We studied the acute effect of ethanol on the hypotensive response to clonidine in conscious spontaneously hypertensive rats. When administered during the hypotensive response to clonidine, ethanol not only reversed the response but also caused a slight but significant short-lived pressor effect. The maximal hypotensive effect of graded doses of clonidine was significantly ($p<0.05$) attenuated by a dose of 1 g/kg ethanol, which resulted in a peak blood ethanol concentration of $54.2\pm6.3$ mg/dl. The data strongly suggest the adverse effect of ethanol on the hypotensive response to clonidine is ethanol mediated and that their antagonistic interaction is both reversible and reproducible because: 1) an equal volume of saline had no effect on the hemodynamic responses to clonidine and 2) crossing over ethanol and saline treatments on days 2 and 3, which allowed longitudinal comparisons, showed that the effect of ethanol was similar both in naive rats (day 1) and in rats that were pre-exposed to ethanol (day 3). Whether this negative effect of ethanol also involves other antihypertensive agents that do not act primarily by a central nervous system mechanism was investigated. The same dose of ethanol had little or no effect on the hypotensive response to hydralazine, suggesting the negative effect of ethanol is selective to centrally acting antihypertensive agents. Although the mechanism by which ethanol reverses the hypotensive effect of clonidine is not known, it is possible that it involves an ethanol-evoked increase in plasma catecholamine levels, which are known to be decreased by clonidine. That ethanol did not reverse the hypotensive effect of hydralazine, which is also known to be associated with increased plasma catecholamine levels, supports this notion. The findings of the present study may explain, at least in part, why regular use of alcohol is associated with an inadequate control of blood pressure in treated hypertensive patients who are regular consumers of alcohol. (Hypertension 1989;14:531–541)

A substantial proportion of treated hypertensive patients are frequent to heavy users of alcohol,¹–³ and in these subjects regular alcohol drinking is associated with inadequate blood pressure control.⁴–⁶ Poor patient compliance with therapy has been blamed for this problem.⁴ However, recent evidence from epidemiological studies⁷ and from controlled crossover studies⁸ has strongly suggested a direct link between alcohol intake and inadequate control of blood pressure of treated hypertensive patients who reported greater than 90% compliance with their therapy but continued to use alcohol.

Many studies have shown that alcohol has a pressor effect both in normotensive and in hypertensive persons.⁸–¹¹ This effect, however, requires at least days to develop,¹⁰ and it is not known whether it contributes to the negative effect of alcohol intake on antihypertensive therapy in treated hypertensive patients. Puddey et al⁶ have shown that reduction of alcohol intake in treated hypertensive patients resulted in a significant lowering of blood pressure during a 6-week trial period. This conclusion was based on the average response of all volunteers who received monotherapy or combined antihypertensive therapy of different types and regimens.⁶ It is not known, therefore, whether the negative effect of alcohol will be more or less noticeable with different types of antihypertensive agents.

One group of antihypertensive drugs that may be adversely influenced by alcohol intake is the cen-
trally acting drugs (e.g., clonidine) because of their directionally opposite hemodynamic and electrophysiological effects. For example, clonidine and guanabenz lower blood pressure and heart rate mainly via a central mechanism of action that involves a decrease in central sympathetic tone.\textsuperscript{12–14} On the other hand, even though alcohol does not change blood pressure after its acute administration,\textsuperscript{15–17} it increases heart rate,\textsuperscript{16–18} sympathetic efferent discharge,\textsuperscript{19} and circulating levels of catecholamines.\textsuperscript{20} Also, both alcohol and clonidine influence differently the baroreceptor reflexes. Whereas clonidine sensitizes the baroreceptor heart rate response,\textsuperscript{21,22} and this effect may contribute to its antihypertensive effect,\textsuperscript{23} alcohol impairs this reflex response.\textsuperscript{15–17,19}

The present study investigates the possibility that ethanol has an adverse effect on the hypertensive response to clonidine in the conscious spontaneously hypertensive rat (SHR). Whether the acute–acute interaction between ethanol and clonidine was reversible and reproducible and whether it involved a pressor effect of ethanol were investigated. Also, the effect of ethanol on the hypertensive response to hydralazine was investigated to determine whether the negative effect of ethanol is specific to centrally acting antihypertensive drugs. Some of these data have been published previously in an abstract form.\textsuperscript{24}

**Materials and Methods**

Male SHR (Charles River Breeding Labs., Research Triangle Park, North Carolina) weighing 300–350 g were used in the study. The method described in our previous study\textsuperscript{16} was used for instrumentation of the rats for measurement of blood pressure and heart rate and for intravenous administration of drugs. The rats were anesthetized by methohexital (Brevital, Eli Lilly and Co., Indianapolis, Indiana; 50 mg/kg i.p). Catheters (PE50) were placed in the abdominal aorta and vena cava via the left femoral artery and vein, respectively, for measurement of blood pressure and intravenous administration of drugs. The catheters were pretreated for 24 hours with tridodecylmethyl ammonium chloride (TDMAC) heparin complex (Poly-science, Warrington, Pennsylvania). The catheters were tunneled subcutaneously to the back of the neck, and the distal ends were plugged by stainless steel pins after they were flushed with heparin. Incisions were closed by surgical clips and swabbed by povidone-iodine solution (Norton Co., Rockford, Illinois), and the rats received penicillin G (20,000 units i.m.) postoperatively. Each rat was then placed in a separate cage and was allowed at least 1 full day for recovery from anesthesia and acclimatization to the environment. On the day of the experiment, the arterial catheter was connected through an extension tubing to a Gould-Statham (Oxnard, California) pressure transducer and blood pressure was displayed on a Grass polygraph (mod-
included. In these rats, phenylephrine injections were omitted, the rats received 10 μg/kg clonidine, and 10 minutes later one group received ethanol (1 g/kg) and the other received equal volume of saline. Whether the adverse effect of ethanol on the hypotensive response to clonidine was reversible and reproducible was investigated by crossing over ethanol and saline treatments on days 2 and 3 as outlined in Table 1.

Occasionally, administration of ethanol and saline treatments was randomized on days 2 and 3; this had no effect on the responses.

**Ethanol–hydralazine interaction.** This experiment examined the effect of ethanol on the hypotensive response to hydralazine, an antihypertensive agent that does not act primarily by a central nervous system mechanism. In two groups of rats (n=6 each), hydralazine (0.5 mg/kg) was administered intravenously, and 10 minutes later either ethanol (1 g/kg) or an equal volume of saline was injected. Ethanol and saline treatments were crossed over on day 2 as was the case in the clonidine experiment.

**Effect of ethanol on baseline blood pressure.** In this experiment, we investigated the effect of the same dose of ethanol on baseline blood pressure and heart rate to determine whether the antagonistic interaction between ethanol and clonidine involved a pressor effect for ethanol. A group of five rats received ethanol, and another group (n=4) received equal volume of saline and served as control. In a third group of rats (n=5), blood ethanol concentration was measured at 5, 10, 15, and 30 minutes after ethanol administration by the method of Bonnichsen and Lundgren26; a 0.2 ml blood sample was drawn through the arterial catheter at the specified time intervals.

### Table 1. Crossover Schedule for Ethanol and Saline Treatments

<table>
<thead>
<tr>
<th>Group</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>Ethanol</td>
<td>Saline</td>
<td>Ethanol</td>
</tr>
<tr>
<td>Group 2</td>
<td>Saline</td>
<td>Ethanol</td>
<td>Saline</td>
</tr>
</tbody>
</table>

Table 2. Baseline Mean Arterial Pressure and Heart Rate

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>MAP (mm Hg) Day 1</th>
<th>MAP (mm Hg) Day 2</th>
<th>HR (beats/min) Day 1</th>
<th>HR (beats/min) Day 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonidine (3 μg/kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1 (saline)</td>
<td>6</td>
<td>147.1±7.3</td>
<td>160.5±8.9</td>
<td>341.2±12.6</td>
<td>330.0±23.5</td>
</tr>
<tr>
<td>Group 2 (EtOH)</td>
<td>5</td>
<td>145.1±2.8</td>
<td>168.8±6.8*</td>
<td>328.6±8.1</td>
<td>316.0±12.2</td>
</tr>
<tr>
<td>Clonidine (10 μg/kg)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1 (saline)</td>
<td>6</td>
<td>157.6±6.1</td>
<td>166.5±5.4</td>
<td>303.2±14.1</td>
<td>324.2±11.6</td>
</tr>
<tr>
<td>Group 2 (EtOH)</td>
<td>7</td>
<td>159.4±5.3</td>
<td>155.2±7.7</td>
<td>310.9±7.8</td>
<td>343.0±8.1</td>
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<tr>
<td>Group 1 (saline)†</td>
<td>6</td>
<td>190.3±2.8</td>
<td>187.6±6.5</td>
<td>410.6±17.3</td>
<td>432.0±16.1</td>
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<tr>
<td>Group 2 (EtOH)†</td>
<td>5</td>
<td>199.6±9.2</td>
<td>178.5±13.7</td>
<td>440.0±13.6</td>
<td>433.8±28.8</td>
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<tr>
<td>Clonidine (30 μg/kg)</td>
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<tr>
<td>Group 1 (saline)</td>
<td>4</td>
<td>162.8±1.0</td>
<td>170.4±9.9</td>
<td>317.5±7.8</td>
<td>373.3±37.6</td>
</tr>
<tr>
<td>Group 2 (EtOH)</td>
<td>5</td>
<td>164.2±11.1</td>
<td>149.1±7.1</td>
<td>335.0±15.0</td>
<td>356.3±18.2</td>
</tr>
<tr>
<td>Hydralazine (0.5 mg/kg)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1 (saline)†</td>
<td>6</td>
<td>181.9±5.2</td>
<td>163.4±8.9</td>
<td>441.3±19.6</td>
<td>433.0±23.8</td>
</tr>
<tr>
<td>Group 2 (EtOH)†</td>
<td>6</td>
<td>183.9±3.4</td>
<td>164.3±4.6</td>
<td>425.0±25.2</td>
<td>438.8±16.4</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Saline and ethanol (EtOH) treatments were crossed over on day 2. MAP, main arterial pressure; HR, heart rate.

* p<0.05 compared with day 1.
† In these rats, phenylephrine injections that were used in other rats to measure baroreceptor reflex control of heart rate were omitted.

### Statistical Analysis

Values presented are the mean±SEM. Student’s t test was used in the analysis of paired and unpaired means. The time-course data were analyzed by repeated-measures analysis of variance (ANOVA) to test for the significance of interaction between ethanol, as compared with saline, and the antihypertensive agent (clonidine or hydralazine). A simple main effects analysis was then performed to test for statistical significance at the different time intervals that followed ethanol or saline administration. These analyses were performed using the Crunch Statistical Package version 3 (Crunch Software Corporation, Oakland, California). A p<0.05 was taken as a measure of significance. Baroreceptor reflex slopes were estimated by linear regression analysis for individual rats.

### Results

**Ethanol–Clonidine Interaction**

Baseline blood pressure and heart rate values were similar in all groups that received different doses of clonidine and subsequently received ethanol or saline (Table 2). Also, there were no significant differences between the values of both variables for the same group on days 1 and 2 of the experiment except for one group that showed a significantly higher blood pressure value on day 2 compared with day 1 (Table 2). This difference had no significant effect on hemodynamic responses to...
clonidine or on responses to subsequent ethanol or saline treatments.

Clonidine produced a biphasic effect on blood pressure; a brief (less than 1 minute) pressor phase that was followed by a longer lasting depressor phase (Figure 1). The heart rate did not show a consistent response, but in most cases, it showed a decrease that coincided with the pressor phase. Both the pressor and depressor effects of clonidine were dose related. Administration of saline (0.13 ml/100 g) during the hypotensive response to different doses of clonidine had no significant effect on blood pressure or heart rate (Figures 1 and 2). Conversely, administration of a 1 g/kg dose of ethanol (same volume as that of saline) not only caused an immediate reversal of the hypotensive response to clonidine but also produced a brief overshoot in blood pressure (Figures 1 and 2). The reversal by ethanol of the hypotensive effect of clonidine and the overshoot in blood pressure were obtained with all doses of clonidine (3, 10, or 30 μg/kg) and was seen on days 1 and 2 of the study (Figure 2). A similar effect for ethanol was also obtained on day 3 (data not shown). Thus, ethanol-clonidine interaction was both reversible and reproducible.

Figure 2 shows the acute effects of ethanol (1 g/kg), or equal volume of saline, on the time course of the hemodynamic responses to clonidine (10 or 30 μg/kg). Ethanol and saline were administered 10 minutes after, but during the depressor effect of, clonidine to the treatment and control groups, respec-
tively, on day 1. On day 2, ethanol and saline treatments were crossed over while the dose of clonidine (10 or 30 \( \mu g/kg \)) remained the same. A repeated-measures ANOVA of the time course of the hemodynamic response to clonidine after ethanol or saline administration indicated that ethanol inhibited the depressor effect of clonidine (Figure 2). A simple main effects analysis demonstrated that ethanol significantly \((p<0.01)\) attenuated the depressor effect of clonidine (10 \( \mu g/kg \)) at 2 minutes after its administration (i.e., at 12 minutes after clonidine administration) on day 1 as shown in Figure 2 (upper panel, left). Similarly, ethanol significantly \((p<0.01)\) attenuated the depressor response of the same dose of clonidine on day 2 at 2, 5, and 15 minutes after its administration (Figure 2; upper panel, right). Ethanol also significantly \((p<0.01)\) attenuated the depressor effect of the 30 \( \mu g/kg \) dose of clonidine at 2 and 5 minutes after its administration on both day 1 (Figure 2; lower panel, left) and day 2 (Figure 2; lower panel, right). Furthermore, comparison of the results of the interaction on days 1 and 2 for both doses of clonidine and with crossover ethanol and saline treatments demonstrated that: 1) the response to clonidine in the saline group on day 2 was very similar to that on day 1 indicating that the adverse effect of ethanol was reversible, and 2) the adverse effect of ethanol on the depressor response to clonidine was qualitatively very similar on days 1 and 2 indicating that the interaction was reproducible.

To investigate the acute effects of ethanol (1 g/kg) on peak depressor responses to clonidine, we compared the maximal decreases in blood pressure evoked by clonidine (3, 10, or 30 \( \mu g/kg \)) before and after ethanol or equal volume of saline administration; these values were taken regardless of the time of occurrence during the course of the experiment. As shown in Figure 3 (upper panel), there were no significant differences between the dose-related depressor responses to clonidine in the treatment (ethanol) and control (saline) groups before ethanol or saline administration. Although a repeated-measures ANOVA showed no statistical interaction between the levels of the dose of clonidine and before treatment and after treatment values in the saline and ethanol groups, the treatment main effect analysis indicated that ethanol significantly \((p<0.05)\) attenuated the depressor response to all three doses of clonidine. The significant attenuation by ethanol of the depressor response to clonidine, as indicated by the significant upward shift of the clonidine dose-response curve (Figure 3; lower panel) cannot be accounted for by volume of injectate or time effect since saline had no effect on the response (Figure 3; middle panel). These findings show that at any clonidine dose the maximal depressor response to clonidine was inhibited approximately 50\% by an acute dose of ethanol (1 g/kg); for example, the maximal depressor response to a 10 \( \mu g/kg \) dose of clonidine was 30 and 15 mm Hg before and after ethanol, respectively (Figure 3; lower panel). Also, a similar finding was obtained on day 2 of the experiment when ethanol and saline treatments were crossed over (see Figure 6).

**Baroreceptor Reflex Control of Heart Rate**

The effect of clonidine (10 \( \mu g/kg \)) on the baroreceptor reflex control of heart rate of conscious SHR is shown in Figure 4. In control rats, which received saline during the hypotensive effect of clonidine, the baroreceptor heart rate response was significantly \((p<0.05)\) augmented (Figure 4); baroreceptor reflex slopes were \(-1.1\pm0.21\) and \(-2.37\pm0.68\) beats/min/mm Hg before and after clonidine (10 \( \mu g/kg \)), respectively. A similar augmentation of the baroreceptor heart rate response was also seen after the 30 \( \mu g/kg \) clonidine dose; clonidine increased baroreceptor reflex slope of saline-treated group from \(-1.18\pm0.53\) to \(-2.12\pm0.48\) beats/min/mm Hg. The 3 \( \mu g/kg \) dose of clonidine had little effect on baroreceptor reflex slopes (data not shown). This augmentatory action of clonidine on the baroreceptor heart rate response was obtained during the hypotensive response to clonidine in control rats. On the other hand, in rats that received ethanol (1
Figure 4. Baroreceptor reflex curves depicting increases in mean arterial pressure (mm Hg) evoked by phenylephrine and concomitant reflex decreases in heart rate (beats/min) in conscious spontaneously hypertensive rats. Control rats (top panel) received 10 μg/kg dose clonidine and 10 minutes later received saline (C+S), and experimental group (lower panel) received same dose of clonidine followed by ethanol (1 g/kg; C+E). Baroreceptor heart rate response, which was very similar in the two groups, was substantially augmented by clonidine treatment in control group and not in ethanol group. Number of rats in each group is shown in parentheses. C, clonidine; S, saline; E, ethanol.

Ethanol–Hydralazine Interaction

Baseline blood pressure and heart rate values of the two groups that received hydralazine and subsequently received ethanol or saline were very similar on days 1 and 2 of the experiment (Table 2). However, an intragroup comparison showed that in both groups the blood pressure values were lower on day 2 as compared with day 1 values (Table 2). In these rats, phenylephrine injections, which were used in the clonidine experiment to measure baroreceptor reflex slopes, were omitted. Therefore, for a better comparison between the effects of ethanol on the hypotensive responses to clonidine and hydralazine, two additional groups were included and received clonidine and ethanol or saline while phenylephrine injections were omitted. The baseline blood pressure and heart rate values of these two groups were very similar to those that received hydralazine (Table 2).

Figure 5. Line graphs showing effect of subsequent ethanol (1 g/kg) administration or equal volume of saline on hypotensive response to 0.5 mg/kg hydralazine (top panel) and 10 μg/kg clonidine (lower panel) in conscious spontaneously hypertensive rat. Ethanol or saline was injected 10 minutes after hypotensive agent, and on day 2 treatments were crossed over while hypotensive agent was kept constant. Phenylephrine injections were omitted in these experiments (compare with data presented in Figure 2). Number of rats in each group is shown in parentheses. *Indicates p<0.05 compared with after-saline values by analysis of variance. Note that effect of ethanol on hypotensive effect of hydralazine seen on day 1 was not reproduced on day 2 (compare with clonidine data and see text for more details).
Hydralazine (0.5 mg/kg) caused a lowering in blood pressure (Figure 5) that was associated with an increase in heart rate (data not shown). The depressor response persisted for the 45-minute duration of the experiment after showing a peak at 15–20 minutes (Figure 5; upper panel), and only partial recovery was seen 24 hours after hydralazine administration (Table 2). The data presented in Figure 5 (upper panel, left) show that on day 1, the depressor response to hydralazine (0.5 mg/kg) was significantly ($p<0.01$) smaller, as compared with after-saline values, during the first 20 minutes that followed ethanol (1 g/kg) administration; a difference of approximately 25 mm Hg was seen 5 minutes after ethanol administration (Figure 5; upper panel, left). It must be noted, however, that a difference of approximately 15 mm Hg existed between the depressor responses to hydralazine in the two groups at the time of ethanol or saline injection. Taken together, the data presented in Figure 5 (upper panel, left) show that ethanol, when compared with saline, caused a small but statistically significant inhibition in the hydralazine depressor effect. Furthermore, on day 2, when the depressor responses to hydralazine were very similar in the two groups, ethanol (1 g/kg) had no effect whatsoever on the depressor effect of hydralazine (Figure 5; upper panel, right). Thus, the small inhibition by ethanol of the depressor effect of hydralazine seen on day 1 was not reproducible (Figure 5; upper panel). This is in marked contrast to the finding obtained with clonidine since, as shown in Figure 5 (lower panel), ethanol significantly ($p<0.01$) reversed and attenuated the depressor response to clonidine on both day 1 and day 2. A simple main effect analysis showed that ethanol significantly ($p<0.01$) attenuated the depressor effect of clonidine (10 $\mu$g/kg) at 2, 5, 10, 30, and 35 minutes after ethanol administration on day 1 (Figure 5; lower panel, left) and at 2, 5, 10, 15, 20, and 30 minutes on day 2 (Figure 5; lower panel, right). Thus, the adverse interaction between ethanol and clonidine shown in Figure 2 and Figure 5 (lower panel) was similar but more long lasting in the latter experiment; the only difference between the two protocols was the omission of phenylephrine injections in the latter experiment (Figure 5).

Figure 6 shows the peak depressor responses evoked by clonidine (10 $\mu$g/kg; upper panel) and hydralazine (0.5 mg/kg; lower panel) before and after ethanol (1 g/kg) or equal volume of saline on days 1 and 2 of the study. The depressor responses to clonidine or hydralazine before ethanol or saline treatments were very similar. After ethanol administration, the depressor response to clonidine was significantly ($p<0.05$) smaller than that attained after an equal volume of saline on day 1, and when the treatments were crossed over on day 2 (Figure 6; upper panel). In contrast, ethanol administration had no significant effect, as compared with saline, on peak depressor responses to hydralazine on days 1 and 2 of the study (Figure 6; lower panel).

**Acute Hemodynamic Effects of Ethanol**

A dose of 1 g/kg ethanol produced a modest increase in baseline blood pressure of conscious SHR; a peak increase of $12\pm3.6$ mm Hg (baseline level $153.4\pm5.2$ mm Hg; $n=5$) occurred within 2–5 minutes after ethanol administration. However, neither the magnitude nor the duration of the increase in mean arterial pressure that followed ethanol administration was significantly different from that obtained after injection of an equal volume of saline, $5.3\pm4.0$ mm Hg (baseline level $155.0\pm3.8$ mm Hg; $n=4$). Heart rate showed inconsistent changes after ethanol saline injections, and the average change from very similar baseline values ($332\pm5.2$ vs. $335\pm10.4$ beats/min) was not significantly different.

**Blood Ethanol Concentration**

In conscious, freely moving SHR, a dose of 1 g/kg ethanol administered intravenously produced a peak blood ethanol concentration of $54.2\pm6.3$
mg/dl 15 minutes after injection. Blood ethanol levels were also high at 5 and 10 minutes after injection during the rising phase as they approached the peak level attained at 15 minutes. Thirty minutes after the injection, blood ethanol level fell to approximately 50% of its peak concentration.

Discussion

The present study provides evidence to show that ethanol has an adverse effect on the hemodynamic responses to clonidine in conscious, freely moving SHR. This finding, which is the first that we are aware of, may provide a new direction for further studies that deal with the problem of inadequate control of blood pressure of treated hypertensive patients. The unique aspects of the present finding include: 1) the reversal occurred at blood ethanol concentrations comparable with those attained after social drinking, 2) the adverse effect of ethanol on the hemodynamic response to clonidine was both reversible and reproducible, 3) the interaction was obtained in conscious rats, and hence a potential effect of anesthesia was ruled out, and 4) the adverse effect of ethanol is not generalizable since it has a small and nonreproducible effect on the depressor response to hydralazine.

Many investigators (e.g., References 4 and 5) have raised the possibility that poor compliance with drug therapy may have contributed to inadequate blood pressure control in treated hypertensive patients who are regular alcohol drinkers. This notion was challenged by more recent findings5,7 that showed even with a greater than 90% compliance with therapy, regular alcohol intake significantly decreased the responsiveness to antihypertensive therapy. Puddey et al6 suggested that a pressor effect of alcohol is involved in its negative effect on antihypertensive therapy. This conclusion was based on the finding that after reduction of alcohol intake, the blood pressure showed a better response to antihypertensive therapy and that in normotensive11 and in hypertensive persons10 chronic alcohol intake has been shown to have a pressor effect. A similar finding has also been obtained in our laboratory28 and by others29 showing a pressor effect for normotensive rats given ethanol on a long-term basis.

In the present study, ethanol was given on a short-term basis in a dose that has little or no effect on blood pressure of normotensive rats15,16,13 and humans.17,18 However, the dose of ethanol used in the present study was shown in our previous study30 to have a pressor effect in anesthetized SHR. Whether this pressor effect of ethanol could be demonstrated in conscious SHR, thus contributing to its ability to reverse the hypotensive effect of clonidine, was investigated. In the present study, ethanol had a modest pressor effect in conscious SHR. It is possible that this pressor effect of ethanol contributed to the reversal of the hypotensive response to clonidine. It is unlikely, however, that this modest pressor effect played a major role in ethanol–clonidine interaction since the same dose of ethanol had no significant effect on the hypotensive response to hydralazine (Figures 5 and 6).

In view of its cardiodepressant31 and central nervous system depressant effects, it may seem surprising that ethanol can reverse the hypotensive effect of clonidine. However, recent findings from our laboratory strongly suggest directionally opposite hemodynamic and electrophysiological effects for ethanol as compared with the well-documented effects of clonidine. Even in doses that had no significant effect on baseline blood pressure, our own data16,17 and those of others18,20 have shown that ethanol increased baseline heart rate. Child et al31 suggested the positive chronotropic effect of ethanol is mediated by sympathetic overactivity that was sufficient to mask its cardiodepressant effect. Other investigators30 have provided a more direct evidence that showed that ethanol caused a relative increase in plasma epinephrine levels during the ascending phase of the blood ethanol curve in normotensive human volunteers. The most direct evidence that shows ethanol increases central sympathetic tone came from our laboratory.19 Ethanol, in the same dose used in the present study, substantially augmented sympathetic efferent discharge measured from the splanchic (preganglionic) nerve.19 Clonidine, on the other hand, lowers arterial pressure via activation of central α2-adrenergic receptors, which leads to suppression of sympathetic outflow.13 It is highly likely, therefore, that these directionally opposite effects of ethanol and clonidine on central sympathetic tone could account for their antagonistic interaction. This conclusion is strengthened further by the findings from the hydralazine experiment. Hydralazine-evoked hypotension is known to be associated by a reflex increase in sympathetic activity unlike a centrally mediated decrease in sympathetic activity that precedes and contributes to the hypotensive effect of clonidine.12-14 The findings that ethanol reversed (Figure 2) and attenuated (Figure 3) the hypotensive effect of clonidine and had little (day 1) or no effect (day 2) on that of hydralazine (Figures 5 and 6) may suggest that an ethanol-evoked increase in sympathetic activity has been involved in ethanol–clonidine interaction.

It is important, however, to comment on the findings of the hydralazine experiment before a conclusion could be made that ethanol has a differential effect on the depressor responses to clonidine and hydralazine. The possibility must be considered that an overall lack of reversal and attenuation of the depressor effect of hydralazine relates, at least in part, to a greater fall in blood pressure seen with the dose employed. In support of this possibility is the finding that both reversal and attenuation of the depressor effect of clonidine seem to be inversely related to the magnitude of fall in blood pressure. When phenylephrine injections were omitted, the same dose of clonidine produced a greater fall in
blood pressure whose inhibition by ethanol was less than that seen in the presence of phenylephrine (compare Figures 3 and 6). Thus, the data suggest that a greater clonidine-evoked depressor response can, at least partly, circumvent the inhibitory effect of ethanol. It must be remembered, however, that phenylephrine or the volume associated with its injection could have contributed to the inhibitory effect of ethanol as discussed below.

Neither a relatively greater depressor response nor the omission of phenylephrine injections in the hydralazine experiment could explain the absence of the inhibitory effect of ethanol with this antihypertensive agent especially on day 2. At the time of ethanol administration, 10 minutes after clonidine or hydralazine administration, a very similar fall in blood pressure of approximately 40 mm Hg was produced by both drugs; reversal and attenuation of the depressor response were only seen with clonidine (Figure 5, right panel). Further, it was interesting to note that a significant inhibition of the depressor response to hydralazine was obtained during the first 20 minutes after ethanol administration on day 1 that coincided with a greater fall in blood pressure. However, the difference between the after-ethanol and after-saline values may be accounted for, at least partly, by the already existing difference between the depressor responses in the two groups at the time when ethanol or saline was injected (Figure 5; top panel). Nonetheless, even if it is assumed that the inhibition of the hydralazine-evoked depressor response on day 1 is ethanol mediated, it must be remembered that the inhibitory effect of ethanol was not only small but was also not reproducible. Finally, a repeated-measure ANOVA, which was followed by multiple comparison analysis, has shown that the after-ethanol values were very similar on days 1 and 2 regardless of the use of phenylephrine and with both doses of clonidine. These findings strongly suggest that the inhibitory effect of ethanol on the depressor response to clonidine is reproducible. Because the same analyses revealed that the after-saline values for the depressor response to clonidine were also very similar on days 1 and 2 even though ethanol and saline treatments were crossed over, the data suggest that the interaction is reversible and that prior treatment with clonidine or ethanol had no bearing on the depressor effect of clonidine on day 2. Taken together, these findings strongly suggest that ethanol has a differential effect on the depressor response to clonidine and hydralazine.

Many investigators have demonstrated an augmentatory action for clonidine on baroreceptor reflexes and suggested this effect may contribute to the hypertensive effect of clonidine.21–23 In the present study and in agreement with reported findings,21–23 we observed that clonidine-evoked lowering of arterial pressure was associated with a substantial increase in baroreceptor reflex slopes. Based on our previous findings, which showed ethanol produced dose-related decreases in baroreceptor reflex slopes of anesthetized and conscious rats15,16,19 as well as normotensive human volunteers,17 we decided to investigate the possibility of whether this effect, which is directionally opposite to that of clonidine,21–23 is involved in ethanol–clonidine interaction. The data of the present investigation clearly demonstrated that ethanol virtually abolished the augmentatory action of clonidine on baroreceptor reflexes (Figure 4) along with attenuating its hypotensive effect (Figures 2 and 3). Although the study did not establish a cause and effect relation between the increase in baroreceptor reflex slope and the decrease in blood pressure evoked by clonidine, the data can suggest a contributory role for baroreceptor reflexes in ethanol–clonidine interaction. It must be noted, however, that this conclusion only pertains to the higher doses of clonidine (10 and 30 μg/kg), which increased the baroreceptor reflex slopes. On the other hand, the finding that ethanol attenuated the hypertensive effect of the low dose of clonidine (3 μg/kg) without involving any change in baroreceptor reflex slope suggests a minor contributory role of the baroreceptor reflexes in this interaction.

The timing of the blood pressure change suggests that the observed reversal and attenuation of the hypertensive effect of clonidine are ethanol mediated and do not seem to involve its metabolites. Reversal by ethanol of the hypertensive effect of clonidine occurred within 1–2 minutes of its infusion and in some instances was preceded by a transient fall in blood pressure and heart rate (see Figure 1). Furthermore, the data suggest that neither this transient fall in blood pressure evoked by ethanol nor the use of phenylephrine can account for the observed reversal of clonidine-evoked hypotension by ethanol. The infrequent falls in blood pressure and heart rate were also seen when ethanol was infused during the hypertensive response to hydralazine, but no reversal of the hypotension took place. Reversal of the hypertensive effect of clonidine by ethanol was obtained in the presence (Figure 2) and in the absence (Figure 5) of phenylephrine. It must be noted, however, that the use of phenylephrine (perhaps due to volume loading) reduced the hypotensive effect of clonidine by approximately 45%; mean arterial pressure showed an average maximal decrease of 55 and 30 mm Hg in the absence and in the presence of phenylephrine, respectively, in response to a dose of 10 μg/kg clonidine. It is also possible that the use of phenylephrine has contributed to the overshoot in blood pressure seen when ethanol was administered during the hypertensive effect of clonidine (compare Figures 2 and 5).

A lack of reproducibility of the hypertensive response to the same dose of clonidine in the same rat, which suggests acute tolerance had developed and agrees with the finding of others,32 made it impossible to use each rat as its own control. Thus, the experimental protocol was designed to allow a
cross-sectional comparison between ethanol and saline (control) groups. Although we believe this experimental design was adequate to draw a valid conclusion, it was felt the data would be more meaningful if each rat could be used as its own control. A crossing over of ethanol and saline treatments on days 2 and 3 of the study provided solid evidence to suggest ethanol–clonidine interaction is both reversible and reproducible (Figure 2). It is important, however, to indicate that reversibility of the adverse effect of ethanol on the hypotensive effect of clonidine pertains only to the duration of the experiment (3 days) and to a single dose of ethanol per day. The situation may be different if the interaction is studied on a long-term basis.

In our previous studies, we have shown a negative correlation between the dose of ethanol (or blood ethanol concentration) and baroreceptor reflex sensitivity values. It is possible that larger doses of ethanol would attenuate further the hypotensive effect of clonidine. We decided, however, to use a dose of ethanol that resulted in a blood ethanol concentration of 54.2±6.3 mg/dl, which is comparable to that attained after social drinking. This dose of ethanol, 1 g/kg, produced an upward shift of the clonidine dose-depressor response curve and resulted in a significant attenuation of the depressor response to the same dose of clonidine (Figure 3). Based on this finding, if the dose of clonidine is adjusted to produce the desired decrease in pressure of an alcohol user, care should be taken not to advise abrupt abstinence of alcohol consumption, otherwise an exaggerated depressor response to clonidine may ensue.

In conclusion, the findings of the present study provide evidence to suggest an antagonistic interaction between ethanol and clonidine that may explain, at least in part, the inadequate control of blood pressure in treated hypertensive patients who are regular users of alcohol. The mechanism by which ethanol attenuates the hypotensive effect of clonidine is not known. It is possible, however, that a directionally opposite effect of ethanol and clonidine on sympathetic activity may be involved in the interaction; that ethanol failed to influence the hypotensive effect of hydralazine strengthens this notion. The finding pertains to an acute–acute interaction that was both reversible and reproducible. Whether a similar interaction occurs after long-term treatment with either or both agents remains to be investigated.

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References

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