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Cardiovascular changes in alcoholic patients during withdrawal phase

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Abstract

Background: Haemodynamic changes such as tachycardia, arterial hypertension and elevated cardiac output are usual in alcohol withdrawal syndrome (AWS). Objective: We investigated central haemodynamics in alcoholic patients non-invasively in different phases of AWS parallel to recording AWS symptoms. Material and methods: 22 alcoholic patients during different phases of withdrawal were investigated 1, 2, 3 and 10 days after admission for detoxification. The intensity of alcohol withdrawal syndrome (AWS) was evaluated with a rating scale. Stroke volume (SV) was measured with an impedance cardiogram, systolic (SBP), diastolic (DBP), and mean blood pressures (MBP) were measured with a sphygmomanometer by Korotkoff, and heart rate (HR) was obtained from an electrocardiogram (ECG). Cardiac output (CO) and total peripheral resistance (TPR) were calculated. Results: The intensity of AWS decreased towards Day 10. Concomitantly, MBP decreased which was attributable to a reduction of both SBP and DBP. Changes in TPR were proportional to the level of change in SV. The level of HR measured on Day 10 differed from the HR on Day 1 but not from rates on Days 2 and 3. The CO tended to be maintained at the same level during AWS. Depending on the level of CO on Day 1, the haemodynamic parameters underwent different courses towards the end of AWS. When CO was low (<6 l), TPR decreased and CO tended to be at the same level. The opposite was true when CO was high (> 6 l). Conclusion: These results suggest that the adaptive capacity of haemodynamics appears to be preserved in patients with alcohol withdrawal without evident cardiac diseases. The cardiovascular system of alcoholic patients tends to adapt to the changing level of activity in the sympathetic nervous system during alcohol withdrawal (German J Psychiatry 2000;3:1-6).

Key words: alcoholism, cardiac output, blood pressure, heart rate, haemodynamics, impedance cardiography, substance withdrawal syndrome

Introduction

Alcohol withdrawal syndrome (AWS) is characterised by increased anxiety, tremulousness, paroxysmal sweating and reduced sleep, which develop after cessation of alcohol abuse (Gross et al., 1974, Koch-Weser et al., 1976). Cardiovascular changes as increased systolic (SBP) and diastolic blood pressures (DBP) as well as accelerated heart rate (HR) often follow AWS. Even a single moderate dose of alcohol ingestion in non-alcoholic subjects causes significant changes in haemodynamics. During the phase of rising blood ethanol, HR and cardiac output (CO) increase and total peripheral resistance (TPR) decreases. In contrast, during the declining blood ethanol phase, SBP and stroke volume (SV) decrease (Kupari, 1983).

Pronounced haemodynamic changes are usual in AWS: tachycardia, arterial hypertension and elevated cardiac output (Carlsson, 1971; Beckman et al., 1981; Saunders et al., 1981; Clark and Friedman, 1985). Alcohol abuse and hypertension are strongly associated, with a 50 to 150% higher prevalence in heavy users of alcohol than in abstainers (Clark, 1984; Beevers and Maheswaran, 1988). Alcoholics admitted for detoxification frequently have blood pressure exceeding 140/90 mmHg. In most cases, this appears as a transitory hypertension, with pressures returning to normal a few days after acute withdrawal. If abstinence continues, these alcoholics will usually remain normotensive at rest (Saunders et al., 1981; Clark and Friedman, 1985). However, in some alcoholic subjects the BP elevation during AWS may predict future BP abnormalities (King et al., 1991). The degree of hypertension seen during AWS closely correlates with AWS severity (Potter et al., 1984) and with the amount of alcohol taken during the most recent hard-drinking period (Clark and Friedman, 1985). A transient increase occurs in SBP, but not in DBP during AWS, which decreases with the resolution of the withdrawal symptoms. The degree of change is markedly affected by age. Younger patients have a greatly accentuated lability as compared to the older age-group (Beckman et al., 1981). King et al. (1996) have reported cardiodynamic changes at 3-4 weeks postwithdrawal in alcoholic patients with transitory hypertension during withdrawal. Elevated peripheral resistance, elevated heart rate, and reduced stroke volume were observed during rest and an isometric handgrip task.

Orthostatic hypotension may occur in AWS as a result of impaired blood-pressure control. Thus, Eisenhofer et al. (1985) reported that despite a raised plasma concentration of catecholamines and HR responses to standing, withdrawing alcoholics as a group showed a fall in BP on standing, four out of ten patients having a fall of more than 30/5 mmHg. De Marchi et al. (1986) were unable to confirm these findings; only a small percentage (3.5%) exhibited mild to severe orthostatic hypotension, whereas a significant percentage (56%) of withdrawing alcoholics showed an increase in BP in a standing position.

In this study we investigated central haemodynamics in alcoholic patients non-invasively in different phases of AWS parallel to recording AWS symptoms.

Subjects and Methods

Patients. 22 patients with alcohol dependence in AWS were investigated within 1, 2, 3, and 10 days of admission to an alcohol in-patient unit for detoxification. All fulfilled the DSM-III-R criteria for alcohol dependence and alcohol withdrawal (American Psychiatric Association, 1987). Patients with other psychiatric pathology and substance-abuse, complicated forms of AWS, and alcoholism, as well as evident cardiologic diseases were excluded. All were males under 50 years of age.

The patients underwent a routine clinical and psychiatric examination. Relevant laboratory tests commonly used to evaluate liver and kidney functions (ASAT, ALAT and urea), a blood and urine examination, and an electrocardiogram (ECG) were included. Withdrawal symptoms were treated with oral diazepam 10-20 mg per day as needed. Diazepam was not given at least three days prior to the first examination or three days prior to the examination on Day 10. The characteristics of patients are summarized in Table 1. Informed written consent and institutional approval were obtained.

Table 1. Sample characteristics

Characteristic	Mean ± SEM
Age (yr)	37 ± 1.4
Duration of heavy drinking (yr)	12 ± 1.3
Duration of AWS (yr)	8 ± 1.4
Daily ethanol consumption (g)	351 ± 18
Duration of last alcohol abuse (days)	19 ± 4.1

Rating the alcoholic symptoms. The structure and severity of AWS were studied with the aid of a rating scale, which includes a list of general WS manifestations, viz. alcohol craving, depressed mood, anxiety, suspiciousness, irritability, transient hallucinations or illusions, weakness, insomnia, headache, tremor, polyuria, vomiting, anorexia, diarrhea, thirst, chest pain, tachycardia, elevated blood pressure and hyperemia. The intensity of each symptom was scored as follows: 2 (= symptom present and marked), 1 (= all other types of symptoms present) or 0 (=symptom is absent). The recording of symptoms in accordance with the rating scale was done on Days 1, 2, 3 and 10 of admission to the hospital, at approximately the same time of the day.

Haemodynamic measurements. Cardiodynamic variables were measured by an impedance cardiograph system (RPG 2-02, Russia) using four band-electrodes as described by Kubicek et al. (1966). Two aluminium band

Table 2. Central haemodynamic changes in AWS

Day	HR	SBP	DBP	MBP	SV	CO	TPR	AWS
1	85±4.2	141±4.0	91±2.4	106±2.6	71±8.1	5.8±0.5	1790±168	17±1.0
2	79±3.5	133±3.8	87±2.5	101±2.7	62±4.9	4.8±0.3	1900±164	11±1.1
3	77±2.7	129±3.6	86±3.0	99±3.0	67±5.1	5.1±0.4	1760±136	7.5±0.7
10	72±2.3	119±2.7	79±1.5	92±1.6	83±6.2	5.7±0.4	1410±101	1±0.4
ANOVA F	5.25	17.81	10.80	12.43	4.76	2.08	3.39	102.85
p	<0.01	<0.001	<0.001	<0.001	<0.01	NS	<0.05	<0.001
$p_{1\text{-}10\ Days}$	<0.01	<0.001	<0.001	<0.001	NS	NS	NS	<0.001
$p_{2\text{-}10\ Days}$	NS	<0.01	<0.001	=0.001	<0.001	NS	>0.001	<0.001
$p_{3\text{-}10\ Days}$	NS	<0.01	<0.01	<0.01	=0.02	NS	=0.02	<0.001

Abbrevations: AWS= alcohol withdrawal syndromes (scores); HR= heart rate beat/min); SBP, DBP and MBP= systolic, diastolic and mean blood pressure (mmHg); SV= stroke volume (ml); CO= cardiac output (l/min); TPR= total peripheral resistance (dyne ×s ×cm^{-5})

electrodes, separated as widely as possible, were placed around the neck of the subject. A third electrode band was placed around the thorax just below the xiphoid process, and a fourth electrode about 5 cm below the third one. The outer electrodes were provided with a constant sinusoidal current (4 mA) with a frequency of 100 kHz. The potential changes, which reflect the changes in the impedance between the two inner electrodes, were picked up. The parameters of impedance cardiography were measured with the patient in a supine position after a 10-minute rest separately in the state of unforced breathing, of inspiration, and of expiration (at least 10 epochs for each), and the mean value was taken. Impedance cardiography has been reported to be a reliable method for measuring relative changes in SV and CO (Pushar et al, 1977; Sherwood et al., 1990, Fuller, 1992)

The following parameters were measured or calculated as follows:

(1) SBP and DBP (mmHg) measured with sphygmomanometer by Korotkoff. MBP (mm Hg) calculated from the formula MBP = (SBP + 2 x DBP)/3
(2) HR (beat/min) from the ECG
(3) SV (ml) of the heart by impedance cardiography utilizing the formula of Kubicek-Gundarov (Kubicek et al., 1966; Gundarov et al., 1983)
(4) CO (l/min) refers to HR x SV
(5) TPR (dyne?s/cm^{-5}) calculated from the formula TPR = MBP/CO

Statistics. Results were expressed as the mean ± SEM values. A one-way ANOVA for repeated measures was used for analyzing differences of haemodynamic parameters between days. Pairwise comparisons between groups were performed using a paired t-test. In these cases a Bonferroni correction was used to protect against type I errors. Correlation coefficients (r) were calculated by the Spearman rank test.

Results

It appears that significant overall changes occurred in all haemodynamic parameters studied during AWS, except for CO. The severity of AWS gradually declined towards the end of AWS, and MBP decreased concomitantly with declining AWS. This decrease in MBP was attributable to a reduction of both SBP and DBP. Changes in TPR were proportional to the level of change in SV. The level of HR measured on Day 10 differed from the HR on Day 1 but not from rates on Days 2 and 3. The CO tended to be maintained at the same level during AWS.

The severity of AWS on Day 1 correlated positively with the duration of recent alcohol abuse (r=0.44, p<0.05), with heavy ingestion of alcohol (r=0.56, p<0.01), and with duration of withdrawal syndrome (r=0.60, p<0.001). SBP on Day 1 correlated positively with the severity of AWS (r=0.46, p<0.05). SV and CO correlated positively with daily consumption of alcohol (r=0.52, p<0.05 and r=0.47, p<0.05, respectively). No significant correlations were found between anamnestic characteristics and HR, DBP and TPR on Day 1.

Table 3 shows that an equal decrease in MBP by Day 10 can be associated with differing CO and TPR changes. Thus, in patients with initially low CO, the TPR decreased significantly (t = 2.35; p<0.05), whereas CO did not increase (t = 0.78; p>0.05) by Day 10. In patients with initially high CO, a significant decrease in CO (t = 2.52; p<0.05) occurred, whereas TPR did not increase (t = 1.34; p>0.05). In the first group of patients, lowered MBP led to decreased TPR which was compensated for by increased CO. In the second category of patients, lowered MBP was due to decreased CO.

Table 3. Changes in haemodynamics with different levels of CO on Day 1

Group		MBP	HR	CO	TPR
A	Initial	112±3.5	89±5.8	4.2±0.3	2200±183
A	Change	-16±2.4	-18±4.7	0.8±0.6**	-540±268*
B	Initial	109±5.9	81±8.2	8.5±0.7	1080±131
B	Change	-13±3.5	-14±8.3	-1.4±0.5	29±99

Patients in group A (n=14) showed low CO (<6 l/min) on Day 1; group B (n=8) showed high CO (>6 l/min) on Day 1. *$p<0.05$, **$p<0.01$ in comparison with group B change values. Abbrevations: HR in beats/min; MBP in mmHg; CO in l/min; TPR in dyne ×s ×cm^{-5}.

Discussion

The results confirm the complex structure of alcohol AWS, the evolution of which is characterized by a rapid decline in intensity of WS, including the changes in the cardiovascular system. Our results showed that the adaptive capacity of the cardiovascular system in alcoholic patients during AWS is preserved. During AWS, cardiac output tended to be maintained at the same level. The finding that haemodynamic alterations paralleled changes in AWS severity may suggest that these changes during AWS are due mainly to extracardial effects. The severity of AWS also depends on anamnestic data, such as daily consumption of ethanol, and duration of recent alcohol abuse, and duration of withdrawal syndrome. Mechanisms of lowered MBP differ in AWS, depending on the initial haemodynamic indices at the onset of AWS.

Correlation analysis of haemodynamic parameters (SBP, SV, CO) in alcoholic patients on Day 1 demonstrates that their level depends on the severity of AWS and on heavy ingestion of alcohol. An increase in SBP as well as AWS severity may reflect the degree of activation of the sympathoadrenal system (Hawley et al., 1985). As the alcoholism progresses, there is a risk of toxic myocardiac damage and impairment of the heart's contractile function (Wu et al., 1976).

The exact mechanism of haemodynamic alterations in alcohol withdrawal has not been fully elucidated, but it appears to be complex and may involve central and peripheral systems regulating haemodynamics. The important role of endogenous active substances determining haemodynamic changes is not excluded, the hormones of the hypothalamus-hypophysis-adrenal cortex axis playing the major role. Thus, the cortisol concentration increases and correlates positively with the BP level (Smals et al., 1976; Bannan et al., 1984; Potter et al., 1984). The increase in cortisol level may be caused by stimulation (Gilles et al., 1982) directly or via the secretion of antidiuretic hormone which becomes greater in AWS (Jenkins and Connolly, 1968). This antidiuretic hormone may induce the pressor effect of angiotensin II and catecholamines and enhance the discharge of ACTH (Potter et al., 1984). In contrast to this, Arkwright et al. (1982) reported that hypertensive alcoholics have normal plasma concentrations of cateholamines, angiotensin and aldosterone. There is a reversible decrease in renal sodium excretion which closely correlates with the BP level (De Marchi and Cecchin, 1985).

It is also possible that the direct action of ethanol on the vascular wall is responsible for elevated BP in AWS. Vasoconstriction occurring in AWS is believed to be one of the mechanisms active in the development of the brain insults seen in alcoholic patients (Altura et al., 1983). However, these effects are not identical for all vascular beds. Ethanol depresses the normal spontaneous activity of small arteries and veins and inhibits their contractile responses to the endogenous neurohumoral substances, thus causing vasodilation (Altura and Altura, 1982). The direct action of ethanol on the vascular wall makes it more sensitive to the effects of other vasoactive substances. However, it remains unclear why the alcoholic patient with a high blood ethanol level often has normal BP which becomes hypertensive during AWS (Saunders et al., 1981). Impairment of the baroreceptor reflex has been observed in alcohol-treated rats (Abdel-Rahman et al., 1985), but Rhee et al. (1989) could not confirm this finding. Autonomic nervous damage may in part contribute to withdrawal hypertension (Yokoyama et al., 1991; Murata et al., 1994; Miralles et al., 1995). In alcoholic patients, interaction between sodium, magnesium, and calcium ions has been described as playing a role in the genesis of hypertension (Adeniyi, 1986).

A hyperdynamic circulatory state is often seen in alcoholic patients undergoing withdrawal, and during delirium tremens in particular (Mendelson, 1970; Abraham et al., 1985). Ballas et al. (1982) showed that the SV was not significantly different from normal values, but some of the patients during AWS exhibit decreased SVs not due to any heart diseases. However, the material of that study included patients without severe forms of AWS, and haemodynamic control values were not obtained after AWS developing. Beta-adreno receptor blockers timolol and propranolol tended to normalize elevated HR and CO, and to correct high TPR (Carlsson, 1971; Potter et al., 1984), showing that central and peripheral beta-adrenoreceptors may regulate withdrawal-induced haemodynamic changes in alcoholic patients.

In summary, significant changes were observed in haemodynamics of alcoholic patients during withdrawal, paralleling a decrease in the severity of withdrawal symptoms. The adaptive capacity of haemodynamics appears to be preserved in patients with alcohol withdrawal without evident cardiac diseases. The cardiovascular system tends to adapt to the changing level of activity in the sympathetic nervous system in the alcohol withdrawal state.

References

Abdel-Rahman A-RA, Dar MS, Wooles WR: Effect of chronic ethanol administration on arterial baroreceptor function and pressor and repressor responsiveness in rats. J Pharmacol Exp Ther 232; 194-201: 1985

Abraham E, Shoemaker WS, McCartney SF. Cardiorespiratory patterns in severe delirium tremens. Arch Intern Med 145; 1057-1059: 1985

Adeniyi FA. Interactive roles of monovalent and divalent cations in pathogenesis of hypertension caused by alcohol. J Clin Pathol 39; 1264-1268: 1986

Altura BM, Altura BT, Gergebrevol DA. Alcohol induced spasms of cerebral blood vessels in relation to cerebrovascular accident and sudden death. Science 220; 331-333: 1983

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised, Washington, DC, American Psychiatric Association, 1987

Arkwright PD, Beilin LJ, Rouse L, Vandongen R. The pressor effect of moderate alcohol consumption in man: a search for mechanism. Circulation 66; 515-519: 1982

Ballas M, Zoneraich S, Yunis M, Zoneraich O, Rosner F. Noninvasive cardiac evaluation in chronic alcoholic patients with alcohol withdrawal syndrome. Chest 82; 148-153; 1982

Balldin J, Berggren U, Engel J, Lindstedt G, Sundkler A, Wålinder J: Alpha-2-adrenoceptor sensitivity in early alcohol withdrawal. Biol Psychiatry 31; 712-719: 1992

Bannan LT, Potter JP, Beevers DG, Saunders JB, Walterns JRF, Ingram MC. Effect of alcohol withdrawal on blood pressure, plasma renin activity, aldosterone, cortisol and dopamine-hydroxylase. Clin Science 66; 659-663: 1984

Beckman H, Frank RR, Robertson RD, Brady KA, Coin EJ. Evaluation of blood pressure during early alcohol withdrawal. Ann Emerg Med 10; 32-35: 1981

Beevers DG, Maheswaran R. Does alcohol cause hypertension or pseudo-hypertension? Proc Nutr Soc 47; 111-114: 1988

Carlsson C. Haemodynamic studies in alcoholics in the withdrawal phase. Int J Clin Pharmacol Ther Toxicol 3; 61-63: 1971

Clark LT. Alcohol use and hypertension: clinical considerations and implications. Postgrad Med J 75; 273-276: 1984

Clark LT, Friedman HS. Hypertension associated with alcohol withdrawal: Assessment of mechanisms and complications. Alcoholism: Clin Exper Res 9; 125-130: 1985

De Marchi S, Cecchin E. Alcohol withdrawal and hypertension: evidence for a kidney abnormality. Clin Science 69; 239-240: 1985

De Marchi S, Cecchin E. Are orthostatic hypotension and impaired blood pressure control common features of alcohol withdrawal syndrome? Clin Science 70; 213-214: 1986

Eisenhofer G, Whiteside EA, Johnsson RH. Plasma catecholamine responses to change of posture in alcoholics during withdrawal and after continued abstinence from alcohol. Clin Science 68; 71-78: 1985

Eisenhofer G, Szabo G, Hoffman PL: Opposite changes in turnover of noradrenaline and dopamine in the CNS of ethanol-dependent mice. Neuropharmacology 29; 37-45: 1990

Fuller HG. The validy of cardiac measurement by thoracic impedance: a meta-analysis. Clin Invest Med 15; 103-112: 1992

Gilles GH, Linton EA, Lowry PL. Corticotropin releasing activity of the new CRF is potentiated several times by vasopressin. Nature 299; 355-357: 1982

Gross MM, Lewis E, Hastey J. Acute alcohol withdrawal syndrome. In: Biology of alcoholism. Vol 3. Clinical Pathology. New York, Plenum Press, pp 191-263, 1974

Gundarov IA, Pushkar YT, Konstantinov YI. The central haemodynamic norms determined by impedance cardiography. Ther Arch 55; 26-28: 1983

Jenkins JS, Connolly J. Adrenocortical response to ethanol in man. Br Med J 2; 804-805: 1968

King AC, Errico AL, Parsons OA. Blood pressure dysregulation associated with alcohol withdrawal. Alcohol Clin Exp Res 15; 478-482: 1991

King AC, Bernardy NC, Parsons OA, Lovallo WR. Hemodynamic alterations in alcohol-related transitory hypertension. Alcohol 13; 387-393: 1996

Koch-Weser J, Sellers EM, Kalant H. Alcohol intoxication and withdrawal. N Engl J Med 294; 757-762: 1976

Kubicek WG, Karnegis JN, Patterson RP, Witsoe DA, Mattson RH. Development and evaluation of an impedance cardiac output system. Aerospace Med 37; 1208-1212: 1966

Kupari M: Acute cardiovascular effects of ethanol. A controlled non-invasive study. Br Heart J 49;174-82: 1983

Mendelson JH, Ogata M, Mello NK. Adrenal function and alcoholism. I. Serum cortisol. Psychosom Med 33; 145-57: 1971

Miralles R, Espadaler JM, Navarro X, Rubies-Prat J. Autonomic neuropathy in chronic alcoholism: evaluation of cardiovascular, pupillary and sympathetic skin responses. Eur Neurology 35; 287-292: 1995

Murata K, Araki S, Yokoyama K, Sata F, Yamashita K, Ono Y. Autonomic neurotoxicity of alcohol assessed by heart rate variability. J Autonomic Nervous System 48; 105-111: 1994

Potter JF, Bannan LT, Beevers DG. Alcohol and hypertension. Br J Addiction 79; 365-373: 1984

Pushkar YT, Bolshov VM, Yelisarova NA. Determination of the cardiac output by impedance cardiography. Cardiology 17; 85-90: 1977

Rhee HM, Valentine JL, Hendrix D, Schweisthal M, Soria M. Hemodynamic responses to vasoactive compounds in chronically alcohol treated rats. Adv Exp Med Biol 248; 629-639: 1989

Saunders JB, Bevers BC, Paton A. Alcohol induced hypertension. Lancet 2; 653-656: 1981

Sherwood A, Allen MT, Fahrenberg J, Kelsey RM, Lovallo WR, van Doornen LJP. Methodological guidelines for impedance cardiography. Psychophysiology 27; 1-23: 1990

Smals AG, Kloppenberg PW, Njo T, Knoben JN, Ruland CM. Alcohol-induced Cushingoid syndrome. Br Med J 2; 1298-1299: 1976

Yokoyama A, Takagi T, Ishii H. Impaired autonomic nervous system in alcoholics assessed by heart rate variation. Alcohol Clin Exp Res 15; 761-765: 1991

Wu CF, Sudhaker M, Ghazanfar J, Ahmed SS, Regan TJ. Preclinical cardiomyopathy in chronic alcoholics: a sex difference. Am Heart J 91; 281-6: 1976

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