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# Altered Sleep-Related Blood Pressure Profile in Hypocretin-Deficient Narcoleptic Patients

Commentary on Grimaldi et al. Abnormal sleep-cardiovascular system interaction in narcolepsy with cataplexy: effects of hypocretin deficiency in humans. SLEEP 2012;35:519-528.

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Hypocretin neurons are located exclusively in the lateral hypothalamus, but project widely throughout the central nervous system, including hypothalamic and brainstem structures known to play a central role in autonomic and cardiovascular regulation.[1] Pharmacological animal studies showed an increased blood pressure (BP), heart rate (HR), oxygen consumption, body temperature, and plasma catecholamine levels after administration of hypocretin, effects being mainly mediated by sympathetic activation.[1-3] Studies on the cardiovascular status in hypocretin-deficient mice showed a lower BP during wakefulness compared to wild mice.[1-3] A more recent study reported a blunted NREM and REM sleep-related BP decrease in animal models of narcolepsy (hypocretin knock-out and hypocretin-ataxin3 transgenic mice) compared to wild mice, with a prominent sleep-related increases in BP during REM sleep.[4]

I read with great interest the manuscript by Grimaldi and colleagues[5] in the issue of *SLEEP*, describing the first results on sleep-related BP and HR profile in hypocretin-deficient patients compared to controls under standardized conditions. They observed a nighttime non-dipping BP pattern for both systolic and diastolic pressure, with a REM sleep state increase of systolic BP, together with an increase in HR across the 24-hour in patients with narcolepsy-cataplexy compared to normal controls. Most of these findings suggest an increased sympathetic activation despite a hypocretin deficiency.

The study reported by Grimaldi et al. is based on a well-designed protocol to assess the 24-hour circadian rhythm, day-night, time and state-dependent changes of BP and HR that include sleep-wake together with Portapress portable recording, stable temperature, and food restriction in bedrest condition during 32-hour duration. However several limitations need also to be addressed before accepting the generalization of the findings: (1) limited number of patients (n = 10) and matched controls (n = 12); (2) primarily male (n = 9) subjects with higher risk of high BP and HR levels; (3) previous psychostimulants intake by most of the patients with potential for a persistent of cardiovascular stimulating effect even after a 15-day withdrawal; (4) increased sleep-wake fragmentation with a larger amount of daytime sleep in patients with narcolepsy, especially in the bedrest condition; (5) associated comorbid conditions such as obesity (not clearly detailed, but the mean BMI was 28 ± 4), obstructive sleep apnea syndrome OSAS (mean AHI was 13 ± 4), and periodic leg movements (mean PLMS was 23 ± 20) with and without associated microarousals; and (6) lack of data concerning other potential cardiovascular risk factors (i.e., dyslipidemia, hypertension, diet, associated cardiovascular treatment, habitual sleep duration, and psychosocial factors).

If the current results described by Grimaldi et al. were further confirmed and not related to the chance of type I errors, the mechanisms underlying these abnormal sleep-cardiovascular system interactions would need to be identified. Despite the title of the manuscript, the potential role of hypocretin deficiency in such interaction could not be definitively confirmed in this study. The duration of daytime and nighttime sleep, sleep fragmentation together with the occurrence of NREM vs REM sleep (characterized by a marked sympathetic activation with BP and HR instability) may also contribute significantly to BP regulation,[6] especially in patients with narcolepsy with highly disturbed nighttime sleep.[7,8] In addition, associated comorbid conditions such as obesity, metabolic syndrome, OSAS, PLMS with or without microarousals, and psychological distress frequently reported in patients with narcolepsy-cataplexy may also confound the non-dipping BP pattern reported.

Although Grimaldi et al.[5] did not consider the influence of most of these factors on their results, they showed a clear interaction between blunted BP nighttime fall and PLMS. Sympathetic overactivity has been associated with PLMS with increased HR and BP coincident with PLMS.[9] We recently studied interactions between sleep and the cardiovascular system through physiologic activations associated with PLMS in patients with narcolepsy-cataplexy.[10] We found a significant reduced magnitude of cardiac activation associated with PLMS with and without microarousals in patients with narcolepsy-cataplexy as compared to controls. We suggested that attenuation of PLM-related HR changes in narcolepsy was related to impairment in both sympathetic and parasympathetic activities due to hypocretin deficiency. The hypocretin system may act as an essential modulator for coordinating autonomic-system circuits, with the predominant sympathetic excitatory effect targeting the autonomic brain centers. Thus, we speculate that there may be a lower amplitude of sympathetic activity response together with an enhanced sympathetic tone at baseline in narcolepsy with cataplexy. However the clinical significance of such findings with regard to yet unproven increased risk of cardiovascular diseases remains unknown.

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The major result of the study of Grimaldi et al.[5] is the "non-dipping BP profile" (defined as a nocturnal BP dip < 10% lower than daytime BP) observed in patients with narcolepsy. Nocturnal BP decline has major clinical implications, and the loss of normal reduction in BP during sleep is associated with high risk of cardiovascular morbidity and mortality even in absence of daytime hypertension.[11] Moreover, a meta-analysis revealed that nighttime BP was a stronger predictor than daytime BP for adverse cardiovascular events.[12] As patients with narcolepsy-cataplexy are frequently obese, exhibit type 2 diabetes or metabolic syndrome, present with a decrease in PLMS-related HR changes, and are taking psychostimulants like modafinil and methylphenidate known to affect the autonomic nervous and cardiovascular systems,[8] the potential higher risk of cardiovascular morbidity and mortality need to be further assessed.

As no study has ever reported an increased risk of cardiovascular morbidity in narcolepsy, we recommend caution before concluding it is an "at risk" profile. In parallel to studies focusing on OSAS and RLS, longitudinal cardiovascular studies need to be performed in narcolepsy to assess the clinical consequences of such discoveries. Studies that include large numbers of patients with narcolepsy (male and female, with and without hypocretin deficiency—the latter corresponds to most patients with narcolepsy without cataplexy) are needed to determine whether the hypocretin system per se impacts the sleep-related BP profile. Once demonstrated, further studies on the 24-h BP pattern taking into account the different comorbidities (OSAS, PLMS, obesity, psychosocial symptoms…), as well as daytime and nighttime sleep, and current and past medication intake, are also required to identify precisely the cardiovascular risks in patients with narcolepsy.

## CITATION

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## DISCLOSURE STATEMENT

Prof. Dauvilliers has received speaker's honoraria and supports for travel to meetings from UCB Pharma, Cephalon, Novartis, and Bioprojet. Prof. Dauvilliers participated in advisory boards of UCB and Bioprojet

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