EFFECT OF ATROPINE ON ESCAPE MECHANISM OF THE SUBSIDIARY PACEMAKERS IN PATIENTS WITH DYSFUNCTION OF THE SINUS NODE

WEN-PIN LIEN, M.D., F.A.C.C., JIN-JER CHEN, M.D.
AND TEH-LU WU, M.D.

Effects of intravenous atropine on postpacing impulse recovery time of the subsidiary pacemakers were studied by incremental atrial pacing in 9 patients with sinus nodal (SN) dysfunction. Patients having either or both of the following anomalies are used: 1) persistent sinus bradycardia (sinus cycle length > 1000 msec), or documented episodes of sinoatrial block or arrest and/or 2) maximum corrected SN recovery time of longer than 525 msec before and after atropine. Seven patients had a history of cerebral ischemic symptoms. The mean $\pm$ SEM of the maximum A-V junctional recovery times (MJRTs) before and after atropine, measured in 5 patients, were $2,485 \pm 825$ msec and $1,164 \pm 281$ msec, respectively ($p < 0.01$). The average percent reduction of the junctional escape times in these 5 patients was 53.2%. In all 9 patients MJRT shortened to less than 1,610 msec after atropine. Moreover, a low atrial pacemaker also was the escape mechanism following pacing in 2 patients after atropine; the maximum atrial recovery times were 2,500 msec and 1,220 msec, respectively. We conclude that atropine can markedly enhance escape mechanism of the subsidiary pacemakers in patients with SN dysfunction.

PATHOLOGICAL changes in the sinus node (SN), perinodal area or also in the atrial tissue, as well as the influence of the autonomic nervous system, may cause various electrophysiologic manifestations in patients included in the category of SN disease. Nevertheless, it is the escape mechanism of subsidiary pacemakers that determines whether or not cerebral ischemic symptoms occur.^{1,2} Studies on the effects of

atropine on escape mechanism of the low atrial or atrioventricular (A-V) junctional pacemakers in this clinical setting are limited to the recent reports with small numbers of patients^{1,2} and data concerning comparative automaticity changes of the SN and subsidiary pacemakers with atropine is not available.

In this study, we used atrial overdrive stimulation technique to evaluate the electrophysiologic effects of atropine on automaticity of the SN and subsidiary pacemakers systematically in 9 patients with SN dysfunction. We found that atropine enhanced escape mechanism of the subsidiary pacemakers to nearly normal level.

Key Words:

Dysfunction of the sinus node
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The Department of Internal Medicine, National Taiwan University, College of Medicine and National Taiwan University Hospital, Taipei, Taiwan

Address for correspondence: Wen-Pin Lien, M.D., 12, Lane 120, Section 1, Shin-Shen S. Road, Taipei 106, Taiwan

TABLE 1 CASE MATERIALS

Case No.	Sex/Age(yr)	Underlying disease	Cerebral ischemic symptoms	ECG manifestations during the study	History of atrial tachyarrhythmias
1	M/60	No OHD	Severe dizzy spells, 2 mos.	SB, SA, JE, JR	—
2	F/49	No OHD	Severe dizzy spells, 1 yr.	NSR, SAB, PACs	—
3	F/22	No OHD	Dizzy spells, 14 yrs.	SB, SAB or SA, AV dissociation	—
4	F/36	No OHD	Dizzy spells, 6 mos.	NSR, SAB	—
5	F/61	Thyrotoxicosis, treated	Syncopal attacks, 4 yrs.	NSR, SB or JR	PSVT (AVJRT), AF
6	F/52	No OHD	Syncopal attacks, 3 yrs.	NSR, SAB	AF
7	M/34	No OHD	—	NSR, SAB or SA	—
8	M/36	No OHD	—	NSR, SAB or SA	—
9	M/46	No OHD	Dizzy spells, 2 yrs.	SB	—

mos = months; yr = year; ECG = electrocardiogram; M = male; F = female; No OHD = No apparent organic heart disease; SB = sinus bradycardia; SA = sinus arrest; SAB = sinoatrial block; JE = junctional escape; JR = junctional rhythm; NSR = normal sinus rate; PACs = premature atrial contractions; AV = atrioventricular; AF = atrial fibrillation; PSVT = paroxysmal supraventricular tachycardia; AVJRT = AV junctional reentrant tachycardia

Atropine can be a useful drug before pacemaker implantation in symptomatic patients with SN dysfunction.

MATERIALS AND METHODS

The study population consisted of 9 patients who were admitted for electrophysiologic studies because of SN dysfunction. They ranged in age from 22 to 60 (mean = 46) with 5 men and 4 women. In the present study, the patients having either or both of the following anomalies were used: 1) persistent sinus bradycardia (sinus cycle length longer than 1,000 msec), or documented episodes of sinoatrial block or arrest, with or without junctional escapes and/or 2) maximum corrected SN recovery time (MCSNRT) of longer than 525 msec before and after atropine administration. A pertinent clinical profile is presented in Table I. Seven patients (Cases 1, 2, 3, 4, 5, 6 and 9) had a history of cerebral ischemic symptoms. The remaining 2 (Cases 7 and 8) were asymptomatic over a follow-up period of 4 and 6 years, respectively. Two of the 7 patients with symptoms had had documented atrial tachyarrhythmias before the studies. All patients had no evidence of organic heart disease.

Electrophysiologic studies were performed in the resting non-sedated postabsorptive state. All patients had taken no cardiac medication within 72 hours of the studies. Informed written

consent was obtained from all patients. His bundle recordings were performed using a bipolar catheter passed through the right femoral vein²⁻⁴. A quadripolar catheter was positioned at the high right atrium in the vicinity of the SN for atrial pacing (distal 2 poles), and also for recording of high right atrial electrograms (proximal 2 poles). Atrial pacing studies were performed with a current strength of twice the diastolic threshold with a duration of 2 msec. Overdrive suppression of SN and low pacemakers was assessed by incremental atrial pacing with an increment of 10 beats/min^{2,3,5}. Each pacing period lasted for 3 min. Atrial effective refractory period and sinoatrial conduction time (SACT) were determined with atrial extrastimulus techniques as previously described³. Recordings were obtained on a 12-channel oscilloscopic photographic recorder (Electronics for Medicine, VR-12) at paper speeds of 100 and 200 mm/sec. Simultaneous multiple surface and intracardiac electrograms were recorded. The studies were also repeated 5 min after administration of atropine (1 to 1.5 mg intravenous single bolus injection).

Maximum corrected SN recovery time (MCSNRT) was defined as the longest SNRT after sudden cessation of atrial pacing minus the average value of the 10 preceding sinus cycle lengths prior to atrial pacing^{2,6}. Atrioventricular junctional impulse recovery time (JRT) was defined as the interval between the His deflection

Fig.1. Recordings before intravenous atropine administration in Case 1 with sinus bradycardia, junctional escapes and junctional rhythm with intact A-V conduction. A) Control tracing. Simultaneous recordings of bipolar electrograms from high right atrium (HRA) and the His bundle (H) region along with 3 standard ECG leads (L1, L3 and V1). The control sinus cycle length (HRA-HRA) ranges from 1,020 to 1,580 msec and the A-V junctional cycle length ranges between 1,240 and 1,270 msec. In sinus beats, intraatrial conduction time (HRA-A) is 20 msec, intranodal conduction time (A-H) is 130 msec and His-Purkinje system conduction time (H-V) is 45 msec. B) Junctional recovery time (H-H) on termination of atrial overdrive pacing for 3 min at a cycle length of 400 msec. On termination of the pacing the first spontaneous escape junctional beat appears at an H-H interval of 1,710 msec, while the first spontaneous sinus beat appears at an HRA-HRA interval of 2,610 msec. C) Sinus node recovery time on cessation of atrial pacing for 3 min at cycle length of 375 msec with an HRA-HRA interval of 2,190 msec. On termination of the pacing the second spontaneous beat is of junctional mechanism, giving an H-H interval of 1,910 msec. Note that 2:1 A-V block (intranodal) develops during atrial pacing in B) and C). All the intervals are indicated in milliseconds.

(H) of the last pacing beat to H of the A-V junctional escape beat (Figs. 1B and 2B). When the first recovery beat was of sinus or atrial mechanism but the second beat was of junctional mechanism, JRT was also measured as the interval between the H of the first postpacing beat (sinus or atrial mechanism) to H of the second postpacing A-V junctional escape beat (Figs. 1C and 2C)^{1,2}. The corrected JRT was measured from average value of JRTs minus average value of the available preceding A-V junctional cycle lengths (usually 10 cycle lengths). In some patients, low atrial escape beat(s) followed cessa-

tion of overdrive atrial pacings. The low atrial recovery time was defined as the interval between the low atrial deflection (A) of the last pacing beat and A of the first postpacing low atrial escape beat (Fig. 2C)². When the first postpacing beat was of sinus mechanism and the second postpacing beat was low atrial escape beat, the A-A interval between the sinus recovery beat and the atrial escape beat was also taken as low atrial recovery time.

Sinoatrial conduction time was calculated as described by Strauss et al.⁷ The one-way conduction time was obtained by measuring the differ-

Fig. 2. Recordings following intravenous atropine administration (1.5 mg) in the same patient (Case 1) as in Fig. 1. A) Control tracing recorded 5 min after atropine showing mostly junctional rhythm with occasional V-A conduction. Both sinus cycle length and junctional cycle length have shortened. The sinus cycle length ranges from 810 to 1,190 msec, while junctional cycle length ranges between 890 and 920 msec. Intraatrial conduction time (HRA-A) and His-Purkinje system conduction time (H-V) remain unchanged from that of before atropine. The intranodal conduction time, however, has shortened (110 msec). B) Shortening of junctional recovery time (1,170 msec) after atropine. The sinus node recovery time is 2,750 msec. On termination of atrial overdrive pacing, the same junctional interval has persisted up to the fourth spontaneous junctional escape beat. C) Low atrial recovery time on termination of atrial pacing at cycle length of 429 msec with an A-A interval of 2,500 msec. On cessation of the atrial pacing, the second spontaneous beat is of junctional escape mechanism and H-H interval is 1,620 msec. The first postpacing high atrial potential (HRA) is probably of sinus mechanism and sinus node recovery time is 2,530 msec. The third HRA on termination of atrial pacing is most likely conducted from a low atrial escape beat.

ence between the A2-A3 and A1-A1 intervals during the zone of reset and then dividing this value by 2. A mean SACT was calculated using all reset responses. A-V nodal effective refractory period was measured during sinus rhythm with atrial extrastimulus technique.³ All electrophysiologic findings noted before and after atropine in 9 patients are summarized in Table II. A part of data from Case 3 was previously reported²

RESULTS

Sinus Nodal Function in the 9 Patients

Electrophysiologically, all 9 patients had SN dysfunction. The mean $\pm$ SEM sinus cycle length was $1,137 \pm 284$ msec before and 699 ± 69 msec after administration of atropine ($p < 0.001$). Maximum CSNRT in 7 of the 9 patients was $2,128 \pm 1,037$ msec (mean $\pm$ SEM) before and $1,324 \pm 1,008$ msec after atropine; the difference was not statistically significant. In the remaining 2 patients, one (Case 5) had A-V junctional escape following overdrive pacing all the times before atropine and in all but twice after atropine. Maximum CSNRT after atropine was 270 msec (Fig. 3). The other patient (Case 9) had a MCSNRT of 860 msec before atropine. However,

TABLE II SUMMARY OF ELECTROPHYSIOLOGIC FINDINGS BEFORE AND AFTER ATROPINE

Case No.	SCL	HRA-A	A-H	H-V	JE Interval	H-H (JR)	MCSNRT	MJRT	SACT	AERP	AVN ERP
1	1130±133 *864±42	20 20	125 110	45 45	1375±60 1145±43	1287±57 1041±84	3656 3540	1995 1610	96 91	260 220	355 310
2	923±175 *659±224	25 30	95 95	40 40	— 850, 850	930, 980 —	2090 1265	1900 1100	No reset zone —	360 —	420 —
3	1783±381 *684±15	20 20	350 135	53 52	— —	1413±148 —	3465 698	2970 850	170 —	435 —	— —
4	1275±309 *667±19	20 15	90 90	45 45	— —	— —	1545 670	1850 1050	120 109	270 180	370 285
5	803±53 *664±5	25 20	75 75	40 40	1332±178 —	1192±153 —	— 270(?)	3710 1210	— —	— —	— —
6	920±63 *660±14	20 20	80 85	35 37	— —	— —	1622 935	— 1610	— 132	— 245	— 295
7	1126±27 *686±25	25 25	80 80	43 45	— —	— —	1590 865	— 1075	143 No reset zone	285 —	355 —
8	1180±34 *656±24	25 25	80 75	40 40	— —	— —	927 1295	— 1510	— —	— —	— —
9	1096±44 *755±66	20 20	80 80	40 40	— —	680 —	860 270(?)	— 1060	85 81	280 240	345 330

All data is expressed in millisecond. *Data obtained after intravenous atropine (1–1.5 mg). SCL = sinus cycle length; JE = junctional escape; JR = junctional rhythm; MCSNRT = maximum corrected sinus node recovery time; MJRT = maximum AV junctional recovery time; MAR = maximum atrial recovery time; SACT = mean sinoatrial conduction time; AERP = atrial effective refractory period; AVNERP = AV nodal refractory period; (?) = SNRT could be measured on only one or two occasions.

Fig.3. Diagrams showing automaticity (postpacing impulse recovery time) of sinus node and/or subsidiary pacemakers before and after i.v. atropine in 9 patients with sinus nodal dysfunction. Before atropine, maximum corrected sinus node recovery time (MCSNRT) could be measured in 8 patients; all disclosed prolongation of MCSNRT (≥ 525 msec) (top panel). In the remainder, junctional escape beats appeared on termination of atrial pacing all the times and no MCSNRT could be measured. Maximum corrected atrioventricular junctional recovery time (MCJRT) and/or MJRT could be measured before atropine in 5 of 9 patients (middle panel). All 5 patients were symptomatic and disclosed MJRT ranging between 1,850 and 3,710 msec. MCJRTs measured in 4 patients were all longer than 200 msec (708 to 2,518 msec). Maximum atrial recovery time (MART) could be measured in 3 patients before atropine (bottom panel). The MARTs were 1,440, 1,480 and 1,900 msec, respectively. After atropine, MCSNRT shortened in 7 patients (top panel). In the remaining 2 (Cases 5 and 9), SNRT could only be measured at one or 2 instances and MCSNRT was 270 msec in each patient (*, **). MCJRT measured after atropine in one patient was 589 msec and all 9 patients disclosed MJRT less than 1,610 msec following atropine administration (middle panel). Low atrial escapes appeared on termination of atrial overdrive pacing in 2 patients after atropine, and MARTs were 2,500 and 1,220 msec, respectively (bottom panel).

SNRT could be measured only once after atropine and the corrected recovery time was 270 msec (Fig. 3). Sinus cycle length uniformly decreased after atropine in all 9 patients; the decrease ranged between 17.3 and 61.6% (average 38.5%) (Fig. 4). Six patients showed a decrease in MCSNRT ranging from 3.1 to 79.9%, and one patient showed a paradoxical prolongation of the recovery time (39.7%) after atropine (Fig. 4). The average percent change of the MCSNRT was a reduction of 37.9%.

Effect of Atropine on Escape Mechanism of the Subsidiary Pacemakers

The changes in escape mechanism of the subsidiary pacemakers after atropine in the 9 patients are shown in Figs. 3 and 4. A-V junctional rhythm was noted before atropine in 4 patients (Cases 1, 2, 3 and 5). Their junctional cycle lengths ranged from 930 to 1,413 msec. A-V junctional rhythm was noted in 2 patients after atropine; their cycle lengths were 680 and 1,041 msec, respectively (Cases 1 and 9). In only

Fig.4. Diagrams showing percent changes in sinus cycle length and recovery times of sinus node and A-V junctional pacemakers following intravenous atropine (1–1.5 mg). Reduction in sinus cycle length (SCL) after atropine ranged from 17.3 to 61.6% with an average of 38.5% (left panel). The changes in corrected maximum sinus node recovery time (MCSNRT) were, however, variable (middle panel). Six out of 7 patients disclosed reduction in MCSNRT, ranging between 3.1 and 79.9%, and one (Case 8) revealed paradoxical prolongation of MCSNRT (an increase of 39.7%) after atropine. The average percent change of MCSNRT was a reduction of 37.9%. Reduction in maximum atrioventricular junctional recovery times (MJRT) after atropine in 5 patients studied ranged from 19.3 to 71.4% with an average of 53.2% (right panel).

Fig.5. Case 5. Electrocardiograms. Sinus bradycardia with ventricular rate of 50 beats/min on June 19, 1980. There was prolonged QT interval (0.56 sec) but serum electrolytes were normal. The cardiac rhythm was auricular fibrillation with slow ventricular rate (about 38 beats/min) on June 21, 1980. Again prolongation of QT was noted. No recurrent ventricular tachyarrhythmia was ever noted.

Fig.6. The same patient as Fig. 5. Electrocardiogram (lead II) on July 4, 1980 showing slow A-V junctional rhythm with frequent premature ventricular beats, single or paired (first strip). Retrograde conduction to the atria was noted following many premature ventricular systoles, and hence, the sinus node was probably frequently reset by the atrial excitation front. After atropine (second strip), the intervals between two A-V junctional QRS complexes that contained one premature ventricular beat in-between had shortened and almost precisely corresponded to twice the R-R intervals of the last 6 beats in the same strip. This suggests that the actual rate of impulse formation in the junctional pacemaker at this moment was about 83/min, and every other junctional impulse was blocked and not conducted to the ventricle because of the premature ventricular systole. Longer junctional cycle length seen when paired premature ventricular beats occurred in the first and second strips would suggest resetting of the A-V junctional pacemaker by retrograde conduction from the ventricles. Note that intravenous atropine (1 mg) accelerated automaticity of the junctional pacemaker prior to the resumption of normal sinus mechanism, 90 beats/min (last strip), and the premature ventricular beats aborted. Shortly before resumption of normal sinus rhythm, the P-P interval was 3.16 sec. The P configuration was identical with that noted in Fig. 5 (lead II).

one patient (Case 1) was A-V junctional rhythm noted before and after atropine. The A-V junctional cycle length shortened from 1,287 to 1,041 msec after atropine ($p < 0.001$). Maximum corrected JRT could also be compared before and after atropine in this patient, and shortened from $2,485 \pm 825$ to $1,164 \pm 281$ msec ($p < 0.01$). All 5 patients who had cerebral ischemic symptoms (Cases 1, 2, 3, 4 and 5) showed maxi-

mum JRTs ranging between 1,850 and 3,710 msec before atropine (maximum corrected JRTs in 4 patients were between 708 and 2,518 msec). The shortening in A-V junctional escape times in these 5 patients was consistent after atropine, ranging from 19.3 to 71.4% (mean of 53.2%). Maximum JRTs after atropine in all 9 patients ranged between 850 and 1,610 msec. Atrial escape rhythm was noted in 3 patients before

atropine (Cases 2, 8 and 9). The maximum atrial recovery times were 1,440, 1,900 and 1,480 msec, respectively. Atrial escape rhythm was noted in 2 patients after atropine (Cases 1 and 5). The maximum atrial recovery times after atropine in these 2 patients were 2,500 and 1,220 msec, respectively.

Following electrophysiologic studies, 6 symptomatic patients were treated with permanent pacemakers. One other symptomatic patient has refused pacemaker therapy and continues to have dizzy spells. The 2 asymptomatic patients have not been treated by pacemakers or any chronotropic medications. All patients are followed clinically at interval of one to 3 months on an outpatient basis.

DISCUSSION

The mechanism of inadequate escapes of the subsidiary pacemakers with resultant cerebral ischemic symptoms in patients with SN dysfunction remains unsolved. In the mammalian heart, the major subsidiary pacemaker is in or near the A-V node-His bundle region.^{8,9} In canine experiments, a consistent mathematical relationship between stable sinus and junctional escape rhythms is found following eserization of the region supplied by the SN artery.¹⁰ A reliable atrial pacemaker can also assume dominance in experimental unanesthetized dogs after exclusion of the SN from all connections to the remainder of the atrium.¹¹ In awake dogs after complete excision of the SN, atrial rhythm is responsive to adrenergic and cholinergic interventions, indicating the presence of sympathetic and parasympathetic regulation of subsidiary atrial pacemaking tissues.¹² Influence of sympathetic tone on automaticity of the A-V junction and SN in dogs was studied by Millar et al.¹³ After overdrive in dogs with SN crushed, the average maximal cycle length of the A-V junction was 2.4 sec. Automaticity of the A-V junction was depressed after stellectomy and the average maximal post-overdrive cycle length was 9.1 sec. Thus, the A-V junction showed greater dependence on sympathetic tone than SN for maintenance of rhythm.

Automaticity of the subsidiary pacemakers can sometimes be measured in patients with SN dysfunction.^{1,2} In some patients with sinus bradycardia or normal sinus rate with sinoatrial block or sinus arrest, junctional escape may be observed following termination of atrial over-

drive pacing, particularly after atropine administration. Narula and Narula, and Lien et al. have recently evaluated the recovery time of the subsidiary pacemakers using atrial overdrive stimulation technique in some selected patients with SN dysfunction.^{1,2} They found that the clinical features of this setting were not uniform and the automaticity of the subsidiary pacemakers might not be as much impaired so as to produce a syncopal attack even in patients with advanced SN dysfunction.

The effects of atropine on escape mechanism of low atrial or A-V junctional escape pacemakers in patients with SN dysfunction are limited to the recent reports with small number of patients,^{1,2} and data concerning comparative automaticity changes of the SN and subsidiary pacemakers with atropine is not available. Narula and Narula studied the effect of atropine on recovery time of junctional pacemakers in 5 patients with SN dysfunction.¹ Of these, JRT was measured in 3 patients before and after atropine; all 3 patients showed shortening of the recovery time to less than 1,300 msec. Our study showed that maximum JRT was shortened to less than 1,610 msec after intravenous atropine in all 9 patients. In 4 of the 9 patients in whom maximum JRT could be measured after atropine, the maximum recovery time was invariably shorter than any SNRT noted before atropine administration, reflecting enhancement of A-V junctional automaticity by atropine. The effects of atropine on sinus cycle length and recovery time were similar to the reported series.^{14,15} Paradoxical prolongation of MCSNRT was noted in one patient with normal sinus rate, sinoatrial block and sinus arrest. Thus, it seems clear that in patients with SN dysfunction with inadequate escape mechanism of the subsidiary pacemakers, the automaticity of the A-V junctional pacemaker can be enhanced to a nearly normal level (junctional rhythm with rates between 40 and 50 beats/min) by parasympathetic blockade. The subsidiary pacemakers are amply supplied with autonomic fibers and the impaired function of the autonomic system seems to be an important cause of inadequate escapes of the subsidiary pacemakers in SN disease.

The positive chronotropic action of atropine on SN and subsidiary pacemakers as determined in this study reflects vagolysis. Since a striking enhancement of automaticity of A-V junctional pacemakers occurs in most patients with SN dysfunction with atropine, atropine can be a

useful drug before pacemaker implantation in symptomatic patients. A clinical representative case (Case 5) is shown in Figs. 5 and 6. This 61-year-old woman had recurrent syncopal attacks, with electrocardiographic manifestations of normal sinus rate (70–80 beats/min), sinus bradycardia (50 beats/min) or auricular fibrillation with slow ventricular rate (about 38 beats/min). She also had documented paroxysmal supraventricular tachycardia (160 beats/min) which was confirmed to be of A-V nodal reentry at time of electrophysiologic study. During her stay in hospital, she developed dizziness and chest discomfort and electrocardiogram showed slow A-V junctional rhythm (30–33 beats/min) with premature ventricular beats (bigeminal fashion). A one mg intravenous injection of atropine resulted in abolition of premature ventricular beats and junctional foci accelerated (82 beats/min) prior to the resumption of normal sinus mechanism (90 beats/min).

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