Antihypertensive Therapy and Circadian Blood Pressure Profiles: A Retrospective Analysis Utilising Cumulative Sums

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The results of previous studies on the effects of antihypertensive agents on circadian blood pressure patterns are inconclusive, possibly due to the lack of a simple, objective, universally accepted method of quantifying circadian blood pressure profiles. In order to investigate for differences in the effects of antihypertensive drugs on circadian changes we utilised a recently described modified cumulative sums technique to quantify circadian alteration magnitude (CAM). CAM is simply calculated as the difference between crest and trough blood pressures, the mean blood pressures of the 6-h periods of highest and lowest sustained pressures respectively. The records from all 24-h ambulatory blood pressure monitoring performed over a 7 year period on subjects either on no medication (1208), or on treatment with a single first-line antihypertensive agent (578), were examined retrospectively. A sample (n = 40) stratified for trough diastolic blood pressure, age and sex was randomly selected from each of the following 5 groups: subjects on no medication, and subjects being treated with bendrofluazide, atenolol, class 2 calcium-channel blockers or captopril alone. Untreated subjects, those on bendrofluazide and those on a class 2 calcium channel blocker had similar circadian patterns. Subjects on atenolol therapy (25.9 ± 1.7/18.3 ± 1.3, systolic CAM ± SE/diastolic CAM ± SE) had attenuated circadian changes (p < 0.05) when compared to the untreated group (29.8 ± 1.8/23.6 ± 1.1), while those on captopril (34.9 ± 2.4/25.7 ± 1.8) exhibited markedly increased systolic and diastolic circadian blood pressure swings, which differed from those of the atenolol treated group (p < 0.01). As the pattern of 24-h blood pressure, quite apart from absolute pressure levels, appears to contribute to morbidity and mortality in hypertensive patients, these findings deserve further prospective evaluation. Key words: blood pressure, circadian rhythm, cumulative sums, ambulatory blood pressure monitoring, antihypertensive drugs, dippers/non-dippers.

INTRODUCTION

The relative day-time blood pressure lowering efficacies of the current first-line antihypertensive drugs, thiazide diuretics, beta-blockers, calcium channel blockers and angiotensin converting enzyme inhibitors appear comparable [1, 2]. A number of reviews of ambulatory blood pressure studies have attempted to clarify the circadian pattern of blood pressure during varied drug treatments [3–5]. However, most ambulatory blood pressure studies only sought the presence or absence of a circadian rhythm by visual inspection of pooled pressure profiles, rather than examining for quantitative effects by antihypertensive agents on circadian profiles. A minority compared day-time versus night-time blood pressure reductions, or utilised Halberg's cosinor method [6], and to date no study has quantified circadian blood pressure patterns by the more complex smoothing techniques such as truncated Fourier analysis [7], or spline functions [8], by square wave fitting [9], nor by the recently described modified cumulative sums technique [10]. This latter method has been proposed as a simple precise objective method of quantifying the extent of circadian blood pressure changes, from raw ambulatory blood pressure data, in a manner that is independent of the timing and duration of inactive or sleep periods.

Using the modified cumulative sums technique, we analysed retrospectively, random samples, which were stratified for age, blood pressure and sex, of ambulatory blood pressure profiles from both untreated subjects and subjects on single first-line antihypertensive agents, recorded over a 7 year period, to ascertain the extent to which antihypertensive agents might perturb circadian blood pressure patterns.

MATERIAL AND METHODS

All 24-h non-invasive ambulatory blood pressure records, performed on subjects referred for assessment of hypertension, recorded by SpaceLabs 90202 or 90207 systems [11, 12], at the Blood Pressure Unit, Beaumont Hospital, from January 1985 to December 1991, were reviewed. The SpaceLabs recorders had been programmed to obtain measurements at intervals of 30 min for a 24-h period, starting between 9 and 11 am. Failed readings automatically triggered a single
remeasurement attempt 2 min later. If blood pressure recordings were repeatedly unsuccessful, resulting in an interval duration (time period between 2 successive successful ambulatory blood pressure recordings) of 2 h or more, or if less than 42 readings over the 24 h were achieved, the ambulatory study was regarded as not suitable for analysis and excluded from the study.

**Quantification of circadian blood pressure patterns**

A modified cumulative sums technique as previously described [10] was utilised to quantify crest and trough pressures, and circadian alteration magnitudes (CAM), for both systolic and diastolic blood pressures from these records. Briefly the method involves construction of a cumulative sum or cusum plot, and cusum-derived statistics are then calculated from this plot. To construct a cusum plot, mean time-weighted 24-h pressure, the reference value, is subtracted from each interval pressure value (mean of the blood pressure readings at the start and finish of the interval) in succession. Any remainder (mmHg) is multiplied by the duration of the interval (h) and then the resultant pressure-time product (mmHg-h) is added to the previous sum. This cusum, plotted against time, is a cusum plot. When the interval pressure is greater than mean 24-h blood pressure the pressure-time product is positive, the cusum increases, and the plot rises. When the interval pressure is less than the reference value, the cusum decreases, and the plot falls. The cusum plot slope for any given time period is defined as the change in the cusum over the period divided by the change in time for that period. It can be proven that the cusum plot slope equals the difference between mean time-weighted blood pressure for that period and mean 24-h blood pressure. Thus crest blood pressure, which is defined as the time-weighted mean blood pressure of the period of at least 6 h duration with the highest time-weighted mean pressure level, can be located in time from the cusum plot as the 6 h (or longer) period with the steepest positive slope. Crest blood pressure is calculated as the sum of this positive slope and mean 24-h blood pressure. In analogous fashion, trough blood pressure, the time-weighted mean blood pressure of the period of at least 6 h duration with the lowest time-weighted mean pressure level, is calculated by the addition of the most negative slope (over 6 h or greater) to mean 24-h pressure. Circadian alteration magnitude quantifies the extent of the circadian pressure change, and is defined as the difference between crest and trough blood pressures. Alternatively CAM may be calculated as the sum of this positive slope and mean 24-h blood pressure. In analogous fashion, trough blood pressures are indicated as is circadian alteration magnitude (CAM).

**Inclusion and exclusion criteria**

Subjects with established diagnoses of secondary hypertension, diabetes, ischaemic heart disease or cardiac failure were excluded, as were hypertensive subjects taking more than one antihypertensive drug. Only records from subjects taking no medication or taking single first-line antihypertensive drug therapy were eligible for inclusion in the study. In the treated groups, drug dosage and schedule had to satisfy the recommendations of the appropriate data sheet for the treatment of hypertension. One thousand, two hundred and eight subjects on no medication and 578 on single first-line antihypertensive drug therapy were identified as having 24-h ambulatory blood pressure records from which cusum-derived statistics could be calculated, and who satisfied all of the above inclusion and exclusion criteria. Of those on treatment 88 were on thiazide diuretics (bendrofluazide 87, chlorothiazide 1), 232 on cardioselective beta-blockers (acebutolol 2, atenolol 105, bisoprolol 4, celiprolol 1, metoprolol 110, 118 on calcium-channel blockers (diltiazem 16, nicardipine 15, nifedipine 63, verapamil 24) and 139 were on angiotensin converting enzyme inhibitors (captopril 64, enalapril 20, lisinopril 4, perindopril 41, spirapril 10).

**Selection of stratified random samples**

As circadian patterns of blood pressure may be influenced by mean level of blood pressure, age, and sex, samples (n = 40) stratified for trough diastolic blood pressure, age and sex were randomly selected from random samples.
alone. In order to exclude subjects with isolated or predominantly systolic hypertension, it was also stipulated that the difference between trough systolic and trough diastolic blood pressure had to be less than or equal to 70 mmHg. As influences on C/A.M might be due to individual drug effects rather than class effects, we attempted to randomly select each sample from patients on a single drug from each class. However, no group of patients on an individual calcium channel blocker was sufficiently large—hence the compromise of selecting from a group of patients taking class 2 calcium antagonists, nifedipine or nicardipine. For the purposes of stratification subjects from each individual drug treatment were subdivided into low and high blood pressure groups (diastolic trough blood pressure 45-74 mmHg and 75-90 mmHg, respectively), into younger and older age groups (age 25-54 years and 55-70 years) and by sex. Thus there were four factors, sex, age group, blood pressure group (each with two levels), and treatment group (five levels) in this randomised block design. Each factor was crossed with each other, resulting in $2 \times 2 \times 2 \times 5 = 200$ cells each with 5 replicates, the number of subjects thus totalled 200.

**Statistical analysis**

Statistical comparisons between the initial treatment groups (untreated, thiazide diuretics, cardioselective beta-blockers, calcium channel blockers, and ACE-inhibitors) were carried out by one-way analysis of variance (ANOVA), followed by Bonferroni $t$-test of differences between group means. Differences between the stratified random samples of subjects ($n=40$) on specific drug regimens (untreated, bendrofluazide, atenolol, nifedipine/nicardipine, and captopril) were compared with the aid of a four-way ANOVA, followed by Tukey's Studentized range test. Results are expressed as arithmetic means with one standard deviation or as arithmetic means with one standard error.

### Table 1. Subject data for whole treatment groups

Values are means $\pm$ standard deviation; ANOVA is one-way analysis of variance followed by Bonferroni $t$-tests of differences between group means.

<table>
<thead>
<tr>
<th></th>
<th>Untreated</th>
<th>Thiazide diuretics</th>
<th>Beta-blockers</th>
<th>Calcium antagonists</th>
<th>ACE-inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$</td>
<td>1208</td>
<td>88</td>
<td>232</td>
<td>118</td>
<td>140</td>
</tr>
<tr>
<td>Male/female</td>
<td>627/581</td>
<td>30/58</td>
<td>117/115</td>
<td>54/64</td>
<td>76/64</td>
</tr>
<tr>
<td>Age (years)</td>
<td>$47.3 \pm 14.3$</td>
<td>$59.3 \pm 12.9$</td>
<td>$51.4 \pm 11.7$</td>
<td>$57.4 \pm 12.6$</td>
<td>$52.2 \pm 12.9$</td>
</tr>
<tr>
<td>Systolic trough BP (mmHg)</td>
<td>$124.6 \pm 16.2$</td>
<td>$128.9 \pm 19.0$</td>
<td>$124.1 \pm 17.3$</td>
<td>$130.9 \pm 18.3$</td>
<td>$124.3 \pm 15.8$</td>
</tr>
<tr>
<td>Diastolic trough BP (mmHg)</td>
<td>$73.9 \pm 11.5$</td>
<td>$73.2 \pm 11.8$</td>
<td>$72.3 \pm 11.4$</td>
<td>$76.5 \pm 11.6$</td>
<td>$74.6 \pm 10.3$</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>$26.5 \pm 4.4$</td>
<td>$26.0 \pm 4.1$</td>
<td>$26.3 \pm 4.4$</td>
<td>$25.8 \pm 4.0$</td>
<td>$27.2 \pm 4.7$</td>
</tr>
</tbody>
</table>

* $p < 0.05$ versus untreated; $b p < 0.05$ versus thiazide diuretics; $c p < 0.05$ versus cardioselective beta-blockers; $d p < 0.05$ versus calcium antagonists; $e p < 0.05$ versus ACE-inhibitors.

### Table 2. Subject data and circadian alteration magnitudes (CAM) on stratified random samples

Values are means $\pm$ standard deviation; $n=40$ for each group; ANOVA is four-way analysis of variance (ns = not significant), followed by Tukey's Studentized range tests of differences between group means.

<table>
<thead>
<tr>
<th></th>
<th>Untreated</th>
<th>Bendrofluazide</th>
<th>Atenolol</th>
<th>Nifedipine/Nicardipine</th>
<th>Captopril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>$51.6 \pm 11.4$</td>
<td>$52.8 \pm 8.9$</td>
<td>$53.5 \pm 8.9$</td>
<td>$53.0 \pm 10.8$</td>
<td>$52.9 \pm 10.1$</td>
</tr>
<tr>
<td>Systolic trough BP (mmHg)</td>
<td>$124.5 \pm 14.5$</td>
<td>$122.7 \pm 14.5$</td>
<td>$125.1 \pm 15.8$</td>
<td>$124.0 \pm 13.9$</td>
<td>$124.2 \pm 13.3$</td>
</tr>
<tr>
<td>Diastolic trough BP (mmHg)</td>
<td>$73.1 \pm 8.9$</td>
<td>$74.4 \pm 10.1$</td>
<td>$74.2 \pm 10.8$</td>
<td>$73.2 \pm 9.5$</td>
<td>$74.4 \pm 10.1$</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>$25.8 \pm 3.6$</td>
<td>$26.8 \pm 4.0$</td>
<td>$27.4 \pm 5.2$</td>
<td>$25.4 \pm 2.8$</td>
<td>$26.5 \pm 4.7$</td>
</tr>
<tr>
<td>Systolic CAM (mmHg)</td>
<td>$29.8 \pm 11.4$</td>
<td>$27.8 \pm 12.6$</td>
<td>$25.9 \pm 10.8$</td>
<td>$30.8 \pm 13.3$</td>
<td>$34.9 \pm 15.2$</td>
</tr>
<tr>
<td>Diastolic CAM (mmHg)</td>
<td>$23.6 \pm 7.9$</td>
<td>$21.8 \pm 10.1$</td>
<td>$18.3 \pm 8.2$</td>
<td>$23.0 \pm 9.5$</td>
<td>$25.7 \pm 11.4$</td>
</tr>
</tbody>
</table>

* $p < 0.05$ versus untreated; $b p < 0.05$ versus bendrofluazide; $c p < 0.05$ versus atenolol; $d p < 0.05$ versus nifedipine/nicardipine; $e p < 0.05$ versus captopril.
RESULTS

Whole treatment groups

Table I shows that there were marked differences in sex, age and blood pressure distribution of the subjects from the whole treatment groups.

Stratified random samples

As expected the selection of random samples from subjects on individual antihypertensive agents, stratified for sex, age and trough diastolic blood pressure, who did not display isolated systolic hypertension, resulted in groups with similar sex, age, systolic and diastolic trough blood pressure and additionally body mass index distributions (Table II). When we analysed these groups for differences in circadian pattern, subjects on atenolol therapy (25.9 ± 1.7/18.3 ± 1.3, systolic CAM ± SE/diastolic CAM ± SE) were found to have significantly attenuated diastolic circadian changes (p<0.05) when compared to the untreated group (29.8 ± 1.8/23.6 ± 1.1), while those on captopril (34.9 ± 2.4/25.7 ± 1.8) exhibited markedly increased systolic and diastolic circadian blood pressure swings which differed from those of the atenolol treated group (p<0.01) (Table II. Fig. 2).

Drug dosages and schedules

Daily dosages of atenolol ranged from 50 mg to 200 mg, and those of captopril from 12.5 mg to 100 mg. While the blunting of circadian rhythm tended to be more marked in patients taking daily doses of atenolol greater than 50 mg (n = 23, 24.1 ± 2.2/16.7 ± 1.5, systolic CAM ± SE/diastolic CAM ± SE) than in those on 50 mg atenolol per day (n = 17, 26.7 ± 2.6/20.5 ± 2.3), these differences were not statistically significant. Circadian alteration magnitudes were similar for patients on 12.5–49 mg captopril daily (n = 13, 36.1 ± 5.0/26.0 ± 3.3), 50 mg daily (n = 15, 35.5 ± 3.8/25.7 ± 2.7), and those on 51–100 mg daily (n = 12, 32.8 ± 4.1/24.7 ± 3.5). All patients on bendrofluazide took it as a single morning dose, and those on nicardipine or nifedipine took their tablets twice or three times daily. The majority of patients taking atenolol followed a once daily regimen (34/40), while most of those on captopril took their medication twice daily (33/40). Thus analysis of the associations between dosage schedule and circadian alteration magnitudes was not possible.

DISCUSSION

Altered patterns of 24-h blood pressure have been suggested as independent influences on cardiovascular morbidity and mortality [13–23]. Kobrin [13], Verdecchia [14], and Shimada [15] have suggested that patients with an average drop in nocturnal systolic and diastolic pressures of greater than 10% may be protected from the development of hypertensive target organ damage, and cardiovascular complications. However, the results of other studies provide evidence which suggests that greater circadian swings might predispose to organ damage rather than act as a protection [16, 17]. It has been shown that there is a circadian pattern to the occurrence of such cardiovascular events as myocardial infarct [18, 19], and stroke [19]—both occurring most frequently during the morning hours, and cardiovascular physicians have speculated that a rapid and substan-
tial rise in morning blood pressure might increase the likelihood of rupture of an atherosclerotic plaque, leading to exposure of thrombogenic collagen [20]. There is at least a theoretical possibility that external diuretics may be at greater risk from nocturnal cardiac and cerebral ischaemia [21, 32]. A recent report, that nocturnal limb pain in patients with severe arterial insufficiency was closely correlated to the extent of the night-time drop in blood pressure [23], strongly supports this suggestion.

While many researchers have realised the advantages of utilising ambulatory blood pressure monitoring in the evaluation of antihypertensive drug efficacy—elimination of white-coat hypertension, lack of placebo response, enhanced reproducibility—few have used ambulatory blood pressure monitoring to satisfactorily assess the impact of drug therapy on circadian pressure profiles. Most investigators who have commented on effects of antihypertensive therapy on circadian rhythmicity only analysed for qualitative changes, seeking the presence or absence of a circadian rhythm by visual inspection of pooled pressure profiles [3–5]. A minority of investigators have compared the differences between day-time and night-time blood pressure means, or used Halberg’s ‘cosinor method’ [6]. Both of these quantitative methods suffer from inherent inaccuracies, utilisation of fixed time periods and assumption of symmetrical blood pressure behaviour respectively [10].

Of six ambulatory blood pressure studies that examined for effects of angiotensin converting enzyme inhibitors on circadian blood pressure rhythms [24–29], four inspected pooled pressure profiles and two compared day-time and night-time pressure reductions, and all observed the persistence of a circadian pattern of blood pressure during angiotensin converting enzyme inhibitor treatment. Of six studies [30–35] on the effects of cardioselective beta-blockers on circadian blood pressure changes, three reported significant blunting of circadian rhythmicity to be associated with cardioselective beta-blockade [31–33]. Only one of these studies compared awake and sleeping blood pressures quantitatively [31], and the remainder drew conclusions based on visual inspection and comparison of pooled pressure profiles.

Our analysis of the records from all 24-h ambulatory blood pressure monitoring performed over a 7 year period on subjects either on no medication, or on treatment with a single first-line antihypertensive agent was performed in order to investigate for possible quantitative differences in the effects of antihypertensive drugs on circadian blood pressure changes. Our study has the disadvantage of being retrospective. Hence patients had not been randomly allocated to the various antihypertensive agents nor to specific dosage schedules. We were concerned by the marked disparity in group sizes, and also that sex, age, and blood pressure level distributions differed greatly between the initial five groups. So as to eliminate the influence of these potentially confounding factors, random samples stratified for sex, age, and diastolic blood pressure were selected from groups of subjects treated with agents that were representative of each drug class, or on no medication. Analysis of variance on these stratified random samples showed that circadian patterns were most blunted in subjects on the beta-blocker atenolol, and more accentuated in those on captopril, an ACE-inhibitor, the difference in the mean circadian change between these two groups being 9.0 mmHg systolic and 7.4 mmHg diastolic. Hypertensive patients treated with class 2 calcium antagonists or bendrofluazide had similar circadian blood pressure patterns to untreated subjects.

Our results do not contradict the results of previous studies but rather illustrate how quantitative analyses, that analyse individual rather than pooled profiles, with independence from fixed time periods, may detect subtle alterations which might be missed by qualitative analyses. Our modified cumulative sums technique is one such quantitative technique, and other examples are the more complex smoothing techniques such as truncated Fourier analysis [7], and spline functions [8], and also the square wave fitting method [9].

The disparity of effects by atenolol and captopril on circadian blood pressure profiles may be due to circadian variations in the susceptibility of the cardiovascular system to the drugs. Sympathetic nervous system activity in man is greater during day-time than night-time hours [36, 37], and therefore sympathetic blockade would be expected to reduce crest/day-time blood pressure to a greater extent than trough/night-time pressure levels. Since the majority of patients taking atenolol followed a once daily regimen, an alternative explanation for its blunting effect could be a duration of action considerably shorter than 24-h. However, despite atenolol having a plasma half-life of only 6 to 9 h, many studies support a longer duration of action [31, 32].

We found that captopril therapy was associated with greater circadian pressure rhythmicity than subjects treated with atenolol. This could result due to an elevation of crest pressures by the angiotensin converting enzyme inhibitor, or could be due to a relatively greater lowering of trough blood pressures than of crest pressures by captopril. The latter appears the more likely explanation. The similarity of trough pressures of the stratified random samples (Table II) is not in conflict with this proposal as the samples were stratified on the basis of trough pressures. If captopril does lower
trough pressures more effectively than crest pressures, this would suggest that the renin-angiotensin-aldosterone system could play a larger role in the maintenance of trough blood pressures than in the generation of pressure crests or peaks.

Whatever the explanation for these varying effects of different antihypertensive drugs, and further prospective studies are necessary to clarify the situation, the fact that some drugs may accentuate circadian swings, that others may blunt the normal pattern and still others have no effect raises important questions in choosing a drug for an individual patient. In patients with an accentuated circadian pattern, it may be advisable to prescribe drugs that are known not to reduce night-time/trough blood pressure excessively, or short acting agents to be taken in the morning. On the other hand, in hypertensive subjects with no or little circadian rhythm, it may be advantageous to attempt to restore a normal pattern by using drugs known to be efficacious in reducing trough blood pressure.

In conclusion, circadian blood pressure patterns may contribute to morbidity and mortality in hypertension. The results of this retrospective study, utilising a new quantitative method of analysing blood pressure patterns, suggest that drugs currently used in hypertension may have varied quantitative effects on circadian pressure changes. Hence judicious choice of specific antihypertensive agents for individual patients may allow normalisation of the circadian pattern of blood pressure over the 24 h in addition to reduction of blood pressure level.

ACKNOWLEDGEMENTS

Support from the Charitable Infirmary Charitable Trust, the Health Research Board (Ireland), the Irish Heart Foundation, ICI Pharmaceuticals and the Royal College of Surgeons in Ireland is gratefully acknowledged.

REFERENCES


Submitted December 12, 1992; accepted April 19, 1993

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