

## VASCULAR DISEASE RISK SYNDROMES AFFECTING BOTH MESOR-NORMOTENSIVES AND MESOR-HYPERTENSIVES: A META-ANALYSIS OF 2039 CASES

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### Abstract

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, as vascular disease risk syndromes. The results from this study fully corroborate earlier findings indicating that CHAT is a disease risk syndrome warranting immediate therapy.

### Key words

Cardiovascular disease risk, Circadian blood pressure amplitude, Essential hypertension, Left ventricular mass index

### INTRODUCTION

Vascular disease risk increases linearly with an increasing mean value of blood pressure, as documented longitudinally in the Framingham study (1). A great vascular disease risk elevation is also associated with an excessive circadian blood pressure amplitude (CHAT, brief for circadian hyper-amplitude-tension) (2, 3; cf. also 4, 5). Independent studies relying on the 24-hour SD of BP also support the increase in vascular disease risk associated with too much BP variability (6). The increase in cardiovascular disease risk associated with a decreased HR variability has also been recognized (7,8,9,10). Too low a SD of HR is one of several chronome alterations of heart rate variability (CAHRVs).

Circadian hyper-amplitude-tension (CHAT) is associated with a large increase in the actual incidence of adverse vascular events in subjects with MESOR-normotension (MN) as well as in treated patients with MESOR-hypertension (MH), as is a chronome alteration of heart rate variability (CAHRV). Using the left ventricular mass index (LVMI) as a surrogate outcome measure that may become elevated long before the actual occurrence of morbid events, we ask

whether CHAT and/or CAHRV are associated with an increase in LVMI, and if so, whether they affect MN and MH subjects alike.

MATERIALS AND METHODS

The around-the-clock blood pressure (BP) and heart rate (HR) profiles of 2039 subjects were analyzed by single cosinor, involving the fit of a 24-hour cosine curve to the data by least squares. Estimates are thus obtained for the MESOR (M), a rhythm-adjusted mean, and for the circadian amplitude (A) and acrophase (f), measures of the predictable extent and timing of change within a day. For each subject, the systolic (S) and diastolic (D) BP M and A were interpreted in the light of chronobiologic reference standards. The upper 95% prediction limit of clinically healthy (Caucasian) peers matched by gender and age but not ethnicity, were diagnosed as MH and/or as having CHAT. Separately for SBP and DBP, the LVMI was compared between subjects with MN vs. MH and with an acceptable (N) or excessive (E) circadian BP-A by 2-way ANOVA, also using age or weight as a covariate. LVMI was also linearly regressed with the 24-hour standard deviation (SD) of HR, used to assess HRV.

RESULTS

LVMI is increased in association with both MESOR-hypertension and CHAT in the untreated subjects ( *Table 1*). A 2-way ANOVA finds both factors to be statistically significant with no interaction. Similar results are obtained when adding either age or weight as a covariate in the analysis.

*Table 1*

Overswinging or CHAT (Circadian Hyper-Amplitude-Tension) rather than non-dipping is associated with an increase in left ventricular mass index (LVMI); an elevated LVMI is observed only in subjects showing a reversal of their circadian blood pressure variation\*

		LVMI (g/m <sup>2</sup> ): Mean ± SE						
Variable Gender		CHAT			DNR (%)			
		No	Yes	P	>10	0 – 10	<0	P <sup>†</sup>
SBP	Men	89.0±0.8	99.4±4.2	0.016	88.4±1.1	89.4±1.2	93.7±3.3	0.140
DBP	Men	89.1±0.8	94.1±3.8	0.189	89.0 ±1.0	90.0±1.5	89.5±3.1	0.883
SBP	Women	87.2±0.9	100.0±3.2	<0.001	88.5±1.3	85.2±1.2	94.6±2.5	0.001
DBP	Women	87.0±0.9	100.8±3.3	<0.001	87.7±1.1	86.0±1.4	94.0±2.6	0.018

<sup>†</sup>from one-way ANOVA comparing all 3 groups; the LVMI of women with a (SBP or DBP) DNR <0 is larger than that of women with a DNR >10% or a positive DNR <10% (P<0.05), whereas no difference is seen between positive DNR values < or > 10% (P>0.05); by contrast, the LVMI of men with a negative DNR of SBP is only slightly larger than that of dippers (P=0.057).

\*SBP: systolic blood pressure; DBP: diastolic blood pressure  
 DNR: day-night ratio (non-dipping is defined as DNR <10%)

A statistically significant negative correlation of LVMI on the 24-hour SD of HR is found for both men ( $r=-0.098$ ;  $P=0.015$ ) and women ( $r=-0.125$ ;  $P=0.003$ ). Overall, the negative relation of LVMI on HR-SD holds for both normotensive (SBP:  $r=-0.060$ ,  $P=0.063$ ; DBP:  $r=-0.096$ ,  $P=0.003$ ) and hypertensive (SBP:  $r=-0.146$ ,  $P=0.036$ ; DBP:  $r=-0.117$ ,  $P=0.068$ ) patients. This result is in keeping with the earlier finding that a decreased HRV is associated with an increase in cardiovascular disease risk. Further analyses suggest that the relation may be nonlinear and that there may be a threshold HR-SD below which LVMI increases sharply.

## DISCUSSION

The risk of adverse vascular events increases linearly with progressively increasing mean values of blood pressure. By contrast, there is no change in risk for a wide range of circadian amplitudes of blood pressure, or of 24-hour SDs of HR, but when these dynamic endpoints exceed a threshold, the risk is drastically and statistically significantly increased, suggesting a nonlinear relation with risk. The same relationship is found in two different studies, one carried out prospectively, the endpoint being the actual incidence of morbid events, the other study being a retrospective analysis of data wherein the LVMI is used as a surrogate outcome measure available for each patient.

CHAT is a risk factor that applies equally to men and women. By contrast, a gender difference characterizes the increase in risk associated with “non-dipping” (11, 12), the condition of a very small circadian amplitude of blood pressure. The incidence of adverse vascular events is compared between “non-dippers” and “dippers” and between patients with “CHAT” vs. patients with an acceptable circadian BP amplitude. Whereas CHAT is invariably associated with a statistically significant increase in risk, the risk of “non-dippers” does not differ with statistical significance from the risk of “dippers” in the overall population or in men, but it tends to do so for women, as can be seen from the only slight overlap by the 95% confidence interval of a relative risk of one, the latter representing equal risk between “dippers” and “non-dippers”. This result suggests that a very small circadian amplitude of BP may also be associated with vascular problems in women, whereas CHAT remains the largest risk factor assessed thus far for both men and women (2, 13).

The fact that a deviant circadian blood pressure pattern can predict vascular disease risk has several implications:

1. There is merit in assessing the dynamic changes in blood pressure, even when they occur within the physiological range, since endpoints such as the circadian amplitude are informative from a clinical viewpoint.
2. Spotchecks of blood pressure in patients with CHAT are likely to result in inadequate decisions to treat or not to treat (14).

3. The current guidelines for screening and diagnosis (15) are inadequate to identify patients with CHAT, who may be at an even higher vascular disease risk than patients with MESOR-hypertension (14, 16).

4. Blood pressure should be measured more than once, preferably systematically around the clock for at least 7 days, to reliably assess the circadian variation and, in certain cases, a one-week record is not conclusive (17, 18, 19).

CHAT and CAHRV are disease risk syndromes associated with an increase in LVMI. Their diagnosis requires the around-the-clock monitoring of BP and HR. Monitoring for at least 2 days and preferably 7 days at the outset is recommended in order to obtain a reliable estimate of the variability in both BP and HR. The diagnosis of CHAT, even in MN patients, may warrant medical attention and the institution of precautionary measures. This status quo is not desirable when an excessive circadian blood pressure amplitude has been shown to carry a large increase in risk of ischemic stroke and other adverse vascular complications.

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#### SYNDROMY RIZIKA VASKULÁRNÍHO ONEMOCNĚNÍ U NEMOCNÝCH MESOR-NORMOTENZIVNÍCH A MESOR-HYPERTENZIVNÍCH - METAANALÝZA 2039 PŘÍPADŮ

#### S o u h r n

Cílem této studie bylo zjistit, zda je index hmotnosti levé komory (LVMI) ovlivňován různými indikátory rizika, včetně překmitnutí (overswinging neboli CHAT - Circadian Hyper-amplitude Tension), nedostatečného poklesu krevního oběhu tlaku během odpočinku a tzv. mesorové hypertenze. Index hmotnosti levé komory byl použit jako náhradní měřítko rizika raného stadia kardiovaskulárního onemocnění. Výsledky studie plně potvrzují nálezy, z nichž vyplývá, že CHAT je rizikový syndrom onemocnění vyžadující okamžitou terapii.

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