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*Research Paper*

# The comparative studies of the influences of Urapidil and Nicardipine on sino-atrial node function, atrio-ventricular node function and hemodynamics

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## Abstract

**Objective:**To investigate the influences of urapidil and nicardipine on rabbit sinus function, atrio-ventricular node function and hemodynamics. **Methods:**Thirty-two Angora's rabbits were selected and randomly divided into four groups. U1 group:urapidil 0.25 mg/kg; U2 group:urapidil 0.5 mg/kg; N1 group:nicardipine 10 μg/kg; N2 group: nicardipine 20 μg/kg. All these medicine were administrated within 30 seconds. Measurements were taken before and after the administration of urapidil or nicardipine for the following data: mean blood pressure(MAP), heart rate(HR), sino-atrial conduction time(SACT), maximal sinoatrial recovery time(SNRTmax) corrected sinus node recovery time(CSNRT) , index of sinus node recovery time(SNRTI), Wenckebach A-V conduction frequency (WB), and P-R interval. **Results:**Significant MAP and HR changes were identified in all of the four groups before and after administration of both urapidil and nicardipine. No significant changes could be found in the rest of the parameters. Intergroup analysis showed that SACT and CSNRT of N1 and N2 groups were shorter than those of the U2 group($P < 0.01$); the MAP decreased($P < 0.01$) and the HR increased drastically($P < 0.01$). **Conclusions:**Neither urapidil(0.25 mg/kg, 0.5 mg/kg) nor nicardipine(10 μg/kg, 20 μg/kg) has any significant influence on rabbit sinus function or rabbit atrio-ventricular node function. Nicardipine could be a better choice than urapidil for parafunctional sinus node patients.

*Key words*: urapidil; nicardipine; sinus function; A-V node function; hemodynamics

## INTRODUCTION

Urapidil and nicardipine are widely used for the treatment of perioperative hypertension and the prevention of cardiovascular side effects during tracheal intubations. Intensive research has already been conducted concerning their homodynamic effects, depressurization mechanisms, as well as the protection and prevention of myocardial ischemia[1-2]. However, few studies have been published about their effects upon sinus and A-V conduction functions. Here, we report the results of the electrophysiological tests using the atria pacing method, which is the most commonly used method to evaluate sinus and atrio-ventricular functions[3]. Research already undertaken in our hospital studied the influence of anesthetic medicine on intracardiac conduction system[4-6]. The results of these studies offer reliable, stable and reproducible evidence that SACT, CSNRT and SNRTI can be used to evaluate sinus node function. The influences of urapidil and nicardipine on sinus and atrio-ventricular function have been investigated in the present study using the frequency increment atria pacing method. The results are as follows;

## MATERIALS AND METHODS

### Materials

Thirty-two Angora's rabbits(male and female), weighting between 2.2 kg and 3.0 kg, were provided by the experimental animal center of Nanjing Medical University. Urapidil was purchased from Byk Gulden drug plants in Germany(batch number of 120191).

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Nicardipine is the product of Yamanouchi pharmaceutical Co. Ltd.(batch number of A017Y01). The multipurpose heart electrophysiological stimulator was manufactured by Chang-Hong Instrument Company China(model number CF-4.)

### Methods

The thirty-two Angora's rabbits were divided stochastically into four groups:group U1:urapidil 0.25 mg/kg; group U2: urapidil 0.5 mg/kg; group N1: nicardipine 10 μg/kg; group N2:nicardipine 20 μg/kg. The rabbits were injected intravenously with thiopental sodium until unconcious. Anesthesia was maintained by intermittent intravenous low dose injections. Tracheotomy was performed under 0.5% lidocaine local infiltration anesthesia and a tracheal tube with 3.5 mm internal diameter was inserted. The autonomous respiration was temporarily maintained(HR frequency 40-60 $min^{-1}$) with the humidity of 80-100 ml. One external jugular vein was cut open and a 4F bipolar pacing catheter was inserted. The catheter was placed upon the upside part of right atrium according to intracavitary ECG waveforms. ECG examinations were performed on all rabbits before urapidil and nicardipine administration. The cardiac electrophysiology stimulator was used to capture atria. Urapidil and nicardipine were diluted to 1 g/L and 50 μg/ml respectively with 0.9% aqueous sodium chloride. The administration of the above dose was finished within 30 s. All electrophysiolgical parameters were determined before and 3 min after the administration, respectively.

### Measurement and parameters

The right atrium was paced at a frequency 20% higher than its normal value. This process was repeated 3 times and the mean value was taken. 2-5 pulses were paced every time. 10 cardiac cycles were recorded before, during and after pacing, among which, the clearest P wave leads were recorded. $A_1$-$A_1$ was sinus cardiac cycle before pacing. 10 cycles' values were selected for the average; $A_2$ was the end bearing premature pulse; $A_3$ was the first sinus P wave after the programmed premature stimulation stopped. SACT=(the $A_2$-$A_3$)-(the $A_1$-$A_1$).

The corrected sinus node recovery time(CSNRT), and the sinus node recovery time index(SNRTI) determination: The atrium was paced for 15 s at a frequency 30 $min^{-1}$ higher than the base heart rate. Each time, the frequency was increased by 30 $min^{-1}$ until the Wenckebach type A-V conduction block occurred. At least 10 cardiac cycles were recorded electrocardiographically before and after pacing, with the interval of 15 s between consecutive ones. The detailed process was:$A_4$ was the end pacing pulse and $A_5$ was the first P wave after pacing stopped respectively. So the SNRT equals the $A_4$-$A_5$. The CSNRT equals(the $A_4$-$A_5$)-(the $A_1$-$A_1$), whilst the SNRTI equals ( the $A_4$-$A_5$)/(the $A_1$-$A_1$).

The Wenckebach A-V conduction frequency(WB) and the P-R interval.

The mean arterial pressure(MAP) and the heart rate (HR).

### Statistical methods

Quantitative data were expressed as mean±standard deviation($\bar{x}\pm s$). The paired *t* test was applied within each group. And the covariance test was done between groups, with the basic values taken as concomitant variables. The difference was considered significant when $P < 0.05$.

## RESULTS

In groups U1 and U2, obvious decrease in the MAP was observed after the intravenous infusion of urapidil ($P < 0.05$). The CSNRT had a tendency to increase, but it was not significant. In groups N1 and N2, the MAP decreased drastically($P < 0.01$), whereas the HR increased($P < 0.05$). No significant changes were found in the SACT, the CSNRT, the SNRTI, the WB or the P- R internals.

Intergroup analyses found that the SACT and the CSNRT of N1 and N2 groups were conspicuously shorter than their counterpart U2 group($P < 0.01$). Also, the MAP decreased sharply($P < 0.01$) and the HR increased apparently($P < 0.01$). Similar results were identified once the data of N2 group were compared with those of N1 group($P < 0.01$ for the MAP and $P < 0.05$ for the HR). No significant differences were observed for neither of these parameters in other inter-group analyses(See ***Tab 1*** and ***2***).

## DISCUSSION

The sinus node(SAN) function mainly includes two meanings, namely the sinus pacing function and the conduction function. The SAN pacing mechanism was very complicated. It is already known that several ion currents are related to pacing, such as $I_K$, $I_f$, $I_{ca\text{-}T}$, $I_{ca\text{-}L}$, $I_{b\text{-}Na}$ etc[7]. The research into the influence of automatic nerve and its transmitter on SAN pacing function has advanced tremendously. When vagus nerve slightly excites, adenylate cyclase is inhibited after acetylcholine and M receptor enter into combination. The cAMP production is reduced and the $I_f$ ion channel is suppressed, causing slow opening speed, single channel opening probability decreases, the left ward curve is activated, $I_f$ width value decreases, and the SAN pacing frequency decreases. When adrenaline combines with β receptor, adenyl cyclase is activated, leading to the increases in both intracelluar cAMP and the SAN pacing frequency through If ion current[7-8]. There are many substances which also regulate sinus function, such as adenosine[9-10],

***Tab 1*** **The comparisons of sinus and atrio-ventricular node functions parameters before and after urapidil/nicardipine administration** (%, $\bar{x} \pm s$)

| Group | *n* | Time point | SACT(ms) | $SNRT_{max}$(ms) | CSNRT(ms) | SNRTI(ms) | WB(bp/min) | P-R internal(ms) |
|---|---|---|---|---|---|---|---|---|
| U1 group | 8 | Before administration | 66.2 ± 10.2 | 84.9 ± 22.0 | 74.4 ± 20.1 | 1.31 ± 0.05 | 435 ± 41 | 67.2 ± 6.2 |
| | 8 | After administration | 66.8 ± 13.8 | 85.1 ± 23.8 | 77.3 ± 25.2 | 1.32 ± 0.14 | 446 ± 30 | 66.0 ± 12.1 |
| U2 group | 8 | Before administration | 68.2 ± 10.6 | 78.8 ± 23.0 | 72.2 ± 22.3 | 1.30 ± 0.09 | 442 ± 37 | 64.1 ± 8.0 |
| | 8 | After administration | 72.7 ± 21.6 | 87.5 ± 29.2 | 79.4 ± 25.6 | 1.33 ± 0.12 | 450 ± 32 | 62.0 ± 13.9 |
| N1 group | 8 | Before administration | 66.0 ± 10.8 | 80.6 ± 23.3 | 72.5 ± 19.9 | 1.28 ± 0.10 | 430 ± 41 | 68.1 ± 7.1 |
| | 8 | After administration | 59.1 ± 12.8$^{\#\#}$ | 76.2 ± 27.6$^{*\#\#}$ | 66.6 ± 17.5$^{\#\#}$ | 1.22 ± 0.30 | 441 ± 32 | 64.0 ± 11.0 |
| N2 group | 8 | Before administration | 70.2 ± 10.3 | 81.6 ± 25.8 | 72.6 ± 24.2 | 1.23 ± 0.06 | 431 ± 36 | 65.9 ± 7.2 |
| | 8 | After administration | 64.3 ± 20.1$^{\#\#}$ | 82.6 ± 32.8 | 64.5 ± 25.6$^{\#\#}$ | 1.21 ± 0.15 | 420 ± 37 | 60.0 ± 18.7 |

Compared with that before administration,$^{*}P < 0.05$, $^{**}P < 0.01$; Compared with U2 group, $^{\#\#}P < 0.01$.

***Tab 2*** **The changes in hemodynamical parameters before and after urapidil/nicardipine administration** (%, $\bar{x} \pm s$)

| Group | *n* | Time point | MBP(mmHg) | HR($min^{-1}$) |
|---|---|---|---|---|
| U1 group | 8 | Before administration | 94.6 ± 13.1 | 255.9 ± 27.5 |
| | 8 | After administration | 84.0 ± 14.2$^{*}$ | 260.3 ± 22.1 |
| U2 group | 8 | Before administration | 95.6 ± 6.2 | 269.6 ± 22.1 |
| | 8 | After administration | 84.5 ± 8.9$^{*}$ | 273.0 ± 32.6 |
| N1 group | 8 | Before administration | 98.2 ± 12.2 | 251.8 ± 32.6 |
| | 8 | After administration | 72.1 ± 11.1$^{**\#\#}$ | 274.3 ± 38.5$^{*}$ |
| N2 group | 8 | Before administration | 95.2 ± 4.8 | 265.7 ± 17.2 |
| | 8 | After administration | 62.9 ± 9.9$^{**\#\#++}$ | 288.8 ± 31.2$^{*\#\#+}$ |

Compared with that before administration,$^{*}P < 0.05$, $^{**}P < 0.01$; Compared with U2 group, $^{\#\#}P < 0.01$; Compared with N1 group, $^{+}P < 0.05$,$^{++}P < 0.01$.

NO[11], and angiotensin[12]. The atrio-ventricular area is not only the potential automatic rhythm center of the heart, but also the unique normal conduction path between atrial and ventricular chamber. Similar to sinus node, its electrophysiological characteristics belong to slow reaction potential.

The depressurization mechanism of uripidil is very distinct, inasmuch as it has peripheral vasodilatation and center depressurization effects[13]. In periphery, it mainly blocks post synapse $\alpha_1$ receptor, then dilates peripheral small arteries to lower blood press ure. Meanwhile, by exciting the 5-hydroxytryptamine receptor, it suppresses the sympathesis and feedback regulation from the cardiovascular center. Accordingly, the tachycardia is prevented. It was found in the present study that the two different dosages of urapidil did not increase the heart rate significantly when lowering blood pressure. The SACT and CSNRT tended to extend with an increased dosage of urapidil, but the difference was negligible. Due to the decrease in the sympathesis and feedback effects of the bulb cardiovascular center, whether urapidil could affect sinus and A-V conduction functions with increasing dosage and prolonged medication time still requires further studies. Liang M et al[2] reported that urapidil could significantly increase serum calcitonin gene-related peptide level and dilate coronary arteries in coronary artery disease patients. It improves high risk patient oxygen supply and requirement balance. Therefore, urapidil can be safely applied to patients with coronary artery diseaser, acute or chronic heart failure. However, Our results indicated that as side effects, cardiac conduction system impairment must be taken into account when it is applied to patients.

Nicardipine is the second generation hydropyridine short-effect calcium channel blocker. Its intravenous effect time is 1-5 min and elimination half life is(40 ± 10)min. It selectively affects vascular smooth muscle and prevents calcium ion inward, then dilates vessels and lowers blood pressure. At the same time, it causes backward heart rate increase. But verapamil and dilthiazem suppress A-V node channel significantly. Their effects upon A-V conduction are much greater than those on myocardial constriction and angiotasis. The present study proved the excellent depressurization effect of nicardipine($P < 0.01$). Heart rate increased significantly($P < 0.05$), while decreasing tendencies were found in both the SACT and the CSNRT after the administration of nicardipine. However, the above differences were still negligible. These results indicated that nicardipine had no side effects on sinus pacing and sino-atrial conduction functions. It might even improve sinus function. The negligible changes of WB and P-R internal also indicated that nicardipine(10 μg/kg, 20 μg/kg) had no side effect on A-V conduction function. The *in vitro* experiment performed by Motomura S et al[14] proved that Nicardipine had a similar depression effect to those of other calcium channel blockers on sinus node function. David D et al[15] found that nicardipine shortened sino-atrial conduction time, AH internal and atrio-ventricular node functional refractory period(AVNFRPs) significantly. These results were not consistent with ours here. Nicardipine may have double effects on sinus node and A-V conduction functions. It improved sinus and A-V conduction functions via reflective sympathesis when blood pressure went down. Meanwhile, it has depression effects as a calcium channel blocker.

The intrinsic differences between *in vitro* and *in vivo* studies, body conditions and dosage may account for the discrepancies.

Several commonly used hypotensive drugs, such as nitroprosside sodium and phentolamine, could affect intracardiac conduction system to some distinct extent. The effects became more obvious when the administration time was elongated or the dosage was increased. Nevertheless, neither urapidil nor nicardipine has any vicious influence on sinus or atrio-ventriculr functions even with an increased dosage. As mentioned above, nicardipine even has the tendency to improve sinus and atrioventricular functions. Nicardipine(10 μg/ kg, 20 μg/kg) SACT and CSNRT was obviously shorter than urapidil (0.5 mg/kg). This indicates that nicardipine is more suitable than urapidil for parafunctional sinus and atrioventricular patients.

Compared to urapidil, the hypotensive effects of nicardipine(10 μg/kg, 20 μg/kg) were much greater, and HR increased more significantly. In practical application, the authors here all agree that they should be used selectively, according to their different hypotensive effects.

In the pre-experiment, we did not disclose any changes in MAP, HR, SACT, CSNRT, SNRTI, WB, and P-R periods after normal saline injection, therefore we did not add another negative control group. Data in each group were analyzed with paired t test referenced to the baseline value. As a result, scientific statistic results could been drawn out with a smaller sample size.

For the reasons discussed above, neither urapidil (0.25 mg/kg, 0.50 mg/kg) nor nicardipine(10 μg/kg, 20 μg/kg) has any vicious side effects on sinus node function or A-V conduction function. For parafunctional sinus node patients, nicardipine is a safer depressor.

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