The need for 24-hour blood pressure control

Dr Mike Mead begins a new occasional series on issues in primary care cardiology. Here he writes about a factor that is very important in terms of cardiovascular risk but is often overlooked – the need for 24-hour control of blood pressure.

Abstract

The current focus of our efforts in treating hypertension is to 'treat to target' using combination therapy. However, 24-hour control of blood pressure (BP) is of crucial importance in reducing cardiovascular risk. There is a circadian rhythm for such risk, with morning peaks in sudden cardiac death, myocardial infarction, unstable angina and ischaemic stroke. There is also a natural circadian rhythm in BP. Lack of a significant nocturnal dip worsens prognosis: patients tend to have increased left ventricular hypertrophy, cardiovascular mortality and cerebrovascular disease. Risk is related to the patient's total BP load.

The implications are that truly long-acting once-daily antihypertensives are needed, with a trough/peak ratio > 50%. Patient compliance is very important. Ambulatory BP monitoring should be used in selected patients. Patients should be advised to take their antihypertensive medication on waking rather than waiting until after breakfast.

Key words: blood pressure, blood pressure control, ambulatory blood pressure monitoring, antihypertensive agents, circadian rhythm, cardiovascular risk.

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Introduction

It is universally accepted that hypertension is one of the major risk factors for ill health, being implicated as a significant risk factor in the pathogenesis of coronary heart disease, stroke, heart failure, renal failure and dementia. Identifying and treating patients with hypertension has now become a key target for practices and primary care trusts (PCTs), partly as a consequence of the agenda set by the National Service Frameworks for Coronary Heart Disease, Older People and Diabetes.

The targets for control of blood pressure (BP) using antihypertensives have been set out by the British Hypertension Society[1] and are reproduced in table 1.

To try and achieve these targets, combination therapy of different antihypertensives is needed. The current focus of our efforts in treating hypertension is to 'treat to target' using combination therapy. However, there is one factor in hypertension that has been afforded less attention, yet is one of the most important in terms of cardiovascular risk – the need for 24-hour control.

'Cardiovascular risk is related to the patient's total blood pressure load'

Mike Mead

Table 1. Target blood pressures (BP) for antihypertensive treatment (clinic readings in mmHg)

	No diabetes	Diabetes
Optimal BP	< 140/85	< 140/80
Audit standard	< 150/90	< 140/85

Footnote: The audit standard reflects the minimum recommended levels of BP control.

The circadian rhythm of cardiovascular risk

It has long been known that there is a circadian rhythm for cardiovascular risk, with a peak of risk as the patient rises and begins to carry out his or her daily activities. In a review of the evidence documenting this circadian phenomenon, Muller[2] presented the data supporting a morning peak for:

- Sudden cardiac death, with a peak incidence between 7 a.m. and 9 a.m. and a low frequency at night. (The risk of sudden cardiac death in the Framingham Heart Study was ≥ 70% greater during the peak interval than the mean risk during the remaining 22 hours of the day).
- Myocardial infarction (MI), with a peak occurrence between 6 a.m. and noon.
- Unstable angina and non-Q-wave acute myocardial infarction (AMI),

with a peak incidence between 6 a.m. and noon.
- Ischaemic stroke, with a frequency peak between 8 a.m. and noon.

Numerous studies have confirmed this morning peak of risk. Stefan *et al*.[3] showed an increased onset of sudden cardiac death in the first three hours after awakening, with a relative risk of 2.6 compared to other times of the day. Muller *et al*.[4] showed that AMI is three times more likely to occur at 9 a.m. than at 11 p.m. Casetta *et al*.[5] found that 44% of ischaemic strokes occur in the morning between 6 a.m. and noon. There are several mechanisms which may explain the increased cardiovascular risk in the morning but a major factor is undoubtedly the circadian variation in BP.

The circadian rhythm of blood pressure

We have a huge body of evidence documenting the natural circadian rhythm of BP. Awakening is accompanied by a surge in systolic and diastolic BP. Millar-Craig *et al*.,[6] for example, used continuous intra-arterial BP monitoring in hypertensive and normotensive patients and found that:
- BP is highest in the morning, then falls progressively throughout the remainder of the day.
- BP is lowest at about 3 a.m. but begins to increase at 5–6 a.m., sharply rising as the patient wakes up and moves around until it reaches a morning peak.
- Heart rate is maximum at midday, falling again progressively until it reaches its lowest rate during sleep, then rising abruptly in the two hours after waking.

The 24-hour readings from normal and hypertensive patients were very similar with regard to the circadian rhythm. Millar-Craig *et al*. noted that it was the 6 a.m. to 9 a.m. period when arterial BP rises rapidly.

Much of this observed circadian BP rise is, in fact, a consequence of physical activity on rising. There is little change in BP between before and after waking if patients remain supine. In shift workers the time and amplification of BP rise mirrors their physical activity and in patients with a prolonged afternoon siesta the afternoon BP approaches that of the night-time drop in patients without a siesta.[7]

The night-time dip in BP is recognised as an important prognostic factor in patients – a dip of < 10% of the day-time level (i.e. the lack of a significant nocturnal dip) worsens prognosis. Non-dippers tend to have increased left ventricular hypertrophy, more severe target organ damage, increased cardiovascular mortality, increased cerebrovascular disease and a greater rate of decline in renal function than those with the normal diurnal variation. Many elderly patients and Afro-Caribbeans do not exhibit a normal nocturnal dip.[8] Black hypertensive subjects, in particular, generally show smaller mean nocturnal dips and have a higher mean left ventricular mass than white patients, despite similar mean 24-hour BPs.[9] Patients with secondary forms of hypertension tend to have a blunted nocturnal dip.[8] Lack of nocturnal dipping on ambulatory BP monitoring should alert the GP to careful consideration of the possibility of a secondary cause for the hypertension.

> ***'Awakening is accompanied by a surge in systolic and diastolic blood pressure'***

The key practical relevance of looking at 24-hour BP readings lies in the fact that cardiovascular risk is related to the patient's total BP load, that is, both the magnitude of the elevation of the BP and the duration over which the raised BP acts. Measuring BPs at our surgeries in the late morning, afternoon or evening once every three months can never give an accurate picture of the patient's BP load. Not surprisingly, the severity of target organ damage in hypertension is more closely related to 24-hour mean BP than to cuff values.[10] Furthermore, target organ damage is also dependent on 24-hour variability of BP. For any given value of 24-hour mean BP, subjects in whom the 24-hour variability is low have a lower prevalence of target organ damage than those in whom 24-hour variability is high.[10]

Other pathological mechanisms

There are several other mechanisms which help to explain the increased cardiovascular risk in the morning. Platelet aggregability increases in the early morning as you get up and start daily activities. There are also other haematological changes that increase the likelihood of thrombosis, including lower levels of tissue plasminogen activator and an increase in blood viscosity. During the waking hours catecholamine and renin levels rise, contributing to a catecholamine-induced vasoconstriction of the coronary and systemic vasculature. Cortisol levels are higher in the morning and increase sensitivity of vessels to catecholamines. As the renin-angiotensin system is activated there is increased production of angiotensin II, one of the most powerful vasoconstrictors. With the BP surge, and these vasoconstrictor responses, shear stresses may precipitate rupture of a vulnerable atherosclerotic plaque, already propagated by the hypercoagulable state.[8]

Significance for therapy

The implications of this new understanding of the circadian cycle of cardiovascular risk are profound. Clearly we need to focus more on 24-hour control, not just surgery readings, if we are to reduce target organ damage. In particular we need to focus on protection from the morning surge in BP to try and reduce the excess of cardiovascular and cerebrovascular events that occur in the post-awakening period. This sharp morning rise in BP, associated with an increased cardiovascular risk, is a new and important risk factor for GPs to consider. Gosse *et al*.[11] showed that

Table 2. Half-lives of some different 'sartans'

Candesartan (Amias®)	9 hours
Eprosartan (Teveten®)	5–9 hours
Irbesartan (Aprovel®)	11–15 hours
Losartan (Cozaar®)	6–9 hours
Telmisartan (Micardis®)	> 20 hours
Valsartan (Diovan®)	9 hours

Source: Summary of Products Characteristics.

Table 3. Half-lives of some ACE inhibitors

Captopril (Capoten®)	8 hours
Enalapril (Innovace®)	11 hours
Lisinopril (Zestril®)	12.6 hours
Perindopril (Coversyl®)	25 hours
Ramipril (Tritace®)	13–17 hours for 5–10 mg dose (longer for lower doses)
Trandolapril (Gopten®)	16–24 hours

Source: Summary of Products Characteristics.

the value of BP on rising in the morning was strongly correlated with left ventricular mass of hypertensive individuals, independently of the 24-hour value. The single BP reading measured by an ambulatory device on rising in the morning was more discriminant of future cardiovascular events in hypertensive patients than the value of BP calculated as the average of three readings taken under standardised conditions in the hospital or office.

Action points for primary care management of hypertension

There are four practical applications of this understanding of the circadian rhythm of hypertension and risk.

1. The need to use truly long-acting once-daily antihypertensives

Covering the full 24-hour period smoothly and consistently, including that early morning period of risk should be our aim. Consistently good control over 24 hours will also reduce the risk of BP variability and may help to normalise circadian patterns in non-dippers.[12]

The obvious thought is to give antihypertensives at night but this risks severe nocturnal hypotension which in some patients (notably the elderly and those with pre-existing coronary heart or cerebrovascular disease) can predispose to myocardial ischaemia and stroke.[8] Absorption of drugs may also decrease at night so you may need a higher dose if you give a drug at night. Once-daily drugs are therefore usually given in the morning. Unfortunately, many antihypertensives will not give satisfactory 24-hour control, losing their efficacy in the critical last four to six hours when the risk may be greatest. Many of our hypertensive patients receiving treatment have high BPs in the early morning hours. Redon *et al.*[13] looked at 290 hypertensive patients who were stable on medication: they found that at least half of patients with well-controlled office BP do not have their BP under control for the period shortly after waking.

> ***'The night-time dip in blood pressure is recognised as an important prognostic factor'***

In respect of 24-hour control of BP there are major differences between different drugs within an antihypertensive class. There are two different ways of looking at longevity of action – the half-lives of the different drugs and trough:peak ratios. The trough effect is the decrease in BP observed at the end of the interdosing interval, immediately before administration of the next dose.[14] The peak effect is the maximum reduction in BP after administration of a drug.[14] For satisfactory smooth BP control over a 24-hour period with a once-daily antihypertensive it should have a trough:peak ratio for effects on BP > 50%.[14]

There have been numerous clinical studies confirming the clinical relevance of half-lives and trough:peak ratios in achieving good 24-hour control of BP. Telmisartan (half-life > 20 hours) has been shown to be significantly more effective in lowering systolic and diastolic BP during the 18 to 24-hour period after dosing, as measured by ambulatory blood pressure monitoring (ABPM), than losartan (half-life 6–9 hours).[15] Bisoprolol (half-life 9–12 hours) maintains significantly better control than atenolol (half-life 6–9 hours) during the final four hours of the dosing interval.[12] Acebutolol once daily (peak trough ratio 0.71) gives more consistent and durable BP control, including the early to mid-morning hours, than once-daily atenolol (trough:peak ratio 0.46).[12] Table 2 lists the half-lives of the 'sartans' (angiotensin II receptor blockers), and table 3 lists the half-lives of some angiotensin-converting enzyme (ACE) inhibitors.

2. The need to ensure patient compliance

Compliance comes in various forms. Clearly the most serious lack of compliance is defaulting on medication altogether but still serious in terms of hypertension load is the patient who forgets tablets on some days, who stops and starts medication and for whom 'once daily' means the tablet is taken at some time during the day but not consistently at the same time. There are several issues in ensuring compliance, including advice to the patient (and relatives!), ensuring proper recall and follow-up and, since side effects are a common cause of non-compliance, ensuring selection of the right antihypertensive (more usually the right combination of antihypertensives) for the patient to minimise side effects. Simplify drug regimes as much as possible – a long-acting once-daily preparation will improve compliance as well as BP control.

3. Increasing the use of ABPM in selected patients

Ambulatory blood pressure monitoring (ABPM) is obviously more time-intensive, but it has a useful role in diagnos-

Key messages

- Remember the importance of 24-hour control and how to measure such control through ABPM readings and home monitoring
- Consider the length of action and dose of different antihypertensives before prescribing
- Make every effort to ensure patients comply with their medication as prescribed
- Give specific advice to patients on taking their medication: once daily should be once in the early morning!

ing and managing hypertension in selected patients, notably those where the BP shows unusual variability, in patients with borderline values, in cases of suspected white coat hypertension, in cases of possible hypotension and in patients with hypertension that is resistant to therapy. ABPM will demonstrate the control of morning levels in those on antihypertensive therapy and allow you to assess both nocturnal dips and non-dippers. Ensuring increased access to ABPM is a key issue for practices and PCTs. Home monitoring will also serve a useful function in improving 24-hour control if patients can take their BPs after rising in the morning to see if there is any poor control at this time. The future for management of hypertension will clearly rest on patients monitoring their own BP at home, just as diabetics monitor their own blood glucose.

'We need to focus more on 24-hour control if we are to reduce target organ damage'

4. Giving specific advice on taking therapy

One of the simplest strategies of all is to advise patients to take their antihypertensives on waking and starting activity rather than waiting until 9 or 10 o'clock, after breakfast. Once-daily should be translated to mean taken once in the early morning. Even a brief summary of the importance of 24-hour control can be incorporated by doctor or practice nurse as part of initial and follow-up consultations.

Conclusion

The control of hypertension over 24 hours is crucial to the reduction of cardiovascular risk. In particular, it is important to control the morning surge in BP which carries an increased risk of stroke and MI.

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Mike Mead
General Practitioner
Forest House Medical Centre,
2a Park Drive, Leicester Forest East,
Leicester, LE3 3FN.
(email: mikemead@talk21.com)