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MERITS OF ASSESSING THE CIRCADIAN AMPLITUDE AND ACROPHASE VERSUS A DAY-NIGHT RATIO.

Some alterations of the circadian pattern of blood pressure (BP) have been associated with an increased cardiovascular disease risk [1]. Risk assessment is better achieved on the basis of a chronobiological classification relying on the circadian amplitude and acrophase as compared to the conventional day-night ratio (DNR) [2, 3]. Melatonin administration reportedly restores an altered circadian system [4]. In order to further investigate the relationship between the circadian rhythms in BP and melatonin, we measured endogenous melatonin production in patients treated for conventionally diagnosed hypertension found to have a DNR below or above 10% ('dippers' and 'non-dippers') [5]. BP was monitored for at least 24 hours with an automatic ambulatory monitor. Plasma melatonin was measured in the middle of the daytime and in the middle of the nighttime by radioimmunoassay. As expected, nocturnal systolic ($P<0.05$), diastolic ($P<0.001$) and mean ($P<0.001$) BP was higher in 'non-dippers' than in 'dippers'. No statistically significant difference was found between the two groups in daytime BP. As expected, mean melatonin concentrations were higher during the night than during the day in both groups. Our earlier analyses showed that for diastolic and mean BP, 'non-dippers' had a lower night/day melatonin ratio than 'dippers' [5]. Herein, we compare the association of the night/day melatonin ratio with the BP DNR on the one hand and the circadian BP amplitude on the other hand. A statistically significant negative correlation is found between the daytime melatonin concentration and the circadian double amplitude (2A) of systolic (S) BP ($r=-0.266$, $P=0.042$), Figure 1. A statistically significant positive correlation is found between the nighttime melatonin concentration and the circadian 2A of heart rate (HR) ($r=0.296$, $P=0.023$), Figure 2. A positive correlation is also found between the night/day melatonin ratio and both diastolic (D) BP-2A ($r=0.348$, $P=0.007$) and HR-2A ($r=0.386$, $P=0.003$), Figures 3 and 4. By contrast, a similar correlation is not statistically significant in

relation to the DNR of DBP, used to define 'dipping' (r=0.116, P>0.20), Figure 5.

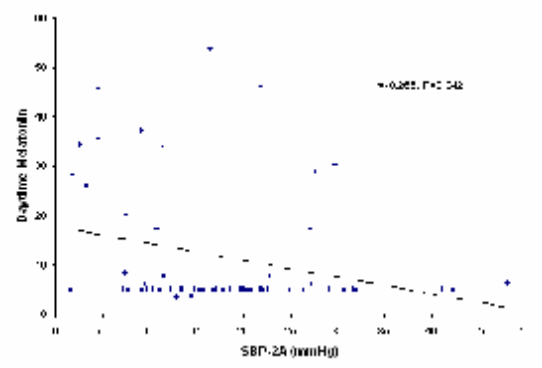

Figure 1

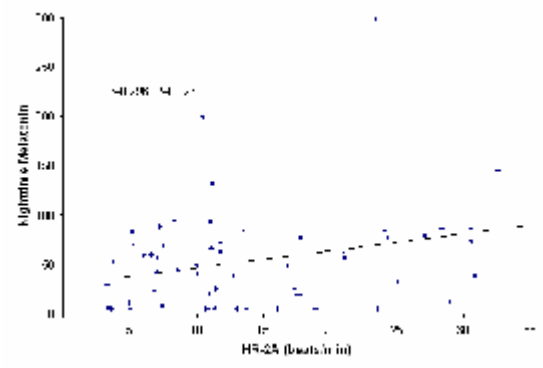

Figure 2

The circadian amplitude of melatonin was not determined herein but the two-timepoint approach used for melatonin determination sufficed to show that the association between the circadian variations in BP and melatonin was more readily apparent in relation to the circadian amplitude of BP than to the BP-DNR.

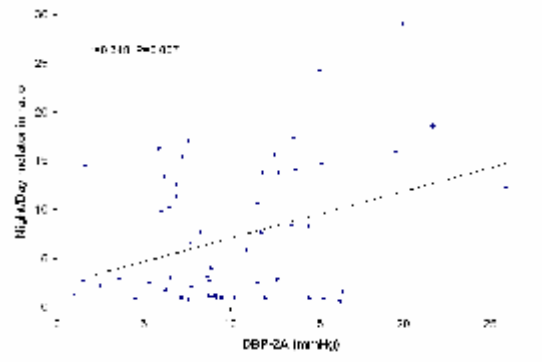

Figure 3

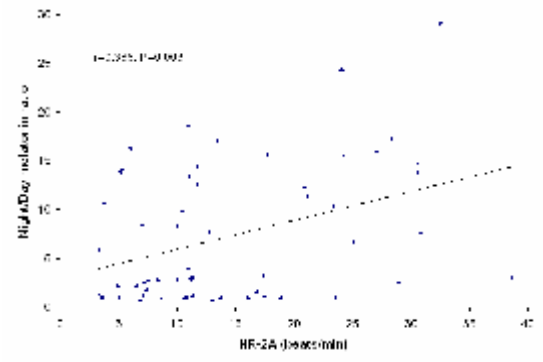

Figure 4

When the circadian rhythm of urinary melatonin excretion is determined, its amplitude correlates with cardiovascular disease risk [6]. Nocturnal melatonin has also been reported to be altered in patients with coronary artery disease [7]. Moreover, melatonin administration in the evening has been shown to lower BP in hypertensive patients, Figure 6, and to improve the condition of patients with heart failure, Figure 7 [8].

Uncontrolled use of melatonin in hypertensive patients is not warranted, however, as it has been suggested that melatonin may impair the antihypertensive efficacy of calcium channel blockers such as nifedipine [9]. It has also been cautioned that no long- term safety data exist for the continued use of melatonin, and the

optimal dose and formulation for any application remains to be clarified [10]. Timing should also be kept in mind both from the viewpoint of optimizing efficacy but also from that of minimizing undesirable effects in view of the involvement of melatonin in feedsidewards [11-13].

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