Reproducibility of arterial pressure measured in the ELSA-Brasil with 24-hour pressure monitoring

ABSTRACT

OBJECTIVE: To determine the reproducibility of casual arterial pressure measurement and to confirm pressure diagnosis by monitoring of participants in the ELSA-Brasil (Estudo Longitudinal de Saúde do Adulto – Brazilian Longitudinal Study for Adult Health).

METHODS: Casual blood pressure was measured with an oscilometric device. A sub-sample of participants (N = 255) from Espírito Santo state (Southeastern Brazil) was reevaluated using the same methodology following one to ten weeks and, in addition, underwent arterial blood pressure monitoring. Diagnosis of hypertension used cut off points of 140/90 mmHg for casual pressure and 130/80 mmHg for arterial blood pressure monitoring. White coat hypertension was defined as the presence of hypertension in casual blood pressure and normal arterial blood pressure monitoring, and converse findings characterized masked hypertension.

RESULTS: Data are from 230 participants that on the two occasions were free from antihypertensive medication (N1 = 153) or under the same antihypertensive regimen (N2 = 77). Normotension was confirmed by arterial blood pressure monitoring in 120 out of 134 participants of the N1 group. In N2, blood pressure control was confirmed by arterial blood pressure monitoring in 43 of 54 participants with controlled hypertension per casual blood pressure. Overall diagnostic concordance between casual blood pressure and arterial blood pressure monitoring was 78% (kappa = 0.44). In the N1 group, six subjects (4%) presented white coat hypertension, and 23 subjects (25%) presented with masked hypertension.

CONCLUSIONS: Diagnostic concordance between casual blood pressure and arterial blood pressure monitoring was moderate. The rigorous standardization of casual blood pressure measurement adopted in the ELSA-Brasil study was able to reduce white coat hypertension. The high frequency of masked hypertension may suggest that pressure values obtained by arterial blood pressure monitoring indicate an elevated degree of stress at work.

INTRODUCTION

Arterial hypertension (AH) is one of the most significant risk factors in developing vascular lesions and contributes to the emergence of dysfunctions in key organs such as the heart, kidneys and brain. From an epidemiological point of view, AH constitutes a serious public health problem, due to its significant contribution to mortality in the adult population of practically all countries including Brazil. Transversal studies carried out in different areas of the country show a prevalence of between 20% and 40% in the population aged over 25.4

Diagnosing AH can be deemed simple, as it depends only on correctly measuring blood pressure. However, blood pressure (BP) is a variable which can be influenced by a series of factors specific to the individual in question, such as the level of stress, time of day, food intake and having a full or empty bladder, among others. Moreover, the measurement obtained is dependent on the place it is taken and the person who takes it.14 With the aim of reducing false diagnosis, the establishment of more precise methods has been sought, including measuring blood pressure outside of the medical offices, in order to obtain a correct diagnosis of the disease or to verify the efficacy of medications aimed at treating it.16 In spite of the large majority of cases of arterial hypertension being incurable, when the disease is controlled the individual may have a life expectancy virtually equal to that of non-hypertensive individuals.4,21 Treatment, however, depends on a correct diagnosis, as unnecessary treatments increase health care costs and may place the patient at additional risk, as anti-hypertensive medications have significant side effects, especially when used over the long term.

Standard diagnosis of AH consists of blood pressure being taken in the medical office. However, in many cases, the measure taken does not represent the individual’s actual arterial pressure, thus calling for repeated measurements in order to confirm the diagnosis.4,20 Stress produced at the moment of taking blood pressure, in many individuals, leads to a false positive diagnosis, a phenomenon known as “white coat hypertension”.12 Ambulatory monitoring of blood pressure (MAPA), or measuring blood pressure at home has been recommended to reduce false diagnoses of high blood pressure.10,14 On the other hand, there are also individuals who have normal blood pressure values during their clinical appointment, but then show high levels when evaluated through MAPA, characterized as “masked hypertension”.18

In the Brazilian Longitudinal Study for Adult Health (ELSA-Brasil), blood pressure measurements will be used to determine the prevalence of AH at the baseline and as a risk factor for cardiovascular outcomes in the cohort monitoring.2 A range of strategies were adopted for obtaining baseline values for pressure within rigorous standardization, aiming to keep false diagnoses to a minimum. However, as there is no method which simultaneously includes 100% of sensitivity and specificity, it was decided to carry out a study on a subsample of ELSA participants in Espírito Santo (ES, southeastern Brazil), aiming to determine the reproducibility of arterial pressure measurements obtained in the study and, in addition, to determine the proportion of individuals exhibiting white coat or masked hypertension, analyzing the MAPA.

METHODS

After carrying out baseline exams, the participants of ELSA-ES (N = 1,055), regardless of the blood pressure (BP) values obtained or use of anti-hypertensive medication, were invited to participate in a supplementary re-evaluation study of BP at another time to be arranged. During the re-evaluation, the casual BP measurement carried out in the baseline of the ELSA would be repeated and, in addition, 24 hours MAPA (MAPA-24h). Invitations were issued according to the availability of MAPA equipment and the new measurements were obtained between one and ten weeks after the baseline exams. A total of 255 participants were included in the supplementary study, of whom 25 were excluded from analysis: in five cases, the minimum number of MAPA measurements needed to validate the exam were not obtained1 (16 measurements while awake and eight while sleeping); 13 were excluded because they had begun to take anti-hypertensive medication after the baseline exams; and seven were excluded because they were taking medication at the time of the baseline exams and had subsequently altered their treatment regime by the time the supplementary study was carried out. The data shown refer, therefore, to the 230 participants who were not taking medication or were following the same anti-hypertensive treatment regime during both BP evaluations.

Casual BP measurement was carried out using the same methodology both times: in the morning, 10 to 14 hours fasting, resting 5-10 minutes in a seated position with feet on the floor and an empty bladder. The cuff used was chosen according to the arm length and circumference. The room in which the measurements took place was quiet and with a temperature between 22°C and 24°C. Baseline exams used the left arm to take measurements. The supplementary study took measurements from both arms; comparison between measurements was based on data for the left arm. The clinical measurement of arterial pressure was obtained using an oscillometric device (Omron705CP Intellisense), with three measurements taken, with a one-minute-interval between each measurement. BP was calculated by the arithmetic mean of the two last results.
In the supplementary study, after the clinical measurement of BP and obtaining additional data through an interview (confirmation of fasting and medications used) the MAPA apparatus (Spacelabs 9075, EUA) was attached to the left arm and the individual instructed to return the next morning. The individuals were instructed to follow their normal routine, albeit avoiding strenuous physical activity. The apparatus was programmed to measure BP every 15 minutes while awake and every 20 minutes while sleeping. Mean blood pressure was calculated for the 24-h period, for waking and for sleeping, according to the patients’ diary records.

The presence of AH or non-controlled BP with the use of antihypertensive medication was assumed for by the presence of AP ≥ 140/90 mmHg in the casual measurement mean. Using MAPA, the cut off points used were mean pressure ≥ 130/80 mmHg in the 24h period or ≥ 135/85 mmHg while awake. The categorical variables are shown as percentages and the Chi-squared test (χ²) was used to test the assumption of homogeneity of the proportions. The Kolmogorov-Smirnov test was used to check the normality of continuous variables. The means for the different pressure measurements was carried out using Anova one-way, followed by the Tukey test. The intra-class correlation coefficient was used to determine reproducibility between the pressure measurements. The degree of agreement between the methods of classifying the individuals’ blood pressure was assessed using the kappa statistic (k) and reproducibility between measurements was obtained using the Bland-Altman method. The continuous variables are shown as mean and standard deviation (sd). Statistical significance was established as p < 0.05. The data were analyzed using the SPSS statistical package, version 17.0.

This study was approved by the Ethical Research Committee of the Centro de Ciências da Saúde of the Universidade Federal do Espírito Santo (nº 140/08) and all participants signed consent forms.

RESULTS

The subsample of 230 participants, of the 1,055 included in the ELSA-ES, maintained the same principal demographics as the whole cohort. Thus, the distribution of characteristics in the ELSA-ES and in the respective subsample were similar (p < 0.05) with regard to the proportion of females (53% versus 54%), mean age (54.0 SD = 9.6 versus 53.3 SD = 8.9 years) and body mass index (27.0 SD = 4.8 versus 26.7 SD = 4.5 kg/m²).

Of the 230 participants (106 men and 124 women) included in the analysis, 153 (66.5%) were not taking anti-hypertensive medication at the time of the two evaluations. Of these, 19 were rated hypertensive according to the ELSA measurements, 21 according to the supplementary study and 33 according to the mean BP values from both MAPA-24h and MAPA-awaking (Table 1). Using the cut off points defined by MAPA, there was an increase in the number of AH diagnoses in individuals not taking medication and a reduction in the number of individuals with hypertension controlled by medication. The proportion of agreement in the diagnoses, considering the ELSA casual measurement and that of the supplementary study, was 87% (k = 0.60). As expected, there was a slight decrease in agreement, to 84%, (k = 0.58) when considering the clinical measurement in the supplementary study and the MAPA, and to 78% (k = 0.44) on establishing diagnosis comparing the measurement of casual AP in the ELSA with MAPA results.

Comparing mean pressure measurements at the three times, both the pressure values and the heart rate were lower in the measurements carried out in the ELSA and greater in the awaking MAPA results (Table 2). With regards to the casual BP measurements, the value was slightly lower for systolic pressure (1.8 SD = 0.8 mmHg; p = 0.02) measured in the ELSA, whereas diastolic pressure showed similar values at both times (0.31 SD = 0.46; mmHg; p = 0.50).

Figure 1 shows the graphics of correlation between casual pressure measurements and the BP means in the MAPA-24h. In all situations, the correlation values

Table 1. Classification of blood pressure according to method and time of measuring.

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Without drug (N = 153)</th>
<th>Under antihypertensive drug (N = 77)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normotensive</td>
<td>Hypertensive</td>
</tr>
<tr>
<td>Casual ELSA</td>
<td>134</td>
<td>19</td>
</tr>
<tr>
<td>Casual Supplementary</td>
<td>132</td>
<td>21</td>
</tr>
<tr>
<td>MAPA 24h</td>
<td>120</td>
<td>33</td>
</tr>
<tr>
<td>MAPA waking</td>
<td>120</td>
<td>33</td>
</tr>
</tbody>
</table>

ELSA: Brazilian Longitudinal Study for Adult Health; AP: arterial pressure; MAPA: Ambulatory Arterial Pressure Monitoring
were above 0.70 (p < 0.01). Higher correlation values (generally above 0.80) were found between casual pressure measurements obtained in the supplementary project and the mean blood pressure in the MAPA-24h (Figure 2). The analysis was carried out separately for individuals who were taking medication at both times and for those who were not. Greater discrepancies were found in the values for the casual measurement and that of the MAPA with regards to systolic pressure, for individuals both taking and not taking medication. In the upper panels, it can be seen that the majority of those taking medication for hypertension had their pressure under control in both the casual measurement and the MAPA and the proportion of individuals with their pressure controlled in the casual measurement and high blood pressure in the MAPA (pseudo pressure control) was greater than the other way around. There were six cases of white coat hypertension, almost all falling into this category due to high systolic pressure and normal values in the MAPA. The prevalence of masked hypertension was greater than white coat hypertension, due to finding high values for systolic and diastolic pressure in the MAPA-24h in individuals with casual pressure within normal limits. A marked difference was that, whereas for white coat hypertension the differences in pressure were small in relation to the cut off points, in masked hypertension the differences between the casual value and the MAPA values were greater.

Figure 2 shows graphics of correlation between the casual blood pressure measurement in the supplementary study and the mean pressures obtained in the MAPA-24h. In this situation, it can be seen that the number of individuals who presented white coat hypertension and masked hypertension was smaller than that observed in the ELSA.

Reproducibility between casual arterial pressure measurements from the ELSA and the MAPA corresponding to the waking period were analyzed using the Bland-Altman diagram (Figure 3). The data show satisfactory reproducibility for both systolic and diastolic arterial pressure, as around 95% of the measurements are located within range of two standard deviations of the means of the differences between the methods. The means of the differences were, respectively, 4.43 mmHg for systolic and 3.81 mmHg for diastolic measurements. In other words, the estimate of the degree of systematic error between the measurements would be within acceptable limits, bearing in mind the precision with which arterial pressure is determined in a clinical environment and independent of the pressure means. Dispersion between the points shown in the graphic shows a small amount of random error, as, in both situations, uniform distribution around the mean is observed.

**DISCUSSION**

Because of its high level of accessibility, casual blood pressure measurements taken during a doctor’s appointments have been the traditional method of diagnosing AH and controlling the pressure of hypertensive patients. Despite this being a practical and accessible method from an economic point of view, permanent monitoring is needed regarding the fragility of this method. BP is a physiological parameter which undergoes continuous fluctuations around a mean value due to changes in the venous return, cardiac output and peripheral vascular resistance. Thus measurements obtained during a doctor’s appointment may not represent the individual’s true BP and deviations of between 5 and 10 mmHg are common when the patient’s conditions, the atmosphere in which the measurement is taken and the method of taking pressure are modified.

The arrival of MAPA represented a key step forward in evaluating true BP values as it enables a high number of measurements to be taken over a long period of time, outside of the doctor’s office, thus contributing to reduce diagnostic errors. MAPA, however, is expensive, which limits its use, especially in the public health care network. More recently, self-measurement of blood pressure was introduced as an alternative, lower cost method. This technique, however, still requires a more rigorous standardization for its wider clinical use to be possible.

Comparing MAPA data with that obtained in a clinical environment, two new situations arise: white coat hypertension, first described by the Mancia.
The first is characterized by the presence of elevated casual blood pressure values taken in the doctor’s office and normal values in the MAPA. High casual blood pressure would depend, mainly, on activation of the sympathetic nervous system due to the stress of measurement. The origin of masked hypertension is less certain and is the result of normal values when measured during a medical consultation and elevated levels in the MAPA. Some of these patients already present lesions to the target organs similar to those found in hypertensive patients. However, there are authors who recommend that patients with masked hypertension should receive appropriate treatment aiming to protect against adverse events.

These new situations should be taken into account when establishing the prevalence of AH in a population in which it is still not adequately determined. White coat hypertension appears more frequently in the elderly and, principally, in individuals who present borderline pressure values when measuring casual blood pressure, a fact confirmed in our study. Therefore, the frequency of this situation would depend primarily on the profile of the individuals evaluated, appearing more common in studies in which the proportion of individuals in the initial stage of the
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Longitudinal monitoring of white coat hypertensive individuals shows a high propensity to develop established hypertension, accompanied by typical lesions to target organs. However, those suffering from white coat hypertension constitute a specific group of individuals who require more frequent primary and systematic health care, aiming to establish early diagnosis of established hypertension.

Various outcomes to be monitored in the ELSA-Brasil cohort include AP as an important factor in causality. Given the importance of this marker for the study, obtaining values for blood pressure was rigorously standardized and an oscilometric device was used to reduce bias. In this study, the two measurements of pressure were carried out under identical conditions and with a mean interval of 30 days. The results show a high level of reproducibility between the two measurements of casual blood pressure.

Comparing the casual measurements with those of MAPA, discrepancies can be observed in relation to those found in the literature. In our study, only six cases were characterized as white coat hypertension, all of which had casual blood pressure values close to the cut-off point (140/90 mmHg). In the study Pressioni 6

Note: The horizontal and vertical lines indicate the cut off points for high blood pressure for MAPA-24h and for the casual blood pressure (respectively). In the upper panels, A and D show individuals with pseudo blood pressure control and B and C those individuals whose blood pressure is not controlled and is controlled, respectively. The lower panels show real normotensive (VN) and hypertensive (VH) individuals and those suffering from white coat hypertension (JB) and masked hypertension (HM). CCI: intra-class coefficient of correlation

Figure 2. Correlation between casual systolic arterial pressure (PAS) and diastolic arterial pressure (PAD) measured in the supplementary project and the MAPA-24h in individuals taking anti-hypertensive medication (upper panels) and those not taking medication (lower panels).
Arteriose Monitorate E Loro Associazioni (PAMELA), carried out in the general population of the north of Italy, white coat hypertension was detected in 9% of individuals. In a study carried out in a primary health care clinic, with 345 patients not taking anti-hypertensive medication, and using the same cut off points to define white coat hypertension, Martinez et al.\textsuperscript{13} (1999) detected this situation in 39% of individuals examined. Being female and with a low-socio-economic level were positively associated with this finding. If MAPA is considered to better reflect BP values for a specific individual, it can be surmised that high levels of white coat hypertension suggest clinical measurements with high levels of stress.

The presence of a large number of individuals with slight hypertension, especially when only systolic pressure is found to be within the 140 to 145 mmHg range, would also be factors which would elevate the number of false positive diagnosis, as fluctuations in pressure in this category are common under any type of mental stress.\textsuperscript{6,18} Therefore, when comparing ELSA data with the literature, it can be inferred that the small proportion of individuals identified as suffering from white coat hypertension is probably due to the rigorous measures taken to standardize casual BP measurement. It is worth noting that casual BP was measured in fasting during the morning period, conditions which are not always present in other studied. Moreover, measurement was carried out in a quiet environment and pressure was taken by a health care professional, not a doctor. It is important to highlight that the majority of publications report using the auscultatory method of measuring BP.\textsuperscript{12,15,19} Therefore, some of the differences between this study and the literature may be due to different methods of obtaining casual BP measurements. Our results show that correct measurement of arterial pressure in a clinical environment is the most appropriate method for avoiding false positive diagnoses of arterial hypertension. This should be a basic goal of all primary health care services aiming to reduce the costs arising from unnecessary treatment of normotensive individuals, and also avoiding side effects from using anti-hypertensive medication.\textsuperscript{3,15}

Masked hypertension, on the other hand, was more frequent in this cohort compared to other studies. The blood pressure values from the MAPA are usually, lower than those of casual BP, even when only the waking period is considered,\textsuperscript{1,3,10,13} which was not the case in this study. There is still controversy concerning which MAPA values most adequately correspond to casual BP measurements. Cut off points of 135/85 mmHg mean waking BP, or 135/85 mmHg mean 24h pressure have been adopted based on population studies.\textsuperscript{11,13,16} One difficulty found in establishing this correspondence is due to the fact that, if factors connected to stress and to the environment can be controlled in the casual measurement, the same is not true for MAPA. In this case, BP measurements taken throughout the day depend on exposure to environmental stress and, in the case of 24h mean, on drops during the night.\textsuperscript{19} In our study, the MAPA monitor was fitted in the morning (between 8 and 9 am) and the participant was recommended to keep all their normal routine activities throughout the day, although

\begin{figure}
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\includegraphics[width=\textwidth]{figure3}
\caption{Reproducibility of systolic blood pressure (SBP) and diastolic blood pressure (DBP) in the two measuring methods (casual measuring in clinic and in MAPA waking).}
\end{figure}
avoiding strenuous physical activity. The BP monitoring in the work environment may have contributed to the higher number of cases of masked hypertension in this study. This interpretation is reinforced by the fact that within individuals taking anti-hypertensive medication we observed an important number with controlled BP in the casual measurement but with uncontrolled BP values during MAPA-24h. Some authors recommend that masked hypertension should be considered as hypertension\textsuperscript{9,13} and, as such, the individuals should receive the appropriate treatment.

It can be concluded that the methodology of clinical blood pressure measuring adopted in the ELSA was effective in reducing false positive diagnoses of hypertension since the prevalence of white coat hypertension was lower than those of similar studies in the general population.
REFERENCES


