Ethanol Causes Epicardial Coronary Artery Vasoconstriction in the Intact Dog

Sharonne N. Hayes, MD, and Alfred A. Bove, MD, PhD

Ethanol produces in vitro vasoconstriction of coronary arteries and can precipitate angina in patients with coronary obstructive disease. To demonstrate the in vivo effect of ethanol on coronary dynamics, baseline measurements of left anterior descending (LAD) coronary artery dimension by quantitative angiography, hemodynamics, arterial and coronary sinus blood gases, and blood ethanol levels were obtained in 14 closed-chest mongrel dogs. Three ethanol levels were established by intravenous bolus followed by 1-hour maintenance infusions. All measurements made at baseline were recorded every 30 minutes. Phentolamine (5 mg i.v.) and nicardipine (0.15 mg/kg i.v.) were given to evaluate constrictor mechanisms. Blood ethanol levels achieved at 60, 120, and 180 minutes were 649 ± 48, 1,285 ± 81, and 2,546 ± 130 μg/ml, respectively. LAD cross-sectional area was reduced significantly from control at the end of each of the three dosing periods (−24 ± 5%, −40 ± 3%, and −53 ± 3%; p<0.004). α-Adrenergic blockade had no effect on LAD cross-sectional area, while nicardipine partially reversed the ethanol-induced vasoconstriction. No significant change in vessel cross-sectional area took place in control dogs. These data suggest that ethanol induces epicardial coronary artery vasoconstriction in dogs at clinically important blood levels. α-Adrenergic blockade does not alter or reverse ethanol-induced vasoconstriction, while calcium channel blockade appears to be an effective vasodilator of ethanol-constricted vessels. (Circulation 1988;78:165–170)

Effects of ethanol on the heart and circulatory system are varied. Heavy ethanol use causes myocardial depression and congestive cardiomyopathy,1,2 cardiac arrhythmias,3,4 hypertension,5,6 and an increased incidence of sudden death.7,8 Conversely, many large-scale epidemiological studies have demonstrated an inverse correlation between moderate ethanol use and coronary artery disease,9–14 perhaps due to favorable effects on lipoprotein levels.15

Despite findings that suggest there may be a protective level of alcohol consumption between the extremes of abstention and drinking more than 3–4 drinks each day, there is evidence that ethanol use can provoke angina in patients with preexisting coronary artery disease.16–19 Several studies of patients undergoing coronary angiography, primarily for symptoms of unstable angina and recent myocardial infarction, have demonstrated a lesser degree of atherosclerotic narrowing in heavy drinkers compared with light drinkers.20–22 This has been interpreted as evidence for a protective effect of ethanol on the coronary arteries. However, because the severity of symptoms leading to angiography in both groups was similar, these data could alternatively be interpreted to show that ethanol causes an earlier presentation of coronary artery disease because of some destabilizing or exacerbating effect.

This effect is likely to be coronary vasoconstriction. Altura et al23 demonstrated sustained dose-dependent vasoconstriction of isolated canine coronary arteries by ethanol that was not affected by pretreatment with phentolamine, methysergide maleate, diphenhydramine hydrochloride, metiamide, propranolol, or indomethacin. Although low-to-intermediate concentrations of ethanol cause vaso-dilation of precapillary sphincters, muscular venules, arterioles, and superficial cutaneous vessels in vivo,24,25 these levels cause vasoconstriction of the vessels of human forearm musculature after oral or intra-arterial administration.26 The vasodilation observed appears to be sympathetically mediated, while the vasoconstriction is independent of sympathetic innervation. Other blood vessels, for example, femoral, intrapulmonary, renal, and cerebral, have also shown only contractile responses to ethanol that cannot be altered by most vasoactive mediators.27,28 Theoretically, narrowing of coronary artery diameter, either chronically or with spasm, can decrease blood flow to a level that would induce ischemia. In people with atheroscle-
rotic coronary disease, such narrowing of the lumen by ethanol could increase the relative stenosis caused by a lesion and precipitate clinical manifestations earlier than they would otherwise appear. Thus, proximal coronary vasoconstriction could be one mechanism by which ethanol is associated with a lower threshold for angina and increased incidence of myocardial infarction, particularly, fatal events.

This study was designed to evaluate the integrated effects of intravenous ethanol on epicardial vessel responses in the intact canine heart and to determine whether ethanol at blood levels that are achieved during social drinking causes significant vasoconstriction of the coronary vasculature.

**Materials and Methods**

**Animals and Anesthetics**

Fourteen male mongrel dogs (23.7 ± 0.7 kg) were anesthetized with a combination of 0.2 ml/kg Innovar Vet i.m. (0.4 mg/ml fentanyl and 20 mg/ml droperidol) and 70% nitrous oxide in oxygen ventilated with a mechanical volume respirator (model 807, Harvard Apparatus, South Natick, Massachusetts) through a cuffed endotracheal tube. Adequacy of ventilation was ascertained by arterial blood gas determinations. This anesthesia has been shown to have minimal effects on myocardial function and does not produce significant alterations in the state of the autonomic nervous system. Thus, resting heart rates and blood pressures were in the normal range and allowed all studies to be performed at similar heart rates established by atrial pacing.

**Experimental Preparation**

The left carotid artery, left femoral vein and artery, and right external jugular vein were dissected. Under fluoroscopic guidance, the coronary sinus was catheterized through a branch of the right jugular vein for pressure monitoring, blood sampling, and for atrial pacing by a 6F bipolar pacing catheter connected to a pulse generator set at approximately 85 beats/min. After a single intravenous bolus of 2% lidocaine (40 mg), a specially designed coronary catheter was advanced from the left carotid artery to the orifice of the left coronary artery for measuring proximal coronary arterial pressures and for injecting radiopaque contrast medium. A transseptal left atrial catheter was inserted into the jugular vein for injecting radioactive microspheres. An infusion catheter was placed in the left femoral vein, and a femoral artery catheter was placed in the abdominal aorta for sampling blood and recording aortic pressure. Pressures were measured with a Statham P23DG (Los Angeles, California) strain-gauge manometer with zero reference taken as the midpoint in the supine position. The pressures and electrocardiogram were monitored continuously and recorded during each stage of the experiment.

**Experimental Procedure**

After positioning the catheters, baseline heart rate, blood pressure, arterial blood gas, coronary sinus and arterial oxygen saturation, and blood ethanol level were measured, and an angiogram of the left coronary artery was performed. Six dogs had microsphere blood flow determinations that were performed before contrast administration. These measurements constitute a "data set." After the control measurements, 8 g ethanol in 50% normal saline solution was infused through the femoral vein during a 15-minute period by a Harvard pump followed by a maintenance infusion of 0.22 ml/min. This rate was based on expected ethanol metabolic rates and calculated so that blood ethanol levels would remain constant throughout each infusion. At 60 minutes, another bolus of 8 g ethanol was given, and at 120 minutes, a bolus of 16 g ethanol was given; each bolus was followed by the maintenance ethanol infusion. The control animals received equal-volume boluses and infusions of normal saline. Ethanol is metabolized by dogs in a fashion similar to that in humans, and the doses of ethanol were designed to approximate blood levels comparable to those achieved after consumption of 1–2, 3–4, and 6–8 cocktails. At 30 and 60 minutes after the start of each bolus infusion, all measurements made at baseline were repeated. Microsphere blood flows were performed only at 0, 60, 120, and 180 minutes to avoid excessive small vessel occlusion (Figure 1).

To determine the effect of α-adrenergic blockade on the ethanol-treated arteries, phentolamine (5 mg i.v.) was given at the high ethanol dose followed by a data set recorded 20 minutes later. To determine the effect of calcium channel blockade, nicardipine (0.1 mg/kg i.v.) was given and was followed by a final data set. The dogs were killed with an intracoronary injection of potassium chloride, and the heart of each was excised.

**Measurement of Epicardial Coronary Dimensions**

Changes in coronary artery reactivity were measured in the right anterior oblique projection by injecting 4–6 ml meglumine diatrizoate into the guide catheter and taking a single roentgenogram on film exposed at 85 kV for 35 msec in mid-diastole with an electrocardiographic trigger system. The opacified luminal edges of the coronary artery were manually traced and digitized with a quantitative angiography program on a PDP 11/34 computer (Digital Equipment, Marlboro, Massachusetts). This program calculates luminal diameter and cross-sectional area (CSA) at 1-mm intervals along the measured artery.29 A representative 10-mm section of each scanned artery was used to evaluate the results. This method of analysis has been previously tested by measuring pieces of metal wire, contrast-filled polyethylene tubing, and implanted plastic plugs with known dimensions and has been
found to produce accurate in vitro and in vivo measurements.30

**Measurements of Myocardial Blood Flow**

Blood flow was determined with 15-μm radioactive microspheres (New England Nuclear, Boston, Massachusetts) labeled with 57Co, 113Sn, 46Sc, or 85Sr in the control state and after 60 minutes of a given ethanol-infusion level. The microspheres (1.4 million suspended in 2 ml normal saline) were rapidly injected into the left atrium while blood was sampled at 7.64 ml/min from the femoral artery with the use of a constant-rate withdrawal pump (Harvard Apparatus) for 2 minutes. No electrocardiographic changes or hemodynamic alterations were produced during injection or withdrawal.

After death, the atria and great vessels were separated from the ventricles, which were then weighed, placed in 10% buffered formalin for 3–4 days, and sectioned into 36 left and 18 right ventricular pieces according to a standard map.31 Each piece was weighed and placed into a counting vial. All tissue samples and the reference blood were counted in a three-channel automatic gamma counter. The data were corrected for energy overlap with standard linear equation techniques. To further reduce any error that might be introduced by contaminant activity contributed by accompanying isotopes and background, the order of isotopes was altered for each experiment. Regional flows were calculated by computer and expressed as flow per gram tissue.

Arteriovenous oxygen differences (ml/dl) were calculated by taking the difference between arterial and coronary sinus blood oxygen content. Oxygen content was calculated as hemoglobin level (g/dl) × 1.34 ml O2/g × oxygen saturation, which was measured by a Co-oximeter.

Myocardial oxygen consumption (ml O2/min/100 g) was calculated by left ventricular blood flow (ml/min/100 g) × the arteriovenous blood oxygen difference.

**Data Analysis**

Results are reported as mean ± SEM. Changes in vessel cross-sectional area, myocardial blood flow, blood pressure, heart rate, and myocardial oxygen consumption over time are expressed in absolute values and as percent change from control values. Data were analyzed with Wilcoxon’s signed rank test and two-way analysis of variance. Statistical significance was assumed at the p<0.05 level.

**Results**

**Effects of Intravenous Ethanol on Epicardial Conduccance Vessels**

Ethanol caused dose-dependent vasoconstriction of the left anterior descending artery (LAD). Vasoconstriction became measurable after 30 minutes at each blood ethanol level and became maximal at 1 hour. Blood ethanol levels achieved at 60, 120, and 180 minutes were 649 ± 48, 1,285 ± 81, and 2,546 ± 130 μg/ml, respectively (Figure 1). Blood levels drawn 30 minutes after the start of each infusion were similar and demonstrate that a stable blood ethanol level was maintained throughout the infusion. LAD cross-sectional area was reduced significantly from control at the end of each infusion.
period at 60, 120, and 180 minutes (-24 ± 5%, -40 ± 3%, and -53 ± 3%, respectively; p < 0.004). In addition, significant vasoconstriction occurred between 60 and 120 minutes (-22 ± 3%; p < 0.0003) and between 120 and 180 minutes (-19 ± 3%; p < 0.0003) (Figure 2). The left circumflex artery displayed similar changes. Phentolamine, given at the highest blood level, had no effect on LAD cross-sectional area. Nicardipine partially reversed the ethanol-induced vasoconstriction (Table 1). In three control animals that were instrumented but given only normal saline infusions, there was no change in LAD cross-sectional area during the 180-minute period, demonstrating that the ethanol effect was not an artifact of experimental procedure.

**Effect of Ethanol on Heart Rate, Blood Pressure, Arteriovenous Oxygen Differences, and Blood Flow**

Heart rate was controlled by pacing and remained constant throughout the study (Table 2). Mean aortic pressure and, therefore, the rate-pressure product also did not change. Myocardial oxygen consumption declined in a dose-dependent manner and did not reach statistical significance. In six animals in which blood flow was measured, flow was reduced by 14 ± 5%, 26 ± 9%, and 28 ± 14% at 60, 120, and 180 minutes, respectively. The 120- and 180-minute values are statistically significant at the p < 0.03 level. Because of varied blood flow responses among individual animals, conclusions about the effect of intravenous ethanol on coronary blood flow cannot be drawn from this study.

**Discussion**

**Major Findings**

This study demonstrates epicardial coronary artery vasoconstriction in dogs in response to ethanol at blood levels commonly achieved during social drinking by humans. The degree of epicardial coronary vasoconstriction observed at even low blood ethanol levels was significant in the normal canine coronary artery. This investigation supports in vitro, in vivo, and clinical findings that indicate that ethanol is a coronary vasoconstrictor. α-Adrenergic blockade did not alter or reverse ethanol-induced vasoconstriction, but calcium channel blockade was an effective vasodilator of ethanol-constricted epicardial coronary vessels.

**Comparison With Other Studies**

Although no work has previously documented the effect of ethanol on epicardial coronary size in the intact model, many of the in vitro and in vivo studies support our findings. Clinically, ethanol was widely accepted as treatment for the symptoms of angina pectoris for many years. However, in 1950, Russek et al 32 tested this hypothesis in five patients with stable angina who underwent standardized exercise tests before and after ethanol and nitroglycerin. Both ethanol and nitroglycerin relieved the chest pain associated with exercise, but ethanol consumption, unlike nitroglycerin, did not alter the ischemic electrocardiographic changes observed during exercise. Therefore, ethanol masked the symptoms of myocardial ischemia but did not affect the pathophysiology. More recently, others have documented the effect of ethanol on exercise tests performed by individuals with stable angina. Conway 33 exercised five patients before and after ethanol until the development of angina. New or worsened electrocardiographic changes occurred in three patients after ethanol. In 12 patients with stable angina and angiographically defined coronary lesions who were exercised until angina developed after 0, 2, or 5 oz ethanol, there was a significant decrease in exercise duration after

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**Table 1. Effects of α-Adrenergic and Calcium Channel Blockade on Ethanol-Induced Vasoconstriction**

<table>
<thead>
<tr>
<th>Constriction</th>
<th>Ethanol Control (high dose)</th>
<th>Ethanol + Phentolamine</th>
<th>Ethanol + Nicardipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD CSA (%)</td>
<td>0</td>
<td>53 ± 3</td>
<td>50 ± 5</td>
</tr>
<tr>
<td>LAD CSA, left anterior descending coronary artery cross-sectional area.</td>
<td></td>
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</tr>
</tbody>
</table>

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**Table 2. Effect of Ethanol on Hemodynamics, Myocardial Oxygen Consumption, and Blood Flow in the Intact Dog**

<table>
<thead>
<tr>
<th>Hemodynamic variable</th>
<th>Time (min)</th>
<th>0</th>
<th>60</th>
<th>120</th>
<th>180</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>87 ± 4</td>
<td>88 ± 4</td>
<td>84 ± 3</td>
<td>82 ± 4</td>
<td></td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>79 ± 3</td>
<td>79 ± 4</td>
<td>83 ± 3</td>
<td>80 ± 4</td>
<td></td>
</tr>
<tr>
<td>LAD CSA (mm²)</td>
<td>5.43 ± 0.31</td>
<td>4.10 ± 0.28*</td>
<td>3.21 ± 0.23*</td>
<td>2.61 ± 0.19*</td>
<td></td>
</tr>
<tr>
<td>Coronary blood flow (LAD) (ml/min/100 g LV)</td>
<td>94 ± 3</td>
<td>80 ± 6</td>
<td>69 ± 7*</td>
<td>67 ± 11*</td>
<td></td>
</tr>
<tr>
<td>AV O₂ difference (ml O₂/100 ml)</td>
<td>5.72 ± 0.32</td>
<td>5.95 ± 0.40</td>
<td>6.21 ± 0.33</td>
<td>6.30 ± 0.37</td>
<td></td>
</tr>
<tr>
<td>MVO₂ (ml O₂/min/100 g)</td>
<td>5.42 ± 0.30</td>
<td>5.19 ± 0.44</td>
<td>4.55 ± 0.68</td>
<td>4.70 ± 0.98</td>
<td></td>
</tr>
<tr>
<td>Coronary vascular resistance (mm Hg/ml/100 g · min)</td>
<td>0.86 ± 0.04</td>
<td>0.96 ± 0.09</td>
<td>1.18 ± 0.14</td>
<td>1.30 ± 0.24</td>
<td></td>
</tr>
</tbody>
</table>

LAD CSA, left anterior descending coronary artery cross-sectional area; LV, left ventricle; AV O₂, arteriovenous oxygen; and MVO₂, myocardial oxygen consumption.

* p < 0.004; † p < 0.03.
both ethanol doses as well as a dose-dependent increase in the degree of ischemic ST segment depression after angina occurred.34 Other studies have shown that ethanol causes significant myocardial dysfunction and blood flow reductions in recently infarcted or experimentally ischemic tissue compared with normal myocardium.35,36

There have been multiple reports of ethanol-induced Prinzmetal’s variant angina occurring several hours after oral ingestion.16-19 In some of these patients, ethanol was the only stimulus that could induce angina, and angina was reproducible with rechallenge in others. Ethanol-induced angina occasionally occurred when ethanol levels were near zero, leading investigators to suspect a metabolite of ethanol or delayed release of a mediator rather than ethanol itself as the cause of symptoms. Rogers et al (unpublished data) have demonstrated this finding in the intact canine model by inducing vasoconstriction of the epicardial coronary arteries after a single intravenous bolus of ethanol. Vasoconstriction continued to increase for 2 hours even as blood ethanol levels were declining. Ethanol consumption has not been consistently associated with changes in plasma norepinephrine, epinephrine, and serotonin levels that could account for symptoms, and its major metabolite, acetaldehyde, appears to be a vasodilator of coronary vessels.28,37,38

Regan et al39 report 12 chronic alcoholics with documented recent myocardial infarction, 10 of whom had no history of heart disease and whose only risk factor was smoking. Seven of these patients had completely normal coronary arteries at angiography or postmortem examination, and none of the other three had more than a single lesion that obstructed over 50% of vessel diameter. Perhaps ethanol-induced vasospasm was related to these cardiac events.

Although it appears that moderate ethanol consumption confers some cardioprotective effects, heavy use of ethanol may destabilize preexisting coronary obstructive disease. In Sweden and the United States in twin pairs concordant for smoking but discordant for drinking, the incidence of angina was higher in the drinking twin.40 In angiographic studies, heavy and regular drinkers have lesser degrees of occlusive atherosclerotic disease than light drinkers or nondrinkers with similar symptoms.20-22 Drinkers also appear to have an increased percentage of acute coronary events that occur as sudden death rather than as nonfatal myocardial infarction when compared with nondrinkers.8,41

These data suggest that alcohol is a risk factor for ischemic coronary events that are unassociated with significant anatomic obstruction. These patients may have ethanol-induced coronary vasoconstriction leading to premature angina, myocardial infarction, and sudden death.

Clinical Implications

The results of this study imply that previous clinical observations of ethanol-associated angina, reduction in exercise tolerance, and premature presentation of ischemic symptoms with minor anatomic disease in drinkers may be related to a direct constrictor effect of ethanol on the epicardial coronary arteries. Although a reduction in luminal cross-sectional area of the magnitude observed in this study might not cause ischemia at rest to myocardium supplied by a normal coronary artery, a 50% reduction in area by ethanol of an already partially stenosed vessel would cause symptoms.

Methodological Considerations

The use of anesthesia might cause changes in vessel responses and in the autonomic system; however, the anesthesia used in this study did not affect vessel cross-sectional area in the control dogs or in previous control studies from our laboratory using similar techniques.42 Although vessel responses to ethanol might have been altered by anesthesia to some degree, the vasoconstriction observed in this study is in accordance with ethanol-induced vasoconstriction seen in other preparations.23-28 Further, the intravenous route of ethanol administration is not “physiological.” The significant difference that intravenous administration made was a more rapid achievement of steady-state blood levels that made administration of doses and interpretation of data more simple. Use of oral doses would have been impractical with results dependent on individual absorption rates.

α-Adrenergic blockade and calcium channel blockade effects must be interpreted carefully because phentolamine and nicardipine were administered at a relatively high blood ethanol level after significant vasoconstriction had already occurred. Their effects might differ if administered before the ethanol infusion or at a lower blood ethanol level. Although it is possible that phentolamine and nicardipine may have had a synergistic effect in vasodilating the ethanol-affected arteries, nicardipine does have a vasodilating effect of its own. In three additional animals that had similar ethanol infusions but received no phentolamine, nicardipine induced a marked vasodilation of ethanol-constricted arteries. In these studies, the average ethanol-induced reduction in cross-sectional area was 47%. After nicardipine, vessel cross-sectional area increased to an average of 8% greater than control. Further studies would need to be performed to clearly delineate the individual drug effects.

In summary, we have demonstrated epicardial coronary artery constriction induced by ethanol at clinically important blood levels. The application of these data may lead to recognition of ethanol-induced angina in patients with coronary disease and could aid the clinician in making recommendations regarding ethanol use by patients with symptomatic coronary artery disease.
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References


KEY WORDS • quantitative angiography • blood ethanol levels • calcium channel blocker
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