SCRIPTA MEDICA (BRNO) – 75 (2): 87–94, *April 2002*

CHAT (CIRCADIAN HYPER-AMPLITUDE-TENSION) AND CSDD-HR (CIRCADIAN STANDARD DEVIATION DEFICIT OF HEART RATE): SEPARATE, SYNERGISTIC VASCULAR DISEASE RISKS?

CORNÉLISSEN G.[1], OTSUKA K.[2], BAKKEN E.E.[3], HALBERG F.[1], SIEGELOVÁ J.[4], FIŠER B.[5]

[1]Chronobiology Center, University of Minnesota, Minneapolis, MN, USA, [2]Department of Medicine, Tokyo Women's Medical University, Tokyo, Japan, [3]North Hawaii Community Hospital, Kamuela, HI, USA; [4] Department of Functional Diagnostic and Rehabilitation, Faculty of Medicine, Masaryk University, Brno, [5]Ministry of Health, Prague, Czech Republic

A b s t r a c t

Adverse vascular outcomes recorded during 6 years were related to abnormalities in the variability of blood pressure and heart rate of 297 patients. Each was monitored for 48 hours at 30-min intervals at the beginning of the study. Patients with circadian amplitude of blood pressure and a 48-hour standard deviation of heart rate within acceptable limits constituted the reference group. As compared to the reference group, patients with either too large circadian amplitude of blood pressure (CHAT) or too low a standard deviation of heart rate had an increase in cardiovascular disease risk. When both conditions coexisted, the increase in risk was larger than the addition of both risks. CHAT and reduced heart rate variability are two separate synergistic disease risk conditions, detected by a chronobiologic approach, even when they occur within the conventional normal range.

K e y w o r d s

Blood pressure, Hypertension, CHAT (circadian hyper-amplitude-tension), CSDD-HR (circadian standard deviation deficit of heart rate), Vascular disease risk

INTRODUCTION

CHAT, short for „**c**ircadian **h**yper-**a**mplitude-**t**ension", is a condition defined by an excessive circadian amplitude (A) of blood pressure (BP), above a threshold approximated by the upper 95% prediction limit of clinically healthy peers matched by gender, age and ethnicity (*1,2*). This condition is associated with a large increase in vascular disease risk, notably in the case of cerebral ischaemic events and nephropathy (*1,2,3,4,5*). CAHRVs, short for „**c**hronome **a**lterations of **h**eart **r**ate **v**ariability", constitute another set of conditions associated with an increased risk of developing vascular diseases. In particular for heart rate (HR), a lowered 24-hour standard deviation (SD), also called circadian SD deficit (CSDD-HR), is associated with an increased cardiovascular disease risk (*6,7*). As reported earlier for the patients studied herein, CSDD-HR is associated with an

increased risk not only of coronary artery disease but also of cerebral ischaemic events (*8*). Whether CHAT and CSDD-HR, characterised by altered dynamic (circadian patterns) of BP and HR, are two aspects of the same syndrome and/or whether constitute disease risks in their own right, is investigated herein.

MATERIALS AND METHODS

Systolic (S) and diastolic (D) BP and HR were measured at 15-min intervals for 2 days on 297 (121 normotensive and 176 treated hypertensive) patients, who were followed-up at 6-month intervals for 6 years. The incidence of coronary artery disease, cerebral ischaemic events, nephropathy and retinopathy was recorded. The relative risk (and 95% confidence interval, CI) of morbidity associated with CHAT and CSDD-HR, occurring separately or in combination, was computed (*9*). A linear regression analysis was also performed between the diastolic (D) BP-A and HR-SD.

RESULTS

Of the 297 patients, 39 experienced a morbid event within 6 years. There were 16 cases of coronary artery disease, 14 cerebral ischaemic events, 18 cases of nephropathy and 16 cases of retinopathy. As illustrated in *Fig. 1*, out of the 39 patients who experienced a morbid event, 20 had a DBP-A and HR-SD within acceptable limits, seven had DBP-CHAT but not CSDD-HR, eight had CSDD-HR but not DBP-CHAT, and four had both DBP-CHAT and CSDD-HR. Of the remaining 258 patients who had no morbid event, 233 had a DBP-A and HR-SD within acceptable limits, whereas 13 had DBP-CHAT but not CSDD-HR, 11 had CSDD-HR but not DBP-CHAT, and only one had both DBP-CHAT and CSDD-HR.

Using the patients with neither DBP-CHAT nor CSDD-HR as reference, the relative risk (RR) of patients with DBP-CHAT-only or with CSDD-HR-only was increased from less than 8% to over 40%. When both conditions, DBP-CHAT and CSDD-HR, were present simultaneously, the risk was increased further to 80% (*Fig. 1* and *Table 1*).

In order to see whether the increase in risk, when both conditions are present, was higher than when only one condition was present, the relative risk of patients with combined DBP-CHAT and CSDD-HR was calculated by comparison with the patients who had either DBP-CHAT-only or CSDD-HR-only. The relative risk was estimated to be 2.08 (95% CI: 1.15–3.76) (c^2 = 3.117; P=0.0775), the relatively small number of patients notwithstanding.

Similar results are obtained when morbid outcomes are further specified by diagnosis, particularly for the case of cerebral ischaemic events and nephropathy, conditions for which both DBP-CHAT and CSDD-HR have been shown earlier to be risk factors (*Table 2*).

These results suggest that DBP-CHAT and CSDD-HR constitute separate risk factors. This finding is corroborated by the fact that DBP-A and HR-SD are not

Table 1

Relative risk of morbid event associated with DBP-CHAT and CSDD-HR, singly or in combination*

Group	DBP-CHAT-only	CSDD-HR-only	DBP-CHAT and CSDD-HR
No. of patients	20	19	5
No. of patients with outcome	7	8	4
χ^2,(1) (P-value)	15.268 (<0.001)	22.385 (<0.001)	30.206 (<0.001)
RR [95% CI]	4.43 [2.13–9.19]	5.33 [2.71–10.46]	10.12 [5.51–18.58]

*In the reference group consisting of 253 patients, 20 patients experienced an adverse event within 6 years.

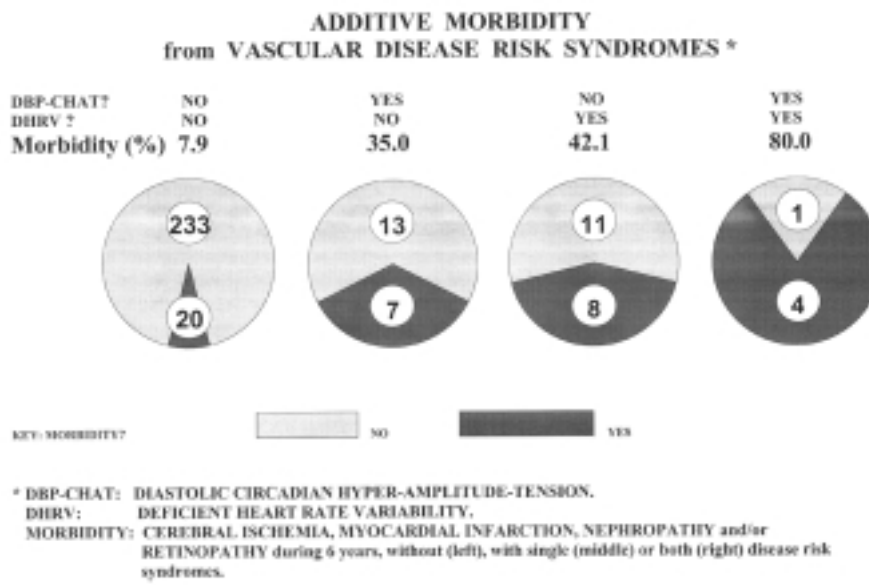

Fig. 1
Pie charts comparing the incidence of morbid events between the patients with abnormalities in blood pressure and/or heart rate variability and those without them (© Halberg).

Table 2
Relative risk of coronary artery disease (CAD), cerebral ischaemic event (CIE), nephropathy (NP) and retinopathy (RP) associated with DBP-CHAT and CSDD-HR, singly or in combination

Group		1. No DBP-CHAT or CSDD-HR	2. DBP-CHAT only	3. CSDD-HR-only	4. DBP-CHAT and CSDD-HR
CAD	Yes	8	2	5	1
	No	245	18	14	4
CIE	Yes	4	3	4	3
	No	249	17	15	2
NP	Yes	8	4	3	2
	No	245	16	16	2
RP	Yes	12	2	1	1
	No	241	18	18	4
Comparison		2 vs. 1	3 vs. 1	4 vs. 1	4 vs. (2+3)
CAD	χ^2,(1)	2.456	20.818	4.129	0.013
	(P)	(0.117)	(<0.001)	(0.042)	(0.911)
	RR	3.16	8.32	6.32	1.11
	[95% CI]	[0.72; 13.91]	[3.01; 22.97]	[0.96; 41.49]	[0.17; 7.28]
CIE	χ^2,(1)	13.359	23.472	63.394	4.462
	(P)	(<0.001)	(<0.001)	(<0.001)	(0.035)
	RR	9.49	13.32	37.95	3.34
	[95% CI]	[2.28; 39.49]	[3.61; 49.11]	[11.35; 126.9]	[1.25; 8.92]
NP	χ^2,(1)	12.505	7.262	38.806	4.462
	(P)	(<0.001)	(<0.001)	(<0.001)	(0.035)
	RR	6.32	4.99	18.97	3.34
	[95% CI]	[2.08; 19.20]	[1.44; 17.30]	[7.06; 50.99]	[1.25; 8.92]
RP	χ^2,(1)	1.053	0.011	2.385	0.812
	(P)	(0.305)	(0.918)	(0.123)	(0.367)
	RR	2.11	1.11	4.22	2.60
	[95% CI]	[0.51; 8.78]	[0.15; 8.09]	[0.67; 26.50]	[0.33; 20.46]

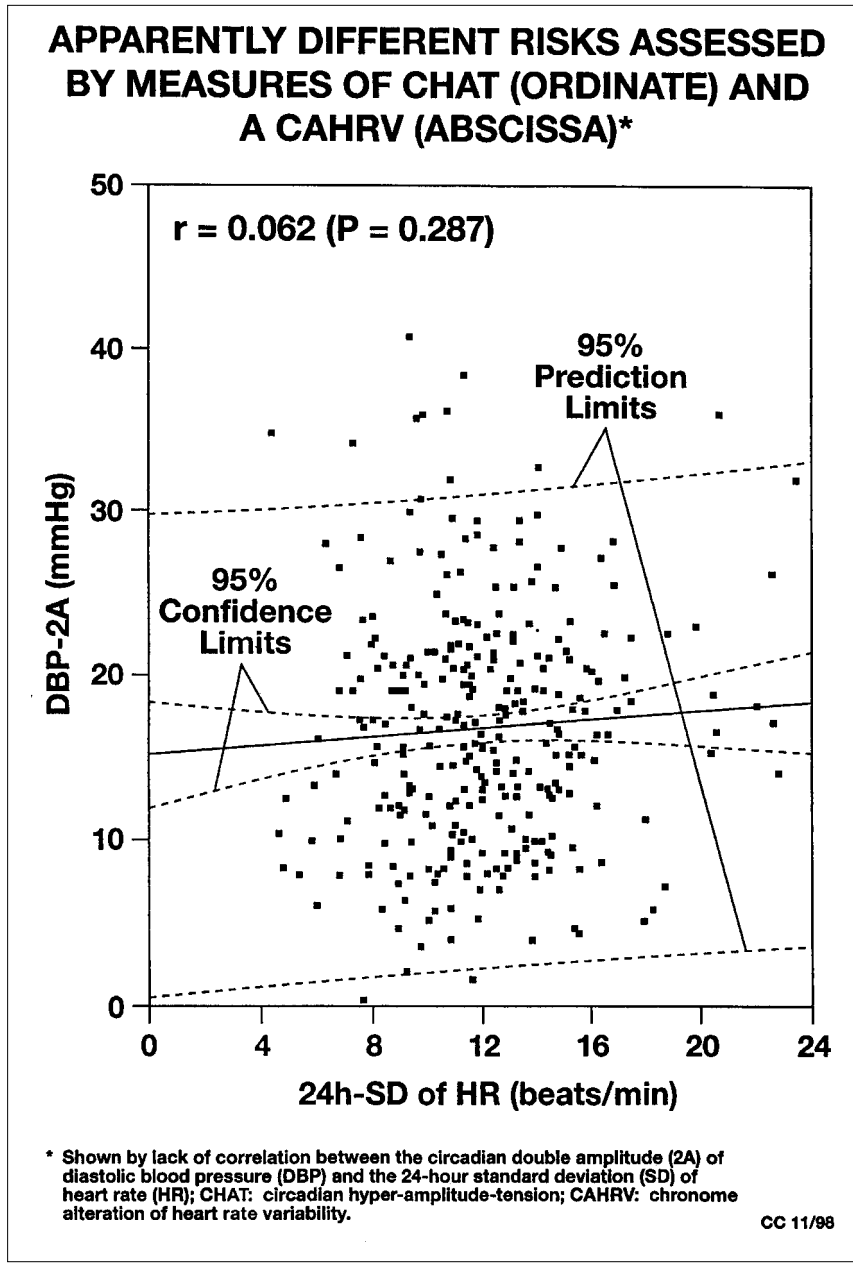

Fig. 2
Lack of relation between the circadian amplitude of blood pressure and the standard deviation of heart rate, indices reflecting variability in these variables (© Halberg).

correlated (10). The relation between DBPA and HR-SD was not statistically significant (r=0.062; P=0.287; *Fig. 2*).

DISCUSSION

Earlier work suggested that only CSDD-HR increased the risk of coronary artery disease with statistical significance, whereas neither DBP-CHAT nor CSDD-HR was found to be associated with an increased risk of retinopathy (*8*). There is only very little overlap between the patients diagnosed with DBP-CHAT and those diagnosed with CSDD-HR (10.2% of those who had a morbid event and 0.5% of those who remained event-free for 6 years). In view of the overall lack of relation between the two dynamic parameters serving to diagnose DBP-CHAT and CSDD-HR, and the increase in risk of morbid events, cerebral ischaemic events and nephropathy in particular, observed when both conditions were present as compared to when only DBP-CHAT or CSDD-HR was present, it is suggested that DBP-CHAT and CSDD-HR are two separate, synergetic disease risk conditions.

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

The study was supported by the U.S. Public Health Service (GM-13981; FH); Dr. h.c. Dr. h.c. Earl Bakken Fund (FH, GC) and the University of Minnesota Supercomputing Institute (FH, GC).

Cornélissen G., Otsuka K., Bakken E.E., Halberg F., Siegelová J., Fišer B.

CHAT (CIRCADIÁNNÍ NAPĚTÍ S HYPER-AMPLITUDOU) A CSDD-HR (CIRCADIÁNNÍ DEFICIT SRDEČNÍ FREKVENCE SE STANDARDNÍ ODCHYLKOU): SAMOSTATNÁ, SYNERGISTICKÁ KARDIOVASKULÁRNÍ RIZIKA

S o u h r n

Nepříznivé výsledky v oblasti kardiovaskulárních chorob zaznamenané během 6 let souvisely s abnormalitami ve variabilitě krevního tlaku a srdeční frekvence u 297 pacientů. Každý z nich byl na začátku studie monitorován po dobu 48 hodin ve 30-minutových intervalech. Pacienti s normální cirkadiánní amplitudou krevního tlaku a 48-hodinovou standardní odchylkou srdeční frekvence v přijatelných mezích tvořili referenční skupinu. Ve srovnání s referenční skupinou docházelo u pacientů, kteří měli buď příliš velkou cirkadiánní amplitudu krevního tlaku (CHAT) nebo příliš malou standardní odchylku srdeční frekvence, ke zvýšení rizika kardiovaskulární choroby. Při společném výskytu obou podmínek bylo zvýšení rizika ještě vyšší. CHAT a snížená variabilita srdeční frekvence jsou dvě samostatná synergistická rizika choroby, zjištěná chronobiologickým přístupem, i když se vyskytují v běžném normálním rozsahu.

REFERENCES

1. *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.
2. *Cornélissen G, Halberg F, Schwartzkopff O et al.* Chronomes, time structures, for chronobioengineering for „a full life“. Biomed Instr Technol 1999; 33: 152–187.
3. *Otsuka K, Cornélissen G, Halberg F.* Predictive value of blood pressure dipping and swinging with regard to vascular disease risk. Clin Drug Invest 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 Med Eng Technol 1997; 21: 23–30.
5. *Cornélissen G, Schwartzkopff O, Halberg F, Otsuka K, Watanabe Y.* 7-day ambulatory monitoring for adults with hypertension and diabetes [letter]. Am J Kidney Dis 2001; 37: 878.
6. *Kleiger RE, Miller JP, Bigger JT, Jr, Moss AJ.* Multicenter Post-Infarction Research Group. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 1987; 59: 256–262.
7. *Tsuji H, Venditti FJ, Manders ES et al.* Reduced heart rate variability and mortality risk in an elderly cohort. The Framingham Heart Study. Circulation 1994; 90: 878–883.
8. *Otsuka K, Cornélissen G, Halberg F.* Circadian rhythmic fractal scaling of heart rate variability in health and coronary artery disease. Clin Cardiol 1997; 20: 631–638.
9. *Agresti A.* Categorical Data Analysis. New York: John Wiley & Sons, 1990.
10. *Cornélissen G, Otsuka K, Chen C-H et al.* Nonlinear relation of the circadian blood pressure amplitude to cardiovascular disease risk. Scripta med 2000; 73: 85–94.