Chapter-V
Summary, Conclusions and Recommendations
INTRODUCTION

The work included in this thesis entitled, “Circadian heart rate and blood pressure variability in apparently healthy subjects using ABPM” has been divided into five chapters. Chapter I contains a review of the studies conducted on variability in blood pressure (BP) and heart rate (HR) in normotensive and hypertensive subjects. It further highlights the work carried out on association of menstrual cycle with BP and HR variability. This chapter also includes objectives of the studies. Chapter II concerns with circadian variability in BP and HR in apparently healthy subjects belonging to the South-Eastern India as function of age, gender and type of job. Chapter III aims at enumerating the circadian variation in BP and HR in hypertensive subjects. Chapter IV includes investigations of the effects of different phases of menstrual cycle on circadian rhythm characteristics of BP and HR in young healthy female subjects. Chapter V (this chapter) deals with the summary of each of the previous chapters. This also includes conclusions and recommendations those are drawn/emanated in/from this doctoral dissertation.

Chapter I: Review of literature

Blood pressure fluctuates over a 24-h period and exhibits reproducible patterns of peaks and troughs in response to mental and physical activity (Redon, 2004). Nowadays clinicians are taking interest in the study of temporal organization in the blood pressure profile (Lambert et al., 2001). Circadian rhythm in BP has been widely studied in normotensive and hypertensive subjects (Seo and Oh, 2002; Vaidya et al., 2011). Apart from circadian rhythms, other multi-frequency rhythms, namely circannual, circaseptan and circasemiseptan have also been described for normotensive and hypertensive human subjects (Rawson et al., 2000; Sothern et al., 2005). However, there has been considerable debate regarding endogenous nature of BP rhythm (Shea et al., 2011). Nevertheless, in humans, BP dips considerably during sleep and remains elevated during the waking period with a characteristic surge in early morning hours (Redon, 2004). The characteristics of blood pressure rhythm are known to alter in diseased person. Excessive circadian amplitude is known as circadian hyper-amplitude–tension (CHAT) (Halberg et al., 1998). CHAT has been
related with the largest known risk of cerebral ischemia disease and also with a high risk of myocardial infarction, neuropathy and retinopathy.

Blood pressure variability (BPV) is a complex phenomenon. BPV is one of the recognized risk factor for different types of cardiovascular diseases. Further, day-night variability in BP in normotensive individuals and subjects suffering from various diseases has been examined extensively (Boggia et al., 2007). Moreover, night time reduction of BP is one of the most specific characteristics of circadian BP in healthy subjects (O’Brien et al., 1988). Prognostic significance of nocturnal dipping in BP has already been established for stroke, cardiovascular mortality, and progression to microalbuminuria in type-1 or type-2 diabetes (Brotman et al., 2008). The variability in rhythm parameters of BP has been evaluated in healthy human subjects with reference to age, gender, and ethnicity (Harshfield et al., 1989; Suzuki et al., 1993).

High blood pressure or hypertension is a common disease in all developing countries. Circadian rhythm in blood pressure has been observed in people with chronic hypertension (Seo and Oh, 2002), and the nocturnal BP fall is even amplified in some cases (Sawyer et al., 1981). Hypertensive subjects without nighttime BP fall (non-dipper) were more likely to suffer from serious end organ damage as compared to those hypertensive people whose blood pressure falls (dipper) during the night (Verdacchia et al., 1990; Imai et al., 1996). In hypertensive subjects, variability in BP is an independent risk factor of cardiovascular complications, particularly in stroke (Widimský, 2011).

Further, HR exhibits 24-h variability. Extreme fluctuation in HR is often associated with ailments. Measurements of heart rate variability (HRV) are increasingly used as markers of cardiac autonomic activity, diabetic neuropathy and other diseases (Al-Hazimi et al., 2002).

Several physiological functions have been found to change during the menstrual cycle. It has been proposed that examination of variability in BP and HR during different phases of the menstrual cycle in premenopausal apparently healthy women may be helpful in understanding the effect of hormones on BP regulation (Tsai et al., 2003).
Now-a-days clinicians rely on ambulatory blood pressure monitoring to improve the diagnosis and treatment of hypertension and cardiovascular diseases. Ambulatory blood pressure monitor (ABPM) is a device, which records blood pressure in humans in ambulatory condition and sleep period (Lambert et al., 2001). It is suggested that measuring blood pressure with the help of ABPM for continuous 24-h duration in longitudinal time scale may provide a useful outcome (Schwartzkopff et al., 2005).

“Cardiovascular diseases (CVDs) will be the largest cause of death and disability by 2020 in India” (The World Health Report, 2002). The prediction is alarming and is based on unequivocal scientific evidence. There is least doubt about the fact that hypertension is one of the primary risk factors for heart disease and stroke - the leading causes of death worldwide. India is the worst sufferer as it witnesses an increasing trend in the occurrence of hypertension and cardiovascular diseases among its citizens in recent times. Further, we do not have any baseline data on blood pressure variability on human populations of Indian sub-continent. Therefore, there is an urgent need to initiate a nation-wide program to study BPV in both healthy and hypertensive human subjects. A humble attempt has been made in the present Ph.D. dissertation to fill the void at least partially with the following objectives: (1) to study circadian variability in blood pressure (BP) and heart rate (HR), using ABPM, in a population of apparently healthy human subjects belonging to the South-Eastern India as function of age, gender, type of job, and dipping pattern; (2) to examine the circadian variability and nocturnal dipping patterns in blood pressure (BP) and heart rate (HR) in hypertensive subjects with and without medications, using ABPM; (3) to assess the differences in daytime and nighttime blood pressure in the population of normotensive and hypertensive subjects; and (4) to evaluate circadian rhythm characteristics of blood pressure (BP) and heart rate (HR) in young healthy female subjects as function of phases of their menstrual cycles.

Chapter II: Circadian rhythm in blood pressure and heart rate in apparently healthy subjects as function of age, gender and type of job

Circadian variability in blood pressure (systolic blood pressure, SBP & diastolic blood pressure, DBP) and heart rate (HR) was monitored in 114 randomly selected
normotensive human subjects, consisting of 57 females (age range: 20 – 50 y, median: 27 y) and 57 males (age range: 21 – 50 y, median: 30 y). Variables were monitored non-invasively using ambulatory blood pressure monitor (ABPM, TM 2430, A&D, Japan) for at least 2-4 consecutive days in each subject. Measurement durations were every 15-minute during daytime (between 07:00 and 22:00) and every 30-minute during night time (between 22:00 and 07:00). Mean arterial pressure (MAP) and double product (DP) were derived from the SBP, DBP, and HR. Nocturnal dipping in BP; and 24-h, daytime, and nighttime averages of SBP, DBP, MAP, and HR were also obtained separately for each subject.

It is evident from the results that a statistically significant circadian rhythm, gauged by a null amplitude hypothesis test, was documented for most of the studied variables, namely SBP, DBP, MAP, DP and HR, irrespective of age, gender, work type and dipping pattern. However, the rhythm detection ratio in all studied variables was lower in older subjects and non-dippers. Further, gender-linked variability was observed for circadian Mesors (24-h averages) of most of the studied variables. Values of SBP, DBP and MAP were significantly higher in males than that of females, however, *vice versa* was noticed for HR. Results of one-way ANOVA demonstrate that the factor dipping pattern produced significant effect on amplitudes of SBP, DBP, MAP, and DP. Amplitudes of all these variables were significantly higher in extreme dippers (ED) than those of the dippers (D) and non-dippers (ND). Further, the prevalence of non-dippers in this study was about 32%. We further validated that the characteristic of day-night variability of blood pressure and heart rate are influenced by the factors, such as age, gender, dipping pattern, body surface area, and body mass index.

On the basis of present findings we can conclude that variability in BP may be associated with factor gender, whereas nocturnal dipping in BP is independent of gender. Interestingly in the present study, about 32% subjects were non-dippers that may be an indication of higher risk of cardiovascular diseases among individuals belonging to younger generation of this region. Information on day-night variation in BP, reported in the present study, using ABPM in human subjects may be paramount in clinical diagnosis.
Chapter III: Circadian variability in blood pressure and heart rate in hypertensive subjects

In India, information on circadian variability in blood pressure and heart rate in hypertensive patients is meager. The present study therefore, aimed at investigating the circadian variability and nocturnal dipping pattern in SBP, DBP, MAP, DP, and HR in hypertensive subjects. In addition, the differences in daytime and nighttime blood pressure in the said population were also studied. Thirty two randomly selected ambulatory hypertensive human subjects, consisting of seven females (age range: 33 – 65 y, median: 55 y) and twenty five males (age range: 21 – 65 y, median: 49 y), from the Chhattisgarh region, participated in the present study. Of the total subjects, 11 subjects were accidentally diagnosed as hypertensive and were not receiving any medications throughout the period of study. This was perhaps a rare opportunity for the investigators to test the null hypothesis that the circadian timing system (CTS) in respect of blood pressure variability of the hypertensive subjects without medication would not differ from their counterparts on medication. The variables were monitored in each subject following the protocol mentioned in Chapter-II.

Results demonstrate that the rhythm detection ratio of all studied variables, except DBP, was high in subjects with medication. In both groups the ratio was low in DBP. Further, the ratio was low in SBP, DBP, and MAP in non-dippers. Results further indicate a statistically significant higher Mesors of all studied variables, except HR, in subjects without medication than that of subjects with medication. Results of one-way ANOVA demonstrate that factor dipping pattern produced significant effect on amplitudes of SBP, DBP, MAP, and DP. Amplitudes were significantly higher in ED than those of D and ND. In this study the prevalence of non-dippers was higher among the hypertensive subjects without medications (45.45%) as compared to their counterparts (33.33%) who were on medication. Two-way ANOVA was employed to examine the effects of factors medication (with vs. without) and time (daytime vs. nighttime) on SBP, DBP, MAP, and HR. Both the factors produced a statistically significant effect on all these variables.

We concluded that the prevalence of non-dippers is remarkably higher in hypertensive subjects without medication than that of subjects with medication.
However, the limitation of our study is the smaller sample size, particularly in the group of subjects without medication. Therefore, studies including larger human population of India should be carried out to strengthen the above findings.

Chapter IV: Blood pressure and heart rate variability as function of ovarian cycle in young women

Studies on relationship between different phases of menstrual cycle and circadian variability in BP and HR are inadequate. Therefore, in this study we examined the effects of different phases of menstrual cycle on circadian rhythm characteristics of blood pressure (BP) and heart rate (HR) in young healthy women. Thirteen normotensive females (age range: 22 - 32 y; median: 25 y) with regular menstrual cycle were randomly selected for the present study. Variables were recorded with the help of ABPM during a 48-h period on days 1, 8, 15, and 22 of the menstrual cycle, approximately representing the beginning of menstruation, follicular, ovulation, and luteal phase, respectively. Monitoring procedure in each subject followed the protocol mentioned in Chapter-II.

Results of the present study demonstrated a statistically significant circadian rhythm for most of the studied variables, irrespective of phases of menstrual cycle. However, the rhythm detection ratio of all studied variables was low during follicular phases as compared to other phases. The factor phase did not produce any significant effect on Mesors of SBP, DBP, MAP, DP, and HR. Nonetheless, decrement in amplitudes of all rhythms was observed during follicular phase as compared to other phases. Further, day/night ratio of SBP declined significantly during follicular phase than luteal phase.

In conclusion, we report low rhythm detection ratio, reduced day/night ratio and decrement in amplitude during follicular phase. This observation may have a bearing during the diagnosis of hypertension especially in young human females. However, the above conjecture needs further validation.
RECOMMENDATIONS

In recent times there has been an alarming increase in the incidence of hypertension and cardiovascular diseases (CVD) in India. It is presumed that the phenomenon could be attributed to concomitant prevalence of abnormality in the blood pressure variability (BPV). Surprisingly, studies on BPV from chronobiological point of view have not yet been started in the country. Therefore, we recommend that a nation-wide program be initiated to study BPV in Indian population consisting of both healthy and hypertensive subjects.

We aspire that the results obtained and documented in this thesis will provide the scientific community with the novel data on BPV in human population of India that has never been studied earlier. In addition, a comparative account of BPV among healthy and hypertensive subjects may contribute significantly to the existing knowledge on the discipline. The outcome of the study might help in: (a) establishing the standard values of blood pressure and heart rate with special reference to gender and age, (b) assessing the relative role of predictors of hypertension, and (c) delineating plans to curb various cardiovascular diseases in India.