

Reduced baroreflex sensitivity in acute alcohol withdrawal syndrome and in abstained alcoholics

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Abstract

Acute alcohol withdrawal is often associated with increased sympathetic activity, and a decreased baroreflex sensitivity (BRS) can be assumed. Parameters of heart rate variability (HRV), blood pressure variability (BPV), BRS as well as cardiac index (CI), left ventricular work index (LVWI) and total peripheral resistance (TPR) were investigated in 20 patients undergoing acute alcohol withdrawal and matched controls. Measures were obtained during the peak of withdrawal symptomatology prior to treatment as well as 2 and 24 h under continuous clomethiazole treatment. Alcohol withdrawal scores were obtained and correlated with autonomic measures. In addition, parameters were assessed in 15 subjects who abstained from alcohol after long-term intake. We found a severe down-regulation of BRS during acute alcohol withdrawal and to a milder extent in abstained alcoholics. Furthermore, HRV and BPV did not unequivocally reveal signs of elevated sympathetic activity. Non-linear parameters of HRV and parameters of BRS correlated with the severity of AWS. The distinct decrease of BRS in AWS and in long-term abstained subjects described here is of importance since similar alterations have been identified as independent prognostic factors for cardiac mortality in other diseases.

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1. Introduction

The acute alcohol withdrawal syndrome (AWS) is associated with observable autonomic changes such as tachycardia, hypertension and increased body sweat rate (Kahkonen, 2003a). Many of these symptoms might be explained on the basis of increased peripheral (Banerjee et al., 1978) and central adrenergic activity (French et al., 1975) as well as increased catecholamine release (Carlsson and Haggendal, 1967; Potter et al., 1983). To date, most studies examining acute alcohol withdrawal have employed neurochemical methods, showing concentrations of noradrenaline and its major central metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) in the cerebrospinal fluid and in serum to be higher at the onset of AWS than during the decline of symptoms (Eisenhofer et al., 1990; Hawley et al.,

1994; Kahkonen, 2004). Further support for involvement of the adrenergic system is demonstrated by the capacity of propranolol to induce changes of hemodynamic parameters during different stages of AWS (Kahkonen, 2003a) and by rebound β -adrenergic hypersensitivity seen in AWS (Kahkonen, 2003a; Sellers et al., 1976).

To date, few studies have investigated the autonomic balance in acute alcohol withdrawal using neurophysiological methods such as assessment of heart rate variability (HRV, Agelink et al., 1998a; Ingjaldsson et al., 2003; Rechlin et al., 1996), blood pressure variability (BPV) or baroreflex sensitivity (BRS). The latter has been shown to be reduced after chronic alcohol administration in animals, assumedly due to specific ethanol interactions with brain stem nuclei such as nucleus tractus solitarius (Abdel-Rahman et al., 1985; Wang and Abdel-Rahman, 2004). Most studies in humans and in animals have investigated the acute effect of alcohol on HRV, and some have reported a decrease of HRV in chronic abstained alcoholics (Agelink et al., 1998b; Ingjaldsson et al., 2003; Weise et al., 1986). To our knowledge, no study to date has investigated HRV, BPV and especially BRS

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in the acute phase of alcohol withdrawal although autonomic dysfunction and an increased heart rate are core features of alcohol withdrawal.

HRV reflects the interplay between sympathetic and parasympathetic input on the cardiac pacemaker. Peripheral control of HRV is mediated mainly via the parasympathetic cholinergic vagal nerve (Low, 1997). In healthy subjects, a high degree of HRV can occur, whereas a significant decrease has been shown in patients with low parasympathetic tone (Bar et al., 2004, 2005). Low HRV is associated with poor prognosis after acute coronary events (Janszky et al., 2004).

Blood pressure displays continuous physiological fluctuation due to the influence of spontaneous rhythmical variations such as respiration. Furthermore, effects of superimposed physical and mental activity and of a large number of behavioral and environmental factors such as posture or exercise add to its essential variability and complexity. Beat-to-beat analysis of systolic or diastolic blood pressure changes allows the estimation of blood pressure variability (BPV).

In addition, baroreflex sensitivity (BRS) is a powerful beat-to-beat negative feedback mechanism regulating absolute blood pressure. Baroreceptors indirectly sense changes of systemic blood pressure, which are then transmitted to the central nervous system where they trigger reflex adjustments leading to effects buffering or opposing alterations. Thus, a rise in blood pressure elicits reflex parasympathetic activation and sympathetic inhibition with a subsequent decrease of heart rate, cardiac contractility, vascular resistance and venous return. Conversely, the latter parameters are increased when a decrease in pressure is sensed.

Impedance cardiography is a non-invasive technique based on the measurement of phasic changes in transthoracic electric resistivity accompanying left-ventricular ejection of blood into the ascending aorta (Sherwood et al., 1990), and permits the assessment of hemodynamic parameters such as cardiac output (CO) or total peripheral resistance (TPR). CO indicates the blood volume being ejected by the heart in a defined time, therefore resembling an important factor for the determination of cardiac effectiveness and for adequate blood supply to different organs. It is widely used for assessing and monitoring heart failure or inadequate circulation. By definition, two major factors contribute to CO: the heart rate and the stroke volume (blood volume which is ejected upon contraction). Increases of the heart rate therefore effectively increase CO, as long as sufficient time is given for diastole. Mechanisms for increasing the stroke volume include higher preload, lower afterload and increased myocardial contractility (Frank–Starling law). In the few studies that employed impedance cardiography during alcohol withdrawal a preserved adaptive capacity of hemodynamic regulation as well as an adaptation to the changing level of sympathetic nervous activity was found (Kahkonen, 2003b; King et al., 1996).

To characterize and quantify cardiac sympatho-vagal balance in acute alcohol withdrawal we investigated a group of patients with acute, moderate to severe alcohol withdrawal and compared them to matched controls. In order to differentiate between acute withdrawal effects and autonomic changes due to long-term alcohol intake, a second control group consisting

of abstained alcoholics was additionally assessed. Measures of time and frequency domains of HRV and BPV as well as modern non-linear parameters were applied. We calculated BRS using linear and non-linear algorithms to obtain information on fine tuning of heart rate and blood pressure. Impedance cardiography (ICG) was used to allow the estimation of actual cardiac work and TPR as well as their regulation in the disease. We hypothesized that abnormalities of autonomic function in AWS should be found using these methods. Parameters were obtained during the peak of withdrawal before patients were treated, as well as 2 and 24 h after receiving clomethiazole for withdrawal symptoms. Alcohol withdrawal scores were obtained and correlated to autonomic measures.

2. Materials and methods

2.1. Subjects

Thirty-three male patients admitted for alcohol detoxification were screened, of which 26 patients were investigated and 20 patients were included in our study (Table 1). All patients had a history of alcohol dependence according to DSM-IV criteria and suffered from a severe acute alcohol withdrawal syndrome for which they were treated with clomethiazole according to hospital routine. In addition to a clinical interview on the detoxification unit, several scales were applied to confirm the diagnosis (Munich alcoholism test, MALT (Feuerlein et al., 1979) and Lübecker Alkoholentzugs-Risiko-Skala (Lübecker alcohol withdrawal risk scale, LARS, Wetterling, 1994)). Patients scoring lower than 11 points on the MALT were not included in the study. To quantify the severity and progression of the AWS, the “Alcohol Withdrawal Scale” (AW scale, Wetterling et al., 1997) and the Banger score (Banger et al., 1992) were used. The AW scale considers autonomic and mental symptoms and is a suitable instrument to quantify alcohol withdrawal (Wetterling et al., 1997). The Banger score can be used to determine doses of clomethiazole based upon the severity of withdrawal symptoms (4–6 points: 6 ml clomethiazole per hour; 6–8 points: 12 ml clomethiazole per hour). According to in-house guidelines no further medication apart from clomethiazole was administered during withdrawal. A physical examination, routine ECG and blood diagnostics as well as toxicological screening (blood and urine) were performed. Patients with a history of drug or substance abuse or any evidence of drugs or illegal substances in the toxicological investigation were excluded from the study. In particular, none of the patients included tested positive for blood alcohol. Furthermore, we excluded patients with a history of severe alcohol-related diseases such as liver cirrhosis ($n=4$), peripheral neuropathy ($n=2$) and any sign of cardiomyopathy. All participants gave written informed consent; the protocol was approved by the Ethics Committee of the Friedrich-Schiller-University, Jena. Patients were investigated after admission during the peak of the AWS just before treatment with clomethiazole (investigation A), 1 h after the second application of clomethiazole (equal to approximately 2–3 h after the initial application, investigation B) and after being on clomethiazole treatment for 24 h (investigation C).

Patient data were compared to results from 20 age-matched male controls. Control subjects were recruited from hospital staff and medical students. In order to differentiate whether the autonomic changes assessed are related to acute alcohol withdrawal or due to long-term alcohol intake, an additional 15 male subjects were investigated who had a history of alcohol dependence, but abstained from drinking for a significant time (Table 1). Patients and controls had to be free from any medical or additional psychiatric disease and none of them were in receipt of any interfering medication (e.g. cardiac medications or tranquilizer). Participants were asked to refrain from smoking, heavy eating or exercising 2 h prior to the investigation. Controls were also interviewed to assure the absence of a psychiatric disorder or any alcohol related disease.

2.2. Data acquisition and preprocessing

Examinations were performed between 3 and 10 p.m. in a quiet room which was kept comfortably warm (22–24 °C). Subjects were asked to relax, breath

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