Blood pressure variability and pedigree analysis of nocturnal SBP dipping in Kumbas from rural Chhattisgarh, India

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Family is the smallest unit of people to share most of the lifestyle, environmental and genetic factors. They are likely to have similarity in many physiological and behavioural aspects. Therefore, we designed a protocol to test the effect of large rural Indian families living together (Kumbas), on blood pressure variability. We also investigated the hypothesis that ‘nocturnal dipping’ in systolic blood pressure (SBP) is not heritable. Members of two families (1 and 2) consisting of 3-4 generations willingly participated in the study. Both families (natives of Chhattisgarh) belong to reasonably peaceful rural area and are financially stable. Farming is the main occupation of the members of both families. Few members of the families had jobs or small business. The null hypothesis regarding heritability of nocturnal dipping trait was accepted based on data emanating from either of the studied families. Hourly-averaged values depicted less variation in males and females of family 1 from midnight to early morning at around 06:00, as compared to that in males and females of family 2. The 24 h averages of BP in family 2 were significantly higher as compared to that in family 1. Further, in family 2 the peaks of SBP, diastolic blood pressure (DBP) and mean arterial pressure (MAP) occurred significantly earlier as compared to that in family 1. The peak spread of SBP, DBP, heart rate (HR), MAP and pulse pressure (PP) among the members of family 1 was narrower than that for the members of family 2. Arbitrary cut-off values for classification of dipping, small sample size, and age dependency of nocturnal dipping might have marred outcome of the pedigree analysis of nocturnal dipping trait in this study. We have a hunch that the family shares typical temporal ups and downs in 24 h BP and HR. The above hypothesis needs confirmation based on studies with large data set involving subjective and objective assessment of the effects of psychosocial factors on BP and HR variability.

Keywords: Circadian, Kumbas - large Indian families, Pedigree analysis inheritance of nocturnal dipping, Variability in BP

Blood pressure is influenced by several factors, such as stress, emotions, depression, physical work, temporal physiological changes, food habits, alcohol, tobacco and genes. As these factors are temporally superimposed, it is extremely difficult to observe their effects, in isolation, on BP dynamics. Secondly, these factors may produce different effects on different persons. Often, it is practically difficult to group the subjects in a random population based on the role of each factor. There are also some factors that produce universal effects irrespective of traits of the subjects. The ‘time of the day’ factor is one among them.

The blood pressure variability along 24 h time scale has been well studied. ‘Nocturnal dipping’ is the most studied characteristic of temporal BP variation. It has been established that for each 10 mm Hg increase in night time systolic blood pressure, the mortality risk increases by 21%. Nocturnal dipping between 10 and 20% is accepted as normal; however, deviations from this cut off is considered as abnormal and are termed as non-dipping (<10% nocturnal dip in systolic blood pressure, SBP), extreme dipping (>20% nocturnal dip in SBP) and rising (elevated nocturnal SBP than corresponding day time SBP). Abnormal nocturnal dipping is common in primary and secondary hypertension and is often associated with higher prevalence of strokes, cardiovascular mortality and most importantly poor response to antihypertensive treatment.

Non-dipping is the most studied abnormality. It is highly associated with severe cardiovascular damage, poor vascular prognosis and higher risk for cardiovascular morbidity. Non-dipping is particularly associated with enhanced carotid intima-media thickening and thereby target organ damage, ischemic stroke and myocardial infarction. Poor long-term survival of non-dipper makes this category more vulnerable. In addition, other abnormalities, such as rising signifies high risk of fatal strokes,
intracranial hemorrhage, target organ damage and cardiovascular mortality and extreme dipping is associated with lacunar stroke, silent myocardial ischemia, silent cerebrovascular lesion and ischemic stroke. Study on inheritance pattern of such an import BP characteristic (nocturnal dipping) is meager.

Thus, 24 h BP measurement has prognostic and diagnostic significance. However, the ambulatory BP recordings in free living conditions are likely to be influenced by environmental and lifestyle factors that may mislead the investigators. Approximately two decades before Spitzer et al. found that BP is the lowest when person is with family as compared to when he is with friends, professionals or strangers. However, a solitary study on effect of family size on hypertension by Bani documented higher prevalence of hypertension in large families. Investigations of this nature have not yet been carried out for 24 h BP variations.

Therefore, we designed a study protocol to check the hypothesis that the members of the large families (Kumbas) living together, sharing most of the environmental and life style factors will exhibit similar pattern in 24 h BP variability. We also tested the hypothesis that ‘nocturnal dipping’ is not heritable. We selected two large rural families in our studies to test the above hypotheses.

**Material and Methods**

**Selection of subjects and situation**—Two families living in a small semi-rural place, Kasdol (Latitude: 21° 37' 05" N. Longitude: 82° 26' 49" E), 114 km away from State headquarters – Raipur, were chosen (Fig. 1). The area is calm, pollution free, surrounded by forest and many tourist places. Locals are basically farmers, but internet, television, mobile phones, and other electronic gadgets are available and are being used by some affluent villagers. Most people, except older ones, are literate. Daily routine is quite undisturbed, relatively less demanding and nights are silent enough supporting a good sleep. Overall the environment is favourable for studying inheritability of nocturnal dipping in free living conditions. The prevalence of hypothyroidism and diabetes in the selected families is very low. We did not exclude one or two members from the studied population, who are suffering from metabolic disorders, as our basic interest was to see 24 h variability in BP.

**Details of family 1 (Jagat family) —**This family consists of 4 generations. Most of the members live together. The food habits, time of food intake and timings of sleep-wake schedule are similar for almost all the members of the family. The eating habits are traditional consisting of moderately low fats, more seasonal vegetables, and fruits, and unpolished rice. Most of the members in the family, including women, youngsters and teens, are farmers. Most of the members are literate and some of them occupied government job. The socio-economic status of the family is moderately strong. One of the members was ‘Surpanch’ of the place. Although the family belongs to scheduled tribe, no economic backwardness was observed. Overall life style was found to be healthy and socially peaceful.

**Details of family 2 (Banjare family) —**This family consists of 3 generations. Most of the members live together. The food habits, time of food intake and timings of sleep-wake schedule are similar for almost all the members of the family. They follow traditional methods of cooking involving seasonal vegetables. They consume fruits and appear healthy. The most of the members are well-educated. The members are traditionally farmers but few of them also work in government offices and run petty business. Their socio-economic status seems to be strong.

The average sleep and wake times of both the families are similar; they go to bed at around 22:00 hrs and wake up at 06:00 hrs. Their lunch and dinner times are also comparable and were recorded between 12:00 to 13:00 hrs, and 20:00 hrs, respectively.

**Objective and subjective recordings**—The subjects were provided with Ambulatory Blood Pressure Monitor (ABPM). The BP and HR were monitored continuously for at least over two consecutive days. The recording was automated at every 15 min during the waking period and at every half hour during sleep period. The data were downloaded to a personal computer for further statistical analysis. Biographical information on each subject was gathered and tabulated (Table 1). Derived variables, such as mean arterial pressure (MAP), double product (DP) and pulse pressure (PP) were computed.

The ABPM recordings were made between June and August for the members of the family 1 and between April and May for the family 2. All members of family 2 were studied during the
pre-monsoon period; while in the family 1, in 21 subjects [out of 44] recordings were made before onset of monsoon. Therefore, we divided subjects of family 1 into two groups, i.e., pre-monsoon group and monsoon group and compared averages, amplitudes and acrophases of rhythms in all variables of both groups to ascertain if monsoon alters BP and heart rate (HR) variability.

Data analysis—The data were retrieved by A&D software. Cosinor rhythmometry\textsuperscript{18,19} was employed to evaluate the parameters of circadian rhythm ($\tau=24$ h) in systolic blood pressure (SBP), diastolic blood pressure (DBP) and HR. Other statistical techniques, namely ANOVA followed by Duncan’s multiple range test were used whenever pertinent. The data were further analyzed via PC based statistical software like, Excel ToolPak, and SPSS (Version - 10.0).

The pedigree charts were made for two families. All the subjects were classified on the basis of nocturnal dipping of SBP. The patterns of inheritance dipping were observed for each family.

Result

Distribution in the pattern of BP variability—

Family 1: Out of 44 family members, 23 were dippers, 12 were non-dippers, 7 were extreme dippers and 2 were risers (Table 1). Rhythm detection ratio for SBP, DBP and HR was lower among non-dippers and risers (Table 2).

Family 2: Out of 11 family members, 5 were dippers, 4 were extreme dippers and 2 were risers. Rhythm detection ratio for SBP, DBP and HR was higher among dippers and extreme dippers of the family. Out of two risers in the family, one displayed insignificant rhythm in DBP and HR (Table 2).

Table 1—Biographical summary of family 1 and family 2

<table>
<thead>
<tr>
<th>Family</th>
<th>Age (y)</th>
<th>Age – Median (y)</th>
<th>BSA (Unit)</th>
<th>BMI (Unit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family 1</td>
<td>28.37 ± 2.98</td>
<td>26.54 ± 4.31</td>
<td>1.40 ± 0.05</td>
<td>21.25 ± 0.67</td>
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<tr>
<td>Family 2</td>
<td>26.54 ± 4.31</td>
<td>1.48 ± 0.13</td>
<td>23.73 ± 1.45</td>
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</tr>
</tbody>
</table>

Nocturnal Dipping Status

<table>
<thead>
<tr>
<th>Family</th>
<th>D</th>
<th>ND</th>
<th>ED</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family 1</td>
<td>23</td>
<td>12</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Family 2</td>
<td>5</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2—Rhythm detection ratio of family 1 and family 2

<table>
<thead>
<tr>
<th>Subject group</th>
<th>Nocturnal Dipping Status</th>
<th>SBP (%)</th>
<th>DBP (%)</th>
<th>HR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family 1</td>
<td>D</td>
<td>0.82</td>
<td>0.78</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td>ND</td>
<td>0.43</td>
<td>0.50</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td>ED</td>
<td>1.00</td>
<td>0.71</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>0.00</td>
<td>0.50</td>
<td>0.50</td>
</tr>
<tr>
<td>Family 2</td>
<td>D</td>
<td>1.00</td>
<td>0.60</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td>ED</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>1.00</td>
<td>0.50</td>
<td>0.50</td>
</tr>
</tbody>
</table>

D=Dipper; ND=Non-dipper; ED=Extreme dipper; R=Riser

Pedigree analysis—The visual analysis of pedigree charts showed no inheritance pattern for the trait ‘Nocturnal dipping’ in either of the studied families (Fig. 1).

24 h BP and HR variation

Males of family 1 and 2: Data on BP and HR in males of each family were pooled separately and plotted against clock hour. A more smoothness in SBP, DBP and HR variability was observed in males of family 1 as compared to that in males of family 2. The night-time period between 00:00 and 06:00-08:00 hrs was also very composed in males of family 1 as compared to that in males of family 2. A prominent afternoon dip at around 1500 to 1600 hrs in BP and HR were observed in males of both the families (Fig. 2).

Females of family 1 and 2: Data on BP and HR in females of each were pooled separately and plotted against clock hour. A more smoothness in SBP, DBP and HR were observed in females of family 1 as compared to that in females of family 2. The night time period between 00.00 and 06:00-08.00 hrs was also very composed in females of family 1 as compared to that in females of family 2. The afternoon dip in females of both the families was not as prominent as of their respective male counterparts (Fig. 2).
Mesor—The factor ‘family’ produced a significant effect on 24 h averages of SBP, DBP, MAP, DP and PP. The 24 h averages of SBP, DBP, MAP, DP and PP in family 2 were significantly higher as compared to that in family 1 (Fig. 3). No significant effect of the factor ‘family’ was documented for HR.

Amplitude—No significant change was documented in amplitudes of any of the studied variables as function of ‘family’ (Fig. 4).

Peak occurrence and peak spread—The factor ‘family’ produced significant effects on peaks of SBP, DBP and MAP (Fig. 5). In family 2, the peaks...
of SBP, DBP and MAP were detected at around 1130 hrs. The peaks occurred significantly earlier as compared to that in family 1 observed in late afternoon; at around 1400 hrs. The peak spread of SBP, DBP, HR, MAP and PP, except DP, among the members of family 1 was significantly narrower than that among the members of family 2. The highest peak spread was noticed in HR (19.97 h) of family 2, and the lowest was noticed in SBP (0.62 h), PP (1.14 h) and MAP (1.93 h) of family 1.

Monsoon and BP variability—The ABPM recordings in the family 2 was conducted prior to the onset of monsoon. Comparison of averages (Mesors), amplitudes and acrophases of rhythms in all variables between pre-monsoon and monsoon groups of family 1 revealed a significant decline in the average of PP and an increase in the amplitude of HR in the latter (Fig. 6). The peak in the SBP rhythm occurred earlier in the monsoon group as compared with that of the pre-monsoon group (Fig. 6). Apart from the above no changes were noticed in other studied variables.

Discussion
Hypertension is growing faster among urban dwellers due to stressful, sedentary and fast lifestyle. On the other hand the rural dwellers are no longer untouched from this health problem. However, rate of increase in hypertensive cases is comparatively slower in rural population. Among rural population the causes of hypertension differ and are attributed to poor socio-economic conditions, under nutrition and illiteracy. Indian families, especially in rural areas are traditional. With reference to their food habits, rituals, festivals and other important daily activities, they follow their traditions, without knowing the exact reason for such practices. For example, in rural Chhattisgarh area most of the villagers are farmers. They wake up early and go to bed early. Nevertheless, they are relatively less stressed. In addition, junk food habits are less common among the youngsters. It was that the lifestyle and environmental factors as well as the previously studied causal factors of hypertension for rural dwellers (mentioned above) are much less in farmer families of rural Chhattisgarh. Therefore, these types of population were selected for studying BP variability and heritability of nocturnal dipping trait.

Fava et al.20 found partial recessive inheritance in nocturnal dipping. In the present study, the visual assessment of pedigree charts revealed no pattern of inheritance (Autosomal or Sex-linked inheritance) in the studied families. Therefore, the inheritance of nocturnal dipping of SBP could not be confirmed in either of the studied families. Arbitrary cut-off values, small sample size and age dependency of nocturnal dipping could possibly interfere with the human pedigree analysis of nocturnal dipping pattern. Thus, it is difficult to assess the inheritance of nocturnal dipping pattern from overt rhythms in ambulatory conditions.

Secondly, along with the genetic factors, non-genetic factors are reported to produce blood pressure variations21. Previous reports on Victorian family
heart study indicate that along with the genetic factors familial environment is associated with cardiovascular risk factors. Although in the present study both families displayed a significant circadian variation for all the studied parameters, the raw data plotting suggests less variation in males and females of family 1 from mid-night to early morning at around 0600 h, as compared to that in males and females of family 2. Blood pressure and heart rate of family 2 seemed to be disturbed especially during sleep time. This signifies that disruption of pattern in circadian blood pressure could be initiated by social interactions. Circadian clocks were evolved in response to environmental conditions. Apart from physical standards of time (mainly sunlight), social interactions also play as zeitgeber for entrainment of biological clocks, especially for social animals like humans. “Social rhythm stability hypothesis” put forth by Ehler et al. suggests that the disruptive social events either major ones like death and break-ups or minor ones like disturbance in normal routine of person or of those around him can affect a person’s circadian rhythm. Human beings are psychologically and emotionally attached to their families. They become insecure and are prone to diseases when their family passes through some sorts of turmoil.

Two possibilities arise from the above discussion. Firstly, the 24 h variations documented in families could be genetic. Secondly, typical familial situation produces positive or negative modulation of 24 h blood pressure variations. Bani reported that large family size contributes to hypertension; however, it needs further confirmation.

Therefore, for studying the impact of lifestyle factors on blood pressure, subjects of a family may be more suitable than randomly selected subjects with special reference to investigation of the pattern of 24 h blood pressure profile. The observed disorganized fluctuations in blood pressure within the family could be ascribed to psychosocial or any other familial factor. At this moment it is difficult to ascertain the exact cause of impaired pattern in BP and HR.

There are number of reports that have documented seasonal variation in blood pressure. The cardiac disease-related mortality has been reported to be more among elderly subjects in winter as compared to summer. These reports prompted us to compare the pattern of blood pressure variability between pre-monsoon and monsoon groups belonging only to the family 1, as all members of the family 2 were monitored prior to the onset of monsoon. The effects of monsoon did not produce any wide spread effect on the pattern of blood pressure variability at least at the group level. The average of PP decreased and amplitude of HR increased in the monsoon group as compared with that of the pre-monsoon group. No peer studies are available for comparison especially regarding changes observed in PP, amplitude of HR and advancement in the occurrence of peak in SBP. However, the averages of SBP, DBP and HR remained unchanged as function of timing of ABPM recordings pre- and post-onset of monsoon. The present findings neither contradict nor support earlier reports that have highlighted seasonal variation in BP, especially since, unlike this study that spanned over a period of three months only, earlier studies were conducted along longitudinal time scale covering 12 or more consecutive months. There are also contradictory reports regarding seasonal variation in BP. Fine did not find any seasonal variation in blood pressures of patients on hemodialysis.

Conclusion
Arbitrary cut-off values for classification of dipping, small sample size, and age dependency of nocturnal dipping might have marred pedigree analysis of nocturnal dipping trait. The social or familial influence documented on the characteristics of circadian blood pressure rhythm may provide more insights to 24 h BP and HR as members of the large joint families share most of the lifestyle, environmental, psychosocial and genetic factors. We have a hunch that the family shares typical temporal ups and downs in 24 h BP & HR. This hypothesis needs confirmation based on studies with large data set involving subjective and objective assessment of the effects of psychosocial factors on BP & HR variability.

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