Electrophysiological Studies In the Denervated Transplanted Human Heart

RESPONSE TO ATRIAL PACING AND ATROPINE

By David S. Cannom, Anthony F. Graham, and Donald C. Harrison

ABSTRACT

To date, no studies have documented the conduction characteristics of the atrioventricular conduction system in the transplanted human heart. Three patients who had undergone cardiac transplantation 1–2 years previously formed the basis of this study. All were functional class I symptomatically and had normal hemodynamics and coronary arteriograms at the time of study. Each patient was in sinus rhythm with a normal P-R interval and QRS configuration. None was taking medications known to affect the atrioventricular conduction system. Using the His bundle technique, all were shown to have normal base-line atrium–His bundle (AH) and His bundle-ventricle (HV) conduction times. Recordings were made of both the donor (AD) and the recipient (AR) electrograms. The AD rate was more rapid than the AR rate by an average of 24 beats/min. Right atrial pacing to a rate of 170 beats/min resulted in a progressive lengthening of the AH interval to an average of 205 msec, a result comparable to that in normal patients. At the cessation of rapid pacing, AD recovery time averaged 770 msec, which is normal. The administration of 1–2 mg of atropine increased the AR rate by an average of 28% but did not alter the AD rate; the AH intervals did not change. We conclude that (1) the normal AH intervals at rest and the increased AH intervals during pacing demonstrate the inherent conduction delay imposed by the atrioventricular node independent of autonomic influence, (2) the AD recovery time after overdrive is an inherent property of the AD sinus node, and (3) the absence of change in the AD rate or the AH interval after administration of atropine suggests that parasympathetic reinnervation has not occurred in these patients.

Prior studies analyzing the intrinsic properties of cardiac conduction have used either transplanted or denervated canine hearts or isolated in vitro preparations of appropriately prepared conducting tissue. Human cardiac transplantation has provided a unique experimental model for studying both the intrinsic and the autonically mediated conduction characteristics of the heart. This study is the first systematic investigation of the conduction properties of the atrioventricular conduction system in the transplanted human heart.

Three long-term survivors of cardiac transplantation were studied using standard His bundle recording techniques. In these studies two interventions—right atrial pacing and atropine administration—were applied. The data obtained from this unique physiological preparation provide the basis for this report.

Methods

Three patients who had received transplanted human hearts 1–2 years previously formed the basis of this study. At the time of study all of the patients were clinically well (functional class I of the New York Heart Association) and were admitted to the hospital as part of the ongoing routine evaluation of our population of surviving cardiac transplant patients. The clinical profile of each patient is summarized briefly in Table 1. None was taking any medication known to alter the conduction characteristics of the atrioventricular conduction system.

In each patient the surgical technique employed at the time of transplant was that previously described by Stinson et al. (1). The donor heart was excised by opening a wide lateral incision in the right atrium to...
STUDIES IN THE TRANSPLANTED HEART

TABLE I

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Pretransplant cardiac disease</th>
<th>Date of transplant</th>
<th>Date of study</th>
<th>Medications</th>
<th>Coronary arteriogram</th>
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<td>1/5/72</td>
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CAD = coronary artery disease, RHD = rheumatic heart disease, LV = left ventricular, q.d. = every day, q.i.d. = four times a day, and q.o.d. = every other day.

which the recipient atrium was sutured. As a result, the donor sinus node was not included in the atrial suture line, and its function was not susceptible to postoperative healing. The recipient sinus node remained in its original location, and it was separated by a suture line from the donor atrium. Consequently, the transplanted heart had two independently functioning sinus nodes whose activity will subsequently be referred to as that of the recipient atrium (A_R) and that of the donor atrium (A_D).

The voluntary nature of the current studies was explained to each patient, and informed consent was obtained in each case. All of the patients were given systemic antibodies (penicillin and methicillin) the night before and the day of the study. However, concern about infection in these patients receiving immunosuppressive therapy limited the interventions performed on any one patient. Each patient tolerated the procedure well with no evidence of postcatheterization infectious complications.

The electrophysiological studies were made approximately 20 minutes after determination of each patient's hemodynamic status and study of his coronary arteries by the Judkins technique. For these studies, the right femoral artery and the right femoral vein were used. At the conclusion of the studies, a femoral artery cannula was left in place for drug administration, and the right femoral vein pressure catheter was exchanged for a quadrupolar electrode catheter which was positioned in the right atrium and abutting the donor sinus node. The catheter was manipulated until stable atrial electrograms of the donor and the recipient atria were recorded. The distal two terminals of the quadrupolar catheter were attached to a battery-powered pacemaker (Medtronic 5837) which delivered impulses 2 msec in duration and was used for right atrial pacing. Using techniques previously described (2), a tripolar catheter was inserted into the left femoral vein and positioned to record the His bundle electro gram.

The signals from the proximal terminals of the atrial catheter and the His bundle electro gram were transmitted to the a-c input of an electrocardiographic (ECG) amplifier with filter frequencies set between 40 and 500 Hz. A standard ECG lead II was recorded, and all signals were simultaneously displayed on a switched-beam Electronics-for-Medicine oscilloscope and recorded on photographic paper at a paper speed of 100 mm/sec.

Initial base-line measurements were made in each patient of the A_E cycle length, the A_D cycle length, the atrium—His bundle (AH) conduction interval, and the His bundle—ventricle (HV) conduction interval. Standard definitions for measuring AH and HV times were used.

Atrial pacing was performed in patients 1 and 3, beginning at a rate slightly greater than the A_D rate and gradually increasing the rate by 10 beats/min until a rate of 170 beats/min was reached. The patient was then paced at 155 beats/min for 2 minutes, and the pacemaker was abruptly turned off and the recovery time of the donor sinus node measured. A stable atrial pacing position could not be found in patient 2, and this phase of the study was not carried out in this patient.

After the patient's heart rate had stabilized to control values, atropine was administered through the indwell ing arterial line. Patient 2 received 1 mg and patients 1

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and 3 received 2 mg slowly over 2 minutes. The subsequent rate response of the recipient and the donor atria, as well as the AH and the HV intervals, were continuously monitored for the next 10 minutes.

**TABLE 2**

<table>
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<th>Patient</th>
<th>Control values (msec)</th>
<th>Rate (beats/min)</th>
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<th>Time (min)</th>
<th>Atropine (msec)</th>
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<td>170</td>
<td>210</td>
<td>7</td>
<td>750</td>
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</table>

*Pacing experiments were not done on this patient.

**FIGURE 1**

Twelve-lead electrocardiogram of patient 1 at time of study.

*Cannom, Graham, Harrison*
Results

The experimental data obtained in these studies are summarized for each patient in Table 2. The hemodynamic data for each patient were normal, including left ventricular end-diastolic pressure (<12 mm Hg), pulmonary artery pressure (<30/15 mm Hg), pulmonary artery wedge pressure (<12 mm Hg mean), and cardiac output (>4.5 liters/min). Also, all of the patients had normal coronary arteries as demonstrated by coronary arteriography.

A standard 12-lead electrocardiogram taken during the hospitalization period is shown for each patient in Figures 1-3. Each patient was in sinus rhythm, and the activity of the recipient atrium, which can often be seen on standard electrocardiograms in transplanted hearts, was not discernible in these tracings. The P-R intervals were all normal, and the QRS complex was of normal duration. The electrocardiograms of the patients in Figures 1 and 2 showed left anterior hemiblock.

The corresponding His bundle electrograms recorded during the control state for each patient are shown in Figures 4-6. The values for the AH and the HV times were all within normal limits for our laboratory (Table 2). In patients 1 and 2 it was possible to record the activity of the donor and the recipient atria via the right atrial catheter (Figs. 4, 5). In patient 3 only the activity of the recipient atrium was recorded; this activity was clearly independent of the sinus P wave preceding each QRS complex (Fig. 6). In each patient the intrinsic rate of the donor atrium was faster by 150 to 320 msec/cycle than that of the recipient atrium, accounting for the resting tachycardia noted in these patients.

In patients 1 and 3, in whom atrial pacing was performed, the AH interval lengthened successively as the pacing rate was gradually increased (Table 2). There were no changes in the HV interval during the pacing sequence. Pacing was continued to a rate of 170 beats/min with gradual lengthening of the AH interval but with no evidence of atrioventricular block, as is frequently observed in normal hearts at these rates.
Figure 7 demonstrates the changes seen with pacing in patient 1. Although the A_H to His bundle interval increased at faster pacing rates, there was no effect on the A_A rate: the recipient atrium fired independently at its base-line rate.

Figure 8 illustrates the recovery time of the donor sinus node in patient 1 after rapid atrial pacing. After an interval of 790 msec the donor atrium initiated a normal sinus beat which was conducted in an antegrade manner. The sinus node recovery time for patient 3 was 750 msec. Both of these values are within the limits reported from other laboratories in which rapid atrial pacing has been performed on groups of normal patients (3).

The response to atropine administration in the three patients is summarized in Table 2. The rate of the recipient atrium increased 24-30% (average 28%) with little or no change in the rate of the donor atrium. The AH and the HV intervals did not change. The response to 2 mg of atropine for patient 1 is shown in figure 9.

Discussion

This paper presents the first studies of the atrioventricular conduction system in the transplanted human heart and permits (1) a comparison of the conduction properties of the homografted heart with those of the normal human heart and (2) an analysis of the effects of denervation on atrioventricular conduction with particular reference to prior studies in the denervated canine heart. In addition, this study demonstrates that standard His bundle techniques can be safely employed in the study of the cardiac transplant patient.

The 3 patients selected for study were among the longest survivors of the 42 patients who have undergone transplantation at Stanford. None of the patients had postoperative conduction abnormalities, and they all had normal hemodynamics and coronary arteriograms at the time of their cardiac catheterization. Symptomatically the 3 patients were considered to be functional class I (New York Heart Association classification).
Control measurements of the AH and the HV intervals in the three patients were within normal limits for our laboratory and represented average values for normal patients similarly studied. These findings are in agreement with the prior work of Wallace et al. (4), who found that in dogs denervation did not affect atrioventricular conduction time. The normal AH times in the denervated heart support the hypothesis that under baseline conditions the atrioventricular node is influenced little, if any, by parasympathetic innervation but rather that there is inherent delay in conduction velocity at the atrioventricular node which is independent of vagal influence (5). The HV interval has not previously been shown to be affected by vagal tone and was normal in each patient after cardiac transplant (5).

The intrinsic rate of the donor atrium at rest was more rapid than that of the recipient atrium by an average of 24 beats/min. Although not previously documented by intracardiac electrograms, a resting tachycardia is typically observed in the transplanted heart. The increased rate of the donor atrium at rest suggests that the sinus node is more responsive than
the atrioventricular node at rest to the absence of vagal tone. These observations also support the contention that at rest the normal sinus node is under more parasympathetic than sympathetic influence.

The effect of increasing the heart rate by right atrial pacing in two patients to 170 beats/min was to lengthen the AH interval from 90 msec to 210 msec (patient 3) and from 100 msec to 200 msec (patient 1). These results are comparable to earlier studies by Damato et al. (6) in subjects with normal P-R intervals and suggest that inherent antegrade conduction delay imposed by the atrioventricular node is more important in prolonging atrioventricular conduction—the AH interval—at faster pacing rates than is the presence of excess cholinergic tone or diminished adrenergic tone. The prolongation of the AH interval was more pronounced the faster the atrial rate. Although the development of second degree heart block (type 1) is common in normal patients at pacing rates above 140 beats/min, this phenomenon was not noted in our patients. Atrial pacing, using less than 5 ma, did not allow capture of the recipient atrium (Fig. 7), presumably because the suture line separating the two atria blocked capture.

When rapid atrial pacing was abruptly terminated in the two patients, the donor sinus node recovery time was 750 msec (patient 3) and 790 msec (patient 1). These values are comparable to the results seen in normal patients in whom overdrive suppression has been studied (3). We conclude that sinus node recovery time after overdrive suppression is an intrinsic property of the spontaneously depolarizing sinus node and not a function of autonomic influence at the sinus node. These observations are comparable to the recent studies of Millar et al. (7), who noted that sinus node recovery time in dogs was not affected by bilateral stellectomy.

The systemic administration of atropine had a comparable effect in all three patients. In each the rate of the recipient atrium increased by an average of 25%. The rate of the donor atrium did not change during atropine administration.

Prior studies by Cooper et al. (8) in the denervated canine heart did not show a chronotropic response to systemic atropine. The absence of a response in rate by the donor atrium in the transplanted human hearts is comparable to the results of Cooper et al. and is compelling evidence that the transplanted sinus node is not under autonomic control in these patients.

The absence of an effect on the AH interval after atropine administration in these patients suggests that parasympathetic influence is also absent at the atrioventricular node. Other workers (6) have shown a shortening of the AH interval after 0.5 mg of atropine was given intravenously, presumably due to the vagolytic effect of atropine at the atrioventricular node. However, in our patients AH intervals were not shortened even when atropine was given in doses four times those used in prior work, supporting the thesis that vagal innervation is not operant at the atrioventricular node in the transplant patients.
FIGURE 7

A–C illustrate the right atrial pacing sequence for patient 1. Shown are lead II of the standard electrocardiogram (LII), the high atrial electrogram (AE), and the two His bundle electrograms (HBE). Donor atrial activity (AD) and recipient atrial activity (AH) are labeled. The pacing stimulus is seen in lead II (S). As the donor atrial rate is increased from a rate of 120 beats/min in A to 162 beats/min in C, the AH interval increases from 120 msec to 190 msec. The HV interval remains constant at 50 msec. Note that the recipient and the donor atrial activity remain independent at even the fastest rates. No atrioventricular block is noted.
From studies on these patients we conclude that reinnervation of the transplanted heart has not occurred at 1–2 years after transplantation. However, unless they represent a species difference, these data are at variance with the study by Willman et al. (9). In their study of dogs that underwent orthotopic autotransplantation, it was possible to demonstrate slowing of the heart by stimulation of the cervical vagus nerve. At 1 year, this effect was considered to be evidence of vagal activity at the sinus node. Other interventions used by Willman et al. to demonstrate reinnervation, including infusions of tyramine and norepinephrine (which caused unusual degrees of augmentation of rate on the denervated heart), should be employed in future studies of long-term survivors of cardiac transplantation.

Recent studies have described the pathology of the conduction system in the transplanted canine heart (10). Twenty dogs underwent cardiac transplantation and were treated with minimal doses of immunosuppressive drugs. Twelve of the 20 dogs died of acute rejection, surviving an average of 9 days. These deaths were associated with a high incidence of cardiac arrhythmias, and at necropsy impressive changes in the conduction system were noted in all, ranging from cellular infiltration to frank necrosis of the atrioventricular node and bundle branches.

These observations were extended in a pathologic study of the first 12 patients dying at Stanford after cardiac transplantation (11). Although not the cause of death, pathologic features of rejection were noted in all patients. Again, there was a high association of cardiac arrhythmias with marked changes in the morphology of the conducting system. A variety of changes was noted in the coronary arteries with the only consistent change being obliterator intimal proliferation which was time dependent and related to the number of treated rejection episodes.

These early findings are in marked contrast to the status of the three patients included in this study. This difference in proven coronary disease and conduction abnormalities may be related to the more aggressive management of rejection episodes recently employed. In the overall series of patients who have died at Stanford after transplantation with proven coronary artery disease, there has been an average of 3.3 episodes of rejection, 1.8 of which were judged moderate or severe. In contrast, those ten patients who have been shown to have normal coronary arteries at arteriography at an average of 16 months after the transplant have had an average of 2.3 episodes of rejection, of which only 1.1 were moderate or severe. The three patients in this study are part of the latter group with fewer rejection episodes. The lower incidence of rejection episodes in these latter patients, which contrasts with the earlier Stanford experience cited above, may
A–C record the response of patient 1 to 2 mg of systemically administered atropine. Labeling is the same as in Figure 7. A: Control tracing. B: Record at 1 minute. C: Record at 10 minutes. After 1 minute the interatrial rate of the recipient atrium (AR) has increased from 700 msec (A) to 500 msec (B), but the donor atrium (AD) rate has not changed. By 10 minutes the recipient atrial rate has decreased to 530 msec, while the donor atrial rate is still 650 msec.

account for the normal coronary arteries and the absence of conduction abnormalities postoperatively. Also, their conduction systems, when evaluated by current methods, appear normal although...
without reinnervation and suggest that the widespread anatomic changes in the atrioventricular conduction system noted in earlier patients are not present in these long-term survivors.

Acknowledgment

The authors gratefully acknowledge the technical assistance of Mr. Carl Simpson in the performance of these studies.

References


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