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DOES OVERSWINGING PROVIDE AN EARLY WARNING OF CARDIOVASCULAR DISEASE RISK WHEN NON-DIPPING MAY FAIL? A META-ANALYSIS OF 2039 CASES

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A b s t r a c t

Using the left ventricular mass index (LVMI) as a gauge of early cardiovascular disease risk, the study was aimed at examining how this surrogate outcome measure is affected by various risk indicators, including overswinging or CHAT (circadian hyper-amplitude-tension), non-dipping (a deficient blood pressure decline during rest) and MESOR-hypertension. The results from this study fully corroborate earlier findings indicating that CHAT is a disease risk syndrome warranting immediate therapy.

K e y w o r d s

Essential hypertension, Overswinging of blood pressure, Non-dipping of blood pressure, Cardiovascular disease risk, Left ventricular mass index

INTRODUCTION

Adverse vascular events are associated with an elevated mean value of blood pressure *(1).* An excessive circadian variation gauged the amplitude of blood pressure, also warns of an increase in vascular disease risk. This amplitude can be computed by the fit of a 24-hour cosine curve *(2),* e.g., to data obtained automatically every 30 minutes for 7 days with ambulatorily functioning monitors. Irrespective of whether the mean value of BP is elevated or not, too large a circadian amplitude of BP carries a large vascular disease risk *(2,3,4),* larger than any of the other risk factors assessed concomittantly *(5, 6).* Whereas the relation to risk is linear for the BP MESOR, it is nonlinear for the case of the circadian BP amplitude *(7, 8).*

Because BP varies greatly, the conventional diagnosis of "hypertension" vs. "normotension" can be associated with a large error *(9).* For this reason, MESOR-hypertension has been defined as an elevation of the chronome (time structure)-adjusted mean values of BP above the upper 95% prediction limit of clinically healthy subjects of the same gender and ethnicity in the same age group *(10, 11).*

Similarly, CHAT has been defined as a circadian amplitude exceeding the upper 95% prediction limit for clinically healthy peers matched by gender, age and ethnicity *(5, 6)*.

Using the left ventricular mass index (LVMI) as a gauge of early cardiovascular disease risk, to examine how this surrogate outcome measure is affected by various risk indicators, including overswinging or CHAT (circadian hyper-amplitude-tension), non-dipping (a deficient blood pressure decline during rest), MESOR-hypertension, an elevated pulse pressure, and age.

MATERIALS AND METHODS

The around-the-clock ambulatory blood pressure (BP) profile of 2039 subjects was analyzed by single cosinor. The day-night ratio (DNR) was also computed as an index which we chronobiologically qualify as changing in part as a consequence of an altered timing of the circadian BP rhythm. Hence, we separated patients who had less than a 10% BP decrease by night according to whether their DNR was positive or negative, the latter subgroup also characterized by circadian ecphasia. Changes in LVMI as a function of age, the MESOR (M) and circadian amplitude (A) of systolic (S) and diastolic (D) BP, pulse pressure (PP) and the DNR of SBP and DBP, were examined by linear regression and analyses of variance. Some of the analyses were carried out on the subgroup of 424 subjects investigated earlier.

RESULTS

As expected, in the subgroups of 196 and 93 untreated men and women, LVMI increases with age ($P<0.001$), and is elevated in the presence of MESOR-hypertension ($P<0.005$). An elevated PP (>60 mm Hg) is also associated with a larger LVMI (men: 106.3(5.3 vs. 90.2(1.3 g/m2, $t=3.080$, $P=0.002$; women: 104.7(3.4 vs. 91.9(1.5 g/m2, $t=3.813$, $P<0.001$). In the larger cohort of 2039 subjects, including 617 and 562 untreated men and women, CHAT was associated with an elevated LVMI, but non-dipping was not *(Table 1)*. Extreme non-dipping, defined as a negative DNR (and corresponding to a reversal of circadian variation), was, however, associated with an elevated LVMI in women but not in men *(Table 1)*.

Regression analyses further indicate that the relation of LVMI to the circadian BP amplitude is a nonlinear one, suggesting the existence of a threshold beyond which risk increases.

DISCUSSION

According to our previous results, the „Circadian Hyper-Amplitude-Tension, CHAT“ is a disease risk syndrome of cardiovascular medicine (*6*). The availability of analyses of systolic and diastolic blood pressure data in the light of ethnicity-, time-, gender- and age-specified reference values and of ambulatory blood pressure monitors at a reasonable price for research in practice through the University of Minnesota.

Table 1
Increase in left ventricular mass index (LVMI) in association with both MESOR-hypertension and CHAT (Circadian Hyper-Amplitude-Tension)*

				LVMI: Mean ± SE (g/m^2)			
		F	(P)	MN-AN	MN-AE	MH-AN	MH-AE
SBP	M	97.085	(<0.001)	(942)	(29)	(178)	(29)
	A	6.601	(0.010)	85.8±0.6	93.1±3.2	100.5±1.7	106.4±3.5
interaction		0.061	(0.808)				
DBP	M	47.452	(<0.001)	(908)	(27)	(202)	(41)
	A	5.139	(0.024)	86.4±0.6	88.2±3.4	95.7±1.5	104.3±3.2
interaction		1.891	(0.169)				

*SBP: systolic blood pressure; DBP: diastolic blood pressure
M: MESOR (rhythm-adjusted mean value)
A: circadian amplitude
MN: MESOR-normotension; MH: MESOR-hypertension
AN: acceptable amplitude; AE: excessive amplitude (CHAT)
Numbers in ( ) are numbers of subjects per group

The results from the study mentioned above fully corroborate earlier findings based either on LVMI or on the actual incidence of adverse outcomes, indicating that CHAT is a disease risk syndrome warranting medical attention and immediate precautionary measures, such as autogenic training, even in MESOR-normotensive subjects.

An increase in LVMI associated with CHAT is mostly apparent from the nonlinear regression of LVMI on BP-A. The existence of a threshold value for BP-A beyond which LVMI increases is clearly seen by computing average LVMI values for subjects with an increasingly elevated BP-A. A somewhat lesser discrimination is obtained by a Student's t-test comparing subjects with a circadian amplitude that is either acceptable or excessive by Caucasian (white) standards. The relative merits of these different approaches suggest that the available reference limits may need further adjustment in screening the Taiwanese. The fact that the subjects studied herein were monitored for only 24

hours may also play a role since the reference standards were mostly obtained on the basis of 48- to 168-hour profiles. A reversal of the circadian BP rhythm, rather than a positive DNR less than 10%, seems to be associated with an elevated LVMI. This result is in keeping with reports by others and ourselves that circadian ecphasia, notably in patients with diabetes, is the underlying risk determinant and/or indicator. The lack of an increase in LVMI for positive DNR values less than 10%, even for women (this gender difference also replicates earlier results), suggests that „non-dipping" at best may be a stage in the progress of disease occurring only later on if at all, and that CHAT may constitute in any event the earlier, if not the critical warning sign.

A c k n o w l e d g e m e n t

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JE „OVERSWINGING" KREVNÍHO TLAKU ČASNÝM VAROVÁNÍM PŘED RIZIKEM KARDIOVASKULÁRNÍHO ONEMOCNĚNÍ? METAANALÝZA 2039 PŘÍPADŮ

S o u h r n

Cílem studie bylo zjistit, zda různé formy hypertenze („overswinging" krevního tlaku a MESOROVÁ hypertenze) ovlivňují index masy levé komory jako měřítka kardiovaskulárního rizika. Výsledky této studie jsou v naprostém souladu s našimi dřívějšími nálezy, které ukazují, že „overswinging" krevního tlaku jako forma hypertenze je rizikovým syndromem vyžadujícím okamžitou léčbu.

REFERENCES

1 *Kannel WB, Castelli WP, McNamara PM, Sorlie P.* Some factors affecting morbidity and mortality in hypertension: The Framingham Study. Milbank Mem Fund Q 1969;47:116–142.
2 *Cornelissen G., Halberg F.* Chronomedicine. In: Armitage P, Colton T, eds. Encyclopedia of Biostatistics. Chichester, UK: John Wiley & Sons Ltd., 1998:642–49.
3. *Otsuka K, Cornélissen G, Halberg F.* Predictive value of blood pressure dipping and swinging with regard to vascular disease risk. Clinical Drug Investigation 1996;11: 20–31.
4. *Otsuka K, Cornélissen G, Halberg F, Oehlert G.* Excessive circadian amplitude of blood pressure increases risk of ischemic stroke and nephropathy. J Medical Engineering & Technology 1997;21:23–30.
5. *Halberg F, Cornélissen G.* Resolution from a meeting of the International Society for Research on Civilization Diseases and the Environment (New SIRMCE Confederation, Brussels, 1995). Medtronic Chronobiology Seminar 1995;8:1–12.
6. *Halberg F, Cornélissen G, Halberg J et al.* Circadian Hyper-Amplitude-Tension, CHAT: a disease risk syndrome of anti-aging medicine. J Anti-Aging Med 1998;1:239–259.
7. *Chen CH, Cornelissen G, Halberg F.* Left ventricular mass index as „outcome" related to circadian blood pressure characteristics. Scripta medica 1998;71:183–89.
8. *Cornélissen G, Otsuka K, Chen C-H., Kumagai Y, Watanabe Y, Halberg F.* Nonlinear relation of the circadian blood pressure amplitude to cardiovascular disease risk. Scripta medica 2000;73:87–96.

9. *Cornélissen G, Halberg F*. Impeachment of casual blood pressure measurements and the fixed limits for their interpretation and chronobiologic recommendations. In: Portaluppi F, Smolensky MH, eds. Time–dependent Structure and Control of Arterial Blood Pressure. Ann. N.Y. Acad. Sci. 1996;783:24–46.
10. *Halberg F, Cornélissen G, Halberg E et al.* Chronobiology of human blood pressure. Medtronic Continuing Medical Education Seminars, 1988;4:1–242.
11. *Cornélissen G, Otsuka K, Halberg F*. Blood pressure and heart rate chronome mapping: a complement to the human genome initiative. In: Otsuka K, Cornélissen G, Halberg F, eds. Chronocardiology and Chronomedicine: Humans in Time and Cosmos. Tokyo: Life Science Publishing, 1993:16–48.