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NEED FOR CHRONOBIOLOGIC REFERENCE VALUES (CHRONODESMS) SMOOTHED OVER AGE: A PROBLEM AWAITING A BIOCOS SOLUTION

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A b s t r a c t

Because gender differences and age trends have been amply documented to characterize blood pressure (BP) and heart rate (HR) in health, it is not appropriate to use fixed limits (such as 140/90 mm Hg SBP/DBP) for screening and/or diagnosis of adults 18 years and older, as is the current practice. Chronobiologic reference standards have been derived that are specified by gender and ethnicity for specified age groups. The improvement they offer over the status quo notwithstanding, such limits pose problems when longitudinal series from individuals crossing the boundaries of consecutive age groups need to be interpreted. New strategies for developing reference values are proposed.

K e y w o r d s :

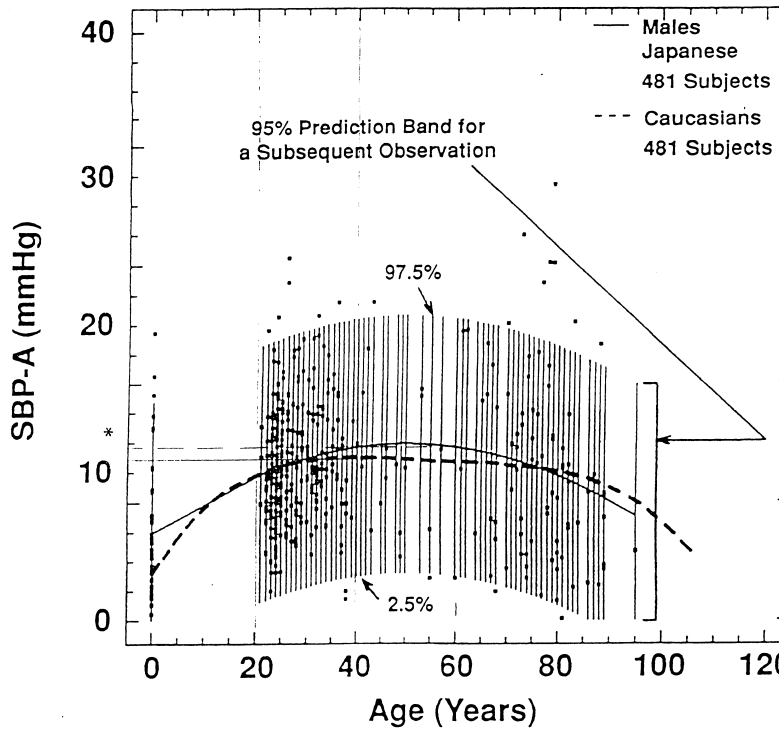
chronobiologic reference value, blood pressure, heart rate, circadian rhythm,

Abbreviations

MESOR midline-estimating statistic of rhythm, 2A - double amplitude (measure of the extent of predictable change within a cycle), CHAT - circadian hyperamplitude tension of blood pressure

INTRODUCTION

In current medical practice, only single measurements of blood pressure (BP) and heart rate (HR) are taken on which decisions are based for the long-term treatment of patients with a deviant BP (*1*). Chronobiologic recommendations (*2-4*) have been made to collect data serially around the clock in order to obtain information concerning the dynamic characteristics of change in BP (or HR), in addition to getting a better estimate of the mean value. Further, it was advocated *(5-7)* to obtain such data on clinically healthy people in order to derive time-specified reference values (chronodesms) as well as reference values for dynamic endpoints such as the circadian amplitude and acrophase. These data bases have revealed gender differences as well as age trends, illustrated in *Fig. 1* for Japanese



*Note smooth rather than abrupt transition.

Fig. 1.
Changes in circadian amplitude (A) of systolic blood pressure (SBP) as a function of age*

and Caucasian men (*6, 8, 9*). In the current implementation of the chronobiologic recommendations, reference values have been specified for clinically healthy peers of a given gender and ethnicity in different age groups.

When individuals advance in age while they monitor themselves longitudinally for vascular disease risk assessment, they will eventually be subject to a switch from one age group's reference values to those of a different age group, since the reference values as a function of age are not (yet) gathered longitudinally on the same population. Thus, when reference limits from one age group, e.g., 20-40 years, to the next, e.g., 40-60 years, are independently computed for the interpretation of single values, there is no smooth transition from one reference group to the next. The same problem of an abrupt change from

one 20-year reference group to another applies to reference standards for the MESOR and for the circadian (or other, such as about-weekly) amplitude and acrophase. Such rather abrupt changes in limits of acceptability found between consecutive age-qualified reference groups do not mimic the much smoother age changes seen in individuals who monitor longitudinally on a very long-term basis.

METHODS

Table 1 describes a clinically healthy man at high familial risk for high BP and related vascular diseases. This unusually motivated cardiologist started around 35 years of age to monitor himself at 15- to 30-minute intervals for over 8 years. He still monitors: his record now covers over 11 years, but the data summarized in Table 1 suffice to make the point of this paper. The data were analyzed by chronobiologic serial section and other rhythmometric techniques (Halberg cosinor analysis).

RESULTS

Illustrative case

In consecutive 48-hour profiles up to 40 years of age, he is found to have an elevated MESOR of systolic (S) and diastolic (D) BP about 29% and 59% of the time, respectively. But after 40 years of age, these incidences are reduced to less than 1% and 29%, respectively. By contrast, the diagnosis of CHAT (**c**ircadian **h**yper-**a**mplitude-**t**ension), a condition associated with a large increase in vascular disease risk (*4*, *10*-*12*,*16*), is made only in 13% and 12% of the SBP and DBP profiles, respectively, before 40 years of age, but these incidences change to 26% and 8% after 40 years of age, *Table 1*. These changes in diagnosis stem primarily from the contemporaneous change in chronodesmic limits associated with the switch from one reference group to another.

DISCUSSION

Where do we go from here ?

The vagaries here reported suggest the need for systematic monitoring longitudinally for lifetimes. Test pilots who monitor themselves and provide these values should be motivated and/or compensated for this task, until automatic, preferably implanted monitors and reference values become available.

In the interim, the current chronobiologic recommendations could be improved by assuring a smoother transition from one age group to the next. This could be achieved by relying on logistic regression techniques applied to the reference data base as a whole rather than on local analyses performed for specified age groups (for each gender and ethnic background), formed on the basis of results from analyses of variance on the original reference data banks.

Another advantage of using regression techniques over an analysis of variance approach is the possibility of accounting for other sources of variation that may affect the chronodesmic limits, such as the circannual variation that modulates the usually predominant circadian rhythm.

Table 1
Artifactual changes resulting from different reference values for peers above vs. below 40 years of age*

Monitoring Year	Age (years)	N of 48-h profiles	MESOR-hypertension SBP N+ (%)		MESOR-hypertension DBP N (%)		CHAT SBP N (%)		CHAT DBP N (%)	
1987	34	62	6	(9.68)	41	(66.13)	1	(1.61)	1	(1.61)
1988	35	161	33	(20.50)	109	(67.70)	8	(4.97)	8	(4.97)
1989	36	154	57	(35.85)	94	(59.12)	4	(2.52)	4	(2.52)
1990	37	152	62	(40.79)	45	(29.61)	6	(3.95)	1	(0.60)
1991**	38	158	21	(13.29)	71	(45.57)	6	(3.80)	4	(2.53)
1992**	39	101	29	(28.91)	59	(58.92)	13	(12.81)	12	(11.88)
1993***	40	133	1	(0.75)	39	(29.32)	34	(25.56)	11	(8.27)
1994	41	134	0	(0)	47	(35.00)	33	(24.81)	7	(5.26)
1995**	42	115	0	(0)	21	(18.26)	32	(27.83)	14	(12.17)
1987 (8/26) to 1995 (9/2)		1175	209	(17.80)	527	(44.89)	137	(11.67)	62	(5.28)
Total N of days monitored		2350	418		1054		274		124	

*Presented to emphasize need for peer-group reference standards smoothed over age for the interpretation of results from long-term monitoring. Tabulated are incidences of an elevated rhythm-adjusted mean (MESOR) of systolic (S) or diastolic (D) blood pressure (BP) (MESOR-hypertension) and of overswinging (namely circadian hyperamplitudetension; CHAT) in consecutive 2-day profiles of a clinically healthy man at high familial risk of cardiovascular disease, who monitored himself automatically for more than 8 years with few interruptions, using an ABPM-630 from Colin Electronics (Komaki, Japan).

**Subject changed employment on April 1 from St. Marianna University in Kanagawa Prefecture near Tokyo to Amamoto Hospital in Tokyo. One month later (May 1), he moved to Tokyo Women's Medical College (now University), where he remained employed throughout the monitoring span. On July 6, he married a wife who cooked salt-free meals. With his wife, he had emotional episodes, at some times of a positive, at other times of a negative nature, which prompt him to regard marriage as a load. On October 19, 1992, a son was born at 11:52. On April 29, 1995, he arrived in Minnesota, USA, for a first 7-month span of research (ending about November 30).

***The use of a dividing line in reference values above and below 40 years of age prompts reference to a new 95% prediction limit whereby systolic MESOR-hypertension appears to be practically eliminated while SBP CHAT is nearly trebled. A linear regression in this case reveals no statistically significant change in SBP MESOR ($P=0.285$), a small increase in the MESOR of mean arterial pressure ($P=0.030$), and a decrease in the MESOR of DBP ($P<0.001$), while both the linear regression and a self-starting cusum control chart reveal a statistically highly significant increase in circadian amplitude for SBP, MAP and DBP.

+N=N of 48-h profiles; for total N of monitoring days multiply N by 2 for each item in the two columns headed with N, as shown in the bottom rows of these columns only.

In summary, the current chronobiologic approach, by accounting for gender and ethnic differences and for trends as a function of age, provides more realistic limits of acceptability (*10-13*) than the fixed limits used indiscriminately under the current WHO guidelines (*1*). The chronodesms presently available on tolerance (*14*) or prediction (*15*) intervals seem to be acceptable as a reference standard for the interpretation of relatively short profiles from patients monitored for one or a few weeks at a time. Shortcomings become apparent when longer series or a series straddling an age associated with a change in reference values need to be interpreted. These limitations could be overcome by using logistic regression techniques to derive chronodesmic limits from the reference data banks and eventually by applying such techniques to longitudinal data series collected on the same individuals whose clinical health is ascertained both by their longevity and their demise.

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POTŘEBA CHRONOBIOLOGICKÝCH REFERENČNÍCH VĚKOVĚ ZPRŮMĚRNĚNÝCH HODNOT: PROBLÉM REŠENÝ V RÁMCI BIOCOS

S o u h r n

Vzhledem k tomu, že rozdíly pohlaví a věkové trendy byly bohatě dokumentovány pro charakterizování hodnot krevního tlaku a srdeční frekvence u zdravých osob, není vhodné používat pevné limity (jako je 140/90 STK/DTK) pro vyhledávání a diagnostiku dospělých ve věku 18 let a starších, což je současná praxe. Byly odvozeny chronobiologické referenční normy, specifikované podle pohlaví a etnicity pro určité věkové skupiny. Navzdory zdokonalení ve srovnání se status quo přinášejí tyto limity problémy, když je třeba interpretovat longitudinální sérii u jednotlivců, překračujících hranice věkových skupin. Navrhují se nové metody vytváření referenčních hodnot.

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