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Electrophysiologic Study of Sinus Node Function in Isolated Rabbit Sinoatrial Preparation

WU Jianyi* and SHIH YUshu*

Summary

Using standard microelectrode techniques, this study investigated the affected factors for evaluating sinus node function and the effects of autonomic nervous system on sinus node function in 44 isolated rabbit sinuatrial preparations. We found that: 1) Overdrive pacing directly depressed the pacemaker automaticity and SNRT dependent on the complex interactions among automaticity, conductivity and refractoriness in sinus node. 2) All indirected methods for estimating SACT might be affected by the depression of automaticity and the shift of primary pacemaker site. 3) Echo response would complicate the estimation of SNERP. 4) Besides the positive and negative effects of isoprenaline and acetylcholine separately, ATP decreased sinus rate by a reduction of phase 4 slope, increased SNERP by a lengthening of action potential duration, and had not significantly effect on SACT, which could not be modified by atropine.

Key words: Sinus node function, Electrophysiologic study, SNRT, SACT, SNERP

*From the Department of Cardiology, Second affiliated Hospital, Tianjin Medical College

In recent years, the electrophysiologic test of sinus node function, including sinus node recovery time (SNRT), sino-atrial conduction time (SACT) and sinus node effective refractory period (SNERP) have been proved to have two problems: the limitation of each testing method[1)-10)] and the effects of autonomic nervous system[1)-10)].

Studies in cellular electrophysiology about these problems have been reported, but there are controversies[11)-18)]. The present investigation was designed to determine the affected factors of each testing method in evaluating SNRT, SACT and SNERP; and to assess the effects of autonomic nervous system on sinus node function.

Methods

Animal preparation

Rabbits weighed 2-3 Kg were anesthetized with sodium pentobarbital (30 mg/Kg, iv). The hearts were rapidly excised in cool oxygenated, modified Tyrode's solution. The right atrium including sinus node was carefully dissected free and pinned with the endocardial surface uppermost to the wax bottom on a lucite chamber. The tissue was superfused at a constant rate of 8 m*l*/min with modified Tyrode's solution that was equilibrated with 95% oxygen and 5% carbon dioxide. The temperature of

the bath was maintained at 3±0.5℃ and the pH of the solution was 7.3±0.05. (Fig. 1)

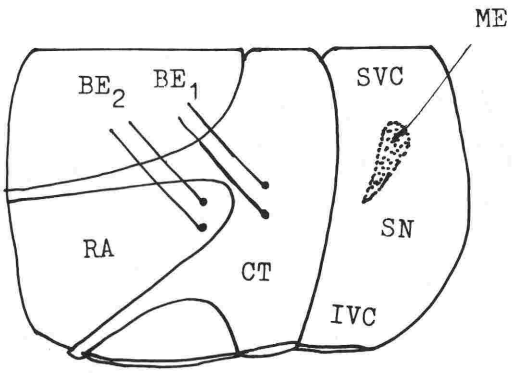

Fig 1. Diagram of sinoatrial preparation. SN=sinus node; CT=crista terminalis; RA=right atrial muscles; SVC=superior vcna cava; IVC=inferior vena cave; ME=microelectrode; BE=bipolar electrode.

Standard microelectrode techniques

One bipolar electrode was placed on the proximal end of the crista terminalis to stimulate the preparation and a second bipolar electrode on the midportion of crista terminalis for recording the surface electrogram. Glass microelectrode filled with 2.7 M KCL (resistance 15-30 MΩ) were used to measure the transmembrane potentials. The electrogram and transmembrane potential were displayed on a dual-beam oscilloscope. The signals were frozen for photography or measurment.

Location of the pacemaker site

The prepration was allowed to equilibrate for 1 hour. The region of sinus node was then systematically mapped. Cell which was referred to the primary pacemaker cell must show the following characteristics: 1) the earliest activation; 2) the smooth transition from phase 4 to phase 0; 3) an action potential amplitude of at least 50 mV; 4) the steepest slope of diastolic depolarization.

Protocols and definitions

44 preparations were classified into 6 groups. The numbers and procedures in each group were summarised in table 1 and table 2.

The following variables were measured for analysis. 1) transmembrane potential variables were referred to figure 2; 2) electrophysiologic variables included SNRT, SACT and SNERP.

The transmembrane potential parameters are as follows:

MDP: maximum diastolic potential; Slope of phase 4; threshold of transmambrane potential; APA: amplitude of action potential; APD duration of action potential (90% of repolarization). (Fig. 2)

The electrophysiologic parameters are:

A_1A_1: basic cycle length; A_1A_2: coupling time of extrastimulation; A_2A_3: first recovery time; A_3A_4: second recovery time.

SNRT: recovery time after overdring depression; SNRT-A: the sinus recovery time

Table 1 The numbers and procedures in each group

	Goup 1 (n=8)	Group 2 (n=12)	Group 3 (n=6)
1)	overdrive pacing for 1 minute	directly measuring SACT	analysing the responses**
2)	reversing pacing time and order	comparing three indirect methods*	estimating SNERP**
3)	perfusing with atropine (1 mg/L)	analysing the affected factors	

*including strauss's[13] and Narula's methods[3], another method is premature atrial stimulation during continuous atrial pacing (PASDCAT)[9),15)].

**by the method of PASDCAP[9),15)].

Table 2 The numbers and procedures in each group

	Group 4 (n=6)	Group 5 (n=6)	Group 6 (n=6)
1)	control	control	control
2)	isoprenaline (1×10^{-6}M)	Ach (5×10^{-6}M)	ATP (3×10^{-5}M)
3)	propranolol (1×10^{-6}M)	atropine (1×10^{-6}M)	atropine (1×10^{-6}M)

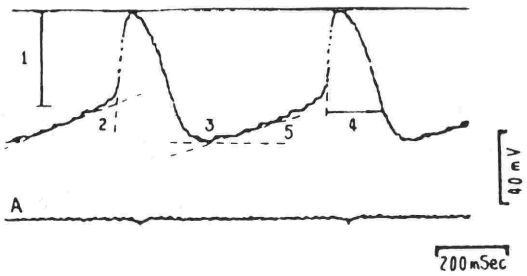

Fig 2. Variables measured from transmembrane potential in primary pacemaker cell. 1) APA: action potential amplitute; 2) TR: takeoff potential; 3) MDP: maximum diastolic potential; 4) APD: action potential duration at 90%; 5) Slope: slope of diastolic depolarization; A: atrial surface electrogram.

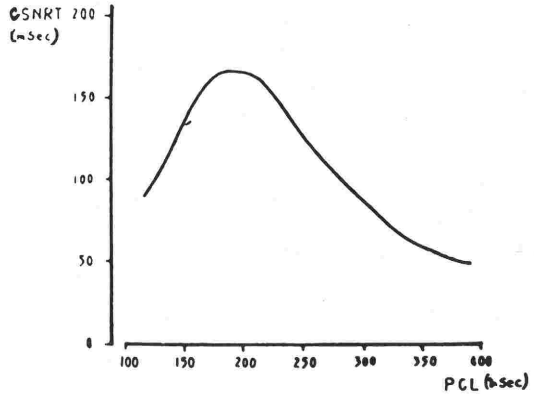

Fig 3. Effect of atrial pacing cycle length (PCL) on corrected sinus node recovery time (CSNRT). PCL was decreased from 400 msec to 120 msec in steps of 20-40 msec. Each pacing period lasted 1 minutes and the duration between two pacing periods was 2 minutes.

measured by atrium depolarization; SNRT-SN: the sinus recovery time measured by sinus node transmembrane potential.

SACT: measured by A_2A_3-A_1A_1 or by A_2A_3-A_3A_4

SNERP: the longest A_1A_2 of incomplete interpolation of primary pacemaker cell.

Refractory period of perisinus region: the shortest A_1A_2 when the ratio of amplitude of action potential of perisinus AP_2/AP_1 more than 1/3.

Refractory period of atrium: the longest A_1A_2 when atrium was not depolarized.

Results

Group 1. SNRT

The relationships of SNRT to pacing cycle length, atrio-sinus conduction and SNERP were studied.

Fig. 3 summarized the relationship between pacing cycle length (PCL) and SNRT in all 8 preparations. To compare data from different preparations with varying basic cycle length, we plotted CSNRT on the ordinate. As PCL was decreased in steps of 20-40 ms in consecutive trials, the CSNRT prolonged continuously and then reached a maximum value. With further decrease of PCL, CSNRT no longer increased but shortened slightly.

We also found that as the decrease of PCL, SACT prolonged until atrio-sinus block occurred. So we assessed the relationship of SNRT to atrio-sinus conduction. Tab. 3 shows the results from a typical case. Similar results were seen in all other experiments. It showed that as soon as the atrio-sinus conduction block occurred (240 ms) or developed (160 ms), SNRT shortened markedly, but during the zone in

Table 3 Relationship of SNRT to atrio-sinus conduction.

PCL (msec)	conduction pattern	conduction of last beat	SNRT-SN (msec)	SNRT-A (msec)	A3A4 (msec)
360	1 : 1	(−)	490	554	460
320	1 : 1	(−)	514	576	464
280	1 : 1	(−)	566	628	483
240	2 : 1	(−)	545	607	476
200	2 : 1	(−)	574	638	504
200	2 : 1	(+)	576	442	504
160	3 : 1	(−)	538	612	464
120	4 : 1	(−)	515	576	462

Sinus cycle length in this preparation was 440 msec.

which the same conduction pattern was present (1:1 from 260 ms to 280 ms; and 2:1 from 240 ms to 200 ms), SNRT prolonged as PCL decreased.

To explore the genesis of atrio-sinus conduction block, we assessed the SNERP in each experiment, and found that the PCL, at which atrio-sinus block occurred, were close to the SNERP. Fig. 4 was recorded from a typical experiment, SNERP in this case was 185 ms, 2:1 atrio-sinus block occurred, in which a low-voltage depolarization was seen in every two impulses. The numbers of impulse reaching the primary pacemaker site were decreased, while SNRT was shortened.

The effects of pacing time, pacing order and atropine superfusion are as follows. Pacing at different times (15 sec to 15 min) reversing pacing order from short to long cycle or random order, and pretreating with atropine (1 mg/l) did not significantly affect SNRT and similar relationship described above remained in all experiments.

Group 2. SACT

Mechanisms for estimating SACT:

Fig. 5 showed an experimental recording, in which three methods of estimating SACT were compared in the same preparation. Similar results were seen in all twelve experiments. Though the procedures of atrial pacing were different, the mechanisms of estimating SACT were same,: 1) reset the primary pacemaker

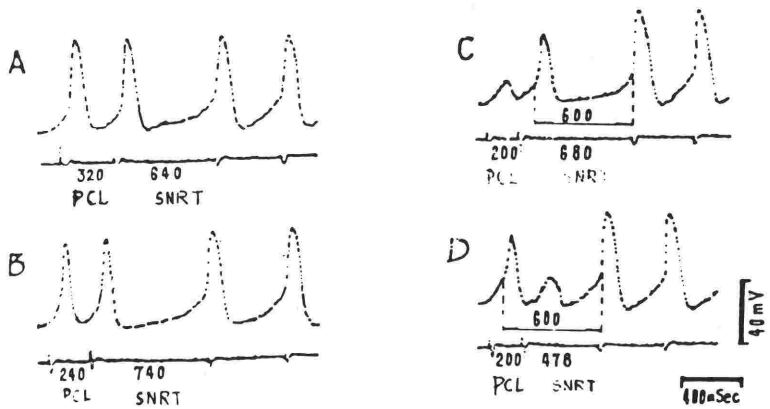

Fig 4. Transmembrane potentials recorded from a cell in the primary pacemaker site at different PCL: (A) PCL=320 msec, SNRT-A=640 msec; (B) PCL=240 msec, SNRT-A=740 msec; (C) and (D). PCL=200 msec, 2:1 atriosinus block occured and SNRT-A decreased; which resulted from a low-voltage action potential amplitute.

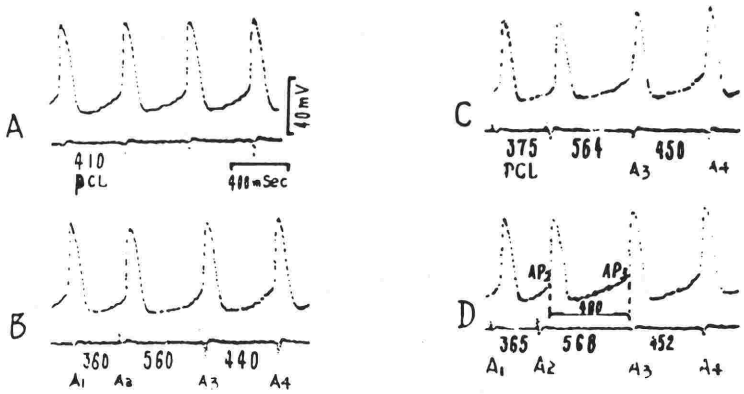

Fig 5. Transmembrane potentials recorded from a cell in the primary pacemaker site with different methods estimating SACT: A) Basic sinus rate (SCL=410 msec); B) Strauss's method (A1A2=360 msec); C) Narula's method: Constant atrial pacing length was 375 msec; D) The method of PASDCAP: Basic pacing length was 375 msec, A1A2 was 365 msec.

Table 4 The affected factors of estimating SACT.

	retrograde conduction time	recovery sinus cycle	antegrade conduction time
before pacing	34.8±8.4	462.0±53.6	40.6±8.5
after pacing	35.1±7.7 p >0.05	503.2±52.5 p <0.05	31.3±6.9 p <0.05

Note: mean±SD (msec) n=12

Table 5 Compared estimated SACT with measured SACT.

	SCL	Measured			Estimated*	
	(msec)	Ante-CT	Retro-CT	Total	A2A3-A1A1	2A3-A1A1
			(msec)		(msec)	
1	470	43	35	78	79	75
2	504	35	27	62	120	71
3	453	49	40	89	151	94
4	482	39	30	69	157	80
5	523	41	27	68	110	85
6	521	45	45	90	93	95
7	441	29	29	58	57	57
8	362	42	29	71	58	58
9	479	53	52	105	81	82
10	379	26	26	52	56	56
11	513	51	41	92	160	103
12	418	34	31	65	114	73
	462± 54	41± 8	34± 8	75±16	103± 39	78±16

*By the method of PASDCAP.

rhythm by atrial pacing (premature stimulation); 2) calculating SACT by A_2A_3, which was composed of retrograde conduction time (A_2AP_2), recovery interval of sinus rhythm (AP_2-AP_3), and antegrade conduction time (AP_3-A_3); 3) a tendency of depression of automaticity (AP_2-$AP_3 > A_1$-A_1).

Affected factors for estimating SACT:

Since SACT was calculated from A_2A_3, we used the method of PASDCAP (pacing with S_1 as the base and programmed extrastimulation) to analyse the three variables in A_2A_3. Tab. 4 summarized the results of 12 experiments. It showed that: 1) retrograde conduction time was not significantly affected by the method; 2) automaticity was depressed (AP_2-$AP_3 > A_1A_1$), which would lead to an overestimation of SACT.; 3) antegrade conduction time would shorten after atrial pacing, which had been referred to the shift of primary pacemaker site and would lead to an underestimation of SACT.

SACT calculated by A_2A_3-A_3A_4:

As the effects of depression of automaticity may extend to the second recovery interval ($A_1A_1 = A_3A_4 = AP_2AP_3$), we compared the estimated SACT with the true SACT (be measuring) to determine whether SACT calculated by A_2A_3-A_3A_4 would be more correct than that by A_2A_3-A_1A_1. Tab. 5 was the results of 12 experiments. Compared to the true SACT, SACT calculated by A_2A_3-A_1A_1 has a difference (p 0.05), conversely SACT calculated from A_2A_3-A_3A_4 had no significant difference (p 0.05). Therefore, using A_3A_4 to calculate the SACT would decrease the effects of depression of automaticity. In addition, measured ante-CT and retro-CT were not equal (p 0.05).

Group 3. SNERP

Responses following premature stimulation:

In order to understand the mechanisms of estimating SNERP by the method of PASDCAP (Kerr), we analysed the responses following premature atrial stimulation in pacemaker site. There were 4 types of responses, but echo response was seen in 2 preparations out of 8. Fig. 6 showed a typical result which was recorded in the same praparation. In this experiment sinus cycle length (SCL) was 440 ms, basic pacing cycle length (PCL) was 415 ms. and spontaneous recovery cycle without premature beat was 640 ms. (A) Reset: A_1A_2 was 400 ms., A_2 reseted the primary pacemaker rhythm. A_2A_3 was equal to a spontaneous recovery cycle without premature beat (640 ms.). (B) Echo: A_1A_2 was decreased to 240 ms. A_2 entered the primary pacemaker site and induced and re-entry action potential. It propagated again to atrium (A_3). A_2A_3 was less than the SCL (440 ms.). (C) Incomplete interpolation: A_1A_2 was 195 ms. A_2 did not set the

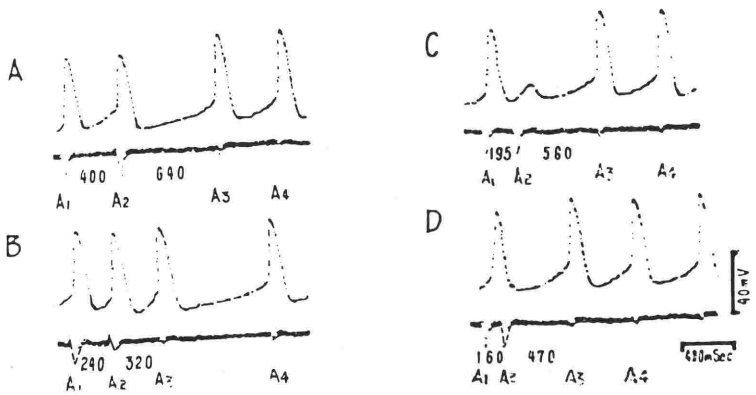

Fig 6. Four types of responses following premature atrial stimulation in the same preparation. From A to D: reset, echo; incomplete interpolation and complete interpolation. Refer to the main text for details.

primary pacemaker cell but resulted in a low-voltage potential which only caused delay in AP_3. So, A_2A_3 (560 ms.) was shorter than that of reset (640 ms.), but longer than SCL (440 ms.). (D) Complete interpolation: A_1A_2 was 160 ms., A_2 was blocked between primary pacemaker and pacemaker and atrium. It did not affect on sinus cycle rhythm. A_2A_3 (470 ms.) was less than that of incomplete interpolation (560 ms.) and A_1A_3 (678 ms.) was similar to the spontaneous cycle length without premature beat (640 ms.).

Relationships of SNERP to incomplete interpolation:

In all preparations, we found that the action potential amplitude in the primary pacemaker cells decreased markedly while incomplete interpolation occurs (Fig. 6), it demonstrated that premature atrial impulse entered the primary pacemaker site and met the refractoriness. Therefore, SNERP would be represented by the longest A_1A_2 in the zone of incomplete interpola-

Table 6 The effects of isoprenaline on SN function.

	control* (msec)	isoprenaline** (msec)	propranolol*** (msec)
SCL	465±50	387±25	480±50
CSNRT	146±33	117±18	149±31
Ante-CT	43± 9	26±14	44±11
SNERP	163±24	140±16	164±23

p value: * to **: <0.005 ; <0.01 ; <0.05 ; <0.05.
** to ***: all same to above.
* to ***: all >0.05.

Table 7 The effects of isoprenaline on SN function.

	control*	isoprenaline**	propranolol***
MDP (mV)	60±3	58±1	58±1
TP (mV)	42±3	48±2	42±3
APA (mV)	44±4	53±4	44±3
APD (mV)	173±17	142±9	172±17
Slop (V/S)	0.47±0.03	0.60±0.09	0.46±0.09

p value: ** to * >0.05, <0.05, <0.05, <0.01, <0.005 ;
** to *** all same to above;
* to *** all >0.05.

Table 8 The effects of Ach on SN function.

	control* (msec)	Ach** (msec)	atropine*** (msec)
SCL	471±52	615±25	469±50
CSNRT	157±22	237±18	162±26
Ante-CT	39±9	52±9	40±9
SNERP	158±56	286±46	158±24

p value: ** to * <0.001, <0.005, <0.05, <0.001 ;
** to *** all same to above;
* to *** all >0.05.

Table 9 The effects of Ach on transmembrane potential.

	control*	Ach**	atropine***
MDP (mV)	59±4	67±6	60±3
TP (mV)	44±5	43±5	44±4
APA (mV)	48±4	43±5	47±5
APD (msec)	155±15	202±16	154±13
Slope (V/S)	0.46±0.11	0.25±0.05	0.46±0.01

p value: ** to * <0.001, >0.05, <0.05, <0.001, <0.001;
** to *** all same to above;
* to *** all>0.05.

Table 10 The effects of ATP on SN function.

	control* (msec)	ATP** (msec)	atropine*** (msec)
SCL	425±54	556±54	550±48
CSNRT	163±23	198±26	197±32
Ante-CT	42±11	42±10	43±11
SNERP	163±21	201±24	204±25

p value: ** to * <0.05, <0.005, >0.05, <0.005;
* to *** all>0.05;
** to *** all same to above.

Table 11 The effects of ATP on transmembrane potential.

	control*	ATP**	atropine***
MDP (mV)	60±3	60±5	60±3
TP (mV)	43±3	44±3	43±3
APA (mV)	46±4	45±4	45±4
APD (mV)	152±15	183±14	186±15
Slope (V/S)	0.48±0.07	0.35±0.07	0.36±0.06

p value: ** to * >0.05, >0.05, >0.05, <0.05, <0.01;
** to *** all same to above;
* to *** all>0.05.

tion, during which echo response was also present.

Groups 4-6: The effects of autonomic nervous system:

Tab. 6 to 11 summarized the effects of sympathetic, parasympathetic and purinergic nerves on sinus node function and transmembrane potential in the primary pacemaker cells.

Briefly, (1) Isoprenaline increases sinus rate by increasing phase 4 slope and shifting TP to more negative, reduces SACT by increasing APA and shortens SNERP by decreasing APD; (2) Acetylcholine decreased sinus rate by increasing negatively MDP and decreasing phase 4 slope, increased SACT by decreasing APA and lengthens SNERP by increasing APD. (3) The effects of ATP were independent of parasympathetic nerves, because atropine can not affect its effects.

Discussion and conclusion

1. The affected factors of SNRT

There have been three hypotheses about the mechanisms of overdrive suppression: 1) suppression is mediated by the release of acetylcholine; 2) rapid atrial pacing induces the ischemia of sinus node, which results in the pacemaker suppression; 3) overdrive atrial pacing disrupts directly intrinsic mechanisms of pacemaker automaticity. The results of our experiments support the third hypothesis, which depends on the following observations: 1) overdrive suppression could not be abolished by atropine pretreatment; 2) pacing for a long time did not lengthen SNRT, which reject the hypothesis of ischemia in sinus node; 3) SNRT depends on the number of impulses reaching the primary pacemaker site.

Prior studies have suggested that SNRT was affected by the conductivity.[11)-12)] The present study demonstrated that SNRT was the results of interactions among automaticity, conductivity and refractoriness in the sinus node. Therefore it seems reasonable to conclude that any factors which affect SACT and SNERP may affect SNRT as well.

2. The affected factors of SACT

Strauss's method, Narula's method and the method of PASDCAP have been suggested to estimate SACT on clinical electrophysiology testing of sinus node function.[1)-10)] Since there are different opinions about the errors in estimating SACT[1),2)13)-18)], it is necessary to determine the mechanism and affected factors in each method. To assess the overall value, we compared the 3 methods under the same experimental conditions. Our findings suggested that the mechanisms and affected factors of three methods were similar and SACT would be over or under-estimated by these methods. In addition, the view that SACT must be calculated by A_3A_4 instead of A_1A_1 was receptible.

3. The affected factors of SNERP

Recent studies[15),9)] have suggested that incomplete interpolation response arises from enchroachment of that premature beat on SNERP. Therefore measurment of the premature interval, at which the transition from reset to incomplete interpolation occurs, would provide an estimation of SNERP. But whether SNERP can be derived from echo response has not been clarified. Kirkorian et al[9)] proposed that SNERP can be derived from interpolation and echo response. Our studies opposed to this suggestion and supported the opinion to exclude the effect of echo response in measuring SNERP. The reasons are that: 1) the action potential amplitude of primary pacemaker cell do not decrease when echo occurs; 2) the mechanism of echo is re-entry which may occur in pacemaker site or perinodal zone or atrium. Therefore, the time at which echo is present, may be before or during or after SNERP. (that is overlap). Considering the effects of echo response may account for the complicated phenomenon in determining SNERP, such as the transition between zone 2 and 3 is less sharp.

4. Effects of autonomic nervous system:

Although the effects of sympathetic and parasympathetic nerves on the sinus node function have been considerably investigated and proved to have positive and negative effects separately, the corresponding changes in transmembrane potential are still less clear[19)-21),25)]. Our findings suggested that: 1) Isoprenaline increases sinus rate by increasing phase 4 slope and shifting TP to more negative, reduces SACT by increasing APA and shortenes SNERP by decreasing APD; 2) Acetylcholine decreased sinus rate by increasing negatively MDP and decreasing phase 4 slope, increases SACT by decreasing APA and lengthens SNERP by increasing APD.

To assess the hypothesis of purinergic nerves[22)-25)], we studied the effects of ATP, which have been considered as the purinergic transmitter in recent studies. We found that ATP decreases sinus rate by slowing phase 4

slope, increases SNERP by lengthening APD and has no significant effect on SACT. The effects of ATP appeare to be independent of parasympathetic nervus, because atropine can not modify its effects. Therefore, it seems reasonable to consider that ATP mediates extracellular purinergic receptors to exert its electrophysiologic effects.

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References

1) Li Zhongcheng, Shih Yushu: The value of SNRT, and SACT in diagnosing sick sinus syndrome. Tianjin Medical J. **7**: 387, 1983.
2) Liu Kequiang, Shih Yushu: The persistent sinus node electrograms during postpacing atrial pauses S-A block vs sinus quiescence. Tianjin Medical J. **11**: 651, 1986.
3) Onker S. Narula: A new method for measurement of sinoatrial conduction time. Circulation **58**: 706, 1978.
4) Jawahar M. Desal: Electrophysiologic effects of combined autonomic blockade in patients with sinus node disease. Circulation **63**: 953, 1981.
5) Pritpal S. Kang: Role of autonomic regulatory mechanisms in sino-atrial conduction and sinus node automaticity in sick sinus syndrome. Circulation **64**: 832, 1981.
6) Paolo Alboni: Electrophysiology of normal sinus node with and without autonomic blockade. Circulation **65**: 1236, 1982.
7) J. A. Reiffel: Indirectly estimated sinoatrial conduction time by the atrial premature stimulus technique: patterns of error and the degree of associated inaccuracy as assessed by direct sinus node electrography. Am Heart J **106**: 459, 1983.
8) Nicholas Z. Kerin: Interractions among the critical factors affection sinus node function: the quantitative effects of the duration and frequency of atrial pacing and of vagal and sympathetic stimulation upon overdrive suppression of the sinus node. Am Heart J **105**: 215, 1983.
9) Gilbert Kirkorian: Premature atrial stimulation during regular atrial pacing: a new approach to the study of the sinus node. Am J Cardiol **54**: 109, 1984.
10) Sam L. Teichman: The value of electrophysiologic studies in syncope of undetermened origin: report of 150 cases. Am Heart J **110**: 469, 1985.
11) Gerhard Steinbeck: Effects of atrial pacing on atrio-sinus conduction and overdrive suppression in the isolated rabbit sinus node. Circ Res **46**: 859, 1980.
12) Charles R. Kerr: The nature of atriosinus conduction during rapid atrial pacing in the rabbit heart. Circulation **63**: 1149, 1981.
13) Augustus O. Grant: The estimation of sinoatrial conduction time in rabbit heart by the constant atrial pacing technique. Circulation **60**: 597, 1979.
14) Ralph haberl: Comparison between intracellular and extracellular direct current recordings of sinus node activity for evaluation of sinoatrial conduciton time. Circulation **70**: 760, 1984.
15) Charles R. Kerr: Characterization of refractoriness in the sinus node of the rabbit. Circ Res **47**: 742, 1980.
16) George J. Rozanski: Functional characteristics of sinoatrial and subsidiary pacemaker activity in the right atrium. Circulation **67**: 1378, 1983.
17) Stephen L. Liqsius: Electrotonic interactions in delayed propagation and block within the guinea pig SA node. Am. J. Physiol. **245**: H7, 1983.
18) George J. Rozanski: Electrophysiology of functional subsidiary pacemakers in canine right atrium. Am. J. Physiol. **249**: H594, 1985.
19) Victor A. J. Slenter: Vagal control of pacemaker periodicity and intranodal conduction in the rabbit sinoatrial node. Circ Res **54**: 436, 1984.
20) Eric N. Prystowsky: An analysis of the effects of acetylcholine on conduciton and refractoriness in the rabbit sinus node. Circ Res **44**: 112, 1979.
21) Takashi Taniguchi: Effect of acetylcholine on the norepinephrine-induced positive chronotropy and increase in cyclic nucleotides of isolated rabbit sinoatrial node. Cire Res **45**: 493, 1979.
22) Takao Katoh: The cellular electrophysiologic mechanism of the dual action of disopyramide on rabbit sinus node funciton. Circulation **66**: 1216, 1982.
23) Luiz Belardinelli: Effects of adenosine and adenine nucleotides on the atrioventricular node of isolated guinea pig hearts. Circulation **70**: 1083, 1984.
24) Amir Pelleg: Comparative electrophysiologic effects of adenosine triphosphate and adenosine in the canine heart: influence of atropine, propranolol, vagotomy, dipyridamole, and aminophylline. Am. J. Cardiol. **55**: 571, 1985.
25) William J. Mandel: Cardiac arrhythmia 107-144, by J. B. Lippincott Company. 1980.