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DEFICITS OF RESPIRATORY-CARDIAC COUPLING IN HEAVY DRINKERS

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Abstract

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1. Physiological evidence of chronic alcohol abuse prior to the onset of clinical signs of alcohol dependence is difficult to obtain. The purpose of this study was to search for possible non-invasive indicators for chronic alcohol consumption yielding information in addition to conventional biological markers
2. The authors investigated the relationship between respiratory-cardiac coupling and blood alcohol concentration (BAC) in male subjects who lost their driver's license from drunk driving.
3. We found that subjects who had a high BAC level (0.16-0.31% at the time of offense) show altered respiratory sinus arrhythmia (RSA) and, in particular, an altered heart-rate response to auditory stimulation and compared them to a control group of social drinkers. Normal subjects showed a pronounced acoustic heart-rate response, i.e., particularly during expiration there was a difference between the interbeat-interval (IBI) traces with and without auditory stimulation. Subjects who had lost their driver's license from drunk driving had an overall severely reduced heart-rate response, that was even absent particularly in the subgroup having high BAC values (0.21-0.31%). The authors also found some evidence that in the latter subgroup IBI, RSA, and acoustic heart-rate responses partially recover after a six-month period of abstinence.
4. Specific parameters of the acoustic heart-rate response are changed in our group of alcohol abusers presumably, due to impairment of vagal function. These parameters may therefore be useful to serve as a non-invasive measure of alcohol abuse.

Keywords: acoustic heart-rate response, alcohol, heart-rate, respiratory sinus arrhythmia

Abbreviations: alanin-amino transferase (ALT), aspartat-amino transferase (AST), blood alcohol concentration (BAC), gamma-glutamyl transferase (GGT), interbeat-interval (IBI), mean corpuscular volume (MCV), heart-rate reaction to auditory stimulation (RA) and respiratory sinus arrhythmia (RSA).

Introduction

Chronic alcohol consumption precedes alcoholism and constitutes a major risk for traffic safety. Driving under the influence of alcohol is a major problem worldwide and the dominant risk factor for serious crashes (Hurst et al., 1994) Although people who have a high tolerance for alcohol are still able to drive a car under acute alcohol intoxication, the probability for careless action is sharply increased. It is difficult, however, to secure a diagnosis of chronic alcohol abuse because a subject will typically deny excessive drinking habits, thus limiting the validity of the widely used questionnaires or interviews in expert assessments (Fuller et al., 1988, Conigrave and Saunders, 1995; Cyr and Wortman, 1988). The need for such assessments will arise when a person is caught drunk driving and requests his suspended driver's license back, in which case it is important to determine if the person in question has a history of alcohol abuse (Kunkel, 1976). A decreased heart-rate variability has often been reported in chronic alcoholics (Malpas et al., 1991; Yokoyama et al., 1991). This decrease has been attributed to reduced parasympathetic activity (Beilin et al , 1992; Murata et al , 1994, Reed et al., 1999) and parasympathetic functioning might thus be the key to pinpointing long-term alcohol effects. A physiological mechanism that has long been proposed as indicative of parasympathetic activity (Katona and Jih, 1975) is the respiratory sinus arrhythmia (RSA), i.e., the variation of heart rate with the rhythm of breathing, since it seems largely mediated by the vagus nerve (Grossman and Kollai, 1993). We were thus interested in the question of whether or not RSA-related parameters would be changed in drinkers with alcohol abuse. Physiological evidence of chronic alcohol abuse is difficult to obtain. Even though the abuse will eventually harm the liver, heavy drinkers usually show normal liver function when assessed with standard laboratory tests (Saunders and Conigrave, 1990) Furthermore, liver function tests are sensitive not only to alcohol-related diseases but also to a multitude of other factors (Lum and Gambino, 1972). In addition to the classical biochemical markers, therefore, a measure of chronic alcohol abuse, based on autonomic function, would be of high practical value (Burke et al , 1992). We applied a measure that assesses central-nervous-system control of respiratory-cardiac coupling as observed in the respiratory sinus arrhythmia (RSA) (Warzel and Krell, 1984). Respiratory-cardiac coupling seems almost exclusively mediated by parasympathetic heart-rate control, involving brain-stem cardiac and respiratory centers (Langhorst et al., 1975; Korpelainen et al., 1996; Eckberg, 1983). Spontaneous and baroreflex-induced firing of central cardiovagal neurons is inhibited during inspiration and reaches a maximum during early expiration (Berne and Levy, 1992). Since RSA is mediated through the vagus nerve, parameters of the RSA seem a suitable non-invasive measure of parasympathetic activity (Duncan et al., 1980, Weise et al., 1985, Johnson and Robinson, 1988, Cohen et al ,1988; Newlin et al., 1990) In Warzel and Krell's (1984) approach, the underlying concept is that the brain-stem centers which control breathing- and heart-rate cycles receive input from higher cortical areas

(Danielsen et al., 1989; Spyer, 1989) Here, an acoustic stimulus is presented at defined points of time in the combined respiratory-cardiac cycle and the modulation of the RSA stemming from the tone is observed Normal healthy subjects show such auditory RSA modulation It occurs predominantly during the expiration phase and we therefore restricted our study to that phase.

With blood-alcohol concentrations above 0.16%, drivers in Germany who are caught in traffic controls are referred to expert assessment for judging their competence of safe driving. With such excessive blood-alcohol concentrations, low-consumption drinkers show severe symptoms of intoxication (whereby they lose their ability to drive a car safely) A high BAC with only *moderate* symptoms of intoxication therefore signifies tolerance that has developed from excessive chronic use or abuse. For example, subjects caught drunk driving with BAC values above 0.25% (55 mmol/liter) were found to be heavy drinkers on the basis of gamma glutamyl transferase (GGT) measurements (Gjierde, 1987). Conversely, social drinkers who had not developed alcohol tolerance were found to be unable, due to effects of intoxication, to achieve excessive blood alcohol concentration and showed BAC levels of not more than 0.13% (Stephan, 1988). Tolerance is generally defined as a decreased effect of the same quantity of alcohol after repeated use and/or that a comparable effect requires an increased quantity of alcohol (Kalant et al., 1971; Bennett et al., 1993) People caught drunk driving with high BAC at the time of their offense thus constitute a suitable group of at-risk drinkers, to study possible effects in this subgroup of alcohol abuse (Hasin et al., 1999) In the present study the authors compared offenders, i.e., subjects with BAC>0 16%, to normal control subjects. We were interested in whether or not (1) they show a different extent of auditory RSA modulation, i.e., an indicator of parasympathetic control; (2) whether such an effect would be related to the BAC level at the time of offense; and (3) in case we find such a relation, whether there is an observable recovery of these vagal-function parameters after half a year of abstinence from alcohol consumption.

Methods

Subjects

There were 28 male subjects who had lost their driver's license from drunk driving (BAC range 0.16% to 0.31%). Of these, 17 were involved in an accident and 11 were caught in routine police traffic controls (Table 1). Subjects were referred to our institution for the expert assessment of whether their driver license should be withheld or could be granted back. On average the offense and BAC measurements took place 17±5 months before the study In accordance with German legal regulations, the BAC levels at offense are

corrected for resorption, based on the Widmark formula (Gilg, 1995). This correction for resorption is routinely done by the hospitals forensic medicine departments The computational guideline guarantees the comparability of BAC levels of drunk drivers caught under varying situational conditions. The physical status of the subjects was examined, considering in particular medical signs of alcoholism as defined by American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM IV, 1994). None of the offenders had clinical evidence of alcoholism in routine medical diagnostics, which included a clinical (in-depth) interview, the measurement of alcohol-sensitive blood parameters as well as neurological and internistic examination. Though not having medical signs of alcoholism, subjects with BAC values above 0,20% will be considered likely to be heavy drinkers, according to Gilg (1995). No indication of heart disease or withdrawal symptoms were found. Subjects with diabetes mellitus or intake of beta blockers were excluded from the study. Control subjects (n=11, all male) were recruited from newspaper announcements or were employees at the Medical Faculty Controls were occasional or social drinkers as classified on the basis of a questionnaire (devised by the authors) and were inconspicuous in liver-enzyme parameters, particularly in GGT values. Test subject and control groups were matched in age (offenders: 42±10 years, controls 39±12 years). Written informed consent was obtained from all participants and the study was approved by the local ethics committee.

Table 1

Comparison of the Both BAC-Groups in Age, Age at Onset of Drinking, Prevalence of Accidents vs. Routine Traffic Controls at Offense

	High BAC Group BAC>0.21% (n=14)	Middle BAC Group BAC<0.21% (n=14)	Controls (n=11)
age	42±11	42±11	39±12
age at onset of drinking	17±3	16±2	-
caught at accident	6 (43%)	11 (79%)	-
caught in routine traffic-control	8 (57%)	3 (21%)	-

[a] Each value represents the mean of the group ± standard deviation (SD)

Apparatus and Materials

Standard Einthoven electrocardiogram (ECG) recording were employed. The amplitude of RSA is defined as the mean difference between the minimum and the maximum of IBI-duration. Central nervous

system control of respiratory-cardiac coupling in Warzel and Krell's method (1984) is defined as the momentary change of the RSA-amplitude to auditory stimuli which occur at defined time points in the respiratory cycle. Stimuli were a 90-dB white-noise pulse of 750-ms duration presented through head phones Subjects followed a rhythm of breathing paced by an oscilloscope. Auditory stimuli were triggered by the first R-wave occurring after a change in respiratory cycle (start of inspiration or of expiration). Twelve sequential inter-beat intervals (IBI's) following the respiratory phase change were recorded as one period of measurement. Forty-eight of these periods of measurement were selectively averaged into four separate groups of 12 periods each: (1) and (2) expiration with and without stimulation; (3) and (4) inspiration with and without stimulation. The auditory stimuli were administered in a pseudo-random sequence to minimize effects of anticipation by the subjects and to guarantee an equal distribution of the four periods of measurement. An averaging technique was used to remove the influence of phase variance between the heart-rate and respiratory cycle and thus achieve a phase-independent measure of the RSA amplitude (Warzel and Krell, 1984). The variance in the temporal phase delay between respiratory phase change and IBI response occurs both intra- and interindividually, and it partly results from the fact that the auditory stimulation is not triggered by respiration itself but by the first R-wave after respiratory phase change. For the removal of phase variance, the reference point of the IBI-scale was displaced in each respiratory cycle The shortest IBI during inspiration and the longest during expiration, respectively, were labeled as No.1; the IBI's preceding these new reference points were labeled as 0, -1, and those following the reference as 2, 3, 4 etc. Interbeat-intervals having the same label were then averaged within a subject, and group means were obtained from these. From the mean within-subject IBI traces, with and without auditory stimulation, the difference curve was calculated, the amplitude of which we term "reaction amplitude" (RA). Negative differences correspond to a shortening of IBI-duration following stimulation, that is, to heart-rate increase. The RA is our indicator of the acoustic heart-rate response. It captures the momentary effect of acoustic stimulation, i e , that which occurs immediately within the next and the subsequent beats, independent of a phase delay between the heart-rate and respiratory cycle. Note that as a consequence of removing phase variance, the precise beginning of expiration and inspiration is not defined in the mean IBI trace. Warzel and Krell (1984) showed that the auditory effect is only present for stimulation in the early expiration phase: efferent cardiac parasympathetic activity is either blocked or highly diminished during inspiration. This was taken as evidence that the RA during expiration can be used as an indicator of the vagal influence on the respiratory-cardiac coupling. In our study, therefore, we restricted the analysis to the expiration phase. Analysis of respiratory arrhythmia based on spectral analysis has become a powerful and well-established tool (Mulder, 1988; Jorna, 1992). By the above described averaging method we have chosen analysis in the time domain rather than in the frequency domain for two reasons For one, the acoustic heart-rate response constitutes a short-term response that is more easily

seen in a time-based analysis Second, the separation of inspiration and expiration phase which proves valuable to assess central (medullar) control mechanisms amounts to a non-linear approach (a non-linearity in the respiration to heart-rate transfer function) (Clynes, 1969) that prohibits simple conversions between time-domain and frequency-domain analyses. Subjects were fitted with a breathing mask and the change of respiratory cycle was monitored by a thermo element that allows reliable measurement without a hindrance of breathing. Systolic and diastolic blood pressure were measured by finger photoplethysmography (Finapres 2300, OHMEDA, Louisville, USA) To assess the influence of chronic alcohol consumption on general attention, the subjects' selective-attention capacities were measured by the d2-test (Brickenkamp, 1994) The purpose of the task is to quickly and correctly discriminate between 16 different graphical elements, the 16 elements being combinations of the letters *p* or *d*, with 1, 2, 3, or 4 commas attached to the letter's top and/or bottom. A test has 14 rows with 47 symbols each. The task is to mark all *d*s having two commas.

Statistical Analysis

The comparison between the alcohol-tolerant and control group was evaluated by the unpaired Student's *t*-test For analysis, we employed a one-way analysis of variance (ANOVA) and subsequent LSD (least significant difference) test using standard statistical software (Statistica for Windows, 1993). The alpha level was set at .05 for all statistical tests. The follow-up data were analyzed by dependent-samples *t*-test.

Results

Physiological and Psychological Parameters for the BAC and the Control Group

Table 2 summarizes the results for all physiological and psychological parameters for the two subject groups (BAC group vs controls). Alcohol and control groups showed a similar capacity of selective attention as assessed by the d2 test. The cardiovascular measures showed diastolic blood pressure to be significantly elevated in the alcohol group ($p<.02$). Mean IBI duration, RSA, and RSA reaction amplitude (RA) were significantly reduced. The liver enzymes aspartat-amino transferase (AST) and alanin-amino transferase (ALT) did not differ between the groups. The gamma-glutamyl transferase (GGT) and also the mean corpuscular volume (MCV) were significantly elevated in the alcohol group as compared to our controls, but at 25 U/l and 89 fl, respectively, they were still within the standard range and are therefore considered clinically inconspicuous

Table 2

Summary of Physiological and Psychological Parameters for the BAC and Control Group

	BAC Group $n = 28$		Controls $n = 11$	Student's t- test
age (in years)	42±10		39±12	n.s.
d2 concentration test (GZ-F)	383±65		423±65	n.s.
systolic blood pressure	143±18mmHg		132±14mmHg	n.s. ($p = .08$)
diastolic blood pressure	98±13mmHg		86±16mmHg	$p = .02$
mean IBI	724±144 ms		920±146 ms	$p = .001$
RSA without stimulus	64±70ms		114±83 ms	n.s. ($p = .07$)
RSA with stimulus	63±67 ms		124±89 ms	$p = .03$
reaction amplitude, (RA)	18±15 ms		30±13 ms	$p = .02$
Liver enzyme		*Clinical Cut Off Value*		
Aspartat-Amino Transferase (AST)	11±5 U/l	*18 U/l*	10±3 U/l	n.s.
Alanin-Amino Transferase (ALT)	13±7 U/l	*24 U/l*	11±3 U/l	n.s.
Gamma-Glutamyl Transferase (GGT)	25±15 U/l	*28 U/l*	11±4 U/l	$p = .001$
Mean corpuscular volume (MCV)	89±4 fl	*78-98 fl*	85±2.2 fl	$p = .004$

[a] The groups were matched in age, and do not differ in subjects' psychological-intellectual capacity (d2-test of selective attention, raw score shown). [b] Each value represents the mean of the group ± standard deviation (SD). Group differences were assessed by Student's t-test. Significance level is at $p<.05$.

Cardiovascular Parameters and BAC levels

We now asked whether the difference in the cardiovascular parameters is dependent upon BAC at the time of the offense On the basis of studies on chronic alcohol abuse and cardiovascular alterations high BAC levels are expected to lead to decreased heart-rate variability.

BAC and RSA. There is a moderate correlation between BAC level and RSA ($r=-.32$, $p<.05$; one-tailed). A scatter plot of RSA versus BAC suggested a non-linear relationship. Since the correlation coefficient only captures linear covariation and to study the variation of cardiovascular reactivity with BAC, we further applied the median-split method to our data. The BAC median was at 0.21%; we termed the two resulting groups "middle" versus "high" BAC group, respectively (n=14 each). The split at 0 21% corresponds well with clinical experience reported by Gilg (1995) who found 0,2% a critical value above which severe alcohol problems are common. The middle-BAC subjects further seemed more prone to accidents. eleven subjects of the middle-BAC group, compared to six of the high-BAC group, were caught

at an accident. This corresponds well with our assumption that the subjects in the latter group had developed higher functional tolerance against alcohol effects (Tabakoff et al., 1986). The authors compared the averaged IBI within one respiratory cycle of both alcohol groups to that of the controls. Figure 1 shows the group mean trace.

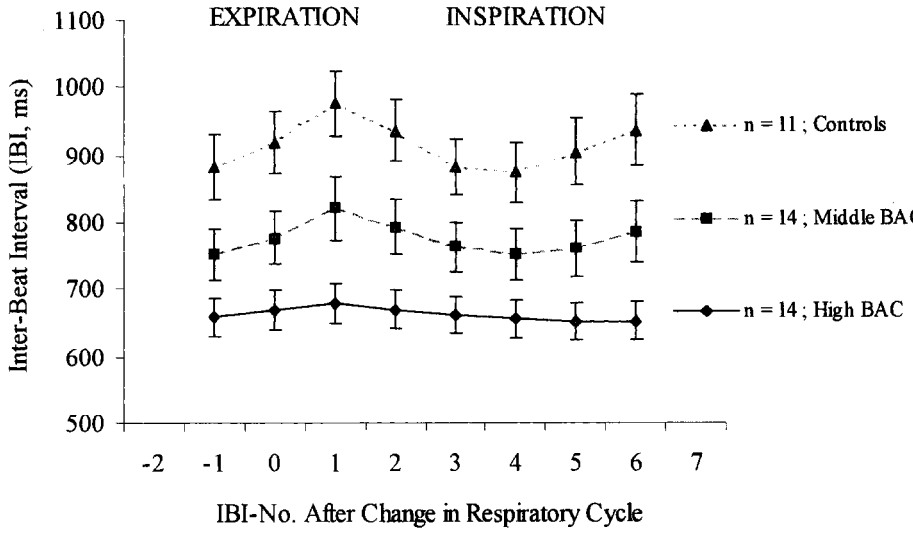

Fig.1 IBI Traces of the Controls, Middle-BAC and High-BAC Groups During a Respiratory Cycle without Acoustic Stimulation . [a] Each value represents the mean of the group ± S.E.M.

Between-Group Differences of Cardiovascular Parameters

Systolic blood pressure was equal between the groups but there was a highly significant difference in diastolic blood pressure [$F(2, 36)=5.07$; $p<.01$]. Comparison of the means using the LSD (least significant difference) test revealed that the high-BAC group had an elevated diastolic blood pressure in comparison with both the middle-BAC ($p<.05$) and the control group ($p<.01$). Furthermore, there was a main effect for the IBIs [$F(2, 36)=9.39$, $p<.01$], i.e., the individual subjects' mean IBI differs significantly between

subjects. Comparison of means (LSD test) indicated that both the differences of the high-BAC and middle-BAC groups to controls were highly significant ($p< 01$); whereas the difference between the two alcohol groups was not significant. There was also a main effect for the individual subjects' IBI standard deviation (SD) [$F(2, 36)=7\ 59$, $p< 01$]. Comparison of means (LSD test) showed that the variance of the high-BAC group was significantly reduced in comparison to the middle-BAC group ($p<.02$) and to the control group ($p<.01$) The difference between the middle-BAC group and controls was not significant. An analysis of variance revealed a significant main effect [$F(2, 36)=4.85$, $p<.01$] for the RSA. Comparison of the high-BAC and control group with post-hoc tests (LSD test) showed a significantly diminished RSA for the high-BAC group ($p<.01$). There was no difference between the middle-BAC and controls, but RSA was significantly less diminished in the middle-BAC compared to the high-BAC group ($p<.02$) We next studied the heart-rate reaction-amplitude (RA) by taking the difference curve of the IBI traces with and without stimulation Normal subjects show a pronounced heart-rate reaction to the stimulation. The effect is restricted to the expiration phase and heart rate returns to the pre-stimulation state in the inspiration phase (Gonschorek, 1996). The ANOVA yielded a significant main effect for the reaction amplitude (RA) [$F(2, 36)=6.28$, $p<.01$] Post-hoc comparison of means (LSD test) indicated that the group with high BAC levels had a significantly reduced RA in comparison to the control group ($p<.01$). Although there was no significant difference between the middle-BAC group and controls, we found that the high-BAC group had also significantly reduced RA in comparison to the middle-BAC group ($p< 02$). Table 3 summarizes the results.

Table 3

Between-Group Differences of Cardiovascular Parameters

	high BAC group BAC > 0.21% (n=14)	middle BAC group BAC < 0.21% (n=14)	controls (n=11)	one-way ANOVA[a]
SBP (mmHg)	146±20	140±15	132±14	n.s.
DBP (mmHg)	103±14	93±10	86±16	F(2, 36)=5 07[b]
IBI (ms)	676±124	772±150	920±146	F(2, 36)=9.39[b]
SD of IBI (ms)	26±13	51±33	70±35	F(2, 36)=7.59[b]
RSA (ms)	33±22	96±88	114±83	F(2, 36)=4.85[b]
RA (ms)	11±9	24±17	30±13	F(2, 36)=6.28[b]

[a]Group differences were assessed by using separate one-way analyses of variance (ANOVAs) [b]Significance level is at $p< 01$. Legend: SBP systolic blood pressure, DBP diastolic blood pressure, RSA respiratory sinus arrhythmia without auditory stimulation, RA reaction amplitude

Table 4

Follow-up Data of Clinical Blood and Cardiovascular Parameters in Subgroups with High (> 0.21%) and Middle (< 0.21%) BAC

high BAC group (n = 7)	at interview	at follow up	dependent-samples t-test
AST	14±8	12±4	n.s.
ALT	19±7	16±6	n.s.
GGT	35±15	19±5	p=.03
IBI (ms)	720±58	785±100	p=.03
SD of IBI (ms) between - subjects variability	32.4±22	40 5±23	n.s
RSA (ms)	39±33	71±49	p=.02
RA (ms)	9±8	16±13	p=.03
middle BAC group (n = 5)			
AST	10±5	9±2	n.s.
ALT	11±5	10±2	n.s.
GGT	14±4	14±3	n.s.
IBI (ms)	833±132	759±123	p= 05
SD of IBI (ms) between - subjects variability	40.4±18	39 8±23	n.s
RSA (ms)	56±39	67±57	n.s
RA (ms)	20±15	21±22	n.s

Follow-up differences were assessed by dependent-samples t-test. Significance level is at p<.05.

Follow-up Analysis

Six-months after the initial assessment, subjects were seen for re-evaluation. To investigate if there is a recovery of autonomic parameters in those subjects who underwent a period of abstinence in the meantime, we repeated the above analysis, of all subjects seen, twelve subjects were selected who had voluntarily attended a self-help course and medical control of blood parameters in that six-months period, with the goal of achieving alcohol abstinence. All subjects in the clinical follow-up interview reported, e g., to feel more drive in the morning, to have higher motivation and productivity at work and better skills of communication in their family. The group was divided at the same split-point BAC as the total group; seven subjects (mean age 42±11 years) had a BAC at the time of offense above 0.21% (mean BAC=0.23), and five subjects were below 0.21% (mean BAC=0.17). For this follow-up assessment we again analyzed IBI, RSA, RA and the clinical blood parameters. The results are shown in Table 4. For the group with BAC>0.21%, we found between the two measurements (first assessment and follow-up after six months) a significant change in IBI-interval, RSA, and RA. The marked decrease observed in the GGT value between

the first (35±15 U/l) and the second interview (19±5 U/l) supports the subjects' claim in their interview to have discontinued alcohol consumption after the first assessment In contrast, the middle-BAC follow-up subgroup (n=5; mean age 37±10 years) showed a change only in IBI-interval (p=.05) between the first and the second measurement (Table 4). The pre values of the RSA and RA in the middle-BAC subgroup for this pre/post comparison were close to the controls, so that there was little room for further improvement. This is particularly evident for RA In the high-BAC subgroup the value had improved from 9±8 ms (pre) to 16±13 ms (post), so that the pre value for the middle-BAC group, at 20±15ms, is already better than these and it is not surprising that it does not improve any further. Likewise, the GGT pre-value, at 14 U/l, was much better than that in the high-BAC group (35 U/l). Thus, consistent with our hypothesis, only the high-BAC subjects showed an improvement in their autonomic parameters from the first to the second interview, e.g. after a period of alcohol abstinence.

Discussion

Changed Autonomic Activity in Alcohol Abusers

In the present study, the authors found that autonomic activity in chronic alcohol abusers differs systematically from that of controls Alcohol abusers showed high diastolic blood-pressure values as would be expected from the generally-found correlation of blood pressure with level of alcohol consumption (Beilin, 1995; Choudhury et al., 1995). Abusers in our study further, however, showed increased heart rate, decreased RSA, and a decreased heart-rate response to acoustic stimulation Until now, changes in cardiovascular parameters had been reported in patients with alcohol dependency (Duncan et al., 1980, Malpas et al., 1991; Murata et al., 1994). Yokoyama et al (1991) reported that chronic alcoholics had lower variations in their beat-to-beat intervals than healthy volunteers, and observed a return towards normal after a period of abstinence (after thirty days) during hospitalization. The male subjects we tested had lost their driver's license from drunk driving and we were able to show that these persons had a reduced acoustic heart-rate response. According to the hypothesis that the heart-rate reaction-amplitude is indicative of parasympathetic activity, mediated through the vagal nerve, the diminished amplitude in persons with high BAC levels may represent an inhibitory effect of ethanol on vagal function. In particular, we used a method in which the acoustic signal was timed within both cardiac and respiratory cycles (Warzel and Krell, 1984) The presentation of an auditory stimulus with an intensity of 90-dB produces a heart-rate acceleration in the beginning of the expiration phase superimposed upon deceleration from RSA, in contrast to only a slight acceleration in the inspiration phase. Since it seems to be vagal activity that

dominates heart-rate control during expiration (Kollai and Koizumi, 1979) the effect of sensory afferents is thus presumably caused by an inhibition of the cardial vagus during the expiration phase Even though cardiac acceleration is often associated with a defensive response and thus with sympathetic activity (Sokolov, 1963; Grossman, 1983; Graham et al., 1983) other sources question such a link, particularly when the stimulus is not sufficiently aversive and not extremely loud (Young and Leaton, 1994). A *relative* acceleration from the tone — during a phase of absolute deceleration as in our paradigm — can therefore result from a reduced vagal heart-rate down-regulation. We thus interpret our finding of a reduced reaction amplitude in high-BAC persons as indicative of a chronic modification of these medullar brain-stem centers where vagal heart-rate control originates, and that are in turn influenced by sensory stimulation.

Situational Components. The expert assessment performed during the measurements might be a stressful situation for our subjects because they all had a high interest to get their driver's license back. It is well known that stressors can modulate the sensitivity of the baroreceptor heart-rate reflex (Ditto and France, 1990). Such an effect from the emotional excitement would confound the differences in cardiovascular parameters between the experimental and the control group. In the within-group comparison, however, we also found significant heart-rate acoustic response differences between the two alcohol groups (BAC>0.21% vs. BAC 0.16–0.21%) whereas heart rate itself (IBI) did not differ between the groups. Since these subgroups were in the same stressful situation of expert assessment and reacted similarly in heart rate, it is unlikely that situational components accounted for differences in heart-rate reaction amplitude between these two subgroups The present results, therefore, suggest a persistent, vagally-induced deficit of respiratory-cardiac coupling in persons with extreme alcohol tolerance. Unlike conventional biochemical markers, these indicators of respiratory-cardiac coupling may thus be sensitive to long-standing alcohol abuse It is inherently difficult to obtain reliable information about a subject's status of alcohol drinking at the time of RSA measurements. It may be that most of the subjects had temporarily reduced their drinking habits between the time of offense and when the expert assessments took place. To check for a recent alcohol abuse, we also measured conventional biological markers. Although the mean value of GGT was significantly elevated in the alcohol group relative to our controls — the latter strictly selected to be highly seldom drinkers — all of these conventional biological markers were, on average, still within the normal range.

Recovery from Abuse

Even though for our follow-up analysis the number of subjects was low and it is required to have more empirical data, our limited follow-up data suggest recovery in the RSA and RA, and would point towards

a vagal functional damage being reversible after prolonged (≥ six months) abstinence by the high-BAC group The middle-BAC group seemed recovered already in the first interview or perhaps they never developed impaired vagal function which thus remained unchanged at follow-up. We attach little importance to the increase of heart rate at follow-up in the middle-BAC group since heart rate is rather sensitive to situational components and the increase is not accompanied by changes in either RSA, RA or blood alcohol parameters like GGT. More data on the consequences of abstinence are desirable to further test that proposition of vagal damage being reversible.

Conclusion

The results suggest that the RSA and acoustic heart-rate responses are suitable for indicating differences in vagal functioning caused by chronic alcohol consumption in the distant past Further investigations are needed, however, to test the repeatability and robustness of our findings. Respiratory-cardiac coupling might serve as an objective measure of alcohol abuse prior to the onset of clinical signs of alcohol dependence.

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