Accentuated Vagal Antagonism of β-Adrenergic Effects on Ventricular Repolarization

Evidence of Weaker Antagonism in Hostile Type A Men

Shin Fukudo, MD; James D. Lane, PhD; Norman B. Anderson, PhD; Cynthia M. Kuhn, PhD; Saul M. Schanberg, MD, PhD; Nancy McCown, RN; Motoyasu Muranaka, MD; Jinichi Suzuki, MD; and Redford B. Williams Jr., MD

Background. Prior research has suggested a weaker parasympathetic antagonism of sympathetic effects on the heart in type A (coronary-prone) men. To confirm this phenomenon and extend our understanding of it, we investigated the effects of prior muscarinic blockade on the electrocardiogram T wave and other cardiovascular and neuroendocrine responses to isoproterenol in type A and type B (non-coronary-prone) men.

Methods and Results. Responses to two 5-minute intravenous isoproterenol infusions (0.01 µg/kg/min and 0.02 µg/kg/min) were evaluated in six type A and six type B men after pretreatment with either dextrose placebo or atropine (1.2 mg). Atropine significantly potentiated T wave attenuation in the recovery period after isoproterenol infusion (0.30±0.07 mV) compared with placebo (0.54±0.09 mV, p<0.001). Atropine also potentiated the heart rate increase to isoproterenol (39±3 beats per minute versus 20±2 beats per minute after placebo). Atropine enhanced decreases in systolic, diastolic, and mean arterial pressures as well as pulse pressure to isoproterenol. Atropine enhancement of many of these responses was increased among subjects with high scores on various hostility/anger scales. Isoproterenol alone produced greater T wave attenuation in type A than in type B men. However, atropine enhancement of T wave attenuation and blood pressure falls by isoproterenol was present only in type B men.

Conclusions. These findings indicate that there is accentuated parasympathetic antagonism of T wave attenuation and blood pressure responses induced by β-adrenergic stimulation. Relative weakness of this antagonism of sympathetic effects on the heart in hostile type A individuals may contribute to their higher coronary disease risk. (Circulation 1992;85:2045–2053)

Key Words • T wave • atropine • coronary-prone behavior • isoproterenol

The autonomic nervous system plays a central role in modulating circulatory responses to physical and psychological stressors. Sympathetic arousal-induced stress has long been known to cause dramatic changes in cardiovascular function.1 The T wave of the electrocardiogram has been considered to reflect such cardiac sympathetic effects on ventricular repolarization processes.2–4 Thus, systemic or intracoronary administration of catecholamines produces decreased T wave amplitude.5,6 Although vagal influences on T wave amplitude have been less well defined,7 atropine is reported to cause T wave attenuation in humans.7 Though not particularly strong under low levels of sympathetic drive, effects of vagus nerve stimulation on cardiac function have been shown to be enhanced during sympathetic excitation.8,9 This increasing vagal effect with increasing sympathetic drive has been termed “accentuated antagonism.”10 Recent research in cardiovascular physiology also demonstrated the presence of such accentuated vagal antagonism during intravenous isoproterenol infusion11 and investigated its impact on ventricular performance.12

Findings in a recent study in our laboratory13 suggest that T wave attenuation during isoproterenol infusion is subject to accentuated vagal antagonism. Moreover, this vagal antagonism of isoproterenol effects on T wave amplitude was less pronounced in coronary-prone type A individuals14 than in non-coronary-prone type B individuals. Additional evidence for weaker vagal tone in type A's came from a second study15 showing weaker vagally mediated heart rate slowing during drive reflex elicitation in type A's compared with type B's. It has been supposed that type A's have high coronary risk because of their exaggerated adrenergic tone and sympathetic reactivity to stress.16–19 Type A's have also been shown to exhibit greater T wave attenuation during emotional stress,20,21 which was interpreted as yet another manifestation of sympathetic hyperreactivity. Based on our recent findings, we have hypothesized
that type A’s are placed at increased risk for coronary heart disease not only by enhanced sympathetic excitation but also by reduced vagal antagonism of sympathetic effects on the heart.

Therefore, the purpose of the current study was to document the presence of stronger accentuated vagal antagonism of sympathetic stimulation effects on T wave amplitude among type B as contrasted to type A men. We evaluated the effects of isoproterenol infusions on T wave and other physiological responses after pretreatment with either placebo or atropine. To the extent that atropine exerted a larger effect on T wave responses to isoproterenol among type B’s, it would support our hypothesis of stronger vagal antagonism in type B’s.

Methods

Subjects

Fifteen healthy Caucasian men aged 18–29 years were recruited through advertisements and gave informed consent using human subjects committee–approved procedures. Any organic or functional disorder was excluded by complete medical history, physical examination, standard electrocardiogram, chest x-ray, urinalysis, hematological analysis, and blood chemical analysis including plasma electrolytes, proteins, blood urea nitrogen, uric acid, glucose, lipids, and enzymes.

Procedures

Subjects were instructed to refrain from any intake of alcohol, caffeine, nicotine, or other drugs and to avoid heavy exercise from 6 PM on the day before the study. All subjects participated in the experiment on two different days. The atropine pretreatment was administered before isoproterenol infusion on one day, and the placebo treatment (equal volume of 5% dextrose solution) was administered on the other. Treatment order was counterbalanced, and both subjects and laboratory staff were blind to the pretreatment condition. All experiments began at 1 PM after the subjects had consumed a light lunch. During the study, the subjects lay supine in a quiet, temperature-controlled (22°C) room.

A Teflon catheter was placed into the right median cubital vein, and the intravenous line was kept open with a slow drip of 5% dextrose solution. Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate (HR) were measured using a Dinamap Vital Signs Monitor (Critikon model 845 XT, Tampa, Fla.). Forearm blood flow (FBF) was measured from the left forearm using the mercury strain-gauge method of venous occlusion plethysmography. These measurements were recorded concurrently at approximately 1-minute intervals throughout the experiment. The subject’s electrocardiogram (lead II) was continuously recorded throughout the experiment (model 7D polygraph, Grass Medical Instruments, Quincy, Mass.). After a 15-minute period of calibration and recovery from catheterization, baseline measurements were taken for 20 minutes.

After baseline measurements, either 1.2 mg of atropine sulfate (Elkins-Sinn, Cherry Hill, N.J.) or the same volume of 5% dextrose was administered intravenously through the venous line. Laboratory staff and subjects were blind as to whether atropine or dextrose was in the syringe. On the atropine day, the total dose of 1.2 mg was given as follows: an initial test dose of 0.2 mg was given, followed 2 minutes later by the remaining 1.0 mg. A similar smaller test dose followed by the full dose of placebo was given on the placebo day. After 8 minutes of physiological recording, the intravenous infusion of isoproterenol hydrochloride (Elkins-Sinn) was begun, initially at a dose of 0.01 μg/kg/min for 5 minutes, then at a dose of 0.02 μg/kg/min for 5 minutes. Measurements continued for 20 minutes after the end of infusion to evaluate recovery from the effects of isoproterenol.

Samples of venous blood were collected at the end of the baseline, atropine, isoproterenol, and recovery periods. Samples were immediately cold-centrifuged (3,000 rpm, 10 minutes), and the plasma was frozen at −20°C until assays were performed.

Assay Procedures

Plasma levels of norepinephrine and epinephrine were determined with high-performance liquid chromatography with electrochemical detection after batch alumina extraction. Plasma cortisol was assayed by standard radioimmunoassay. Cyclic AMP (cAMP) was measured by radioimmunoassay with a commercial kit (Amersham).

Assessment of Type A/B

All subjects were assessed as type A, B, or X by both the structured interview technique and the Jenkins Activity Survey (JAS) on the day of medical screening. A subject was categorized as type A when his JAS A/B score was more than one half SD above the mean for our population (JAS >12) and when he was rated by two independent auditors as a type A1 or A2 on the structured interview. Subjects were categorized as type B when the JAS A/B score was one half SD below the population mean (JAS A/B <5) and when they were rated as B1 or B2 on the structured interview. Subjects whose scores did not meet these stringent criteria were rated type X and omitted from the analyses comparing A’s and B’s but included in analyses of atropine effects in all subjects. By these procedures, six subjects were classified as type A, six as type B, and three as type X.

Subjects also completed a variety of questionnaires that assess aspects of type A behavior related to an increased risk of coronary disease comprising Cook-Medley Hostility Scale, Spielberger’s State-Trait Personality Inventory and Anger Expression Scale, Crowne-Marlowe Social Desirability Scale, and Buss-Durkee Hostility Inventory. As shown in Table 1, there were no differences among the types in age or weight. As expected, however, the type A’s showed higher scores than the type B’s on several of the scales related to the dimension of hostility/anger.

Data Analysis

At approximately 1-minute intervals, the following cardiovascular measures were obtained. T wave amplitude was determined for 10 QRST complexes beginning with the start of each FBF venous occlusion slope, as measured from the midpoint of the isoelectric PQ interval to the peak of the T wave. The average of 10 measurements of T wave amplitude was used as the T
wave amplitude value for that set of cardiovascular measurements (i.e., SBP, DBP, MAP, HR, and FBF). Forearm vascular resistance (FVR) was calculated from MAP divided by FBF (FVR=MAP/FBF). Rate–pressure product (RPP) was calculated as the product of HR and SBP divided by 100.\textsuperscript{35} Subtraction of DBP from SBP gave pulse pressure. The sets of cardiovascular data as described above were averaged to yield values for three baseline periods (B1, B2, B3), two atropine/placebo periods (A1, A2 or P1, P2), two isoproterenol infusion periods (I1, I2), and three recovery periods (R1, R2, R3). The data were analyzed using three-way analysis of variance (ANOVA) with type A/B as a between-groups effect and with treatment condition (atropine/placebo) and period included as repeated-measures effects.

Where ANOVA revealed significant effects, post hoc analyses using paired \( t \) tests were used to evaluate specific period and atropine/placebo effects. The \( t \) test was also used to explore type A/B differences in response to atropine pretreatment after calculation of difference scores that contrasted specific periods within the experiment (for example, I2–A2, I2–P2, R1–A2, etc.). Differences in response to isoproterenol after atropine versus placebo pretreatment were tested using paired \( t \) tests comparing change scores (\( \Delta \)) in the placebo session to change scores (\( \Delta \)) in the atropine session—i.e., [(I2–A2)–(I2–P2)] or [(R1–A2)–(R1–P2)]. Correlational analyses by Pearson's coefficient were done to clarify the bases of the important findings from the primary analyses described above. Values were expressed as mean±SEM, and a probability value of less than 0.05 defined statistical significance.

Although the small sample size raises the question of sampling error, this problem is reduced by using a within-subject design and by using only extreme type A’s and B’s.

**Results**

### Effect of Isoproterenol in All Subjects

With placebo pretreatment, infusion of the two doses (0.01, 0.02 \( \mu g/kg/min \)) of isoproterenol caused significant increases in HR (\( p<0.01 \); Figure 1a). SBP, DBP, and MAP significantly increased after isoproterenol infusion (\( p<0.005 \); Figure 1b). Pulse pressure increased both during (\( p<0.05 \)) and after (\( p<0.001 \)) isoproterenol infusion. The infusion produced an increase in FBF (\( p<0.001 \)) and a decrease in FVR (\( p<0.05 \)). T wave amplitude decreased in dose-dependent fashion from 0.66±0.08 mV to 0.58±0.08 mV (0.01 \( \mu g/kg/min \), \( p<0.005 \)) and 0.46±0.08 mV (0.02 \( \mu g/kg/min \), \( p<0.001 \); Figure 1c). Moreover, the T wave became inverted in two cases during isoproterenol infusion. Plasma norepinephrine levels increased (\( p<0.001 \)) during isoproterenol infusion (Figure 1d), whereas epinephrine levels showed a slight but significant decrease (\( p<0.05 \)) followed by a rebound increase (\( p<0.05 \)) during recovery. Plasma cortisol was not changed by isoproterenol.

### Differential Effect of Isoproterenol in Type A and Type B

The ANOVA revealed a significant difference in T wave response to isoproterenol in the type A and type B groups after placebo pretreatment (type A/B times period interaction, \( p<0.05 \)). As shown in Figure 2, T wave amplitude decreased more during isoproterenol infusion in type A’s than in type B’s, and recovery was also delayed more in type A’s. In addition, both cases of T wave inversion during isoproterenol infusion occurred in type A subjects. However, there were no significant differences between type A’s and B’s in the other cardiovascular or neuroendocrine responses to isoproterenol after placebo pretreatment. These findings replicate those from our earlier study.\textsuperscript{13}

### Effect of Atropine in All Subjects

Low-dose (0.2 mg) atropine did not affect HR, but after the total dose (1.2 mg) of atropine, there was a significant increase in HR both before (\( p<0.001 \)) and after (\( p<0.001 \)) the isoproterenol infusion (Figure 1a). The HR increase caused by isoproterenol infusion was significantly higher after atropine pretreatment (I2–A2=39±3 beats per minute) than after placebo pretreatment (I2–P2=20±2 beats per minute, \( p<0.001 \)), documenting an accentuated antagonism of the HR response to isoproterenol by the vagus. Atropine (1.2 mg) also caused a significant increase in FBF (\( p<0.01 \)) and a decrease in FVR (\( p<0.05 \)) but did not affect the FBF and FVR responses to isoproterenol.

As shown in Figure 1b, atropine alone induced a slight but significant rise in DBP and MAP compared with placebo (\( p<0.05 \)). Compared with placebo, atropine pretreatment also significantly reduced SBP (\( p<0.001 \)), DBP (\( p<0.01 \), and MAP (\( p<0.001 \)) during

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**Table 1. Subject Characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>All subjects (n=15)</th>
<th>Type A (n=6)</th>
<th>Type B (n=6)</th>
<th>Type X (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>21.6±0.6</td>
<td>22.2±1.0</td>
<td>21.8±0.9</td>
<td>20.0±0.6</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78.6±2.1</td>
<td>80.3±4.7</td>
<td>77.4±1.9</td>
<td>77.6±4.0</td>
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<tr>
<td>JAS A/B</td>
<td>7.6±1.6</td>
<td>14.5±1.1†</td>
<td>2.8±0.4</td>
<td>3.3±0.9</td>
</tr>
<tr>
<td>SI</td>
<td>1.3±0.3</td>
<td>2.6±0.1†</td>
<td>0.1±0.1</td>
<td>1.3±0.3*</td>
</tr>
<tr>
<td>Hostility</td>
<td>14.6±1.7</td>
<td>19.7±2.7*</td>
<td>10.8±2.1</td>
<td>12.0±0.0</td>
</tr>
<tr>
<td>Cynicism</td>
<td>3.9±0.6</td>
<td>5.5±0.7*</td>
<td>2.5±0.7</td>
<td>3.3±0.9</td>
</tr>
<tr>
<td>Anger</td>
<td>18.5±1.4</td>
<td>22.3±2.1*</td>
<td>14.7±1.2</td>
<td>18.3±2.3</td>
</tr>
<tr>
<td>BD total</td>
<td>21.3±2.0</td>
<td>26.7±2.9†</td>
<td>14.2±1.6</td>
<td>24.7±2.0†</td>
</tr>
</tbody>
</table>

All data are expressed as mean±SEM: JAS A/B, type A score from Jenkins Activity Survey\textsuperscript{23}; SI, assessments based on structured interview\textsuperscript{24}; Hostility and Cynicism, from Cook-Medley Hostility Scale\textsuperscript{25}; Anger, Spielberger State-Trait Personality Inventory\textsuperscript{26}; BD Total, total score from Buss-Durkee Inventory that indicates intensity of hostility.\textsuperscript{30}  

*\( p<0.05 \), †\( p<0.01 \), ‡\( p<0.001 \); significant difference from type B’s.
the infusion of isoproterenol but only at the higher dose (I2). Atropine pretreatment decreased pulse pressure both during \(p<0.01\) and after \(p<0.001\) isoproterenol, effects that were significantly different \(p<0.01\) from responses after placebo.

T wave amplitude was slightly but significantly decreased by atropine alone \(p<0.01;\) Figure 1c). Atro-

FIGURE 2. Graph shows that isoproterenol infusion after placebo pretreatment reduces T wave amplitude (percent change from baseline, mean±SEM) more in type A than in type B subjects \(n=6\) per group. Periods: B1, B2, B3, baseline; P1, P2, placebo administration; I1, isoproterenol infusion \(0.01 \mu g/kg/min\); I2, isoproterenol infusion \(0.02 \mu g/kg/min\). R1, R2, R3, recovery. ANOVA reveals significant type A/B by period interaction \(p<0.05\).

Pine reduced T wave amplitude significantly during the 0.01-\(\mu g/kg/min\) isoproterenol infusion \(p<0.01\) and throughout the recovery periods. The atropine effect was especially pronounced in the R1 period, when T wave amplitude continued to decrease after atropine \(0.30±0.07\) mV, but had already begun to recover on the placebo day \(0.54±0.09\) mV, \(p<0.001\). The T wave decrease from the level after full atropinization to the first recovery period \(R1−A2=−0.24±0.04\) mV was larger \(p<0.05\) than that observed on the placebo day \(R1−P2=−0.13±0.02\) mV. ANOVA documented a significant drug pretreatment times period interaction for T wave amplitude \(p<0.001\). Thus, accentuated vagal antagonism was demonstrated in the T wave response to isoproterenol infusion. T wave inversions during isoproterenol infusion were again observed in the same two subjects who showed inversions on the placebo day, as well as in two additional subjects—one type A and one type B.

As shown in Figure 1d, atropine treatment caused a fall in plasma norepinephrine and significantly attenuated the norepinephrine increase to isoproterenol in comparison with placebo treatment. Atropine had no effect on either levels or isoproterenol responses of plasma epinephrine or plasma cortisol. cAMP increased after isoproterenol infusion \(p<0.001\), but this increase did not differ as a function of type A/B group or atropine/placebo pretreatment condition.

Regression analysis revealed no relations between atro-

Differential Effects of Atropine Versus Placebo on Responses of Type A and Type B Subjects to Isoproterenol

As shown in Figure 1, atropine pretreatment significantly enhanced the heart rate response to isoproterenol despite the higher starting HR caused by atropinization alone. ANOVA failed, however, to document a
Recent research indicates that type B's are more pronounced in their accentuation of the vagal antagonism of heart rate response to isoproterenol compared to type A's. This pattern of effects suggests that greater vagal antagonism of β-adrenergic effects on the T wave is present in type B subjects.

The effects of atropine pretreatment to enhance blood pressure and pulse pressure responses to isoproterenol were also greater in type B subjects. As shown in Figure 4, the SBP fall during high-dose isoproterenol (I2) infusion was larger in type B's than in type A's. Particularly dramatic is a fall in pulse pressure during I2 on the atropine day that is present only in type B subjects.

Relation of Other Psychological Traits to Accentuated Antagonism

The subjects in this study were selected to be extreme type A or type B subjects, and the findings just described indicate that accentuated vagal antagonism of T wave and blood pressure (SBP and pulse pressure) responses to isoproterenol are more pronounced in type B's. Recent research indicates that it is only those aspects of type A behavior related to hostility and anger that are pathogenic\(^{26}\); therefore, we felt it worthwhile to explore the relations between the various hostility/anger scales assessed in these subjects and a measure of the atropine enhancement of cardiovascular responses to isoproterenol.

To accomplish this goal, we computed Pearson correlation coefficients between the hostility/anger measures and change scores representing the difference in cardiovascular responses to isoproterenol infusion observed after atropine compared with placebo pretreatment. A large negative difference represents a large atropine enhancement of the response to isoproterenol and thus implies a larger vagal antagonism of the response when the pretreatment was placebo. Therefore, positive correlations between hostility measures and this difference measure would suggest that hostility is associated with weaker vagal antagonism.

As shown in Table 2, this exploratory analysis revealed several significant correlations between hostility/anger measures and atropine effects on cardiovascular reactivity to isoproterenol, and all were in the predicted positive direction except for the Crowne-Marlowe Social Desirability score, in which negative correlations are predicted. Thus, smaller atropine enhancement of the T wave decrease during R1 after isoproterenol was correlated with higher scores on the Buss-Durkee irritability \((r=0.61)\), verbal assault \((r=0.56)\), and total \((r=0.55)\) scores and higher scores on the following components rated during the structured interview: total hostility \((r=0.54)\), intensity of hostility \((r=0.53)\), and...
hostile attitude toward interviewer ($r=0.58$). Similar positive correlations indicated that higher scores on hostility/anger measures were associated with weaker atropine enhancement of several other cardiovascular responses to isoproterenol during both I2 and R1 periods (see Table 2).

Given the exploratory nature of this analysis and that many correlations were computed, these results must be interpreted with some caution. Nevertheless, of 120 correlations that were run, 36 were significant at the 0.10 level, and all were in the predicted direction. As with our earlier finding that hostility/anger measures correlate with slower T wave recovery to isoproterenol infusion, this pattern of correlations suggests that, in addition to type A behavior, high levels of hostility and anger are also associated with less pronounced vagal antagonism of sympathetic effects on cardiovascular function.

**Discussion**

The major finding of this study is that prior muscarinic cholinergic blockade with atropine causes a greater enhancement (relative to placebo pretreatment) of both T wave attenuation and SBP and pulse pressure decreases resulting from isoproterenol infusion in young type B men than it does in their type A counterparts. In the placebo condition of this study, we have replicated our earlier finding of larger and more prolonged T wave attenuation in response to isoproterenol infusions among type A compared with type B men. Thus, this phenomenon has been confirmed in an independent sample.

A second study, which used the dive reflex as a means of eliciting increased vagal tone, also supported our hypothesis that type B's have more robust vagal responsivity. In the present study, we have now added to the evidence supporting this hypothesis by showing that muscarinic blockade leads to enhanced T wave attenuation and blood pressure falls due to isoproterenol infusions in type B but not type A men. Post hoc analyses of other psychological data obtained in the present study also suggest that atropine’s enhancement of cardiovascular responsivity to isoproterenol infusions is also stronger in those with lower levels of hostility and anger, factors that other research indicates are the aspects of type A behavior that account for increased coronary risk.

The present findings indicate that accentuated vagal antagonism does occur for heart rate increases as well as T wave and blood pressure responses occurring in
response to isoproterenol infusion, because all effects were made larger when vagal influences were removed via prior atropinization. Because the atropine effects on T wave and blood pressure responsivity were stronger among type B's (especially those who are nonhostile), the present findings provide strong support for our hypothesis that, at least for T wave and blood pressure responses, accentuated vagal antagonism of sympathetic influences on the cardiovascular system under normal conditions is more robust in nonhostile type B men than it is in hostile type A men.

Our findings are in accord with other research documenting parasympathetic-sympathetic interactions with respect to myocardial function. Morady et al. reported, for example, that cholinergic blockade by atropine shortens ventricular refractoriness regardless of background sympathetic activity, but that the magnitude of atropine's effect on ventricular refractoriness is greater in the setting of β-adrenergic stimulation via infusion of 0.05 μg/kg/min isoproterenol than it is during β-blockade. With intravenous isoproterenol infusions at a four-fold to fivefold higher dose than in the present study, Biberman et al. observed during the first minute of infusion a decrease in T wave amplitude followed by a return to control levels after 2–3 minutes. Our finding in the present study that this recovery is slowed by prior atropinization (see Figure 1c) suggests that this later-phase recovery of T wave amplitude to control levels is mediated by accentuated vagal antagonism.

It is unclear at present why this accentuated parasympathetic antagonism of sympathetic effects is more pronounced in nonhostile type B subjects for T wave and blood pressure responses but not for the HR responses to isoproterenol infusion. Differential activation of vagal input to the sinus node versus ventricular myocardium could be responsible. Thus, Morady et al. observed accentuated antagonism between β-adrenergic and cholinergic effects on ventricular refractoriness but not sinus cycle length and concluded that “the interaction between sympathetic and intrinsic cholinergic activity in the sinus node may differ from the interaction that occurs in ventricular myocardium” (Reference 36, p 296). Despite the T wave recovery during the later phase of isoproterenol infusion in the Biberman et al. study, the RR interval remained just as shortened as it had been during the early phase when T wave amplitude had been decreased. Such a divergence of HR and T wave responses could be explained by a differential vagal antagonism of sympathetic effects at the atrial versus the ventricular levels.

A recent study demonstrating differential effects of right and left vagus nerves on atrial versus ventricular functions does suggest at least one possible anatomic substrate whereby such differential activation of parasympathetic components might occur, perhaps to antagonize sympathetic effects on ventricular inotropic but not atrial chronotropic responses. This differential activation of right as contrasted to left vagal influences on the heart in type B's could underlie their accentuated vagal antagonism of T wave but not heart rate responses to isoproterenol. Although speculative and hard to demonstrate in humans, it would be possible in animal studies to document whether stimulation of right and left vagi has differential effects on chronotropic and T wave responses to isoproterenol infusions.

Besides accentuated vagal antagonism, the differential T wave effects in type A and type B men in this study could involve HR effects on T wave amplitude and/or possible induction of myocardial ischemia by the atropine/isoproterenol combination. Overdrive right atrial pacing in both placebo and atropine pretreatment conditions would have enabled us to discount the HR explanation but was not done in this study. However, other research has failed to find any T wave change associated with increased HR caused by right atrial pacing. This explanation becomes even more unlikely in light of the observation that even with overdrive atrial pacing at the rate of 175 beats per minute, catecholamine infusions still produce a progressive and dose-dependent decrease in T wave amplitude.

Because all of our subjects were healthy young men, we also consider it unlikely that induction of myocardial ischemia is responsible for the T wave effects we observed. Nevertheless, it is possible that even with normal major coronary arteries, isoproterenol could have induced subendocardial ischemia. However, much larger doses of isoproterenol (e.g., 0.25 μg/kg/min) than we used have not been found to produce impairment in coronary flow reserve. Although isoproterenol doses in the range we used have been found to induce myocardial ischemia in the setting of latent coronary stenosis, with normal coronary arteries, no ischemic ST changes were detected in either the surface or endocardial ECG in conscious dogs. Nevertheless, it remains a possibility that induction of myocardial ischemia in the microcirculation could have played some role in our T wave findings.

The effects of atropine to cause blood pressure and pulse pressure decreases during infusion of 0.02 μg/kg/min of isoproterenol is in agreement with similar observations by others, but neither they nor we have a ready explanation for these effects. Our finding that the atropine effect on the blood pressure responses to isoproterenol is significantly correlated with the atropine effect on T wave but not heart rate responses suggests the possibility that the blood pressure effects reflect inotropic rather than chronotropic effects, but unmeasured vascular effects of parasympathetic-sympathetic interactions could also be involved. Whatever the ultimate explanation, it is clear in Figure 4 that accentuated parasympathetic antagonism does occur with respect to blood pressure responses to β-adrenergic stimulation, and that such antagonism is more pronounced in nonhostile type B men than in hostile type A men.

Whatever the ultimate explanation for the underlying basis of the weaker parasympathetic antagonism of sympathetic effects on cardiovascular function that we observed among hostile type A men in the present study, such deficient parasympathetic responses could play a role in the pathogenesis of coronary disease and its clinical outcomes. Conversely, a more robust parasympathetic antagonism of sympathetic effects on the cardiovascular system, which the present study suggests is present among nonhostile type B's, might contribute to a reduction in coronary risk. Several observations support this hypothesis. Lower HR reactivity to stress was associated with diminished coronary atherosclerosis in monkeys fed an atherogenic diet and subjected to chronic stress. Lower HR as a result of sinoaortic
derivation was also associated with less severe coronary atherosclerosis in monkeys fed an atherogenic diet in another study. A lower casual HR was a strong predictor of lower coronary risk in the Seven Countries study. Although factors other than increased vagal tone (e.g., decreased sympathetic tone or reactivity) might underlie these relations between lower HR and coronary disease, they are at least consistent with the vagal protection hypothesis. Prospective studies assessing vagal tone in healthy persons will be required to document the pathogenic/protective role of weak/strong vagal tone in coronary disease.

More direct evidence for a protective role of vagal influences on the heart comes from clinical studies of coronary patients. In a prospective study of 808 post-MI patients, vagally mediated HR variability was the strongest single predictor of mortality, especially that attributed to sudden death. Moreover, experimental studies in dogs have documented protective effects of stronger vagal tone against ischemia-induced ventricular fibrillation after experimental myocardial infarctions.

In summary, β-adrenergic stimulation after muscarinic blockade reduced T wave amplitude more than β-adrenergic stimulation alone, and this effect was more pronounced in nonhostile type B men than in hostile type A men. Similar effects were observed for blood pressure but not HR responses to β-adrenergic stimulation. These findings are consistent with our hypothesis that accentuated vagal antagonism of sympathetic effects on the cardiovascular system is more robust in nonhostile type B men than in their hostile type A counterparts. There is both clinical and experimental evidence that deficient vagal tone may be playing an important role in both the pathogenesis and course of coronary heart disease. Thus, differences in vagal antagonism of sympathetic effects on the cardiovascular system may account for the increased coronary risk observed among hostile type A men and the reduced risk associated with nonhostile type B behavior.

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