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Sinus node function in the denervated human heart[1] *Effect of digitalis*

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Evaluation of sinus node function was performed in 5 patients with an intact cardiac autonomic nervous system (group 1), and in 8 patients with a transplanted, denervated heart (group 2). After baseline data were recorded, the electrophysiological studies were repeated in all group 1 patients and in 6 of the 8 group 2 patients, 45 to 60 minutes after the administration of digoxin 1.25 mg intravenously. Baseline cycle length, sinus node recovery time, and sinoatrial conduction time were significantly shorter in the transplanted heart than in those with intact autonomic innervation, but correction of the sinus node recovery time and sinoatrial conduction time for heart rate abolished these differences. Digoxin produced a small increase in cycle length, sinus node recovery time, and sinoatrial conduction time which did not reach statistical significance in this small study group of patients with innervated hearts. In the denervated, transplanted patients, no change in cycle length occurred after digoxin in any patient. The sinus node recovery time was unaffected by glycoside administration in 3 of 6 patients, while the sinoatrial conduction time was unchanged in 4 of 6. In one group 2 patient, digoxin produced first degree sinoatrial nodal exit block, and in a second patient, 2:1 sinoatrial nodal exit block developed. The mechanisms responsible for these effects in the denervated heart are not clear.

Recently, the evaluation of sinus node function in the *in situ* human heart has been attempted by two methods. Rapid atrial stimulation resulting in overdrive suppression of the sinus node has been used to evaluate its automatic pacemaker function (Mandel *et al.*, 1971) and varying the prematurity of a stimulated atrial depolarization through the cardiac cycle permits the calculation of the sinoatrial conduction time (Strauss *et al.*, 1973). These techniques have been applied for the evaluation of patients with the clinical diagnosis of sinus node disease ('sick sinus syndrome') and for the assessment of drug effects in these patients (Bond, Engel, and Schaal, 1974). While important insight into sinus node function has been gained through investigation of such patients, two important factors limit the conclusions that can be drawn from such studies: they are most often done in patients with organic heart disease, and autonomic innervation of the heart is intact.

In order to evaluate sinus node function in the human, independent of pre-existing heart disease or autonomic innervation, we have recently studied 8 patients who had undergone successful cardiac transplantation.

Methods

Two groups of patients were included in our study. Group 1 consisted of 5 patients ranging in age from 34 to 68 years, with various cardiac diagnoses and intact autonomic nervous control of the heart (Table 1). Three had mitral valve prolapse, one had paroxysmal supraventricular tachycardia with no other evidence of cardiac disease, and one had an idiopathic congestive cardiomyopathy. All patients were functionally NYHA Class I, except for the cardiomyopathy patient who was NYHA Class II. Drugs acting on the heart were withheld for 72 hours before study. Group 2, with totally denervated hearts, consisted of 8 patients ranging in age from 26 to 54 years, who had undergone cardiac transplantation at least one year before evaluation (Table 1). All were functionally NYHA Class I and were taking no cardioactive drugs; however, routine immunosuppression with corticosteroids and azathioprine was continued up to the time of study. We have previously shown the trans-

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TABLE 1 *Clinical data for both groups of patients*

Case No.	*Age (yr)*	*Sex*	*Cardiac diagnosis*	*Heart rate (beats/min)*
Group 1				
1	35	M	MV prolapse	75
2	68	F	PSVT	92
3	50	M	CM	80
4	34	F	MV prolapse	70
5	42	F	MV prolapse	68
Group 2				
1	26	M	Tx	115
2	40	M	Tx	107
3	32	M	Tx	83
4	52	M	Tx	95
5	48	M	Tx	126
6	54	M	Tx	128
7	52	M	Tx	90
8	32	M	Tx	105

Abbreviations: MV prolapse = mitral valve prolapse; PSVT = paroxysmal supraventricular tachycardia; CM = idiopathic congestive cardiomyopathy; Tx = cardiac transplant.

planted human heart to be completely denervated (Stinson *et al.*, 1972a, b).

The patients were studied in the Cardiac Catheterization Laboratory in the non-sedated, postabsorptive resting state using techniques previously described (Goldreyer and Damato, 1971; Mandel *et al.*, 1971; Strauss *et al.*, 1973). Informed consent was obtained from all patients studied. Briefly, a quadripolar electrode catheter was positioned in the high right atrium near the sinus node in order to record the earliest possible atrial depolarization. The two distal electrodes were used to pace the atrium, and the proximal electrode pair was used to record the atrial electrogram in the region of the sinus node. The atrial electrogram, as well as two surface electrocardiographic leads, were simultaneously recorded with 100 and 1000 ms time lines on a multichannel oscillographic recorder (Electronics for Medicine DR-16) at paper speeds of 100 and 200 mm/s, filtered at 40 to 500 Hz. After a resting recording was made, sinus node recovery times were determined in triplicate following the abrupt termination of rapid atrial pacing at 150 to 180 impulses/min (Narula, Samet, and Javier, 1972; Chadda, Banka, and Helfant, 1973). Premature atrial stimuli of 2 ms duration and twice diastolic threshold were then introduced after every eighth spontaneous sinus cycle for the determination of sinoatrial conduction time, using a programmable stimulator (manufactured by M. Bloom, Philadelphia) and a Tektronix pulse generator. Initially, the stimuli were introduced late in diastole, and then moved progressively earlier in 20 ms steps until atrial refractoriness was encountered. In the transplanted heart, only the donor atrium was paced.

As described by Strauss *et al.* (1973), the following intervals were measured: 1) the spontaneous sinus cycle length (A-A) occurring just before the atrial premature depolarization and just after the return cycle (see below); 2) the interval between the last spontaneous sinus impulse, as recorded by the intra-atrial electrogram and the atrial premature depolarization, i.e. the test cycle length ($A\text{-}A_T$); 3) the interval between the atrial premature depolarization and the subsequent spontaneous sinus impulse, as recorded by the intra-atrial electrogram, i.e. the return cycle ($A_T\text{-}A_R$). Reset of the sinus node by an atrial premature depolarization occurred when the sum of the test cycle and the return cycle was less than the sum of two spontaneous sinus cycles. Non-reset of the sinus pacemaker by an atrial premature depolarization occurred when the sum of the test cycle and the return cycle equalled the sum of two spontaneous sinus cycles, i.e. the return cycle was fully compensatory. All data were normalized by expressing each interval as a percentage of the resting spontaneous sinus cycle interval. This permitted a comparison of data between patients, despite differences in basic sinus cycle length. The basic spontaneous cycle length did not significantly vary during the entire study in patients with denervated hearts. In all patients, the normalized return cycle was plotted as a function of the normalized test cycle (Fig. 3a). A reference line projected from the y axis at point 1.0 representing one spontaneous sinus cycle was drawn. Progressive shortening of the test cycle was accomplished until the return cycle duration was nearly constant. The distance such points fall above the reference line is assumed to represent the sum of conduction into and out of the sinus node. The sinoatrial conduction time was calculated as one-half the product of this distance and the spontaneous sinus cycle length.

After baseline measurements were made, digoxin, 1.25 mg intravenously, was given to the 5 patients in group 1, and to 6 of the 8 transplant patients. Measurement of cycle length, sinoatrial conduction time, and sinus node recovery time was repeated 45 minutes to 1 hour after digoxin administration. At the termination of the study, blood samples were drawn for serum digoxin level determination. In all patients the serum digoxin level was greater than 6.4 nmol/l (5 ng/ml). Student's t test for paired data was used for statistical analysis.

Results

Table 2 and Fig. 1 and 2 summarize the electrophysiological data in the 5 group 1 patients before and after digoxin. Mean cardiac cycle length was increased from 788 ± 41 ms to 828 ± 31 ms after digoxin. The mean sinus node recovery time also increased, from 917 ± 50 ms to 1000 ± 40 ms, as did the mean sinoatrial conduction time from 107 ± 4 ms to 119 ± 5 ms. All three variables approached but did not reach significance ($P > 0.05$). Because the sinus node recovery time is heart rate dependent, the values obtained were corrected for cycle length in two ways: 1) by dividing the sinus node recovery time by the resting cycle length, and 2) by subtracting the baseline cycle length (Rios *et al.*, 1972; Narula *et al.*, 1972; Chadda *et al.*, 1973) (Table 3, Fig. 1). After digoxin, the corrected mean

TABLE 2 *Electrophysiological data* (Data uncorrected for cycle length)*

Case No.	*CL*		*SNRT*		*SACT*	
	C	*Dig*	*C*	*Dig*	*C*	*Dig*
Group 1						
1	800	880	775	1050	106	118
2	650	720	850	900	99	132
3	750	800	900	910	96	103
4	860	870	1020	1040	113	119
5	880	870	1040	1100	120	120
Mean	788	828	917	1000	107	119
SEM (±)	41	31	50	40	4	5
P<		NS		NS		NS
Group 2						
1	520	520	1005	1122	104	247
2	560	560	700	708	90	84
3	715	715	882	980	46	96
4	630	630	950	835	95	95
5	475	475	583	598	48	48
6	470	470	598	595	56	56
7	570	—	750	—	86	—
8	670	—	725	—	40	—
Mean†	561	561	786	806	73	104
SEM (±)	—	—	75	87	11	30
P<		NS		NS		NS

* All values expressed in ms.
† Mean for patients 1–6 who received digoxin.
Abbreviations: CL = cycle length; SNRT = sinus node recovery time; SACT = sinoatrial conduction time; C = control; Dig = digoxin; NS = not significant; SEM = standard error of the mean. Student's t test for paired data was used to compare cycle length, sinus node recovery time, and sinoatrial conduction time before and after digoxin.

TABLE 3 *SNRT and SACT (corrected for cycle length) before and after digoxin*

Case No.	*SNRTc division*		*SNRTc (ms) subtraction*		*SACTc division*	
	C	*Dig*	*C*	*Dig*	*C*	*Dig*
Group 1						
1	0.969	1.913	−25	170	0.133	0.134
2	1.308	1.250	200	180	0.155	0.184
3	1.200	1.138	150	110	0.121	0.128
4	1.186	1.195	160	170	0.131	0.137
5	1.182	1.264	160	230	0.137	0.138
Mean	1.169	1.208	129	172	0.135	0.144
SEM (±)	0.055	0.023	39	19	0.006	0.010
P<		NS		NS		NS
Group 2						
1	1.932	1.158	485	602	0.200	0.475
2	1.250	1.264	140	148	0.160	0.150
3	1.234	1.371	167	265	0.064	0.134
4	1.508	1.325	320	205	0.151	0.151
5	1.227	1.259	108	123	0.100	0.100
6	1.272	1.266	128	125	0.120	0.120
Mean*	1.404	1.441	225	245	0.132	0.188
SEM (±)	0.114	0.145	60	75	0.020	0.058
P<		NS		NS		NS

* = For Cases 1–6 in group 2.
Abbreviations: SNRTc division = sinus node recovery time corrected by dividing by the basic cycle length; SNRTc subtraction = sinus node recovery time corrected by subtracting the basic cycle length; SACTc division = sinoatrial conduction time corrected by dividing by the basic cycle length; C = control; Dig = digoxin; NS = not significant. Student's t test for paired data was used to compare cycle length, sinus node recovery time, and sinoatrial conduction time before and after digoxin.

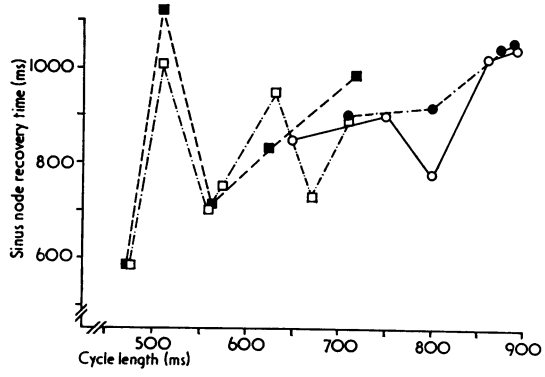

FIG. 1 *Sinus node recovery time as a function of cycle length in group 1 and group 2 patients, before and after digoxin administration. Open circles = group 1, innervated patients. Closed circles = group 1 patients after intravenous digoxin 1.25 mg. Open squares = group 2, denervated patients. Closed squares = group 2 patients after intravenous digoxin 1.25 mg. ms = milliseconds.*

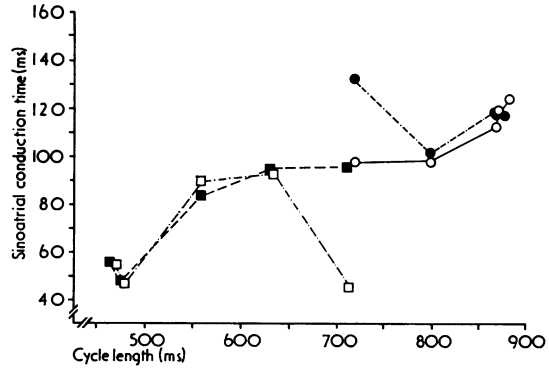

FIG. 2 *Sinoatrial conduction time as a function of cycle length in group 1 and group 2 patients before and after digoxin administration. Notation same as Fig. 1.*

sinus node recovery time obtained by the division method changed from 1.169 ± 0.055 ms to 1.208 ± 0.023 ms, and from 129 ± 39 ms to 172 ± 19 ms when obtained by the subtraction method. These results were again not statistically significant ($P > 0.05$).

Table 2 and Fig. 1 and 2 also summarize the findings in group 2 patients who had undergone cardiac transplantation. The electrophysiological studies were repeated in 6 of the patients after the administration of digoxin. In the group as a whole, mean resting cycle length was 576 ms. In the 6 patients receiving digoxin, mean resting cycle length did not change, remaining 561 ms after digoxin administration. The mean sinus node recovery time was 774 ms for the entire group.

In the digoxin treated patients, sinus node recovery time increased from 786 ± 75 ms to 806 ± 87 ms ($P > 0.05$). Because cycle length did not change after administration of digoxin, no correction was necessary. Mean sinoatrial conduction time was 71 ms in the 8 patients, and increased from 73 ± 11 ms to 104 ± 30.1 ms in the 6 patients receiving digoxin ($P > 0.05$). Fig. 3 illustrates the various effects of digoxin on sinoatrial conduction time in 3 denervated patients. In Case 1, second degree sinoatrial exit block developed after glycoside administration (Fig. 3c). If this patient is eliminated from consideration, the sinoatrial conduction time in the remaining 5 patients increased from 67 ± 11 ms to 76 ± 10 ms ($P > 0.05$) after digoxin.

In order to compare sinus node function in the innervated versus the transplanted denervated heart, the various parameters studied before and after digoxin were compared in the group 1 and group 2 patients. Patient 1 of the group 2 patients was eliminated because he developed sinoatrial block after digitalis.

A comparison of mean cycle lengths both before and after digitalis in group 1 (before 788 ± 41, after 828 ± 31 ms) with group 2 (before 570 ± 47 ms, after 570 ± 47 ms) shows that the difference is significant in both situations ($P < 0.01$ before digoxin, $P < 0.005$ after). The sinus node recovery times in group 1 before (917 ± 50 ms) and after (1000 ± 40 ms) digoxin are also significantly greater ($P < 0.05$ before, $P < 0.01$ after digoxin) than in the group 2 patients (742 ± 74 ms before digoxin, 743 ± 74 ms after digoxin). The corrected mean sinus node recovery time in group 1 patients before (1.169 ± 0.055 by division method, 129 ± 39 ms by subtraction method), and after (1.208 ± 0.023 by division method, 172 ± 19 ms by subtraction method), digoxin was compared with the corrected values in the group 3 patients (1.404 ± 0.114 by division method, 225 ± 60 ms by subtraction method before,

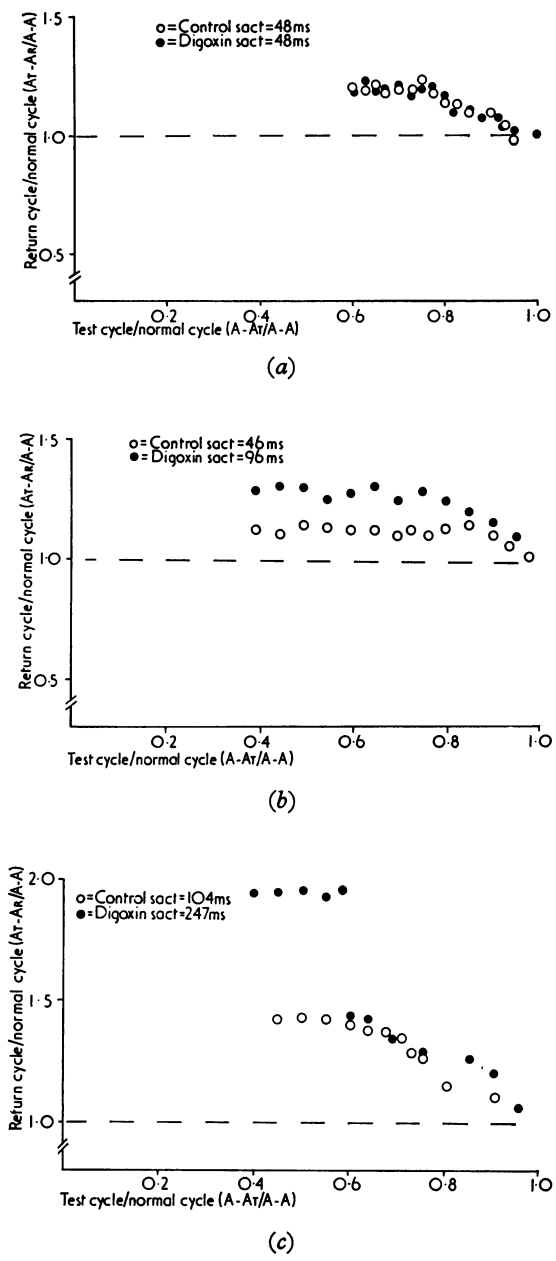

FIG. 3 *Effect of intravenous digoxin 1.25 mg on sinoatrial conduction time (sact) in three transplanted, denervated patients. Return cycle is plotted as a function of the test cycle, normalized for cycle length. (a) No effect on sact, Case 5 of group 2; b) prolongation of the sact, compatible with first degree SA block, Case 3 of group 2; c) prolongation of the sact, compatible with second degree SA block, Case 1 of group 2.*

1.441 ± 0.145 by division method, 245 ± 75 ms by subtraction method after digoxin). Only the sinus node recovery time after digoxin, corrected by the division method, was significantly different between the 2 groups of patients ($P < 0.05$). Mean values for sinoatrial conduction time in group 1 patients before (107 ± 4 ms) and after (119 ± 5 ms) digoxin were both significantly greater ($P < 0.005$ before digoxin, $P < 0.005$ after digoxin) than the comparable values in the transplant patients (67 ± 11 ms before, 76 ± 10 ms after digoxin). Because Fig. 2 suggested that for group 1 and group 2 patients as a whole, sinoatrial conduction time is related to the basic cycle length, these data were also normalized by dividing by the basic cycle length (Table 3). Analysis of the data showed that the effect of digitalis on the normalized sinoatrial conduction time in either group 1 or group 2 patients was not significant ($P < 0.05$), and that the sinoatrial conduction time in group 1 before and after digoxin was not different when compared to the respective results in group 2 patients.

Discussion

The evaluation of sinus node function in man has recently received renewed interest (Mandel *et al.*, 1971; Strauss *et al.*, 1973; Stinson *et al.*, 1972a; Narula *et al.*, 1972). The pacemaker function of the sinus node has been evaluated by observing the degree of postpacing depression after rapid atrial stimulation (Mandel *et al.*, 1971; Narula *et al.*, 1972). Conduction from the sinus node to the atrium has been estimated by the use of premature atrial stimulation (Strauss *et al.*, 1973.)

Definite abnormalities in the sinus node recovery time and sinoatrial conduction time have been observed in patients with the 'sick sinus syndrome' (Engel, Bond, and Schaal, 1973b; Narula *et al.*, 1972). In investigating patients both with and without the 'sick sinus syndrome', it has become obvious that the autonomic nervous system plays an important role in determining the value for the sinus node recovery time (Mandel *et al.*, 1971; Rios *et al.*, 1972). Atropine has usually (Mandel *et al.*, 1971; Engel, Boudoulas, and Schaal, 1973a; Boudoulas, Engel, and Schaal, 1972), but not uniformly (Narula *et al.*, 1972), normalized an abnormal sinus node recovery time. As discussed by others, acetylcholine released locally by pacing, or a reflex increase in parasympathetic tone caused by a pacing rate higher than the control sinus node rate has been suggested as the cause of postpacing sinus node depression (Mandel *et al.*, 1971).

The transplanted human heart has been shown to be denervated (Stinson *et al.*, 1972a, b); and, therefore, offers a unique model to study sinus node function free from autonomic nervous system effects. In the resting state, the heart rate is significantly higher in the transplanted heart (Table 1), probably because of the absence of the usually dominant vagal tone. The uncorrected sinus node recovery time is significantly shorter in the transplanted heart when compared to the innervated heart (Table 2), but when corrected for heart rate only approaches significance (Table 3). In general, the sinus node recovery time increased with increasing cycle length in the transplanted heart as in the innervated heart, suggesting that other factors, in addition to autonomic innervation, modulate this variation (Fig. 1).

Sinoatrial conduction, as estimated by the premature atrial stimulation technique, has been noted to range from 68 to 156 ms (unidirectional conduction) in a group of 4 patients with sinus bradycardia (Mandel *et al.*, 1971) to 169.1 ± 91.6 ms (bidirectional conduction) or approximately 85 ms (unidirectional conduction) in a group of 20 normals (Engel *et al.*, 1973b). Engel and Schaal (1973) noted prolonged sinoatrial conduction in 7 of 13 patients with the 'sick sinus syndrome'.

In our group 1 patients with innervated hearts none of whom had 'sick sinus syndrome', the sinoatrial conduction time (unidirection conduction) was 107 ± 4 ms. The transplanted patients had significantly shorter conduction times of 67 ± 11 ms. Because the sinoatrial conduction time appeared rate dependent (Fig. 2), we normalized the values by dividing by control cycle length (Strauss *et al.*, 1973). This yielded values of 0.135 ± 0.006 in the group 1 patients and 0.132 ± 0.020 in group 2 patients; the difference is not statistically significant ($P < 0.05$). Other authors have similarly not found the sinoatrial conduction time to correlate with baseline cycle length (Engel *et al.*, 1973b).

Digitalis preparations are known to affect sinus node function in the intact human heart. Three possible mechanisms have been suggested: an increase in vagal tone, an antiadrenergic effect, and a direct effect of the drug. Sinus node automaticity is diminished after digitalis administration (Hoffman and Singer, 1964), while the uncorrected sinoatrial conduction time is prolonged (Bond *et al.*, 1974). Resting autonomic tone, as well as the quantitative autonomic responses to various stimuli, are probably important factors in an individual patient's response to digitalis. It has been suggested that autonomic dysfunction plays an important role in patients with 'sick sinus syndrome' (Engel *et al.*, 1973a). Abnormalities in autonomic tone may help to explain the paradoxical shortening of sinus node recovery time after ouabain administration in this type of patient (Engel and Schaal, 1973). Atropine

has been reported to increase sinus node recovery time, possibly by reducing sinoatrial entrance block (Bashour, Hemb, and Wickramesekaran, 1973). Ouabain, in a similar manner, may have decreased sinus node recovery time by increasing sinoatrial entrance block through its vagotonic action.

Unfortunately, in this small group of patients, these changes were not statistically significant. In the denervated, transplanted heart, no change in heart rate occurred after digitalis administration (Table 2). Sinus node recovery time and sinoatrial conduction time were also not significantly changed by digoxin administration; in 3 of 6 patients, sinoatrial conduction time was essentially unchanged. In 2 patients, however, both the sinus node recovery time and sinoatrial conduction time were longer after digoxin administration. In Case 1, the sinus node recovery time approximately doubled, while the sinoatrial conduction time dramatically increased, compatible with the development of 2:1 sinoatrial node exit block (Fig. 3c). In Case 3, the increase in sinus node recovery time was accompanied by a conspicuous increase in sinoatrial conduction time compatible with first degree sinoatrial node exit block (Fig. 3b). It is interesting that in these 2 patients, both the sinus node recovery time and sinoatrial conduction time were affected by digitalis, while in 3 of the 4 other patients, this drug affected neither parameter. The reason for the change in these 2 patients is not clear. The transplanted human heart has been shown to be denervated (Stinson *et al.*, 1972a, b), so that digitalis-induced changes in autonomic tone would not be a factor. In addition, the constant heart rate during the entire study speaks against important changes in circulating autonomic stimulating substances. Perhaps a direct effect of digitalis on the area of the sinus node damaged at the time of surgery or undergoing subclinical cardiac rejection was a factor. In the dog heart, sinus node injury can prolong the sinus node recovery time (Goldreyer and Damato, 1971).

The serum digoxin levels measured in all patients ((> 6.4 nmol/l) (> 5ng/ml)) 45 to 60 minutes after the acute administration of a 1.5 mg intravenous bolus of the drug were undoubtedly obtained before serum tissue equilibration. However, digoxin did have a demonstrable electrophysiological action at this time, as evidenced by its effect on the innervated patient's heart (group 1). In addition, digoxin has been shown to have important electrophysiological effects on atrioventricular conduction 45 minutes after a similarly administered dose of the drug (Przbyla *et al.*, 1974).

The findings of this study indicate the important effect of cycle length in evaluating sinus node function as determined by the rapid overdrive and premature stimulus techniques. Cycle length was the most important factor giving differences in sinus node recovery time and sinoatrial conduction time between the innervated and denervated heart. In general, correction for cycle length rendered these differences insignificant.

These results in the transplanted human heart may have relevance to patients with cardiac disease in general and specifically to those with cardiac decompensation. Eckberg, Drabinsky, and Braunwald (1971) have demonstrated that in patients with heart disease the response to atropine and hypotensive manoeuvres is blunted, an indication of parasympathetic dysfunction. Covell, Chidsey, and Braunwald (1966) and Beiser *et al.* (1968) have shown that in the experimental animal or in the patient with congestive heart failure, the response to sympathetic nerve stimulation is also subnormal. Therefore, the electrophysiological behaviour of the sinus nodes in the patient with heart disease and congestive failure may be expected to resemble that of the denervated human heart. The occasional episodes of sinoatrial block encountered in these patients may be related to their blunted autonomic responsiveness.

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