Diurnal rhythms, the renin-angiotensin system and antihypertensive therapy

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Abstract

The circadian rhythms of the cardiovascular system are related to the risk of events such as myocardial infarction and stroke. The so-called 'morning surge' in heart rate and blood pressure at around the time of waking is a particularly hazardous period. The sympathetic nervous system and the renin-angiotensin system are thought to be the main regulators of these rhythms and a potential target of antihypertensive medication is the blunting of the morning surge through action on these systems. This article reviews some of the mechanisms involved and recent therapeutic approaches to this problem.

Key words: circadian cardiovascular rhythms, morning surge, sympathetic nervous system, renin-angiotensin system, angiotensin II receptor blockers, alpha adrenoceptor blockers.

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Introduction

Circadian rhythms are so obvious that we rarely think about them. We also tend to assume that their mechanism and implications are now more or less fully understood. We would be mistaken. One area where we should certainly take a greater interest as clinicians is the rhythms governing variations in heart rate and, even more importantly, blood pressure. This is relevant from both pathophysiological and therapeutic perspectives. Firstly, the daily rhythms in blood pressure have a major influence on the timing of cardiovascular events, including myocardial infarction, stroke and sudden death. Secondly, arising from this, it must be of importance to control blood pressure to minimise the effect of these fluctuations, especially of rapid rises in individuals with hypertension.

Circadian changes in blood pressure and heart rate

Although it has long been known that blood pressure fluctuates during the day, the amount of data relating to this has hugely increased in recent years since ambulatory blood pressure monitoring became clinically practicable. This has confirmed a consistent pattern in most normotensive and hypertensive subjects, though of course the overall levels are higher in the latter (see figure 1).[1,2] We know that:

- Highest levels of blood pressure occur after 10 am with a peak around noon but often with a plateau extending to 6 pm.
- Leading up to this, there is a rise in pressure from the time of waking or before (about 6 am), with the pressure rising by up to 20/15 mmHg in most people.
- There is a decline in pressure of 10–20% in the late evening and on going to sleep, with a nadir in blood pressure at about 3 am.

Of course this can be modified by changes in patterns of activity, for instance in shift workers, and by other factors such as strenuous exercise and anxiety (as in the white-coat syndrome). This pattern is also modified in some hypertensive patients, who can experience:

- The loss of nocturnal 'dipping', that is to say the decline in blood pressure is less than 10% at night and may be almost non-existent. This is associated with increased target-organ damage and enhanced risk of cardiovascular events.[3,4]
- Extreme dipping, with reductions in pressure of more than 20% in night-time pressures. This too is thought to be harmful, especially with regard to stroke, but this has yet to be fully confirmed.[5]

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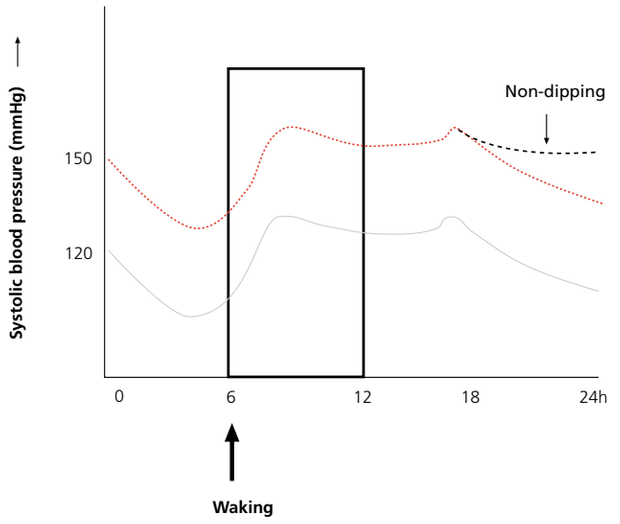
Figure 1. Stylised representation of 24-hour blood pressure rhythm in normotensive (lower curve) and hypertensive (upper curve) individuals. The rectangle indicates period of maximum risk for cardiovascular events



- The morning rise or 'surge' in blood pressure may be exaggerated, not necessarily in the rate of rise in pressure but rather in the level attained.

Broadly, changes in heart rate parallel those in blood pressure.

These changes are influenced by many factors apart from actual activity, including age, gender and ethnicity. For instance, the nocturnal dip is generally diminished in black individuals and older individuals from all races.[6] On the other hand it may be greater in women than in men.

Regulatory mechanisms

The master pacemaker for human circadian rhythms is located in the suprachiasmatic nucleus in the anterior hypothalamus.[7] The main regulatory input is light, while the pineal hormone melatonin seems to be the most important endocrine messenger so far described. It is interesting that melatonin levels decline with age and that cardiovascular circadian rhythms appear to be flattened in the elderly, as noted above. It has recently been reported that exogenous melatonin may lower blood pressure,[8] but the relevance and reproducibility of this have yet to be established.

Much more work has focused on the roles of the autonomic nervous system, and latterly also the renin-angiotensin-aldosterone system, in modulating cardiovascular circadian rhythms. It has been shown that sympathetic activity increases during the day, from or before waking, while the parasympathetic system follows the opposite pattern, with greater activity during sleep.[9] The renin-angiotensin system also appears to follow a rhythm which largely parallels sympathetic activity although this has been somewhat controversial, with some suggestions that the pattern of hormone secretion was driven by blood pressure change rather than helping to initiate it. Although the relevant data are neither as extensive as one might expect, nor as recent, it seems that there is an early morning rise in plasma renin activity, with a peak at around 8 am with similar or slightly delayed peaks in angiotensin II and aldosterone levels. The increase in renin activity actually precedes waking and the possible morning surge in blood pressure, which would be plausible if part of that rise were driven by angiotensin II or even aldosterone. There are also fluctuations in renin level during sleep, with maximal levels during slow wave, non-rapid eye movement sleep.[10,11] It is not clear whether these mechanisms are disturbed in essential hypertension.

Circadian rhythm of cardiovascular events

Regardless of potential mechanisms, there is little doubt that the peak time for cardiovascular events – myocardial infarction, stroke, sudden death, and hypertensive crises – is in the hours between 6 am and noon, although the exact location of the peak varies between studies.[1,2,12,13] It is hard to envisage that this is not related to the changes in heart rate, blood pressure and in the neurohumoral parameters already mentioned. These also promote other potentially harmful changes, for instance in increased coagulation and platelet activation and reduced fibrinolysis. Trying to minimise these 'excess' events must be a valid therapeutic objective.

Implications for antihypertensive therapy – chronotherapeutics

There is no controversy about the need for sustained blood pressure control throughout the day and night.[14] Any antihypertensive drug is assessed for its ability to provide this control, which may be quantitated in a number of ways. The best known is still the trough:peak ratio, while the smoothness index has also been advocated in some studies. Many trials now measure the effects of missing one dose of the medication to be tested.[15] At the same time, all the impetus has been towards the development of once-daily drugs, since this is likely to encourage adherence to treatment. There are now drugs in almost all the major therapeutic classes which will provide 24-hour blood pressure control as measured by the technique mentioned above, but this does not fully address the problem of the morning blood pressure surge. If once-daily medication is taken soon after waking, blood pressure control may be adequate about 24 hours later before the next dose is due, but in fact it needs to be better than adequate: rather it should be at its maximum, providing greatest protection at a time of increased risk. There may be three ways to achieve this:

- To abandon the once-daily approach and to take an additional drug late in the evening to ensure blood pressure control 6–8 hours later.
- To use formulations which may be taken once daily but with delayed release of drug timed for optimal effect.
- To use a drug with high efficacy and a trough:peak ratio close to one.

The term chronotherapeutics has been applied to studies on

the optimisation of the timing of drug delivery to produce the greatest possible efficacy and safety.[16] It is not surprising in view of previous comments that this area of research has been very much focused on hypertension. How then can we apply the three approaches mentioned? Furthermore, how, if at all, do these approaches fit with our knowledge of the rhythms of the sympathetic and renin-angiotensin systems?

The evidence is not as comprehensive as one might like but a considerable amount does exist. To take the above points one by one:

- The alpha$_1$-selective blocker doxazosin may be taken at bedtime and there is evidence that the subsequent morning blood pressure surge is blunted.[17] This complicates the treatment regime but may be particularly useful in patients with prostatic hypertrophy and nocturia. There seems to be little problem with nocturnal hypotension.
- The calcium channel blocker verapamil has seen the greatest research effort with novel formulations. The controlled onset extended release preparation (COER), again taken at bedtime, has been shown to reduce morning rises in both heart rate and blood pressure[18] but an outcome trial was stopped prematurely in somewhat controversial circumstances.[19] It is not clear whether this preparation will be marketed in the near future, or at all.
- Some of the newer angiotensin II receptor blockers (ARBs) have a very prolonged duration of action. Of these, telmisartan is probably the longest acting, and has a half-life of about 24 hours. It may be particularly relevant that there appears to be a biphasic pattern in the elimination of this drug, possibly reflecting secondary release from tissue-binding sites. In comparison with another ARB, losartan, and with the long-acting calcium channel blocker amlodipine, telmisartan (40–120 mg given once daily in the morning) produced greater reductions in blood pressure the following morning.[20] Although the differences were small (approximately 3/1.5 mmHg) they were nonetheless statistically significant and would be expected to have a clinically significant impact on risk reduction.

Conclusions

There is no doubt that circadian rhythms are of importance in determining risk from cardiovascular events and that these are related, at least in part, to changes in blood pressure and heart rate. These, in turn, are partly regulated by the autonomic and renin-angiotensin systems. We also know that the changes in blood pressure can be modified by existing therapies, including those aimed at the sympathetic nervous system and the renin-angiotensin system, specifically the angiotensin AT$_1$ receptor. But there are several important points which are still unclear, of which perhaps the most important is: which of the treatments available is the most likely to improve outcomes and to what extent is the blunting of the early morning rise in blood pressure relevant in any improvement? It is also interesting to speculate whether the timing of drug administration matters, even for long-acting agents, which might perhaps be given in the evening for optimal effect.[21] As ever, one can also ask whether the mechanism of the blood-pressure lowering matters, or just the ultimate effect?

Key messages

- Blood pressure and heart rate typically follow a circadian rhythm, usually including an early morning surge which may be exaggerated in the hypertensive patient
- This is related to the period of greatest risk of cardiovascular events, such as myocardial infarction and stroke
- The main modulators of this rhythm appear to be the autonomic nervous system (particularly the sympathetic), and the renin-angiotensin system
- Several strategies are available for suppressing the morning surge, including alpha$_1$-blockade and the use of a long-acting angiotensin II receptor blocker
- It is not known whether altering the blood pressure profile in this way will lead to improved clinical outcome

Conflict of interest

The author has spoken at meetings organised by several manufacturers of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers and has accepted sponsorship for attendance at international conferences. The companies are: AstraZeneca, Bristol Myers Squibb, Servier and Takeda.

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