The circadian organization of the cardiovascular system in health and disease

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In normal conditions, the temporal organization of blood pressure (BP) is mainly controlled by neuroendocrine mechanisms. Above all, the monoaminergic systems (including variations in activity of the autonomous nervous system, and in secretion of biogenic amines) appear to integrate the major driving factors of temporal variability, but evidence is available also for a role of the hypothalamic-pituitary-adrenal, hypothalamic-pituitary-thyroid, opioid, renin-angiotensin-aldosterone, and endothelial systems, as well as other vasoactive peptides. Many hormones with established actions on the cardiovascular system (arginine vasopressin, vasoactive intestinal peptide, melatonin, somatotropin, insulin, steroids, serotonin, CRF, ACTH, TRH, endogenous opioids, and prostaglandin E2) are also involved in sleep induction or arousal, which in turn affects BP regulation. Hence, physical, mental, and pathological stimuli which may drive activation or inhibition of these neuroendocrine effectors of biological rhythmicity, may also interfere with the temporal BP structure. On the other hand, the immediate adaptation of the exogenous components of BP rhythms to the demands of the environment are modulated by the circadian-time-dependent responsiveness of the biological oscillators and their neuroendocrine effectors.

These notions may contribute to a better understanding of the pathophysiology and therapeutics of hypertension, myocardial ischemia and infarction, cardiac arrhythmias and all kind of acute cardiovascular accidents. For instance, the normal temporal balance between external stimuli and neurohumoral influences with endogenous rhythmicity is preserved in uncomplicated, essential hypertension, whereas it is frequently lost in complicated and secondary forms of hypertension where gross alterations are found in the circadian profile of BP.

When all the gates of the critical physiologic functions are aligned at the same time, the susceptibility, and thus risk, of adverse events becomes extremely high, even in the presence of minor environmental stimuli that could be usually harmless, and circadian rhythms of cardiovascular events are observed. This implies that one cannot afford to miss what happens during day but also night. Moreover, the requirement for preventive and therapeutic interventions varies predictably during the 24 h, suggesting that the delivery of protective or preventive medications should be synchronized in time in proportion to need, as determined by established rhythmic patterns in cardiovascular function as well as risk, in a manner that will avert or minimize their undesired side effects.

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Doctors used to believe until a few decades ago, that cyclic changes in living entities were caused solely by the effects of cyclic changes in the environment. More recently, during the 1950s, it became apparent that organisms do not respond passively to environmental changes, but have internal clocks able to measure time in an accurate manner. Today we have a good understanding of the mechanisms of biological time-keeping (for an updated synthesis see Fabbian et al.)1, and a specific discipline is devoted to studying biological rhythms, their properties and practical implications2. Like all functions and systems in living organisms, the human cardiovascular system is entirely organized into patterns of functional variation, mainly circadian (24 h) and seasonal3, not only in normal conditions but also during disease, as shown by the temporal variation in cerebro-cardio-vascular accidents4. When one analyzes the circadian pattern of common pathological conditions and clinical manifestations of such disease5,6, it becomes apparent that the same neurohumoral mechanisms which control cardiovascular functioning, are also the driving forces of its temporal organization. Above all, the autonomic and, in general, the monoaminergic systems appear to integrate the major driving factors of temporal variability. On the other hand, many clinical manifestations of cardiovascular diseases reflect the temporal structure of the underlying pathophysiological mechanisms. The main sources of temporal variability in cardiovascular physiology and pathophysiology are the external interfering stimuli such as physical and mental activity or stress, the sleep-waking cycle, and...
the endogenous rhythmicity, even though it is often impossible to clearly separate the relative influence of each factor.

Normal circadian rhythms in cardiovascular function

All physiologic variables pertaining to the cardiovascular function fluctuate during the 24 h of the day. In particular, blood pressure (BP) and heart rate (HR) show significant differences between daytime (awake) and nighttime (asleep) levels. Sleep is the major integrator of such differences, and characteristic changes are observed in BP and HR levels during the different stages of sleep. This means that a normal sleep architecture is fundamental for a normal circadian rhythm of BP. Altogether, during sleep BP and HR fall by an average 10-20% from the awake values, and this normal nocturnal BP fall has been translated in the definition of "dippers", i.e. subjects with a normal dip in nocturnal BP values.

Mechanisms of circadian cardiovascular rhythms in physiological conditions

Circadian rhythms in autonomous nervous system activity, as well as in both norepinephrine and epinephrine plasma levels, urinary catecholamine excretion, dopaminergic and serotoninergic turnovers, are all well documented. Altogether, convincing evidence is available suggesting that the circadian variations in the autonomous nervous system activity and biogenic amines are not explained by a single controlling influence. A significant component of the circadian rhythmicity of norepinephrine, dopamine, and serotonin is under control of a circadian oscillator, whereas epinephrine seems more dependent on external stimuli. This is how environmental factors like sleep/activity and light/dark changes, as well as endogenous rhythmicity do contribute to the determination of the circadian variation in cardiovascular physiology and pathology. In other words, cyclic variations in autonomic nervous system activity play an important role not only in the determination of the sleep-wake process, but also in the mediation of the influence of sleep and wakefulness on the cardiovascular function. The detailed analysis of the circadian fluctuations in neurohumoral factors active on the regulation of the cardiovascular system, is beyond the scope of this presentation. It may be found in the above mentioned references. Biogenic amines and the autonomous nervous system are showing circadian rhythms together with the endogenous opioids, the hypothalamic pituitary adrenal system, hypothalamic pituitary thyroid system, the renin-angiotensin-aldosterone system (RAAS), and many vasoactive (either constricting or relaxing) peptides. A key role in this is played by the kidney, which shows circadian rhythmicity in all factors regulating renal hemodynamics, hence renal function.

Circadian rhythm in cardiovascular disease

The normal dipping condition in BP and HR appears to be changed into "nondipping" (i.e., a decrease from awake values inferior to 10%) in many pathological conditions, including complicated and secondary forms of arterial hypertension. This is bound to increase the hemodynamic burden upon the arterial walls, which in turn augments significantly the cardiovascular risk of nondipping subjects. This particular feature is clearly related to higher target organ damage, particularly renal damage, and is made even more severe in those conditions associated with either sleep-disordered breathing or other sleep-related alterations like restless legs syndrome (RLS) and periodic limb movements in sleep (PLMS). Hypertension is almost invariably the underlying condition of the various clinical manifestations of cardiovascular disease, but when nondipping is also present this causal relationship is clearly enhanced.

Another major mechanism of circadian rhythmicity in cardiovascular disease is represented by the circadian fluctuations in myocardial ischemia, which may occur at any time of the day or night but is more frequent in the second part of nocturnal sleep and in the first hours of the day after awakening, which also explains the relative increase in occurrence of arrhythmic events during this part of the day. For the same reasons, during the early hours of the day a significant prevalence is observed in cardiac angina, myocardial infarction, sudden cardiac death, pulmonary thromboembolism, and cerebrovascular disease (both ischemic and hemorrhagic).

In addition to the already mentioned, obvious, importance of circadian variations in sympathetic tone, catecholamine secretion, and blood pressure variations, other mechanisms may play a role as triggering factors for acute cardiovascular accidents: increased platelet aggregability, changes in blood clotting, fibrinolysis, vascular tone and resistance. By taking into account the body’s so-called biological time structure and the associated variability in
physiological status and pathological mechanisms of disease, a new concept emerges of cardiovascular chronorisk, a risk that results in systematic periodicities in the occurrence of morbidity and mortal events along the time domains, particularly that of 24 h.

Clinical implications and conclusions
It is now well established that any therapeutic approach to cardiovascular disease, and hypertension in particular, may not preclude from the appreciation of time-related differences in the effect of drugs. Since the first observation that nondipping is clearly associated to increased target organ damage, it became apparent that there was a possibility that by reinstating a normal nocturnal fall in BP a significant prognostic advantage could be obtained. After the first demonstration that a blunted or even reversed nocturnal BP fall may be normalized (or at least reconducted towards a more dipping pattern) by appropriate temporal administration of a drug, a systematic investigation began to find out any possible difference in the effects of antihypertensive drugs according to the time of their administration. A detailed analysis of those differences, which are now clearly established, can be found in recent reviews on this subject. Above all, the antihypertensive drugs acting on the RAAS (blocking either the angiotensin-converting enzyme or angiotensin receptors) are now known to be more effective when administered at night before going to bed, as compared to in the morning after awakening. Another major breakthrough derived from the results of the MAPEC study, clearly demonstrating significant prognostic advantages are derived by restoring a more dipping BP profile through evening administration of antihypertensive drugs: a simple and inexpensive change, like switching from morning to evening administration of medications, may hence represent a significant improvement in the management of hypertensive patients.

An obvious but often unrecognized implication of the above mentioned chronotherapeutic possibilities is the absolute need to ascertain the complete BP pattern throughout the day and night in the individual hypertensive patients, using ambulatory BP monitoring, with proper differentiation of the time period spent in sleep from that spent in wakefulness. In fact, among the various BP parameters than can be recorded today with either traditional sphygmomanometric or continuous oscillometric methods, the mean nocturnal BP level is the one most closely related to target organ damage and prognosis.

In conclusion, the rhythms of life are not only acting from the external environment upon the human body, but reside in organisms, which is able to measure time through its central and peripheral biological clocks. As a consequence, a temporal variation is present, particularly within the 24 h of the day (the so called circadian rhythms), not only in the pathophysiologic mechanisms that trigger cardiovascular events, but also in the physiological status of the cardiovascular system. The circadian rhythmic organization of the cardiovascular functions is such that the defense mechanisms against disease are incapable of providing the same degree of protection at all times of the day and night. Instead, temporal gates of susceptibility exist, particularly in the morning hours, and in the second half of nocturnal sleep, of unusually low resistance through which the multiple risk factors can trigger vascular events. Moreover, perturbation or loss of the proper coordination of the temporal structure of cardiovascular functions appear to play a role in initiating the clinical onset of cardiovascular events. When all the gates of the critical physiologic functions are aligned at the same time, the susceptibility, and thus risk, of adverse events becomes extremely high, even in the presence of minor environmental stimuli that could be usually harmless.

This implies that the requirement for preventive and therapeutic interventions varies predictably during the 24 h. It suggests that the delivery of protective or preventive medications should be synchronized in time in proportion to need as determined by established rhythmic patterns in cardiovascular function as well as risk, in a manner that will avert or minimize their undesired side effects. Such a chronotherapeutic approach to the cardiovascular system and its diseases should be advantageous for reducing the morbidity and mortality of at risk patients and for enhancing their quality of life. We now have considerable evidence of all of this in hypertension, in myocardial infarction, and in some arrhythmias. Further research in this field is highly warranted and needed.

References
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