Short-term blood pressure variability in renovascular hypertension and in severe and mild essential hypertension

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ABSTRACT

This study was designed to examine short-term blood pressure variability (BPV) in patients with different severity and forms of chronic medically treated hypertension. Power spectral analysis of BPV was performed from continuous finger blood pressure (Finapres) recordings. Ten patients with renovascular hypertension (RVHT), 34 with severe essential hypertension (SEHT) and 29 with mild essential hypertension (MEHT) as well as healthy age- and sex-matched control subjects were studied. The RVHT group was characterized by reduced low frequency (LF) power of both systolic and diastolic BPV ($P = 0.004$ and $P = 0.003$ respectively) when compared with the control group. There was also a tendency to lower total power of diastolic BPV ($P = 0.094$). On the contrary, the SEHT group had increased total power of diastolic BPV ($P = 0.044$). However, in the SEHT group, we found no differences in the LF and high frequency power of systolic and diastolic BPV when compared with controls. The MEHT group presented with lower LF power of systolic and diastolic BPV ($P = 0.028$ and $P = 0.003$ respectively) and, in addition, high frequency power of diastolic BPV was lower than in the control group ($P = 0.020$). When the hypertensive groups were compared with each other, total power and LF power of diastolic BPV ($P = 0.043$ and $P = 0.039$ respectively) were lower in the RVHT group than in the SEHT group. In addition, total power of diastolic BPV was lower ($P = 0.030$) in the MEHT group than in the SEHT group. No differences were observed in BPV between the RVHT and MEHT groups. The results show that BPV in hypertensive patients groups behaved differently. This suggests that both the aetiology and severity of hypertension have a significant influence on short-term BPV measured in laboratory conditions and that different control mechanisms are operating in these clinically distinctly different hypertension groups.

INTRODUCTION

Blood pressure variability (BPV) has been used to evaluate the features of cardiovascular control mechanisms. Blood pressure fluctuates spontaneously and in response to internal and external stimulation. This variability reflects the general cardiovascular regulation in which autonomic nervous system has a significant role [1]. In early stages of hypertension, sympathetic tone is increased [2–4] and parasympathetic activity is decreased [5]. This imbalance is thought to be important in the maintenance of elevated blood pressure and in the development of cardiovascular complications of hypertension. On the other hand, target organ damage has been shown to be

Key words: blood pressure variability, essential hypertension, renovascular hypertension.

Abbreviations: BPV, blood pressure variability; LF, low frequency; LV, left ventricular; LVM, LV mass; LVMi, LVM index; HF, high frequency; MEHT, mild essential hypertension; RVHT, renovascular hypertension; SEHT, severe essential hypertension; VLF, very-LF.

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related to diurnal BPV, and thus BPV may have prognostic value in hypertensive patients.

Medical technology provides reliable tools for non-invasive continuous blood pressure recording and methods for assessing short-term BPV with spectral analysis [6–8]. This technique allows us to describe and quantify the different frequency components that characterize BPV such as influence of respiration and other slower physiological rhythms that are controlled by the autonomic nervous system [9].

There are only few studies on short-term BPV in hypertensive patients [7,8,10–12]. The present study was undertaken in order to evaluate short-term BPV in three clinically distinctively different groups: renovascular hypertension (RVHT) and severe and mild essential hypertension (SEHT and MEHT respectively). In particular, we were interested in investigating whether BPV in subjects with MEHT differs from that of SEHT, and whether BPV in subjects with SEHT differs from that of RVHT.

**METHODS**

**Study design**

Three groups of patients, representing different types and severity of hypertension (RVHT, SEHT and MEHT), were studied and compared with age- and sex-matched healthy control subjects, as well as with each other. All patients underwent a careful assessment of the type of hypertension and measurement of ambulatory and office blood pressure. A clinical history, including vascular and other diseases, medical treatment, duration of hypertension, family history of hypertension and smoking habits, were obtained from every patient. Patients in the RVHT and SEHT groups underwent captopril radionuclide test, renal digital subtraction angiography and clinical routine laboratory tests [13,14].

The study protocol was approved by the Ethics Committee of the Kuopio University Hospital. Patients gave written informed consent before participating in the study.

**Study population**

The clinical characteristics of the hypertensive groups and age- and sex-matched control groups are shown in Table 1.

**RVHT and SEHT**

Patients in the RVHT and SEHT groups were selected from 54 consecutive patients, who were referred for evaluation of possible secondary hypertension to Kuopio University Hospital [15]. They all fulfilled the clinical criteria for moderate or high indication of secondary hypertension [16]. The referral criteria for a moderate indication of hypertension were: office diastolic blood pressure \( \geq 115 \text{ mmHg} \), refractoriness to standard treatment, abrupt onset of hypertension with age under 30 or over 55 years. The criteria for a high indication of hypertension were: malignant hypertension, elevation of serum creatinine during ACE (angiotensin–converting enzyme) inhibitor therapy and known asymmetry in renal size or recurrent left ventricular (LV) failure [17]. The exclusion criteria for the study were known non-vascular nephropathies, Type I diabetes and aortic stenosis. Fourteen patients who had significant renal arterial diameter stenosis (> 50 %) in renal digital subtraction angiography and who were cured or improved after 6 months after renal angioplasty were considered to have RVHT. Four patients were excluded because of inadequate finger blood pressure measurements, thus leaving ten patients for final statistical analysis. RVHT was caused by atherosclerosis in nine patients and fibromuscular dysplasia in one patient. No other forms of secondary hypertension were found.

The remaining 40 patients were classified to have SEHT. Finger blood pressure recordings from 34 of these patients were acceptable for further analysis. Three of these patients had mild coronary artery disease and one had previous stroke.

**MEHT**

In addition, 30 MEHT patients were recruited separately during the run-in phase of an ongoing clinical trial [15,18]. Exclusion criteria for this trial were severe hypertension or any other chronic disease. Generally, their hypertension was in relatively good care. One of the patients had inadequate finger blood pressure recording and was excluded from the final analyses. Two patients had mild coronary artery disease.

**Control subjects**

Healthy age- and sex-matched control subjects were selected for each hypertensive group from another study performed during the same period with similar BPV measurement methods [19]. All control subjects were in good health and free from systemic diseases, and none of them smoked or was taking any cardiovascular medication.

**Assessment of short-term BPV**

Continuous non-invasive finger blood pressure was recorded (Finapres; Ohmeda, Inc., Englewood, CO, U.S.A.) to assess short-term BPV. The middle finger of the right hand was used for the measurements and the right arm was kept at the level of the heart. ECG recordings were obtained simultaneously. The signals were analysed off-line with a menu-driven software package (CAFTS; Medikro Oy, Kuopio, Finland) [19,20]. Mean values of systolic and diastolic blood pressure and a power spectral analysis of systolic and diastolic BPV were obtained from...
steady-state recordings of sinus rhythm containing at least 250 beats.

All recordings were performed in a dim and quiet room between 08:00 and 12:00 in a supine position after 15–30 min rest. When blood pressure and heart rate had stabilized, subjects started to breath with a frequency according to a paced signal for 10 min with normal tidal volume. Recordings from eleven patients were not acceptable due to artefact signals and/or ectopic beats and were excluded.

Frequency domain analysis of BPV was performed using a modified autoregressive model (model order 14). The powers of each frequency bands were calculated as an integral under the respective power spectral density and expressed in absolute units (mmHg$^2$). Total power (frequency range 0–0.5 Hz) was divided into three frequency bands: high-frequency (HF) band (0.15–0.4 Hz), low-frequency (LF) band (0.07–0.15 Hz) and very-LF (VLF) band (< 0.07 Hz). Normalized units (nu) of BPV were calculated as follows: LF$_{nu}$ = LF power/(total power – VLF power), and HF$_{nu}$ = HF power/(total power – VLF power).

Before the assessment of short-term BPV, β-blockers were reduced within 4 days to at least a half, and no β-blockers were taken during the 2 days before measurements. In 16 SEHT patients this was not possible, but the dose was reduced to a quarter of normal. Diuretics and ACE inhibitors were suspended for at least 3 days and at least one week respectively, prior to the measurements.

### Other measurements

Office blood pressure was measured with a standard sphygmomanometer after 10 min rest in the sitting position. A mean of three consecutive blood pressure measurements was used for further analysis. Ambulatory blood pressure monitoring for 24 h was started immediately after the office blood pressure measurements during a typical weekday by using a previously validated recorder (Space Labs 90207; Redmond, WA, U.S.A.) [21,22]. Patients used their normal antihypertensive treatment during the measurements.

ECGs were recorded (Aloka 870; Aloka Ltd., Tokyo, Japan) according to the recommendations of The Biochemical Society.

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**Table 1: Characteristics of the subjects**

Values are means ± S.E.M., numbers of cases or percentages. *P < 0.05, **P < 0.01 and ***P < 0.001 compared with controls. NA, not available.

<table>
<thead>
<tr>
<th>Variable</th>
<th>RVHT Patients (n = 10)</th>
<th>Controls (n = 10)</th>
<th>SEHT Patients (n = 34)</th>
<th>Controls (n = 34)</th>
<th>MEHT Patients (n = 29)</th>
<th>Controls (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>3/7</td>
<td>3/7</td>
<td>20/14</td>
<td>20/14</td>
<td>15/14</td>
<td>15/14</td>
</tr>
<tr>
<td>Age (years)</td>
<td>61 ± 6</td>
<td>60 ± 5</td>
<td>46 ± 2</td>
<td>46 ± 3</td>
<td>59 ± 1</td>
<td>56 ± 2</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166 ± 2</td>
<td>163 ± 3</td>
<td>171 ± 2</td>
<td>171 ± 2</td>
<td>167 ± 1</td>
<td>169 ± 2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65 ± 2</td>
<td>63 ± 3</td>
<td>81 ± 3</td>
<td>71 ± 2</td>
<td>79 ± 2*</td>
<td>68 ± 2</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>21.9 ± 0.7</td>
<td>23.4 ± 0.7</td>
<td>27.5 ± 0.7*</td>
<td>23.9 ± 0.4</td>
<td>27.8 ± 0.6*</td>
<td>24.0 ± 0.4</td>
</tr>
<tr>
<td>Office blood pressure†</td>
<td>Systolic (mmHg)</td>
<td>171 ± 10</td>
<td>151 ± 8</td>
<td>153 ± 4**</td>
<td>140 ± 4</td>
<td>142 ± 3</td>
</tr>
<tr>
<td>Diastolic (mmHg)</td>
<td>96 ± 5</td>
<td>88 ± 3</td>
<td>97 ± 2***</td>
<td>85 ± 2</td>
<td>88 ± 2*</td>
<td>83 ± 2</td>
</tr>
<tr>
<td>Ambulatory blood pressure†</td>
<td>Systolic (mmHg)</td>
<td>151 ± 6</td>
<td>NA</td>
<td>141 ± 2</td>
<td>NA</td>
<td>132 ± 2</td>
</tr>
<tr>
<td>Diastolic (mmHg)</td>
<td>87 ± 5</td>
<td>NA</td>
<td>88 ± 2</td>
<td>NA</td>
<td>84 ± 1</td>
<td>NA</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>67 ± 3</td>
<td>NA</td>
<td>71 ± 2</td>
<td>NA</td>
<td>71 ± 2</td>
<td>NA</td>
</tr>
<tr>
<td>LVMi (g/m²)</td>
<td>171 ± 19</td>
<td>NA</td>
<td>151 ± 10</td>
<td>NA</td>
<td>151 ± 10</td>
<td>NA</td>
</tr>
<tr>
<td>Creatine clearance (ml/min)</td>
<td>57.4 ± 6.5</td>
<td>NA</td>
<td>92.9 ± 5.1</td>
<td>NA</td>
<td>85.8 ± 3.1</td>
<td>NA</td>
</tr>
<tr>
<td>Duration of hypertension</td>
<td>&lt; 2 years</td>
<td>30 %</td>
<td>20 %</td>
<td>4 %</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2–10 years</td>
<td>60 %</td>
<td>--</td>
<td>21 %</td>
<td>41 %</td>
<td>--</td>
<td>-</td>
</tr>
<tr>
<td>&gt; 10 years</td>
<td>10 %</td>
<td>--</td>
<td>59 %</td>
<td>55 %</td>
<td>--</td>
<td>-</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>30 %</td>
<td>0 %</td>
<td>18 %</td>
<td>0 %</td>
<td>10 %</td>
<td>0 %</td>
</tr>
<tr>
<td>Use of antihypertensive drugs</td>
<td>0 %</td>
<td>100 %</td>
<td>11 %</td>
<td>100 %</td>
<td>7 %</td>
<td>100 %</td>
</tr>
<tr>
<td>1</td>
<td>30 %</td>
<td>--</td>
<td>6 %</td>
<td>83 %</td>
<td>--</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>40 %</td>
<td>--</td>
<td>24 %</td>
<td>10 %</td>
<td>--</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>20 %</td>
<td>--</td>
<td>44 %</td>
<td>--</td>
<td>0 %</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>0 %</td>
<td>--</td>
<td>15 %</td>
<td>--</td>
<td>0 %</td>
<td>-</td>
</tr>
</tbody>
</table>

† Obtained under regular antihypertensive treatment.
Continuous finger blood pressure and BPV in the hypertensive and control groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>RVHT Patients (n = 10)</th>
<th>Controls (n = 10)</th>
<th>P</th>
<th>SEHT Patients (n = 34)</th>
<th>Controls (n = 34)</th>
<th>P</th>
<th>MEHT Patients (n = 29)</th>
<th>Controls (n = 29)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic</td>
<td>146 ± 8</td>
<td>122 ± 6</td>
<td>0.059</td>
<td>143 ± 3</td>
<td>123 ± 3</td>
<td>0.001</td>
<td>130 ± 5</td>
<td>120 ± 3</td>
<td>0.157</td>
</tr>
<tr>
<td>Diastolic</td>
<td>70 ± 6</td>
<td>64 ± 4</td>
<td>0.171</td>
<td>74 ± 2</td>
<td>63 ± 2</td>
<td>0.001</td>
<td>60 ± 2</td>
<td>63 ± 2</td>
<td>0.257</td>
</tr>
<tr>
<td>LF</td>
<td>1.4 ± 0.5</td>
<td>3.4 ± 0.7</td>
<td>0.004</td>
<td>3.8 ± 0.6</td>
<td>3.0 ± 0.5</td>
<td>0.737</td>
<td>3.0 ± 0.5</td>
<td>3.9 ± 0.7</td>
<td>0.028</td>
</tr>
<tr>
<td>LFns</td>
<td>0.1 ± 0.01</td>
<td>0.2 ± 0.03</td>
<td>0.022</td>
<td>0.2 ± 0.03</td>
<td>0.2 ± 0.03</td>
<td>0.266</td>
<td>0.1 ± 0.02</td>
<td>0.2 ± 0.02</td>
<td>0.032</td>
</tr>
<tr>
<td>HF</td>
<td>6.8 ± 2.8</td>
<td>6.3 ± 2.0</td>
<td>0.733</td>
<td>5.1 ± 0.9</td>
<td>3.7 ± 0.4</td>
<td>0.202</td>
<td>4.0 ± 0.6</td>
<td>3.7 ± 0.4</td>
<td>0.621</td>
</tr>
<tr>
<td>HFns</td>
<td>0.6 ± 0.2</td>
<td>0.4 ± 0.2</td>
<td>0.430</td>
<td>0.3 ± 0.05</td>
<td>0.2 ± 0.03</td>
<td>0.861</td>
<td>0.2 ± 0.04</td>
<td>0.3 ± 0.07</td>
<td>0.672</td>
</tr>
</tbody>
</table>

American Society of Echocardiography [23]. LV mass (LVM) was calculated using the formula: LVM = 1.04 · [(LV end-diastolic diameter3 + septum3 + posterior wall3) - LV end-diastolic diameter3] - 13.6 g [24]. The LVM index (LVMi) was calculated by dividing the LVM by the body surface area (g/m2) [25].

**Statistical analysis**

Data were analysed by the SPSS for Windows statistical package (version 9.0; SPSS Inc., Chicago, IL, U.S.A.). A logarithmic transformation was performed before statistical analysis if the variable was not normally distributed. Paired Student’s t test and ANOVA were used for group comparisons. Data are expressed as means ± S.E.M., numbers of cases or percentages. Results were considered statistically significant at P < 0.05.

**RESULTS**

**Clinical characteristics**

Clinical characteristics of the study subjects are shown in Table 1. Comparison between hypertensive groups (age, gender and body mass index as covariates) showed that the RVHT and SEHT groups had higher systolic office blood pressure than the MEHT group (both P = 0.002). RVHT and SEHT groups did not differ from each other in this respect. In the RVHT group, 24 h systolic blood pressure was higher than in SEHT and MEHT groups (P = 0.015 and P = 0.007 respectively). According to ambulatory blood pressure measurements, 70 % of patients in the RVHT group, 69 % of patients in the SEHT group and 79 % of patients in the MEHT group were non-dippers (i.e., patients had lower blood pressure during the night-time than during the daytime; comparison between groups was not significant). LV hypertrophy (LVMi > 125 g/m2 [26]) was common in all hypertensive groups (comparison between groups was not significant). In the SEHT group, 11 % of patients had newly diagnosed severe hypertension and therefore did not use any antihypertensive medication. In the RVHT and SEHT groups, 33 % and 30 % of patients respectively, used a quarter of their normal β-blocker dose (difference between groups was not significant).

**BPV**

**RVHT**

In the RVHT group, total power of diastolic BPV tended to be lower than in the control group (Table 2). LF power of both systolic and diastolic BPV were lower in the RVHT group when compared with the healthy control subjects. HF power of systolic and diastolic BPV of the RVHT group and controls did not differ from each other.

**SEHT**

In the SEHT group, total power of systolic BPV tended to be higher, and diastolic BPV was significantly higher when compared with the control group (Table 2). However, the absolute values of LF and HF powers of both systolic and diastolic BPV did not differ from the control subjects.
MEHT
In the MEHT group, total power of systolic and diastolic BPV did not differ from the control group (Table 2). On the other hand, LF power of both systolic and diastolic BPV, as well as HF power of diastolic BPV, were lower in the MEHT group when compared with the control group.

Comparison between hypertensive groups
Systolic and diastolic finger blood pressures did not differ between the RVHT and SEHT groups (Table 2). The MEHT group had lower systolic finger blood pressure than the SEHT group ($P = 0.015$) and lower diastolic blood pressure than the RVHT ($P = 0.009$) and SEHT groups ($P = 0.004$).

Systolic BPV did not differ between the hypertensive groups; however, total power and LF power of diastolic BPV ($P = 0.043$ and $P = 0.039$ respectively) were lower in the RVHT group when compared with the SEHT group, but no significant differences were found between the RVHT and MEHT groups. Total power of diastolic BPV in the SEHT group was higher ($P = 0.030$), and HF power of systolic BPV tended to be higher ($P = 0.058$) than in the MEHT group.

DISCUSSION
Blood pressure shows rhythmic spontaneous oscillation which can be quantified from continuous blood pressure recordings. Most of the previous studies have focused on systolic BPV and data on diastolic BPV are scant. Total power, LF and VLF powers of BPV represent on systolic BPV and data on diastolic BPV are scant. Most of the previous studies have focused which can be quantified from continuous blood pressure recordings. In our present study, short-term BPV was characterized by impaired heart rate variability [31] and BPV [8]. The normal BPV in MEHT patients may indicate that effective antihypertensive therapy results not only in a decrease of blood pressure, but also in normalization of cardiac autonomic regulation. Normalization of autonomic regulation may also contribute to the beneficial effects of antihypertensive therapy on prognosis [32].

There are some confounding factors in the present study that might potentially add statistical noise to the data. The number of patients in the RVHT group remained relatively small. During 4 years, we identified 54 patients with moderate or high indication of secondary ( renovascular) hypertension. Of these, 26 % turned out to have RVHT, which can be considered successful screening for RVHT. Another limitation is the age difference between the hypertensive groups. To overcome this problem, healthy age- and sex-matched control subjects were used and age adjustment was used in statistical analyses. In addition, patient selection is always difficult in case of multipharmacy, because, in severely diseased patients, all medication cannot be removed. When the present study was planned, it was considered neither clinically nor ethically possibly to discontinue all antihypertensive medication in the most severely hypertensive patients. The use of $\beta$-blockers attenuates sympathetic activity and could possibly reduce short-term BPV. However, in our present study, very low $\beta$-blocker medication was used in equal amounts in both
RVHT and SEHT patients and thus, cannot explain the difference between these groups. Most importantly, a great majority of the patients were without any antihypertensive medication.

To evaluate the reproducibility of our BPV measurements, two persons familiar with cardiovascular dynamic analysis performed repeated analysis from a subgroup of hypertensive patients (n = 20). They independently selected a visually estimated stationary series of recordings. Correlation coefficients were generally high and percentage coefficients of variation were low. As regards to systolic and diastolic LF power, the correlation coefficients were 0.992 and 0.919 respectively. For HF powers, the corresponding values were 0.994 and 0.977 respectively. The percentage coefficients of variation were all under 0.5 %.

In summary, our present results suggest that both the aetiology and the severity of hypertension influence short-term BPV. The mechanisms and clinical and prognostic significance of short-term BPV needs to be studied further with a larger patient population.

REFERENCES


