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Research Article

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The Electrophysiologic Effects of Quinidine in the Transplanted Human Heart

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ABSTRACT Using His bundle recording techniques, we examined direct and autonomically mediated conduction system effects of quinidine in five cardiac transplant recipients who have anatomically denervated hearts. We made control conduction interval and refractory period measurements, and then infused 10 mg/kg quinidine gluconate over a 20-min period. At 30 min, we determined the electrophysiologic changes induced by quinidine. Quinidine significantly increased the atrial-His (AH) interval (from 97 ± 9 [SEM] to 108 ± 7 ms, $P < 0.001$), the His-ventricular (HV) interval (from 43.9 ± 1 to 52.8 ± 3 ms, $P < 0.01$), the donor heart sinus cycle length (from 599 ± 38 to 630 ± 56 ms, $P < 0.08$), and the atrial effective refractory period (from 214 ± 14 to 241 ± 11 ms, $P < 0.01$). Quinidine significantly decreased the innervated, remnant atrial sinus cycle length (from 847 ± 104 to 660 ± 96 ms, $P < 0.01$) and the blood pressure. The mean plasma concentration of quinidine at the time that electrophysiologic measurements were repeated was 4.37 ± 0.449 $\mu\text{g}/\text{ml}$. We conclude that quinidine's predominant sinus nodal and atrioventricular nodal effects in man are autonomically mediated and opposite to its direct actions upon these structures. On the other hand, quinidine's prevailing effect on atrial refractoriness and His-Purkinje conduction in man is direct.

INTRODUCTION

The effect of quinidine upon the human cardiac conduction system is controversial because quinidine has both direct and autonomically mediated electrophysiologic activities. Several investigators have attempted to identify these actions separately in animals (1-4). Studies in man, in which His bundle record-

ing techniques were applied (5, 6), could not make this separation because of the subjects' intact cardiac innervation which permitted both actions to occur simultaneously. In one of these investigations, Hirschfeld and his colleagues (5) administered quinidine intravenously to patients with intact cardiac neural supply and found a decrease in the AH interval, but no changes in the HV interval or the spontaneous sinus cycle length after quinidine. Josephson et al. (6), using His bundle recording techniques to study the effects of intramuscular quinidine in patients with intact cardiac autonomic supply, found that quinidine produced decreases in the sinus cycle length and the AH time, and increases in the atrial effective refractory period and His-Purkinje conduction time. In neither of these electrophysiologic studies in humans, however, were the direct and autonomically mediated effects of quinidine separately identified.

Cardiac transplant recipients provide a unique model for studying the heart free of autonomic influences (7-11). In the present study, we examined the effects of quinidine administered intravenously to human cardiac allograft recipients to determine the drug's autonomic and direct conduction system actions.

METHODS

Five cardiac allograft recipients were studied 8-20 mo after transplantation. The study was approved by the Stanford Medical Committee on the Use of Human Subjects in Research, and each patient gave informed, written consent. These patients had had uncomplicated postoperative courses, and at the time of study, were in New York Heart Association Class I functional status and had no evidence of cardiac rejection or of extracardiac disease. All five patients had normal cardiac biopsies, right and left heart hemodynamic studies, and coronary and left ventricular angiograms within 6 mo of this investigation. Patients were catheterized in the post-absorptive state with no sedation, or light diazepam sedation. Atrial electrogram recordings were obtained with a 7F quadripolar recording-stimulating electrode catheter positioned in the high right atrium via the right internal jugular,

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TABLE I
*AH, HV, and QT Intervals, Atrial Cycle Lengths, and Blood Pressure, before, during, and after Quinidine Infusion**

Patient no.	Pacing cycle length†	Measure- ment§	Before quinidine	Minutes after initiation of quinidine infusion			Maximum change
				5	15	25	
1	590	AH	75	80	85	80	+10
		HV	45	45	50	52	+7
		QT	285	370	390	390	+105
		RCL	990	550	700	670	-220
		DCL	640	640	645	645	+5
		MBP	84	72	75	74	-12
2	480	AH	85	85	100	100	+15
		HV	42	45	55	55	+13
		QT	330	340	360	370	+40
		RCL	1,190	1,040	1,040	1,050	-150
		DCL	530	540	570	570	+40
		MBP	72	79	64	66	-8
3	630	AH	110	115	115	115	+5
		HV	45	50	55	60	+15
		QT	325	365	415	435	+110
		RCL	675	645	620	605	-70
		DCL	685	700	755	740	+70
		MBP	83	84	77	81	-6
4	515	AH	115	120	125	125	+10
		HV	47	45	50	55	+8
		QT	315	340	380	400	+85
		RCL	700	620	625	520	-180
		DCL	540	542	540	550	+10
		MBP	113	110	97	98	-15
5	670	AH	100	105	115	115	+15
		HV	40	40	42	40	+2
		QT	335	460	475	475	+140
		RCL	680	650	590	585	-95
		DCL	—	—	—	—	—
		MBP	105	103	95	96	-9

* Electrophysiological intervals in ms, blood pressure in millimeters of mercury.

† Atrial pacing was performed during these electrophysiological measurements (except during recording of the spontaneous donor atrial cycle length) at a cycle length 25–50 ms shorter than the original spontaneous cycle length.

§ Abbreviations: QT, QT interval; RCL, recipient atrial cycle length; DCL, donor atrial cycle length; MBP, mean central aortic blood pressure.

right basilic, or a femoral vein. In the cardiac recipients, as previously reported (7), stable pacing of the donor atrium required looping of the catheter within the atrium in such a way that the distal pair of pacing electrodes were applied to the high anterolateral donor right atrial wall. His bundle recordings were achieved by advancing a 7F tripolar or a 5F bipolar His bundle recording catheter across the tricuspid valve to the vicinity of the common bundle. Three surface electrocardiograph leads (I, aVF, and V₁) were recorded simultaneously with the atrial and His bundle electrograms. Signals from the electrode catheters were transmitted to the AC input of an electrocardiograph amplifier with filter frequencies set between 40 and 500 Hz. Atrial electrograms from both the remnant recipient atrium and the implanted

donor atrium were recorded. Data were displayed on a switched-beam oscilloscope and recorded on photographic paper at a speed of 100 mm/s. Pacing stimuli of 2-ms durations were delivered by a Tektronix pulse generator (Tektronix, Inc., Beaverton, Oreg.) at twice the diastolic threshold. Stimuli were temporally varied by a programmable digital stimulator (M. Bloom, Philadelphia, Pa.). After baseline recordings of the AH, HV, and QT intervals and the spontaneous donor and recipient sinus cycle lengths, the sinus node recovery time was measured three times by atrial pacing at a cycle length of 430 ms for a 1-min duration, followed by abrupt termination of pacing. A base pacing cycle length 25–55 ms shorter than the spontaneous sinus cycle length was then chosen, and AH, HV, and QT inter-

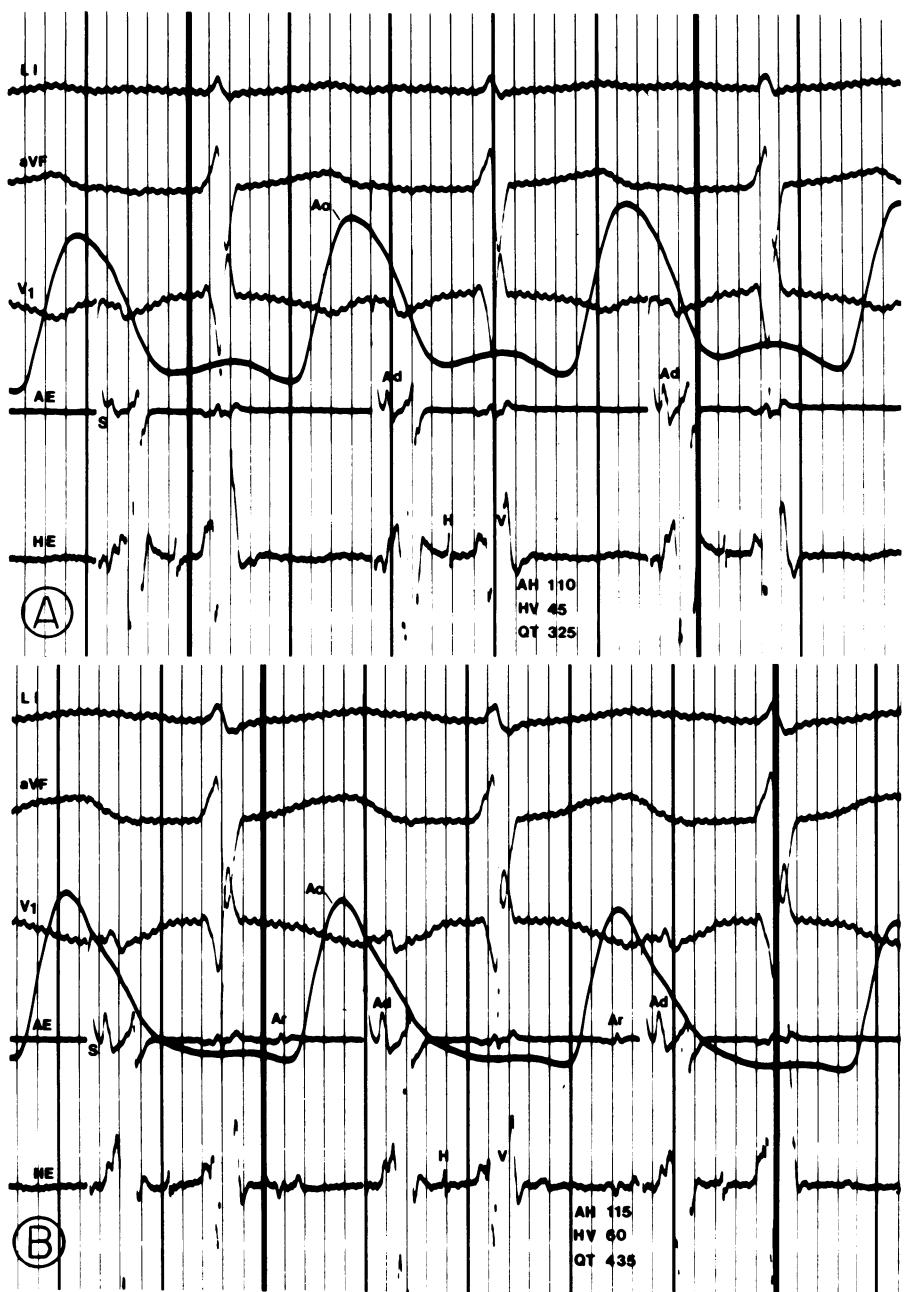


FIGURE 1 Tracings taken before (A) and 25 min after (B) initiation of quinidine infusion. The bold vertical time lines represent 1-s intervals. Three surface ECG leads (LI, aVF and V₁), the aortic pulse (Ao), atrial electrogram (AE), and His bundle electrogram (HE) are shown. Although the recipient atrial electrogram (Ar) is well seen in panel B, it occurred within the donor atrial complex (Ad) in the panel A tracing, and thus cannot be distinguished. "H" indicates the His bundle spike and "V" the ventricular depolarization. In this patient, the AH, HV, and QT intervals (milliseconds) increased respectively from 110, 45, and 325 to 115, 60, and 435 after quinidine administration.

vals were recorded at the spontaneous and the base paced heart rate. The atrial effective refractory period and the refractory periods of the atrioventricular node were determined using the extra-stimulus technique (12). After every eighth paced beat (S₁), a premature stimulus (S₂) was intro-

duced. The S₁-S₂ interval was then reduced by 10-ms decrements until the effective refractory period of the atrium was reached. The atrial effective refractory period was defined as the longest S₁-S₂ interval at which S₂ failed to depolarize the atrium. The AV nodal functional refractory period was

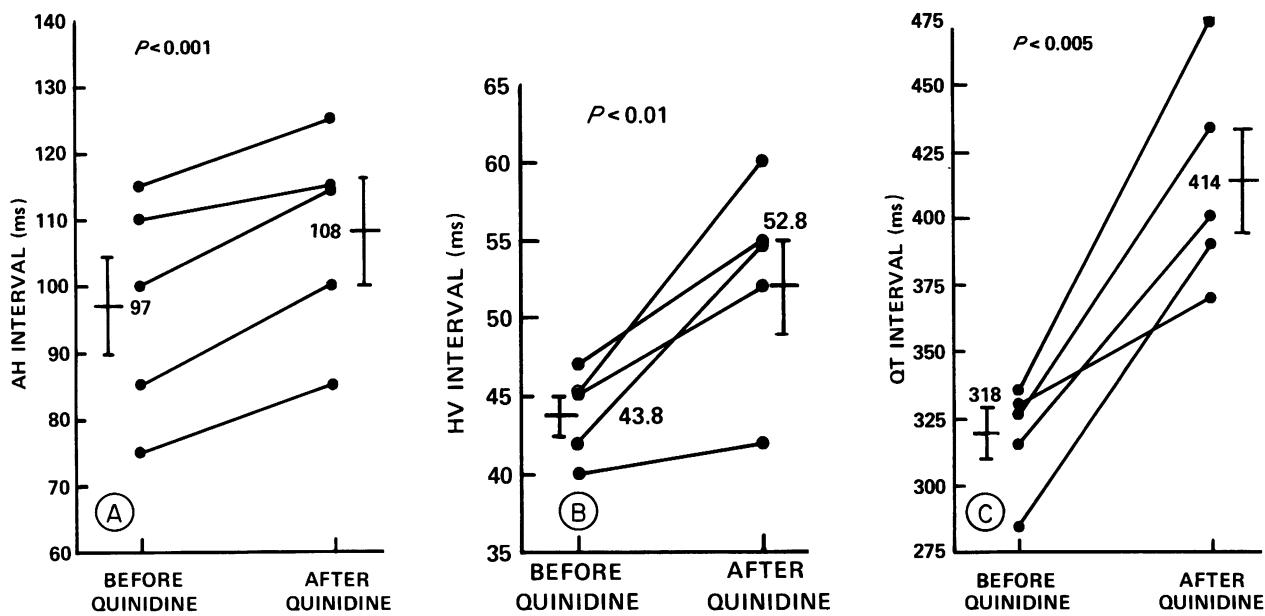


FIGURE 2 Conduction intervals before and after quinidine infusion (Table I). (A) All five patients had a significant rise in the AH conduction time after quinidine ($P < 0.001$). The mean change was +11 ms. The P values, means, and SEMs are indicated in this and subsequent graphs. (B) The HV interval increased after quinidine administration in all patients, and the mean change of +9 ms was significant ($P < 0.001$). (C) The QT interval increased significantly ($P < 0.005$) in all five patients by a mean of +96 ms when measured at a constant paced rate.

defined as the shortest H_1-H_2 interval achieved, and the AV nodal effective refractory period was defined as the longest A_1-A_2 at which A_2 failed to conduct through the AV node to produce a His bundle potential. The spontaneous atrial cycle lengths were recorded as the average, to the nearest 5 ms, of 15 sequential atrial cycles at each data interval. Central aortic blood pressure was measured through a PE 160 catheter placed transfemorally and connected to a Statham P23DB transducer (Statham Instruments Div., Gould Inc., Oxnard, Calif.)

After control measurements, quinidine gluconate salt, in a solution of 16 mg/cm³ of 5% dextrose and water, was administered to a total dose of 10 mg/kg by constant intravenous infusion over 20 min. The AH, HV, and QT intervals, the sinus cycle lengths, and the blood pressure were then remeasured during spontaneous sinus rhythm and during pacing at the previously selected base pacing cycle length at 5, 15, and 25 min after initiation of the infusion. Repeat sinus node recovery times and refractory studies of the AV conduction system were accomplished at 30 min after the initiation of the infusion. Blood samples were obtained for plasma quinidine determinations before, and at 5, 15, 25, 30, and 40 min after the start of drug administration. Quinidine was assayed by the benzene-extraction technique (13).

To confirm persistence of functional cardiac denervation, the day before this investigation all five subjects had shown a delayed heart rate response, in onset and offset, to treadmill exercise testing, and after the study showed absence of a rate response to 1 mg atropine administered intravenously.

Differences between electrophysiologic measurements recorded before and after quinidine administration were analyzed by the two-tailed Student's *t* test for paired data.

RESULTS

Conduction intervals. Table I and Fig. 1 show quinidine's effects upon cardiac conduction intervals during base-rate atrial pacing. In general, maximum changes in the AH, HV, and QT intervals were observed at 15 min of infusion, by which time they had reached a plateau. Maximum changes in these intervals are illustrated in Fig. 2. Despite the small number of patients, the postquinidine mean values were significantly different from control measurements. The AH interval increased in all five patients from 97 ± 8 to 108 ± 7 (SEM) ms ($P < 0.001$). The HV interval was lengthened in all subjects from a mean of 43.8 ± 1 to 52.8 ± 3 ms ($P \leq 0.01$). The QT interval also increased in all five patients from a mean of 318 ± 9 to 414 ± 19 ms ($P < 0.005$).

Effect on sinus nodes. At transplantation, the posterior walls of the recipient atria, with the sinus node intact, are left in place for attachment of the donor atria. Thus, both the recipient and the donor sinus nodes remain functional after transplantation. The implanted donor sinus node is denervated, while the remnant recipient node retains its neural innervation. Separate donor and recipient atrial depolarizations can be detected by surface and intracardiac electrocardiography (14). The effects of quinidine

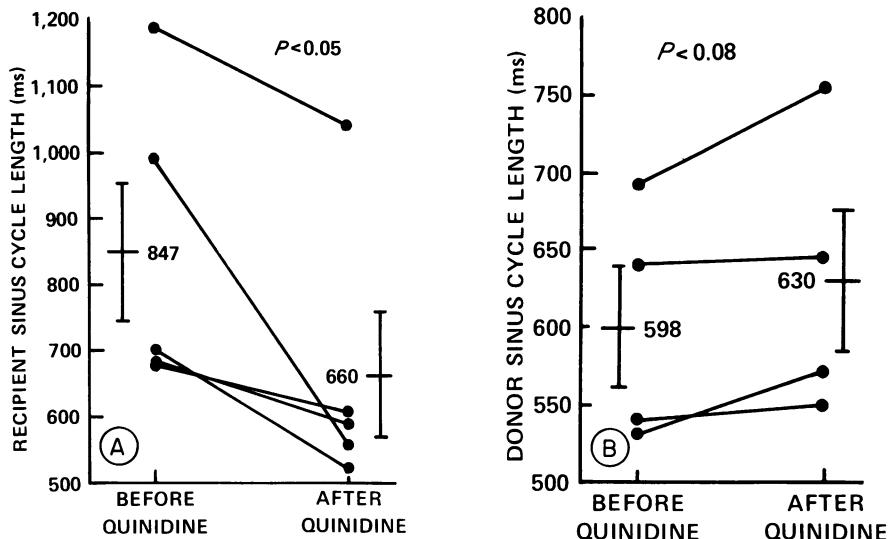


FIGURE 3 (A) The recipient sinus cycle lengths before and after quinidine dosage are shown. Quinidine resulted in a significant ($P < 0.05$) fall in the cycle length (that is, an increased atrial rate) in the recipient atria of all five patients. (B) The cycle length of the denervated donor sinus node was increased (slowed atrial rate) in the four transplant patients in whom sinus rate could be measured (see text).

upon sinus cycle lengths are shown in Table I and Figs. 3 and 4. While the recipient sinus cycle length decreased in all five patients after quinidine from a mean of 847 ± 104 to 660 ± 96 ms, the donor sinus cycle length increased in the four patients in whom

it could be measured from 599 ± 38 to 630 ± 56 ms. (One of the patients has a chronic post-transplantation junctional rhythm due to permanent sinus node arrest.) The donor sinus node recovery time was minimally and inconsistently affected by quinidine (Table II).

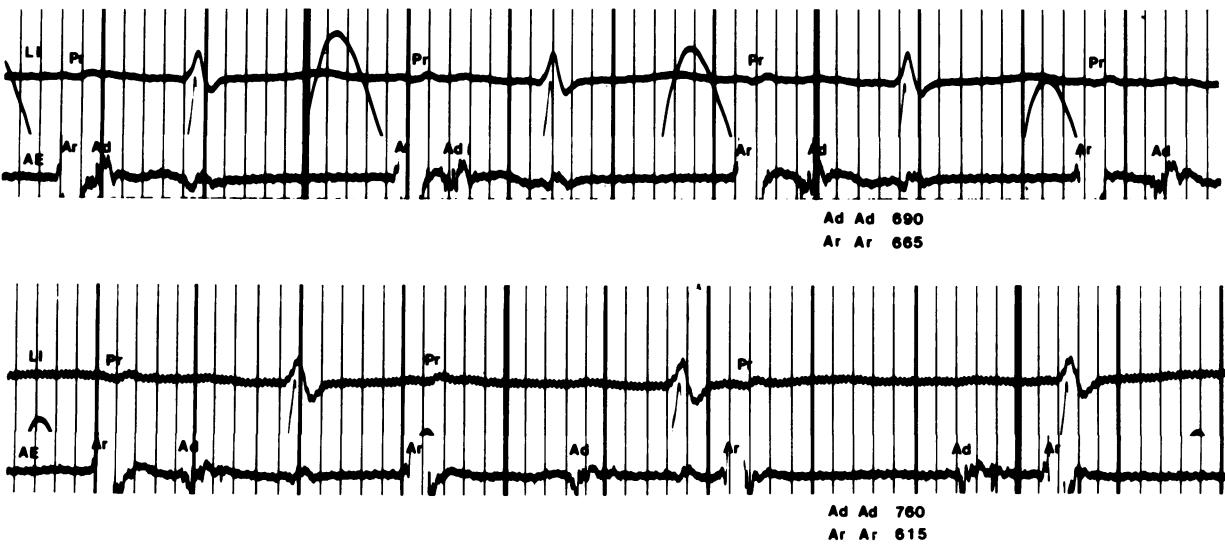


FIGURE 4 These tracings of Lead 1 (L1) and the atrial electrogram (AE) show the recipient (Ar) and donor (Ad) atrial depolarizations and the recipient P wave (Pr) (the donor P wave could not be distinguished in these surface tracings) before (A) and after (B) quinidine infusion. As noted, the donor atrial cycle length, Ad-Ad, increased from 690 to 760 ms, whereas the recipient cycle length, Ar-Ar, decreased from 665 to 615 ms. (The AE has been spliced underneath L1 in these illustrations, with the intervening recordings deleted, to facilitate interpretation. The listed cycle lengths represent direct measurements from the above tracings, rather than the mean cycle lengths obtained at this recording interval).

TABLE II
Sinus Node Recovery Times*

Patient	Quinidine	
	Before	After†
ms		
1	860	808
2	610	615
3	1,095	1,190
4	655	650
5	2,700§	1,350§

* Average of three recovery times obtained after 1 min of atrial pacing at a cycle length of 430 ms.

† 30 min after initiation of infusion.

§ These recovery times refer to the reemergence of this patient's junctional rhythm after atrial pacing.

Effect of atrial and AV nodal refractory periods. The atrial effective refractory period increased in all five patients from a mean value of 214 ± 14 to 241 ± 11 ms ($P < 0.01$) (Fig. 5). The AV nodal functional refractory period was variably affected; it increased in three of the patients, remained unchanged in one, and decreased in the fifth patient (Table III). The AV nodal effective refractory period and the refractory

periods of the His-Purkinje system could not be determined in any of the patients, due to earlier refractoriness higher in the conduction system.

Effect on blood pressure. Sequential changes in mean blood pressure are recorded in Table I. The average mean central aortic blood pressure fell from 91.4 ± 7.6 to 81.0 ± 6.5 ($P < 0.005$) at its nadir after quinidine administration.

Plasma quinidine concentrations. Mean plasma quinidine levels at 5, 15, 25, 30, and 40 min after initiation of the infusion were 2.36, 9.83, 6.12, 4.37, and $3.95 \mu\text{g}/\text{ml}$, respectively. Although a true steady-state condition was not achieved at the time that the repeat refractory determinations and sinus node recovery measurements were made, the plasma quinidine concentrations had almost reached a plateau and the mean concentration of 4.37 ± 0.449 (SEM) $\mu\text{g}/\text{ml}$ (range 3.07 – $5.14 \mu\text{g}/\text{ml}$) is similar to the $4.6 \mu\text{g}/\text{ml}$ level reported by Josephson et al. (6) after intramuscular injections, and is within the range considered therapeutic for chronic oral therapy. One patient experienced a brief episode of nausea, but no other patient reported subjective side effects. Ventricular irritability was not encountered during or after the study, as determined by continuous electrocardiographic monitoring.

DISCUSSION

We have studied the denervated hearts of five cardiac transplant recipients to identify direct electrophysiologic effects of quinidine upon the human cardiac conduction system. Transplant recipients provide a model for the study of cardiac drug actions in a milieu free of direct autonomic nervous influences.

To support the contention that functional autonomic denervation persists in long-term human cardiac transplant survivors, we have shown that the present subjects', and other cardiac recipients', rate responses to exercise are sluggish, both in onset and offset, as is observed in animals with anatomic cardiac denervation (15). Furthermore, those long-term survivors who have suffered myocardial infarctions have not experienced cardiac pain. Finally, pharmacologic interventions with intravenous atropine and tyramine, and inhaled amyl nitrite, which result in tachycardia in subjects with normal cardiac innervation, produce no significant heart rate changes in transplant recipients (7, 15).

Studies of direct electrophysiologic effects in isolated tissue have shown that quinidine alters action potentials of the cells of the cardiac conduction system. Slowing of phase zero (upstroke) and delays of phase two (plateau) and phase three (rapid repolarization) of the action potential are seen (16).

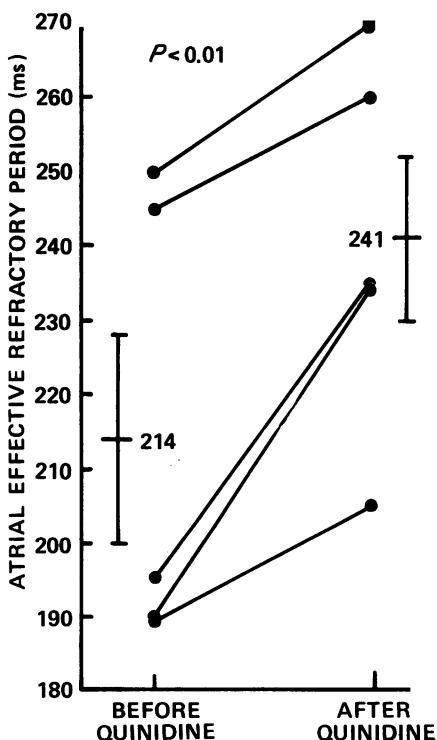


FIGURE 5 The atrial effective refractory period was significantly increased by 27 ms ($P < 0.01$) after quinidine administration.

These effects are clinically evidenced by prolongation of the QRS complex and lengthening of the QT interval of the surface electrogram. In addition, quinidine reduces the rate of diastolic depolarization and inhibits action potentials elicited in early phase three (early in the relative refractory period). These drug actions would be expected to result in prolonged refractory periods, decreased conduction velocities, damped automaticity, and an antiarrhythmic effect in humans treated with quinidine. All of these expected actions, however, are not observed clinically; patients with therapeutic plasma quinidine concentrations, instead, usually show increased sinus rate and decreased AV nodal conduction time (6). Indirect, autonomically mediated effects of quinidine, which have been recognized since 1937, account for these unanticipated findings. Hiatt et al. (1) and Nathanson (2) established, in the experimental animal, that quinidine decreases cardiac vagal tone. James and Nadeau (4), using direct sinus node perfusion, demonstrated that quinidine blocks the effects of both vagal stimulation and acetylcholine infusion upon the sinus node and blocks adrenergic stimuli to a comparable degree. Other investigators have emphasized this sympatholytic action (16-18).

Thus, quinidine produces autonomic nervous system-mediated cardiac effects. These actions must account for the differences between our observations in transplant patients and those reported by Josephson et al. in patients with intact cardiac nerves (6). The quinidine levels which Josephson et al. recorded in their electrophysiologic study are similar to the concentrations which we attained. We make a more detailed comparison of our findings in cardiac transplant recipients with their findings in intact humans below (Table IV).

The innervated sinus node of the recipient's excised heart remains present and intact, and serves as a "control" for comparison with the denervated donor sinus node. This innervated node significantly increased its rate of depolarization after quinidine administration (Fig. 3A) which is consistent with the findings of Josephson et al. of an increased heart rate after intramuscular quinidine administration. On the other hand, the denervated donor sinus rate was slowed by quinidine in all four patients in whom sinus rate could be measured (Fig. 3B). Although this change fell short of statistical significance, ($P < 0.08$), the consistency of the response holds greater weight than statistical analysis in such a small sample. This comparison of the two sinus nodes within the same patient clearly separates quinidine's direct effect, which is to depress sinus node automaticity, from its autonomically mediated acceleratory effect on the sinus node. James and Nadeau (4) concluded, from their direct sinus node perfusion studies in the anes-

TABLE III
AV Nodal Functional Refractory Periods

Patient	Quinidine	
	Before	After
ms		
1	325	345
2	350	350
3	390	450
4	375	340
5	445	460

thetized dog, that quinidine's anticholinergic actions were opposing influences of nearly comparable magnitude at therapeutic levels of the drug. Our results indicate that, in the unanesthetized human, quinidine's predominant action upon the innervated sinus node is autonomically mediated and that this autonomic effect outweighs the direct sinus nodal-depressant effect. Sinus node recovery times after quinidine did not reflect this depression of sinus nodal automaticity. However, factors other than automaticity affect the postpacing recovery times, such as perinodal entrance and exit block (19, 20), local metabolic factors (21, 22), and fiber stretch (22).

Because the mean blood pressure fell by approximately 10 mm Hg in this group of subjects, the possibility of a resultant reflex sympathetically mediated acceleration of the innervated recipient sinus rate (rather than a vagolytic quinidine effect) cannot be entirely dismissed. However, the occurrence of recipient atrial acceleration in the absence of a significant fall, and even in the presence of a rise, in blood pressure at several data points (Table I, patient 2 at 5 min; patient 3 at 5 and 25 min, patient 4 at 5 min, and patient 5 at 5 min after initiation of quinidine infusion) is contrary to this explanation.

AV nodal conduction time, which decreases in normally innervated patients after the administration of

TABLE IV
Electrophysiologic Effects of Quinidine in Transplant Recipients Compared with Normal Patients *

Location	Normal	Transplant
Sinus node	↓ CL	↑ CL
AV node†	↓ CT	↑ CT
Atrium	↑ ERP	↑ ERP
His-Purkinje system	↑ CT	↑ CT

CL, cycle length; CT, conduction time; ERP, effective refractory period; ↓, decreased; ↑, increased.

* Taken from Josephson et al. (6).

† During atrial pacing.

quinidine, increased in the transplant patients (Fig. 2A), indicating that quinidine directly slows AV nodal conduction but that its predominant effect in intact man is to enhance AV nodal conduction by an autonomically mediated mechanism. Once again it can be argued that the mild reduction in blood pressure reported by Josephson et al. (6) (approximately 10 mm Hg, systolic) accounted for the reduction they noted in the AH interval in his innervated patients. While it seems just as likely that vagolytic quinidine effects were responsible, it was not within the scope of their study or the present study to differentiate between these two possibilities.

Our transplant recipients and Josephson and colleagues' normal patients showed similar changes in His-Purkinje conduction time after quinidine administration. Prolongation of the HV interval by quinidine, then, appears to be a direct effect, as it occurs in the absence of autonomic innervation. The possibility still exists that additional autonomic effects of quinidine might influence the human His-Purkinje system, which has sympathetic and histologically demonstrated cholinergic innervation (23). However, since our subjects showed HV interval changes of a magnitude similar to those of patients with intact autonomic innervation, it would appear that the major portion of quinidine's effect upon the His-Purkinje system is direct.

The magnitude of increase in the atrial effective refractory period after quinidine in transplant recipients (Fig. 5) was similar to that which occurs in normally innervated patients. This finding documents the existence of a direct drug effect upon the atrium of man. Quinidine's anticholinergic activity should also prolong refractoriness of atrial tissue. Although both mechanisms probably act in concert in intact man, a similarity in the degree of change in innervated and denervated hearts favors a predominance of the direct effect.

We have drawn four conclusions regarding the cardiac conduction system actions of quinidine in man. These conclusions are supported by previous animal investigations, and represent the first clear separation of quinidine's direct activity and its autonomically mediated activity in man. First, the enhancement of sinus rate seen after quinidine administration in man is a neurally mediated effect, dependent upon an intact cardiac autonomic supply; quinidine's direct effect is to slow the rate of depolarization of the sinus node. Second, the net enhancement of AV nodal conduction by quinidine in man is most likely due to an autonomic effect which opposes and outweighs its direct slowing effect upon the AV node. Third, quinidine decreases His-Purkinje conduction by a direct action which can occur independently of autonomic influences. Fourth, the cardiac autonomic nerv-

ous system is not critically involved in quinidine's prolongation of the atrial refractory period.

ACKNOWLEDGMENTS

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