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ScienceDirect
Drug and Alcohol Dependence 89 (2007) 259–266
DRUG and ALCOHOL DEPENDENCE
www.elsevier.com/locate/drugalcdep

Increased QT interval variability index in acute alcohol withdrawal

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Received 13 September 2006; received in revised form 14 January 2007; accepted 17 January 2007

Abstract

Objective: Acute alcohol withdrawal is associated with increased cardiovascular mortality, most likely due to cardiac arrhythmias. As the QT interval reflects the most critical phase for the generation of reentry and thus for arrhythmia, we examined QT variability in patients suffering from acute alcohol withdrawal.
Methods: High resolution electrocardiographic recordings were performed in 18 male unmedicated patients suffering from acute alcohol withdrawal, 18 matched controls and 15 abstained alcoholics. From these, parameters of beat-to-beat heart rate and QT variability such as approximate entropy and QT variability index (QTvi) were calculated. Measures were correlated with the severity of withdrawal symptoms and with serum electrolyte concentrations.
Results: Heart rate and QTvi were significantly increased in acute alcohol withdrawal. Abstained alcoholics did not significantly differ from controls. While QTvi correlated with the severity of alcohol withdrawal symptoms, the mean QT interval duration showed an inverse relationship with serum potassium concentrations.
Conclusion: Our data indicate increased QT variability and thus increased repolarization lability in acute alcohol withdrawal. This might add to the elevated risk for serious cardiac arrhythmias. In part, these changes might be related to increased cardiac sympathetic activity or low potassium, thus suggesting the latter as possible targets for adjuvant pharmacological therapy during withdrawal.

Keywords: Alcohol withdrawal; Autonomic function; QT interval variability; Arrhythmia; Sudden cardiac death

1. Introduction

An increased incidence of cardiac arrhythmias and sudden cardiac death is associated with acute alcohol withdrawal syndrome (AWS) (Puddey et al., 1999; El Mas and Abdel-Rahman, 2005). Although the cascade of mechanisms leading to this increased mortality is not fully understood, increased sympathetic and/or decreased vagal modulation of heart rate parameters may play a significant role. For instance, peripheral and central adrenergic activity as well as catecholamine release are increased in AWS (French et al., 1975; Banerjee et al., 1978; Potter et al., 1983). Clinically, these alterations are reflected in the signs and symptoms displayed by the patients such as tachycardia, hypertension or increased sweat rate (Kahkonen, 2003).

Electrophysiological assessment of autonomic changes in AWS has shown unchanged or decreased heart rate variability (HRV) (Rechlin et al., 1996; Agelink et al., 1998; Bar et al., 2006a) as well as a significantly reduced baroreflex sensitivity (BRS) (Bar et al., 2006b). Both reduced HRV and BRS correlate with the severity of various kinds of cardiac diseases (Rocco et al., 1987; Peele and Brodsky, 2000; Chapleau, 2003).

However, alterations of HRV reflect the efferent cardiac sympathetic-parasympathetic modulation mainly at the sinus node level. In contrast, beat-to-beat QT interval variability (QTV) reflects the temporal fluctuation in ventricular repolarization, thus providing information on repolarization abnormalities. Not surprisingly, an association between abnormal QTV and

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doi:10.1016/j.drugalcdep.2007.01.010

ventricular arrhythmias and sudden cardiac death has been established in patients after myocardial infarction (Vrtovec et al., 2000; Bonnemeier et al., 2003; Haigney et al., 2004) or in dilated cardiomyopathy (Berger et al., 1997; Atiga et al., 2000). Recently, a novel index normalizing QTV to HRV has been established. The QT variability index (QTvi) is a useful non-invasive marker for cardiac repolarization lability (Berger et al., 1997; Atiga et al., 1998). In healthy subjects, QTvi reveals negative values. An increase in QTvi, caused either by increased QTV or reduced HRV, has been shown to be associated with cardiac disease (Haigney et al., 2004; Desai et al., 2004; Raghunandan et al., 2005; Furukawa et al., 2006), as well as with aging (Piccirillo et al., 2001) and increased sympathetic activity (Yeragani et al., 2000; Piccirillo et al., 2001; Pohl et al., 2003; Furukawa et al., 2006).

Here, we investigated heart rate and QT variability in 18 unmedicated male patients undergoing alcohol withdrawal in the acute stage in comparison to 18 healthy controls as well as 15 abstained alcoholics in order to differentiate between acute withdrawal effects and autonomic changes due to long term alcohol intake. Besides linear techniques (QTvi), we used approximate entropy (ApEn), which is a nonlinear parameter that measures the regularity in a time series (Pincus, 1991). Furthermore, we studied the acute effect of clomethiazole administration, which alleviates AWS symptoms, on the measures described. As the alcohol withdrawal state is associated with heightened sympathetic activity, we sought to test the hypothesis that QTvi will be significantly increased in AWS.

2. Materials and methods

2.1. Subjects

Thirty male patients admitted for alcohol detoxification were screened, of which 24 patients were investigated and 18 patients were included in our study (see Table 1). Most of them were known to the staff psychiatrist. 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 in-house hospital guidelines. Apart from the clinical interview on the detoxification unit, several scales were used 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 in 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 psychological symptoms and is a suitable instrument to quantify alcohol withdrawal and to evaluate its pharmacotherapy (Wetterling et al., 1997). Apart from determining the severity of withdrawal symptoms, the Banger score is used to approximate the amount of clomethiazole treatment with respect to 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. In addition to the physical examination, routine ECG and blood chemistry 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. Patients with a history of severe alcohol-related diseases such as cirrhosis of the liver ($n = 3$), peripheral neuropathy ($n = 2$) and signs of cardiomyopathy ($n = 1$) were excluded. All participants gave written informed consent to a protocol approved by the Ethics Committee of the Friedrich-Schiller-University, Jena. Furthermore, the investigation conforms with the principles outlined in the Declaration of Helsinki. From the routine blood tests performed on admission, serum liver enzyme activities and electrolyte concentrations were documented. Patients were investigated after admission during the acute stage of AWS just before treatment with clomethiazole and 1 h after the second application of clomethiazole (equal to approximately 2 h after the initial application).

Parameters of these patients were compared to the results of 18 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, who had a history of alcohol dependence, but abstained from drinking for a significant time (for demographic and clinical data, see Table 1) were also investigated. Patients and controls had to be free from any medical or additional psychiatric disease (see Table 1) and none of them were in receipt of any medication that may have confounded the results of the study (e.g. cardiac medications or tranquilizer). In addition, controls and abstained alcoholics were tested for acute alcohol intake using a breathing test device. 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

The data were acquired in a quiet room which was kept comfortably warm (22–24 °C) between 3 and 10 p.m. Subjects were asked to relax, breath regularly and move as little as possible.

Similar to previous studies (Bar et al., 2007), the electrocardiogram (high resolution, 1000 Hz) was recorded for 25 min from two separate adhesive monitoring electrodes (CNSystems®, Medizintechnik GmbH, Austria), which were placed on the chest wall to assure maximal R-wave amplitude. In addition, respiratory rate was obtained.

2.3. Data analysis

2.3.1. Measures of RR and QT variability. In order to analyze a recording period with the fewest possible artifacts and errors and maximum stationarity, continuous 256 s segments of ECG were identified from the segment between the 5th and the 15th minute of the original recordings and data from these were used to calculate the RR and QT intervals. For examples of the raw data recorded from patients and controls, see Fig. 1.

2.3.1.1. QT variability. The QT variability algorithm applied here has been described by Berger and co-workers in detail and has been used by his and our groups in previous studies (Berger et al., 1997; Yeragani et al., 2000, 2006). In brief, we used a graphical interface of digitized ECG (sampled at 1000 Hz which gives a precision of 1 ms to measure the RR and QT intervals) in which the time of the 'R' wave is obtained applying a peak detection algorithm. Then the operator provides the program with the beginning and the end of the QT wave template. This algorithm finds the QT interval for each beat using the time-stretch model. If the operator chooses a longer QT template, all the QT intervals will be biased accordingly. The output of this algorithm contains beat-to-beat RR intervals and QT intervals.

The beat-to-beat RR intervals in milliseconds were sampled at 4 Hz using linear interpolation. QT intervals were similarly constructed at 4 Hz. The sampling frequency of 4 Hz was applied to ensure that the same length of time was used for the analysis as the instantaneous RR and QT intervals. In general, RR time series free of ventricular premature beats and noise were used. The RR and QT interval data were then detrended using the best-fit line prior to the computation of spectral analyses.

The mean RR (RR mean), detrended RR variance (Detrend_{RR}), mean QT interval (QT mean), detrended QT variance (Detrend_{QT}) of RR and QT intervals and QT variance corrected for mean QT interval (QT_{VM}) were calculated from the instantaneous RR and QT time series of 1024 points (256 s). Mean RR and mean QT intervals are in milliseconds. The powers are corresponding squared values.