine produced no change in heart rate at all; thus, although the effects of a combined autonomic blockade have not been studied, it seems reasonable to assume that resting heart rate is close to the intrinsic rate. The clinical picture and the hemodynamic findings of a high venous pressure and subnormal cardiac output are in keeping with myocardial failure, the result of repeated episodes of acute or chronic rejection. Unfortunately we have not been able to make full hemodynamic studies to exclude pericardial or other nonmyocardial causes of heart failure, nor is it certain to what extent the steroid immunosuppressive therapy contributes to the high venous pressure and peripheral edema. If our clinical impression of myocardial failure is correct, it is clear that resting heart rate or intrinsic heart rate has not been a good

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<th>5 min after 2.4 mg</th>
<th>Propranolol</th>
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Abbreviations: BP = blood pressure; CO = cardiac output; HR = heart rate.
indication of myocardial dysfunction following cardiac transplantation in this patient. Furthermore, in the second case in which there is no clinical evidence of myocardial dysfunction and there have been no episodes of acute rejection, the resting heart rate is slowed at about 90 beats/min. Steroid therapy may be one of several complicating factors affecting the intrinsic heart rate.

Changes of heart rate during the stress of exercise have been extensively studied in experimental animals following cardiac denervation. The changes in rate during exercise in healthy human subjects following complete autonomic blockade have also been reported. Results indicate that following cardiac denervation, considerable although autonomic control of increases in rate can be during exercise and that this exercise tachycardia can only partially be prevented by beta receptor blockade suggesting that circulating catecholamines released from the adrenal gland and sympathetic nerve endings under the stress of exercise are not the only cause. Donald and Samueloff investigated the role of temperature and blood-borne agents in dogs and concluded that these could not be responsible for the residual increase in rate. The possibility of some direct effect on the rate of sinus node discharge by the increased venous return and increased distention of the right atrium which may occur during exercise under these conditions has been suggested. Such small increases in heart rate have in fact been noted in heart-lung preparations when the venous reservoir is elevated, and may account for the changes in heart rate following sudden increases in venous return, which were previously ascribed to the Bainbridge reflex. Donald and Shepherd, however, concluded that the effect of venous return on heart rate was too delayed and variably to account for
The effect of temperature on heart rate under the influence of propranolol (prop). Heart rate, esophageal temperature, and the bath temperature in degrees F are recorded against time in minutes. There appears to be a linear relationship between heart rate and esophageal temperature under these conditions with a temperature coefficient of 3.5 beats/1°F.

The exercise tachycardia in the denervated dog heart. The cause of the exercise-induced tachycardia in chronically denervated dogs is thus largely unexplained.

In our first patient the slight increase in heart rate from 107 to 120 beats/min was noted on exercise, but we have not studied the effect of exercise under beta blockade. We have, however, investigated other possible mechanisms for increased heart rate which may operate during exercise and have noted an effect of temperature on heart rate. During a pyrexial illness the temperature coefficient was about 8 beats/1°F increase in oral temperature, while under conditions of induced temperature change after beta blockade the effect was less marked with a temperature coefficient of 3.5 beats/1°F increase in the esophageal temperature. Since the temperature increase that occurs during heavy muscular exercise seldom exceeds 35°F and in our first patient was probably much less, the direct effect of temperature on the denervated heart during exercise is probably insufficient to account for the observed rate increase.
An attempt has also been made to ascertain the effect of venous return on heart rate. The Valsalva maneuver produced no change, nor did the rapid change from horizontal to vertical positions although this latter maneuver caused right atrial pressure to fall and cardiac output to decrease by one third. The reverse positional change from the vertical to horizontal also produced no changes in heart rate. It is concluded that in this patient venous return, right atrial pressure, and the degree of right atrial stretch have had no effect on the rate of sinus node discharge. It would, however, be unwise to assume that this is an invariant finding after cardiac denervation. For some time our patient has presented the clinical picture of congestive heart failure, and under these conditions it is often extremely difficult to induce adequate stress; furthermore, cardiovascular adaptations to stress are often very abnormal. Although we appear to have produced an adequate stress with a change of posture, the lack of change in heart rate may be due to some as yet unexplained effect of heart failure or its therapy on the capacity of the sinus node to change its rate of discharge in response to a change in atrial wall tension. In our second case posture again had no effect on rate, but we were unable to monitor the effects of posture on venous return. It thus seems likely that during exercise both catecholamine release and temperature increase may contribute to the increased heart rate. We do not, however, have any evidence that venous return is a factor.

In animal experiments evidence of reinnervation has been found between 3 and 12 months after surgery in both homotransplanted and allotransplanted hearts.\textsuperscript{13-16} The return of sinus arrhythmia has been noted as an early sign. Neither of our patients has shown any evidence of sinus arrhythmia under resting conditions; carotid sinus and eyeball pressure have had no effect on heart rate. In our first case, 15 months after surgery no change in the heart rate followed a full blocking dose of atropine, nor has any change in rate followed significant elevation of blood pressure with phenylephrine, nor a fall in blood pressure followed after amyl nitrite inhalation. Here again, these results must be interpreted with caution because of the presence of congestive heart failure. We have observed several patients in congestive heart failure due to cardiomyopathy, in whom no slowing of the rate followed significant elevation of systemic pressure; they have, however, always responded to an acute amyl nitrite-induced fall in blood pressure with an appropriate tachycardia. The evidence, therefore, suggests that reinnervation has not occurred in case 1.

In case 2 the information is scanty and we have not studied the effects of phenylephrine. Following amyl nitrite inhalation, however, blood pressure fell from 150 to 100 systolic while heart rate increased from 81 to 90 beats/min. This slight increase in heart rate with an adequate drop in blood pressure is less than we had ever observed in either normal patients or in patients with congestive heart failure. Furthermore, the maximum increase in rate occurred some 50 seconds after the peak hypotensive response and remained at this increased level for several minutes after the blood pressure had returned to control levels. We have concluded that the slight increase in rate was not mediated by the baroreceptor reflex but was probably due to circulatory catecholamines released by the acute hypotensive effects of the drug.

\textbf{Acknowledgment}

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