Electrophysiological abnormalities in the transplanted human heart

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SUMMARY Fourteen relatively long term survivors of cardiac transplantation underwent systematic electrophysiological evaluation and ambulatory electrocardiographic monitoring. Six patients had prolonged conduction intervals during sinus rhythm. Sinus node function could be assessed in all donor atria and in 10 recipient atria. Sinus node recovery times were prolonged in four of the donor atria and in six recipient atria. In the donor atria abnormalities of sinus node automaticity were invariably associated with abnormalities of sinoatrial conduction. Four patients showed functional duality of atrioventricular nodal conduction during programmed extrastimulation, but no patient developed re-entrant arrhythmia. During ambulatory electrocardiographic monitoring no pronounced tachyarrhythmias were recorded. Three patients showed abnormalities of sinus node impulse formation. All three patients had abnormal sinus node recovery times during their electrophysiological study. Long term survivors of cardiac transplantation have a high incidence of electrophysiological abnormalities. Abnormalities of donor sinus node function are probably of clinical significance. The clinical significance of abnormalities detected within the atrioventricular conduction system of the denervated heart remains to be elucidated.

The therapeutic and prognostic implications of abnormalities found during invasive electrophysiological testing have been widely reported.¹⁻⁵ Although the sensitivity and specificity of formal testing of sinus node function in man may be limited,^{6,7} abnormalities within the atrioventricular conduction system, particularly in certain subgroups of patients or when associated with other cardiovascular abnormalities, appear to carry greater therapeutic implications.⁸⁻¹⁰ The significance of electrophysiological abnormalities in asymptomatic, apparently normal subjects has obviously not been determined.

Although previous reports from both Stanford University, California, and Papworth Hospital, Cambridge, have indicated a high incidence of both atrial and ventricular arrhythmias in transplant patients^{11,12} together with a relatively high incidence of sinus node

disease,^{13,14} the incidence of abnormalities found during electrophysiological testing has not been reported. The purpose of this investigation was to detail the abnormalities detected during a systematic electrophysiological evaluation and during the ambulatory electrocardiographic monitoring of a group of relatively long term survivors of cardiac transplantation.

Patients and methods

Fourteen cardiac transplant recipients underwent routine electrophysiological evaluation four to 28 (mean 14) months after transplantation. Their ages ranged from 24 to 54 (mean 38) years, and 13 patients were men (Table). The study was performed because of the previous reports of a high incidence of sinus node and conduction system disease in patients after cardiac transplantation,¹¹⁻¹³ which in at least one study has been associated with an increased mortality.¹⁴ All patients were completely asymptomatic with no haematological, biochemical, or electrocardiographic evidence of rejection. All patients were

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Table Patient details and results

Case No.	Sex	Diagnosis before transplant	Age at time of study (years)	Survival at time of study (months)	Abnormal conduction intervals	Abnormal sinus node function tests	Abnormal refractory period
1	M	IHD	43	4	+	-	-
2	M	CM	41	9	-	-	-*
3	M	IHD	44	11	+	-	-
4	M	CM	37	18	-	-	-
5	M	CM	24	17	-	-	-
6	M	CM	24	14	+	-	-*
7	M	IHD	31	22	+	+	-*
8	M	IHD	54	28	+	+	-*
9	F	CM	34	8	-	+	-
10	M	IHD	28	14	-	+	-
11	M	IHD	49	18	-	-	-
12	M	IHD	35	17	-	-	-
13	M	IHD	53	15	+	-	-
14	M	IHD	42	7	-	+	-

IHD, ischaemic heart disease; CM, cardiomyopathy; *, functional duality of atrioventricular nodal conduction; +, present; -, absent.

taking prednisolone and azathioprine as routine immunosuppressive treatment, and no patient was taking cardioactive drugs. Seven patients had implanted epicardial ventricular demand pacemakers, which had been implanted at operation because of the previously reported poor prognosis associated with early sinus node dysfunction after transplantation.¹⁴

ELECTROPHYSIOLOGICAL STUDY

The patients were studied in the non-sedated, postabsorptive state after written informed consent had been given. Prior approval for the study had been obtained from the ethical committee of St Bartholomew's Hospital. All patients were premedicated with intramuscular flucloxacillin, which was continued orally for two days after the electrophysiological study, and there was no appreciable short term or long term morbidity associated with the study. Five pacing electrodes were inserted into the right femoral vein under local anaesthesia and positioned within the heart using fluoroscopic guidance. During orthotopic cardiac transplantation¹⁵ the posterior portions of the recipient atria are left in situ together with the recipient sinus node. A quadripolar electrode was therefore positioned at the junction between the superior vena cava and right atrium to record and stimulate the recipient atrial remnants. Two bipolar electrodes were positioned within the appendage of the donor right atrium for recording and stimulation. An electrode was manipulated across the septal leaflet of the tricuspid valve to record distinct electrograms from the low right atrium, His potential, and the proximal portion of the right ventricular septum. A further electrode was advanced to the apex of the right ventricle for stimulation.

Bipolar endocardial signals from the electrodes were passed through appropriate amplification and filtering and recorded on a Mingograf ink jet recorder

at 100 mm/s, together with four surface electrocardiographic leads. Intracardiac stimulation was achieved using constant voltage, current limited square wave pulses of 1.5–2.5 ms duration at about twice diastolic threshold.

Conduction intervals were measured during sinus rhythm and during constant rate donor right atrial pacing at cycle lengths of 500 ms and 400 ms. The intervals were measured according to previously described definitions¹⁶ and defined as normal or abnormal based on the normal range of values for normally innervated adult man.^{17–20} Sinus node recovery time was assessed by overdrive suppression²¹ and was defined as the maximum sinus pause after stopping right atrial pacing at rates of 110 (if appropriate), 130, 150, and 170 beats/min for periods of 15, 30, and 60 s at each rate. The results were corrected by subtracting sinus cycle length.²² The upper limit of normal for sinus node recovery time was accepted as 1400 ms²³ and for corrected recovery time as 525 ms.²² Both donor and recipient sinus node recovery times were assessed during synchronous pacing of both sets of atria. Sinoatrial conduction time was assessed by introducing programmed atrial beats during sinus rhythm and calculated according to the revised method of Strauss *et al.*²⁴ The upper limit of normal was accepted as 206 ms.²⁵ Both donor and recipient sinoatrial conduction times were assessed.

Anterograde and retrograde conduction characteristics and refractoriness of the donor heart were determined by introducing an extrastimulus after regular donor atrial or ventricular pacing^{26,27} at cycle lengths of 500 ms and 400 ms. Standard definitions^{16,26,27} and normal values^{27–29} were used for estimating the effective and functional refractory periods of the various components of the atrioventricular conduction system.

Functional duality of atrioventricular nodal con-

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duction was considered to be present when, during assessment of atrioventricular nodal refractoriness, there was a discontinuity on the anterograde conduction curve with a sudden jump in the H1-H2 interval, and therefore concomitantly in the A2-H2 interval, at a critical A1-A2 coupling interval.³⁰⁻³² Duality of atrioventricular nodal conduction was defined as a jump in the H1-H2 interval of 40 ms or greater for a decrease of 10 ms in the A1-A2 coupling interval.³² The curve to the right of the discontinuity represents fast atrioventricular nodal pathway conduction and to the left slow pathway conduction.

In one patient the electrophysiological study had to be ended prematurely for technical reasons. Conduction intervals and sinus node function tests from 14 patients and refractory periods from 13 patients are therefore reported below.

AMBULATORY ELECTROCARDIOGRAPHIC MONITORING

Each patient underwent 24 hour ambulatory electrocardiographic monitoring using either four inch reel to reel two channel tape recorders or two channel cassette recorders. The recordings were subjected to automatic and technician analysis to assess the incidence of arrhythmic episodes of any origin or aetiology or evidence of sinus node or conduction system disease.

Results

CONDUCTION INTERVALS

During sinus rhythm four patients had prolonged PA intervals (55 ms, 60 ms, 60 ms, and 70 ms), two patients had prolonged HV intervals (both 60 ms), and two patients had prolonged QRS durations (115 ms and 130 ms) (Fig. 1). Both the patients with prolonged QRS durations had complete right bundle branch block. In one of these patients the abnormality

Fig. 1 Conduction intervals in individual patients. The mean $\pm$ 1 SD is also indicated. Dashed lines indicate the upper limit of normal for normally innervated man.

had been present on the donor electrocardiogram before transplantation. Although eight patients had a prolonged QTc, no patient had a prolonged QT interval measured during sinus rhythm based on normal values.²⁰

SINUS NODE FUNCTION (Fig. 2)

In two patients no electrical activity of the recipient atrium was recorded nor could this atrium be paced despite high pacing energies. In one patient the recipient atrium was fibrillating while the donor atrium remained in sinus rhythm (Fig. 3). In one patient the donor and recipient atria remained synchronised throughout a variety of physiological and pacing manoeuvres. This unique situation has been reported elsewhere.³³ The sinus node function of 14 donor atria and 10 recipient atria could therefore be assessed.

Fig. 2 Results of sinus node function tests in individual patients. The mean $\pm$ 1 SD is also indicated. Dashed lines indicate the upper limit of normal for normally innervated man. SCL, sinus cycle length; SNRT, sinus node recovery time; cSNRT, corrected sinus node recovery time.

Fig. 3 Electrocardiogram illustrating the recipient atrium in atrial fibrillation while the donor atrium remains in sinus rhythm. RAr, recipient atrial electrogram; RAd, donor atrial electrogram; HBE, His bundle electrogram. I, aVF, V1, and V6 are surface electrocardiographic leads.

Fig. 4 Electrocardiogram showing a considerably prolonged recovery time of the donor sinus node. The secondary pause is interrupted by a ventricular escape beat which is almost synchronous with a sinus escape beat. The arrow indicates the last pacing stimulus (pacing both recipient and donor atria). This pause follows pacing at a rate of 130 beats/min for 60 s. RAr, recipient atrial electrogram; RAd, donor atrial electrogram; HBE, His bundle electrogram. I, aVF, V1, and V6 are surface electrocardiographic leads.

Fig. 5 Anterograde conduction curve showing functional duality of atrioventricular nodal conduction. The curve to the right of the discontinuity represents fast pathway conduction and to the left of the discontinuity slow pathway conduction. In this example there is a jump in the A2-H2 interval of 70 ms for a 20 ms decrease in the A1-A2 coupling interval. BCL, basic cycle length.

Fig. 6 Electrophysiological recordings showing the jump in AH interval as the fast pathway becomes refractory. Panel a shows a basic driven pacing cycle length (S1-S1) of 500 ms with an AH interval (A1-H1) of 65 ms followed by an atrial extrastimulus with a coupling interval (S1-S2) of 300 ms. The extrastimulus (S2) conducts through the fast pathway with an AH interval (A2-H2) of 160 ms. In panel b with an S1-S2 interval of 280 ms the refractory period of the fast pathway has been exceeded and the extrastimulus (S2) conducts through the slow pathway with an AH interval (A2-H2) of 280 ms. All measurements are in ms. RAr, recipient right atrial electrogram; LA, left atrial electrogram; RAd, donor right atrial electrogram; HBE, His bundle electrogram. I, aVF, V1, and V6 are surface electrocardiographic leads.

The sinus cycle length was greater than 1000 ms in one of the donor atria and in four of the recipient atria. Sinus node recovery times and corrected recovery times were prolonged in four (of the 14) donor atria and in six (of the 10) recipient atria. In two patients (cases 8 and 9) the donor sinus node recovery time exceeded 2500 ms (Fig. 4). One of these patients (case 9) had an implanted ventricular pacemaker, the other did not. The uncorrected sinoatrial conduction time (measured using the method of Strauss²⁴) of the donor atria was prolonged in four patients (206 ms, 220 ms, 240 ms, and 460 ms) and abnormally short in one patient (5 ms). Four of these five patients had prolonged donor sinus node recovery times. In one patient the dramatically prolonged sinoatrial conduction time (460 ms) was due to considerable sinus node suppression during the zone of reset. Even after correcting this value for sinus node suppression, however, the sinoatrial conduction time was still prolonged at 275 ms. The recipient sinoatrial conduction time was prolonged in four patients (222 ms, 234 ms, 235 ms, and 282 ms), but only two of these patients had prolonged recovery times.

REFRACTORINESS

The atrial, ventricular, and atrioventricular refractory periods estimated at a cycle length of 500 ms were all within normal limits. Four patients had evidence of functional duality of anterograde atrioventricular nodal conduction during assessment of atrioventricu-

lar nodal refractoriness at a pacing cycle length of either 500 ms (three patients) or 400 ms (three patients) (Figs. 5 and 6). Jumps in the A2-H2 interval ranged from an increase of 50 ms for a 10 ms decrease in the A1-A2 coupling interval to an increase of 105 ms for a 5 ms decrease in A1-A2 interval. Only one patient showed functional duality of conduction in the retrograde direction.

From these previous results and the table it can be seen that only four patients (cases 4, 5, 11, and 12) had entirely normal electrophysiology of the transplanted donor heart.

AMBULATORY ELECTROCARDIOGRAPHIC RECORDINGS

A total of 447 hours of ambulatory electrocardiographic recordings were performed in the 14 patients. The period of monitoring ranged from 20 to 70 (mean 31.9) hours. Seven patients had no abnormalities. One patient had flutter of the donor atrium on his first 24 hour recording. He had no clinical, biochemical, or haematological evidence of rejection and underwent DC cardioversion under a general anaesthetic five hours before his electrophysiological study, during which donor sinus node function was normal. There was no abnormality on his second recording. Three patients (cases 1, 3, and 11) had infrequent unimorphological ventricular premature beats (less than one per hour), but in one of these patients (case 1) the premature beats occurred in couplets. Two of these

three patients (case 1 and 3) also had a moderate number of atrial premature beats, which in case 1 occurred in couplets and on one occasion initiated a 3 s run of atrial fibrillation. No episode of ventricular tachyarrhythmia was recorded in any patient.

Three patients (cases 8, 9, and 14) showed relative bradycardias throughout their recordings. Two of these patients (cases 9 and 14) had implanted ventricular pacemakers, the other did not (case 8). All three patients had abnormal donor sinus node function tests during their electrophysiological evaluation. Patient case 8 (corrected sinus node recovery time 1440 ms) showed sudden changes in sinus rate, sometimes by as much as 33 beats/min, with the initial pause interrupted by a junctional escape beat on occasions. The sinus rate fell to 57 beats/min at times, even during waking hours. The recordings in case 9 showed sinus rates less than 80 beats/min at all times and ventricular demand pacing at 70 beats/min for a high proportion of the 24 hours including waking hours. This patient had a corrected donor sinus node recovery time of 1360 ms during her electrophysiological study. The recording in case 14, who had a corrected donor sinus node recovery time of 935 ms, showed several episodes of ventricular demand pacing at 70 beats/min and donor sinus rates never exceeding 85 beats/min. This patient also had sudden changes in heart rate, which usually followed an atrial premature beat. The P wave of the slower atrial rhythm had a different morphology and vector to that of the faster rate, suggesting different sites of origin of the two atrial pacemakers.

Discussion

The incidence and significance of abnormalities of the atrioventricular conduction system found during invasive electrophysiological studies of symptomatic patients and patients with obvious conduction system disease, or during routine surface electrocardiographic screening of asymptomatic subjects, have been well reported.^{3 4 9 10 18 34-37} The incidence and significance of abnormalities of the conduction system detected during electrophysiological evaluations in asymptomatic patients with normal surface electrocardiograms are, naturally, unknown. Similarly, the influence of the denervated state of the transplanted heart on the significance of abnormalities detected is unclear. Other studies from our laboratory (unpublished observations) have shown that the electrophysiological characteristics of the atrioventricular conduction system of the transplanted heart are similar to those of the innervated heart and therefore the significance of conduction abnormalities found in the transplanted heart may probably be equated to that reported for the innervated heart.

Four patients had a prolonged intra-atrial conduction time. Impulse conduction from the sinus node to the atrioventricular junction probably takes place primarily through muscular connections.³⁸ The surgical technique entailed in cardiac transplantation may result in damage to these muscular connections, and this, together with the physical distortion of the donor atrium, may account for the high incidence of intra-atrial conduction delay in these patients. Such conduction delay may result in first degree heart block,¹⁸ but spontaneous higher degrees of block have never been reported. Second degree Wenckebach type block within the atrium has, however, been reported with atrial pacing.^{39 40}

The finding of a slightly prolonged HV interval in two patients, who were asymptomatic and had normal surface electrocardiograms, is probably of no clinical significance. Although the significance of a prolonged HV interval in patients presenting with syncope is well documented,³⁶ in asymptomatic patients, even those with bundle branch block, reports of the prognostic implications of His-Purkinje conduction delay have been conflicting.^{3 4}

Two of the 14 patients had complete right bundle branch block, although in one of these this had been present before operation in the donor heart. This compares with reported prevalences of 0.18% in 122 043 airmen,³⁵ 0.4% in an insurance population of 30 000 subjects,⁴¹ 0.75% in 3983 airmen,³⁴ and 1.15% in 8770 members of an average population.⁴² The long term follow up studies of Mathewson and Varnam,³⁴ Reusch and Vivas,⁴² and Rotman and Triebwasser³⁷ of subjects with right bundle branch block showed that in subjects with no evidence of heart disease and a normal axis the only deaths were due to non-cardiac causes and no cases of advanced atrioventricular block were recorded. Similarly, in the mortality study of Rodstein *et al.*⁴¹ the presence of right bundle branch block did not imply a higher mortality in the absence of other major cardiac abnormalities.

The limitations of invasive electrophysiological testing of sinus node function in normally innervated man^{6 7 25} are well known. There is often a poor correlation between the results of electrophysiological testing and the presence or absence of symptoms.^{6 43} and clinical signs and symptoms may result primarily from escape pacemaker malfunction and not from the sinus node malfunction itself.⁴⁴ The effect of the autonomic nervous system may be important,⁴⁵ and perhaps of prime importance, in terms of the prognosis of sinus node disease, is the coexistence of underlying heart disease.^{24 46}

In the absence of autonomic neural influences formal testing of donor sinus node function in transplant patients may provide a more reliable indicator of true intrinsic sinus node function than in the innervated

heart, as has been suggested from studies using pharmacological autonomic blockade.^{47,48} The spontaneous abnormalities of sinus node function found during ambulatory electrocardiographic monitoring in three of the four patients with abnormal sinus node function tests during invasive testing but in none of the patients with normal sinus node function tests add further credence to this theory. These three patients also showed relative bradycardias during their 24 hour recordings. In the absence of the normally dominant vagal tone⁴⁹ the resting heart rate of the denervated sinus node tends to be faster than in the innervated heart with resting heart rates of 100 beats/min or greater.

The clinical course of the sick sinus syndrome may be variable but tends to be progressive,¹ and its prognosis is uncertain. The ultimate prognosis depends partly on the characteristics and stability of the escape rhythm of lower pacemakers, which may be unreliable in transplant patients.¹⁴ The finding of abnormalities of donor sinus node function during invasive testing in transplant patients may therefore be of greater clinical significance than abnormalities found in patients with normally innervated hearts. The high incidence of recipient sinus node disease may well be related to underlying disease before the operation and to the relative ischaemia induced by the surgery but is probably of limited clinical importance.

Four of the 13 patients in whom atrioventricular nodal refractory periods were assessed showed functional duality of atrioventricular nodal conduction. Dual atrioventricular pathways predispose to atrioventricular nodal re-entrant tachycardia in man^{30,31,50} as originally hypothesised by Moe *et al.*⁵¹ and later shown by Mendez and Moe⁵² in animal experiments, and they are a common finding during electrophysiological testing of patients with supraventricular tachycardia.⁵³ They are also a relatively common finding in arrhythmia free adults⁵⁴ and children.^{32,55} Denes *et al.*⁵⁴ showed dual pathways in 41 out of 397 patients studied. Sixteen of these 41 patients were arrhythmia free. Similarly Thapar and Gillette³² reported an incidence of 29%, and Casta *et al.*⁵⁵ reported an incidence of 35% in arrhythmia free children with a variety of congenital cardiac defects. This high incidence of dual atrioventricular nodal pathways in children may be related to their considerably shorter atrial refractory periods,⁵⁵ which would allow the unmasking and increased expression of dual pathways. The relatively high incidence of dual pathways in transplant patients (31%) may be related to the young age of the donor hearts, to the slightly shorter refractory periods of the atrioventricular conduction system compared with innervated hearts, and, to an unknown extent, to the denervated state of the transplanted heart. All four patients had retrograde

ventriculoatrial conduction, but only one patient had retrograde functional duality of conduction and no patient showed atrial echoes during programmed extrastimulation at either basic pacing cycle length. Hence no patient developed sustained re-entrant tachycardia. Although dual pathways are the electrophysiological substrate for atrioventricular re-entrant tachycardia, its initiation depends on an interplay of many factors. It is not known whether the finding of dual pathways in an arrhythmia free patient is a benign electrophysiological phenomenon representing the normal functional characteristics of the human atrioventricular node or whether these patients are at risk of developing a clinically important arrhythmia. Long term longitudinal studies of such patients are not available.

Although previous studies from Stanford University^{11,12} have reported a high incidence of both atrial and ventricular arrhythmias in asymptomatic transplant patients, this was not borne out by us. Infrequent atrial and ventricular premature beats were recorded in only four patients, and the only appreciable arrhythmia recorded was a short run of atrial fibrillation in one of these patients. The period of recording was obviously relatively short and few conclusions can be drawn about the incidence and significance of arrhythmias in these patients.

Asymptomatic, relatively long term survivors of cardiac transplantation thus have a high incidence of electrophysiological abnormalities. As already indicated, abnormalities of donor sinus node function may well be of clinical significance, although long term follow up studies are required to clarify this point. Limited data from studies in normally innervated man suggest that the abnormalities found within the atrioventricular conduction system are probably relatively benign but obviously it is impossible, and unwise, to make direct comparisons with the innervated heart because of the unique denervated state of the transplanted heart.

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