Electrocardiographic Studies in Homologous Canine Heart Transplantations

By Nicholas P. DePasquale, M.D., George E. Burch, M.D., Edgar Pena, M.D., and Keith Reemtsma, M.D.

Transplantation of the canine heart has been performed by a variety of technics since the original work of Alexis Carrel reported in 1907. The most widely used method was described in 1933 by Mann and associates, who placed an auxiliary heart in the neck of a recipient by means of direct vascular anastomoses. Subsequently other investigators using this technic achieved maximal functional survival of the transplanted heart of six to ten days. A few reports on the electrocardiograms of the transplanted heart have been published, but we are aware of no electrocardiographic studies on the heart of the recipient.

Treatment of the recipient animals with immunosuppressive drugs has produced a maximal survival period of the transplanted heart of approximately one month in our series. This prolongation of survival of the transplanted heart has permitted serial studies of electrophysiologic phenomena in both the transplanted and recipient hearts. This report summarizes observations on the electrocardiograms of animals subjected to heart transplantation and treated with a purine analogue, azathioprine.

Methods

The present observations are based on 10 technically successful homologous canine heart transplantations. In all instances hearts of puppies were transplanted into the neck of adult dogs using a modification of the technic of Mann et al. The donor and recipient animals were anesthetized with pentobarbital administered intravenously in doses of 30 mg/kg body wt. The aorta and pulmonary artery of the graft were anastomosed to the carotid artery and jugular vein, respectively, of the host. Donor animals were mongrel pups weighing 800 to 2400 g. Following transplantation all recipients received azathioprine in doses of 3 to 5 mg/kg/day. Animals were observed daily for presence of pulsation of the heart in the neck, and electrocardiographic tracings were made at intervals of two to three days.

Electrocardiograms of the hearts of the recipient dog were recorded before transplantation and serially thereafter until the transplanted heart ceased beating. In five animals the transplanted heart was removed after function had ceased and electrocardiographic studies of the recipient were continued. Serial electrocardiograms were obtained from five azathioprine-treated animals in which no heart transplantation was performed, and from eleven animals that received kidney transplants and azathioprine but no heart transplants.

Electrocardiographic tracings consisted of standard limb leads, augmented unipolar limb leads, a unipolar precordial lead recorded with the electrode in the fifth intercostal space in the midclavicular line, and a unipolar lead recorded with the electrode placed directly over the transplanted heart in the neck. To insure reproducibility of electrode placement in recording the precordial electrocardiogram, a suture was placed in the skin corresponding to the position of the electrode at the time preoperative tracings were obtained. Postoperative tracings were recorded with the precordial electrode at the site of the suture. Electrocardiograms were recorded at paper speeds of 25 and 50 mm/sec.

All electrocardiograms were recorded with dogs in a supine position on the operating table. Because of lack of fixation of the canine mediastinum, dogs were tilted slightly to the left during the recording of the electrocardiogram to insure a relatively uniform cardiac position during serial recordings.

Hemoglobin and hematocrit level, white blood cell counts, and platelet counts were obtained be-

From the Departments of Medicine and Surgery, Tulane University School of Medicine, New Orleans, Louisiana.

Supported in part by Grants HE-02826, HE-03545, and H-6769 from the U. S. Public Health Service.

Accepted for publication August 10, 1964.

*Supplied as Imuran through the courtesy of Burroughs, Wellcome and Company, Inc., Tuckahoe, New York.
fore transplantation and three times weekly during the post transplantation period. Serum sodium, potassium, and chloride were measured at varying intervals following transplantation.

Results

In this series of animals the period of survival of the transplanted heart ranged from 6 to 21 days. Eventual failure of the transplanted hearts was attributed to graft rejection or death of the recipient from drug toxicity.

Histologic examination of the transplanted hearts revealed variable degrees of necrosis throughout the myocardium. In some instances the architecture of the myocardium appeared well preserved even in animals in which the heart survived more than three weeks. In other instances varying degrees of necrosis, round cell infiltration, and loss of architecture were noted. One of the most consistent findings was the appearance of endothelial hyperplasia of small vessels in the myocardium. This finding appeared approximately one week following transplantation. Recipient hearts appeared grossly normal and histological studies were unremarkable.

ELECTROCARDIOGRAM OF THE RECIPIENT HEART

Cardiac Rate

Immediately after operation there was a transient increase in heart rate. After two or three days the rate became stable but tended to become slower with increasing duration of survival of the transplanted heart. In one dog a 2:1 block developed immediately postoperatively. This reverted to normal sinus rhythm by the fourth day after operation.

Standard Leads

Although slight variations in the direction of the mean electric axis of the P and QRS complexes occurred in some animals, these were attributed to variations in cardiac position. The most striking changes in the standard leads following transplantation involved the S-T segment and the T waves. S-T segment elevation occurred in one or more of the standard leads in four animals (table 1). In five animals the T waves became deeply inverted in leads I and/or aVII (fig. 1), whereas in two animals negative or biphasic T waves in leads aVII and aVIII became positive and peaked (table 1). Elevation of the S-T segment and/or inversion of the T waves did not occur prior to the sixth day following transplantation. All animals in whom the transplant survived more than nine days developed changes involving the S-T segment and/or T waves of the electrocardiogram (table 1).

Precordial Lead

Changes in the precordial lead involved the S-T segment and T wave and were similar to those in the standard leads (table 1). In one animal (no. 8) no significant changes occurred in the precordial lead, whereas the T waves in leads aVII and aVIII became deeply inverted. The changes of the T waves in the precordial lead consisted of either deep in-

<table>
<thead>
<tr>
<th>TABLE 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrocardiographic Changes in the Standard Leads and in a Unipolar Precordial Lead of Recipient Dogs</td>
</tr>
<tr>
<td>Dog no.</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>8</td>
</tr>
<tr>
<td>9</td>
</tr>
<tr>
<td>10</td>
</tr>
</tbody>
</table>

Circulation Research, Vol. XVI, March 1965
version of the T wave or peaking of the T wave (Fig. 1).

In a few instances changes in the amplitude of the QRS complex occurred in the precordial lead which were considered to be due to alterations in cardiac position. Such changes were not associated with QRS changes in the standard or unipolar limb leads. In three animals serial electrocardiograms were recorded from 7 to 12 days after the death and

![Electrocardiogram images](img)

**FIGURE 1**
Serial electrocardiograms from recipient dog before homologous canine heart transplant and seven days after transplant. Seven days after transplant the T wave in lead I has become deeply inverted, whereas the T waves in leads II, III, and the precordial lead have become peaked.

![Electrocardiogram images](img)

**FIGURE 2**
Serial electrocardiograms recorded from recipient dog before and after heart transplant. The S-T segment and T wave changes which occurred following transplantation were no longer present eight days after removal of the transplanted heart and hydrocortisone administration.

*Circulation Research, Vol. XVI, March 1965*
removal of the transplanted heart. In two of these animals the T waves improved but did not return to the preoperative configuration. In two other animals, in addition to removing the nonfunctioning donor heart, hydrocortisone was administered. In both of these animals the T waves returned to their preoperative configurations (fig. 2).

**ELECTROCARDIOGRAM OF THE TRANSPLANTED HEART**

**Cardiac Rate**

The cardiac rate remained relatively stable until shortly before the death of the transplanted heart at which time bradycardia developed. In four animals bradycardia was associated with marked irregularity of the cardiac rhythm.

**Unipolar Neck Lead**

Serial changes in the electrocardiogram from the transplanted heart included 1) progressive decrease in amplitude of the QRS complexes, 2) increased duration of the QRS complex, 3) marked elevation of the S-T segment, and 4) deep inversion of the T wave (table 2, and fig. 3). The earliest changes occurred on the sixth day following transplantation.

**ELECTROCARDIOGRAM OF AZATHIOPRINE-TREATED ANIMALS**

Serial electrocardiograms of five animals treated with azathioprine without organ transplantation showed no significant changes over a 21-day period. In addition, serial electrocardiograms from animals treated with azathioprine and receiving kidney transplants were unremarkable.

**Discussion**

Interpretation of the canine electrocardiogram is difficult. One of the major problems involves the relatively great variations of cardiac electric position recorded from animal to animal, or from tracing to tracing in the same animal. These changes occur because the canine heart is loosely anchored in the mediastinum.

Every effort was made to eliminate such variations of cardiac position as a source of difficulty in the interpretation of the electrocardiograms. The mean electric axis of the QRS complex, as recorded in this study, changed little from tracing to tracing. The electrical position of the heart as determined by the unipolar limb leads also varied only slightly. Thus, the S-T segment and T wave changes observed in the electrocardiograms of the recipient dogs following transplantation were considered to be related to factors other than changes of anatomic or electric cardiac position. These changes were similar to those observed in electrocardiograms from human beings with myocarditis and/or pericarditis. Furthermore, the electrocardiographic findings, including the response to steroids, were not unlike those observed in patients with the postcommissurotomy and postmyocardial infarction syndromes.

Our finding that the recipient hearts ap-

### Table 2

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Decrease in amplitude of QRS complex</th>
<th>Increase in duration of QRS complex</th>
<th>Elevation of S-T segment</th>
<th>Significant T wave changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Unipolar electrocardiogram recorded directly over the transplanted heart in the neck of the recipient dog seven days and eleven days after transplantation. The S-T segment and T wave changes suggest acute myocardial injury. The changes in the QRS complex of the recipient heart are probably related to alterations of cardiac position.

Peared histologically normal is difficult to understand. Either sufficient time had not elapsed to permit the development of structural changes or, more probably, routine histologic preparations are not sufficiently sensitive to demonstrate the lesions responsible for the electrocardiographic changes. It is also not unusual to encounter clinical instances in which S-T segment and T wave alterations are associated with a histologically normal myocardium. Under such circumstances the electrocardiographic findings are often attributed empirically to electrolyte disturbances, even in the presence of normal serum electrolyte determinations.

The possibility that the changes in the recipient electrocardiogram were due to factors other than an immune process was also considered. Administration of azathioprine is associated with toxicity in some animals. However, in five animals treated with azathioprine but in whom homologous heart transplantation was not carried out no significant S-T segment or T wave changes were observed. In addition, no changes were observed in the electrocardiogram of 11 dogs treated with azathioprine for kidney transplantation. Thus, it appears unlikely that either azathioprine itself or toxicity due to azathioprine was responsible for the electrocardiographic changes.

Clinical observations indicated that evidence of toxicity in the dogs consisted primarily of lassitude and anorexia. No significant changes were noted in hematocrit, white blood cell count, or serum electrolytes.

The serial changes in the electrocardiogram of the transplanted heart involved both the QRS complex and the S-T segment and T wave. They were consistent with extensive myocardial damage and necrosis, as rejection of the transplanted heart occurred. The mechanism of rejection of homologous tissue is complex. One wonders, however, whether substances released by the damaged transplanted heart might have produced a reaction in the heart of the recipient. It is noteworthy that in other studies, when kidney rather than heart was transplanted, no changes in the electrocardiogram of the recipient dog's heart were observed.

If an immune mechanism is responsible for changing the S-T segment and T wave of the recipient electrocardiogram, then the electrocardiogram may prove to be useful for determining the adequacy of immunosuppressive therapy while the transplanted heart is still viable. There is a need for further study of the electrocardiographic findings reported.
in this paper including detailed histologic examination of the recipient heart and immunologic studies. It is possible that electron microscopic and histochemical study of the myocardium may demonstrate changes associated with an immune myocardial reaction not easily recognized on routine histologic examination. Such studies would not only provide information on the mechanism of organ rejection but might also contribute to the understanding of the nature of the cardiomyopathies occasionally observed in patients with diseases such as lupus erythematosus in which "auto-immunity" has been postulated.

Summary

1) In a series of ten dogs subjected to heart transplantation, serial electrocardiograms were recorded from the transplanted and the recipient hearts.

2) Approximately one week following transplantation, changes appeared in the S-T segment and the T wave of the electrocardiogram of the recipient heart without significant alteration of the QRS complexes. These findings resembled those associated with myocarditis and/or pericarditis.

3) Electrocardiographic changes did not appear in animals treated with drugs alone or in animals subjected to kidney transplantation. These findings suggest the possibility of release from transplanted hearts of an organ-specific substance or substances which affected the hearts of the recipients.

References

Electrocardiographic Studies in Homologous Canine Heart Transplantations
NICHOLAS P. DEPASQUALE, GEORGE E. BURCH, EDGAR PENA and KEITH REEMTSMA

Circ Res. 1965;16:197-202
doi: 10.1161/01.RES.16.3.197

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1965 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/16/3/197

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/