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Article

The Clinical Significance of Circadian Rhythm and Blood Pressure Variability

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***Abstract*— Sleep-wake cycle is the most evident 24 hour rhythms observed in humans. This circadian variation is a normal biological clock. The physiological phenomenon, however has been able to explain the onset of cardiac events that also tend to occur during certain time of day. It has been known that there is a tendency for major cardiovascular episodes to occur during the mid-morning hours. With the advent of ambulatory blood pressure monitoring, the fluctuations of blood pressure throughout the day are able to be captured. This is called blood pressure variability (BPV). The factors affecting BPV include age, sex, physical activity, mental activity, behavioural and environmental. Recent studies have shown that high BPV is associated with target organ damage, in particular cardiovascular and coronary artery diseases. In the effort to explain the mechanisms related to these complications out of excessive BPV, several studies explored the role of history of family with hypertension, hyperglycaemia and hyperlipidemia towards developing pre-existing condition that lead to high BPV.**

***Keywords*— Blood pressure variability; hypertension; diabetes mellitus; hyperlipidemia; arterial compliance.**

I. INTRODUCTION

Out of many 24 hour rhythms observed in humans, the most evident is the sleep-wake cycle. Major physiological systems are influenced by this component of the biological clock. Prominent variations of functions occur in endocrine, thermoregulatory, cardiac, pulmonary, renal, gastrointestinal and neurobehavioural systems according to the light-dark cycle. There are functions that exhibit rhythmic components passively triggered by behavioural or environmental changes. In the case of blood pressure (BP) for example, it rises in response to the act of physical activities, or, the seasonal variations of BP responding to cold or hot weather, that requires hypertensive patients to adjust their medication according to the seasons of the year. However, there are also physiological functions that are actively driven by the endogenous 24 hour rhythm, for example the circadian variation of plasma cortisol which is maintained regardless of the variations in environment or behavioural conditions.

In mammals, the suprachiasmatic nuclei (SCN) in the hypothalamus acts as the regulatory centre controlling the endogenous circadian rhythm. Studies have shown that the destruction of these nuclei resulted in loss of circadian rhythmicity. SCN genetically determines the period of fluctuations, which is synchronized to the 24-hour light-day cycle. This synchronization or entrainment of human circadian to that of the light-day cycle is mediated by the retinohypothalamic tract.

II. CARDIOVASCULAR EVENTS RELATED TO CIRCADIAN RHYTHM

Over the past decade, epidemiological studies have objectively confirmed the circadian variation in the onset of cardiac events. Since 1960, it has been known that there is a tendency for major cardiovascular episodes to occur during the mid-morning hours [1]. The onsets of acute myocardial infarction, sudden cardiac death ([2], [3]) and transient myocardial ischaemia [4] tend to occur during the morning waking hours as compared with the other times of the day. In the case of acute myocardial infarction, earlier studies have described a circadian periodicity on the onset of chest pain, based on the subjective reports by the patients ([5], [6]). Muller et al., [7] had attempted quantification of the temporal distribution of the acute onset of myocardial infarction on the basis of objective evidence. The records of 985 patients enrolled in the Multicenter Investigation of Limitation of Infarct Size (MILIS) trial were analyzed to determine the time

of the onset of infarct according to serial measurements of plasma creatine kinase-MB activity. It was observed that the frequency of the onset of pain increased significantly between 6 AM and noon and was associated with increased enzymes level, which occurred between 5 AM and 2 PM. This observation was supported by other reports where the incidence of acute myocardial infarction which was documented from the onset of pain between 6 AM and noon was 1.28 times greater than the other three six-hour interval period while the incidence of acute myocardial infarction confirmed enzymatically was 1.43 times greater between 6 AM and noon than the other period of the day [8].

After nearly four decades since the first report of circadian patterns of acute myocardial infarction was made, clinical management have included changing of lifestyles as well as advances in medical therapy to address the issue. However a recent study [9] observed that there was a circadian pattern of ST elevation of myocardial infarction (STEMI) where occurrences coincide with a morning peak at approximately 11:30 AM. This pattern was highly significant in patients who were not using beta-blockers ($P < 0.0001$) and had no history of diabetes ($P < 0.0001$), but was otherwise absent. The circadian pattern appeared to be attenuated, but not abolished, in patients of a younger age, female gender, or who used statins or aspirin. Peak STEMI occurrence was earlier in smokers than non-smokers.

This drives us back to the drawing board to understand the reasons for the surge of these events in specific hours of the day, following the circadian rhythm. We know that humans possess an internal time clock that regulates multiple physiologic factors (chronobiology). It had been acknowledged in late 1970 that the blood pressure (BP) together with the heart rate, surge soon after a patient awakens and commences activity, with a clearly demonstrated trough at night [10]. Data from numerous studies utilizing ambulatory BP monitoring have demonstrated that BP has a very characteristic and reproducible circadian pattern ([11], [12]). The surge of these cardiovascular events in the early morning hours is related to the 'ruptured plaque' theory where, a surge in BP in the early morning would cause rupture of the smooth, relatively stable plaques in the coronary arteries, which is usually well tolerated and asymptomatic [13]. The irregular surface created by the rupture becomes a nidus for platelet aggregation, which has also been reported to have increase of activity in the morning [14]. Furthermore, with the increase in blood viscosity, which was documented to reach its highest value at this period [15], thrombogenesis sets in and vessel occlusion may occur leading to myocardial infarction or sudden death. In addition, circulating catecholamine [14], renin [16] and cortisol [17] which promote vascular constriction have also been known to increase steeply during the morning waking hours.

III. Blood Pressure Variability.

It has been observed that BP and heart rate have a definite circadian pattern [10]. In most individuals, BP is not constant throughout the day. BP is highest during the daytime hours, forming a plateau between 1000 hour and 1800 hour and falls steadily during the evening hours at approximately 0000-0200 hours. This low nocturnal value, then slowly rises again during the early morning hours (between 0400 and 0600 hours, often while the patient is still asleep) until approximately 0600 hours, after which there is an abrupt and steep increase in BP to the daytime value [18]. BP is closely related to the patterns of sleep and wakefulness rather than to the time of day. This was illustrated by one study where the BP rhythm followed the inverted cycle of activity in night-shift workers [19]. BP varies by about 50-60 mmHg over a 24-hour period [20]. The mean BP falls by about 10%-20% from waking to sleeping [21].

Blood pressure fluctuations or variability (BPV) is closely related to the average level of BP, being greatest when pressure is high [20]. In patients with essential hypertension, the diurnal rhythm and the nocturnal fall in BP are preserved ([20], [21]), the pattern being similar to that of normotensive except that it is shifted upward [22].

The nocturnal fall in BP (which is arbitrarily defined as BP reduction equal or greater than 10% of average daytime values) has been reported to be impaired in a number of other conditions such as ageing, snoring, obstructive apnea syndrome and secondary hypertension namely renovascular hypertension, phaeochromocytoma and Cushing's syndrome [23]. The subgroup of patients who has blunted nocturnal fall of pressure is called non-dipper. This subgroup is of interest as it is associated with a higher rate of organ damage and cardiovascular events in hypertensive women [24] and a higher rate of cerebral lacunae infarct in hypertensive elderly subjects [25].

IV. Factors Influencing Blood Pressure Variability.

The factors affecting BP variability include age, sex, physical activity, mental activity, behavioural and environmental [23]. BPV is reported to correlate with age. Elderly subjects tend to have higher BPV as compared to the younger ones [26]. Analysis of subjects by age groups also revealed that BP level and age independently affected BPV [26]. There have been contradictory reports regarding the BPV among sex distribution. In analyzing ambulatory BP recordings from 354 adolescents (age ranging from 7.2 - 30.9 years old) with type I diabetes mellitus, the BPV was found to be higher in male compared to female [27]. In contrast, a community based study where the age ranges from 20 to 70 years old, the result was otherwise [28]. Another study on atherosclerosis which involved the elderly (subjects of 55 years and above), found no difference among gender [26].

The mean level of both ambulatory BP and BPV decrease during rest [29]. Physical activity has been shown to affect BP, such as changing of posture from lying to sitting or standing, causing a change in both systolic and diastolic BP [30].

Mood has been reported to be a potent determinant of BP with changes observed during anxiety, happiness and emotion [29]. Emotion as one of the factors affecting BPV, also has its clinical implication, as sphygmomanometric BP measurement by a physician or a nurse is considered an emotional event for the patient, leading to a rise of BP. This transient pressor response, only reaches the hypertensive values in a subset of patients, is called the white coat hypertension. The white coat hypertension is defined as a condition in which BP is elevated in the presence of a doctor but falls when the subject leaves the medical environment [11]. As many as 15-30% of those diagnosed as hypertensive are actually in this group ([31], [32]).

The ambulatory BP measurement showed an increase of about 11 mmHg systolic and 5 mmHg diastolic within a few minutes of smoking and lasting for about 15 minutes in both normotensives and hypertensives [33]. The power spectral density analyses of heart rate and blood pressure variability revealed elevated HRV and BPV in both the low- and high-frequency ranges during the smoking imagery [34]. Alcohol intake also increased the BP in both normotensive [35] and hypertensive [36]. However, research showed that BPV was not affected by alcohol intake [37].

V. The Clinical Significance Of 24 Hour Blood Pressure Measurement

Risk factors in an individual are becoming essential to be identified and should be taken into consideration in the patient's management. Meta-analysis of recent studies that have examined the impact of hypertension with new drug intervention showed that there was a success in decreasing the incidence of stroke [38]. However, comparatively it was not the case for the incidence of coronary artery disease (CAD) ([39], [40]). This raised the questions of whether considering a measurement of 140/90 mmHg to represent adequately controlled BP is sufficient, for if this criterion is taken, only 50 % of hypertensive patients are being adequately treated [41]. This resulted in new guidelines being proposed [42]. Furthermore, when patients with treated and controlled hypertension were compared with normotensive subjects with similar levels of BP, there was still an approximately 30% higher incidence of CAD among hypertensive patients [43]. It appears that in addition to the inadequate BP control, an important reason for inadequate impact on the incidence of CAD is that there may be multiple features of hypertension, of which high BP is only one of them. Could BPV be another element in hypertension that has not been adequately addressed?

Elevated BPV in hypertensives have been reported in many studies ([18], [20], [21], [44]) and the results have been almost consistent even when different measuring devices and analysis methods were used, such as continuous non-invasive finger BP recording and analyzed by power spectral analysis method [45]. It is however still debatable as to whether these two abnormalities precede or are merely the consequences of sustained elevated BP. Rafidah et al. [46] attempted to explain this through a study which showed that subjects with a family history of hypertension (FHT) showed higher systolic, diastolic and mean arterial BPV during night time analysis as compared to the controls. This suggests that BPV in early phase may contribute to the development of HT later on.

Hyperglycaemia is also associated with the fluctuations of BP. BPV was found to be higher in type II diabetic patients ([47], [48]). This is thought to be due to hyperglycemia affecting the compliance of the arteries. A study reported that type II DM subjects with high BPV had reduced compliance in the small but not the large arteries [48] (Table 1).

Finally, hyperlipidemia has also been associated with BPV, with study reported that hyperlipidemic subjects as defined by a ratio of TC to HDL cholesterol of more than 5 showed a higher 24 hour and daytime BPV [49]. The study, however, did not find significant correlation of arterial compliance in hyperlipidemia subjects. There was however a weak correlation between 24 hour systolic BPV and large arterial compliance in normolipidemia subject suggesting a physiological correlation at a low level of circulating plasma lipid (Figure 1).

VI. Conclusion

Fluctuations of blood pressure or blood pressure variability are normal responses to the haemodynamic changes of human as part of the physiological mechanism to maintain homeostasis. In certain pre-existing disease and disease condition, excessive BPV increase the likelihood of cardiovascular and coronary artery events that may lead to target organ damage. It is important therefore to have more in depth studies with a bigger sample size to investigate how BPV correlates with cardiovascular risk factors such as family history of hypertension, hyperglycaemia and hyperlipidemia to understand the pathophysiology of hypertension better.

TABLE I
THE COMPARISON OF CARDIOVASCULAR HAEMODYNAMIC PARAMETERS BETWEEN TYPE II DM AND CONTROLS. ADAPTED FROM Rafidah et al. [48]

		Controls (n=18)	**Type II DM n=18**
1	Cardiac ejection time (msec)	338 + 17	319 + 35
2	Stroke Volume Index (ml/beat/m2)	44.4 + 5.8	40.7 + 5.9*
3	Estimated Cardiac Output Index (L/min/m2)	2.9 + 0.3	2.8 + 0.3*
4	Large artery elasticity index C1 (ml/mmHg X 10)	13.7 + 3.8	14.4 + 4.8
5	Small artery elasticity index C2 (ml/mmHg X 10)	6.1 + 3.0	4.3 + 2.6*
6	SVR (dyne•sec•cm^{-5})	1576 $\pm$ 356	1572 $\pm$ 359
7	TVI (dyne•sec•cm^{-5})	146 $\pm$ 38	143 $\pm$ 66

Data expressed as mean + standard deviation (SD); SVR=Systemic vascular resistance, TVI=Total vascular impedance

*P<0.05, **P<0.01

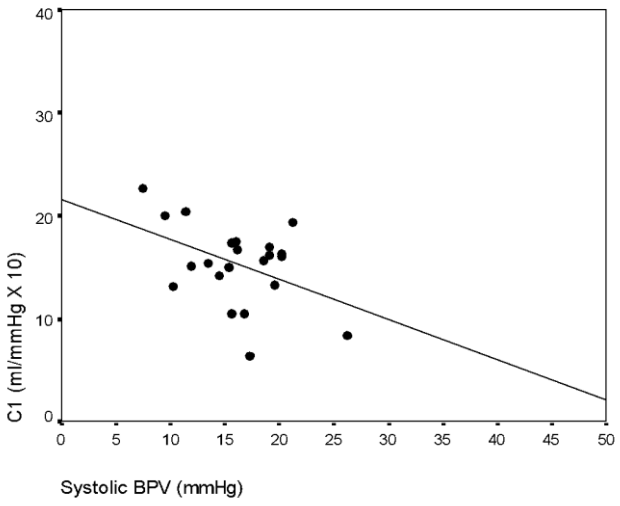

Fig 1. Scatterplot diagram showing the correlation between C1 and 24 hour systolic BPV in normolipidemia subjects. Adapted from Rafidah et al. [49]

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