Chronocardiology and Chronotherapy

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ABSTRACT

Chrono-cardiology is the science which refers to cardiovascular function and dysfunction according to time structure. Guidelines from various agencies for the management of cardiovascular diseases (CVDs) emphasize that the necessity, choice and intensity of treatment should be determined by the individual’s probability of an event (risk) within a given period leading to cardiovascular disease or death. Unfortunately, assessment of the cardiovascular risk, which is based on secondary risk factors such as waist circumference and/or body mass index, blood glucose, blood lipids is subject to bias. The presence of associated clinical conditions and/or end-organ damage are not adequately considered. Primary risk factors; age, sex, family history, sedentary behavior, excess of salt and alcohol consumption, tobacco intake, Western diet, mental load are well known risk factors of CVDs. These risk factors can influence circadian rhythm both in the brain and the body, and the consequences could be fatal. However, the role of an individual’s circadian periodicity in CVDs, which is in turn, influenced by the environment, is still poorly understood. Therefore, the detection of vascular variability disorders (VVDs), and vascular variability syndromes (VVSs), is of significant importance. The role of brain-body interactions, are recent advances in chronocardiology. It is noteworthy that circadian periodicity in blood pressures, have become important due to its influence on chrono-cardiovascular dysfunction which may be pivotal in the prevention of cardiovascular diseases (CVDs) (Figure 1 and 2).

INTRODUCTION

Variability in blood pressures and myocardial function, heart rate, according to time structure particularly on a 7-days scale, has been ignored by most of the experts, despite repeated attempts by Franz Halberg who is considered a pioneer on chronobiology and chronotherapy. The role of variability in blood glucose causing increased risk of target organ damage is now well known. However, recently, a few experts reiterate their viewpoints on various aspects of ambulatory blood pressure (BP) monitoring which appears to be quite interesting, although it is limited 24-hours monitoring. Extended consensus on need and methodology to detect vascular variability disorders (VVDs), and vascular variability syndromes (VVSs), and the role of brain-body interactions, are recent advances in chronocardiology. It is noteworthy that circadian periodicity in BPs, have become important due to its influence on chrono-cardiovascular dysfunction which may be pivotal in the prevention of cardiovascular diseases (CVDs) (Figure 1 and 2).

CHRONOCARDIOLOGY

Chrono-cardiology is the science which refers to cardiovascular function and dysfunction according to time structure. Global guidelines for the management of CVDs emphasize that the necessity, choice and intensity of treatment should be determined by the individual’s probability of an event (risk) within a given period leading to cardiovascular disease or death. Unfortunately, assessment of the cardiovascular risk, which is based on secondary risk factors such as waist circumference and/or body mass index, blood glucose, blood lipids is subject to bias. The presence of associated clinical conditions and/or end-organ damage are not adequately considered. Primary risk factors; age, sex, family history, sedentary behavior, excess of salt and alcohol consumption, tobacco intake, Western diet, mental load are well known risk factors of CVDs. These risk factors can influence circadian rhythm both in the brain and the body, and the consequences could be fatal. Therefore, the detection of vascular variability disorders (VVDs), and vascular variability syndromes (VVSs), is of significant importance. The role of brain-body interactions, are recent advances in chronocardiology. It is noteworthy that circadian periodicity in blood pressures, have become important due to its influence on chrono-cardiovascular dysfunction which may be pivotal in the prevention of cardiovascular diseases (CVDs) (Figure 1 and 2).
rhythms of cardiac events as well as other biological functions which have a periodicity. These physiological functions and their variability according to time structure, may be used as guideline for chronotherapy.

The expression of approximately 10-15% of all myocardial genes oscillate in a time-of-day-dependent manner which is clear from gene expression microarray analysis identified 548 and 176 genes without having any adverse effects of the drug.

Normal myocardial contractile function in vivo, as assessed by echocardiography, was preserved. There was, as we cite, almost verbatim, the finding in mice that the circadian clock influences myocardial contractile function, metabolism, and gene expression. The role of time structure on biochemical and biological function was pointed out by Franz Halberg much before Bartter. He went on conducting research starting from molecular medicine to clinical cardiology which is popularly known as chronocardiology, the name given by him.

**CHRONOTHERAPY**

Chrono-therapy is the method of treatment where time of therapy determines the bioavailability and bioactivity of the modality of treatment. The adverse effects of any therapeutic agent can be eliminated or reduced in extent and bioactivity can be increased by the rescheduling the treatment along the 24-hour scale. The treatment may be modifications of routine activities, diet and/or daily exercise and/or stating or antihypertensive medication. For any non-drug or drug treatment the rescheduling in kind and/or timing of administration being gauged by hours after the habitual awakening time or by other marker rhythms such as continuous ambulatory blood pressure monitoring (Chronobiologically interpreted automatic ambulatory BP and heart rate (HR) monitoring), wrist activity or a human metabolite timetable. Statins can also decrease sympathetic activity. Statin may have adverse effects, if given in higher doses and in combinations, indicating that it may be a two-edged sword. However, if the approach based on timing is used, the dosage of statins may be lowered to achieve greater therapeutic benefit without having any adverse effects of the drug. It is possible that statin therapy if given, according to time structure for example; immediately after awakening, 4 hours, 8 hours or 12 hours after awakening may provide differences in efficacy and bioactivity as well as in incidence of adverse effects. We need to find out the circadian activity of a biological factor such as cytokine or cholesterol around 24 hour scale and administer the drug according to its maximal level in the 24 hour scale. Coenzyme Q10 may be considered in prophylaxis because a decrease in CoQ10 in the muscle in presence of toxicity has been observed in several studies indicating, a reduction in serum levels. Chronotherapy with statins as suggested by Halberg may be used to decrease its therapeutic dosage and increase its efficacy in the prevention of cardiovascular diseases. In an interesting case it has been shown for the first time, how statistically significant results can be obtained by chronotherapy with exercise training, with a simple individualized design, that can be self-applied by everybody to optimize a desired effect by Chronobiologically interpreted automatic ambulatory BP and heart rate (HR) Monitoring) (Figure 3). A 68-year old internist cardiologist monitored himself at half-hourly intervals, with interruptions, for 3- to 7-day sessions (total about 4 weeks). The exercise timing being kept the same within a given session and changed from one session to another. Exercise training in the morning was associated with lowest BP and HR MESORS (Midline Estimating Statistic Of Rhythm, a rhythm-adjusted mean) as compared to exercise done at mid-day.

**Figures 1** MESSR Hypertension (Halberg et al. 2010).

**Figures 2** Effect of environmental factors in the pathogenesis of circadian rhythms.

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late afternoon or in the evening\(^{[29]}\). It seems that exercise effects are circadian stage-dependent and that exercise at the wrong circadian stages can induce a Vascular Variability Disorder (VVD) has been documented earlier\(^{[4,27]}\).

**BLOOD PRESSURE VARIABILITY**

Definition of ambulatory BP targets for diagnosis and treatment of hypertension in relation to clinic BP is based on 24-48 hours records which ignores the presence of circa-septan variability in blood pressures as well as VVS and VVDs\(^{[4,27,28]}\). “The superiority of daytime ambulatory over conventional BP in four populations among 7030 individuals\(^{[25]}\) gave little consideration to night time non-dippers\(^{[27]}\). These studies, although prospective, appear to be only speculations in absence of data on circa-septan increase in blood pressure variability and resultant target organ damage\(^{[24]}\).

Given that conventional health care practice is concerned mainly with high BP and given that other VVDs; circadian over-swinging, excessive pulse pressure, deficient heart rate variability, odd circadian blood pressure timing and MESOR hypertension are not diagnosed but contribute several fold greater risk of CVDs and deaths\(^{[10,11]}\). A recent experimental study published in Nature\(^{[28]}\) suggests that a comprehensive re-examination of circadian behavior and its molecular readouts under simulated natural environmental conditions will provide a more authentic interpretation compared to that observed in the laboratory which is similar to clinic or home BP measurements. If we want to understand exactly how the circadian clock works and how BP variability (BPV) occurs periodically, we are of the firm opinion that it is going to be very useful to have approaches that observe BP of populations living in natural living environment, which is possible only by 7-days ambulatory BP recording (Figure 2)\(^{[29]}\). We cannot simply transfer what we know in the clinic or office into natural conditions. Unfortunately, current management of hypertension strongly relies on clinical BP measurement, although potential evidence indicate that measurement of BP outside the clinic by ambulatory BP and/or home BP devices better represents patients actual BP. Most experts feel that there is only limited information of how to include ambulatory BP monitoring, as a stronger predictor of clinical outcomes, into the diagnosis and management of hypertension\(^{[5-7]}\).

This observation is also in agreement with a cross-sectional survey among 6740 subjects, aged 25 years and above, which reported that pre-hypertension and hypertension are more prevalent in India than assumed before and considered to be a big public health issue\(^{[8]}\).

In a more recent sub-study from India involving “209 subjects (142 men and 67 women) aged 42±18.0 years, in which BPs records were collected for 3-7 days by ambulatory BP monitors, anticipated relationships were found\(^{[7]}\). Namely showing increase in the MESOR of SBP, DBP and heart rate, with age (SBP: \(r=0.260, P=0.001\); DBP: \(r=0.269, P<0.001\); HR: \(r=0.242, P<0.005\)), as well as with body mass index (SBP: \(r=0.232, P<0.005\); DBP: \(r=0.257, P<0.001\)). The MESOR of heart rate also decreased with increased activity (F=5.558, \(P=0.001\)). The MESOR of SBP decreased slightly with increased activity, but the relationship was not statistically significant.” Of particular importance was the effect of consumption of fruits, vegetables and legumes (FVL) on the MESOR of heart rate (\(r=-0.192, P=0.011\)). The circadian double amplitude of HR was also found to be higher among Hindus who prayed (11.7 beats/min) as compared to Hindus who did not pray (8.1 beats/min) (Student t=2.137, \(P=0.035\)) indicating that prayer may have beneficial effect on parasympathetic activity.

The effects of autogenic training and antihypertensive agents on circadian and circa-septan variation of blood pressures have been observed\(^{[30]}\), indicating that both methods of treatment may be complimentary to each other. A few studies have reported an association between pre-diabetes and diabetes with abnormal circadian blood pressure variability which supports the role of glycemia in the pathogenesis of VVSs and VVDs\(^{[3,31,32]}\). It seems that the consensus statement made outlines only limited rationale for the recommended upper limits for daytime, night-time and 24-h SBP/DBP (systolic and diastolic BP) levels determined by ambulatory BP monitoring\(^{[31]}\). Details specific indications for its use, interpretation of the measurements and potential areas of further research are also open to bias because VVSs and VVDs are likely to be missed (Figure 1)\(^{[30]}\). Franz Halberg the father of chronobiology and chronotherapy has laid down guidelines for Chronobiologically interpreted automatic ambulatory BP and heart rate (HR) monitoring in which he has clearly indicated that monitoring should be done for minimum 7-days, otherwise VVDs are likely to be missed\(^{[31]}\).

The role of various environmental factors including nutritional factors which can influence BPV needs further mention (Figure 2). The current guidelines for the diagnosis and management of hypertension in adults also need greater emphasis on blood pressure variability\(^{[34]}\). The guidelines incorporate revised ambulatory BP thresholds for the diagnosis and management of hypertension but ignore the existence
of VVSs and VVDs \[^{23,31,32,34}\].

It is well known that specific features of the 24-h BP pattern are linked to progressive injury of target tissues and risk of CVD events. Several studies have consistently shown an association between blunted asleep BP decline and risk of fatal and nonfatal CVD events. Therefore, most expertise emphasizes to properly control BP during nighttime sleep as well as during daytime activity. The timing of antihypertensive treatment entails to endogenous circadian rhythm determinants of the 24-h BP pattern \[^{39}\]. There have been significant and clinically meaningful treatment-time differences in the beneficial and/or adverse effects of at least six different classes of hypertension medications, and their combinations. Calcium channel blockers (CCBs) are more effective with bedtime than morning dosing, and for dihydropyridine derivatives bedtime dosing significantly reduces risk of peripheral edema. Since renin-angiotensin-aldosterone system is highly circadian rhythmic and activates during nighttime sleep, an evening ingestion of the angiotensin-converting enzyme inhibitors (ACEIs) have been found to exert more marked effect on the asleep than awake systolic (SBP) and diastolic (DBP) BP means. Similarly, the angiotensin-II receptor blockers (ARBs) administered at bedtime, in comparison with morning, ingestion schedule, exert greater hypertensive effect on asleep BP, plus significant increase in the sleep-time relative BPs. There is additional benefit, independent of drug terminal half-life, of converting the 24-h BP profile into a more normal dipping pattern. Such results are also observed for the bedtime versus upon-awakening regimen of combination ARB-CCB, ACEI-CCB, and ARB-diuretic medications.

The chronotherapy of conventional hypertension medications constitutes a new and cost-effective strategy for enhancing the control of daytime and nighttime SBP and DBP levels, normalizing the dipping status of their 24-h patterning, and potentially reducing the risk of CVD events and end-organ injury, for example, of the blood vessels and tissues of the heart, brain, kidney, and retina. However, chronotherapy in consideration of 7-day BP records and considering the time of awakening may double these beneficial effects which has been demonstrated by Franz Halberg in relation to other biomarkers.

CVD morbidity and mortality risk reduction by a bedtime versus upon-awakening treatment schedule has never been evaluated prospectively \[^{36}\]. The MAPEC study was specifically designed to test the hypothesis that bedtime chronotherapy with ≥ 1 hypertension medications exerts better BP control and CVD risk reduction than conventional therapy, i.e., all medications ingested in the morning. A total of 2,156 hypertensive subjects, 1,044 men/1,112 women, 55.6 ±13.6 (mean ± SD) years of age, were randomized to ingest all their prescribed hypertension medications upon awakening or ≥ 1 of them at bedtime. At baseline, BP was measured at 20-min intervals from 07:00 to 23:00 h and at 30-min intervals at night for 48 h. Physical activity was simultaneously monitored every min by wrist actigraphy to accurately determine the beginning and end of daytime activity and nocturnal sleep. Those patients, ingesting medication at bedtime showed at their last available evaluation significantly lower asleep systolic (SBP) and diastolic BP (DBP) means than treatment with those ingesting some (20.0%) or all medications at bedtime (p < 0.001) compared with those ingesting all medications upon awakening. Sleep-time relative SBP and DBP decline was significantly attenuated in patients ingesting all medications upon awakening (p < 0.001). The prevalence of non-dipping was significantly higher when all hypertension medications were ingested upon awakening (68.6%) than when ≥ 1 of them was ingested at bedtime (55.8%; p < 0.001 between groups), and even further attenuated (49.7%) when all of them were ingested at bedtime (p < 0.001). The prevalence of the riser BP pattern, associated with highest CVD risk, was much greater (23.6%) among patients ingesting all medications upon awakening, compared with those ingesting some (20.0%) or all medications at bedtime (12.2%; p < 0.001 between groups). The latter group also showed significantly higher prevalence of properly controlled ambulatory BP (p < 0.001) that was achieved by a significantly lower number of hypertension medications (p < 0.001) compared with patients treated upon awakening. These results indicate that bedtime drug therapy, in conjunction with proper patient evaluation by ABPM to corroborate the diagnosis of hypertension and avoid treatment-induced nocturnal hypotension, should be the preferred therapeutic scheme for type 2 diabetes.

In cardiomyocytes, when a threshold level of reactive oxygen species (ROS) is reached, mitochondrial oscillations are triggered resulting in the cycling of cytoplasmic and mitochondrial proteins between their oxidized and reduced states mainly driven by ROS and the redox potential of the thiols pool \[^{38}\]. Since oxidative stress results from an imbalance of ROS, and mitochondria are the main source of ROS produced by the respiratory chain, a circadian activity of ROS may be important in the pathogenesis of myocardial diseases. This biomarker may be used for the treatment of heart failure, myocardial infarction and cardiomyopathy where oxidative stress is an important...
determinant of cardiac damage.

In brief, chronocardiology and chronotherapy appear to have great potential but need further studies to provide more evidence to establish their role in the management of CVDs. For example, the potential role of self-sustained ultradian rhythms may have in oscillatory redox mechanisms in cellular coherence and survival (as indicated for molecular and cellular function relaxation times following perturbation) is undoubtedly an area of future research (DWW Personal communication Professor Lloyd). It would seem logical to complement circadian and circaseptan time structures with those of ultradians, as well as some of those possibly from ‘solar imprinting’ at the other end of the frequency spectrum.

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