

THE EFFECT OF THE INGESTION OF ETHANOL ON OBSTRUCTION OF THE LEFT VENTRICULAR OUTFLOW TRACT IN HYPERTROPHIC CARDIOMYOPATHY

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ABSTRACT

Background Ethanol causes vasodilatation, which might have an adverse effect, due to increased obstruction of the left ventricular outflow tract, in patients with hypertrophic obstructive cardiomyopathy. We assessed the hemodynamic effects of the ingestion of ethanol, in an amount commonly consumed socially, in patients with hypertrophic cardiomyopathy.

Methods We performed echocardiography in 36 patients before and several times after the ingestion of either 50 ml of 40 percent ethanol or an isocaloric placebo with the aroma of rum. Each patient received both ethanol and placebo, on different days. The patients, but not the physicians, were blinded to the content of the drink. We measured the sizes of the left atrium and left ventricle, the left-ventricular-wall thickness, blood pressure, heart rate, the degree of systolic anterior motion of the mitral valve, and the pressure gradient across the left ventricular outflow tract.

Results The ingestion of ethanol resulted in a significant drop in the mean (\pm SD) systolic blood pressure (from 130.5 ± 18.6 to 122.5 ± 20.3 mm Hg, $P < 0.001$), a significant increase in systolic anterior motion of the mitral valve (from a grade of 2.1 to a grade of 2.5, $P < 0.001$), and a 63 percent increase in the mean gradient across the left ventricular outflow tract (from 38.1 ± 26.5 to 62.2 ± 42.4 mm Hg, $P < 0.001$). These changes, which were not associated with symptoms, did not occur after the ingestion of placebo.

Conclusions The ingestion of a small amount of ethanol caused an increase in the gradient across the left ventricular outflow tract in patients with hypertrophic obstructive cardiomyopathy, which could have an adverse clinical effect. (N Engl J Med 1996; 335:938-41.)

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ETHANOL is a strong myocardial depressant, and its short-term hemodynamic effects have been studied in normal subjects¹⁻⁶ and in persons with a history of excessive intake.⁷ The vasodilatation associated with the intake of ethanol may improve left ventricular function, but it may also be detrimental to patients with hypertrophic cardiomyopathy if it increases obstruction of the left ventricular outflow tract.

We encountered a patient with hypertrophic cardiomyopathy in whom even one drink of alcohol could be predictably associated with dyspnea and

the development of a precordial thrill. We therefore undertook a study to see whether there were adverse hemodynamic effects associated with the ingestion of ethanol in patients with hypertrophic cardiomyopathy.

METHODS

The Patients

All adult outpatients at Beilinson Hospital (Petah Tiqvah, Israel) with a diagnosis of hypertrophic obstructive cardiomyopathy were recruited for the study. All these patients met the entry criteria of having asymmetric septal hypertrophy (defined as a ratio of the thickness of the septum to that of the posterior wall of the left ventricle of not less than 1.3) and systolic anterior motion of the mitral valve seen on an echocardiogram. A total of 36 patients were enrolled, 24 men and 12 women, who were a mean (\pm SD) of 68 ± 11 years of age (range, 37 to 82). All but one patient were receiving medication, which was not discontinued during the study. Twenty-four patients were taking calcium-channel blockers, eight were taking beta-blockers, four were taking disopyramide, two were taking amiodarone, and one was taking an angiotensin-converting-enzyme inhibitor (four patients were taking a combination of two of the above drugs).

Only 4 of the 36 patients had a history of alcohol use; 1 patient had stopped drinking alcohol 10 years before the study and 3 patients each consumed one drink per day.

Data Collection

M-mode, two-dimensional, and Doppler echocardiography (with a Sonos 1000 system with a 2.5-MHz transducer; Hewlett-Packard, Andover, Mass.) was performed in all patients before and 15, 30, 45, 60, and 75 minutes after the ingestion of 50 ml of 40 percent ethanol. On a different day (but at the same time of day), the same regimen of echocardiographic studies was performed before and after the ingestion of 50 ml of an isocaloric placebo that had the odor and taste of rum without the ethanol. The patients were therefore blinded to the ethanol content of the drink, but the physicians were not. All patients were asked to report any symptoms occurring after the ingestion of ethanol or placebo.

The following variables were measured at each echocardiographic study: systolic and diastolic blood pressure, the heart rate and rhythm, the degree of mitral systolic anterior motion, the peak velocity through the left ventricular outflow tract, and the peak pressure gradient across the left ventricular outflow tract as calculated by the modified Bernoulli formula, in which peak gradient = $4 \times (\text{peak velocity})^2$. In addition, left atrial size, left ventricular size, and the thickness of the septum and the left ventricular posterior wall were determined by standard techniques. The degree of mitral systolic anterior motion was graded on a 4-point scale (0 represented no systolic anterior motion; 1, sys-

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tolic anterior motion of less than 50 percent of the diameter of the outflow tract; 2, systolic anterior motion of 50 to 99 percent of the diameter of the outflow tract; and 3, systolic anterior motion during which the mitral valve touched the interventricular septum).

The time at which the maximal change in the left ventricular outflow tract gradient took place after the ingestion of ethanol was recorded, and the values of the observed variables were compared with the values at base line. After the ingestion of placebo, this same period was used for comparison — that is, the changes, if any, in the variables after the ingestion of placebo were recorded at the time at which each patient's gradient had reached its highest value after the ingestion of ethanol.

Statistical Analysis

The data were analyzed with a two-repeated-measures analysis of variance, which tested for the presence of a significant difference between values before and after the ingestion of ethanol and placebo. Values are expressed as means \pm SD. A Pearson's correlation coefficient was computed for the pressure gradient across the left ventricular outflow tract and the systolic blood pressure. In a comparison of the group that had facial flushing after ingesting ethanol with the group that did not, we used one between-groups factor and two-repeated-measures analysis of variance to assess the significance of the relative effects of ethanol and placebo. The changes in left ventricular dimensions were analyzed with a paired, two-tailed *t*-test. A *P* value of less than 0.05 was considered to indicate statistical significance. Data were analyzed with SPSS software (SPSS, Chicago).

RESULTS

M-Mode and Two-Dimensional Echocardiography

Before the ingestion of ethanol, the mean septal thickness for the entire group was 1.7 ± 0.2 cm (range, 1.3 to 2.1) and the thickness of the left ventricular posterior wall was 1.2 ± 0.1 cm (range, 0.9 to 1.4). The mean left atrial dimension was 4.8 ± 0.9 cm (range, 3.3 to 8.1). The mean grade of mitral systolic anterior motion was 2.1 ± 0.7 (range, 0 to 3). These values as measured before the ingestion of placebo were virtually identical ($P \geq 0.05$ for all comparisons). As measured before the ingestion of placebo, the mean septal thickness was 1.6 ± 0.2 cm; the mean posterior-wall thickness, 1.2 ± 0.2 cm; the mean left atrial dimension, 4.8 ± 0.7 cm; and the mean grade of mitral systolic anterior motion, 2.2 ± 0.7 .

In 20 patients, the end-diastolic and end-systolic dimensions of the left ventricle were measured before the ingestion of ethanol and at the time of ethanol's peak effect on the left ventricular outflow tract gradient. The mean end-diastolic dimension was 4.5 ± 0.6 cm before the ingestion of ethanol and 4.3 ± 0.6 cm after ingestion. This difference was statistically significant ($P < 0.001$). The mean end-systolic dimension was 2.6 ± 0.6 cm before and 2.5 ± 0.6 cm after the ingestion of ethanol, also a significant difference ($P = 0.025$).

Heart Rate, Rhythm, and Blood Pressure

Before the ingestion of ethanol, the mean heart rate for the entire group was 64.4 ± 7.1 beats per minute (range, 50 to 88). This did not change appreciably after ingestion (mean after ingestion, 64.3 ± 7.7 beats per minute; $P = 0.119$). The mean heart rate before placebo (63.9 ± 8.5) was not significantly different from that measured before the ingestion of ethanol; it also did not change significantly after the ingestion of placebo (mean after ingestion, 61.8 ± 7.5 ; $P = 0.144$). Two-repeated-measures analysis of variance showed no significant difference in the effects of ethanol and placebo on heart rate ($P = 0.13$). No rhythm disturbances were noted after the administration of either ethanol or placebo.

Two-repeated-measures analysis of variance showed a significant difference in the effects of ethanol and placebo on systolic blood pressure ($P < 0.001$). The mean systolic blood pressure before the ingestion of ethanol was 130.5 ± 18.6 mm Hg. This fell significantly to 122.5 ± 20.3 mm Hg after ingestion. However, there was no fall in blood pressure during the same interval after the ingestion of placebo (the mean systolic pressure before placebo was 124.0 ± 19.2 mm Hg; after placebo it was 126.3 ± 19.3 mm Hg). Similarly, there was a significant drop in diastolic blood pressure after the ingestion of ethanol, but not after the ingestion of placebo (a decrease of 3.3 mm Hg after ethanol vs. an increase of 0.8 mm Hg after placebo, $P = 0.04$).

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Systolic Anterior Motion of the Mitral Valve and Left Ventricular Outflow Tract Gradient

A two-repeated-measures analysis of variance showed a significant difference in the effects of ethanol and placebo on mitral systolic anterior motion ($P = 0.001$). The grade of mitral systolic anterior motion increased after the ingestion of ethanol from 2.1 ± 0.7 to 2.5 ± 0.7 , but it did not change after placebo (2.2 ± 0.7 before ingestion and 2.2 ± 0.7 after).

A two-repeated-measures analysis of variance showed a significant difference in the effects of ethanol and placebo on the left ventricular outflow tract gradient ($P < 0.001$) (Fig. 1). The left ventricular outflow tract gradient increased significantly (by 63 percent) after the ingestion of ethanol, from 38.1 ± 26.5 to 62.2 ± 42.4 mm Hg. The left ventricular outflow tract gradient before the ingestion of placebo was 43.9 ± 31.2 mm Hg; after placebo it was 38.9 ± 29.4 mm Hg.

The increase in the left ventricular outflow tract gradient after the ingestion of ethanol also correlated significantly with the fall in blood pressure after ingestion ($r = -0.5$, $P < 0.01$). There was no obvious relation between the increase in gradient and the patients' sex, age, or medication. None of the patients (who were supine during the study) had chest pain or dyspnea. Thus, after the ingestion of ethanol, there was a statistically significant drop in systolic blood pressure and an increase in the left ventricular outflow tract gradient; the two changes were significantly correlated. There was no change in heart rate.

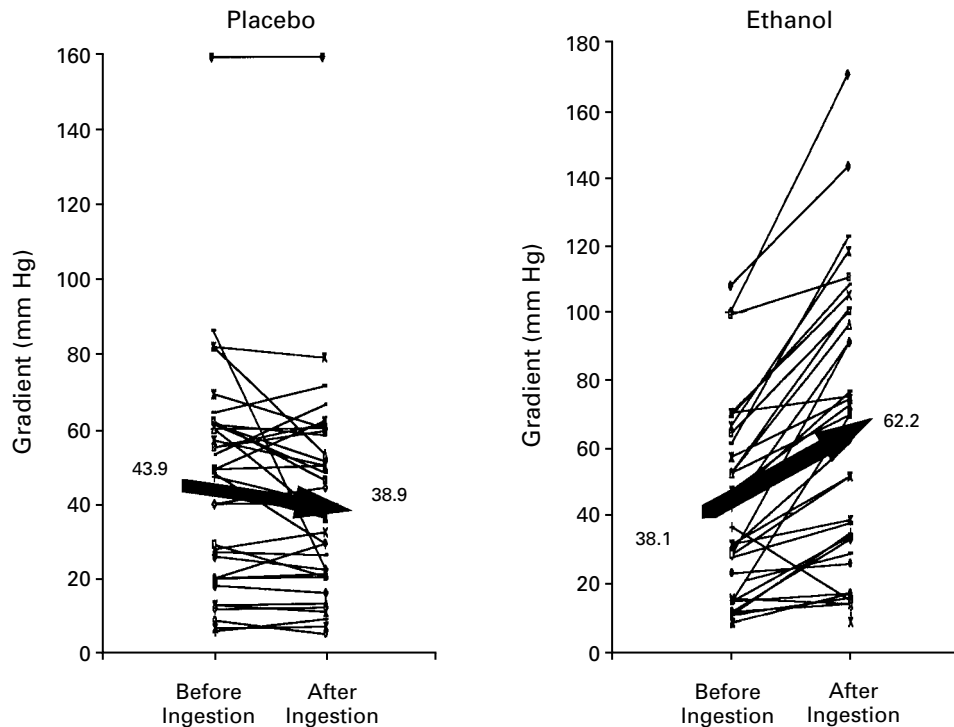


Figure 1. Left Ventricular Outflow Tract Gradient in 36 Patients with Hypertrophic Obstructive Cardiomyopathy.

There was a significant increase of 63 percent ($P < 0.001$) in the left ventricular outflow tract gradient after the ingestion of ethanol (right-hand panel). There was no significant change after the ingestion of placebo (left-hand panel). The direction of the change in the means after ingestion is indicated by the arrows. Values after ingestion were selected as described in the Methods section.

Facial Flushing after the Ingestion of Ethanol and the Left Ventricular Outflow Tract Gradient

Eight patients were observed to have facial flushing after ingesting ethanol. The average increase in the left ventricular outflow tract gradient (40.6 ± 15.5 mm Hg) was more than twice as great in these 8 patients as in the 28 patients who did not have flushing (18.9 ± 20.9 mm Hg). The mean gradient in the eight patients with flushing increased from 45.6 ± 20.3 to 86.3 ± 20.7 mm Hg. In the 28 patients without flushing, the mean gradient increased after the ingestion of ethanol from 35.8 ± 28.0 to 55.0 ± 44.8 mm Hg. This difference between the two groups was statistically significant ($P = 0.04$). No flushing occurred after the ingestion of placebo.

DISCUSSION

The physiologic effects of ethanol may be understood by taking into account ethanol's direct effect on the myocardium as well as its effect on the peripheral vasculature and the autonomic nervous system. The vasodilative effects of ethanol on peripheral arteries were recognized by Cook and Brown in 1932.⁸ Juchems and Klobe recorded a decrease in peripheral vascular resistance accompanied by an increase in heart rate and cardiac output after the in-

gestion of ethanol by a group of healthy subjects.² This finding stands in contrast to the effects of ethanol in the patients with pericarditis or valvular, myocardial, or coronary heart disease who were studied by Gould et al.⁴ These authors found an increase in peripheral vascular resistance, no change in blood pressure, and a decreased cardiac index after the ingestion of 2 oz (60 ml) of 86.8-proof Canadian whiskey by the patients with disease, and a decrease in peripheral vascular resistance with an increase in cardiac index in a group of normal subjects. In other studies, Gould et al. found a dose-dependent effect on myocardial function (systolic time intervals) in normal subjects who ingested ethanol.^{5,9} After drinking 2 oz of Canadian whiskey, the subjects had a decrease in both the preejection period and the isometric-contraction time, as well as an increase in left ventricular ejection time.⁹ These results indicate an improvement in left ventricular function. However, a larger amount of ethanol (4 oz [120 ml]) had the opposite effect — an increase in the preejection period and isometric-contraction time, indicating a reduction in left ventricular function.⁵

An additional effect of ethanol on preload has been described by Kupari, who found a decrease in the left ventricular end-diastolic dimension in a group

of normal subjects.¹⁰ We observed the same phenomenon in our group of patients with hypertrophic cardiomyopathy. This effect may be secondary to decreased venous return due to ethanol-induced venodilation. We also observed a smaller, although still significant, decrease in left ventricular end-systolic dimension after the ingestion of ethanol.

To date, there has been no systematic investigation of the hemodynamic effects of ethanol in patients with hypertrophic obstructive cardiomyopathy. Our study was designed to assess the effects of ethanol, in an amount commonly consumed socially, on hemodynamics in patients with this disorder.

We found that 50 ml of 40 percent ethanol produces a significant drop in systolic blood pressure, presumably because of a fall in peripheral resistance. In patients with obstructed outflow, such a decrease in peripheral vascular resistance will cause an increase in left ventricular contractility and emptying. This increase results in a decrease in the size of the outflow tract in systole and a higher flow velocity across the left ventricular outflow tract. This higher flow velocity is accompanied by an increase in mitral systolic anterior motion because of the Bernoulli effect, which in our patients caused a significant 63 percent increase in the left ventricular outflow tract gradient. This chain of effects is similar to the one provoked by other vasodilative drugs (such as amyl nitrite or sodium nitroprusside) in these patients. Another possible mechanism that can increase obstruction of the outflow tract is a reduction in left ventricular size due to decreased venous return resulting from increased venous capacitance. Our measurements of small, but still significant, decreases in left ventricular end-diastolic dimension and end-systolic dimension support this hypothesis. Except for flushing, our patients (who were supine during the study) did not report any symptoms related to ethanol other than affective ones (specifically, there was no dyspnea, chest pain, or dizziness).

Patients with hypertrophic cardiomyopathy may have chest pain, dyspnea, or syncope or may die suddenly. One mechanism for these effects may be the development of myocardial ischemia, which may, in part, be due to left ventricular outflow obstruction and decreased coronary perfusion pressure.¹¹ Medications used for the treatment of patients with hypertrophic obstructive cardiomyopathy may alter myocardial contractility, peripheral vascular resistance, and the effects of the autonomic nervous system. Such therapy is aimed primarily at the reduction of outflow obstruction. Medical therapy (with negative inotropic drugs such as disopyramide and beta-blockers or calcium-channel blockers), surgical myectomy, and the insertion of a pacemaker are all effective in reducing the left ventricular outflow gradient.¹¹ This reduced gradient, in turn, is associated with an improved prognosis; the incidence of sudden death and

syncope may be lowered by abolishing or reducing the gradient by means of cardiac pacing¹² or myectomy.¹³ Therefore, because of the propensity of even small amounts of ethanol to increase outflow tract obstruction, it is likely that it may be detrimental in patients with hypertrophic cardiomyopathy.

Although we documented the physiologic consequences of the ingestion of ethanol in our patients, our study was not designed to determine the exact mechanism of these changes. Although we found a significant decrease in systolic pressure, we did not measure indexes of contractility or cardiac output. Systemic vascular resistance was therefore not calculated. In addition, we did not measure venous return, another possible mechanism causing decreased left ventricular volume and increased outflow tract obstruction. Furthermore, since all but one of our patients were taking medication at the time of study, our findings reflect the effect of ethanol only on patients undergoing treatment. Nevertheless, we did find ethanol to have a detrimental effect, despite the effects of medications known to improve the hemodynamic condition of patients with hypertrophic cardiomyopathy.

In summary, the ingestion of ethanol in an amount commonly consumed socially in one cocktail was associated in our study with a significant decrease in systolic blood pressure, an increase in mitral systolic anterior motion, and a 63 percent increase in the left ventricular outflow tract gradient in patients with hypertrophic obstructive cardiomyopathy. These changes occurred despite the fact that the patients were taking medications that are prescribed, in large part, to reduce the obstruction of outflow. Patients with this disorder should be cautioned about the potentially harmful effects of this commonly used substance.

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