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Opportunity of detecting pre-hypertension: worldwide data on blood pressure overswinging

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Abstract

Overswinging or CHAT (brief for Circadian Hyper-Amplitude-Tension), that is an excessive circadian variation in blood pressure (BP), has been associated with a large increase in cardiovascular disease risk, present even in the absence of an elevated BP itself. This usually asymptomatic condition is usually overlooked by current practice based on spot-checks, because to be diagnosed, measurements need to be taken around-the-clock, preferably for 7 days at the outset. Once diagnosed, however, a usual circadian BP pattern can be restored by means of certain non-pharmacologic or pharmacologic interventions timed appropriately. Thereby, it is possible to reduce the risk of cardiovascular morbidity and mortality, cerebral ischemic events and nephropathy in particular. For the preparation of guidelines regarding the diagnosis of BP disorders and for the institution of primary as well as secondary preventive measures, it is important to know what the incidence of CHAT is on a global basis. We found 191 cases of CHAT among 1602 mostly 7-day/24-h BP profiles, obtained from several centers in different countries participating in an ongoing project on the BIOsphere and the COSmos (BIOCOS). CHAT incidence is about the same between men and women, but it is diagnosed more often among patients with borderline hypertension or with glucose intolerance. It is also more common among MESOR-hypertensive than among MESOR-normotensive individuals. Priority should be given to the development of an unobtrusive and affordable device to automatically monitor BP and to analyze the data as-one-goes, so that cardiovascular disease risk can be prevented.

Keywords: BIOCOS; Blood pressure; Chat (circadian hyper-amplitude-tension); Glucose intolerance; Pre-hypertension; Worldwide incidence

1. Introduction

The need for an increase in awareness, treatment, and management of hypertension, afflicting over a quarter of the adult population [1] may take second place after efforts targeting primary prevention, our purpose herein. Hypertension is currently diagnosed mostly by means of single or a few measurements during a few consecutive examinations, a single visit in 27 of 30 studies summarized in Table 1 in [1]. This practice can be associated with over 40% false diagnoses [2], due in part to the large variability in BP, as such and in

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response to external factors. A diagnosis based on serial measurements taken at intervals, systematically around-the-clock for several days, obtained by manual or automatic monitoring, reduces misdiagnoses and hence morbidity and/or mortality. Home monitoring, becoming affordable is more widely used. Efforts to render automatic home monitoring within reach are underway [3,4], while the TM-2421 ambulatory monitors from A&D are available with an 80% reduction in cost with free data analyses, interpreted chronobiologically, provided worldwide through the BIOCOS project [5].

As compared to spot-checks or even 24-h profiles, week-long (or longer, once BP abnormality is diagnosed) ambulatory monitoring interpreted by the methods of chronobiology [3–5] provides a less unreliable diagnosis of "MESOR-hypertension", an elevation of the average BP, estimated by accounting for its broad time structure or chronome. The MESOR, or Midline Estimating Statistic Of Rhythm, is a more accurate and more precise estimate of location than the arithmetic mean. We need to diagnose also abnormalities in the variability of BP (and heart rate), not assessable on the basis of single measurements, and associated with an increase in cardiovascular disease risk greater than MESOR-hypertension [3–5]. CHAT, an excessive circadian BP variation, is associated with a large increase in cardiovascular disease risk, notably cerebral ischemic events and nephropathy, observed in normotensive as well as in treated hypertensive patients [3–8], validated in a perspective of up to 28 years based on 144,641 measurements from 2586 patients [9,10], Table 1. Identifying patients with consistent CHAT could relieve the burden of hypertension by prompt-

Table 1: Outcomes of chronobiological screens of blood pressure and heart rate*

N of patients (ref)	N at follow-up	Sampling	N measurements: Total (outcomes)	Finding
10 (1)	10 (up to 5 years)	5/day daily	Up to 9,125 (only partially analyzed)	Among P. Scarpelli's patients, the 4 who died with malignant hypertension had a larger circadian BP amplitude than the 6 who were still alive (SBP: t=1.84; P=0.103; DBP: t=2.99; P=0.017)
63 (2, 3)	21 after 28 years	~q4h for 2 days	756 (252)	9 of 10 subjects without CHAT are alive while 7 of 11 subjects with CHAT are dead 28 years later (chi-square=6.390; PO.01)
56 (4)	56: Concomitant LVM1	q15 min for 24 h	5,376 (5,376)	Classification by Y. Kumagai of patients by LVMI (<100; 100-130; >130 g/m^2) reveals elevation of circadian amplitude at LVMI in 100-130 range whereas MESOR elevation occurs only at LVMI > 130.
221 (5,6)	221 (time of delivery)	q1 h/48h in each trimester of pregnancy (336 profiles)	16, 128 (16,128)	In addition to an 8 mm Hg difference in mean value between women who will or will not develop complications (gestational hypertension, preeclampsia) already observed during the first trimester of pregnancy, the occurrence of complications is also associated with BP profiles characterized by an elevated circadian BP amplitude. In particular, one case (JK) of CHAT where warning was not heeded, was followed 8 weeks later by severe pre-eclampsia, premature delivery and 26 months of hospitalization of offspring at a cost of about $1 million
297 (7-12)	297 after 6 years	q15 min for 48 h	57,024 (57,024)	CHAT or a reduced circadian standard deviation of heart rate, or an excessive pulse pressure (>60 mm Hg) are large risk factors (larger than hypertension) for cerebral ischemic events, nephropathy and coronary artery disease, even when the blood pressure is within acceptable limits.
2039 (13-15)	2039 Concomitant LVMI	Hourly averages for 24 h	48,936 (48,936)	LVMI is increased in patients with CHAT, a reduced circadian standard deviation of heart rate, or an elevated pulse pressure. The relation between LVMI and the circadian endpoints is nonlinear.
23 (16)	12 after 7 years	q15 min for 9 days	19,872 (10,368)	10 of 20 patients with no consistent BP abnormality are alive and well; 2 of 3 patients with consistent BP abnormality reported an adverse vascular event (P=0.015 by Fisher's Exact Test).
80 (17, 18)	80 Response to treatment administered 2 h before daily BP peak vs. control group treated 3 times a day	q4 h for 24 h before and on treatment	960 (960)	With smaller doses of medications, BP was lowered by R. Zaslavskaya to a larger extent and treatment was accompanied by fewer complications. Treatment: propranolol, clonidine, or alpha-methyldopa (P<0.05 for each effect)
18 (19)	18 (12 weeks)	q30 min (≥ 24h) on 3 regimens	≥ 2592 (≥ 2592)	Treating CHAT may prevent adverse vascular events: As compared to placebo, nifedipine (1 mg b.i.d. at 08 & 20) increases and benidipine (4 mg/day at 08) decreases the circadian amplitude of blood pressure. The resulting increase vs. decrease in the incidence of CHAT on nifedipine vs. benidipine may account for the corresponding difference between the number of stroke events of 7.6 vs. 3.5 and the total number of cardiovascular events of 20.4 vs. 8.8 per 1,000 person-years.
Totals:				
2,807	2.754		160.769 (>141.636)	

*SBP and DBP: Systolic and Diastolic blood pressure; HR: heart rate; CHAT: Circadian Hyper-Amplitude-Tension, a condition defined by a circadian amplitude exceeding the upper 95% prediction limit of acceptability (in healthy peers matched by gender and age); LVMI: left ventricular mass index. By comparison with several classical studies, the number of measurements in chronobiological work completed thus far is likely to be larger, and confounding by inter-subject variability smaller (20).