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Effects of atropine on atrial refractoriness and its dispersion in humans

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Abstract. To evaluate the influence of atropine on atrial refractoriness and its dispersion, we studied ten subjects with sinus bradycardia who were otherwise healthy. Effective and functional refractory periods were measured at three sites of the right atrium (high, middle, and low in the lateral wall), in sinus rhythm and during atrial pacing (120/min), before and after i.v. administration of 0.04 mg/kg of atropine. Both before and after administration, dispersion of atrial refractoriness was determined from the range of refractory periods measured at the three atrial sites as the longest minus the shortest refractory period.
Our data indicate that atropine was able to significantly reduce refractoriness and its dispersion. The study protocol allowed us to exclude the possibility that cycle length played a role. The antivagal effect of atropine seemed to explain our findings, even if the possibility that the drug had a direct effect could not be excluded.

Key Words: atropine – atrial refractoriness – sinus bradycardia

Introduction

The ability of atropine to increase heart rate and facilitate A–V conduction by its vagolytic action [Rudolf and Bulmer 1924, Nefelski and Brown 1950, Gravenstein et al. 1969, Rosen et al. 1971, Dhingra et al. 1976a] is well known. Less well known are the effects of this drug on atrial electrophysiologic properties. Previous studies on humans [Akhtar et al. 1974; Bissett et al. 1975; Dhingra et al. 1976a, b] are few and also conflicting. Moreover, in the above-mentioned studies refractoriness was evaluated only at one atrial site. In our opinion this is not sufficient since

1) recent papers [Luck and Engel 1979, Franchi et al. 1981, Michelucci et al. 1981] indicate the possibility of obtaining useful information about the mode of recovery of atrial excitability in clinical electrophysiology;

2) atropine is thought to reduce dispersion of refractoriness in humans by incrementing heart rate [Das et al. 1975];

3) atropine has been proved to prevent [El-Sherif 1972, Coumel et al. 1979] or abolish [Cannata and Narbonne 1958] atrial fibrillation in humans and to exert other favorable effects on cardiac rhythm [Robinson and Draper 1912, Goel and Han 1970].

For these reasons and because of the frequent clinical use of this drug, we decided to assess refractoriness at more than one atrial site to further clarify the clinical cardiac electrophysiologic effects of atropine.

Material and methods

The study group consisted of ten subjects (seven males and three females), mean age 59 ± 8 years (range 48–69 years), who underwent an electrophysiologic study following a history of sinus bradycardia. Physical examination, resting ECG, response to multistage treadmill stress test, chest X-ray, echocardiogram, and Holter monitoring were normal. Atrial extrastimulation was performed on all subjects in the resting, nonsedated and postabsorptive state after informed consent had been obtained. None was receiving cardioactive drugs.

Stimulation and recording techniques

Two electrodes, number 6F USCI quadripolar and number 6F USCI tripolar, were inserted percutaneously via a right antecubital vein and a right femoral vein, respectively. The quadripolar catheter was first positioned close to the parasinusal zone to determine corrected sinus node recovery time and total sinoatrial conduction time by using previously described techniques [Narula et al. 1972, Strauss et al. 1973]. The tripolar catheter was initially placed across the tricuspid valve to record the His bundle electro-

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gram and evaluate the manner of atrioventricular conduction, both in the resting state and during atrial pacing.

Subsequently the distal pair of electrodes of the quadripolar catheter was positioned at the mid-point of the lateral wall of the right atrium. Thus, the proximal pair of electrodes was close to the high portion of the lateral wall of the right atrium (HRA), near its junction with the superior vena cava. Also the tripolar catheter was repositioned, and its two distal electrodes placed close to the lower part of the lateral wall. Particular care was given to avoid shifting of the catheters. Each pair of electrodes was used alternately to stimulate the atrium, while the other pair was used to record two atrial electrograms on an Elema-Schonander Mingograph 62–6 channel ink-jet recorder at a paper speed of 100 mm/s and filter settings of 30–500 Hz. The first deflection in amplified recordings of the atrial electrograms was taken as the onset of atrial depolarization, so as to best reflect the timing of the onset of depolarization at the stimulating site. Surface leads I, II, III, and V_1 were also recorded. Overdrive and premature programmed atrial stimulation were performed using an electrically isolated battery-powered Medtronic 5325 stimulator. The pulse width was 2 ms and its amplitude was adjusted at each atrial site to twice diastolic threshold. Atrial extrastimuli were applied at 10-ms decrements after every eight sinus beats or, alternatively, after eight beats of atrial pacing at a rate of 120 bpm, until refractoriness was determined at each of the three atrial sites.

Atrial functional refractory period (AFRP) was the shortest coupling interval recorded on the atrial electrogram. Atrial effective refractory period (AERP) was the longest interval from the atrial electrogram (sinus rhythm) or stimulus artifact (atrial pacing) to the extrastimulus failing to propagate. AFRP and AERP were first obtained during the sinus rhythm, and then with atrial pacing for every subject. Dispersion of atrial refractoriness (D) was determined from the range of refractory periods measured in each subject at the three atrial sites as the longest minus the shortest refractory period. Evaluation of refractoriness according to the above-described protocol was then repeated in each subject after i.v. administration of 0.04 mg/kg of atropine. Measurements were initiated after 5–10 min and completed within 30 min of administration of atropine.

Statistical analysis was performed utilizing values of refractoriness at HRA, mean values of the refractory periods obtained at the three atrial sites ($\bar{x}$), and values of D. Values are expressed in ms and as mean ± standard deviation. Refractoriness was compared at the two rates (sinus rhythm and 120 bpm) and also before and after atropine by paired t test. The same test was performed to evaluate changes in the sinus cycle length. Significance was defined at the 90% level.

Results

Corrected sinus node recovery time, total sinoatrial conduction time, and atrioventricular conduction proved to be normal in each subject. Single values of atrial refractoriness and of its D before and after atropine during sinus rhythm are reported in Table 1. Single values of atrial refractoriness and of its D before and after atropine during paced rhythm are reported in Table 2. Mean values of sinus cycle length before and after atropine administration were 1162 ± 137 and 674 ± 75, respectively ($p < 0.0005$).

Table 1 Values (ms) of atrial refractoriness and of its dispersion during sinus rhythm, before (B) and after (A) atropine. Values (ms) of sinus cycle length are also given.

Patient No.	Sinus Cycle length		AERP HRA		$\bar{x}$		D		AFRP HRA		$\bar{x}$		D	
	B	A	B	A	B	A	B	A	B	A	B	A	B	A
1	1050	670	300	290	327	282	60	20	400	325	352	305	80	35
2	1030	510	290	250	287	258	30	25	330	300	345	310	95	25
3	1280	700	360	270	350	297	30	40	470	340	450	353	30	20
4	1300	740	400	250	360	277	70	40	480	330	425	342	90	25
5	1140	770	390	330	360	323	90	20	510	360	443	360	130	20
6	1030	600	340	240	310	327	50	10	380	280	333	283	80	10
7	1100	670	415	290	365	293	115	90	500	320	450	343	90	70
8	1030	700	370	310	358	307	25	10	410	350	390	346	45	30
9	1240	730	340	320	367	333	40	40	370	340	403	363	60	60
10	1300	650	360	280	360	290	80	50	420	330	430	346	70	40
$\bar{x}$			362	283	344	299	59	34	427	327	402	335	77	33
SD			35	31	27	24	30	24	60	23	45	26	28	19
B vs A: p <			0.0005		0.0005		0.005		0.0005		0.0005		0.0025	

AERP = atrial effective refractory period; AFRP = atrial functional refractory period; D = dispersion of atrial refractoriness; HRA = higher site of the lateral wall of the right atrium; $\bar{x}$ = mean value of the refractory periods obtained at the three atrial sites.

Table 2 Values (ms) of atrial refractoriness and its dispersion during paced rhythm (120/min), before (B) and after (A) atropine.

Patient No.	AERP HRA		$\bar{x}$		D		AFRP HRA		$\bar{x}$		D	
	B	A	B	A	B	A	B	A	B	A	B	A
1	320	240	277	267	70	40	330	290	323	300	20	20
2	270	240	250	233	40	40	295	300	272	287	45	40
3	310	290	317	290	40	20	390	340	367	327	50	20
4	380	260	307	247	140	20	420	310	350	302	120	20
5	300	280	283	267	50	40	350	310	327	297	40	20
6	320	250	307	230	120	40	330	300	320	270	110	55
7	360	310	327	280	80	70	395	330	378	317	25	20
8	310	280	288	263	50	30	340	300	315	283	55	30
9	320	280	303	277	90	50	330	290	307	287	90	50
10	290	270	290	260	40	20	340	320	340	320	20	0
$\bar{x}$	318	270	295	261	72	37	352	309	330	299	57	27
SD	32	22	22	20	35	16	38	17	31	18	37	17
B vs A: p <	0.0025		0.0005		0.01		0.0005		0.0025		0.01	

For abbreviations see Table 1.

Atropine reduced significantly AERP and AFRP at HRA, respectively, from 362 ± 35 to 283 ± 31 ($p < 0.0005$) and from 427 ± 60 to 327 ± 23 ($p < 0.0005$) during sinus rhythm (Table 1) and, respectively, from 318 ± 32 to 270 ± 22 ($p < 0.0025$) and from 352 ± 38 to 309 ± 17 ($p < 0.0005$) at the same driven frequency (Table 2). The same behavior was observed for AERP$\bar{x}$ and AFRP$\bar{x}$, which decreased, respectively, from 344 ± 27 to 299 ± 24 ($p < 0.0005$) and from 402 ± 45 to 335 ± 26 ($p < 0.0005$) during sinus rhythm (Table 1) and, respectively, from 295 ± 22 to 261 ± 20 ($p < 0.0005$) and from 330 ± 31 to 299 ± 18 ($p < 0.0025$) at the same driven frequency (Table 2).

Finally, also D of AERP and of AFRP showed a significant reduction after atropine: from 59 ± 30 to 34 ± 24 ($p < 0.005$) and from 77 ± 28 to 33 ± 19 ($p < 0.0025$), respectively, during sinus rhythm (Table 1) and from 72 ± 35 to 37 ± 16 ($p < 0.01$) and from 57 ± 37 to 27 ± 17 ($p < 0.01$), respectively, at the same driven frequency (Table 2).

The variation of cycle length (from sinus rhythm to atrial pacing) while reducing significantly atrial refractoriness both before (AERP at HRA: $p < 0.0005$; AERP$\bar{x}$: $p < 0.0005$; AFRP at HRA: $p < 0.0005$; AFRP$\bar{x}$: $p < 0.0005$), and after (AERP$\bar{x}$: $p < 0.0025$; AFRP at HRA: $p < 0.05$; AFRP$\bar{x}$: $p < 0.0005$) atropine, did not produce any significant variation of D (Table 3).

Discussion

Dhingra et al. [1976a, b] showed previously that atropine shortens atrial refractoriness in normal individuals, but does not induce a variation in patients with sinoatrial dysfunction. The other studies in normal humans [Akhtar et al. 1974, Bissett et al. 1975] have not confirmed these findings. Therefore, we decided to study further the influence of atropine on atrial electrophysiologic properties.

We evaluated more extensively than before [Akhtar et al. 1974, Bissett et al. 1975, Dhingra et al. 1976a, b] atrial refractoriness, testing three atrial sites. This also allowed us to evaluate, according to previous studies [Luck and Engel 1979, Franchi et al. 1981, Michelucci et al. 1981], the degree of homogeneity of atrial excitability. Considering that different doses of

Table 3 Effects of cycle length (statistical significance indicates in each case a reduction induced by paced rhythm).

		AERP HRA	$\bar{x}$	D	AFRP HRA	$\bar{x}$	D
Before atropine	p <	0.0005	0.0005	N.S.	0.0005	0.0005	N.S.
After atropine	p <	N.S.	0.0025	N.S.	0.05	0.0005	N.S.

For abbreviations see Table 1.