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CIRCADIAN ASPECTS OF IMMIGRANT INDIANS BLOOD PRESSURE AND HEART RATE IN THE USA

A Thesis

Presented to

The Faculty of the Department of Biological Sciences

San Jose State University

In Partial Fulfillment

of the Requirements for the Degree

Master of Science

by

Balasasikumar Sundaram

May 2008

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Balasasikumar Sundaram

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Approved for the department of Biological Sciences

Dr. Daniel Holley, Professor
Department of Biological Sciences
San Jose State University, San Jose, CA, USA

Dr. Michael Sneary, Professor
Department of Biological Sciences
San Jose State University, San Jose, CA, USA

Dr. Franz Halberg, Professor
Halberg Chronobiology Center
University of Minnesota, Minneapolis, MN USA

APPROVED FOR THE UNIVERSITY

ABSTRACT

CIRCADIAN ASPECTS OF IMMIGRANT INDIANS BLOOD PRESSURE AND HEART RATE IN THE USA

by Balasasikumar Sundaram

Time structurally (chronomically) interpreted half- hourly monitoring of blood pressure and heart rate for 7 days could be used for a diagnosis of blood pressure (BP) and assessment of cardiovascular risk. 30 clinically healthy subjects underwent 7-day monitoring and provided a series of findings, including the detection of Circadian Hyper-Amplitude-Tension (CHAT), which is blood pressure over swinging that carries a high risk of cardiovascular events. Five subjects were diagnosed with CHAT and two subjects were found to have systolic MESOR (Mean Estimating Statistic of Rhythm) - hypertension. MESOR of systolic BP increases with age and double amplitude of diastolic BP increases with increasing severity of family history. The results bear upon, specifically, Asian-Indian immigrants and show that their cardiovascular disease risk increases with family history of cardiovascular diseases including hypertension, duration of stay in the USA, and with age. Such monitoring for prehabilitation may eventually reduce the need for rehabilitation.

ACKNOWLEDGEMENTS

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- Dr. Daniel Holley, my graduate advisor at San Jose State University, who opened the doors for my research interests as a masters student. His research expertise and his critical feedback of my work will always be a good source of education for me and I thank him for that.
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- Dr. Germaine Cornelissen for her enthusiastic support and valuable assistance in doing the statistical analyses for this thesis project.
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Background and significance

High Blood pressure (BP) is a serious health problem in developing, as well as developed countries. It is estimated that 65,000,000 people in the USA (32.3%) have high BP. The health care costs due to high BP are estimated to be $59.7 billion and the overall death rate from complications of high BP in 2000 was 17.1% of all deaths (American Heart Association [AHA], 2005).

The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High BP, convened by the National Heart, Lung, and Blood Institute, states that "Repeated blood pressure measurements will determine whether initial elevations persist and require prompt attention or have returned to normal and need only periodic surveillance" (National Heart, Lung, and Blood Institute [NHLBI], 1997). The Scottish Intercollegiate Guidelines Network (SIGN), an affiliate of the Royal College of Physicians of Edinburgh, recommends at least three-repeated BP measurements over a span varying from days to months before diagnosing high BP (Scottish Intercollegiate Guidelines Network [SIGN], 2005). The detection and confirmation of high BP by looking at single or occasional measurements is unwise, however, even if it is officially sanctioned (Chobanian et al., 2003; Halberg & Cornelissen, et al. 1995; NHLBI, 1997; SIGN, 2005; Zarnke, Levine &

McAlister, 2001), because of a high chance of false positive and false negative diagnoses. National and international meetings have addressed the clinical importance of the outcomes of ambulatory monitoring studies, and have emphasized the need for their incorporation into clinical diagnostic and prognostic guidelines. The SIGN (SIGN, 2005) states that ambulatory BP monitoring has proved useful in certain circumstances, like borderline hypertension, suspected "white coat" hypertension, i.e., in patients defined as those whose BP is consistently elevated in the clinic but normal at other times, and apparent refractory hypertension .

The British Hypertension Society recommends use of the ambulatory BP monitoring when clinic BP shows unusual variability and when symptoms suggest the possibility of hypertension (Ramsay et al., 1999). The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (NHLBI, 1997) and other researchers (Appel & Stason, 1993; Perloff, Sokolow & Cowan, 1983) have mentioned that, among persons with hypertension, there is "an extensive and very consistent body of evidence" indicating that ambulatory BP correlates more closely than clinic BP with target organ damage such as left ventricular hypertrophy. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation,

and Treatment of High Blood Pressure (Chobanian et al., 2003) suggests that Ambulatory Blood Pressure Monitoring (ABPM) is warranted for evaluation of (white-coat) hypertension in the absence of target-organ injury and is helpful to assess patients with apparent drug resistance, hypotensive symptoms with antihypertensive medications, episodic hypertension, and autonomic dysfunction". The 2000 Canadian recommendations for the management of hypertension (Zarnke et al., 2001) suggests ABPM should be considered when an office induced increase in blood pressure is suspected and, for 1) untreated patients with mild to moderate clinical blood pressure elevations, and without target organ damage, 2) treated patients with apparent resistance to drug therapy, symptoms suggestive of hypotension, or fluctuating office blood pressure readings. For patients in who elevated clinic pressure is the only abnormality, ambulatory monitoring may identify a group at relatively low risk of morbidity (Perloff, Sokolow & Cowan, 1983; Perloff, Sokolow & Cowan, 1989; Verdecchia, Porcellati & Schillaci, 1994). Pickering (1995) reported that ambulatory BP monitoring is "most clinically helpful and most commonly used" in patients with suspected "white coat hypertension" and in patients with apparent drug resistance, hypotensive symptoms with antihypertensive medications, episodic hypertension, and autonomic dysfunction.

I chose immigrant Indians (Asian Indians) living in California, USA as our study population because migration has been shown to influence BP (Brown & James, 2000; Green & Peled, 1992; Kaplan, Chang & Newsom, 2002; Lizarzaburu & Palinkas, 2002; Powles, Hopper & Gregory, 1993; Rosenthal & Grossman, 1993; Salmond, Prior & Wessen ,1989), and their numbers have been increasing over the past 10 years as many come for jobs in California's high-tech industry. A study by Rosenthal and Grossman (1993) on Ethiopian immigrants in Israel found high BP which was thought to be due to effects of urbanization. Brown and James (2000) reported a study claiming to have evaluated the effects of "Americanization" (the adoption of American life style and culture) in Filipino American immigrant nurses found high Diastolic Blood Pressure (DBP) low dips in BP during sleep, and high norepinephrine, considered as the presence of physiological measures of a load ("stress") . Though the exact reasons behind an immigration-induced elevation of BP are still unclear, environmental factors like diet, climate, and exposure to chemical and biologic agents, and indirect psychosocial factors might play a role. Immigrant Indians who were born and raised in a traditional setting are now living in an entirely new environment, experiencing different cultures, life style, work style, and food habits.

I note that in other parts of the world (Singapore, Trinidad, South Africa, and Fiji) Asian Indians have a three-fold higher prevalence of cardiovascular disease (primarily coronary artery disease) than the corresponding native population (Adelstein, 1963; Balarajan, 1991; Beckles, Miller, Kirkwood, Alexis & Carson, 1986; Danaraj, Acker, Danaraj& Ong, 1959; Enas, Yusuf& Mehta, 1992; McKeigue& Marmot, 1985; Mckeigue, Miller& Marmot, 1989; Toumilehto, Ram, Eseroma & Zimmet, 1984). A report on South Asian-Americans' health by the South Asian Public Health Association(2002) states that in the USA, heart disease has a higher prevalence in Asian Indians than in other Asians and non-Hispanic whites, and that one of the top chronic illness concerns is high BP. Because migration is such a widespread phenomenon, studies of the effects of accompanying life change on the health and well being of the migrant have special significance in areas like California that support large migrant communities, but a desirable monitoring of people before and after migration was not possible for me. My research seeks to explore the circadian variations of BP and heart rate (HR) in immigrant Indians in the light of reference values from Caucasians, clearly a compromise with practicability.

Subjects and methods

Following advertisement for immigrant Indian subjects through fliers posted at San Jose State University, religious places where Indians gather in large numbers, Silicon Valley companies where immigrant Indians work in large numbers, and Indian grocery stores, 19 men and 11 women volunteered to participate in this study. The study was approved by the Institutional Review Board at San Jose State University. Before data collection, each subject was briefed on the use of the equipment and signed an informed consent form. All subjects also filled out a BP family history and risk questionnaire, asking routine questions about the subject's dietary habits, family, and personal medical history.

The subjects wore the TM-2421 ambulatory BP monitor from A&D (Tokyo, Japan) for 7 consecutive days, mostly 24 hours per day. The monitor took BP and HR measurements once per 30 minutes during the day (06:00 to 22:00) and once per hour during the night (22:00 to 06:00). Schaffer et al., (2001) and Watanabe et al., (1997) showed the importance of a 7-day monitoring to secure reliable estimates of circadian rhythms. The BP and HR data were stored in the monitor's memory and downloaded to a personal computer at the end of the 7

days. The procedures followed by the subjects have been used by a wide range of individuals in several other research studies (Cornelissen et al., 1989; Halberg, Cornelissen, Halberg, Fink, et al., 1998; Halberg, Cornelissen, Schwartzkopff, et al., 2005; Halberg, Cornelissen, Wall, et al., 2002; Otsuka, Cornelissen& Halberg, 1996; Otsuka, Cornelissen, Halberg& Oehlert, 1997; Scarpelli, Gallo& Chiari, 2000; Schaffer et al., 2001; Watanabe et al., 1997).

The data were analyzed by *sphygmochron* (Cornelissen, Otsuka, Halberg, 1993; Halberg et al., 1990), which provides both a parametric and a non-parametric assessment of the data. Based on a 2-component model consisting of cosine curves with periods of 24 and 12 hours, the parametric endpoints considered herein are: the Mean Estimating Statistic Of Rhythm (*MESOR*), a rhythm-adjusted mean value; the *double circadian amplitude*, a measure of the extent of predictable change within a day; and the *circadian acrophase*, a measure of the timing of overall high values (from the fitted cosine curve) recurring each day. Estimates of these parameters for each subject were compared with 90% prediction limits for clinically healthy Caucasian peers matched by gender and age. The non-parametric endpoints are obtained by comparing each subject's profile with time-specified reference limits (chronodesms) derived from

clinically healthy Caucasian peers matched by gender and age (Cornelissen et al., 1993; Halberg et al., 1990).

Regression analyses was done to correlate the MESOR and circadian double amplitude of systolic blood pressure(SBP) and diastolic blood pressure (DBP) and HR with a cardiovascular disease risk score based on family history , body mass index (BMI, body wt in kg/height in m^2), age, and duration of stay in the USA (Cornelissen et al., 1989).

Results

Based on Caucasian reference limits, out of 30 subjects, 2 women and 1 man were found to have systolic CHAT, two men to have diastolic CHAT, and two women to have systolic MESOR- hypertension. The excessive variation in SBP of the 27-year-old woman, who has both systolic CHAT and systolic MESOR-hypertension, is illustrated in Figure 1. Interviews of subjects with CHAT revealed the presence of worries and other loads. The 27-year-old woman, whose data are shown in Figure 1, reported a weight loss of 22 pounds over 24 months prior to monitoring, whereas the 31-year-old man with diastolic CHAT reported a drop in his physical activity resulting in a weight gain of about 3 pounds over 24 months prior to monitoring.

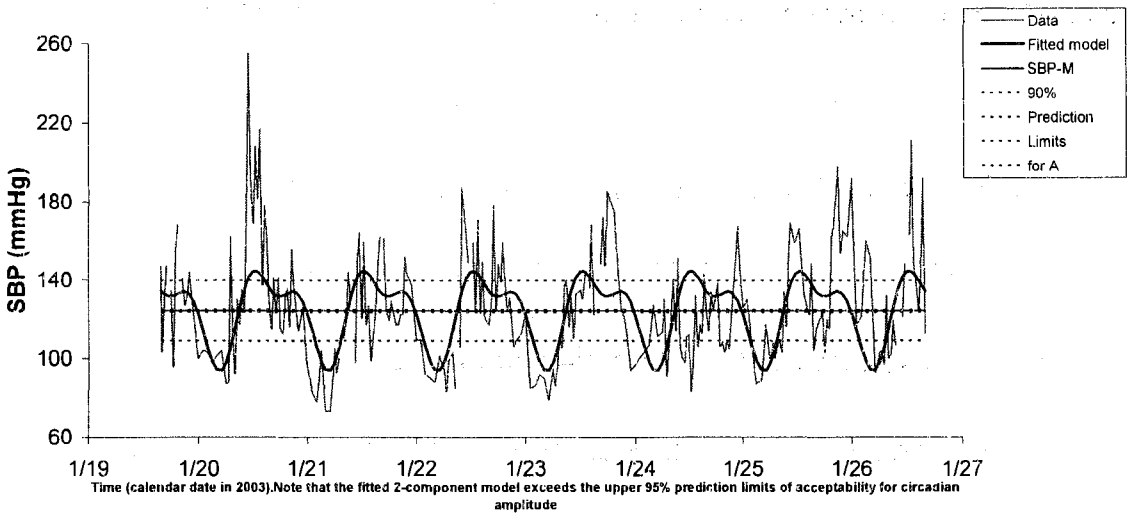

Figure 1. Systolic Blood Pressure (SBP) profile of subject diagnosed with systolic CHAT (DH028, 27 year old female).

Regression analyses indicate that MESOR of DBP tends to correlate positively with duration of stay (p=0.03, R= 0.390), as shown in Figure 2, which could mean that the longer duration of stay could increase cardiovascular risk.

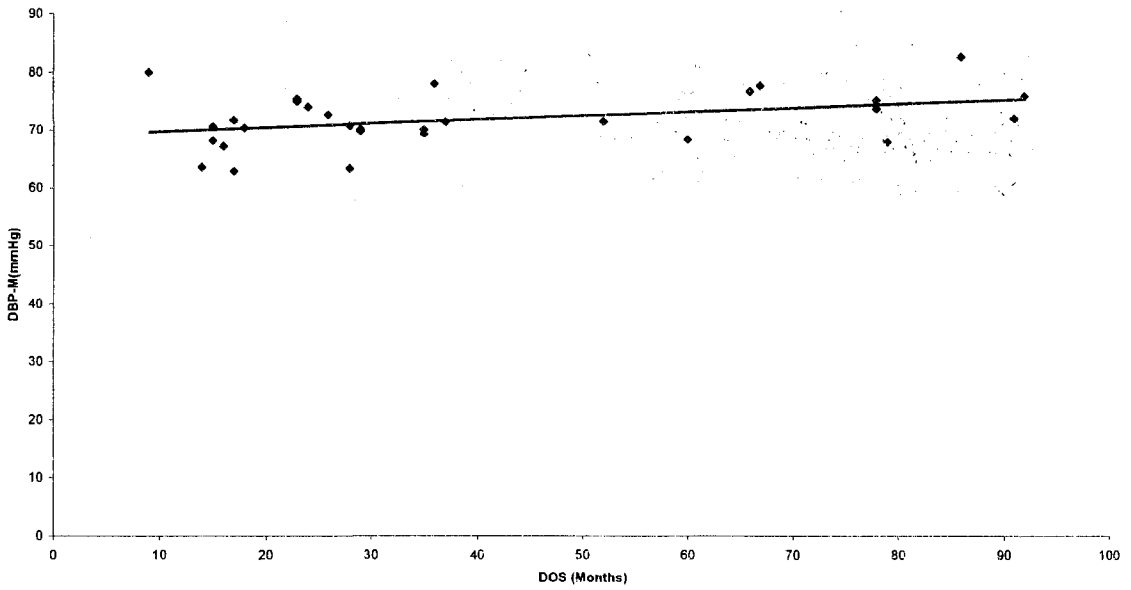

Figure 2. Higher MESOR of Diastolic blood pressure (DBP-M) associated with longer duration of stay (DOS).

MESOR of diastolic blood pressure also correlates positively with age (p= 0.01, R= 0.617), as shown in Figure 3.

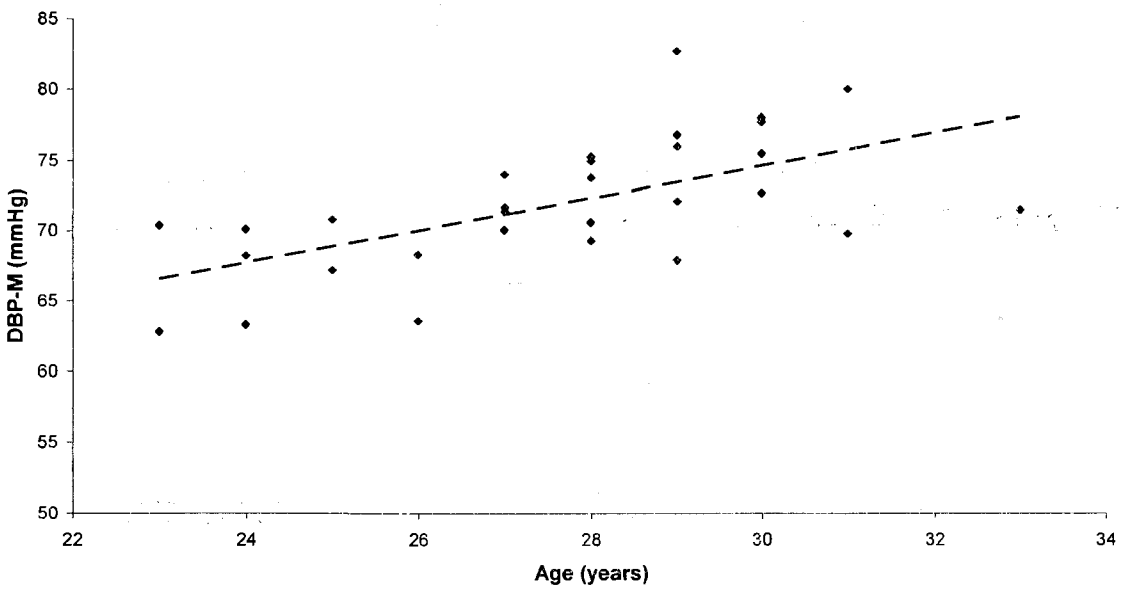

Figure 3. MESOR of Diastolic blood pressure (DBP-M) increases with age.

Double circadian amplitude of heart rate correlates negatively with family history risk score (p= 0.02, R=0.403), as shown in Figure 4, and this may mean that decreased heart rate variability is seen in families with increased cardiovascular risk.

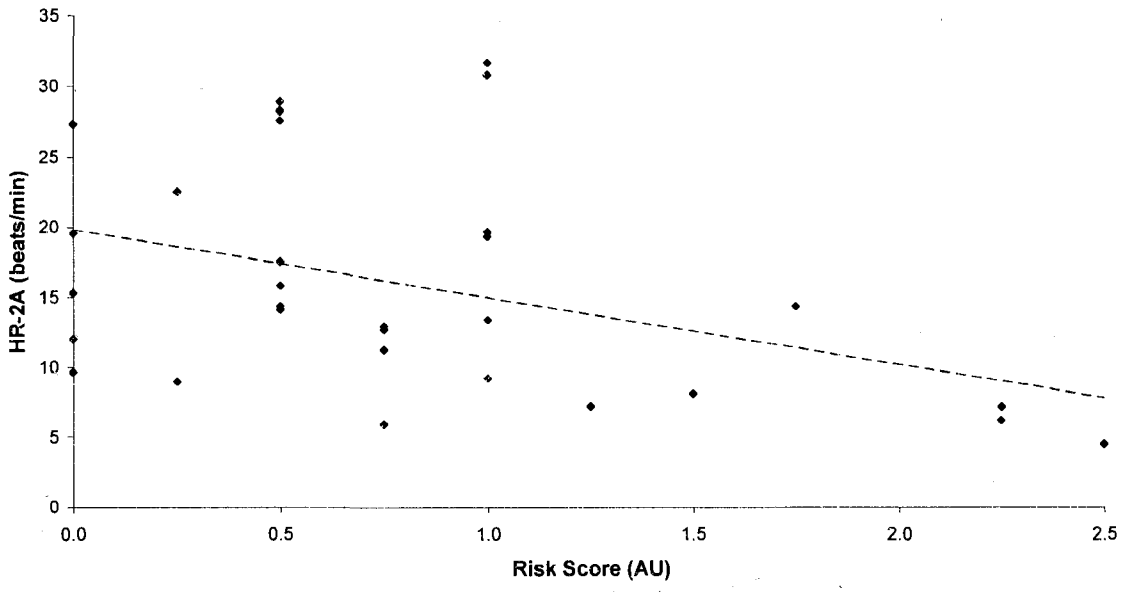

Figure 4. Lower double amplitude of heart rate (HR-2A) associated with higher family history cardiovascular disease risk score.

The double amplitude of SBP increases with increase in family history risk score (p=0.01, R=0.462), as shown in Figure 5, and decreases with increase in BMI (p= 0.01, R=0.44), as shown in Figure 6.

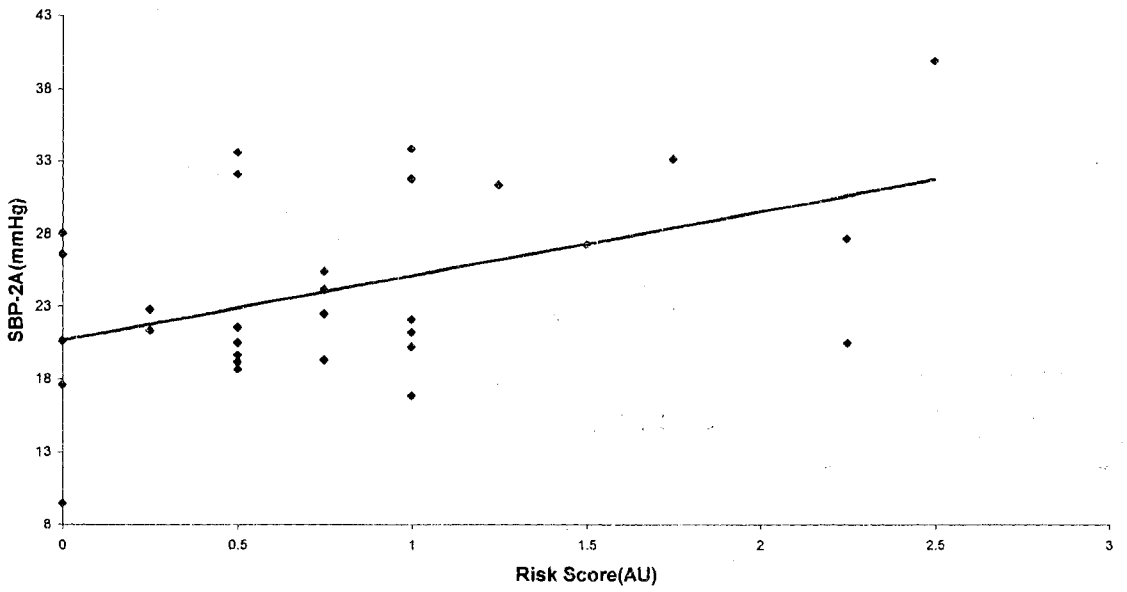

Figure 5. Higher double amplitude of systolic blood pressure (SBP-2A) associated with higher family history cardiovascular disease risk score.

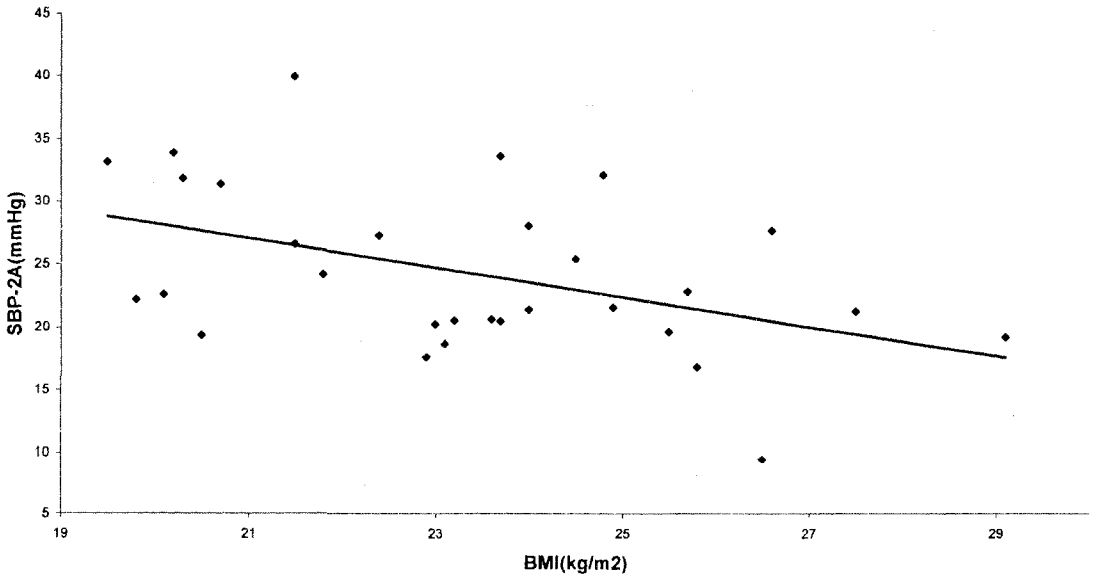

Figure 6. Lower double amplitude of systolic blood pressure (SBP-2A) with increased Body Mass Index (BMI).

The double amplitude of DBP also correlates negatively with BMI (P= 0.05, R=0.355), as shown in Figure 7, and this inverse relationship of BMI with both diastolic and systolic double amplitude goes along with the observation that obesity is slightly protective against a cerebral ischemic event (44).

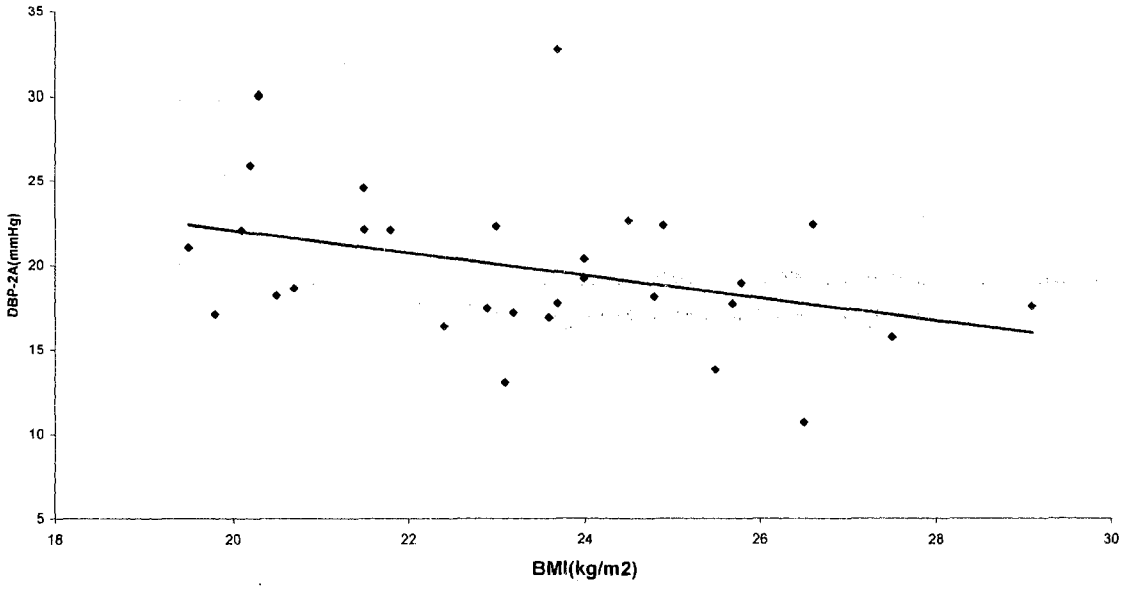

Figure 7. Lower double amplitude of diastolic blood pressure (DBP-2A) with increased body mass index (BMI)

Discussion and summary

In this study, circadian BP and HR data were collected from 30 subjects. The results show that:

1) Five subjects were diagnosed with CHAT (Circadian Hyper-Amplitude- Tension) and two subjects were found to have systolic MESOR-hypertension.
2) Double circadian amplitude of SBP increases with the presence of a family history of cardiovascular disease and/or high BP (P= 0.01), a statistically highly significant observation in earlier studies on other populations (Cornelissen, Kopher, et al., 1989; Cornelissen, Otsuka, et al ., 1993; Halberg, Bakken, et al ., 1990; Halberg, Cornelissen, Halberg, et al ., 1998; Halberg, Cornelissen, Schwartzkopff, et al ., 2005; Halberg, Cornelissen, Wall, et al ., 2002; Otsuka, Cornelissen& Halberg , 1996; Otsuka, Cornelissen, Halberg& Oehlert , 1997; Scarpelli, Gallo& Chiari, 2000; Scarpelli, Marz, Cornelissen, Romano& Livi, 1985; Wan, Wang, Cornelissen& Halberg, 1994).
3) MESOR of DBP correlates significantly with age (P=0.01). This is consistent with studies which observed that older hypertensive subjects have more DBP fluctuations, and age had significant linear

correlation with BP variability (Cicconetti, Migliori, Lorido, & Ciotti, 2000), and even in normotensive, healthy subjects age correlates with mean and amplitude of BP variability (Cugini, Derosa,Pellegrino & De Laurentis, 2000).

4) Double amplitude of SBP decreases with increasing BMI (P=0.01) and so does the double amplitude of DBP, albeit with borderline statistical significance (P= 0.05). This inverse relationship was observed in an observational study in which higher body mass index was found to be slightly protective against ischemic events (Otsuka, Cornelissen & Halberg, 1996). BMI was found to have inverse relationship with nocturnal fall of BP in hypertensive men in the Northwick Park Hospital Database Study (Acharya, Heber, Dore & Raftery, 1996).

5) MESOR of DBP was found to be increased in subjects who had stayed in USA for longer (P=0.03). This is consistent with at least one study, which concluded that longer-term immigrants are more likely than recent immigrants to report hypertension (Green& Peled, 1992). The duration of stay varies between 9 months to 92 months with an average of 46.5 months. However, the MESOR of DBP increases with

age too. The average age of our subjects is 28 years and it varies from 23 to 33. Since I found positive correlation of MESOR of DBP with both duration of stay, and age, I think that both age and duration of stay, alone or in combination, would increase the cardiovascular risk of immigrants. This is particularly important in case of younger immigrants, who constitute the majority of our study population, who, if choose to stay for longer duration, may increase their cardiovascular risk because of elevated circadian parameters of BP.

6) Double circadian amplitude of heart rate decreases with increasing family history risk score (P= 0.02). Earlier studies (Cornelissen, Kopher, et al., 1989; Cornelissen, Otsuka, et al ., 1993; Halberg, Bakken, et al ., 1990; Halberg, Cornelissen, Halberg, et al ., 1998; Halberg, Cornelissen, Schwartzkopff, et al ., 2005; Halberg, Cornelissen, Wall, et al ., 2002; Otsuka, Cornelissen& Halberg , 1996; Otsuka, Cornelissen, Halberg& Oehlert , 1997; Scarpelli, Gallo& Chiari, 2000; Scarpelli, Marz, Cornelissen, Romano& Livi, 1985; Wan et al., 1994) show that decreased heart rate variability increases cardiovascular risk. The data from this study shows that subjects with higher cardiovascular risk, based on family history, are

exhibiting decreased heart rate variability. This is important since decreased heart rate variability adds more to a subject's cardiovascular risk load, when present along with stronger family history.

Two of the five subjects with CHAT report considerable subjective loads ("stress") related to work, school, and family. The average family history risk score of this study population is 0.776 with a standard deviation of 0.711. The family history risk score is 2.5 for one woman with systolic CHAT (which is more than two standard deviations above the mean), 1.25 for another woman with systolic CHAT (which is almost one standard deviation above the mean) and 0.5 for one of the men with diastolic CHAT. This is noteworthy if we take into account the statistically significant relationship between the double amplitude of SBP and the family history score observed herein and in earlier studies (Halberg, Bakken, et al., 1990; Halberg, Cornelissen, et al., 1998; Otsuka, Cornelissen& Halberg, 1996; Otsuka, Cornelissen, Halberg&Oehlert, 1997).

Ambulatory Blood Pressure Monitoring (ABPM) allows the measurement of the variability of BP and HR throughout out the day and night, which is used to categorize patients into 1) dippers (> 10%), 2) non-dippers (0-10%), and 3) reverse dippers (< 0%) (Kario, 2004; Lee, Blann& Lip, 2005; Mousa, El-sayed,

Motawea, Salama& Elhendy, 2004; Von Kanel et al., 2004). Previous research studies have shown that non- dipping is directly associated with cognitive impairment/ vascular dementia (Yamamoto, 2005), and influences cardiovascular risk by altering hemostasis /endothelial function (Lee et al., 2005; Von Kanel et al., 2004). Research studies have also shown that non-dipping is independently associated with Left Ventricular Mass Index (LVMI) even after adjustment for mean BP, and angiographic coronary artery disease (Mousa et al., 2004; Rahman, Griffin, Heyka& Hoit, 2005),and has a positive correlation with stroke incidence/ silent cerebral infarcts (Kario, 2004). Researchers have evidence to prove that BP variability in general and non-dipping in particular, has a consistently reproducible pattern (Rahman et al., 2005; Stenehjem& Os, 2004; Cuspidi, Meani, Salerno& Valerio, 2004). Though this type of categorization potentially serves to increase the validity of risk stratification and mortality/morbidity prediction, researchers have demonstrated that chronobiologically derived parametric endpoints such as CHAT represent a greater and clinically more important risk factor than non-dipping (Cornelissen, Otsuka, Chen, Singh& Halberg,[unpublished manuscript]; Otsuka, Cornelissen& Halberg , 1996). Figure 8 shows that CHAT is a better predictor of morbidity than "non-dipping".

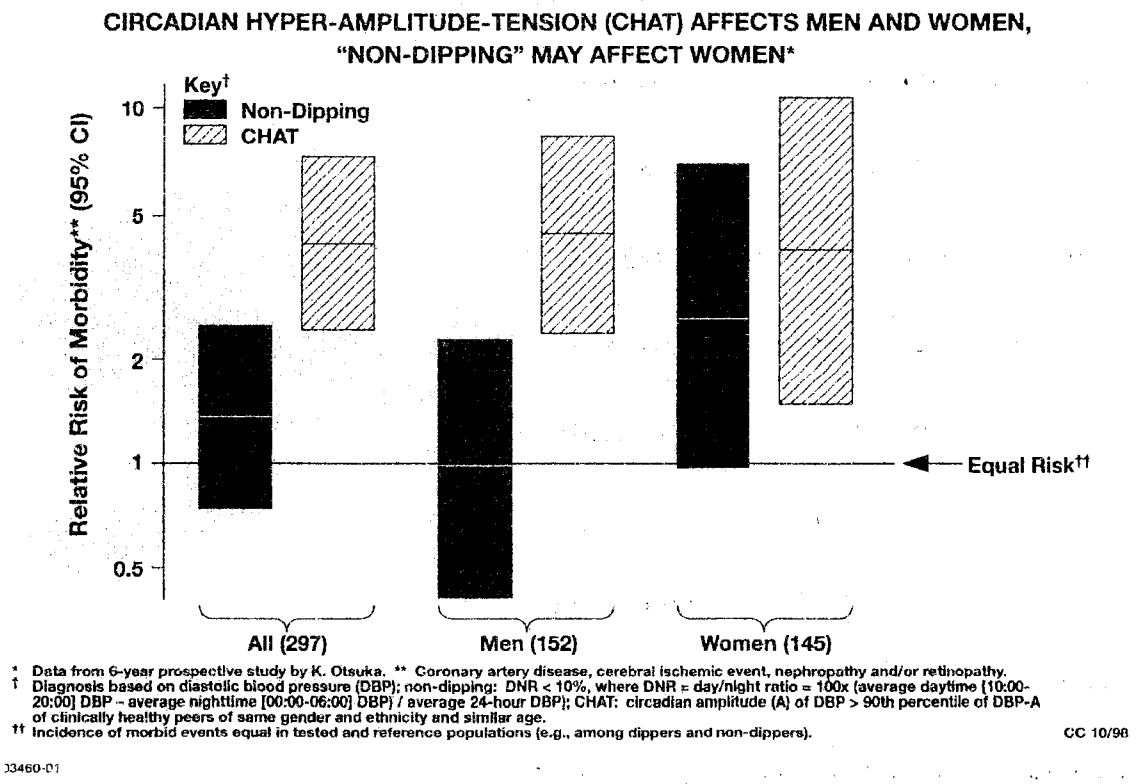

Figure 8: (Reprinted with permission of the author). The relative risk (RR) of morbidity occurring within 6 years of monitoring of 297 patients in Tokyo, Japan, associated with diastolic CHAT (Circadian hyper-amplitude-tension) is statistically significant for men and women, as well as overall, as evidenced by the 95% confidence intervals of RR values not overlapping one (equal risk). By contrast, the relative risk associated with "non-dipping" (day-night ratio less than 10%) is only marginally elevated, and only so for women and not for men.

From "Circadian Hyper-Amplitude-Tension (CHAT) and an Elevated Pulse Pressure are Separate Cardiovascular Disease Risk Factors" by G. Cornelissen, K. Otsuka, CH-H. Chen, R.B. Singh, F. Halberg. Unpublished Manuscript.

A research study in Spain showed the usefulness of ABPM in predicting incidence of gestational hypertension and preeclampsia as early as first

trimester (Hermida, Diana, Artemio& Fernandez, 2003). Also, anti-hypertensive treatment may be less effective when based on clinic BP rather than ABPM (Hoshide, Kario, Schwartz& Hoshide, 2002.

ABPM analysis combined with chronobiology allows us to obtain refined diagnoses namely MESOR- hypertension when the chronome-adjusted mean value (MESOR) of BP is above the upper limit of acceptability, excessive pulse pressure(EPP) when difference in MESOR between the systolic and diastolic BP is too large, CHAT (Circadian Hyper-Amplitude Tension) when the circadian BP amplitude is excessive, DHRV (decreased heart rate variability) when the standard deviation (SD) of HR is below acceptable range, and/or ecphasia when the overall high values recurring each day occur at an odd time (a condition also contributing to the risk associated with "non- dipping"). This approach further serves as a guide to optimize the efficacy of any needed treatment by timing its administration (chronotherapy) and normalizing abnormal patterns in BP and HR.

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