Electrocardiograms of Dogs with Heart Homografts

By Richard R. Lower, M.D., Eugene Dong, Jr., Capt., M.C., U.S.A.F., and Frederic S. Glazener, M.D.

Two aspects of the electrocardiogram, rhythm and voltage, have proved to be of particular importance in the management of dogs with orthotopic cardiac homotransplants. Arrhythmias are frequent in the early postoperative course as the heart recovers from the anoxic insult and adjusts to the denervated state and again in the later stages of cardiac rejection. Changes in the electrocardiographic voltage allow the early detection of threatened rejection, and these voltage changes generally revert after appropriate adjustments in immunosuppressive drug therapy. In this communication the electrocardiographic findings on 50 homografted hearts that survived longer than 4 days will be presented to emphasize the value of this modality in monitoring the cardiac transplant.

Method

Daily electrocardiographic limb lead tracings were taken on 50 dogs with orthotopic cardiac homografts, all of which survived more than 4 days after transplantation. Twelve of the animals received no drug therapy; the remaining 38 received immunosuppressants in variable dosage. Seventeen of the latter group survived from 1 to 12 months after operation. None of the animals received digitalis preparations.

Observations

Early Postoperative Period

In the immediate posttransplant period after electrical defibrillation, 26 (52%) of the hearts demonstrated normal sinus rhythm at a rate ranging from 75 to 150 which was adequate in all cases to permit prompt recovery from the operative procedure. The remaining 24 (48%) demonstrated some form of aberrant rhythm, usually a bradycardia due to atrial arrest with slow nodal or idioventricular rhythm at a rate of 40 to 70. Three animals demonstrated sinus bradycardia, two had complete A-V dissociation, and one had nodal tachycardia. In the majority of the group with bradycardia the rate was insufficient to maintain blood pressure and cardiac output at acceptable levels. Five animals were treated with a pacemaker for 1 to 4 days, and the others received a slow intravenous drip of norepinephrine (1 to 4 μg per minute) which increased the cardiac rate sufficiently to allow full recovery. In about half of the 18 animals demonstrating atrial arrest with slow nodal rhythm, this rhythm alternated with periods of sinus rhythm at which time the rate and blood pressure would markedly improve. The norepinephrine was discontinued in 1 to 6 hours after operation by which time animals with nodal rhythm had an increased rate. The factors responsible for the presence or absence of sinus rhythm after defibrillation of the transplanted heart have not been clearly identified. It appears that cooling the heart below 4 C may result in cold injury to the sinus mechanism, but this has not been established. Occasionally air embolism in the coronary arteries may result in atrial arrest or atrioventricular dissociation.

Within the first 2 days, all transplanted hearts except three demonstrated sinus rhythm at a rate of 92 to 160. One of the three required pacing for 4 days because of persistent heart block, and the other two remained in nodal rhythm at a rate of 92 to 110 for several days; all three subsequently reverted to sinus rhythm. As a result of denervation, all hearts characteristically demonstrated absence of sinus arrhythmia with
the R-R interval remaining constant for long periods when the animal was in the resting state. In the majority of cases the P waves were smaller than normal and frequently were diphasic resembling the deflections encountered in coronary sinus rhythm. The altered P waves are presumably a consequence of sutures placed in the heart graft at the level of the sino-atrial node. One particular arrhythmia of brief duration was seen in 22 (44%) of the animals, usually during the first or second postoperative day. The electrocardiogram (fig. 1) in most instances resembled a ventricular tachycardia or nodal tachycardia with intraventricular block, attended by a deep notched S wave in lead II, prolongation of the QRS to 0.08 to 0.10 second (normal dog mean 0.06 ± 0.01 S.D.) and a peaked upright T wave. The rate was generally 120 to 164, occasionally as high as 240, but was not accompanied by evidence of clinical deterioration. In a few instances in which it was determined, the serum potassium was well within normal range, and none of the animals received digitalis pre-

![Figure 1](attachment:image1.png)

**Figure 1**

This arrhythmia that occurred transiently on the second postoperative day resembles ventricular tachycardia or nodal tachycardia with intraventricular block. It produced no obvious alteration in the clinical status of the animal.

![Figure 2](attachment:image2.png)

**Figure 2**

A progressive fall in QRS voltage preceded death from cardiac rejection on the eighth postoperative day. No drug therapy was administered.

![Figure 3](attachment:image3.png)

**Figure 3**

An episode of threatened rejection was treated with methylprednisolone 200 mg daily on days 14, 15, and 16. Four hundred milligrams of azathioprine were administered during the same 3 days. Note the reversion to more normal voltage by day 17.
HOMOGRAFTED CANINE HEARTS

Changes in Cardiac Rejection

Electrocardiographic abnormalities which appeared beyond the fourth postoperative day were presumed in most instances to be manifestations of homograft rejection. Two changes which correlated well with the histological findings of rejection were a decrease in the QRS voltage and the late occurrence of arrhythmias, particularly conduction disturbances producing bradycardia. A decrease in the voltage of the QRS complexes (fig. 2), seen best in the R wave of limb lead II, occurred in all transplants which demonstrated the morphological changes of acute cardiac rejection, namely pronounced vascular congestion of the myocardium, interstitial edema, and marked infiltration with immunocytes. Fourteen of the animals demonstrated one or more episodes of decreasing QRS voltage which were reversed by initiating or increasing immunosuppressive drug therapy (fig. 3), presumably indicating recovery from threatened rejection. Eight of these had several episodes of low voltage reversed by drugs.

This graph represents a transplant which survived 107 days on immunosuppressants. During the latter half of the course, the R-wave voltage became less responsive to therapy.

Circulation, Volume XXXIII, March 1966
The effectiveness of drugs, particularly steroids, in correcting the voltage decline has been maximal during the first month or two; later episodes of threatened rejection have generally been less successfully treated. Figure 4 illustrates the course of a cardiac transplant which survived for 107 days. Voltage dips in the first 60 days responded well to therapy, but during the last 40 days low voltage persisted despite high dosage of drugs. Postmortem studies in this dog revealed extensive myocardial fiber degeneration with foci of calcification and scattered arterial and arteriolar necrosis. There was only a minimal infiltration by immunocytes, and presumably the myocardial and vascular damage resulted from the numerous bouts of threatened rejection which were incompletely reversed by therapy.

Abnormalities of cardiac rhythm and rate were frequent in animals which at postmortem examination demonstrated the morphological changes of rejection. In all 50 transplants, sinus rhythm was predominant after the first few days, but in 29 (58%) some form of arrhythmia appeared late in the course and was considered related to rejection. In 12 of these the abnormality of rhythm was clinically benign and consisted of occasional dropped beats, or bouts of bigeminal (fig. 5) or trigeminal rhythm. Nodal tachycardia occurred in one and intraventricular block in another. None of this group showed a change in clinical status attributed to the arrhythmias; however, the onset of the arrhythmia probably served as a warning of incipient rejection.

Seventeen animals (34%) developed a more serious arrhythmia at the time of rejection manifested by episodes of bradycardia or brief periods of asystole (figs. 6 and 7). The onset of this form of arrhythmia was frequently preceded by dropped beats similar to those in the previous group. Seven of the animals with a bradycardia of 40 to 65 had slow sinus or slow nodal rhythm; three animals demonstrated complete atrioventricular block. The remaining seven demonstrated episodes of arrest of the sinus mechanism with a few seconds of asystole terminated by the onset of ventricular escape beats or resumption of sinus rhythm. These animals each had one or more typical Stokes-Adams attacks of syncope, occasionally followed by a convulsion. Postmortem examination in this group showed myocardial damage in the form of focal necrosis, calcification, or myocytolysis (fig. 8).

The interpretation of atrioventricular dissociation seen on the electrocardiogram is at times difficult because of the persistence of an electrical impulse from the posterior wall of the host atrium which is retained and to which the heart transplant is sutured. The impulse can be frequently seen as a small P wave dissociated from both the atrial and
HOMOGRAFTED CANINE HEARTS

Myocardial lesions seen in a transplant rejected at 35 days. Despite therapy with hydrocortisone and 6-mercaptopurine, various arrhythmias occurred including atrioventricular dissociation. Postmortem examination revealed the lesions of myocytolysis, scattered calcifications, and infiltration with immunocytes which are characteristic of cardiac rejection.

VENTRICAL IMPULSE OF THE HOMOGRAFT

Two examples in which the impulse (A) from the retained autologous atrium of the host is visible and is dissociated from the atrial (P) and ventricular impulses of the homograft.

Comment

It is apparent from the frequency and severity of the electrocardiographic abnormalities occurring in cardiac homografts that careful electrocardiographic monitoring will be of importance when clinical cardiac transplantation becomes feasible. The atrioventricular conduction problems resulting either from surgical injury or from homograft rejection indicate that artificial pacing should be readily available presumably via an implanted wire electrode.

The voltage of the QRS complex remains the only practical determination for detecting the early onset of cardiac rejection, and thus it provides an indispensable guide for the administration of immunosuppressants. Additional parameters, however, need to be defined if possible to permit an accurate diagnosis of rejection, particularly when arrhythmias or low voltage persist despite high dosage of drugs.

Summary

Serial electrocardiograms from 50 dogs
which survived 4 days to 12 months with orthotopic cardiac homografts have been evaluated. Although sinus rhythm is the basic mechanism in all homografted hearts, arrhythmias are frequently encountered early in the post-transplant period and later during episodes of threatened rejection. The decrease in QRS voltage which consistently ac-
companies impending rejection makes the electrocardiogram indispensable in monitoring the cardiac homograft.

Reference


100 Years Ago: A Campus Riot Described

To the Scottish system of extramural university life the objection has been made of a laxity of discipline favourable to immorality, vice, and insubordination. . . . Of more serious acts of general insubordination, approaching in character to riot, there have been in my time only two: . . . The first, eclipsed by the subsequent one, and now almost forgotten happened in January 1829, when the body of the arch-murderer Burke was brought to the anatomical rooms after execution, to be dissected according to his sentence. Two thousand students took it into their heads that they should like to see him. But the College Bailie—the name of the civil magistrate who, under our old constitution, had charge of the police of the University—took it into his head to resist this wish. Presently he found it necessary to back his resistance by a force of police. A conflict of course at once arose; wounds were interchanged; the police at last were hemmed in at the anatomy corner; and matters began to look uncommonly serious. No aid was asked from the professors. Even Dr. Monro was not communicated with. But a professor, who chanced to be in the quadrangle, volunteered the simple advice to put down the disturbance by granting the students their wish. The irate magistrate at first treated his adviser as a ringleader for recommending such weakness, and even spoke of committing him on the spot. But soon better thoughts prevailed. The students were allowed to file past the dead criminal that afternoon; and the privilege was extended during the next two days to 40,000 of the populace, who, like the students, behaved with the utmost decorum. This was a simple case of something like a riot, arising from nothing else than blundering punctilio and dogged mismanagement.—Graduation Address to the Gentlemen who obtained their Medical Degree in the University of Edinburgh, 1st August 1866, delivered by Professor Christison, Promoter. Edinburgh M J, 12: 195, 1866-67.
Electrocardiograms of Dogs with Heart Homografts
RICHARD R. LOWER, EUGENE DONG, JR., CAPT. and FREDERIC S. GLAZENER

Circulation. 1966;33:455-460
doi: 10.1161/01.CIR.33.3.455
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1966 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/33/3/455

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation 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 is online at:
http://circ.ahajournals.org//subscriptions/