Clinical electrophysiological effects of propranolol on normal sinus node function

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SUMMARY In 35 patients aged 18 to 69 years (mean 48) with clinical, electrocardiographic, or electrophysiological evidence of normal sinus node function, the effect of intravenous propranolol (0.1 mg/kg) was assessed on 3 indices of sinus node function. The drug significantly prolonged sinus node cycle length (12%), slightly prolonged the corrected sinus node recovery time (15%), and slightly but insignificantly lengthened sinuatrial conduction time. Propranolol may be administered safely in patients with normal sinus node function without the fear of producing severe sinus bradycardia, sinuatrial block, sinuatrial pauses, or prolonged sinus asystole, after spontaneous or stimulation-induced conversion of a tachycardia.

For over a decade, propranolol has been used extensively in the management of patients with arrhythmias (Rowlands *et al.*, 1965; Bath, 1966). Several studies have reported the electrophysiological effects of propranolol in isolated tissue preparations (Davis and Temte, 1968; Pollen *et al.*, 1969), in the intact animal (Priola, 1973), and in man (Seides *et al.*, 1974). Despite a large number of publications, there is little information on the electrophysiological effects of propranolol on the sinus node function in man (Grendahl *et al.*, 1975; Strauss *et al.*, 1976b). Previous studies (Seides *et al.*, 1974) in general analysed the effect of propranolol on only one index of sinus node function, that is the changes in sinus node cycle length or rate. Except for a preliminary report (Chuquimia *et al.*, 1977) from this laboratory, few data are available on the effects of propranolol in patients with normal sinus node function, in particular on the response of the sinus node to overdrive suppression and on sinuatrial conduction time. Recently Strauss *et al.* (1976b) have reported their results on the effect of propranolol in 10 patients with sinus node dysfunction. It is difficult to view their results with a proper perspective without the knowledge of its effects on normal sinus node function.

In view of its extensive clinical use in patients with various types of arrhythmias, especially atrial

fibrillation, atrial flutter, or supraventricular tachycardia, which inherently produce overdrive suppression of the sinus node, the necessity to learn the effects of propranolol on various indices of normal sinus node function was realised. The purpose of this study was to analyse the effect of intravenous propranolol on sinus node function in patients with clinical and electrophysiological evidence of normal sinus node function.

Subjects and methods

Electrophysiological studies were performed in 35 patients. Patients ranged in age from 18 to 69 years (mean 48), with 16 men and 19 women. A complete history and physical examination were recorded. In each patient routine laboratory data, a standard 12 lead electrocardiogram, and a chest x-ray film were obtained. The patients included in this study consistently showed resting normal heart rates (> 60/min) on serial electrocardiograms and showed no electrocardiographic (standard electrocardiogram and Holter recordings) or clinical evidence of sinus node dysfunction. In addition, none of the 35 patients had any evidence of sinus node dysfunction during electrophysiological studies which were performed for symptoms of syncope, dizziness, and/or palpitations. The standard electrocardiogram was normal in 11 patients and showed a pattern of bundle-branch block in 9 patients. The remaining

15 patients showed various arrhythmias, that is paroxysmal re-entrant supraventricular tachycardia (7), ventricular arrhythmia (7), and 2° type 1 atrioventricular nodal block (1). In the cases with paroxysmal supraventricular tachycardia, the site of re-entry was either in the atrioventricular node or resulted from bypass tracts. None of the 35 patients showed any evidence of atrial fibrillation or atrial flutter. In 24 patients there was no clinical evidence of associated heart disease, besides the arrhythmia or the bundle-branch block pattern. One patient had arteriosclerotic heart disease and 10 had associated systemic hypertension. At the time of study all cardioactive drugs had been discontinued for an interval exceeding 3 drug half lives. In all patients informed consent was obtained. The patients were studied in the postabsorptive state after premedication with 100 mg pentobarbitone sodium administered intramuscularly half an hour before the study.

Under fluoroscopic control and intracardiac electrographic monitoring, a bipolar electrode catheter, 5 French in size with ring electrodes 10 mm apart was introduced precutaneously from a femoral vein and placed in the His bundle region. His bundle electrograms were recorded as described previously (Narula *et al.*, 1970). A second quadripolar pacing catheter with electrodes 10 mm apart was introduced into the right atrium via an antecubital vein, and positioned so that the proximal electrode pair was located in the region of the sinus node for recording high right atrial electrograms and the distal pair was used for atrial stimulation.

All recordings were made on a multichannel oscilloscopic photographic recorder at paper speeds of 100 mm/s for analyses of AH and HV intervals, and paper speeds of 50 to 100 mm/s were used during studies of sinus node function. Multiple electrocardiographic leads representing the 3 planes of the electrocardiogram were recorded simultaneously with the intracardiac recordings. Atrial stimulation studies were performed at double the diastolic threshold with stimuli 2 ms in duration. Atrioventricular conduction was analysed during sinus rhythm and atrial pacing.

After catheter placement, control observations of spontaneous sinus rhythm were made for a period of 10 minutes. During the last minute of the control period, 10 consecutive sinus cycles were measured to calculate the mean sinus cycle length (mean A_1A_1). Single premature atrial beats were induced during sinus rhythm after every 8th sinus cycle for evaluation of sinuatrial conduction time. The entire sinus cycle was scanned by the placement of premature atrial beats of increasing prematurity in steps of 10 to 20 ms until the atrial refractory period

was reached. After the sequence of premature atrial beats, spontaneous sinus rhythm was observed for another period of 2 minutes before analysis of sinus node recovery time. The sinus node recovery time was measured as previously described (Narula *et al.*, 1972) by atrial pacing at 2 different cycle lengths (500 and 430 ms) for a period of 2 minutes at each level. Atrial pacing at cycle lengths shorter than 430 ms was not used, as previous studies (Mandel *et al.*, 1971) have reported a decrease in sinus node recovery time with shorter pacing cycle lengths. Immediately after atrial pacing was stopped, 10 spontaneous sinus cycles were recorded and analysed. A rest period of 2 minutes was provided between each atrial pacing rate to permit sinus rhythm to return to control levels. In our study, the sinus cycles usually returned to control levels in less than 1 minute.

After control determinations were completed, propranolol was administered intravenously in a dosage of 0.1 mg/kg bodyweight at a rate of 1 mg/min. Total dose ranged from 5 to 10 mg. This dosage regimen has been reported (Seides *et al.*, 1974) to produce average plasma levels of 13.6 ng/ml for 45 to 60 min after administration of propranolol. Ten minutes after the infusion of the last drop of propranolol, 30 sinus cycles were recorded to obtain the post-propranolol mean sinus cycle length. Thereafter, studies were repeated as in control to measure sinuatrial conduction time and sinus node recovery time. These studies were usually completed in ≤ 30 minutes after the last dose of propranolol was given.

The blood pressure was carefully monitored throughout: the drop in systolic pressure was ≤ 10 mmHg in all cases. No complications requiring treatment occurred in any patient either during or after the study. The atrial stimulation studies (regular atrial pacing or premature atrial beats) did not produce any bouts of atrial fibrillation or flutter throughout the study. In none of the cases with a history of supraventricular tachycardia was the measurement of sinus node recovery time or sinuatrial conduction time affected by atrial stimulation studies. Regular atrial pacing at cycle lengths used for sinus node recovery time did not initiate supraventricular tachycardia. During scanning of the sinus cycle by premature atrial beats, supraventricular tachycardia was initiated (3 out of 7) with very early premature atrial beats and not during the zone of sinus node reset used for estimating sinuatrial conduction time. In order to enhance relaxation, patients were studied in a quiet atmosphere and a relatively dark room using as little light as was necessary for the operation of the stimulator and the physiological recorder.

In each patient the intervals between successive atrial depolarisations were measured from the bipolar high right atrial electrogram. During the sequence of premature atrial beats, the following intervals were measured: (1) A_1A_1 which is defined as the interval between the 2 consecutive sinus cycles; (2) A_1A_2 the interval between the atrial electrograms of sinus origin and the premature atrial beat; (3) A_2A_3 (return cycle) the interval between the premature atrial beat and the succeeding sinus beat. The estimated sinuatrial conduction time was calculated by the recently described method of Strauss *et al.* (1976a) based on a mean of A_2A_3 intervals falling in the latter portion of zone II (reset zone). Sinuatrial conduction time = $A_2A_3 - A_1A_1$. The value thus obtained represents the sum total of conduction time into and out of the sinus node.

Sinus node recovery time was measured from the last paced atrial electrogram to the first escape atrial electrogram of sinus origin or the longest post-pacing pause. The corrected sinus node recovery time was obtained by deducting from the sinus recovery time the mean of 10 consecutive spontaneous sinus cycles, recorded immediately preceding each atrial pacing cycle length. The statistical significance of the difference in values of spontaneous sinus node cycle length, corrected sinus node recovery time, and estimated sinuatrial conduction time determined under control and after propranolol were tested using the paired *t* test.

Results

(1) SINUS CYCLE LENGTH

During control the sinus node cycle length ranged from 559 to 955 ms (mean and SD 766 $\pm$

Fig The effects of propranolol on the 3 indices of sinus node function. NS, statistically not significant.

102) and after propranolol it ranged from 705 to 1090 ms (mean and SD 860 $\pm$ 107). After propranolol the sinus node cycle length increased by a range of 6 to 295 ms (mean 94) or by a mean of 12 per cent; this increase was statistically significant ($P < 0.005$) (Fig.). None of the patients manifested any electrocardiographic evidence of 2° sinuatrial block or sinuatrial pauses after propranolol administration.

(2) SINUATRIAL CONDUCTION TIME

In 2 patients (cases 26 and 32), the sinuatrial conduction time during control was 175 and 118 ms, and it could not be calculated after propranolol as the zone of sinus node reset could not be defined (Table). In the remaining 33 patients, the control sinuatrial conduction time ranged from 70 to 246 ms (mean 166 $\pm$ 49) and after propranolol it ranged from 100 to 285 ms (mean 182 $\pm$ 49). With propranolol, the sinuatrial conduction time was shortened (range 7 to 92 ms) in 12 and lengthened (range 2 to 110 ms) in 21 patients. The changes in sinuatrial conduction time after propranolol were not statistically significant.

(3) CORRECTED SINUS NODE RECOVERY TIME

On stopping atrial pacing, the first escape sinus node cycle was the longest in all except 4 of the 35 patients, in whom it was noted to be the second or the third sinus node cycle (Table).

The control corrected sinus node recovery time after atrial pacing at cycle length of 500 ms ranged from 83 to 520 ms (mean 247 $\pm$ 113) and after propranolol ranged from 90 to 605 ms (mean 284 $\pm$ 115) (Fig.). After propranolol, the corrected sinus node recovery time at this atrial pacing rate was unchanged in 2, prolonged in 23 (range 15 to 415 ms, mean = 97), and shortened in 10 patients (range 20 to 175 ms, mean = 93). The control corrected sinus node recovery time after atrial pacing at a cycle length of 430 ms ranged from 10 to 525 ms (mean 235 $\pm$ 137) and after propranolol ranged from -55 to 494 ms (mean = 262 $\pm$ 106). After propranolol, the corrected sinus node recovery time at this atrial pacing rate was unchanged in 1, lengthened in 23 (range 25 to 276 ms, mean = 102), and shortened in 11 patients (range 5 to 345 ms, mean = 125). After propranolol 17 (49%) of the 35 patients showed a shortening in corrected sinus node recovery time at both atrial pacing cycle lengths. Before beta-blockade, in 8 of these 17 patients, the corrected sinus node recovery time had shortened during control as the atrial pacing rate was increased.

Table Electrophysiological effect of propranolol on normal sinus node function

No.	Age	and sex	Other electrocardiographic features	Sinus cycle length (ms)		Sinuatrial conduction time (ms)		Corrected sinus node recovery time (ms)			
				Pre	Post	Pre	Post	AP CL = 500		AP CL = 430	
								Pre	Post	Pre	Post
1	18	F	Normal PR, QRS, and axis	710	830	150	100	90	90	185	150
2	18	M	Lown Ganong Levine syndrome, supraventricular tachycardia	611	717	119	223	146	243	157	212
3	21	F	WPW and supraventricular tachycardia	559	757	78	123	237	357	235	337
4	23	F	Premature ventricular contractions	870	990	175	200	125	245	85	305
5	26	F	Normal PR, QRS, and axis	900	1005	160	235	520	605	290*	-55
6	29	M	Normal PR, QRS, and axis	892	1020	131	114	265	158*	10	112*
7	30	F	Normal PR, QRS, and axis	682	740	188	190	273	340	234	343
8	36	F	Ventricular tachycardia	950	968	165	172	367	293	525	347
9	38	M	Type 1, 2° atrioventricular block	740	855	210	197	180	215	205	350
10	40	M	Supraventricular tachycardia	915	940	245	215	145	260	180	320
11	42	F	Left bundle-branch block	775	850	205	285	215	380	295	350
12	43	F	WPW and supraventricular tachycardia	700	720	170	120	175	195	130	105
13	45	F	Supraventricular tachycardia	629	718	113	147	95	510	120	310
14	45	F	Left bundle-branch block	764	770	246	265	297	255	114	167
15	46	F	Normal PR, QRS, and axis	787	815	120	230	235	370	182	257
16	50	M	Normal PR, QRS, and axis	680	705	170	245	110	180	60	160
17	52	F	Normal PR, QRS, and axis	728	820	157	120	275	205	150	145
18	52	M	Supraventricular tachycardia	700	850	180	220	380	250	500	210
19	52	F	Ventricular tachycardia	830	880	210	170	280	205	125	290
20	53	M	Right bundle-branch block and left axis deviation	875	955	190	205	430	515	290	360
21	54	M	Left bundle-branch block	700	760	85	170	152	247	125	170
22	55	M	Normal PR, QRS, and axis	898	926	158	130	245	310	400	380
23	55	F	Prolonged QT, premature ventricular contraction	710	790	110	110	140	240	185	250
24	55	M	Ventricular tachycardia	680	790	240	250	400	440	460	410
25	57	F	Right bundle-branch block and left axis deviation	700	750	70	140	300	300	275	360
26	57	F	Ventricular tachycardia	760	960	175	ND	290	380	520	250
27	58	F	Right bundle-branch block and left axis deviation	725	795	230	235	231	324	216	245
28	60	M	Normal PR, QRS, and axis	710	737	180	173	410	325	260	305
29	60	M	Right bundle-branch block and left axis deviation	730	855	100	190	83	105	25	50
30	64	M	Right bundle-branch block and left axis deviation	860	980	165	180	165	145	200	180
31	65	F	Left bundle-branch block	955	1000	155	125	128	264	218	494
32	65	M	Premature ventricular and atrial contractions	927	1090	118	ND	305*	130	320	410
33	68	M	Normal PR, QRS, and axis	730	840	210	195	285	320	470	235
34	69	M	Normal PR, QRS, and axis	705	910	242	150	460	310	320	320
35	69	F	Supraventricular tachycardia	715	1010	135	200	215*	230	140	240
Mean ± SD				766 ± 102	860 ± 107	164 ± 49	182 ± 49	247 ± 113	284 ± 115	235 ± 137	262 ± 112

*Longest escape sinus cycle was 2nd or 3rd cycle.

AP, atrial pacing; CL, cycle length; ND, not definable.

With propranolol, the increase (15%) in mean corrected sinus node recovery time (from 247 to 284) after atrial pacing at a cycle length of 500 ms was statistically significant ($P < 0.025$). However, the increase in corrected sinus node recovery time (from 235 to 272 ms) after atrial pacing at a cycle length of 430 ms was not statistically significant. In addition, when the data of maximum or the longest corrected sinus node recovery time at either of the atrial pacing cycle lengths are reviewed, the maximum time: (a) increased from a mean of 284 ± 130 to 317 ± 112 ms and (b) lengthened in 25 and shortened in 10 patients after propranolol. In this

study of patients with normal sinus node function, there was no difference in response to propranolol related to the presence or absence of associated arrhythmias.

Discussion

In the past 6 years, atrial pacing studies have been extensively used for electrophysiological evaluation of sinus node function in man, both for investigative and clinical purposes. With the increasing use of such techniques, it has become apparent that at times in patients with previously documented sinus node

dysfunction, the evaluation of sinus node function by electrophysiological means is within normal limits at the time of the study. These observations raise questions as to whether the electrophysiological testing procedures are inadequate and unreliable or whether the laboratory results return to normal because of an increase in release of stored catecholamines resulting from the stress of cardiac catheterisation. If the latter possibility is true, then it may be argued that patients requiring evaluation of sinus node function for clinical purposes may be analysed with greater accuracy by blocking the effect of increased catecholamines with propranolol administration.

Recently Strauss *et al.* (1976b) attempted to evaluate this consideration in 10 patients who were thought to have symptomatic sinus node dysfunction. However, only 2 of the 10 patients had abnormal corrected sinus node recovery time during control and both showed a severe prolongation of corrected sinus node recovery time after propranolol. In 5 other patients, the corrected sinus node recovery time changed by ≤ 58 ms with propranolol. Since the effect of propranolol on normal sinus node function was not known, their observations cannot be reviewed from a proper perspective and have failed to satisfy the questions raised above. Their study left several questions unanswered. Does propranolol have a significant effect on sinus node recovery time in both patients with normal and abnormal sinus nodes? Is the severe prolongation of sinus node recovery time noted in 2 of the 10 cases an unusual response, or is it indicative of severe sinus node dysfunction?

Our data in patients with normal sinus node function show that with propranolol sinus cycles lengthened significantly ($P < 0.005$) with an average increase of 12 per cent. This prolongation in sinus cycle length is slightly less as compared with 16 per cent (Seides *et al.*, 1974) and 22 per cent (Stern and Eisenberg, 1969) reported by others. The difference between our results and those of others may be explained by the fact that our patients were premedicated with pentobarbitone sodium whereas others obtained their data in non-sedated patients, possibly with higher levels of released catecholamines. The greater the beta-adrenergic stimulus, the greater the response to beta-adrenergic blockade. In our patients, the control sinus cycle lengths noted at the time of the study were usually similar to those noted on routine electrocardiograms. This suggests that possibly there was no obvious increase in catecholamine release during the electrophysiological study.

After propranolol, though the mean corrected

sinus node recovery time lengthened after each of the atrial pacing levels (120/min and 140/min), it was statistically significant only after atrial pacing at 120/min. In addition, in 49 per cent of the patients the corrected sinus node recovery time, at either of the pacing cycle lengths, decreased after propranolol. Previous studies (Breithardt and Seipel, 1976) have indicated a faster conduction into the sinus node with sympathetic stimulation or with parasympathetic blockade after atropine. Therefore, the converse is also possible, that is an increased conduction delay or entrance block into the sinus node with sympathetic blockade. A decrease in corrected sinus node recovery time with propranolol may be explained on the basis of an enhanced entrance block into the sinus node and which, compared with the control levels, was manifested in some at lower atrial pacing rates. However, a lack of significant increase in sinuatrial conduction time with propranolol fails to support such a possibility.

If, in fact, propranolol enhances entrance block into the sinus node, it may possibly obscure the demonstration of sinus node dysfunction and may mask prolongation of the sinuatrial conduction time. Recently reported observations (Strauss *et al.*, 1976b) of a distinct prolongation of corrected sinus node recovery time with propranolol in some and not all of the cases with clinically diagnosed sinus node dysfunction may suggest that: (a) if in patients with sinus node dysfunction, as discussed above, a protection from overdrive suppression does exist, it does not apply to all of the cases with sick sinus node; and (b) depending upon the response to propranolol, it may be possible to differentiate the various underlying mechanisms responsible for sick sinus syndrome, that is abnormalities of sinuatrial conduction and of the generator function of the sinus node.

During experiments in isolated tissues, it has been previously noted (Rosenbleuth, 1950) that in order to produce slower sinus rates or asystole it is necessary to affect all sinus node pacemaker fibres by acetylcholine, whereas only a few sinus node pacemaker fibres need be accelerated by norepinephrine to produce an increment in the heart rate. Therefore, it may be reasoned that in patients with sick sinus node, only a few sinus node pacemaker fibres may be functioning under the influence of available catecholamines which are sufficient to sustain sinus rhythm. In such patients, a withdrawal of catecholamine influences and beta-adrenergic blockade with propranolol may not only result in slower sinus node rates but also show a pronounced suppression to overdrive pacing or a distinct prolongation of the sinus node recovery time.

In our series, the maximum corrected sinus node

recovery time at either of the atrial pacing rates showed a mean prolongation of 33 ms (11%) with propranolol. None of the patients showed a severe prolongation in corrected sinus node recovery time similar to that observed by Strauss *et al.* (1976b) in 2 of their 10 cases with sinus node dysfunction. On the basis of present data, it may be suggested that in the dosage used in this study and in therapeutic doses, propranolol may be safely administered when required to patients with electrophysiologically normal sinus node function without affecting it adversely. Accordingly, the evaluation of sinus node recovery time with and without propranolol may be clinically useful, before the institution of propranolol therapy, for detecting patients in whom a distinct adverse effect on sinus node function may occur, though extrapolation to patients on long-term oral treatment with propranolol may not be valid.

In all but 4 of the cases in our series, the first escape sinus node cycle after cessation of atrial pacing was the longest, both during control and after propranolol. This suggests that the secondary pauses are not common in cases with normal sinus node function and, when noted, may be suspicious of an overt or latent sinus node dysfunction. It may also be indirectly concluded that after propranolol administration a conversion of supraventricular tachycardia when associated with a long period of asystole probably indicates a sick sinus node. The asystole should not be interpreted merely as an expected side effect of propranolol. Such patients should be further investigated, in the absence of propranolol to confirm the diagnosis of sick sinus syndrome.

Previous workers (Breithardt and Seipel, 1976) have shown that sinoatrial conduction time is affected by autonomic influences, that is shortened by parasympathetic blockade or sympathetic stimulation. Our data show that though after propranolol there was a slight increase in the mean sinoatrial conduction time for the entire group, it was not statistically significant. It is difficult to evaluate properly the effect of propranolol on sinoatrial conduction time because of the limitations inherent in the present technique for its estimation (Strauss and Wallace, 1976).

The dosage of propranolol used in this study is similar to that used by others during electrophysiological studies in man (Seides *et al.*, 1974; Strauss *et al.*, 1976b). Propranolol in these doses produces 20 to 30 per cent blockade of exercise-induced sinus tachycardia and requires a tenfold increase in the dose of isoprenaline to produce a given level of sinus tachycardia (Coltart and Shand, 1970). The plasma level resulting from this dosage

regimen has been shown to have a significant beta-adrenergic blocking effect. Mean serum levels of 13.6 ng/ml have been reported 45 to 60 minutes after propranolol administration with this dosage regimen (Seides *et al.*, 1974). Our studies were generally completed within 30 min of the last dose of propranolol. In addition, this dosage regimen was selected to avoid unnecessary side effects or complications, that is hypotension which in turn may artificially alter the sympathetic and parasympathetic influences and thereby confuse the interpretation of the results. The results of the present study of an increase in sinus node cycle length, lengthening of corrected sinus node recovery time, and a possible prolongation of sinoatrial conduction time may all be explained on the basis of the beta-adrenergic blocking effect of propranolol on the sinus node and the atrial myocardium.

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