# Effect of Autonomic Blockade on Ventricular Refractoriness and Atrioventricular Nodal Conduction in Humans

## Evidence Supporting a Direct Cholinergic Action on Ventricular Muscle Refractoriness

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**SUMMARY** In humans, the parasympathetic nervous system predominates over the sympathetic nervous system in control of heart rate, but little is known about the relative influences of cholinergic and adrenergic tone on the electrophysiological properties of the ventricle and atrioventricular (AV) node. Thirteen subjects were studied using standard electrophysiological testing techniques in the control state and after propranolol (0.15 mg/kg, iv) plus atropine (0.03 mg/kg, iv) to assess the effect of autonomic blockade on ventricular and AV nodal refractoriness and AV nodal conduction. Eight subjects received propranolol first (group A) and five were given atropine first (group B). For groups A and B, the spontaneous sinus cycle length significantly decreased from control after administration of propranolol and atropine [813 ± 107 (SD) to 613 ± 57 msec and 842 ± 188 to 637 ± 115 msec, respectively]. Ventricular effective (ERP) and functional (FRP) refractory periods insignificantly increased from control after propranolol was given (group A); however, both ventricular ERP and FRP significantly shortened to less than control values after atropine was added (238 ± 23 to 218 ± 19 msec and 261 ± 22 to 243 ± 17 msec, respectively). Similar results for ventricular refractoriness occurred after administration of atropine and propranolol in group B subjects. The shortest atrial pacing cycle length sustaining 1:1 AV nodal conduction after administration of propranolol and atropine did not significantly change from control values (386 ± 109 to 372 ± 74 msec). These data suggest that (1) resting vagal tone exerts a significant effect on human ventricular refractoriness and the effect can occur in the presence of β-adrenergic blockade, and (2) in contrast to the markedly predominant effect of the parasympathetic nervous system on sinus nodal automaticity, vagal and adrenergic tone exert a balanced effect on resting AV nodal conduction. *Circ Res 49: 511-518, 1981*



The autonomic nervous system exerts important effects on electrophysiological characteristics of the heart. The sinoatrial (SA) and atrioventricular (AV) nodes receive multiple inputs from the sympathetic and parasympathetic nervous systems (Tcheng, 1951; James and Spence, 1966; Levy and Zieske, 1969; Spear and Moore, 1973; Schmid et al., 1978). In the human and animal SA node, the parasympathetic nervous system predominates over the sympathetic nervous system in control of heart rate (Jose and Taylor, 1969; Levy and Zieske, 1969). However, in animals, autonomic influence on AV nodal function is more balanced, and the effect of simultaneous stimulation of the parasympathetic and sympathetic nervous systems on AV nodal conduction appears to be additive algebraically (Levy and Zieske, 1969). The relative influence of both limbs of the autonomic nervous system on AV nodal conduction has not been defined for humans.

The effect of the sympathetic nervous system on electrophysiological characteristics of the ventricle has been known for years. In contrast, the functional significance and even the anatomical presence in the ventricle of the parasympathetic nervous system has been questioned. Recent data demonstrate the presence of ventricular cholinergic innervation by anatomical methods (Hirsch et al., 1965; Smith, 1971; Kent et al., 1974; Fields et al., 1978), by analysis of acetylcholine content and choline acetyltransferase activity (Roskoski, et al., 1974; Brown, 1976), and by changes in ventricular contractility and/or refractoriness during parasympathetic stimulation (DeGeest et al., 1965; Levy et al., 1966; Daggett et al., 1967; Wildenthal et al., 1969; Watanabe and Besch, 1975; Kolman et al., 1976; Bailey et al., 1979; Martins and Zipes, 1980; Blair et al, 1980). Furthermore, the vagus has been

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shown to affect ventricular function directly (Daggett et al., 1967; Wildenthal et al., 1969; Blair et al., 1980) or indirectly by modulating existing sympathetic activity (Levy et al., 1966; Watanabe et al., 1975; Kolman et al., 1976; Bailey et al., 1979; Martins and Zipes, 1980).

It is quite clear that both limbs of the autonomic nervous system interact and may in certain circumstances and on specific tissues exert opposing effects (Levy, 1971). In many studies, the parasympathetic nervous system appears to modulate the effects of the sympathetic nervous system (Watanabe and Besch, 1975; Kolman et al., 1976; Bailey et al., 1979; Martins and Zipes, 1980). Such interaction may affect significantly the development and maintenance of cardiac arrhythmias (Kent et al., 1973; Rabinowitz et al., 1976; Waxman and Wald, 1977). Yet, detailed studies of the interactions of the parasympathetic and sympathetic nervous system on AV nodal conduction and ventricular refractoriness in humans have not been performed. The purpose of this study was to assess in humans the relative contributions of parasympathetic and sympathetic tone on AV nodal conduction and right ventricular refractoriness by administration of atropine and propranolol to produce autonomic blockade.

## Methods

Thirteen subjects were studied electrophysiologically before and after autonomic blockade, in the postabsorptive nonsedated state. Subjects entered this protocol after giving informed written and oral consent if they (1) had no contraindication to the administration of atropine and propranolol, and (2) were taking no medications known to affect the heart or autonomic nervous system. In all subjects three catheters were inserted percutaneously into the femoral vein, and guided fluoroscopically to the high right atrium and right ventricular apex and across the tricuspid valve in the area of the His bundle. The catheter positions remained unchanged throughout the period of data accumulation.

A programmable stimulator (Medtronic 5325) was used to pace the heart with stimuli 1.8 msec in duration and twice late-diastolic threshold; the latter was determined before and after drug administration. AV nodal conduction was evaluated by pacing the right atrium through the distal bipolar pair of the right atrial quadripolar catheter at cycle lengths just shorter than spontaneous sinus cycle length (SCL), and the pacing cycle length was decreased by 10- to 20-msec intervals until AV nodal block occurred. Ventriculoatrial (VA) conduction was assessed by using the same stimulation protocol during pacing through the distal bipolar pair of the quadripolar catheter situated in the right ventricular apex. The extrastimulus technique (Krayer et al., 1951) was used to determine refractoriness, and for each patient, the pacing cycle length (PCL) was the same for control and after drug interventions. Since cycle length influences refractoriness, we avoided variations in cycle length by pacing the ventricle for 30 seconds before assessing refractoriness; after 30 seconds, premature stimuli were induced early in diastole after every eighth paced beat without interrupting the basic drive train. The premature coupling interval was increased by 5- to 10-msec intervals until ventricular capture occurred. In this fashion, the heart was paced at an uninterrupted fixed cycle length until the refractory period was determined. Each premature interval was tested twice, and the effective refractory period (ERP) was defined as the longest $S_1S_2$ interval at which $S_2$ consistently did not result in ventricular capture. The ventricular electrograms were recorded on the proximal bipolar pair of a quadripolar catheter, and the distal bipolar pair was used to stimulate the heart. The $V_1V_2$ interval was measured from the first rapid deflection in the ventricular electrograms. The ventricular functional refractory period (FRP) was defined as the shortest obtainable $V_1V_2$ interval. The AV nodal ERP was defined as the longest $A_1A_2$ interval at which $A_2$ consistently did not result in His depolarization. The AV nodal FRP was defined as the shortest obtainable $H_1H_2$ interval. The SCL was taken as the mean of 20 consecutive sinus cycles.

Data from multiple surface and intracardiac leads were recorded on an oscilloscopic recorder (Electronics for Medicine VR 12) at paper speed 100 mm/sec. Signals from the ECG surface leads were filtered at 0.1–20 Hz and from the intracardiac leads at 30–500 Hz. Repeated measures analysis of variance was used to compare subjects on the three treatments (control, propranolol or atropine, propranolol and atropine). When the analysis of variance was significant, comparisons with control values were made by using the Bonferroni method. Paired *t*-tests were performed when only one measurement was compared to the control value. Data are reported as mean ± 1 SD. Linear regression analysis was used to compare the changes in SCL, with AV nodal conduction (Fig. 4).

### Drug Studies

All subjects were given atropine (Elkins-Sinn, Inc.) (0.03 mg/kg) and propranolol (Ayerst) (0.15 mg/kg) intravenously following collection of control data. Eight received propranolol first and five received atropine first. Propranolol was administered at 1.0 mg/min and the atropine dose was given during a period of 3 minutes. The doses used have been shown to block effectively the influence of the autonomic nervous system on sinus nodal automaticity in humans (Jose and Taylor, 1969; Jose and Collison, 1970). For all subjects, the total time required to perform single and combined drug studies was less than 30 minutes.

In addition to the 13 subjects who received propranolol and atropine, two were studied to evaluate

whether propranolol (0.15 mg/kg, iv) blocked the effects on ventricular refractoriness of increased sympathetic tone. Refractoriness was determined at the right ventricular apex, and then isoproterenol (Breon Laboratories, Inc.) was given as a constant intravenous infusion in a dose that resulted in a 25% increase in sinus rate and refractory period determinations repeated. Subsequently, propranolol (0.15 mg/kg, iv) was given and refractory periods reevaluated with continued isoproterenol infusion, and then 10 minutes after termination of isoproterenol infusion. Thus, refractory periods were determined in the control state and during administration of isoproterenol, isoproterenol and propranolol, and propranolol alone.

## Results

### Characteristics of Subjects

Thirteen subjects, mean age 37.9 ± 15.6 years, were studied to determine the cause for their clinical symptoms and/or to define their arrhythmias (Table 1). Historically, six had ventricular and two supraventricular tachyarrhythmias; four had bradyarrhythmias, and no arrhythmias were identified in one. Subjects 5, 8, and 13 had a history of AV block but did not have spontaneous AV block at the time of study. Two subjects had demonstrable heart disease, but in 11 no heart disease was detected by history, physical examination, chest x-ray, ECG, or echocardiogram.

### Sinus Nodal Automaticity

Eight subjects were given propranolol first (group A), five received atropine first (group B), and all subjects received atropine and propranolol (Table 2; see Methods). For all subjects, insignificant changes in blood pressure occurred with one or both drugs. The effect of autonomic blockade on SCL is shown in Figure 1. For group A, SCL was significantly different at the three measurements ($P < 0.001$) by repeated measures analysis of variance. Comparison with control values showed that SCL significantly increased from control after administration of propranolol (813 ± 107 to 875 ± 98 msec, $P < 0.01$) and significantly decreased after administration of atropine and propranolol (813 ± 107 to 613 ± 57 msec, $P < 0.01$). For group B, SCL significantly changed following drug administrations ($P < 0.001$). SCL decreased after administration of atropine (842 ± 188 to 458 ± 85 msec, $P < 0.05$) and increased after administration of propranolol, but the value after administration of atropine and propranolol was still significantly less than control (842 ± 188 to 637 ± 115 msec, $P < 0.05$). These results confirm the well known predominance of cholinergic over sympathetic tone on SA nodal automaticity.

### Ventricular Refractoriness

Ventricular refractory period data are listed in Table 2. Ventricular ERP values were different from control on propranolol and propranolol plus atropine for group A by repeated measures analysis of variance ($P < 0.001$). After propranolol infusion (group A), ventricular ERP increased in five, decreased in one, and did not change in two subjects, and for the entire group there was no significant change from control values in ventricular ERP (238 ± 23 to 243± 17 msec). The administration of atropine decreased ventricular ERP values significantly from control (238 ± 23 to 218 ± 19 msec, $P < 0.05$)

TABLE 1 *Subject Characteristics*

| Subject no. | Age | Sex | Heart disease | Arrhythmias | ECG intervals* (msec) R-R | PR | QRS | QT$_c$ |
|---|---|---|---|---|---|---|---|---|
| 1 | 61 | M | ASHD | VT | 825 | 170 | 80 | 440 |
| 2 | 22 | F | MVP | PVCS | 880 | 140 | 70 | 420 |
| 3 | 50 | M | None | Ectopic atrial tachycardia | 870 | 145 | 70 | 410 |
| 4 | 53 | F | None | VT | 890 | 115 | 80 | 410 |
| 5 | 23 | M | None | Type I (2° AV block) | 800 | 330 | 70 | 390 |
| 6 | 45 | M | None | SSS | 710 | 170 | 70 | 380 |
| 7 | 19 | F | None | VT | 850 | 170 | 70 | 350 |
| 8 | 48 | F | None | Type II (2° AV block) | 630 | 175 | 120 | 440 |
| 9 | 21 | F | None | None† | 1050 | 155 | 70 | 360 |
| 10 | 27 | F | None | PVCS | 710 | 130 | 70 | 420 |
| 11 | 30 | M | None | SVT | 680 | 135 | 80 | 390 |
| 12 | 61 | F | None | VT | 1090 | 150 | 85 | 430 |
| 13 | 33 | M | None | Type I (2° AV block) | 820 | 220 | 85 | 430 |

Abbreviations. ASHD = atherosclerotic heart disease; AV = atrioventricular; MVP = mitral valve prolapse; PVCS = premature ventricular complexes; SSS = sick sinus syndrome, SVT = supraventricular tachycardia; VT = ventricular tachycardia.

* Intervals obtained from admission ECG

† Subject with history of syncope.

TABLE 2 *Effect of Autonomic Blockade on Ventricular Refractoriness (msec)*

| Subject no | SCL C | SCL P or A | SCL P + A | PCL | Ventricular ERP C | Ventricular ERP P or A | Ventricular ERP P + A | Ventricular FRP C | Ventricular FRP P or A | Ventricular FRP P + A |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | *Group A—Propranolol first* | | | | | | |
| 1 | 840 | 920 | 690 | 600 | 270 | 270 | 260 | 300 | 300 | 270 |
| 2 | 880 | 880 | 530 | 500 | 250 | 260 | 220 | 265 | 270 | 250 |
| 3 | 760 | 880 | 555 | 400 | 260 | 240 | 210 | 270 | 260 | 230 |
| 4 | 910 | 950 | 620 | 500 | 240 | 250 | 210 | 270 | 280 | 230 |
| 5 | 950 | 1020 | 680 | 400 | 230 | 240 | 200 | 250 | 255 | 230 |
| 6 | 690 | 800 | 640 | 400 | 200 | 220 | 200 | 225 | 235 | 225 |
| 7 | 830 | 860 | 610 | 400 | 230 | 230 | 220 | 260 | 260 | 260 |
| 8 | 645 | 695 | 575 | 400 | 220 | 230 | 220 | 245 | 265 | 250 |
| Mean | 813 | 875 | 613 | | 238 | 243 | 218 | 261 | 266 | 243 |
| ± SD | ±107 | ±98 | ±57 | | ±23 | ±17 | ±19 | ±22 | ±19 | ±17 |
| | | | | *Group B—Atropine first* | | | | | | |
| 9 | 970 | 357 | 570 | 400 | 220 | — | 210 | 230 | — | 225 |
| 10 | 650 | 400 | 545 | 400 | 230 | — | 200 | 230 | — | 215 |
| 11 | 680 | 445 | 605 | 400 | 220 | 200 | 210 | 240 | 220 | 230 |
| 12 | 1090 | 550 | 835 | 400 | 220 | 210 | 215 | 250 | 230 | 225 |
| 13 | 820 | 540 | 630 | 400 | 225 | 200 | 215 | 250 | 225 | 235 |
| Mean | 842 | 458 | 637 | | 223 | — | 210 | 240 | — | 226 |
| ± SD | ±188 | ±85 | ±115 | | ±4 | | ±6 | ±10 | | ±7 |

Abbreviations A = atropine; C = control, ERP = effective refractory period; FRP = functional refractory period; PCL = pacing cycle length, P = propranolol; SCL = spontaneous cycle length.

(Fig. 2). The effects of autonomic blockade on the ventricular FRP were similar to those in the ERP.

Five subjects received atropine first (group B), but two could not tolerate the increase in heart rate and were given propranolol prior to electrophysiological testing. In the three subjects tested after receiving atropine alone, the ERP and FRP are significantly different at the three measurements by repeated measures analysis of variance ($P < 0.05$) (Table 2, Fig. 2). Possibly because of small sample sizes ($n = 3$), significant difference between control and atropine alone could be demonstrated only for ventricular FRP ($P < 0.05$). After propran-

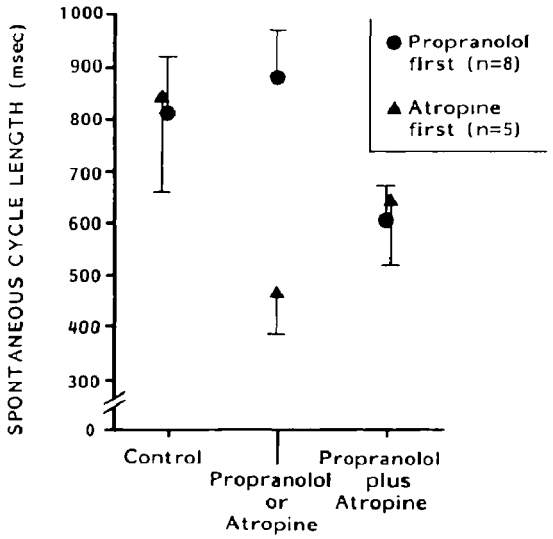


FIGURE 1 *Effect of autonomic blockade on SCL. For all subjects, mean SCL significantly decreased from control values after administration of propranolol and atropine. The vertical bars signify 1 SD. See text for further detail.*

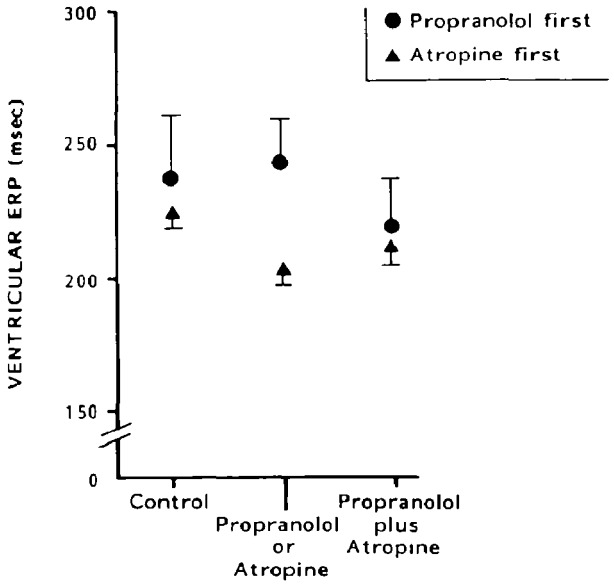


FIGURE 2 *Right ventricular refractoriness before and after autonomic blockade. For all subjects, the mean ERP of the right ventricular apex significantly shortened from control values after administration of propranolol and atropine. The vertical bars signify 1 SD. See text for further detail.*

olol administration, the ERP and FRP increased in these three subjects, but remained shorter than control values (Fig. 3). For all five subjects, the ERP and FRP after propranolol and atropine was less than control (223 ± 4 to 210 ± 6 msec, $P < 0.05$, and 240 ± 10 to 226 ± 7 msec, $P < 0.02$, respectively) (Fig. 2).

Two additional subjects were tested to determine the effect of propranolol (0.15 mg/kg) on enhanced sympathetic tone (see Methods). In both, ventricular refractoriness was evaluated during ventricular pacing at a cycle length of 400 msec. The ventricular ERP before drugs and during administration of isoproterenol, isoproterenol and propranolol, and propranolol alone was 230, 200, 235, and 235 msec, respectively, for the first subject, and 225, 205, 235, and 235 msec, respectively, for the second.

## AV Nodal Conduction and Refractoriness

The shortest atrial PCL sustaining 1:1 AV nodal conduction increased from 393 ± 122 msec before to 433 ± 128 msec after propranolol administration in group A subjects ($P < 0.02$, paired $t$-test) (Table 3). In all three subjects tested after receiving atropine alone (group B), AV nodal conduction improved. After administration of propranolol and atropine, 1:1 AV nodal conduction occurred at a shorter PCL than control in seven subjects, at a longer PCL in four, and was unchanged in two. For all subjects, the change from control was not significant (386 ± 109 to 372 ± 74 msec). AV nodal ERP was limited by atrial refractoriness in many subjects and statistical analysis could not be performed. However, in eight subjects AV nodal ERP before and after administration of propranolol and atropine could be compared, and in six the ERP decreased.

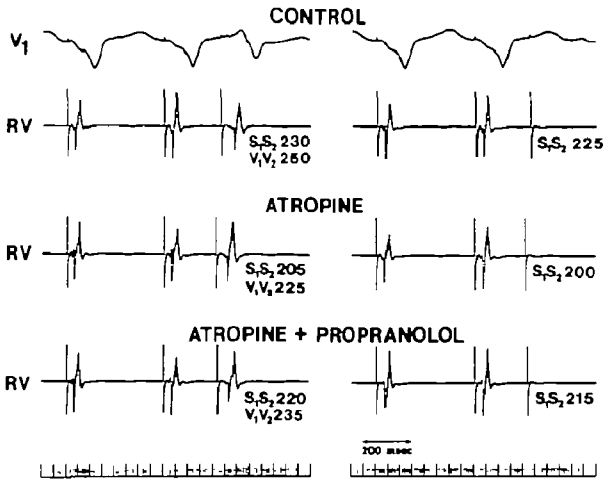


FIGURE 3 *Changes in ventricular refractoriness after atropine and atropine and propranolol (subject 13). Standard ECG lead $V_1$ is shown for control and the right ventricular (RV) electrogram is shown for control and drug studies. Ventricular FRP is shown on the left and ventricular ERP on the right. During control, the ventricular FRP was 250 msec and the ERP was 225 msec. Atropine was given, and the ventricular FRP and ERP decreased to 225 and 200 msec, respectively. Propranolol was added, and the FRP and ERP increased to 235 and 215 msec, respectively. Note that after propranolol and atropine administration the ventricular FRP and ERP are less than control values.*

A comparison of the percent changes from control after administration of propranolol and atropine between SCL and AV nodal conduction revealed a significant, but weak correlation (Fig. 4). For example, subjects who had the largest increases

TABLE 3 *Effect of Autonomic Blockade on AV Nodal Function (msec)*

| Subject no. | Shortest PCL with 1:1 AV nodal conduction | | | Shortest PCL with 1:1 VA conduction | | | PCL | AV nodal ERP | | | AV nodal FRP | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | C | P or A | P + A | C | P or A | P + A | | C | P or A | P + A | C | P or A | P + A |
| | | | | | | | *Group A—Propranolol first* | | | | | | |
| 1 | 350 | 400 | 350 | 310 | 310 | 310 | 400 | 330 | — | 300 | 360 | — | 380 |
| 2 | 380 | 390 | 340 | 390 | 420 | 350 | 500 | 280 | 320 | <200 | 400 | 410 | ≤355 |
| 3 | 370 | 390 | 330 | 300 | 370 | 300 | 400 | 280 | 320 | <255 | 380 | 385 | 340 |
| 4 | 340 | 330 | 310 | 280 | 380 | 310 | 500 | <220 | <240 | <270 | ≤350 | ≤380 | ≤350 |
| 5 | 680 | 740 | 560 | VA dissociation | | | — | — | — | — | — | — | — |
| 6 | 290 | 380 | 300 | 300 | 490 | 310 | 500 | 255 | 310 | <245 | 340 | 400 | ≤320 |
| 7 | 410 | 450 | 360 | VA dissociation | | | 450 | 320 | — | — | 430 | — | — |
| 8 | 320 | 380 | 340 | VA dissociation | | | 500 | 260 | 280 | 260 | 350 | 370 | 355 |
| | | | | | | | *Group B—Atropine first* | | | | | | |
| 9 | 400 | — | 390 | VA dissociation | | | 450 | 340 | — | 330 | 385 | — | 400 |
| 10 | 280 | — | 280 | 400 | — | 410 | 500 | <240 | — | <270 | ≤330 | — | ≤310 |
| 11 | 290 | 260 | 400 | 360 | 330 | >430 | 400 | 300 | 230 | >360 | 350 | 290 | CNM |
| 12 | 390 | 330 | 430 | VA dissociation | | | 500 | 360 | — | 350 | 420 | — | 415 |
| 13 | 520 | 280 | 440 | VA dissociation | | | — | — | — | — | — | — | — |

Abbreviations: A = atropine; AV = atrioventricular; C = control; CNM = cannot measure; ERP = effective refractory period; FRP = functional refractory period; P = propranolol, PCL = pacing cycle length; VA = ventriculoatrial.

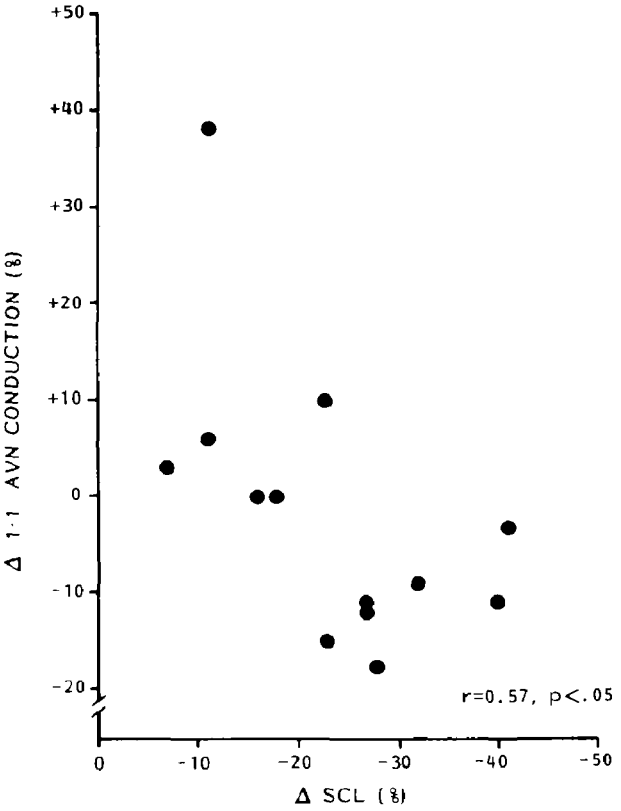


FIGURE 4 *A comparison of changes in AV nodal conduction and sinus nodal automaticity after autonomic blockade. The percent change from control after atropine and propranolol in AV nodal conduction (ordinate) is plotted as a function of the percent change from control in SCL (abscissa). Each symbol represents one subject. A significant correlation occurred between changes in SA nodal automaticity and AV nodal conduction.*

in heart rate following autonomic blockade also tended to have the most improvement in AV nodal conduction. Of note, after propranolol and atropine the changes in AV nodal conduction were much less than the changes in sinus nodal automaticity; most subjects had more than a 20% reduction in SCL, but the changes in AV nodal conduction were usually only ± 10%.

## Discussion

### Ventricular Refractoriness

The most important finding in this study is that elimination of tonic muscarinic cholinergic activity shortens ventricular refractoriness determined in the right ventricular apex in humans. When propranolol was given to group A subjects minimal changes in ventricular refractoriness occurred. This finding is consistent with previously published data in humans and animals (Davis and Temte, 1968; Wellens et al., 1977; Jaillon et al., 1980). Since β-adrenergic tone shortens ventricular refractoriness (Martin and Zipes, 1980), the small changes in ventricular ERP and FRP after propranolol administration indicate a lack of significant background sympathetic tone on ventricular fibers at the right ventricular apex.

Data obtained after atropine administration suggest that resting vagal tone exerts a significant effect on ventricular refractoriness. In the patients given propranolol first, the ventricular ERP and FRP shortened after atropine was given, which demonstrates that background cholinergic tone was present and suggests that it prolonged ventricular refractoriness. Since the effect of atropine occurred during β-adrenergic blockade, it appears that muscarinic cholinergic activity does not require background sympathetic (β) tone to exert its effect on the human right ventricle, and can prolong directly ventricular refractoriness. The dose of propranolol we used is sufficient to block β-sympathetic effects on SA nodal automaticity (Jose and Collison, 1970), and in the two subjects we studied, this dose of propranolol also was sufficient to block β-sympathetic effects on ventricular refractoriness. In 11 of 13 subjects the ERP and FRP of the ventricle shortened below control values after administration of propranolol and atropine, and these data suggest that the parasympathetic nervous system exerts a predominating effect over the sympathetic nervous system on resting human ventricular refractoriness.

Our data suggest that the parasympathetic nervous system can prolong ventricular refractoriness by a direct action, and agree with the findings of Blair et al. (1980), but are contrary to the results from other studies (Kolman et al., 1976; Martins and Zipes, 1980). The discrepancies may be due to species differences (Smith, 1971) and the fact that we studied nonsedated conscious patients, rather than anesthetized animals without an intact nervous system. Of note is that our subjects had shown a variety of arrhythmias and conduction disturbances, and it is unknown whether the results can be extrapolated to the general population.

The results from this study support previously published data on the effects of vagal stimulation on ventricular arrhythmias in humans. Waxman and Wald (1977) terminated ventricular tachycardia by enhancing vagal tone. If one assumes reentry as the mechanism for ventricular tachycardia in Waxman and Wald's patients, enhanced vagal tone could increase ventricular ERP in one limb of the reentrant circuit, causing the propagating wavefront of depolarization to encroach upon incompletely recovered tissue and terminate the reentrant excitation.

The effects on the autonomic nervous system of some antiarrhythmic drugs may account in part for the success or failure of a drug to suppress ventricular arrhythmias. For example, although quinidine and procainamide have similar electrophysiological properties in vitro (Bigger, 1980), quinidine has more potent anticholinergic properties (Fields et

al., 1978; Mirro et al., 1980). Thus, procainamide, but not quinidine, might suppress ventricular tachycardia occurring in a patient in whom the electrophysiological effects of vagal tone are antiarrhythmic.

### AV Node

The present study confirms the negative dromotropic effect of propranolol and the positive dromotropic effect of atropine on AV nodal conduction (Berkowitz et al., 1969; Akhtar et al., 1974). However, AV nodal conduction was unchanged after administration of atropine and propranolol (Table 3). Interpretation of these data suggest a balanced effect of the parasympathetic and sympathetic nervous systems on resting AV nodal conduction in humans. This contrasts with the marked predominant effect of the parasympathetic nervous system on SA nodal automaticity (Fig. 1).

Cholinergic effects on AV nodal conduction predominated in seven and sympathetic effects predominated in four subjects (Table 3). After administration of propranolol and atropine, the changes from control in AV nodal conduction correlated with the changes in SA nodal automaticity (Fig. 4), suggesting that the tonic modulating influence of autonomic tone on both nodes was related. However, quantitative differences exist because, following a similar degree of autonomic blockade, the percent increase in SA nodal discharge rate far exceeded the percent changes in AV nodal conduction time. One possible interpretation of the data is that the rate of sinus nodal automaticity is primarily under parasympathetic control while AV nodal conduction time is more equivalently controlled by both parasympathetic and sympathetic tone.

The lack of vagal predominance on AV nodal conduction may explain in part the apparently greater effect of verapamil on AV nodal than SA nodal function (Rinkenberger et al., 1980). Verapamil transiently decreases blood pressure and results in a reflex withdrawal of parasympathetic tone and an increase in sympathetic tone, responses that increase sinus nodal automaticity and may offset the direct negative chronotropic effects of verapamil. The effects of the autonomic nervous system are more balanced on the AV node, and the reflex changes occurring after verapamil administration may have a minor effect on AV nodal conduction, and the direct negative dromotropic action of verapamil would predominate. This hypothesis is supported by a recent study on the effects of verapamil on SA nodal function before and after autonomic blockade (Breithardt et al., 1978).

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# Blood Pressure Response to Central and/or Peripheral Inhibition of Phenylethanolamine *N*-Methyltransferase in Normotensive and Hypertensive Rats

JESSIE BLACK, BERNARD WAEBER, MARGARET R. BRESNAHAN, IRENE GAVRAS, AND HARALAMBOS GAVRAS

**SUMMARY** **We studied the effects on blood pressure and heart rate of two different phenylethanolamine *N*-methyltransferase (PNMT) inhibitors in normotensive, in two-kidney renal hypertensive, and in deoxycorticosterone-salt (DOC-salt) hypertensive rats. One compound (SK&F 64139) blocks the conversion of norepinephrine to epinephrine in both the central and the peripheral nervous system, whereas the other (SK&F 29661) does not cross the blood-brain barrier and therefore is active mostly in the adrenal glands. In the rats given SK&F 29661, practically no acute blood pressure changes were observed. Central PNMT inhibition with SK&F 64139 induced only a minor blood pressure and heart rate response in normotensive and two-kidney renal hypertensive rats. However, in DOC-salt hypertensive rats, it reduced arterial pressure to approximately normal levels and concomitantly slowed pulse rate. There was a close correlation between the magnitude of the blood pressure response observed in all SK&F 64139-treated animals and the control plasma norepinephrine ($r = -0.795$, $P < 0.001$) and epinephrine ($r = -0.789$, $P < 0.001$) levels. These results suggest an important role for central epinephrine in regulating the peripheral sympathoadrenomedullary and the baroreceptor reflex activity, particularly when the maintenance of the high blood pressure is not renin-dependent.** ***Circ Res 49: 518–524, 1981***

CENTRAL catecholaminergic neurons are thought to participate in the regulation of normal blood pressure and in the development and maintenance of high blood pressure in several types of experimental hypertension (Chalmers, 1975). At least some of the brain areas involved in cardiovascular homeostasis are located in the brain stem (Doba and Reis, 1974; Chalmers, 1975). Such areas not only are innervated richly with catecholaminergic cell bodies and terminals (Fuxe, 1965; Bolme et al., 1972), but also have the highest activity of phenylethanolamine *N*-methyltransferase (PNMT) (Saavedra et al., 1974), the enzyme which catalyzes the last step in epinephrine formation (Axelrod, 1962).

A neurogenic component has been proposed as a pathogenic factor in the hypertension induced by mineralocorticoids and salt (Nakamura et al., 1971;

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# Effect of autonomic blockade on ventricular refractoriness and atrioventricular nodal conduction in humans. Evidence supporting a direct cholinergic action on ventricular muscle refractoriness.

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