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RESEARCH ARTICLE

Opposite effects of sleep deprivation on the continuous reaction times in patients with liver cirrhosis and normal persons

Mette Munk Lauridsen · Jesper Frøjk · Ove B Schaffalitzky de Muckadell · Hendrik Vilstrup

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Abstract The continuous reaction times (CRT) method describes arousal functions. Reaction time instability in a patient with liver disease indicates covert hepatic encephalopathy (cHE). The effects of sleep deprivation are unknown although cirrhosis patients frequently suffer from sleep disorders. The aim of this study was to determine if sleep deprivation influences the CRT test. Eighteen cirrhosis patients and 27 healthy persons were tested when rested and after one night's sleep deprivation. The patients filled out validated sleep quality questionnaires. Seven patients (38 %) had unstable reaction times (a CRTindex<1.9) compatible with cHE. In these patients, the wakefulness improved or normalized their reaction speed and CRTindex (p= 0.01). There was no change in the other patients' reaction speed or stability. Seven patients (38 %) reported poor sleep that was not related to their CRT tests before or after the sleep deprivation. In the healthy participants, the sleep deprivation slowed their reaction times by 11 % (p<0.0001) and in 7 persons (25 %) destabilized them. The acute sleep deprivation normalized or improved the reaction time stability of the patients with a CRTindex below 1.9 and had no effect in the patients with a CRTindex above 1.9. There was no relation between reported sleep quality and reaction time results. Thus, in cirrhosis patients, sleep disturbances do not lead to 'falsely' slowed and unstable reaction times. In contrast, the acute sleep deprivation slowed and destabilized the reaction times of the healthy participants. This may have negative consequences for decision-making.

Keywords Sleep · Hepatic encephalopathy · Continuous reaction time · Liver cirrhosis

M. M. Lauridsen (✉) · J. Frøjk
Sydvestjysk Sygehus Esbjerg, Esbjerg, Denmark
e-mail: mettelauridsen@gmail.com

O. B. S. de Muckadell
Odense University Hospital, Odense, Denmark

H. Vilstrup
Aarhus University Hospital, Aarhus, Denmark

Introduction

The continuous reaction times (CRT) test has long been used for assessing global cerebral impairment. The test predominantly describes arousal functions and the individual's sustained and stable attention and inhibitory control. The ability to deliver an adequate and stable motor response to a sensory stimulus is a key function in many daily life activities, cannot be trained, and has been found not to fatigue during a 10-min test session (Ennio De Renzi 1965; Lauridsen et al. 2013). The effects of sleep disturbances are not known.

The continuous reaction time stability can be assessed by the CRTindex (50 percentile/(90-10 percentiles)) and a CRTindex lower than 1.9 in a patient with liver disease indicates covert hepatic encephalopathy (cHE) (Elsass et al. 1985). A disturbed sleep-wake pattern occurs in up to 2/3 of patients with liver cirrhosis (Cordoba et al. 1998; Marchesini et al. 2001; Montagnese et al. 2009c) but its effects have not been studied although they might confound the CRT test results and lead to false diagnoses of cHE.

Our a priori expectation was that sleep deprivation would slow and destabilize the reaction times both in cirrhosis patients and in normal persons. The aim of the work was to determine if sleep deprivation influences the CRT test. This was done by conducting the CRT test repeatedly in well rested and overnight wakeful cirrhosis patients and normal persons. The patients also answered sleep disturbance questionnaires.

Methods

Participants

Patients with liver cirrhosis The patients were recruited from the medical outpatient clinic of Hospital of South West Jutland, Denmark. Patients were invited by mail and of 32 invited

persons 25 responded and 18 of these accepted to participate (14 men and 4 female). Patients were aged on average 62 years. Ten were in Child-Pugh clinical liver status class A, 7 in group B and 1 in group C. Actual overt HE was an exclusion criterion. None had it but 7 had experienced previous episodes. All filled out the Epwort Sleep Questionaire about daytime sleepiness and the Sleep Timing and Sleep Quality Screening (STSQS) questionnaire. They agreed to undergo one night of in-hospital sleep deprivation, monitored by medical staff from 11.00 pm to 09.00 am the following morning. To mimic the sleep deprivation of the healthy participants (cf. below), the patients were allowed no more that 2 h' rest and no evening rest before coming to the hospital. Also, the patients were kept mobile and entertained during the night to mimic the normal persons' night duty (cf. below). Before and at the termination of the sleep deprivation, patients were tested with the CRT method by the same assessor.

Healthy participants The healthy participants were recruited among junior resident doctors from the Hospital's department of medicine. Exclusion criteria, that none fulfilled, were: Chronic medical conditions, intake of psychoactive substances (alcohol, medication) and psychiatric disorders. Moderate intake of coffee was allowed. Twenty-seven (13 male and 14 female) persons were recruited. No compensation was given for participation. The participants all had maximum five years of clinical training and were aged 27 to 39 years. They started their night duty after 7 h of sleep the previous night and had on average a total of 2.5 h of intermittent rest episodes during the duty. All reported normal sleeping habits and quality. They were tested with the CRT method by the same operator that tested the patients, before and after the night duty. They were not informed about the study hypothesis.

The study was approved by The Regional Committee on Health Research Ethics.

The continuous reaction times (CRT) test

The method is a computerized psychometric test, lasting 10 min. The test person is seated in an undisturbed location and equipped with a set of headphones and a trigger button in the dominant hand. The computer software (EKHO, Bitmatic, Aarhus, Denmark) generates repeated 400 Hz sound stimuli (beeps) at 90 dB at random intervals of 2 to 6 s. The test person must react to the sound by pressing and releasing the trigger button as fast as possible. After a run-in of 15 beeps the person completes 150 reaction time measurements and each reaction time is registered. The 10, 50 and 90 percentiles and the CRTindex (50 percentile/(90-10 percentiles)) are calculated. The 10 percentile represents the fastest reaction times, the 50 percentile the median, and the 90 percentile the slowest reaction times. The CRTindex corresponds to a variation coefficient and is a measure of the intra-personal reaction time stability, i.e. it decreases with low stability. The normal limit is above 1.9 (Elsass et al. 1985).

Sleep timing and sleep quality screening questionnaire (STSQS)

This single-sheet questionnaire assesses sleep timing and subjective sleep quality. It has been tested against the more elaborate Pittsburg Sleep Quality Index and found to be useful as a screening for delayed sleep habits and poor sleep quality. With the threshold>3 the STSQS identifies "poor sleepers" with a sensitivity of 83 % and a specificity of 70 % (Montagnese et al. 2009b).

Epworth sleepiness scale (ESS)

This short questionnaire assesses day-time sleepiness and persons are asked to rate the likelihood of them dozing off or falling a sleep in certain situations. The scores can range from 0 to 24 and a score of≥11 is considered indicative of excessive daytime sleepiness.

Statistical analyses

Our aim was to determine if sleep deprivation influences the CRT test. Under stable conditions the CRTindex intrapersonal day-to-day variance is 6 % (0.12) in patients with liver cirrhosis. The sample size needed was $n=16$ based on a desire to detect a 15 % change in CRTindex (power 80 % and significance level 5 %). Firstly, we performed analysis of the group of patients as a whole. We also post hoc stratified the patient group into a non-cHE group with CRTindex above 1.9 and cHE group with CRTindex below 1.9. We used GraphPad Prism for Mac. D'Agostino-Pearson Omnibus K2 normality test showed that our primary end-point, namely differences in CRTindices before and after sleep deprivation, did not follow Gaussian distribution and we used the non-parametric Wilcoxon matched pairs test. Differences in reaction time percentiles showed Gaussian distribution. We performed intra-group comparison of the CRT results (raw percentiles and CRTindex) before and after sleep deprivation. Correlation between the rested CRTindex and the change in CRTindex was described by Pearson's r.

Results

Patients with cirrhosis

In the whole group of patients the sleep deprivation did not change the CRT measures The median rest to sleep deprived

change in the CRTindex was small (2 %, CI 95 %: −14 % to 10 %). However, in the seven patients (38 %) with a baseline CRTindex<1.9 (indicating cHE) the sleep deprivation decreased (improved) their CRT 10-, 50-, and 90-percentile (by 19, 37, and 42 %, respectively (Table 1 and Fig. 1a)), increased (improved) their CRTindex on average by 24 % (Table 1) including a normalization in 3 (43 %) of them. For the 11 patients with a rested CRTindex>1.9 (normal), the sleep deprivation had no systematic effect on any CRT percentile or the CRTindex (Table 1 and Fig. 1b). Within the group the effect of the sleep deprivation on the CRTindex was linearly related to the baseline CRTindex (Pearson r=0.67) so that a low rested index was associated with an improvement in CRT index and a higher rested index was associated with a worsening of the CRTindex. The rested index corresponding to no change in CRTindex was 2.0 (Fig. 2). One outlier whose CRTindex was more than 2.5 SDs from the group mean was not include in the construction of the regression line.

The CRT measures were unrelated to the reported sleep quality Seven patients (38 %) had a sleep quality score of> 3, defining them as poor sleepers. Two of those had a CRTindex<1.9 (cHE). The sleep deprivation changed neither their reaction times nor CRTindex (2.3 to 2.2, p=0.7) and the sleep score was also not different in the patients with a rested CRTindex<1.9 (3.0 vs. 4.1, p=0.09) or in those who improved their CRTindex. Four patients (14 %) had a daytime sleepiness score of≥11, defining excessive daytime sleepiness. Two of those had a CRTindex <1.9 (cHE). Also for that score, there was no relation to the reaction times, the CRTindex (1.8 vs. 1.9, p=0.9), or to the effects of the sleep deprivation (7.8 vs. 6.2, p=0.7).

Healthy control participants

The sleep deprivation slowed and destabilized the reaction times Both the 10-, 50-, and 90- percentiles increased (slowed) (by 6, 11, and 14 %, respectively) (table 1) and the CRTindex decreased (deteriorated) by on average 15 %. Seven (25 %) developed a CRTindex<1.9 (unstable) (Table 1 and Fig. 1c (p=0.001)). These effects became more marked the fewer hours spent with rest the previous 24 h (p=0.02).

Discussion

The salient findings of this study are that the acute sleep deprivation improved the reaction time measures in the cirrhosis patients with an abnormal CRTindex below 1.9, had no effect in the patients with a normal CRTindex above 1.9, and slowed and destabilized the reaction times of the healthy participants. There was no relation to the patients' self-reported sleep quality.

Our findings, thus, in the patients were contrary to our expectations. Particularly the improvement of reaction time stability in the patients with a low CRTindex, indicative of cHE, was surprising. The findings in the healthy controls were as expected. The implications of our findings are different in the patients and the healthy controls.

Table 1 Mean CRTindex changes and 95 % CI in patients with cHE (mean age 64 years n=7) or no cHE (mean age 61 years, n=11) and healthy persons (mean age 31 years, n=27)

	10 percentile/ms	50 percentile/ms	90 percentile/ms	CRTindex
Cirrhosis+cHE				
Rested	174	235.9	**344.6**	**1.43**
	(108–241)	(117–354)	**(192–497)**	**(1.2–1.6)**
Sleep deprived	140.7	172.4	**242.1**	**1.77**
	(124–157)	(145–200)	**(198–286)**	**(1.5–2.1)**
P-value	0.15	0.09	**0.01**	**0.01**
Cirrhosis - cHE				
Rested	148	178	221	2.63
	(140–156)	(166–190)	(205–238)	(2.3–3.0)
Sleep deprived	158	196	253	2.44
	(121–195)	(134–258)	(164–342)	(1.9–2.9)
P-value	0.85	0.75	0.83	0.41
Normal persons				
Rested	**136**	**159**	**200**	**2.62**
	(130–141)	**(153–167)**	**(192–208)**	**(2.39–2.86)**
Sleep deprived	**144**	**176**	**227**	**2.22**
	(138–149)	**(169–183)**	**(215–239)**	**(2.00–2.44)**
P-value	**0.0004**	**< 0.0001**	**< 0.0001**	**0 001**

Bold entries mark statistically significant results

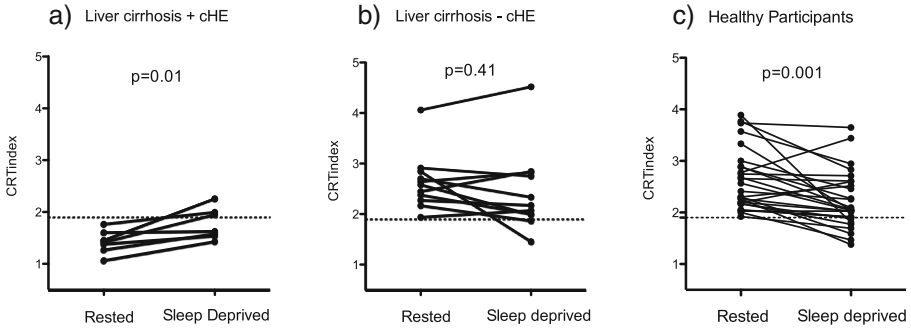

Fig. 1 CRTindex before and after one night's sleep deprivation in 7 patients with liver cirrhosis and cHE (*panel a*), 10 patients with no cHE (*panel b*), and 27 normal persons (*panel c*). The dotted line is the normal CRTindex cut-off at 1.9 (lower values are abnormal)

The differences in the effects of the sleep deprivation on the CRT outcomes among the patients with psychometric results indicative of cHE and healthy participants were not merely chance findings, as can be ascertained from the statistical analyses and from the visual impression of Fig. 1. It is evident that the configuration of the CRTindex data is really different among the groups. The wakefulness, therefore, had different psychometric effects.

One strength of our study is that exposing persons to sleep deprivation is a direct way to assess how the CRT test is affected by lack of sleep but to our knowledge this has not been done with any of the other psychometric test used to diagnose cHE. We were careful in planning and executing the over night wakefulness of the patients in a way that closely resembled the situation for the doctors on duty. Although we could obviously not in detail mimic the stress factors of duty activities including the necessary internal self- regulatory drive, we are confident that such differences were unlikely to account for the measured differences between the groups.

The limitations of our study are that our cirrhosis group was older, comprised more men, and was unemployed. We have shown that younger persons and males have slightly faster reaction times (Lauridsen et al. 2012) but these age and gender effects are of a much smaller scale than the slowing of (rested) reaction times we measured in the cirrhosis group. We have also shown that neither gender nor age in normal persons or in patients with cirrhosis influence the CRTindex (Lauridsen et al. 2012). The importance of employment status is not known but intelligence and educational level have no effect on reaction time performance (Renzi 1965). In any case, the possible effects of such differences should be seen in the light of the main goal of our study being comparisons within each study group.

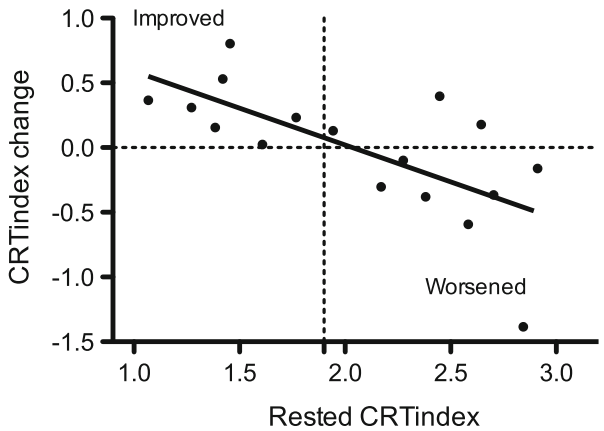

Fig. 2 The change in CRTindex plotted against the rested CRTindex in all 18 cirrhosis patients. The dotted vertical line is the CRTindex 1.9 and the dotted horizontal line the ordinate zero. The full line is the linear regression line (Pearson r=0.67, ordinate interception point 2.03)

The rested cirrhosis patients had slower and less stable reaction times than the healthy participants, and more than one third of them fulfilled the established CRT criteria for cHE. These findings correspond well to earlier reports (Lauridsen et al. 2011, 2012; Maldonado-Garza et al. 2011; Mittal et al. 2011), and they confirm that a large fraction of out-clinic cirrhosis patients may suffer from cHE. This underscores the need for detailed validation of the tests used to diagnose the condition.

The most striking observation was that in the patients who fulfilled the CRT criteria for cHE the acute sleep deprivation improved all their CRT measures, including the diagnostic CRTindex<1.9 - and in some of them actually normalized their CRTindex and thus psychometrically reversed cHE. The linear relationship between the rested CRTindex and the effect of the sleep deprivation suggests that the effect was in fact present for all the cirrhosis patients—but evidently opposite for those with a low CRTindex (abnormal) and those with a high CRTindex (normal). Interestingly, the theoretical ordinate interception point of 2.0 is very close to the suggested diagnostic cHE CRTindex cut-off of 1.9. The same relationship was not present for the healthy control participants (not shown).

Our data do not in themselves give any clue to the mechanism of the effect of the sleep deprivation in the patients. However, many patients with chronic liver disease have delayed sleep pattern and patients with cHE seem to suffer from excessive daytime sleepiness. These disturbed circadian patterns may be caused by deranged neurotransmission (Montagnese et al. 2009a, c). In analogy, in patients with depression and circadian disturbances, sleep deprivation has

rapid acting short term antidepressant effects (Wichniak et al. 2013), thought to be related to immediate changes in neurotransmission (Hefti et al. 2013; Murck et al. 2009). Because the improvement in CRTindex was unexpected we did not screen for depression but no patient used antidepressants.

As for the use of the CRT method as a clinical tool for diagnosing and grading cHE it is valuable information that the method, despite our a priori worries, does not lead to false diagnoses of cHE neither in patients exposed to sleep deprivation nor in patients with subjective poor sleep quality or excessive daytime sleepiness. This also supports the use of such tests for identifying a group of liver patients that is biologically different and at high risk of experiencing overt HE (Kappus and Bajaj 2012). However, the sleep deprivation effect may still confound the CRT test but the other way round: patients awake over night may not show CRT signs of cHE although they suffer from it in all other settings. This may be relevant when using the CRT method for monitoring effects of treatment. In clinical practice we believe the effect is not important because patients rarely spontaneously remain wakeful and active all night before a routine clinical visit.

In the healthy participants, in case doctors on night duty, the clear detrimental effects of the sleep deprivation on their reaction times call for other considerations. Again, the effects are not likely to be random. It has been shown that the ability to deliver a motor reaction to a sensory impulse is not weakened during the continuous test session even when longer test runs are used and does not fatigue at repeated tests (unpublished data). It is also quite plausible that the sleep deprivation should result in loss of arousal and attention, considering the profound psychological and neurological effects of wakefulness (Arnedt et al. 2005; Barapatre et al. 1990; Doran et al. 2001; Lim and Dinges 2008; O'Brien et al. 2012; Taheri and Arabameri 2012). As well the reaction speed as its stability suffered from the sleep deprivation. Some of the healthy participants even passed the suggested CRTindex threshold for cHE. In their case, however, by definition the CRTindex did not indicate cHE but sleep deprivation. In fact, the CRT test might be used to identify significant sleep deprivation in normal persons, but this would require further validation of the test's sensitivity and specificity in this situation.

The practical consequences of the compromised reaction times depend on the context. After duty the doctors might be less safe drivers (Marcus and Loughlin 1996; Ware et al. 2006). The most relevant issue is the possible implications for their clinical decision-making towards the end of their night duty. Expectably, the doctor's loss of arousal and attention as measured by their CRT test results should influence the way they make their decisions. It is not known whether this very complex process looses quality or just speed, but it has been shown that doctors on long duties make more errors of judgement (Landrigan et al. 2004).

In conclusion, acute sleep deprivation resulted in improvements and even normalization of CRT measures in cirrhosis patients with signs of cHE, and did not change the measures in patients without signs of cHE. Self reported sleep quality did not interfere with these results. This means that the method's diagnostic utility is not confounded by sleep disturbances. It remains unknown whether sleep deprivation has any therapeutic potential. In contrast, in most healthy participants all CRT measures deteriorated by the sleep deprivation, and this may have negative consequences for e.g. decision making.

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