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Chronobiology of arterial hypertension

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Abstract

Many biological phenomena follow a cyclical variation and show a certain rhythm, which functions according to a "biological timer". These biological rhythms are seen as adaptive adjustments to cyclical environmental changes that occur throughout the day, over a month, or seasonally. Chronobiology studies physiological differences by hour, month or even year and has been little studied to date. Cardiovascular parameters (heart rate and blood pressure) are not a set of fixed values, but on the contrary, they know a sinusoidal oscillation within 24 hours, defined by the concept of circadian variability or rhythm. The development of automated data processing tools for blood pressure and 24-hour has allowed over the past years to come to a fullest understanding of the notion of circadian rhythm of cardiovascular parameters within the wider scientific domain, referred to suggestively as chronobiology. The data thus obtained determined the physiologists to accept unanimously the existence of a rhythmic variation in blood pressure. Circadian rhythms have a well-established molecular basis and are genetically influenced.

Keywords: chronobiology, arterial hypertension, circadian rhythm, variability, pathophysiological mechanisms

Chronobiology of blood pressure

The chronom is a concept launched by Halberg F. as a "epitome of the temporal characteristics of the physiological variables, just as the genome encompasses the functional and morphological characteristics of living organisms." [1]

Chronodesm is a term that defines the time-dependent reference limit obtained by computerized data analysis of a circadian parameter evaluated in a reference population (e.g., automatically measurement of blood pressure) - provides predictive information about a biological rhythm.[1]

The variability of blood pressure and heart rate is expressed in both normal and hypertensive patients, not only as a circadian profile but also in a diurnal form (from one day to the next), or by a spectral evaluation, beating. A seasonal variability has recently been described.

Blood pressure variability is dependent on a long list of physiological factors and pathological conditions.

Blood pressure physiological variability is influenced by endogenous and exogenous stimuli.

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Endogenous factors – implications in circadian blood pressure variability

Endogenous factors are not fully known.

Experimental studies on strains of spontaneously hypertensive rats (SHR and WKY) involve the region of the suprachiasmatic nucleus and / or locus coeruleus in the hypothesis of a genuine "endogenous circadian clock" in this neuroendocrine area. Genes of the circadian clock have been demonstrated in most mammalian cells. [2]

It has been experimentally proven that many circadian rhythms persist in the absence of the central nervous system. Into a previous study, 22 patients with hypothalamic syndrome and arterial hypertension were evaluated in which, through pressure monitoring and oral temperature, the circadian rhythm of the thermoregulation was discarded but the circadian rhythm of blood pressure and heart rate was preserved [3].

Melatonin (pineal hormone) appears to be the most important endocrine messenger involved in circadian rhythm regulating mechanisms. Recently, exogenous melatonin has been shown to be hypotensive. Interestingly, circulating levels of melatonin decrease with age and cardiovascular rhythms appear more flattened in the elderly.

Other possible factors involved, which recognize a release and nictemeral action, are circulating catecholamine levels, activity of the renin-angiotensin-aldosterone system, serum endothelin-1, cyclic AMP.[4]

These may contribute to a certain hemodynamic variability in cardiac output, HR, peripheral resistance, blood pressure, both in the diurnal and in the resting hours.

The involvement of genetic factors in the blood pressure and heart rate profile is possible and documented relatively recently. An assessment of the circadian profile of blood pressure was performed on a batch of 28 monozygotic twins and 16 dizygotic twins; blood pressure and heart rate were measured at a 10-minute interval for 24 hours. Surprisingly, monozygotic twins have been found with higher blood pressure values. [2]

Age-based pressure dependence is one of a continuous type. From the age of childhood and adolescence, blood pressure is specifically adapted by increasing both systolic and diastolic values, accompanied by a similar increase and pressure variability.

Initial systolic pressure, adipose center excess in childhood, and maternal cardiovascular status could potentially contribute to the adult's subsequent pressure profile.

Also, humoral factors, renal-controlled homeostasis, cardiovascular response to sympathetic stimuli, and some neuro-regulatory mechanisms can be considered responsible for the variability of blood pressure and heart rate as early as childhood and subsequently mitigated with somatic growth and maturation of subjects.

At adulthood (35-55 years) we witness a significantly higher increase in diastolic blood pressure, while in the 55-65 age group, increases are mainly systolic blood pressure. [2]

Due to the multiple situations that contribute to the definition of the circadian arterial blood pressure profile, the difficulty of diagnosing high blood pressure is more and more evident in subjects with slightly or moderately elevated blood pressure levels at extreme ages.

It is therefore necessary that, in these cases, at least two measurements of blood pressure be carried out within three consecutive days. In individuals with high and intermittent oscillations, the number of pressure measurements must necessarily be increased for the safe diagnosis of arterial hypertension.

The influence of sex on blood pressure values has been established in several studies. Thus, in a study conducted on elderly hypertensive patients, Damian and colleagues established that there are significant differences in circadian rhythms in males and females, differences that strongly correlated with the level and nature of daily activities.[5]

It has been observed that men have higher blood pressure levels during the afternoon and evening, while women show higher values in the morning.

The mean diastolic blood pressure was higher in female sex, indicating a possible difference in the cardiovascular profile compared to male patients.

It can not be said, however, whether the increase in blood pressure in elderly patients is, in addition to changing the elasticity of elderly age, and the result of other exogenous factors such as salt-rich diet, defi-

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ciency of trace elements in the body, stress, smoking, obesity or alcohol consumption [2].

Exogenous factors that influence blood pressure variability over 24 hours

A number of influences of everyday life can cause certain pressure fluctuations. Increased physical and / or mental activity, pain perception, physician visit, anxiety and panic attack, type of occupation, may cause occasional increases in both systolic blood pressure> 140 mmHg and diastolic > 90 mmHg [3], but not should be confused with genuine arterial hypertension.

Physical activity and rest contribute to the variability of blood pressure values in both normal and hypertensive [4]. In both groups there are no differences between the pressure parameters of the working and resting phases.

Surprisingly, cardiovascular parameters undergo major influences in variability, more in resting than in activity [5]. Extremely large differences were found and difficult to interpret between the blood pressure and cardiac variability and the levels of physical activity performed.

A good correlation was found between blood pressure and the average physical activity performed about 15 minutes. before the time of the parametric determinations [5]. In a analysis, physical activity levels, blood pressure and heart rate, showed a similar circadian variation [6].

Acute and intense pain can trigger high blood pressure values. By using stimuli of pulp dental pain and evaluating concurrently the pain tolerance threshold and the blood pressure levels by semi-automatic monitoring, a consistent correlation between pain perception and 24-hour pressure mean values was found.

Physician visit and the psycho-neurogenic reaction induced by an affective and catecholamine component have been increasingly described in recent years and become "white coat syndrome". This may result in documented episodic and moderate arterial hypertension they may later be mitigated or even disappear.

Often, a decrease in systolic values of 10 to 30 mmHg and diastolic values of 5 to 10 mmHg may occur between the first visit to the physician and subsequent controls [7].

In the HDFP study, over 30% of the untreated subjects and found with a diastolic blood pressure greater than 95 mmHg at baseline had postmarked values less than 90 mm Hg one week after the first assessment.

These observations were also reinforced by the results noted in the elderly hypertensives evaluated in the SHEP study. The percentage of those with systolic blood pressure variability between initial medical visit and subsequent controls, in the absence of treatment, was 36% of the cases. Of those who were reconfirmed as hypertensives at the second visit, only 30% were randomized to the third medical visit.

Also, in the SYST-EUR study, the differences found between blood pressure values in doctor's office and ambulatory were unexpectedly high, more than 20 mmHg [8].

In another study conducted on 111 subjects, blood pressure measurement in the medical cabinet on two different occasions at 8 days showed that the mean blood pressure value decreased significantly between the two assessments .Individuals who experienced a significant blood pressure decline between the two visits to the physician had a higher anxiety score (labile blood pressure). Only one determination tends to overestimate the blood pressure value and the frequency of arterial hypertension. Some training of subjects exposed to these assessments may be useful in preventing the obtaining of erroneous data and abusive framing in the diagnosis of arterial hypertension [9].

The influence of daily stress and the pathology induced by it, particularly neuropsychological, is often much higher than originally thought. In a study of subjects hospitalized for panic disorder and with a frequency of 3.7-6.8 weekly attacks and hypertensive crisis triggers, a circadian rhythm, diurnal / nocturnal ratio and significant variability were observed for systolic and less for diastolic blood pressure values compared to control subjects [10].

Also, subjects experiencing transient sleep disorder associate the change in cardiovascular circadian rhythm with higher diurnal, nocturnal blood pressure and cardiovascular variability [10]. The demanding professions, characterized by sustained activity, are associated with an increased risk of systolic hypertension [11], especially in association with other risk factors such as smoking and overweight.

Work-related stress is associated with an increased secretion of catecholamines and an increased variability of blood pressure over the course of the day [12].

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Adaptation to the environmental conditions in which these professional activities take place, in addition to age, diet, family status, ethnic or socio-economic characteristics, may be inductive factors of blood pressure variability and the timeliness of essential arterial hypertension [12].

Professional stress triggers more frequent arterial hypertension in men than in women. The latter may, however, be affected to the extent that the professional requirement is added to the marital responsibilities [13].

Marital status can have an effect on blood pressure. The results of a recent study (5th Sustainable Forum on Quality of Outcome and Research on Cardiovascular Disease and Stroke) conducted on 30,534 adults , showed that widowed, divorced or separated more commonly found with high blood pressure during daily activities than married persons [14].

Alcohol consumption was associated with increased blood pressure, more closely with systolic than 24-hour diastolic values, and during professional activities. The relationship is valid for amble sexes, even for normotensives [15].

The acute effect of smoking is to increase blood pressure and heart rate. However, in most epidemiological studies, smokers have been found with blood pressure values similar to those of non-smokers.

Two collectives of researchers [10, 16] note an eloquent association between chronic cigarette smoking and ambulatory systolic-diastolic blood pressure values, but not with clinical blood pressure values. This increase in blood pressure values is accompanied by a faster heart rateover the diurnal interval.

By Cesaris R (1992) evaluated the cardiovascular response to 10 normotensives and 10 smoking hypertensives of over 20 cigarettes / day. They were monitored during the smoking period of 4 cigarettes within 1 hour and after the smoking period. Each cigarette smoked induced a similar and statistically significant increase in blood pressure and heart rate, both in normotensive and hypertensive patients, accompanied by increased variability of these cardiovascular parameters [17].

Postural changes do not significantly affect physiological pressure values, a variation in diastolic blood pressure of not more than 5 mmHg in the orthostatic position is not the exception.

Higher fluctuations from the clinostatic to the orthostatic position, with particularly significant diastolic increases, are often signals of an adaptation of increased systemic arterial resistance and the presence of essential arterial hypertension.

Orthostatic blood pressure increases in hypertensives are partially correlated with HR variability components, which are less attenuated by a diminished sympathetic response [10].

However, variations between 10 and 20 mmHg were found in both normal subjects and hypertensives monitored in lateral decubitus, inexplicable by hydrostatic pressure variations, and which can greatly influence the results [10].

Seasonal variability in blood pressure could be demonstrated recently, after monitoring hypertensive patients by three means; clinically, automatically and at home in all four seasons of the year [18].

In a study carried out between December 1990 and May 1993 on an urban area in northern Italy, Sega et al. [19] find significant seasonal differences in blood pressure values. Systolic and diastolic blood pressure values were found to be lower in the summer and higher in the cold season, with January being characterized by the highest pressure values, regardless of the method of determination, and by July with the lowest arterial pressure. Pressure variations were noted during day and night, both among hypertensives treated and untreated.

Seasonal variations have been reported in normotensive subjects aged 28 and 63 years [20], thus seeking an explanation for the high prevalence of cardiovascular death during the winter and the possible impact on the diagnosis and therapy of cardiovascular diseases.

It is known that during the exposure to cold, the vascular skin network contracts, causing increased peripheral resistance and blood pressure. Moreover, the pressure variability is also dependent on the type of seasonal physical activity and the microclimate conditions of the dwelling.

Circadian profile of blood pressure

The circadian profile of blood pressure is characterized by two diurnal peaks, at 9.00-11.00 and 18.00-19.00, and by a night collapse around 3.00 [21]. Changes in circadian rhythm have been noted between a group of hypertensives and another group of normal. In normal

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subjects, there were two vertices and two edges of the systolic blood pressure circadian profile, with a difference of less than 40 mmHg, whereas in hypertensives this difference exceeded 50 mmHg.

Analysis of the data collected by intra-arterial manometry , showed in both hypertensive and at normal individuals that the blood pressure begins to increase before the time of rising, thereby indicating that the waking and physical activity can not be the major determinants of the crochet hook of morning blood pressure (morning surge) . This morning's "blood pressure wave" is more common among subjects over the age of 60, both normal and hypertensive, and has definite prognostic implications [22].

In a study outpatient conducted on normotensive patients , who watched profile circadian heart rate , was observed a peak around 13.00 and a progressive decrease to a minimum at around 4.00 a.m, followed by another increase before awakening morning [21]. Changes in the pulse were also observed during nighttime sleep.

Combined pulse and blood pressure value ("double-product"), increased in the early morning hours was considered to have a "physiological trigger" effect. This hemodynamic parameter may be related to the increased frequency of cardiovascular events occurring at this time of day [23].

The "beat-to-beat" variability of blood pressure and heart rate is a relevant predictor of autonomic nervous tone and cardiovascular risk [24]. It can be analyzed by computerized signal processing consisting of amplification, filtering and analog-to-digital conversion processes.

Autonomic nervous system – influences on blood pressure circadian variability

Using spectral blood pressure methodology, recently results sustain the hypothesis of sympathetic pathogenic role in essential arterial hypertension, at least in the initial stage of the disease.

In hypertensive patients, these data suggest an alteration of both the sympathetic-vagal balance and baro-receptors mechanism activity.

The neuro-vegetative control of blood pressure in hypertensives is dominated by the sympathetic path accentuation, spectral analysis revealing higher values for both diastolic and mean blood pressure values.

An analysis of spectral parameters in the frequency domain of continuously evaluated pressure values provides somewhat similar information to those derived from heart rate variability analysis in hypertensive subjects.

The results thus obtained estimate the following areas of physiological interest: blood pressure variability, autonomic function, sympathico- vagal balance and baro-reflex sensitivity [10,15]. There is already a good relationship between the blood pressure variability and the circadian rhythm. The higher the presidential decrease is nocturnal, the higher the signs of sympathoadrenergic activity.

This variability is attenuated by the use of beta-blockers [27]. Baroreflex sensitivity determined during Valsalva maneuver is consistently low in hypertensive patients compared to normal subjects.

The alteration of this physiological parameter correlates positively with the reduction of the proto-diastolic filling of the left ventricle, which is associated with an increased risk of cardiac death [28].

The spectral variability of heart rate and blood pressure, as well as baroreflex sensitivity, are also modified in other patient categories: heart failure, myocardial infarction or in pure or associated autonomous failure.

Blood pressure variability increases with increasing pressure values, being much lower in normal than in hypertensive patients.

In uncomplicated arterial hypertension, ambulatory blood pressure variability is in close proximity to baroreflex sensitivity, independent of the level of pressure values.

Blood pressure variability increases with age and systolic pressure. In contrast, baro-reflex sensitivity diminishes with the age and value of systolic blood pressure and is significantly related to ambulatory blood pressure variability [29].

The magnitude of blood pressure variability and impaired baroreflex sensitivity in hypertensive patients spontaneously or induced by some antihypertensive drugs may have real prognostic consequences, contributing to morphofunctional deterioration of target organs [30].

Conclusions

The diagnosis of arterial hypertension and its management for decades has been based mainly on unique measurements of arterial blood pressure during the

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day. However, ambulatory blood pressure monitoring (ABPM) shows that blood pressure is consistently variable in 24 hours, characterized in normotensive and uncomplicated hypertensives, by increasing morning TA with 2 peaks - 2-3 hours after waking and the other early in the evening, and a 10-20% decrease in mean blood pressure during sleep compared to the average recorded during the wakefulness.

An increasing number of clinical trials confirm the correlation between blood pressure values and target organ damage. Risks of vascular and cardiovascular complications strongly correlate with mean nocturnal blood pressure compared to daytime values.[30]

The practical applicability of these observations has led to the development of a new concept, the chronotherapy of arterial hypertension, which has led to the observation that the administration of at least one hypotensive drug at bedtime, in order to obtain optimal blood pressure control during sleep, reduces total CVD events by 61% and major events (CVD death, myocardial infarction, ischemic and haemorrhagic stroke) by 67% compared to previous practice that prescribed the administration of hypotensive drugs ate the sime time, usually in the morning. Therefore, we are facing a need to review the definition of arterial hypertension and the need for a modern diagnostic and management approach.

Conflicts of interest

The authors confirm that there are no conflicts of interest.All authors have equal contribution to this paper.

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