Methodological considerations in the evaluation of the duration of action of antihypertensive therapy using ambulatory blood pressure monitoring

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We review the potential limitations of the two current methodologies for evaluating the duration of action of antihypertensive therapy: the smoothness index (SI) and the trough : peak ratio (TP). We propose a simple correction factor for the SI. The correction factor prevents the SI from reaching erroneous high values in situations in which the reduction in blood pressure (BP) is inadequate but very homogeneous. We refer to the corrected index as the SI_n (normalized SI). ***Blood Press Monit*** **10:111–115 © 2005 Lippincott Williams & Wilkins.**

Blood Pressure Monitoring 2005, **10**:111–115

Keywords: ambulatory blood pressure monitoring, trough : peak ratio, smoothness index, normalized smoothness index, antihypertensive therapy

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Sponsorship: This research was supported in part by grants from Xunta de Galicia (PGIDIT03 PXIB-32201PR), and Vicerrectorado de Investigacion, University of Vigo.

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Received 27 September 2004 **Revised** 1 December 2004
Accepted 10 December 2004

Introduction

Since the introduction of ambulatory blood pressure monitoring (ABPM), the efficacy of antihypertensive treatments is commonly determined from ABPM recordings. ABPM has drastically improved the ability to assess the efficacy of antihypertensive treatment in clinical studies and in medical practice [1–4]. ABPM offers a number of advantages over clinic sphygmomanometric readings obtained casually in the examiner's office. ABPM is characterized by higher reproducibility, is not subject to observer bias and white-coat effect, allows the testing of the effectiveness of a given antihypertensive drug in daily life conditions, and enables the estimation of the pharmacodynamics of antihypertensive drugs [5–7].

There are several methods available to assess the duration of action of an antihypertensive drug. These methods aim at quantifying the efficacy of the antihypertensive drug by taking into account the duration and homogeneity of its antihypertensive effect. The underlying idea is based on the contention that optimal control and management of blood pressure (BP) should be based upon therapeutic strategies that consistently reduce BP in a homogeneous or smooth manner. The two indices most commonly used are the trough : peak ratio (TP) and the smoothness index (SI) [6,8–13].

The TP is obtained by dividing the BP reduction at the end of the between-dose interval (trough) by the BP at the time of maximal drug effect (peak). Despite this simple definition, the application of TP to ABPM recordings raises several methodological questions. These include how to select the optimal time window for calculation of BP changes at peak and trough, the exact definition of the peak and trough effects, whether to limit the TP calculation only to responders, and other methodological considerations caused by the lack of more specific methodological requirements for its calculation [9]. As a consequence, the application of the TP has resulted in inconsistencies and discrepancies caused by the use of different methodologies for its calculation. These have called into question the validity of the index altogether. In general, to obtain the TP, peak changes are calculated by averaging the values of (1) the hour after the drug intake in which the BP reduction compared with the corresponding baseline value was maximal, and (2) the adjacent hour in which the BP fall was greater. Trough changes are calculated by averaging the differences between baseline and after treatment BP values over the last 2 h of the inter-dose period [9]. In addition to these methodological issues, other concerns about the potential theoretical limitations of the index have also been expressed. The most significant of these limitations are: (1) it makes use of only a small portion of the 24 h ABPM recording; (2) even though individual peak and trough changes in ABPM follow a normal distribution with narrow scatter, TPs exhibit pronounced scatter and do not follow a normal distribution; (3) TP has no relation to variability of BP; (4) there is a small placebo effect at peak; and (5) it has limited reproducibility and clinical value [11,12]. Nonetheless, the TP is still used and there is convincing evidence that it is a useful index when employed in an appropriately conducted study and

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interpreted correctly [10]. However, as pointed out by Myers, since better measures of antihypertensive efficacy over 24 h or longer are available the use of the TP should be reconsidered and probably abandoned [14].

The SI was proposed in an attempt to overcome some of the potential theoretical and practical limitations of the TP [11]. The SI is defined as the ratio between the average of the 24 hourly reductions in BP induced by treatment and the standard deviation of these hourly reductions [15,16]. In contrast to the TP, the SI is derived from the analysis of 24 h BP profiles obtained before and during drug treatment, and takes into account all 24 h BP differences between baseline and treatment. This allows for a more comprehensive evaluation of the homogeneity of 24 h therapeutic coverage. The SI has been found to have a normal distribution with narrow scatter [11,12] and exhibits greater reproducibility in comparisons between medium- and long-term treatment when compared with TP [10,11,16]. Furthermore, the SI has been shown to have clinical validity, since SI has been reported to be associated with changes in left ventricular mass and with changes in carotid artery wall thickness under antihypertensive treatment [17,18].

The SI incorporates two effects in a single number, namely, the mean BP reduction and its homogeneity. The main limitation of this definition is that a drug with a negligible BP reduction could still have a very high SI, provided that the reduction is very homogeneous. In fact, the index tends to infinity regardless of the BP reduction as the standard deviation tends to zero.

The relative advantages and limitations of these two different indices for assessing the efficacy and duration of action of antihypertensive drugs have been addressed in several studies [9,10,13,19]. However, despite their widespread use, their implementation in a clinical setting is still mainly restricted to research, and at the moment inferences on the clinical superiority of a particular treatment over another based on a higher TP or SI are still considered speculative in nature [12]. The significance of assessment of antihypertensive treatment and the need for a new index have been very well established in the literature [12,13,15].

We propose a correction factor for the SI which prevents the index from reaching erroneously high values in situations when the reduction in BP is inadequate but very homogeneous. We refer to this corrected SI index as the SI_n (normalized SI).

Methodology

Given two ABPM recordings, let us denote the vector containing the raw BP values before treatment (baseline) as $\mathbf{x}$, and the vector containing the raw BP values after treatment as $\mathbf{y}$. In general, these time series are not uniformly sampled. ABPM monitors are commonly configured so that the sampling frequency is higher during daytime than at night, and it can also happen that the patient may need to take out the monitor for some period of time.

We divide the 24-h period in M containers (categories) numbered from $k = 1$ to M, where $k = 1$ corresponds to the first time (i.e. wake up, drug intake time). For the purposes of this paper we will assume we have 24 categories ($M = 24$). Each BP sample belongs to one and only one container. Using this notation let us define a set of 24 ABPM vectors at baseline as

$$\mathbf{x}_1 = (x_1^1, x_2^1, \ldots, x_{L_1}^1)$$
$$\mathbf{x}_2 = (x_1^2, x_2^2, \ldots, x_{L_2}^2)$$
$$\ldots$$
$$\mathbf{x}_{24} = (x_1^{24}, x_2^{24}, \ldots, x_{L_{24}}^{24})$$

where L_k denotes the number of BP samples in the class k at baseline. In general, the dimension of vectors from different classes is not equal, that is, $L_k \neq L_j$. The set of 24 ABPM vectors after treatment is defined analogously as

$$\mathbf{y}_1 = (y_1^1, y_2^1, \ldots, y_{L'_1}^1)$$
$$\mathbf{y}_2 = (y_1^2, y_2^2, \ldots, y_{L'_2}^2)$$
$$\ldots$$
$$\mathbf{y}_{24} = (y_1^{24}, y_2^{24}, \ldots, y_{L_{24}}^{24})$$

where L'_k denotes the number of BP samples in the class k after treatment. In general, $L_k \neq L'_k$, that is, the dimension of the vector before treatment corresponding to the class k, $\mathbf{x}_k$, is not necessarily equal to the dimension of the vector after treatment corresponding the same class $\mathbf{y}_k$.

For a given patient we can compute the average at each container, before and after treatment, to obtain

$$\overline{\mathbf{x}} = (\overline{x}_1, \ldots, \overline{x}_{24}) \text{ where } \overline{x}_k = \frac{\sum_{i=1}^{L_k} x_i^k}{L_k} \text{ (average of container } k)$$

$$\overline{\mathbf{y}} = (\overline{y}_1, \ldots, \overline{y}_{24}) \text{ where } \overline{y}_k = \frac{\sum_{i=1}^{L'_k} y_i^k}{L_k} \text{ (average of container } k)$$

and their differences

$$\mathbf{d} = \overline{\mathbf{x}} - \overline{\mathbf{y}} = (d_1, \ldots, d_{24}) = (\overline{x}_1 - \overline{y}_1, \ldots, \overline{x}_{24} - \overline{y}_{24})$$

According to the standard definition, the SI is calculated as the ratio between the mean of the hourly reductions and the standard deviation of these, that is

$$\mathrm{SI} = \frac{\overline{d}}{S_\mathrm{d}}$$

where $\overline{d}$ denotes the sample mean of the class-by-class differences (reductions) and S_d is the sample standard deviation

$$\overline{d} = \sum_{k=1}^{24} \frac{d_k}{24}$$

$$S_d = \sqrt{\sum_{k=1}^{24} \frac{(d_k - \overline{d})^2}{23}}$$

Usually high values of SI are preferred. However, a high value of SI can be obtained if S_d is very small, independently of the value of $\overline{d}$. To overcome this limitation we propose a normalized index (SI_n) defined as

$$SI_n = \frac{\overline{d}}{\alpha + S_d}$$

Unlike SI, SI_n does not tend to infinity as S_d tends to zero, instead it tends to a fraction of $\overline{d}$. Even though any α can be selected, we propose to use $\alpha = 1$. For $\alpha = 1$, the best SI_n possible is $\overline{d}$, which is only reached when the reduction is constant ($S_d = 0$). This correcting factor also has the benefit that it removes outliers (i.e. very high SI values due to $S_d \approx 0$).

Illustrative example

The following selected example demonstrates some of the advantages and limitations of each of these indices and compares the proposed SI_n with the TP ratio and the SI. In Figure 1 we show an illustrative example of potential problems with the TP ratio and the SI. Figure 1a shows a plot of simulated BP reductions used for pedagogical purposes, and the calculated TP ratio and SI. In this example we obtained ($T = 0.5788$; $P = 0.6408$, $\overline{d} = 0.5713$, $S_d = 0.0561$). From the graph of the BP reductions we can see how these are negligible BP reductions but very homogeneous ones. Note that the mean reduction is insignificant ($\overline{d} = 0.5713$ mmHg). However, since the TP ratio is defined as a ratio of two BP reductions (trough over peak reduction), the index can in principle give very high values even though there is almost no reduction at all, as long as the reduction at peak and that at trough are very close. This is precisely what happens in this example. The TP ratio is very close to one (TP = T/P = 0.5788/0.6408 = 0.903), since the reduction in BP at trough is very close to the reduction at peak.

A similar problem happens with the SI. This index incorporates two effects (i.e. mean BP reduction and reduction homogeneity) in a single number. Given a high SI we cannot determine if it is due to a considerable BP reduction or if the reduction is very homogeneous. From the definition of SI we can see that in the case of a nearly constant reduction, SI would be very large, regardless of how significant the BP reduction is. Figure 1a illustrates this problem. Even though the antihypertensive treatment is having no reduction, the SI results in a very high value ($SI = \overline{d}/S_d = 0.5713/0.0561 = 10.191$) due to the homogeneity of this reduction, indicating a good overall drug effect. Note, however, how the SI_n provides a more accurate assessment of the drug efficacy ($SI_n = \overline{d}/(1 + S_d) = 0.5713/(1 + 0.0561) = 0.541$). Figure 1b shows an example of good antihypertensive coverage (T = 31.5252, P = 27.4501, $\overline{d} = 27.2771$, $S_d = 4.0559$). In this case the drug induces a significant BP reduction with 24-h coverage ($\overline{d} = 27.2771$ mmHg, $S_d = 4.0559$). However, according to the TP and the SI indices (TP = 0.871, SI = 6.725) the treatment efficacy in this case would be lower than for the treatment in Figure 1a. The SI_n indicates a considerable difference between both treatments [$SI_n = 0.541$ in (a) versus $SI_n = 5.395$ in (b)], providing a better assessment of drug efficacy. This example illustrates a potential limitation of the TP ratio and the SI. These indices are sensitive to treatment efficacy but they are not specific. That is, they give high values in cases where the antihypertensive drug causes a considerable and homogeneous BP reduction (Fig. 1b), but they can also give high values in situations where the BP reduction is inadequate (Fig. 1a). A simple solution to correct this potential limitation is to normalize the SI (SI_n), which results in a better estimate of the combined reduction/homogeneity effect.

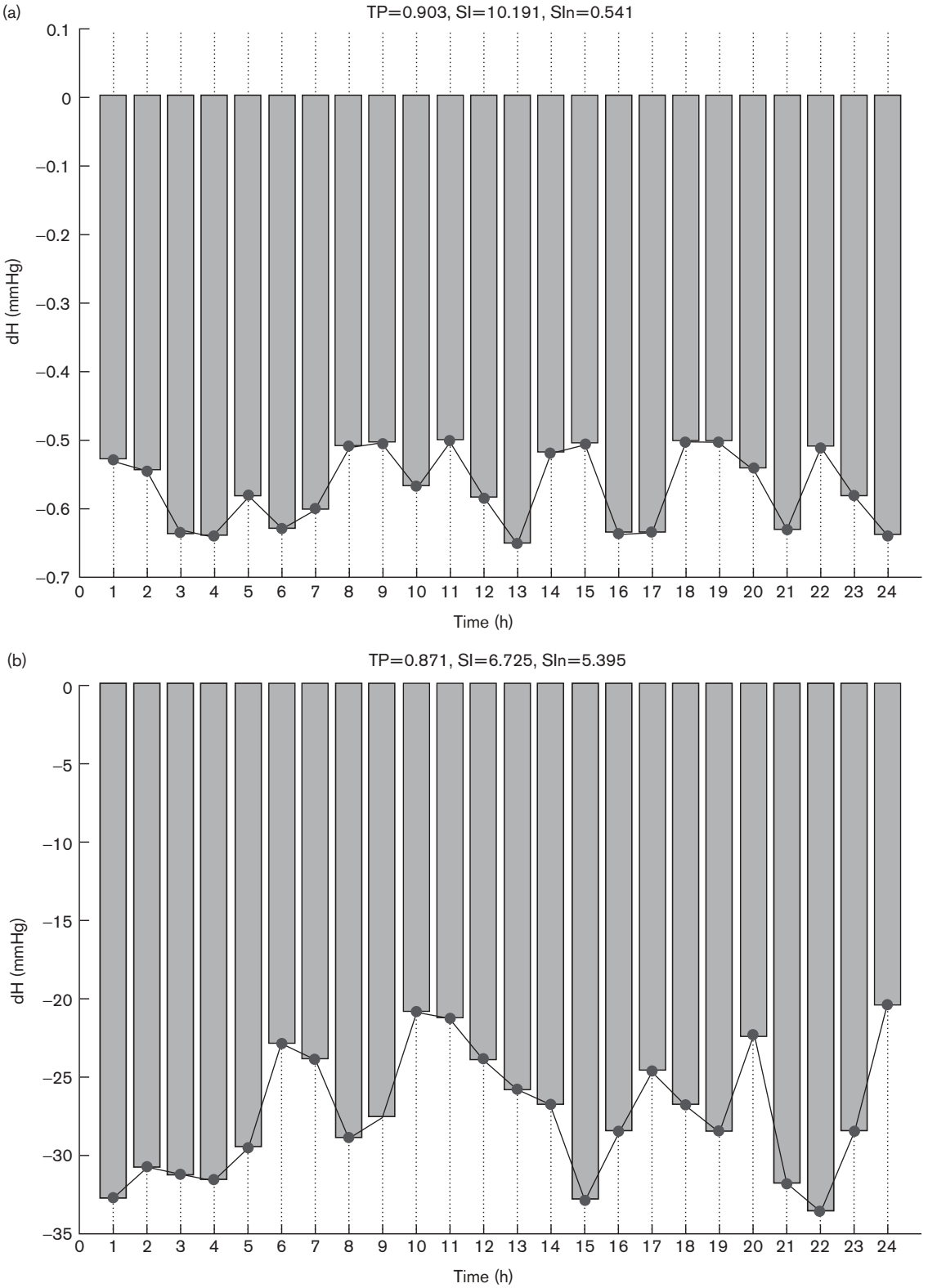
Discussion

The TP and SI are indices commonly used to assess the duration of action of an antihypertensive drug. However, both have significant limitations. Specifically, both indices are based on the BP reduction comparing two profiles, but do not assess the statistical significance of these reductions [12]. In this methodological paper we proposed a correction factor for the SI (resulting in the SI_n) to solve a specific problem with this index. However, it is important to recognize the intrinsic limitations of single number indices for the task of assessing the drug effect of antihypertensive drugs.

In the evaluation of antihypertensive therapy we must take into account two effects: (1) the BP reduction; and (2) the homogeneity of this reduction. In order to study antihypertensive effectiveness we must know how much the BP is reduced. Furthermore, it is also important to study the consistency of the BP reductions along the time interval between doses. The SI combines these two effects into a single number (the ratio of the mean BP reduction over the standard deviation of the BP reduction). In order to interpret the SI it is necessary to know the mean reduction of BP, since a high SI may be due entirely to a high degree of homogeneity, independently of the BP reduction. The SI_n has the advantage that it is bounded. Its maximum possible value is precisely the mean BP reduction.

Other researches have documented a normal distribution for SI and the advantages that this reports [17].

Fig. 1



Comparison of the TP, SI and the proposed SI_n. Negative *d* values indicate reduction in BP (Note the plot is showing $-d$). (a) Plot of the BP hourly reductions of an antihypertensive drug. Note the reduction is negligible (average $d=0.5713$ mmHg), and that both the TP ratio and the SI give very high values (TP=0.903 and SI=10.191), indicating an adequate antihypertensive coverage. SI_n, however, provides a more appropriate assessment of the antihypertensive effect ($SI_n=0.541$). (b) Plot of the BP hourly reductions of another antihypertensive drug and TP, SI and SI_n. Note that in this case the reduction in BP is more considerable and relatively homogeneous. However, the TP ratio and the SI are lower than in case (a). The SI_n gives a much higher value compared with the previous case, which is a more appropriate assessment of the antihypertensive effect.

Normality enables us to perform parametric statistical test and compute averages and confidence intervals for population SI. It is expected that the SI_n follows the same distribution of the SI_n, with the additional advantage that it removes outliers due to high homogeneity of the BP reduction. Other indexes, like TP, are not characterized by this normal distribution, but also it is possible to perform non-parametric statistical tests and summarize their population characteristics using the median as the measure of central tendency [11]. From this point of view, the statistical distribution of a given index is secondary. In general, normality is desirable but not indispensable.

The correction factor for the SI presented earlier does not eliminate all of the possible problems with this index. This is especially true when comparing the duration of action of antihypertensive drugs. This is somewhat expected. After all, it is almost impossible to capture the complexity of antihypertensive drug effect by means of a single number. Despite these limitations, numerical indices are still very relevant. These indices enable us to perform quantitative analysis and have been proven very useful in hypertension research. The SI, for instance, has been shown to have significant clinical validity, correlating with changes in left ventricular mass and with changes in carotid artery wall thickness under antihypertensive treatment [17,18].

A possible solution to this problem is for the research community to start considering the use of vector indices to convey more and better information about the drug effect. A good tradeoff between amount of information and index compactness is to use vector indices of three components. This enables to incorporate information about the reduction, homogeneity, and duration of antihypertensive drugs, as well as their statistical significance. TP, SI and SI_n are obtained from analysis of the mean hourly BP reductions $\mathbf{d}$. However, what is important are not the absolute BP differences (i.e. reductions $\mathbf{d}$ in mmHg), but on whether or not these reductions are significant when we take into account the intrinsic variability of the BP at each of the 24 categories before and after treatment. By means of statistical inference the statistical significance of each hourly reduction can be tested. Other researchers have also suggested the possibility of performing statistical analysis of ABPM recordings over various time periods to develop indices or provide values for descriptive data and for assessing the statistical significance of BP mean differences between the drug versus baseline or between different periods after dosing [14].

In this paper we have illustrated the potential usefulness of the SI_n index using selected examples. We have only addressed the problem of evaluating the antihypertensive drug efficacy for a given patient. The full development and application of such an index to populations of hypertensive patients to assess antihypertensive drug efficacy still requires further research.

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