Effect of Antihypertensive Agents on Blood Pressure Variability
The Natrilix SR Versus Candesartan and Amlodipine in the Reduction of Systolic Blood Pressure in Hypertensive Patients (X-CELLENT) Study

Yi Zhang, Davide Agnoletti, Michel E. Safar, Jacques Blacher

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Abstract—To investigate the effect of different antihypertensive agents on blood pressure (BP) variability (BPV) and the underlying mechanism, we analyzed the ambulatory BP monitoring data of 577 patients before and after 3-month antihypertensive treatment, in the Natrilix SR Versus Candesartan and Amlodipine in the Reduction of Systolic Blood Pressure in Hypertensive Patients (X-CELLENT) Study, a multicenter, multinational, randomized, double-blind, placebo-controlled study with 4 parallel treatment arms (placebo, candesartan, indapamide sustained release, and amlodipine). Within-subject mean and SD of 24-hour BP, weighted by time interval between consecutive readings, were calculated in 3 time frames (daytime, nighttime, and 24 hours) to evaluate BP and BPV. The mean 24-hour heart rate (HR) and HR variability were calculated with the same algorithms. We found that the 3 antihypertensive drugs had a similar BP-lowering effect ($P < 0.001$ for all), but amlodipine ($P < 0.007$) and indapamide sustained release ($P < 0.04$) were the only agents associated with a significantly decreased BPV after 3-month treatment. On the other hand, the major determinants of BPV at baseline were age, mean BP, and the corresponding HR variability. However, the reduction in BPV by amlodipine was significantly associated with the reduction in BP ($P < 0.006$) and the reduction in HR variability ($P < 0.02$), whereas the corresponding reduction by indapamide sustained release was only associated with the reduction in HR variability at night ($P = 0.004$). In summary, 3-month amlodipine or indapamide sustained release treatment was associated with a significant reduction in BPV, and the mechanism of those reductions was possibly attributable to lowering BP or ameliorating the autonomic nervous system regulation or both. The combination of the 2 agents might help to optimize such properties. 

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Key Words: ambulatory blood pressure monitoring ■ calcium channel blocker ■ diuretics ■ blood pressure variability ■ heart rate variability

For many decades, the main goal of antihypertensive treatment was to lower blood pressure (BP) to a defined level. Recently, several investigators have shown that BP variability (BPV) is another critical cardiovascular risk factor, which should also be emphasized in the treatment of hypertension. Mancia et al. were the first to report a close association of BPV, assessed by 24-hour ambulatory BP monitoring (ABPM), with target-organ damage in hypertensive patients. Carotid artery damage and increased left ventricular mass index were, therefore, investigated in the first instance. However, the predictive value of BPV concerning cardiovascular and all-cause mortality has long been a matter of debate. More recently, nighttime BPV was considered to be a more pronounced risk factor than daytime BPV. Finally, Rothwell showed that visit-to-visit BPV was an independent and strong predictor of cardiovascular events, such as stroke and coronary heart disease, and calcium channel blockers and nonloop diuretics were the most effective antihypertensive agents in reducing BPV and in preventing stroke.

However, the unique effect of these agents in terms of BPV reduction is still unproved in the setting of randomized, double-blind, placebo-controlled study. Similar observations can be made regarding other antihypertensive agents as diuretics, β-blocking agents, and blockers of the renin-angiotensin-aldosterone system. Finally, the determinants of BPV remain unclear, and the underlying mechanism of BPV

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From the Paris Descartes University (Y.Z., D.A., M.E.S., J.B.), Assistance Publique-Hôpitaux de Paris, Diagnosis and Therapeutic Center, Hôtel-Dieu, Paris, France; Centre for Epidemiological Studies and Clinical Trials (Y.Z.), Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China.

Correspondence to Michel E. Safar, Centre de Diagnostic et de Thérapeutique, Hôtel-Dieu, 1, Place du Parvis Notre-Dame, 75181 Paris Cedex 04, France. E-mail michel.safar@htd.aphp.fr

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reduction has never been elucidated precisely in subjects with hypertension.

We analyzed the ABPM data of 577 patients before and after 3-month antihypertensive treatment, in a multicenter, multinational, randomized, double-blind, placebo-controlled study with 4 parallel treatment arms (the Natrilix SR Versus Candesartan and Amlodipine in the Reduction of Systolic Blood Pressure in Hypertensive Patients [X-CELLENT] Study), to investigate the effect of different antihypertensive agents on BPV and the underlying mechanism.

**Methods**

**Study Design**

The X-CELLENT Study was conducted in 2370 outpatients (aged between 40 and 80 years) with essential hypertension. The inclusion criteria included 150 mm Hg ≤ systolic BP <180 mm Hg and 95 mm Hg ≤ diastolic BP <110 mm Hg or 160 mm Hg ≤ systolic BP <180 mm Hg and diastolic BP <90 mm Hg. The exclusion criteria were a history of coronary artery disease, heart failure, stroke or transient ischemic attack, left ventricular hypertrophy, diabetes mellitus (type 1 or type 2), and renal failure. A total of 608 subjects were excluded from the study because of BP criteria not met (n=341), medical reasons (n=197), and nonmedical reasons (n=70). After a 4-week selection and run-in placebo period, 1762 subjects were randomized to receive placebo, indapamide (1.5 mg) sustained release (SR), candesartan (8.0 mg), or amlodipine (5.0 mg), all given once daily in the morning for a treatment period of 12 weeks. Further information concerning the study design can be found in a previous publication. The study protocol was approved by the ethics committees of each country involved, and written informed consent was obtained from each study participant.

**Ambulatory BP Monitoring**

A total of 577 patients participated in an ABPM ancillary study, and 496 of them underwent repeat ABPM after 3-month antihypertensive treatment. The ABPM was performed with SpaceLabs 90202 or 90207 (SpaceLabs, Redmond, WA), 4±3 days before the week 0 and week 12 visits and according to the European Society of Hypertension recommendations. Reproducibility of the ABPM measurements had been reported before. The frequency of the ABPM was every 15 minutes throughout the whole day, and the sleep and wake-up times were reported by participants and recorded for further calculations. Daytime and nighttime were defined as from wake-up to sleep time and from sleep to wake-up time, respectively, for each participant.

**Calculation of BP and Heart Rate Variability**

To minimize the effects of recording errors during the 24-hour ABPM, we used the within-subject mean and SD, weighted for the time interval between consecutive validated readings, to evaluate BP and BPV. Considering nighttime dipping, mean and SD were calculated for the times awake and asleep, as daytime mean, daytime SD, nighttime mean, and nighttime SD. The overall mean and SD, as daily mean and daily SD, were assessed using the following 2 formulas: (1) daily mean=(daytime mean×AT+nighttime mean×ST)/(AT+ST) and (2) daily SD=(daytime SD×AT+nighttime SD×ST)/(AT+ST), where AT and ST stand for awake time and sleeping time in hours.

Another parameter, read-to-read average real variability (ARV), recently proposed by other investigators, was also used to evaluate BPV, as calculated by the following formula:

\[
ARV = \frac{1}{n} \sum_{i=1}^{n} w_i \times |BP_i - BP_{i-1}|
\]

where \(k\) ranges from 1 to N, \(w\) is the time interval between \(BP_{i-1}\) and \(BP_i\), and \(n\) is the number of BP readings in 24 hours.

The mean value of 24-hour heart rate (HR) and HR variability (HRV) were assessed with the same algorithms as the BP.

**Statistical Analysis**

Quantitative and qualitative parameters were presented as mean±SD and absolute number with percentage in parentheses, respectively. We used the ANOVA to compare the mean and variability of BP, as well as biochemical variables, between subjects with different antihypertensive treatments at baseline, and applied the Student t test.
and the generalized linear regression to compared BPV between treatment and placebo groups, before and after adjustment for corresponding BP reduction. Multivariate linear regression analysis was used to investigate determinants of BPV and the reduction in BPV by indapamide SR and amlodipine, separately. Statistical analysis was performed using SAS software, version 9.1 (SAS Institute, Cary, NC). P<0.05 was considered as statistically significant.

**Results**

Table 1 shows the characteristics of subjects at baseline according to randomized antihypertensive therapy. There was no significant difference between groups. After 3-month antihypertensive treatment, 496 subjects underwent a second ABPM, and there was no significant difference in characteristics between subjects with (n=497) or without the repeat ABPM (n=82).

In Table 2, compared with placebo, all 3 of the antihypertensive agents significantly decreased systolic BP in the 3 time frames, daytime, nighttime, and 24 hours (P<0.001 for all), whereas amlodipine and indapamide SR were the only antihypertensive agents to significantly decrease systolic BPV. Specifically, amlodipine significantly decreased systolic BPV in the 3 time frames (P<0.008 for all), and indapamide SR significantly decreased systolic BPV in the daytime (P=0.03) and 24 hours (P=0.03). However, candesartan did not reduce systolic BPV in any time frame. The similar findings are presented in the Figure. In addition, although no significant difference in systolic BPV was observed in the 24-hour read-to-read ARV mode after 3-month different antihypertensive treatments (P=0.08), the reduction in ARV by amlodipine also reached statistical significance (P=0.007). Furthermore, even after adjustment for the corresponding mean BP reduction, the present findings remained unaltered, except that the reduction in daily BPV by indapamide lost its previous significance (P=0.06).

When subjects at baseline were investigated, the determinants of systolic BPV were studied in different modes, such as daytime, nighttime, and 24 hours (P<0.03). However, candesartan did not reduce systolic BPV in any time frame. The similar findings are presented in the Figure. In addition, although no significant difference in systolic BPV was observed in the 24-hour read-to-read ARV mode after 3-month different antihypertensive treatments (P=0.08), the reduction in ARV by amlodipine also reached statistical significance (P=0.007). Furthermore, even after adjustment for the corresponding mean BP reduction, the present findings remained unaltered, except that the reduction in daily BPV by indapamide lost its previous significance (P=0.06).

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as in the daytime, nighttime, 24-hour, and 24-hour read-to-read ARV modes (Table 3). Age, mean systolic BP, and HRV evaluated by the corresponding mode were major determinants of systolic BPV.

As shown in Table 4, the reduction in systolic BPV by amlodipine in different time frames and modes was largely attributable to the reduction in mean systolic BP \( (P<0.006) \) and the reduction in the corresponding HRV \( (P<0.02) \), whereas the corresponding reduction by indapamide SR was only attributed to the reduction in HRV at night \( (P=0.004) \) and mean BP \( (P=0.003) \).

**Discussion**

In the present study, the 3 main findings were as follows: (1) although no effect on BPV was noted for candesartan, 3-month amlodipine treatment decreased systolic BPV in the daytime, nighttime, and 24 hours, and 3-month indapamide SR therapy reduced systolic BPV in the daytime and 24 hours; (2) the major determinants of baseline systolic BPV were age, mean systolic BP, and HRV; and (3) the reduction in systolic BPV by amlodipine was attributable to the reduction in mean systolic BP and in HRV, whereas the cause of the corresponding reduction by indapamide SR was largely unknown.

In the literature, several investigators have shown that calcium channel blockers significantly reduce BPV, as assessed by the SD of 24-hour BP\(^{17-19}\) and which is in line with the present study. However, some of these investigators also reported that, when BPV is assessed by coefficient of variability, calculated as SD divided by mean BP, the previous significant reduction is absent\(^{17,19}\). In this respect, we preferred to assess BPV by using SD, for 2 main reasons. First, from a statistical point of view, it is not valid to evaluate the reduction in BPV independent of BP level with a robust division as using coefficient of variability, because some statistical efficacy would be lost. For instance, in the present study, we did not find a significant decrease of BPV in terms of coefficient of variability, but the statistical significance was preserved when we compared the after-treatment BPV between different treatment groups, after adjustment for the mean value of BP (data not shown). Second, from a prognostic viewpoint, a close association of target-organ damage, cardiovascular events, and mortality with SD of 24-hour BP has frequently been reported in various population-based studies\(^{1-4,8,10,11}\) but the prognostic value concerning the coefficient of variability of BP is very limited in literature. Accordingly, we assessed the BPV by SD of 24-hour BP and found that amlodipine and indapamide SR were effective antihypertensive agents in reducing BPV, independent of mean BP, in different time frames and modes.

BPV is a multifaceted phenomenon influenced by human activity, psychology, compliance to antihypertensive treat-

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**Table 3. Determinants of Systolic Blood Pressure Variability in Subjects at Baseline**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Daytime SD</th>
<th></th>
<th></th>
<th>Nighttime SD</th>
<th></th>
<th></th>
<th>Daily SD</th>
<th></th>
<th>ARV</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \beta )</td>
<td>Partial ( \chi^2 )</td>
<td>( P )</td>
<td>( \beta )</td>
<td>Partial ( \chi^2 )</td>
<td>( P )</td>
<td>( \beta )</td>
<td>Partial ( \chi^2 )</td>
<td>( P )</td>
<td>( \beta )</td>
</tr>
<tr>
<td>Age, y</td>
<td>0.06</td>
<td>0.03</td>
<td>&lt;0.001</td>
<td>0.07</td>
<td>0.03</td>
<td>&lt;0.001</td>
<td>0.07</td>
<td>0.06</td>
<td>&lt;0.001</td>
<td>0.05</td>
</tr>
<tr>
<td>Mean SBP, mm Hg</td>
<td>0.06</td>
<td>0.05</td>
<td>&lt;0.001</td>
<td>0.01</td>
<td>0.01</td>
<td>0.14</td>
<td>0.05</td>
<td>0.06</td>
<td>&lt;0.001</td>
<td>0.04</td>
</tr>
<tr>
<td>HR SD, bpm</td>
<td>0.21</td>
<td>0.02</td>
<td>&lt;0.001</td>
<td>0.29</td>
<td>0.04</td>
<td>&lt;0.001</td>
<td>0.17</td>
<td>0.01</td>
<td>0.003</td>
<td>0.25</td>
</tr>
</tbody>
</table>

*Age, sex, and body mass index, as well as mean systolic blood pressure, mean heart rate, and its variability calculated with the same algorithm in the same period as blood pressure variability, were considered in the linear regression models. SBP indicates systolic blood pressure; HR, heart rate; ARV, the read-to-read average real variability, which was calculated by the formula mentioned in the Methods. Daytime SD=time-weighted SD of 24-h systolic blood pressure readings during awake time; nighttime SD=time-weighted SD of 24-h systolic blood pressure readings during sleeping time; Daily SD=(daytime SD×awake time + nighttime SD×sleeping time)/(awake time + sleeping time).*
duration. However, with the significant reduction in BPV small number of subjects and the relatively short therapeutic frames and modes. The study's limitations were the relatively son among the 4 treatment groups, and in 4 different time double-blind, placebo-controlled design, enabling compari-

dening. The similar finding was also achieved in sinoaortic-creased BPV was significantly associated with arterial stiff-

ment, and the nervous and humoral systems, and reflects the magnitude of BP fluctuation. The determinants of BPV were investigated in several population studies, in which age, BP, HR, and sex were frequently reported. In the present study, we also indicated that age and BP were major determinants of BPV. We also took HRV into account and found that it was another important factor of BPV. From a physiological point of view, autonomic nervous system (ANS) regulates BP and HR synchronously and, therefore, contributes to stabilizing their fluctuation. The close association of BPV with HRV in different time frames is probably a universal phenomenon, which could be a consequence of the ANS regulation. Furthermore, the significant relationship between the reduction in BPV and in HRV, consistently observed in the present study, indicates a proportional decrease in the fluctuation of both BP and HR, which is probably attributable to amelioration of the ANS regulation. However, the pharmaceutical mechanism is still unknown.

In literature, there is limited information concerning the underlying mechanism of reduction in BPV. In the amlodipine group of the present study, we found that the reduction in BPV was mainly attributed to the reduction in BP and the reduction in HRV. On the other hand, in the indapamide SR group, we only found limited information with regard to determinants of the reduction in BPV. This difference indicates the distinct mechanism of those 2 antihypertensive agents. In the present study, we found that the effect of amlodipine on BPV was probably attributable to lowering BP and ameliorating the ANS regulation, whereas mechanism of indapamide SR in reducing BPV is largely unknown. Dabire et al. reported that, in spontaneous hypertensive rats, increased BPV was significantly associated with arterial stiffening. The similar finding was also achieved in sinoaorticedenervated rats by Lacolley et al. However, whether indapamide SR could possibly reduce BPV through arterial destiffening is still unclear, and further studies are warranted.

The strengths of the present study include the randomized, double-blind, placebo-controlled design, enabling comparison among the 4 treatment groups, and in 4 different time frames and modes. The study’s limitations were the relatively small number of subjects and the relatively short therapeutic duration. However, with the significant reduction in BPV after 3-month treatment, we had sufficient statistical power to confirm our findings.

Perspectives

In this study, we have shown that age, BP, and HRV were the major determinants of BPV. Amlodipine and indapamide SR were the only effective antihypertensive agents in decreasing BPV by lowering BP or ameliorating the ANS regulation or both. Their combination might help to optimize such properties. However, the mechanism underlying the reduction in BPV has yet to be clarified, especially its potential interaction with arterial stiffness and/or reflection waves. Given the increasing importance of BPV in the prevention of stroke, as well as other target-organ damage, further studies are undoubtedly warranted.

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Disclosures

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Table 4. Determinants of the Reduction of Systolic Blood Pressure Variability by Amlodipine and Indapamide Sustained Release

<table>
<thead>
<tr>
<th>Variables</th>
<th>Daytime SD Reduction</th>
<th>Nighttime SD Reduction</th>
<th>Daily SD Reduction</th>
<th>ARV Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta$</td>
<td>Partial R²</td>
<td>P</td>
<td>$\beta$</td>
</tr>
<tr>
<td>Subjects taking amlodipine (n=123)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean SBP reduction, mm Hg</td>
<td>0.08</td>
<td>0.06</td>
<td>0.005</td>
<td>0.02</td>
</tr>
<tr>
<td>HR SD reduction, bpm</td>
<td>0.19</td>
<td>0.04</td>
<td>0.02</td>
<td>0.46</td>
</tr>
<tr>
<td>Subjects taking indapamide SR (n=133)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean SBP reduction, mm Hg</td>
<td>0.04</td>
<td>0.02</td>
<td>0.14</td>
<td>0.01</td>
</tr>
<tr>
<td>HR SD reduction, bpm</td>
<td>0.01</td>
<td>0.01</td>
<td>0.89</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Age, sex, body mass index, as well as systolic blood pressure reduction and the reduction of heart rate variability calculated with the same algorithm in the same period as blood pressure variability, were considered in the linear regression models. Reduction indicates the after-treatment value minus the corresponding value at baseline. SBP indicates systolic blood pressure; HR, heart rate; ARV, the read-to-read average real variability, which was calculated by the formula mentioned in the Methods. Daytime SD=time-weighted SD of 24-h systolic blood pressure readings during awake time; nighttime SD=time-weighted SD of 24-h systolic blood pressure readings during sleeping time; daily SD=(daytime SD×awake time+nighttime SD×sleeping time)/(awake time+sleeping time).


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