The Electrophysiological Effects of Ouabain on Sinus Node and Atrium in Man

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ABSTRACT Electrophysiological studies were performed in 16 patients before and 30 min after intravenous administration of ouabain (0.1 mg/kg). P-A interval (mean±SEM) was 40±2.1 ms before and 44± 1.5 ms after ouabain ($P < 0.001$). Atrial effective and functional refractory periods (ERP and FRP) were measured in all patients during sinus rhythm and during driving at equivalent paced rates in 12 patients. The mean atrial ERP and FRP during sinus rhythm were, respectively, 244±10.5 and 307±11.0 ms before and 253±9.7 and 318±11.4 ms after infusion of ouabain (NS). Mean atrial ERP and FRP during driving were, respectively, 231±15.3 and 264±14.9 ms before and 266±18.6 and 296±19.7 ms after ouabain ($P < 0.01$ and $P < 0.01$). Mean sinus cycle length and sinus recovery times were, respectively, 887±31.2 and 1,113± 38.7 ms before and 905±38.2 and 1,008±30.7 ms after infusion of ouabain (NS and $P < 0.005$). Calculated sinoatrial conduction times before and after ouabain were 90±6.8 and 110±8.5 ms, respectively ($P < 0.005$).

In summary, ouabain produced depression of intra-atrial conduction as manifested by increase in P-A interval and atrial effective and functional refractory periods. Ouabain significantly increased calculated sinoatrial conduction time wtihout significant effect on spontaneous sinus cycle length.

INTRODUCTION

Experimental studies in animals and man suggest that digitalis depresses atrioventricular nodal conduction without effect on intraventricular condition (1–5). There is limited data available concerning the effects of digitalis on atrium and sinus node. Studies in intact canines have demonstrated a negative chronotropic effect of digitalis on sinus node with slowing of intra-atrial conduction and shortening of atrial refractory periods (1, 2, 6–8). Engel and Schaal (9) found no demonstrable effects of ouabain on sinus node automaticity and intra-atrial conduction in patients with sick sinus syndrome. Preliminary reports by Bond, Engel, and Schaal (10, 11) suggest that digitalis prolongs calculated sinotrial conduction time in man. Reiffel, Bigger, and Giardina (12), in another preliminary report, described variable effects on calculated sinoatrial conduction time in patients with sinus bradycardia after ouabain administration. Data concerning the effects of digitalis on human atrial refractory periods are not available.

In the present study we have used atrial stimulation techniques to systematically examine the effects of ouabain on human atrium and sinus node. Our results suggest that ouabain slows intra-atrial conduction with prolongation of atrial effective and functional refractory periods. In addition, ouabain prolongs calculated sinoatrial conduction time and decreases sinus node recovery time without significant change in spontaneous sinus rate.

METHODS

The study group consisted of 16 patients undergoing electrophysiological studies because of intraventricular conduction defects (six patients), recurrent palpitation (eight patients), or recurrent dizziness (two patients). In all patients, electrocardiographic tape recorder monitoring (Holter Dynamic EKG System, Avionics Research Products, Los Angeles, Calif.) had no demonstrated paroxysmal tachyarrhythmia, severe sinus bradycardia (heart rates of 55/min or slower), sinoatrial block, or sinus arrest. In addition, electrophysiological studies did not demonstrate induction of paroxysmal tachycardia, prolonged sinus recovery time, or prolonged calculated sinoatrial conduction time (13, 14).

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TABLE I
Clinical Data

Patient no.	Age	Sex	Diagnosis or symptom	Electrocardiogram P-R	Electrocardiogram QRS duration	Electrocardiogram QRS morphology
				s	*s*	
1	50	M	Palpitation	0.14	0.08	Normal
2	49	F	Palpitation	0.16	0.09	Normal
3	41	F	Palpitation	0.16	0.08	Normal
4	32	F	Palpitation	0.18	0.09	Normal
5	27	F	Palpitation	0.14	0.08	Normal
6	80	F	Palpitation	0.16	0.08	Normal
7	51	M	Cor pul. palpitation	0.15	0.08	Normal
8	43	M	Palpitation	0.18	0.08	Normal
9	50	M	HCVD	0.16	0.14	RBBB, LASH
10	57	M	PCD	0.18	0.12	RBBB, LASH
11	50	M	ASHD	0.16	0.12	RBBB, LPH
12	70	M	HCVD	0.16	0.13	RBBB, LASH
13	69	M	Dizziness	0.18	0.10	LASH
14	60	M	ASHD	0.16	0.14	LBBB
15	62	M	HCVD	0.14	0.12	RBBB, LASH
16	31	F	Dizziness	0.18	0.08	Normal

ASHD, arteriosclerotic heart; Cor pul., cor pulmonale; HCVD, hypertensive cardiovascular disease; LASH, left anterior superior hemiblock; LBBB, left bundle branch block; LPH, left posterior hemiblock; PCD, primary conduction disease; RBBB, right bundle branch block.

There were 10 males and 6 females with ages ranging from 27 to 80 yr (mean±SEM 51±4.0 yr) (Table I). All patients were in sinus rhythm, had normal P-R intervals, and none were on cardiac medication at the time of study.

Informed written consent was obtained from all subjects. His bundle electrograms were recorded using previously described catheter techniques (13). A quadripolar catheter was positioned at the high right atrium near the vicinity of sinus node for atrial pacing (two poles) and for recording high right atrial electrograms (two poles). Recordings were obtained on a multichannel oscilloscopic photographic recorder (DR-20, Electronics for Medicine, White Plains, N. Y.) at paper speeds of 100 and 200 mm/s. Simultaneous electrocardiographic leads I, II, III, and V_1 were also recorded. P-A interval (normal 9–45 ms) was measured from the onset of the P wave to the first rapid deflection of the low right atrial electrogram recorded from the His bundle catheter, reflecting conduction time from high to low right atrium (13). If the onset of the P wave could not be well delineated, the onset of the high right atrial electrogram was utilized. The measurements of P-A interval were made at 200 mm/s paper speed and reflect the average of 10 consecutive beats.

Atrial pacing was performed at increasing rates. Sinus node recovery time was defined as the interval between the last paced P wave to the first spontaneous P wave after sudden cessation of pacing at a rate of 130/min. (13). Three sinus recovery times were determined and then averaged in each patient. Effective and functional refractory periods of the atrium were measured with atrial extrastimulus technique during sinus rhythm, as previously described (15). The following definitions were used in regard to atrial refractory periods: A_1 was the atrial electrogram of spontaneous sinus or driven beats (S_1), while A_2 was the atrial electrogram in response to the extra-stimulus (S_2). The atrial effective refractory period was the longest S_1-S_2 interval at which S_2 did not result in atrial capture. The atrial functional refractory period was the shortest attainable propagated A_1-A_2 interval. In 12 patients, a driven cycle length approximately 20–25% faster than the sinus rate was also utilized so that refractory periods could be measured at identical cycle lengths before and after administration of ouabain.

Sinus node responses to atrial extra stimuli (A_2) were categorized into four types of responses by noting the occurrence of first spontaneous sinus beat (A_3) following A_2 (14, 16–19): (*a*) Nonreset due to sinus interference was defined when A_3 occurred at an A_2-A_3 interval of more than spontaneous sinus cycle (A_1-A_1) and A_1-A_3 equalled $2 \times A_1$-A_1 (Zone 1 response) (16); (*b*) Sinus reset was defined when A_2-A_3 was either equal to or more than A_1-A_1, and A_1-A_3 was less than twice A_1-A_1 (Zone 2 response) (16); (*c*) Sinus interpolation was defined when A_2-A_3 was less than A_1-A_1, and A_1-A_3 was either equal to A_1-A_1 (complete interpolation) or more than A_1-A_1 (incomplete interpolation); (*d*) Sinus echoes were defined when A_1-A_3 interval was less than A_1-A_1, and P wave morphology of A_3 approximated that of the normal P wave with a high to low sequence of atrial activation.

Each patient was categorized as to whether or not he had the above zones of nonreset due to interference, reset, interpolation, and echoes. In each patient, a zone could be defined by its longest and shortest A_1-A_2 coupling interval and in terms of its absolute duration. When considering all patients with a given zone, the zone could be described in terms of its mean longest and shortest A_1-A_2 coupling intervals as well as in terms of its mean absolute duration.

Sinoatrial conduction time was calculated utilizing atrial extra stimulus technique (16, 18, 19). For each patient, this was obtained by measuring the difference between A_2-A_3 and A_1-A_1 interval during reset and dividing by two. A mean sinoatrial conduction time was calculated for each patient using all reset responses.

Ouabain was administered intravenously in a dose of 0.01 mg/kg to each patient after control recordings. Electrophysiological studies were initiated approximately 30 min after the infusion. Statistical analysis of data was performed using the student *t* test for paired values.

RESULTS

Intra-atrial conduction (Tables II and III). P-A interval was measured in all patients. The mean P-A interval±SEM was 40±2.1 ms before and 44±1.5 ms after administration of ouabain ($P < 0.001$). Atrial effective and functional refractory periods (ERP and FRP)[1] were measured in all patients during sinus rhythm. The mean atrial ERP was 244±10.5 ms before and 253±9.7 ms after administration of the drug (NS). The mean atrial FRP was 307±11.0 ms before and 318±11.4 ms after ouabain (NS). The mean atrial ERP at identical driven cycle lengths in 12 patients was 231±15.3 ms before and 266±18.6 ms after drug administration ($P < 0.01$) (Fig. 1). The mean FRP of the atrium at identical driven cycle length was 264± 14.9 ms before and 296±19.7 ms after administration of ouabain ($P < 0.01$) (Fig. 1). No measurable change

[1] *Abbreviations used in this paper:* ERP, effective refractory periods; FRP, functional refractory periods.

TABLE II

*Effect of Ouabain on Sinus Node and Atrial Conduction Intervals with Refractory Periods**

Patient no.	Sinus cycle length		SRT		Calculated SACT		P-A		Refractory periods: Sinus rhythm AERP		Sinus rhythm AFRP		Driving at identical CL: Driving CL	Driving at identical CL AERP		Driving at identical CL AFRP	
	C	O	C	O	C	O	C	O	C	O	C	O		C	O	C	O
1	810	800	1,115	1,020	115	103	42	46	200	210	300	300	—	—	—	—	—
2	920	1,020	1,110	1,100	70	129	50	50	200	190	280	280	667	210	260	250	270
3	850	820	1,310	1,170	60	105	25	35	210	270	300	350	667	190	235	260	310
4	1,020	1,210	1,300	1,093	110	100	46	54	270	330	340	410	850	260	250	290	300
5	730	840	1,050	1,000	102	114	33	38	210	190	240	290	600	210	195	215	200
6	1,050	950	1,340	1,310	142	202	50	51	280	290	370	400	—	—	—	—	—
7	820	770	1,060	920	73	86	45	44	260	240	340	300	690	240	270	285	300
8	750	650	870	815	70	110	34	43	280	240	330	280	—	—	—	—	—
9	1,070	760	1,370	950	95	110	52	52	350	260	390	300	850	305	295	310	300
10	750	810	940	860	88	110	29	36	240	230	290	270	600	320	400	330	420
11	840	940	1,220	960	87	110	45	44	210	260	260	320	667	180	240	200	250
12	720	770	970	920	120	130	42	48	200	230	270	300	600	170	180	210	210
13	860	1,040	1,155	1,065	60	72	30	35	230	260	270	270	690	295	375	360	420
14	1,030	1,100	980	1,040	78	101	32	37	230	260	300	330	850	230	260	250	310
15	1,060	1,080	1,015	1,005	45	40	37	47	250	280	270	300	850	170	240	210	270
16	920	925	1,005	910	128	140	48	48	290	310	370	390	—	—	—	—	—

AERP, atrial effective refractory period; AFRP, atrial functional refractory period; C, control; CL, cycle length; O, ouabain; SACT, sinoatrial conduction time; SRT, sinus node recovery time.
* In milliseconds.

in P wave duration or morphology was noted after infusion of ouabain.

Effect on sinus node

Sinus rate and recovery times (Table II and III). The mean cycle length during sinus rhythm was 887±31.2 ms before and 905±38.2 ms after administration of ouabain (NS). Sinus node recovery times decreased significantly after ouabain administration. Mean recovery times before and after infusion of ouabain were 1,113±38.7 ms and 1,008±30.7 ms, respectively ($P < 0.005$).

TABLE III

Summary of Electrophysiological Findings after Administration of Ouabain

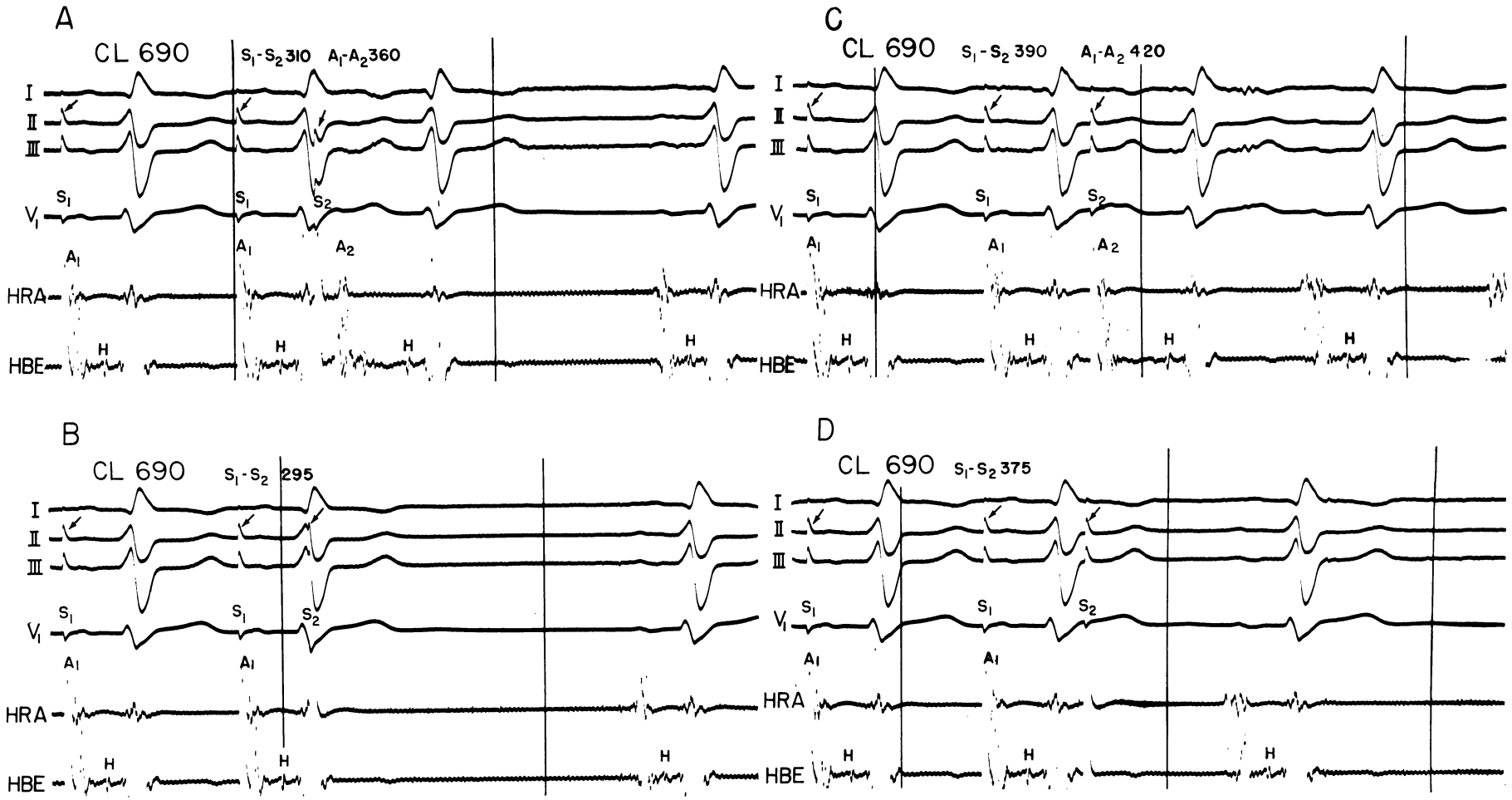
	n‡	State	Mean±SEM	P value
Sinus cycle length*	16	C	887±31.2	NS
		O	905±38.2	
SRT*	16	C	1,113±38.7	<0.005
		O	1,008±30.7	
SACT*	16	C	90±6.8	<0.005
		O	110±8.5	
P-A interval*	16	C	40±2.1	<0.001
		O	44±1.5	
Atrial ERP (NSR)*	16	C	244±10.5	NS
		O	253±9.7	
Atrial FRP (NSR)*	16	C	307±11.0	NS
		O	318±11.4	
Atrial ERP (during atrial driving)*	12	C	231±15.3	<0.01
		O	266±18.6	
Atrial FRP (during atrial driving)*	12	C	264±14.9	<0.01
		O	296±19.7	

C, control; NSR, normal sinus rhythm; O, ouabain; SACT, sinoatria conduction time; SRT, sinus recovery time.
* Milliseconds.
‡ Number of patients.

Sinus responses to extra stimulus. A zone of interference was defined in all 13 patients in whom the extra stimulus (S_2) was delivered late in sinus cycle. The mean zone of interference in these patients was between 860 (outer limit) and 708 ms (inner limit) with an absolute duration of 152 ms at a mean sinus cycle length of 860 ms. The zone increased significantly after ouabain administration, ranging from 890 (outer limit) to 632 ms (inner limit) with an absolute duration of 258 ms at a mean sinus cycle of 890 ms ($P < 0.005$) (Fig. 2). This zone accounted for the last 18% of the sinus cycle length before ouabain and 28% of sinus cycle length after ouabain ($P < 0.005$).

The effect of ouabain on sinus reset responses was evaluated in all 16 patients. The mean zone of reset in these patients was between 716 (outer limit) and 342 ms (inner limit) before ouabain, with an absolute duration of 374 ms. The mean zone of reset after ouabain was between 657 (outer limit) and 359 ms (inner limit), with an absolute duration of 298 ms ($P < 0.005$) (Figs. 2 and 3). The zone of reset accounted for 41% of sinus cycle length before and 32% after ouabain ($P < 0.005$).

Sinus interpolation (total or partial) was defined in four patients before ouabain administration. In two of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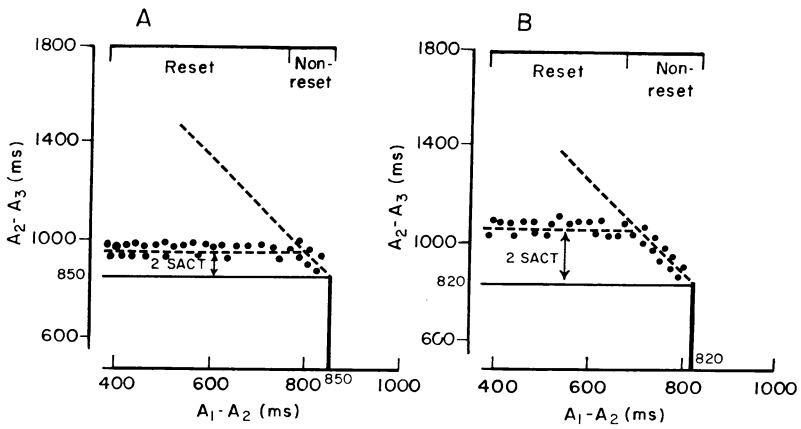

FIGURE 2 Graphic representation of sinus node responses and zones to extrastimulus during sinus rhythm in Case 3. The return cycles (A_2-A_3) are plotted on the ordinate as a function of the test cycles (A_1-A_2) on the abscissa. (Panel A, before ouabain) The sinus cycle is 850 ms. The zone of nonreset due to interference (Zone 1 response) ranges from 850 to 750 ms. The zone of reset (Zone II) is between 740 and 300 ms. The sinoatrial conduction time (SACT) is 60 ms. (Panel B, after ouabain) The sinus cycle is 820 ms. The zone of nonreset ranges from 820 to 640 ms, and the zone of reset is between 650 and 350 ms. The sinoatrial conduction time is 105 ms.

these patients, interpolation responses were abolished with ouabain. In the remaining two patients there was no significant change in the zone of interpolation with ouabain. One patient developed interpolation responses only after ouabain.

The effect of ouabain on sinus echoes was similar to that of interpolation. Sinus echo zones were present in three patients before drug administration. Ouabain abolished the sinus echo responses in one of these. In the other two patients there was no significant change in the zone of sinus echo after ouabain infusion.

Calculated sinoatrial conduction time. The effect of ouabain on calculated sinoatrial nodal conduction time was evaluated in all patients (Figs. 2 and 3). Mean sinoatrial conduction time was 90±6.8 ms before and 110±8.5 ms after administration of ouabain ($P <$ 0.005).

DISCUSSION

Experimental dog studies by Mendez and Mendez (1) revealed that ouabain shortened atrial refractory periods in innervated hearts and lengthened these in denervated hearts. In another study, Mendez and Mendez (2) demonstrated a slowing of atrial conduction velocity with digitalis despite decrease in atrial refractory periods.

There are limited data available in man regarding the effect of ouabain on intra-atrial conduction with no in-

FIGURE 1 Measurements of atrial refractory periods before and after administration of ouabain in Case 13. Shown are electrocardiographic leads I, II, III, and V_1, a bipolar intracardiac high right atrial electrogram (HRA), and a His bundle electrogram (HBE). Paper speed is 100 mm/s, and time lines are at 1-s intervals. The cycle length (CL) of the basic drive (S_1) is 690 ms and the extrastimulus and atrial coupling intervals (S_1-S_2 and A_1-A_2) are listed at the top of the each panel. A_1 is the atrial electrogram induced by S_1, and A_2 is the atrial electrogram of the extrastimulus S_2. A and B are control recordings, C and D were obtained after administration of ouabain. (A) At a coupling interval of 310 ms, S_2 is conducted to the atrium. The A_1-A_2 interval is 360 ms and is the shortest attainable A_1-A_2 interval, defining the functional refractory period of the atrium before administration of ouabain. The atrial latency at this coupling interval is 50 ms. (B) S_2 fails to capture the atrium at a coupling interval of 295 ms. This defines the effective refractory period of the atrium before ouabain. (C) At a coupling interval of 390 ms, S_2 is conducted to the atrium. The A_1-A_2 coupling interval is 420 ms and is the shortest attainable A_1-A_2 interval, defining the functional refractory period of the atrium after administration of ouabain. The atrial latency of 30 ms is less than before ouabain administration. This reflects the fact that the atrial functional refractory period was achieved at a longer S_1-S_2 coupling interval after ouabain. (D) S_2 fails to capture the atrium at a coupling interval of 375 ms. This defines the effective refractory period of the atrium after ouabain administration.

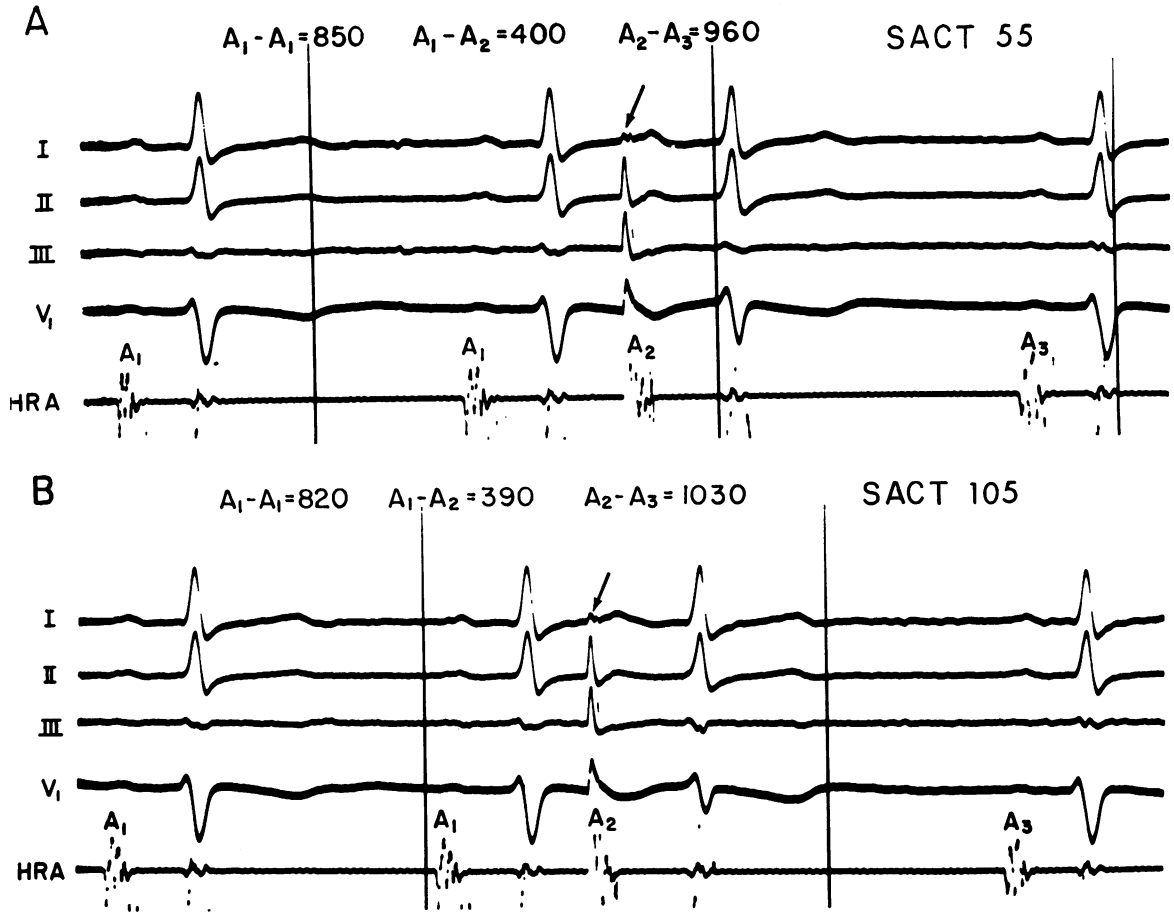

FIGURE 3 Measurements of sinoatrial conduction time before and after administration of ouabain in Case 3. The sinus cycle length (A_1-A_1), atrial coupling interval (A_1-A_2), return cycle length A_2-A_3, and calculated sinoatrial conduction time (SACT) are listed at the top of each panel. A is control recording, and B was obtained after ouabain administration. (A) Sinus rhythm at A_1-A_1 of 850 ms. At a coupling interval of 400 ms, A_2-A_3 is 960 ms, which is more than A_1-A_1, while A_1-A_3 of 1,360 ms is less than twice A_1-A_1. The sinus node is reset by A_2. The sinoatrial conduction time can be calculated by noting the difference between A_2-A_3 (960 ms) and A_1A_1 (850 ms) and dividing by two. The calculated sinoatrial conduction time is 55 ms before administration of ouabain. (B) Sinus rhythm after ouabain with A_1-A_1 of 820 ms. At a coupling interval of 390 ms, A_2-A_3 is 1,030 ms with reset of the sinus node. The calculated conduction time is 105 ms.

formation available concerning the effect on atrial effective and functional refractory periods. Engel and Schaal (9) demonstrated no significant change in P-A interval after administration of ouabain in nine patients with sick sinus syndrome. In contrast, our results suggest that ouabain depresses intra-atrial conduction as evidenced by a slight but statistically significant increase in P-A interval. In addition, ouabain significantly increased atrial functional and effective refractory periods at equivalent driven cycle lengths.

Ten Eick and Hoffman (6) and also Scherlag, Abelleira, Narula, and Samet (7) demonstrated a negative chronotropic effect of ouabain on the sinus node in intact animal hearts. Engel and Schaal (9) observed no appreciable effect of ouabain on the sinus rate in 14 patients with sinus node disease. The data from our study are in agreement with the observations of Engel and Schaal. Sinus rates were not changed significantly with ouabain administration in our patients.

Preliminary observations in our laboratory (unpublished) suggest that atropine facilitates atrial conduction in man. The effects of ouabain in this study are opposite and are thus consistant with a vagally mediated digitalis effect. We cannot exclude the presence of direct atrial effects of ouabain.

Sinus node responses to atrial extrastimuli have been recently categorized in both animals and man (14, 16–19). Responses described include nonreset due to interference of impulses delivered late in the sinus cycle, reset, interpolation, and sinus echoes. In patients without sinus node disease, nonreset and reset zones are universally present (14). Zones of interpolation and echo are much less common (14).

Data concerning the effects of ouabain on these sinus node responses in man are limited to preliminary reports concerning the effect of this agent on calculated sinoatrial conduction time (calculated during the zone of reset) (10–12). Bond and coworkers (10, 11) described a 53 ms lengthening of sinoatrial conduction time after ouabain administration in five patients. Reiffel et al. (12), studying 10 patients with sinus bradycardia, demonstrated shortening of sinoatrial conduction time in 5 and lengthening in 3 patients after ouabain administration, with a mean change ranging from − 22 to + 37 ms. Calculated sinoatrial conduction time was not affected in the two remaining patients. The results of the present study, a significant increase in calculated S-A conduction after ouabain administration, is in agreement with preliminary reports of Bond and associates.

The zone of interference, which represents a period late in atrial diastole in which the incoming impulse (S_s) collides (probably in the perisinuous tissue) with the outgoing impulse (sinus beat) causing nonreset of the sinus node, was lengthened after administration of ouabain in our patients. Since the magnitude of this zone is approximately twice the sinoatrial conduction time, prolongation of the latter would lengthen the zone of interference (14). Prolongation of sinoatrial conduction time and the zone of nonreset due to interference with ouabain may reflect increased refractoriness of the perinodal fibers surrounding the sinus node (17, 20).

In the present study, the zone of reset was contracted after the infusion of ouabain. This appeared to reflect encroachment of the outer limit due to a lengthened zone of interference and encroachment of the inner limit due to prolongation of atrial functional refractory period.

Zones of interpolation (unidirectional sinus entrance block) and echoes probably reflect refractoriness of perinodal fibers (14, 17, 20). Theoretically, ouabain should have potentiated demonstration of these zones, since the drug probably depresses perinodal conduction as suggested by prolongation of sinoatrial conduction time. The lack of this potentiation may have reflected the simultaneous increase in atrial functional refractory period, protecting the sinus node and perinodal fibers from impulses occurring at close coupling intervals.

Previous workers demonstrated a decrease in sinus node recovery time in patients wtih sinus node disease receiving ouabain (9). In the present study, we have found a similar shortening of the sinus recovery time with ouabain in patients without clinically diagnosed sinus node disease. The abbreviation of sinus recovery time after ouabain could be due to increased refractoriness of perinodal fibers, allowing fewer driven atrial impulses to penetrate the sinus node (sinus entrance block) resulting in pseudoshortening of recovery time.

Clinical implications. Acute intravenous administration of ouabain produced slight but statistically significant slowing of intra-atrial conduction and increased atrial effective and functional refractory periods. The most important finding in our study was the increase in sinoatrial conduction time and zone of interference. This probably reflected a direct or vagally mediated effect of ouabain on perinodal fiber conduction.

These electrophysiological effects of ouabain, in addition to being of pharmacological interest, may relate to some of the electrocardiographic manifestations of digitalis intoxication, e.g., sinoatrial block, sinus arrest, and atrial standstill (21). The increase in atrial refractoriness noted with digitalis may contribute to conversion of atrial fibrillation or flutter to sinus rhythm and suggests the possibility that digitalis could be of prophylactic value in patients with these atrial dysrrhythmias. Despite recent reports stressing the safety of digitalis in patients with sinus node disease, the demonstration of prolonged sinoatrial conduction time suggests that this drug is potentially hazardous in this group of patients (22–24).

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