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Introduction and a mini review
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Revolution of the earth on its own axis gives rise to the spectacular and the most predictable geophysical phenomenon – the day and night. The rotation of the earth around the sun generates splendid and recurring seasonal cycles. The more complex movement of the moon in relation to the earth and the sun gives rise to the lunar month and to the tidal cycle (Saunders, 1977; Pati, 2001). The planet earth is rhythmic. All living organisms – microbes, plants, animals and human, on this planet have been evolved to maximize their chances of survival by integrating rhythms in various processes of biological organization at different levels, such as cells, tissues, organs, organ system and whole body. These rhythms are called biological rhythms (popularly – *biological clocks*).

The study of biological rhythms fall in the domain of Chronobiology, which is relatively new multidisciplinary branch of life science that examines periodic (cyclic) phenomenon in living organisms and their adaptation to rhythms in the geophysical realm (Redfern and Lemmer, 1997; Pati, 2001; Berger, 2004; Jha and Bapat, 2004). Biological rhythms are ubiquitous phenomena that are driven by the master (central) clock among most higher vertebrates, including humans (Pati, 2001). In the later, the circadian clock is located in the suprachiasmatic nuclei (SCN) in the hypothalamus. The SCN plays a role as a master pacemaker that coordinates other rhythmic systems.

The clock plays important role in animal behavior and predicts rhythmic changes in their surrounding environment and synchronizes their activities appropriately. All living organisms, from single cell to human being, exhibit multi-frequency rhythms (Chandrashekaran *et al.*, 1991; Pati, 2001). In humans, hundreds of biological functions have been identified that exhibit circadian rhythm. These functions include both physiological (body temperature, hormone production, sleep-wake cycle, blood pressure, heart rate, immune function, enzyme activity in serum & tissues, secretion of reproductive hormones, peak expiratory flow rate, and nutrition) and psychological/ psychophysiological variables (cognitive performance, memory, random number addition speed, subjective drowsiness, fatigue, and attention) (Moore-Ede *et al.*, 1982; Chandrashekaran *et al.*, 1991; Redfern and Lemmer, 1997; Liebmann *et al.*, 1998; Campos *et al.*, 2001; Pati, 2001; Pati *et al.*, 2001; Sothern *et al.*, 2003; Berger, 2004; Redon, 2004; Kennaway, 2005). The periods of biological
rhythms are ranged from milliseconds to much longer cycles with periodicities of several hours, days, or even years. Based upon the period, biological rhythms are generally classified into three types, namely ultradian rhythm ($\tau < 20$ h), circadian rhythm ($\tau = 24$ h ± 4 h) and infradian rhythm ($\tau > 28$ h) (Halberg et al., 1977). In addition, organisms may exhibit multifrequency rhythms, such as weekly (circaseptan), monthly (circamensual), annual (circannual), tidal (period = 12.4), and lunar (period 29-days). Sleep cycle (90-min periodicity) and blinking of eyes (24 blinks min$^{-1}$ periodicity) are the suitable examples of ultradian rhythm (Anonymous, 1999). Estrus cycle in mammals, migration in birds, hibernation & molting in insects, and annual flowering in plants are the examples of infradian rhythm. Apart from this extremely low frequency rhythms, such as flowering in bamboo (about 40 years) and appearance of spots in the sun (about 10-11 years) are also present. So far, circadian rhythm have attracted the attention of Chronobiologists the most and have been studied extensively (Menaker, 1969).

**Properties of circadian rhythms**

A rhythm is defined as a regular incident that is distinguished by three features, such as period, amplitude and acrophase. The period is the length of time necessary to complete one full cycle (e.g., the time required to go from peak to peak). Amplitude is roughly the height of the peaks relative either to the troughs or to the zero crossings. Acrophase is the temporal relationship between specific identifiable point on the cycle and a point on a reference cycle (Pati, 2001). These rhythm parameters can be influenced by multiple factors, such as alteration of day and night, changes in temperature, working habits, meal times, noise, age, social, and sleep hours (Houdas and Sauvage, 1971; Pati, 2001). The following are some important characteristics or properties of the circadian rhythms that have been well described by Pati (2001):

1. Circadian rhythms continue to persist under constant conditions. This phenomenon is called free running and rhythms exhibit period ($\tau_{FR}$) that is slightly greater or shorter than 24 h.
2. The endogenous period is temperature compensated within the physiological range; it means that at different ambient temperature the period length of the clock remains the same with $Q_{10}$ equals to 1.0.

3. They are under genetic control. It has been documented that single mutation can profoundly affect the period length of biological clocks. Mutation in gene causes shortening or lengthening of circadian period in fruit fly to become arrhythmic.

4. Biological clocks are entrained to an exact period by environmental time cues or zeitgebers.

The circadian rhythms also provide temporal organization and ensure that internal changes take place in synchronization with one another (Vitaterna et al., 2001). Desynchronization of the internal temporal organization with external environmental rhythms might produce health problems in an individual, such as those associated with jet lag and shift work (Vitaterna et al., 2001). A number of diseases and their symptoms appear periodically that have remarkable circadian connotation.

**Circadian rhythms - Importance in clinics**

It is noteworthy that the implications of circadian rhythm research are immense in the clinics and in the management of the effects of transmeridian flight, shift work, and seasonal affective disorders. Further, the onset and severity of several medical conditions exhibit daily variations. Therefore, at present greater attention is being paid to utilize the principles of circadian rhythms for the treatment of diseases, like cancer, asthma, hypertension, etc. Thus, a particular diseased state could be improved by giving drugs at carefully selected times of the day through achieving a balance between their desired (the maximum efficacy) and undesired (the least toxicity) effects. This has given birth to a new sub-discipline called “chronotherapy”.

**Blood pressure**

Blood pressure (BP) is the pressure exerted by circulating blood upon the walls of blood vessels, and is one of the principal vital signs. During each heartbeat, BP varies
between a maximum (systolic) and a minimum (diastolic) pressure. A person's BP is usually expressed in terms of the systolic pressure over diastolic pressure (mmHg), for example 140/90 mmHg (Figure 1.1). BP may be influenced by several physiological factors, such as diet, exercise, disease, drugs or alcohol, stress, and obesity. When BP rises on account of various factors, it is called high blood pressure or hypertension.

**Blood pressure variables and heart rate**

**Systolic blood pressure (SBP):** Systolic blood pressure is the maximum arterial pressure exerted against the cardiovascular system when the heart contracts, the time at which ventricular contraction occurs is called systole. "Systolic" word originates from the Greek word *systole*, i.e., "a drawing together or a contraction". The term has been in use since the 16th century to denote the contraction of the heart muscle. Increase of the SBP has been recognized as self-determining risk factor associated with elevated diastolic blood pressure in patients with hypertension (Stamler et al., 1993). Isolated systolic hypertension (ISH) is a cardiovascular disorder normally defined when the SBP is greater than 140 mmHg and diastolic blood pressure is less than 90 mmHg (Staessen et al., 1997). ISH is associated with an increase in all forms of cardiovascular morbidity and mortality (Vardan and Mookherjee, 2000). Several studies revealed that lower SBP is associated with reduced cardiovascular disease mortality and frequency (Lawes et al., 2002; Okayama et al., 2006).

**Diastolic blood pressure (DBP):** Diastolic blood pressure is the amount of force that blood exerted against the cardiovascular system while the heart rest. DBP is represented by the bottom number in a blood pressure reading. When the DBP is less than 60 mmHg, the value is considered as a low DBP. An elevated diastolic value has been associated with increase coronary heart diseases (CHD). A negative relationship of age with DBP and cardiovascular heart disease has been reported (Hansson et al., 1998).

**Mean arterial pressure (MAP):** It is an average blood pressure in an individual. MAP is derived from the SBP and DBP. MAP has clinical and physiological
significance in both the representation of perfusion pressure and its utilization in the calculation of homodynamic variables (Zheng et al., 2008).

**Pulse pressure (PP):** It is the difference between SBP and DBP. The increased pulse pressure is always indicating the vascular difficulty in patients with isolated systolic hypertension (ISH). Several studies have proved that a higher pulse pressure is an independent marker of cardiovascular risk (White, 2002; Gjata et al., 2011).

**Double product (DP):** Double product is an estimation of myocardial work (heart muscle) and is related to myocardial oxygen consumption (Hermida et al., 2001). It is used as an important factor for functional state of the cardiovascular system (Makarova, 2002). DP is measured by SBP multiplied by the HR.

**Heart rate (HR):** Heart rate defines as a number of times the heart beats per minute.

Further, hypertension is classified as either primary (essential) hypertension or secondary hypertension. About 90–95% of cases are categorized as "primary hypertension," which means high blood pressure with no obvious medical cause (Carretero and Oparil, 2000). The remaining 5–10% of cases (secondary hypertension) is caused by other conditions that affect the kidneys, arteries, heart or endocrine system. Various other types of hypertension have been described below:

**White-Coat hypertension:** One of the most important indications of ambulatory blood-pressure monitoring is white-coat hypertension. It is defined as a clinic pressure of 140/90 mmHg. Diagnosis of white-coat hypertension is important because it has relatively low risk and unlikely to benefit from antihypertensive-drug treatment. Several studies have documented that drug treatment of white-coat hypertension reduced the clinic blood pressure. However the effect of ambulatory blood pressure monitoring is insignificant (Pickering et al., 1994). Continuous hypertension may build up in some patients with white-coat hypertension and the risk of stroke can increase after six years (Verdecchia et al., 2005). Therefore, long-term record with repeated ambulatory blood pressure monitoring or home monitoring is essential for detection of white coat-hypertension.
Labile Hypertension: It is characterized by sudden and ongoing fluctuations in blood pressure rising from a normal to a high reading at different times of the day. Labile hypertension is something of a miscomprehension, because all hypertension is labile. However, ambulatory blood pressure monitoring may provide evidence in some patients with a history of paroxysmal hypertension. The common cause of labile hypertension is panic attacks, which have been shown to be accompanied by surges in both blood pressure and heart rate (Shear et al., 1992). Currently, in the patients with labile hypertension over a period of 24-hour, the blood-pressure variability is not determining the standard averages of BP greater than normal.

Resistant Hypertension: In resistant hypertension the white-coat effect may be suspected in some patients whose clinic blood pressure remains high even though they are taking three or more antihypertensive drugs in a day. Previous studies have documented that subgroup of patients with resistant hypertension according to criteria of clinic blood-pressure have normal ambulatory blood pressure and a benign diagnosis (Redon et al., 1998; Pierdomenico et al., 2005).

Masked Hypertension: In the past few years, interest has increased in the phenomenon of masked hypertension. In masked hypertension, clinic blood pressure found to be within normal range and ambulatory blood pressure is high. This condition is the reverse of white-coat hypertension. The clinic blood pressure of patients with masked hypertension may underestimate the risk of cardiovascular complications. Other prospective studies have reported that masked hypertension in patients with untreated and undiagnosed hypertension is associated with an increased rate of target-organ damage (Liu et al., 1999) and an adverse prognosis (Bjorklund et al., 2004). In future the prevalence of masked hypertension in the general population could be as high as 10 percent (Pickering, 2003). White-coat hypertension and masked hypertension may be assumed on the basis of high blood pressure measurements taken at the home (Bobrie et al., 2004).
Figure 1.1 Blood pressure chart (fromVaughns-I-Pagers.com)

Postural Hypotension: It is a common form of low blood pressure. The blood pressure of patients with postural hypotension is unusually labile and depends on their body position. When such patients were lying down with the face, the blood pressure may be moderately high, during the sleep period (Mann et al., 1983). It has been proposed that the use of ambulatory blood-pressure monitoring (ABPM) is essential for evaluating optimal blood pressure control in postural hypotension patients (Mann et al., 1983).
Circadian rhythm in blood pressure

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 blood pressure (BP) has been widely studied in normotensive and hypertensive subjects (Chen et al., 2001; Gonzalez et al., 2002; Halhuber et al., 2002; Mitsutake et al., 2002; Singh et al., 2002; Cornélissen et al., 2003; Halberg et al., 2004; Pickering et al., 2005; Sothern et al., 2005; Shea et al., 2011; Vaidya et al., 2011). Apart from circadian rhythm, other multi-frequency rhythms, namely circannual, circaseptan and circasemiseptan have been described for normotensive and hypertensive human subjects belonging to the temperate regions of the world (Rawson et al., 2000; Chen et al., 2001; Gonzalez et al., 2002; Halhuber et al., 2002; Mitsutake et al., 2002; Cornélissen et al., 2003; Halberg et al., 2004; Sothern et al., 2005). In case of circaseptan rhythm, acrophase of blood pressure usually occurred in mid week than during weekends (Siegelova et al., 2003). However, there has been considerable debate regarding endogenous nature of BP rhythm (Kerkhof et al., 1998; Van Dongen et al., 2001; Shea et al., 2011). Questions have been raised from time to time regarding contribution of endogenous circadian clock to the daily variability in BP. In a recent paper Shea et al. (2011) categorically demonstrated that BP exhibits robust endogenous circadian rhythm. These authors followed constant routine and forced synchronization protocols to prove the point. Nevertheless, in humans, BP dips considerably during sleep and remains elevated during the waking period with a characteristic surge in early morning hours (Halberg et al., 1988; Redon, 2004). It is known that circadian rhythm of blood pressure is synchronized with the sleep-wake cycle. Blood pressure rhythm also shows parallel variability with that of the heart rate rhythm (Redon, 2004).

The characteristics of blood pressure rhythm are known to alter in diseased person. Mitsutake et al. (2002) documented that circadian amplitude of negative mood was positively related with means of SBP and DBP. Similarly, Rawson et al. (2000) also reported that Mesors of SBP and DBP were lower when mood rating was lower. A delay in circadian acrophase of blood pressure and heart rate was also associated with lower mood ratings. Abnormal circadian blood pressure pattern was
occurred in patients with essential hypertension, diabetic patients and patients with chronic renal disease (Covic and Goldsmith, 1999; Schömig et al., 2000). Kohno et al. (1998) demonstrated that the pattern of circadian BP was similar in normotensive subjects and normotensive patients with mild hyperthyroidism, however, heart rate decreased during nighttime in normotensive group only but not in the hyperthyroid group. Higher pulse pressure was also noticed to be a risk factor for cardiovascular morbidity and mortality (Fernández-Fresnedo et al., 2003). An excessive circadian variation determines the amplitude of blood pressure, which notify an increased risk of cardiovascular diseases. This 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. CHAT can be tamed by non-pharmacological or pharmacological intervention (Watanabe et al., 1996; Shinagawa et al., 2001). Broder et al. (1999) observed that ambulatory blood pressure is significantly higher in subjects with Williams syndrome as compared to controls. They also observed that both children and adults with Williams syndrome have higher mean BP and higher frequency of hypertension than healthy controls (Broder et al., 1999).

**Circadian Blood Pressure Variability**

“Blood pressure variability (BPV) is a complex phenomenon that includes both short-term and long-term components, which can be estimated by the standard deviation of the blood pressure values over a defined period of the day or by the night-to-day blood pressure ratio, respectively. Blood pressure variability remains an elusive prognostic index (Hansen et al., 2009)”.

BPV is one of the recognized risk factor for different types of cardiovascular diseases. It is a consequence of complex interaction between multiple cardiovascular control mechanisms, being highly affected by central neural influences, sympathetic vascular modulation, arterial baroreflexes and other cardiovascular reflexes, mechanical factors (respiration) and hormonal influences (plasma catecholamines, rennin-angiotensin system, vasopressin and endothelial factors) (Parati et al., 1995, 1996; Mancia et al., 1997). Several studies have documented that the assessment of
24-h blood pressure profile is not only important as a research tool in investigating the pathophysiology of hypertension, but it may be also relevant in the clinical estimation of hypertensive patients and in the assessment of the effects of antihypertensive treatment (Thomas et al., 2006). It has been documented that the end-organ damage associated with hypertension is closely related to the 24-h average of the blood pressure (Sokolow et al., 1966; Floras et al., 1981). Variation in the characteristics of circadian blood pressure rhythm has been reported. Changes in blood pressure have been observed with the increasing age in school going children (Prabhajot et al., 2005). The acrophase and amplitude of the normal rhythm of blood pressure is influenced by the intrinsic factors, such as physical activity and nutrition. Behavioral influences, such as mental activity and emotional state, and life style factors, such as smoking and alcohol habit can also affect the natural rhythm in blood pressure (James and Pickering, 1993; Pickering and James, 1993). Further, blood pressure variability was found to be higher in hyperlipidaemic subjects as compared to normolipidaemic subjects and the large arterial compliance was negatively correlated with SBP in hyperlipidaemic subjects (Rafidah et al., 2008).

Cardiovascular variability is a complex physiological phenomenon and is associated with the cardiovascular diseases in humans. Elstad et al. (2011) demonstrated physiological relationship and low frequency fluctuation in heart rate, cardiac output and mean arterial pressure in humans. They reported that total peripheral resistance (TPR) and cardiac output (CO) oscillations produce fluctuations in MAP and HR. Recently, it has been suggested that blood pressure was affected by the common polymorphisms of the beta-2 adrenoreceptor gene leading to glycine for arginine substitution at position 16 or glutamic acid for glutamine substitution at position 27. Tank et al. (2011) reported that beta-2 adrenoreceptor genotype may affect coupling between resting sympathetic nerve traffic and systolic blood pressure.

**Variability in day-night blood pressure**

Further, day-night variation in BP is another important parameter that can be useful in the assessment of BPV. Day-night variability in BP in normotensive individuals and subjects suffering from various diseases has been examined extensively (Mancia et al., 1983; Broadhurst et al., 1990; Staessen et al., 1999;
Boggia et al., 2007). Numbers of factors, such as physical activity level at daytime, quality of sleep, body position at night, and the position of the cuffed arm relative to the heart at night, have been found to affect the day-night variation in BP (Parati, 2000). Differences on daytime and nighttime blood pressure have also been evaluated with reference to age, gender, and ethnicity (Broadhurst et al., 1990; Harshfield et al., 2002; Wang et al., 2006, 2009).

Day versus nighttime blood pressure has shown prognostic significance (Palatini et al., 1992; Staessen et al., 1999; Kikuya et al., 2006; Boggia et al., 2007; Thijs et al., 2007). Nighttime BP averages are found to be more reliable predictor of cardiovascular mortality than daytime or 24-h BP averages (Staessen et al., 1999; Dolan et al., 2005; Kikuya et al., 2005). However, Boggia et al. (2007) suggested that prognostic accuracy of the day and nighttime BP depends on the end points under investigation. They accentuated that the night-time BP predicted better the fatal endpoint as compared to daytime BP. However, for fatal combined with non-fatal outcomes the daytime BP was found to be better predictor. The authors also observed a higher mortality in patients with elevated nighttime BP than daytime BP (Boggia et al., 2007). Moreover, the day-night BP variability was also found to be associated with nocturnal blood pressure fall in normotensive and hypertensive subjects (Verdecchia et al., 1994; Staessen et al., 1999; Ohkubo et al., 2002; Parati et al., 2003).

**Nocturnal dipping in blood pressure**

The BP circadian rhythm is usually characterized by minor fluctuations during the daytime and nighttime with an overall decrease (or dipping) that occurs during the night. Nocturnal dipping in BP is a normal phenomenon. Normotensive and mild-to-moderate hypertension subjects typically show a 15% to 20% reduction in BP during sleep. Night time reduction of BP is one of the most specific characteristics of circadian blood pressure in healthy subjects (O’Brien et al., 1988). However, this fall in BP during sleep does not always occur (Larochelle, 2002). On the basis of the nocturnal dipping in blood pressure, human subjects can be classified into extreme dippers, dippers, non-dippers, and risers. In dippers, blood pressure registers a decline of about 10-20% during sleep hours; while in non-dippers it is only about 0-10%
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(Thomas et al., 2006). The extreme dippers exhibit more than 20% dipping and the risers register increase in BP during the period of sleep. Nocturnal dipping in BP is computed using method of dipping criteria based on SBP (Kario et al., 2000):

\[(1 - \text{night time SBP/day time SBP}) \times 100\]

However, Boggia et al. (2007) speculated that classification of dipping categories on the basis of SBP or DBP or both may be conflicting in the same person. This speculation was based on the data obtained from the subjects from Europe (Omboni et al., 1998) and Asia (Mochizuki et al., 1998). In both studies low reproducibility, up to 40%, in dipping status was reported. Boggia et al. (2007) also illustrated that the classification according to dipping status is vulnerable to antihypertensive drug treatment. Nonetheless, a lack of nocturnal BP dipping was found to be more prevalent among subjects with various diseases (Loredo et al., 2004). 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 (Verdecchia et al., 1994; Staessen et al., 1999; Ohkubo et al., 2002; Dolan et al., 2005; Pistrosch et al., 2007; Brotman et al., 2008). These studies observed that high risk of target organ damage in non-dippers leads to increased incidence of fatal and non-fatal cardiovascular events. In addition, some of the specific sleep disorders, such as insomnia and sleep apnea, are characterized by non-dipping pattern of BP (Routledge et al., 2007). One prospective study has found that non-dipping pattern of BP is an independent risk factor for evolution of renal diseases (Timio et al., 1995). Parati et al. (1992) documented that lack of nocturnal dipping in blood pressure among normotensive adult may make them vulnerable to cardiovascular diseases. Hajjar et al. (2010) suggested that nocturnal dipping in BP should be taken into consideration in the clinical evaluation of individuals those are at the risk of cerebrovascular disease.

Factors affecting rhythm characteristics of blood pressure

The variability in rhythm parameters of blood pressure has been evaluated in healthy human subjects with reference to age, gender, and ethnicity (Harshfield et al., 1989; Suzuki et al., 1993; Driziene et al., 2008). Suzuki et al. (1993) reported increased Mesor, decreased amplitude and advancement in acrophase of SBP and DBP with
advancing age. Suzuki et al. (1993) also documented gender-linked variability in circadian blood pressure rhythm. They reported that the 24-h average of SBP increased with advancing age in women; however in case of men, the Mesor of SBP was higher in older group only. Observation of Otsuka et al. (1990) and Vaidya et al. (2011) supported the above speculation. Further, Otsuka et al. (1990) documented an increase in circadian amplitude of SBP with increasing age in women only. In contrast, Suzuki et al. (1993) reported that amplitude of SBP decreased with advancing age in men. Vaidya et al. (2011) did not find any significant differences for the circadian amplitudes of the BP variables and HR as function of gender. Moreover, the effects due to ethnicity on diurnal blood pressure rhythm have been reported (Profant and Dimsdale, 1999). The Africans experience higher levels of SBP and DBP, both at night and during the day as compared to Caucasian Americans (Profant and Dimsdale, 1999). It is proposed, therefore, that the circadian rhythm of blood pressure should always be examined with reference to sex-, age- and race-matched reference values (Harshfield et al., 1989; Suzuki et al., 1993; Drziene et al., 2008).

Furthermore, an association between obesity and hypertension in children from different ethnic and racial group has been demonstrated. In obese children, high blood pressure and a greater prevalence of hypertension have been reported (Sorof and Daniels, 2002; Salman et al., 2010). Children who were overweight or obese had a 4.5- and 2.4-fold greater chance of having high SBP and DBP, respectively (Freedman et al., 2001). Weight has an important association with obesity and BP. It has been documented that weight gain increases the BP (Bath et al., 2003), whereas vice versa was reported with the weight loss (Bacon et al., 2004).

Further, menopause causes high BP in women; however, relatively men had higher BP than premenopausal women independent of age (Reckelhoff, 2001). Circadian rhythm of blood pressure during pregnancy was studied by Cheryl and Yeo (2000). The authors convincingly demonstrated that circadian blood pressure rhythm during pregnancy was same as in the non-pregnant women, with a nocturnal fall during night. However, a decrease in nocturnal BP may be less evident in patients with mild preeclampsia – pregnancy related condition that includes elevated blood pressure (Seligman, 1971; Murnaghan et al., 1980; Sawyer et al., 1981; Halligan et
al., 1996). Women with severe preeclampsia may have a reversed circadian rhythm in blood pressure that increased during sleep (Redman et al., 1976; Sawyer et al., 1981).

Redon (2004) stated that acrophase of blood pressure rhythm occurred in the early morning shortly after awakening. The onset of cardiovascular events and stroke shows a parallel pattern with the highest events of attacks in the early morning hours.

**Circadian blood pressure rhythm in hypertensive subjects**

High blood pressure or hypertension is a common disease in all developing countries. Prevalence of hypertension in developing countries is different from that of the developed countries. Singh et al. (2000) reported a rapid increase in mortality due to stroke and prevalence of hypertension in developing countries of Asia. Kearney et al. (2004) documented that studies conducted between 1980 and 2003 indicate that the prevalence of hypertension has decreased in developed countries, whereas it has been increased in developing countries. Mathers and Loncar (2006) predicted that about 85% of the global cardiovascular death will occur in low- and middle-income countries by the year 2030. However, recently Pereira et al. (2009) did not find any significant differences in the mean prevalence, awareness, treatment and control of hypertension between developed and developing countries, with an exception of a higher prevalence among men in developed countries.

Hypertension is regularly diagnosed and treated on the basis of single spot check. However, the significance of ambulatory blood pressure monitoring (ABPM) has been always emphasized (White, 2007). Hypertension has been established as a risk factor for heart diseases (Howson et al., 1998). The quantity of target organ damage encouraged by hypertension is more closely related to the average value based upon a 24-h profile of the BP than a single one time BP measurement (Kumagai et al., 1992). 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 (Verdecchia et al., 1990; Imai et al., 1996). However, wide variation occurred in the circadian blood pressure rhythm in hypertensive patients (Verdecchia et al., 1998).
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Circadian rhythm in blood pressure has been observed in people with chronic hypertension (Redman et al., 1976; Murnaghan et al., 1980), and the nocturnal BP fall is even amplified in some cases (Seligman, 1971; Redman et al., 1976; Sawyer et al., 1981). Furthermore, the interactions of circadian/diurnal rhythms with hypertension have been evaluated by Smolensky and Haus (2001). Most of the cardiovascular diseases, such as myocardial infarction, heart attacks, angina, strokes, arrhythmias, and sudden cardiac death are time dependent and found in the morning hours (Cohen et al., 1997; Elliott, 1998). Circadian variation was also found in heart rate response to awakening (Hilton et al., 2001). The cardiovascular events are also more likely around the time of awakening. Endogenous and exogenous factors are responsible for this process. Cardiovascular risk has been altered in persons with diabetic mellitus (Felício et al., 2010). Individuals with diabetes have a loss of the normal nocturnal decrease in blood pressure (Bernardi et al., 1992; Monteagudo et al., 1996).

Association of obstructive sleep apnea (OSA) with hypertension has already been established and this association was found to be independent of the confounding factors, such as age and obesity (Lavie et al., 1984; Escourrou et al., 1990; Peter et al., 1991; Fischer and Raschke, 1993). These alterations might contribute to the increased mortality in patients suffering from severe OSA (Pankow et al., 1997). Numerous authors have studied the circadian patterns of ambulatory blood pressure in untreated hypertensive patients with and without metabolic syndrome and they reported a strong association between metabolic syndrome and increased risk of end-organ damage, coronary heart diseases, cardiovascular diseases, stroke, and cardiovascular mortality (Isomaa et al., 2001; Ridker et al., 2003; Schillaci et al., 2004; Ayala et al., 2009).

Licht et al. (2009) observed that depressive disorder is associated with low SBP and less hypertension, whereas the use of antidepressants was associated with both high SBP & DBP, and hypertension. High blood pressure, which is a risk factor for cardiovascular disease (CVD), is more common in psychopathology (Stokes et al., 1989; Markovitz et al., 1993; Flack et al., 1995; Carroll et al., 2001; Matthews et al., 2004; Williams, 2006; Scuteri, 2008). However, some of the studies investigated that association between blood pressure and psychopathology does not produce reliable results particularly for the two major classes of psychiatric ailments, i.e., anxiety
disorder and major depressive disorder (Markovitz et al., 1993). Some more studies reveal increased hypertension or high blood pressure among persons suffering from depression and anxiety disorder (Paterniti et al., 1999; Routledge and Hogan, 2002; Scherrer et al., 2003). Symptoms of anxiety and depression can predict the low blood pressure (Paterniti et al., 1999; Hildrum et al., 2007, 2008).

Hypertension in children is an emerging public health issue attracting the medical professionals worldwide. In hypertensive children, a strong correlation between the various factors, particularly bodyweight and high BP has been shown (Paradis et al., 2004; Sorof et al., 2004; Kelishadi et al., 2006; Raj et al., 2007). Excess weight in hypertensive children deserves instant awareness in large developing economies like India, China and Brazil (Wang et al., 2002; Sorof et al., 2004; Ji, 2007). Diverse population demonstrates that the track of BP from childhood to adulthood is very strong (Chen and Wang, 2008). In adulthood, blood pressure is strongly and directly associated to vascular as well as overall mortality (Lewington et al., 2002). A lot of predictable risk factors, like smoking, high blood pressure, increase in BMI, diabetes mellitus and advancing age have been demonstrated to predict coronary artery disease (CAD) (Kalra et al., 1990; Dominiczak, 2001; Rhee et al., 2007). Body mass index is an independent predictor of long term mortality where a better outcome was observed in overweight and obese patients (Rhee et al., 2007).

In hypertensive subjects, variability in BP is an independent risk factor of cardiovascular complications, particularly in stroke (Widimský, 2011). In clinical practice antihypertensive drugs have been used for suppression of blood pressure variability that might have additional impact on the cardiovascular risk (Widimský, 2011). Recent studies suggest that BPV can be decreased by the calcium channel blockers (CCB) than other antihypertensive drug (Widimský, 2011).

Circadian Rhythm in heart rate

Heart rate has close relationship with blood pressure. Variability in heart rate has been studied in human populations of the Northern hemisphere. It exhibits 24-h variability. Extreme fluctuation in heart rate is often associated with ailments. Under normal free-living conditions heart rate remains high during the period of activity and slows down
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during the period of rest, usually night hours. Heart rate has also been known to vary as function of age. Elderly people usually have lower heart rate than their younger counterparts (Redon, 2004). Standard reference intervals for blood pressure and heart rate rhythms have already been constructed for the Caucasians (Redon, 2004). However, such reference intervals have not yet been constructed for humans belonging to other ethnic background.

Massin et al. (2000) documented a circadian rhythm in heart rate and heart rate variability in infants and children. 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). It has been reported that decrease amplitude of HR indicates low mortality but high risk of cardiac problem. Spectral analysis of HRV in the standing and the lying positions has been studied as function of age and the results depict that dependency of parameters on age is not homogenous. It varies at different period of age from more to less age-dependent or could run a completely independent course (Šlachta et al., 2002). Spectral analysis is the conventional method for the HRV for evaluation of the autonomic nervous system (ANS) activity. It is well known that cardiovascular autonomic diabetic neuropathy (CADN) is related to a loss of HRV (May et al., 2000; Vinik and Mehrabian, 2003). HRV is one of the prognostic markers for diabetic neuropathy in Saudi patients (Al-Hazimi et al., 2002). Analysis of HRV using the time domain analysis method shows the mean of heart rate was reduced in diabetic patients as compared to normal controls and decrease parasympathetic activity is responsible for high heart rate usually reported in patients with diabetic autonomic neuropathy (Al-Hazimi et al., 2002).

**Association of menstrual cycle with blood pressure and heart rate variability**

Several physiological functions have been found to change during the menstrual cycle. Cyclic hormonal variation is an important determinant of variability for some physiological phenomenon, such as blood pressure, heart rate and pulse transit time (Kaplan and Keil, 1990; Dunne et al., 1991). Values of these variables appear to vary systematically across the menstrual cycle. However, hemodynamic and hemostatic
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responses to psychological stress may be elevated during the luteal phase (Jern et al., 1991; Manhem et al., 1991; Tersman et al., 1991).

Driziene et al. (2008) determine the gender-related differences in 24-h arterial blood pressure in healthy adolescent girls during various phases of their menstrual cycle and boys. The authors reported that the nocturnal SBP dipping was higher in boys as compared to girls in different phases of their menstrual cycle. In follicular phase diurnal SBP in boys was higher than in girls. However, dipping pattern did not exhibit any significant differences during different phases of menstrual cycle among girls.

Cardiovascular diseases in women are among the leading causes of death (Murphy, 2000). High blood pressure documented risk factor for different type of cardiovascular diseases in them. Prospective studies have been reported that female sex hormones and their withdrawal play a role in the pathogenesis of hypertension (Rosenthal and Oparil, 2000).

Ambulatory blood pressure monitoring

In clinics the physician uses mercury sphygmomanometer as standard method of blood pressure monitoring. It has been discovered that a single spot check of blood pressure is not reliable. The variability in blood pressure cannot be predicted on the basis of single spot checking. It is well know that most of the cardiac stroke occurs during night time or early morning hours in the patients suffering from cardiovascular disease. But in case of non-dipping the blood pressure remains elevated during sleep period also, which leads cardiovascular diseases (Profant and Dimsdale, 1999). Moreover, hypertension is prevalent in all age groups from children to elderly people (Kotchen et al., 1982; Prabhajot et al., 2005). Therefore, 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).
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Use of ABPM is growing in the pediatric population and some aspects regarding its use need to be improved over the next few years (Lurbe and Redon, 2000). Such improvement may facilitate the early identification of various cardiovascular complications, such as different types of hypertension, 24-h control of hypertension, and the detection of subtle BP variability. The refinement of ABPM for the management of hypertension and for clinical research should be mandatory for the pediatric age (Lurbe and Redon, 2000). ABPM is reliable to determine the drug therapy for diabetic patients and resistant hypertension. Common use of ABPM will likely follow data showing enhanced outcomes for patient (Thomas et al., 2006). Furthermore, ABPM provides information regarding rhythm parameters, such as 24-h average, amplitude and peak of blood pressure and heart rate (Thomas et al., 2006). The main purpose of ABPM trial is to identify whether an antihypertensive drug is affecting the nighttime blood pressure (Goldstein et al., 2005; White, 2007).

Research in the area of blood pressure rhythm using the latest device ABPM is receiving greater attention. However, in India inadequate efforts have been made in this direction. To the best of our knowledge the present study is among a few that has attempted to examine circadian variability in BP variables and HR in the population of normotensive and hypertensive subjects inhabiting the Southeast India. We presume that the results of this Ph.D. dissertation will provide the scientific community with database on blood pressure circadian rhythm and comparative profiles of apparently healthy and hypertensive subjects. The findings of the present study might be helpful in establishing the standard values of blood pressure and heart rate with special reference to gender and age. In addition, the outcome of the study might be helpful to assess the relative role of predictors of hypertension and to construct time-specified reference intervals in BP and HR for Indians. The rhythm profile could be taken into consideration to plan dosing time for improvement of health status in hypertensive subjects. In India, studies on rhythms in blood pressure and heart rate using ABPM in human subjects are meager. Therefore, in the present research, attempts have been made to study the circadian blood pressure variability in normotensive and hypertensive individuals by using the latest device ambulatory blood pressure monitor (ABPM). The expected findings of this study might help to delineate plans to curb various cardiovascular diseases in India.
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Section-II
Objectives
OBJECTIVE S

“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 (refer foregoing review of literature). 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. This report is based on sporadic scientific studies. A scientific dissection of prevalence of hypertension – the main culprit, its causes and consequences is overdue. The prognostic significance of blood pressure variability (BPV) is not well defined. 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.

4. to evaluate circadian rhythm characteristics of blood pressure (BP) and heart rate (HR) in young healthy women as function of phases of their menstrual cycles.