In the emergency room, we often find patients with syncope after alcohol consumption. This is similar to neurocardiogenic syncope (NCS) with prior symptoms such as palpitation, cold sweats and difficulty in standing up.

The head-up tilt test (HUT) has been used for diagnosing NCS. The HUT protocol recommended by the American College of Cardiology (ACC) expert consensus document is widely used for assessing syncope. If NCS does not occur with HUT alone, the HUT is repeated after administering isoproterenol (ISP) or nitroglycerin. ISP is a $\beta$-adrenergic stimulator that induces vasodilation via a mechanism mediated by $\beta_2$-adrenergic receptors and intensifies cardiac contraction by means of a $\beta_1$-adrenergic-receptor-mediated mechanism. Nitroglycerin also induces vasodilation as a NO donor and is known to induce reflex tachycardia due to sympathetic nerve activation. Alcohol consumption also induces vasodilation and reflex tachycardia. We therefore hypothesize that alcohol will induce NCS. To determine the alcohol-induced syncope mechanism, the present study was performed with patients who had experienced syncope after drinking alcohol.

Methods

Patients

Twenty-five patients (20 men and 5 women; mean age 56.6±16.6; range 35–75 years) with unexplained syncope after alcohol consumption, who had visited our hospital between March 1999 and January 2004, were enrolled. All patients underwent physical examination and routine laboratory testing. We also arranged 12-lead ECG, 24-h ambulatory ECG monitoring, exercise stress testing, 2-dimensional echocardiogram, brain computerized tomography and electroencephalogram in order to exclude any other cause of syncope.

Study Protocol

HUTs were performed before and after alcohol consumption. Our HUT test protocol is in line with the principal recommendations of the ACC expert consensus document. In brief, HUT was performed using a tilt table with a foot board. We arranged continuous 3-lead ECG recording and non-invasive beat-to-beat blood pressure (BP) monitoring using radial tonometry (JENTOW). An ANS 508 system (Japan Colin Co Ltd) was used to record and analyze BP and R–R intervals of ECG during the HUT study. After 30 min of supine rest, patients were tilted upright at 80° until they gave a positive response or, failing that, for 30 min. A positive response is defined as induction of syncope or presyncope associated with a marked hypotension (systolic BP <70 mmHg). The type of tilt-induced NCS was determined using a modified version of the classification proposed by Sutton et al. If there was no positive response during the 30-min HUT, patients were returned to the supine position and given alcohol in a quantity equal to the amount ingested.
before syncope occurred in the clinical situation; this amount was determined by self assessment, up to an intake of 40 ml. After drinking the alcohol, the patients were again tilted upright at 80° until they gave a positive response or, failing that, for 30 min.

Blood Sampling for Measurement of Plasma Catecholamine, Renin Activity and Vasopressin

An indwelling catheter was placed in an antecubital vein for drawing blood. Ten milliliters of blood was collected 30 min after the baseline supine position was adapted and after 15 min at 80° of upright tilt. Blood sampling was repeated before and 15 min after the alcohol was ingested at 80° upright tilt. If syncope occurred before 15 min at 80° upright tilt, the blood was drawn during return to the supine position. Blood samples were immediately transferred into chilled polyethylene tubes containing 10 mg EDTA-2Na and centrifuged at 4°C and 3,000 rpm for 15 min. Epinephrine and norepinephrine were measured using high-pressure liquid chromatography. Plasma renin activity (P-RA) and arginine vasopressin were measured using radioimmunoassay. Saline was supplemented during the HUT (1 ml/min) to maintain the hydration status. All 25 patients gave advance informed consent for the HUT test and blood sampling.

Statistical Analysis

Values are expressed as mean ± standard deviation (SD). The non-parametric Mann-Whitney U test was used for comparison of unpaired data, and the non-parametric Wilcoxon signed-ranks test was used for comparison of paired data. P values <0.05 were taken to be statistically significant. For the comparison of proportion of patients between alcohol-negative (AN) group and alcohol-positive (AP) group, chi-square analysis was used. All statistical calculations were performed using Stat View software (version 5.0; SAS Institute Inc, Carry, NC, USA).

Results

Syncope was not induced by HUT prior to alcohol consumption in any patient. After consuming of alcohol, HUT induced NCS in 11 patients (AP group: 52.3±17.8 years old, 7 males, mixed type syncope in 5 patients and vasodepressor type in 6 patients), but did not induce NCS in 14 patients (AN group: 59.9±15.3 years old, 11 male). In the AP group, syncope occurred after an interval of between 6 min to 25 min (average: 15.3±6.5 min) of HUT following alcohol consumption. The amount of alcohol ingested before HUT was similar in the AN and AP group (AN group:

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AN, alcohol-negative; BP, blood pressure; HR, heart rate; HL, hyperlipidemia; PAf, paroxysmal atrial fibrillation; SSS, sick sinus syndrome; PMI, pacemaker implantation; HT, hypertension; DM, diabetes mellitus; Af, atrial fibrillation; Chr, chronic.

AP, alcohol-positive; Frequent, 10 times or more; GERD, gastroesophageal reflux disease. Other abbreviations see in Table 1.
Background of the Patients
Tables 1 and 2 show complicating diseases, customary alcohol intake, amount of alcohol consumed prior to syncope and number of syncope episodes in each patient. There was no significant difference between the 2 groups in the amount of alcohol ingested before syncope. The proportion of patients involved in social drinking was significantly higher in the AP group (6/14 in AN group and 10/11 in AP group, p<0.01, chi-square analysis). The number of episodes of syncope after drinking alcohol was larger in the AP group (see Tables 1 and 2: 2 or more syncope episodes occurred in 3/14 in the AN group and 7/11 in AP group, p=0.03, chi-square analysis).

Effect of Alcohol Drinking on BP and Heart Rate (HR) in the Supine Position
BP and HR in the supine position before and after alcohol consumption are shown in Tables 1 and 2 (in each patient) and Table 3 (average of the 2 groups). HR in the supine position was significantly increased after drinking alcohol in both the AN group and AP group; however, BP in the supine position did not change after alcohol consumption.

Changes in BP and HR During HUT Before and After Alcohol Consumption
Systolic BP decreased significantly during HUT before and after alcohol consumption in both the AN group and AP group. Diastolic BP also fell significantly during HUT after alcohol consumption, and before alcohol consumption in the AN group. HR increased significantly during HUT before alcohol consumption in both groups and after in the AN group.

BP and HR in the supine position and during HUT did not differ between the 2 groups before and after alcohol consumption, except BP during HUT after drinking alcohol.

Effects of Alcohol Consumption on Plasma Levels of Norepinephrine and Epinephrine (P-NE and P-E) During HUT (Figs 1 and 2)
The P-NE level increased significantly during HUT in
both the AN group and AP group before and after alcohol drinking. There were no significant differences between the AN group and AP group in P-NE level in the supine position, and during HUT before and after alcohol consumption.

The P-E level increased significantly during HUT before and after alcohol consumption in both the AN group and AP group.

Before alcohol consumption, the P-E level was significantly higher in the AP group than in the AN group in the supine position, although within the normal range (less than 100 pg/ml) in all patients, and not significantly different between the 2 groups during HUT (supine position: AN, 28.5±18.7 vs AP, 44.1±25.4 pg/ml; p<0.05, at 15 min, of HUT: AN, 54.4±28.6 vs AP, 90.4±73.1 pg/ml; NS).

After alcohol consumption, the difference in P-E level was clear between the AP group and AN group, and the P-E level was much higher in the AP group during HUT (supine position: AN, 39.3±21.0 vs AP, 103.6±97.7 pg/ml; p<0.05, at 15 min, of HUT: AN, 70.9±35.1 vs AP, 258.0±

Fig 2. Plasma epinephrine level at supine position and at 15 min of HUT before and after alcohol consumption in AN group and AP group. *p<0.05. Abbreviations see in Fig 1.

Fig 3. Plasma arginine vasopressin level at supine position and at 15 min of HUT before and after alcohol consumption in AN group and AP group. *p<0.05. Abbreviations see in Fig 1.
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179.2 pg/ml; p<0.05).

Effects of Alcohol Drinking on Plasma Levels of Arginine Vasopressin (P-AVP, Figs 3 and 4)

P-AVP increased significantly during HUT before and after alcohol consumption in both the AN group and AP group. After alcohol consumption, P-AVP was greatly enhanced during HUT in the AP group.

P-RA increased significantly during HUT before and after alcohol drinking in both the AN group and AP group. P-RA during HUT after drinking alcohol tended to be higher in the AP group than the AN group, but the difference between the 2 groups was not significant.

Discussion

The hemodynamic and hormonal responses to HUT were determined before and after alcohol consumption in 25 patients who experienced syncope after drinking alcohol. The 5 main results are as follows: (1) HUT did not provoke NCS in all patients before drinking alcohol, but provoked NCS in 11 patients after drinking alcohol (the AP group). In 14 patients, NCS was not provoked by HUT even after drinking alcohol (the AN group). (2) The alcohol consumption significantly increased HR in the supine position, but did not change BP in the supine position in either groups. (3) P-NE did not differ between the 2 groups in the supine position or during HUT before and after drinking alcohol. (4) P-E in the AP group was (2.6 times) higher than in the AN group in the supine position and during HUT (3.6 times) after drinking alcohol. (5) P-AVP was significantly higher in the AP group than the AN group during HUT after drinking alcohol.

Effects of Alcohol on BP and HR

BP in the supine position did not change, but the HR in the supine position increased significantly with alcohol drinking in both groups. Reports exist of acute effects of alcohol on BP and HR. Several studies have found that alcohol intake does not change BP.6 Other studies reported that BP increased or decreased after drinking alcohol.7–10 The differences between these reports may stem from differences in the degree of vasodilator action by alcohol and the degree of compensatory sympathetic nerve activation in different groups of subjects.

Alcohol-Induced Hypotension During HUT

Syncope attack due to hypotension during HUT was not induced before drinking alcohol in any patient. Syncope was dependent on drinking alcohol.Orthostatic hypotension is diagnosed when the hypotension occurred just after adopting the head-up position. In the present study, syncope with severe hypotension occurred abruptly at 6 min or later during HUT in AP group. The syncope observed in the present study was therefore regarded as alcohol-induced NCS and not as orthostatic hypotension. Five of 11 patients, in whom bradycardia was complicated with hypotension, were diagnosed with mixed-type NCS, and 6 patients were diagnosed with vasodepressor-type NCS.

Tateoka et al also performed HUT after alcohol consumption in 12 patients with alcohol-related syncope.11 None of the subjects (0/12) exhibited a positive response in the control HUT, and only one subject had a positive response (1/12; 8.3%) in the ISP HUT. However, strong positive results (9/12, 75%) were observed in the alcohol HUT. Tateoka et al's protocol differed from the present one; for example, they administered 17.5 ml alcohol (350 ml of beer with 5% alcohol) in all patients. In the present protocol, a varying amount of alcohol (10–40 ml), according to the quantity ingested before the syncope in clinical situation, was administered to the patients. Our protocol may reproduce the clinical situation but their protocol may be more suitable as a clinical evaluation test.
Effects of Alcohol on P-NE and P-E at Rest and During HUT

Sra et al investigated plasma catecholamine changes during head-up tilt testing in NCS patients and control subjects. They compared catecholamine changes in syncpe during HUT in NCS and after 15 min of HUT in control subjects. They found a fivefold increase in epinephrine levels in NCS patients relative to control subjects, whereas norepinephrine levels before and during head-up tilting were similar in control subjects and NCS patients. A previous study found similar results. Epinephrine is primarily secreted from the adrenal medulla, and simultaneous norepinephrine release accounts for 20% of the total catecholamine output. Both studies point in the same direction, namely increased adrenomedullary activity and reduced neuronal sympathetic activity despite a significant decrease in BP during HUT in NCS.

The present study found that the P-E level was higher in the AP group than in the AN group after drinking alcohol. After alcohol consumption, the P-E level in the AP group was 2.6 times higher in the supine position, and 3.6 times higher during HUT, than in the AN group. P-NE did not differ between the 2 groups in the supine position or during HUT before and after drinking alcohol. We therefore consider that the different increases in adrenomedullary activity and neuronal sympathetic activity was produced by drinking alcohol alone before starting HUT, and was further intensified by HUT in the AP group.

Factors likely to be relevant to alcohol-induced NCS are: active vasodilation due to ß-adrenergic stimulation as a result of increased adrenomedullary activity (in other words, a larger increase in P-E); direct action of alcohol; and passive vasodilation due to diminished neuronal sympathetic activation. The exaggerated cardiac contraction due to ß-adrenergic stimulation as a result of increased adrenomedullary activity trends to increase the neural traffic in unmyelinated C-fibers and, consequently, induce centrally mediated sympathetic withdrawal and increased vagal activity. Such changes constitute the so-called Bezold–Jarisch reflex.

Effects of Alcohol on P-AVP and P-RA at Rest and During HUT

In the AP group there was a clear increase in P-AVP during HUT after drinking alcohol. We believe that the increase in P-AVP was due to counter regulation against hypotension during the HUT. Imai et al, however, reported that P-AVP plays an important role in the neurocardiogenic reflex induced by hemorrhage observed in male homozygous Brattleboro rats with hereditary hypothalamic diabetes insipidus. Arginine vasopression (AVP) inhibitors, which prevent that P-AVP plays an important role in the neurocardiogenic reflex, however, are not currently available in Japan, may provide further information about the role of AVP in NCS.

P-RA increased significantly during HUT before and after alcohol drinking in both the AN group and AP group. We speculated that P-RA might be also higher in the AP group than the AN group during HUT after drinking alcohol as a result of the counter regulatory action against hypotension. P-RA during HUT after alcohol consumption tended to be higher in the AP group than the AN group, but the difference between the 2 groups was not significant. Many factors are known to influence the P-RA level. None of the patients were taking drugs, specifically antihypertensives, which affect renin activity. Sodium intake and hydration status might be major determining factors for renin activity in the present study. Harrison et al reported P-RA in the state of normal hydration is lower than under dehydration, and that increases in P-RA during HUT are attenuated following rehydration. Our subjects were asked to take a light lunch on the day of HUT, but breakfast was not restricted and several patients took no lunch on the day of HUT. The extent of sodium loading and hydration status consequently differed between individuals according to their eating habits despite supplementation with saline (1 ml/min) during the HUT; this could influence the results. The time for hypotension seemed to be short for full activation of P-RA, for which at least an hour might be needed.

We were not able to determine the causes of syncpe in the AN group. One of the reasons why the syncpe was not inducible by our protocol may be that amount of alcohol consumed was not enough in AN group, in which customary alcohol intake was larger than AP group. Although, we administered varying amounts of alcohol according to the quantity ingested before the syncope in clinical situation, we set the upper limit of loading dose of alcohol as 40 ml, which may not be enough to induce NCS in the AN group.

We also consider that we could not reproduce the clinical situations through alcohol ingestion alone. In addition to alcohol drinking, several factors that might induce hypotension including NCS were present in several patients, including overwork, dehydration, overheating and mental stress. We could not exclude the possibility of syncpe due to these factors.

Study Limitation

Since all subjects in the present study had experienced syncope only after alcohol consumption, we performed HUT without and with alcohol drinking. HUT with the administration of ISP or nitroglycerin was not performed. Consequently, NCS was not completely ruled out in the AN group patients, and we do not know whether these drugs also induce NCS in the AP group.

We experienced a case of alcohol-induced NCS, which was prevented using oral treatment with the ß-blocker inderal, but we do not know what kinds of drugs are best for preventive therapy. Temperance is the only sure therapy, but in practice further study of how to treat this type of NCS will be needed, including preventative drugs.

Conclusion

We found that NCS was inducible using HUT with alcohol consumption in 11 of 25 patients who experienced syncope only after drinking alcohol. Alcohol-induced imbalance between increases of adrenomedullary sympathetic nervous activity, expressed through the P-E level, and peripheral sympathetic nerve activity, expressed through the P-NE level, may play a crucial role in alcohol-induced NCS.

References


