The population RDH index: a novel vector index and graphical method for statistical assessment of antihypertensive treatment reduction, duration, and homogeneity

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Current indices used in the evaluation of antihypertensive treatment duration and homogeneity such as the trough–peak, smoothness index, and normalized smoothness index were designed to be applied to ambulatory blood pressure monitoring recordings from individual participants. Evaluation of antihypertensive treatment in populations is often carried out by calculating these individual indices for each of the participants and providing summarizing statistics about the population, such as the mean and median. We describe a new population vector index and graphical method for the statistical assessment of antihypertensive treatment reduction, duration, and homogeneity (RDH) from ambulatory blood pressure monitoring. The population (RDH) was specifically designed as a tool to evaluate and compare blood pressure coverage offered by antihypertensive drugs over 24 h in populations. The population RDH is a three-component vector index that incorporates information about the reduction, duration, and homogeneity of antihypertensive treatment, as well as their statistical significance over the 24 h period. In addition to defining the RDH index, in this paper we also demonstrate its usefulness and advantages as an index and graphical method for antihypertensive treatment duration and homogeneity assessment by using it to analyze two data sets. *Blood Press Monit* 11:143–155 © 2006 Lippincott Williams & Wilkins.

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Introduction

The development of a population index to evaluate antihypertensive treatment duration and homogeneity is significant, because none of the current indices used for this purpose were designed to be applied to populations. Duration and homogeneity of antihypertensive drugs are commonly quantified by the computation of the trough : peak ratio (TP) and the smoothness index (SI) [1–7]. Normally, both the TP and the SI are calculated from ambulatory blood pressure monitoring (ABPM) recordings obtained from individual participants, and not from entire populations. As a consequence, these indices have important limitations when applied to populations. Additionally, the lack of a well-defined population index has resulted in methodological inconsistencies regarding the description of antihypertensive drug effect at the population level. Currently, researchers do not follow a standardized methodology to conduct and report results on populations. This limits, in part, the comparability and reproducibility of results involving the evaluation of antihypertensive treatment.

Both the TP and SI have established definitions in the literature for their evaluation on individual participants. Most studies involving assessment of antihypertensive effects, however, are based on populations, and require researchers to report an index to characterize the population or the specific antihypertensive treatment under study. The typical approach to solve this problem has been to evaluate the TP and SI for each individual participant in the sample population under study, and to use summarizing statistics such as the mean or median to report results to characterize the population. Another approach has been to adapt and/or redefine individual indices so that they can be calculated directly from the population, leading to the concept of population indices (i.e. indices calculated directly on the population) versus individual indices (i.e. indices calculated on individual participants).

Before the introduction of the SI in 1998, the TP was the only established index used for the assessment of antihypertensive treatment. Initially, the characterization of populations was carried out by reporting the mean of the individual indices; that is, the mean of the TPs [1,8]. As the TP does not, however, follow a normal distribution, Omboni *et al.* [5,9,10] proposed to characterize the

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population by providing the median of the individual TPs. In addition to the median of the individual TPs, it was later proposed by Meredith, Stergiou, and Mancia that a measure of dispersion such as the range of the individual TP values [4], the interquartile range [7], or the 5th and 95th percentiles [11,12] also be provided. This methodology was not universally adopted by the research community, and recent studies have used the mean to characterize the population and, in some cases, the mean of responders [13,14]. Additionally, there is another methodology proposed by Stewart that consists in calculating the so-called population TP as the ratio of the mean of all the individual troughs and the mean of all the individual peaks [15,16].

In the case of the SI, since its introduction it was reported to follow a normal distribution [17]. As a consequence, it is most commonly reported on populations by providing the mean of the individual SIs and the standard error [5,7,11–14,17].

The need to provide an accurate characterization of antihypertensive drug effects on populations requires vector indices and standardized statistical graphical plots specifically designed for this purpose. It is important to emphasize the fact that we had already started to use vector indices. For instance, in order to characterize antihypertensive drug effects on a population on the basis of the TP, it is necessary to provide at least three numbers (e.g. median, 5th, and 95th percentiles), that is, we use a vector index of three components. In the case of the SI, three numbers are also commonly reported [i.e. SI, standard error, and mean blood pressure (BP) reduction]. Reporting the mean BP reduction is important, as the SI cannot be interpreted in the absence of this information, because negligible BP reductions can result in misleading high SI values in situations in which the reduction is very homogeneous. As the standard deviation of the BP reductions tends to zero, the SI tends to infinity regardless of the mean BP reduction for any nonzero mean BP reduction. The normalized SI (SIn) avoids this limitation by adding one to the denominator [18].

In this paper, we define the population reduction, duration, and homogeneity (RDH) index and present the procedure to calculate it. The population RDH is a three-component vector index specifically designed for statistical assessment of antihypertensive treatment RDH on populations. Its definition and interpretation is identical to that of the individual RDH index [19], that is, the population RDH components quantify: (1) the total number of statistically significant BP reductions, (2) the maximum number of consecutive statistical significant reductions, and (3) the maximum number of consecutive nonsignificant reductions over the 24 h. Additionally, in this paper we also demonstrate its usefulness and advantages as an index for antihypertensive treatment duration and homogeneity assessment by using it to analyze two data sets.

Methodology

Notation and definitions

In this section, we introduce notation and precise definitions that will be used in subsequent sections to define the population RDH index precisely.

Given an individual ABPM recording, we denote each of the time categories by an index k, where $\{k\}_{k=1}^{K}$. For the purposes of this paper, we will assume that we have 24 categories ($K = 24$) corresponding to 24 h. Let L_k represent the number of BP samples in the kth class at baseline. In general, the dimension of vectors from different classes is not equal, that is, $L_k \neq L_j$, where k and j denote the index of the kth and jth class. Analogously, let L_k' represent the number of BP samples in the k-th class after treatment. In general, $L_k \neq L_k'$, that is, the dimension of the vector before treatment corresponding to the kth category is not necessarily equal to the dimension of the vector after treatment corresponding to the same category. Let $\mathbf{x}$ denote the vector containing the individual BP values before treatment, and let $x_{k,i}$ denote the ith sample belonging to time category k,

$$\begin{aligned} \mathbf{x}_1 &= (x_{1,1}, x_{1,2}, \ldots, x_{1,L_1}) \\ \mathbf{x}_2 &= (x_{2,1}, x_{2,2}, \ldots, x_{2,L_2}) \\ &\vdots \\ \mathbf{x}_{24} &= (x_{24,1}, x_{24,2}, \ldots, x_{24,L_{24}}) \end{aligned} \tag{1}$$

The vector $\mathbf{y}$ containing the BP values after treatment for the same participant is defined analogously,

$$\begin{aligned} \mathbf{y}_1 &= (y_{1,1}, y_{1,2}, \ldots, y_{1,L_1'}) \\ \mathbf{y}_2 &= (y_{2,1}, y_{2,2}, \ldots, y_{2,L_2'}) \\ &\vdots \\ \mathbf{y}_{24} &= (y_{24,1}, y_{24,2}, \ldots, y_{24,L_{24}'}) \end{aligned} \tag{2}$$

Let $\bar{x}_k$, $\bar{y}_k$ denote the sample mean of the ABPM vector corresponding to the kth category before and after treatment,

$$\bar{x}_k = \sum_{i=1}^{L_k} \frac{x_{k,i}}{L_k}, \; \bar{y}_k = \sum_{i=1}^{L_k'} \frac{y_{k,i}}{L_k'},$$

and let $\overline{\mathbf{x}}$, $\overline{\mathbf{y}}$ be vectors containing sample means before and after treatment,

$$\begin{aligned} \overline{\mathbf{x}} &= (\bar{x}_1, \bar{x}_2, \ldots, \bar{x}_{24}), \\ \overline{\mathbf{y}} &= (\bar{y}_1, \bar{y}_2, \ldots, \bar{y}_{24}). \end{aligned} \tag{3}$$

The vector containing the class-by-class differences is denoted as $\mathbf{d}$,

$$\begin{aligned} \mathbf{d} &= \overline{\mathbf{x}} - \overline{\mathbf{y}} \\ &= (\bar{x}_1, \bar{x}_2, \ldots, \bar{x}_{24}) - (\bar{y}_1, \bar{y}_2, \ldots, \bar{y}_{24}) \\ &= (d_1, d_2, \ldots, d_{24}). \end{aligned} \tag{4}$$

In order to define the population RDH, we define x_k^j to be x_k for participant j. Given J participants in the population under study, we have

$$\begin{aligned}
\mathbf{x}_1^1 &= (x_{1,1}^1, x_{1,2}^1, \ldots, x_{1,L_{1,1}}^1) \\
&\vdots \\
\mathbf{x}_{24}^1 &= (x_{24,1}^1, x_{24,2}^1, \ldots, x_{24,L_{24,1}}^1) \\
\mathbf{x}_1^2 &= (x_{1,1}^2, x_{1,2}^2, \ldots, x_{1,L_{1,2}}^2) \\
&\vdots \\
\mathbf{x}_{24}^2 &= (x_{24,1}^2, x_{24,2}^2, \ldots, x_{24,L_{24,2}}^2) \\
&\vdots \\
\mathbf{x}_1^J &= (x_{1,1}^J, x_{1,2}^J, \ldots, x_{1,L_{1,J}}^J) \\
&\vdots \\
\mathbf{x}_{24}^J &= (x_{24,1}^J, x_{24,2}^J, \ldots, x_{24,L_{24,J}}^J),
\end{aligned} \tag{5}$$

the vector $\mathbf{y}_k^j$ is defined analogously.

Classical scalar indices: TP, SI, and SIn

In this section, we provide definitions for the classical scalar indices using the notation previously defined. These precise definitions serve as descriptions of our implementation of these indices, which we used for comparison with the population RDH in this study.

(1) *SI and SIn*: The SI is calculated as the ratio between the mean of the hourly reductions and the standard deviation of these,

$$\mathrm{SI} = \frac{\bar{d}}{s_d}, \tag{6}$$

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

$$\begin{aligned}
\bar{d} &= \sum_{i=1}^{24} \frac{d_i}{24}, \\
s_d &= \sqrt{\sum_{i=1}^{24} \frac{(d_i - \bar{d})^2}{23}}.
\end{aligned} \tag{7}$$

The SI incorporates two effects in a single number, namely, the mean BP reduction $\bar{d}$ and its homogeneity s_d. 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. The SI tends to infinity for any nonzero BP reduction as the standard deviation s_d tends to zero.

To overcome this limitation, we have recently proposed an SIn [18] defined as

$$\mathrm{SIn} = \frac{\bar{d}}{1 + s_d}. \tag{8}$$

Unlike SI, SIn does not tend to infinity as s_d tends to zero, instead it tends to $\bar{d}$. The best SIn possible is $\bar{d}$, which is reached only 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 owing to $s_d \approx 0$).

The characterization of a population on the basis of the SI is typically based on the mean and standard error,

$$\overline{\mathrm{SI}} = \sum_{j=1}^{J} \frac{\mathrm{SI}_j}{J}, \tag{9}$$

$$\widehat{se}_{\overline{\mathrm{SI}}} = \sqrt{\frac{\left\{ \sum_{j=1}^{J} (\mathrm{SI}_j - \overline{\mathrm{SI}})^2 / (J-1) \right\}}{J}}. \tag{10}$$

The characterization of a population on the basis of the SIn is analogous to the SI.

(2) *TP*: The TP is calculated as the ratio of the mean BP reduction at the end of the between-dose interval (trough) and the mean BP reduction at the time of maximum drug effect (peak). The exact method for calculating the trough T and peak P differs among researchers. One of most commonly used methods was proposed by Omboni *et al.* [3,5]. The peak P effect is calculated by considering the interval between the second and eighth hour after drug intake. The average is computed over 2 h time windows as follows:

$$\mathrm{TP} = \frac{T}{P}, \tag{11}$$

where T is the average of the BP differences over the last 2 h of interdose period, P is the 2 h average around the peak effect [19].

The characterization of a population on the basis of the TP is most commonly based on the median operator med, and the interquartile range iqr

$$\mathrm{TP}_P = \mathrm{med}\{\mathrm{TP}_1, \mathrm{TP}_2, \ldots, \mathrm{TP}_J\}, \tag{12}$$

$$\mathrm{TP}_R = \mathrm{iqr}\{\mathrm{TP}_1, \mathrm{TP}_2, \ldots, \mathrm{TP}_J\}. \tag{13}$$

Development of the population reduction, duration, and homogeneity

As in the case of the individual RDH [19], the population RDH can be calculated on the basis of parametric or nonparametric statistics. The advantage of the nonparametric RDH is that it minimizes the number of assumptions made.

(1) *Parametric population RDH*: For each category k, the population RDH takes as an input the set of before $\{\mathbf{x}_k^j\}_{j=1}^J$ and post-treatment $\{\mathbf{y}_k^j\}_{j=1}^J$ ABPM recordings, and generates a three-component vector index according to the following algorithm:

• Calculate the mean of each category k for each participant j before and after the treatment

$$\bar{x}_k^j = \sum_{i=1}^{L_{k,j}} \frac{x_{k,i}^j}{L_{k,j}}, \qquad \bar{y}_k^j = \sum_{i=1}^{L'_{k,j}} \frac{y_{k,i}^j}{L'_{k,j}}. \tag{14}$$

• Create population composites of category k, before $\mathbf{x}_k$ and after treatment $\mathbf{y}_k$,

$$\mathbf{x}_k = (\bar{x}_k^1, \bar{x}_k^2, \ldots, \bar{x}_k^j, \ldots, \bar{x}_k^J), \tag{15}$$

$$\mathbf{y}_k = (\bar{y}_k^1, \bar{y}_k^2, \ldots, \bar{y}_k^j, \ldots, \bar{y}_k^J). \tag{16}$$

• Create the vector containing the BP differences,

$$\mathbf{d}_k = \mathbf{x}_k - \mathbf{y}_k = (\bar{x}_k^1 - \bar{y}_k^1, \bar{x}_k^2 - \bar{y}_k^2, \ldots, \bar{x}_k^J - \bar{y}_k^J) = (d_1, d_2, \ldots, d_J). \tag{17}$$

• Perform a paired-sample t-test to test whether the mean BP reduction in category k is greater than zero,

$$t_k = \frac{\bar{d}_k}{\widehat{se}_{\bar{d}_k}} = \frac{\sum_{j=1}^{J} \frac{\bar{x}_k^j - \bar{y}_k^j}{J}}{\sqrt{\frac{s_{d_k}^2}{J}}}, \quad s_{d_k}^2 = \sqrt{\sum_{j=1}^{J} \frac{(d_j - \bar{d})^2}{J-1}}, \tag{18}$$

that is, for each category k, $k = 1, \ldots, 24$, we assess the statistical significance of the mean BP reduction by dividing the mean BP difference $\bar{d}_k$ for category k over its standard error $\widehat{se}_{\bar{d}_k}$.

• We define the population RDH vector as RDH = (c_1, c_2, c_3) where

c_1 = Total number of statistically significant reductions
c_2 = Maximum number of consecutive statistically significant reductions
c_3 = Maximum number of consecutive statistically nonsignificant reductions

As in general $J > 30$, the t-distribution approximates the normal distribution, and the threshold of 1.645 from the normal distribution can be used to establish statistical significance.

(2) *Nonparametric population RDH*: The nonparametric population RDH is based on *bootstrap* to estimate the probability density function of the mean BP differences for category k across the population and to perform a nonparametric test [20]. The nonparametric population RDH takes as an input the set of before $\{\mathbf{x}_k^j\}_{j=1}^J$ and $\{\mathbf{y}_k^j\}_{j=1}^J$ ABPM recordings and generates a three-component vector index according to the following algorithm:

• Create vector containing the BP differences,

$$\mathbf{d}_k = \mathbf{x}_k - \mathbf{y}_k = (\bar{x}_k^1 - \bar{y}_k^1, \bar{x}_k^2 - \bar{y}_k^2, \ldots, \bar{x}_k^J - \bar{y}_k^J). \tag{19}$$

Note that even though the probability model of $\mathbf{x}_k$ and $\mathbf{y}_k$ follows the two-sample model, the probability model for the interpopulation RDH follows a one-sample model,

$$T_k \rightarrow \mathbf{d}_k = (d_{k,1}, d_{k,2}, \ldots, d_{k,J}),$$

where as previously defined

$$d_{k,j} = \bar{x}_k^j - \bar{y}_k^j$$

and T_k is the distribution function for category k.

• Calculate the statistic of interest from $\mathbf{d}_k$, $\hat{\theta}_k = s(\mathbf{d}_k)$, which in this case is the mean BP reduction $\bar{d}$.

$$\hat{\theta}_k = s(\mathbf{d}_k) = \sum_{j=1}^{J} \frac{d_{k,j}}{J}. \tag{20}$$

• Use the empirical distribution $\hat{T}_k$ to obtain bootstrap samples

$$d_k^* = (d_{k,1}^*, d_{k,2}^*, \ldots, d_{k,J}^*)$$

by random sampling of

$$\hat{T}_k \rightarrow \mathbf{d}_k^* = (d_{k,1}^*, d_{k,2}^*, \ldots, d_{k,J}^*)$$

from which we can calculate bootstrap replications of the statistic of interest $\hat{\theta}_k = s(\mathbf{d}_k^*)$ to estimate the probability distribution $\hat{\theta}_k^*$.

• Use the histogram of $\hat{\theta}_k^*(b)$, $b = 1, 2, \ldots, B$ as an estimate of the probability density function of the mean BP differences for category k across the population. The bootstrap confidence intervals for the population BP reduction in class k are obtained as

$$\hat{\theta}_{k_{lo}} = 100 \cdot \alpha th \text{ percentile of } \hat{\theta}_k^{*'}\text{s distribution},$$
$$\hat{\theta}_{k_{lo}} = 100 \cdot (1-\alpha) th \text{ percentile of } \hat{\theta}_k^{*'}\text{s distribution}. \tag{21}$$

If this interval contains zero, it cannot be assumed with $(1-2\alpha)$ confidence that the parameters of the two populations are statistically different.

• Define the nonparametric population RDH vector as RDH = (c_1, c_2, c_3) analogous to the parametric case.

This method of estimating confidence intervals with bootstrap is known as the percentile bootstrap method and it requires at least 1000 replicas [20]. In the following examples, we used 2000 replicas.

Application example

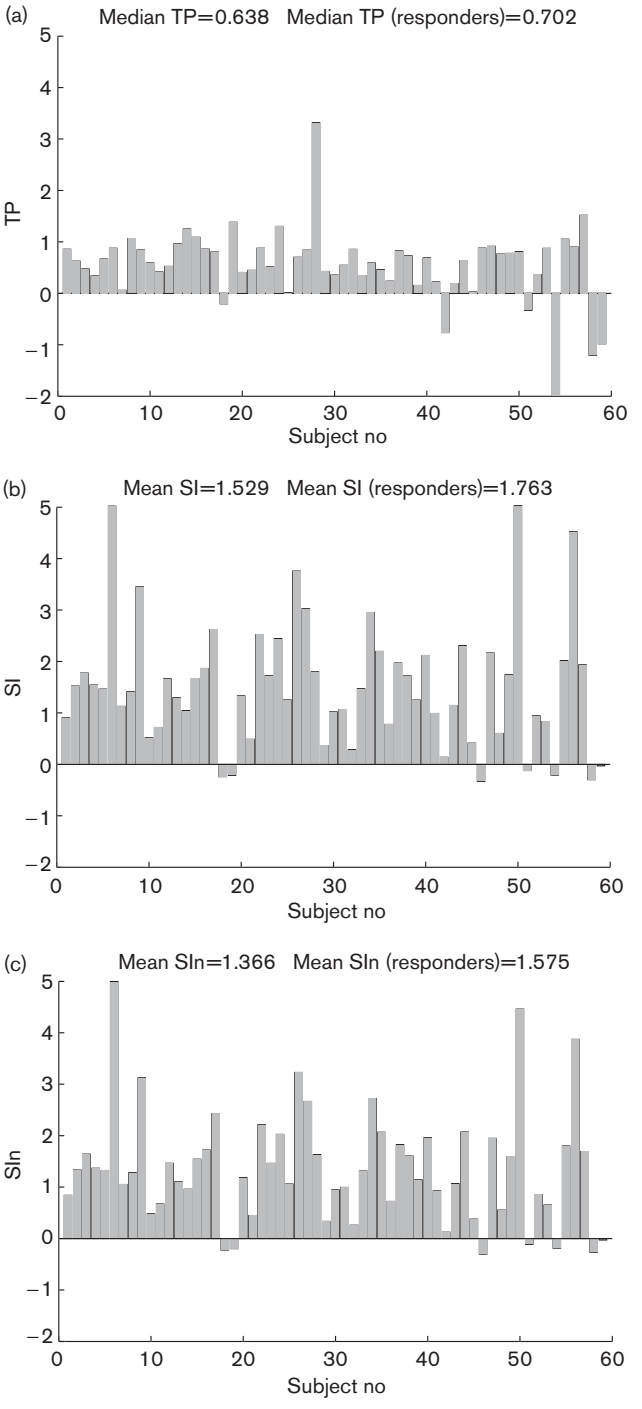
Subjects

(1) *Hypertensive individuals*: We studied 59 white subjects aged 49.3 ± 12.3 years (37 men, 22 women), with mild to moderate (grade 1 or 2) essential hypertension based on the criteria of the European Society of Hypertension–European Society of Cardiology guidelines [21] for conventional cuff BP measurements [systolic BP (SBP) between 140 and 179 mmHg or diastolic BP (DBP) between 90 and 109 mmHg], and corroboration by ABPM at the time of recruitment. A positive diagnosis of hypertension based on ABPM required that either the 24-h mean SBP/DBP be above 130/80 mmHg, the diurnal mean be above 135/85 mmHg, or the nocturnal mean be above 120/70 mmHg [22].

All the participants received their routine medical care at the Hypertension and Vascular Risk Unit, Hospital Clinico Universitario, Santiago de Compostela, Spain. They participated in a clinical trial on the antihypertensive efficacy of 160 mg/day valsartan, as previously reported [23]. Specific details on the participants and the design of this clinical trial have been provided previously [23]. The SBP and DBP, and the heart rate (HR) of each participant were automatically measured every 20 min from 0700 to 2300 h and every 30 min during the night for 48 consecutive hours with a validated Space Labs 90207 device (SpaceLabs Inc., Issaquah, Washington, USA) [24]. Participants were studied by ABPM under baseline conditions when participants were free of medication before and, again, after 3 months of therapy (valsartan taken at wake-up time). During 48-h ABPM, each participant wore a MiniMotionLogger actigraph (Ambulatory Monitoring Inc., Ardsley, New York, USA) on the dominant wrist to monitor physical activity every minute. This compact device, about half the size of a wrist watch, functions as an accelerometer. The internal clocks of the actigraph and the ABPM devices were synchronized through their respective interfaces by the same computer. The actigraphy data were used to determine the onset and offset times of diurnal activity and nocturnal sleep so as to accurately determine the diurnal and nocturnal BP means of each participant. The mean activity for the 5 min before each BP reading was then calculated for further statistical analysis on circadian variability of activity, according to previous studies on this area [25,26]. Each individual's clock hour BP and HR values were first re-referenced from clock time to hours after awakening from nocturnal sleep, according to the information obtained from wrist actigraphy. This transformation avoided the introduction of bias due to differences among participants in their sleep/activity routine [27]. BP and HR time series were then edited according to conventional criteria to remove measurement errors and outliers [28].

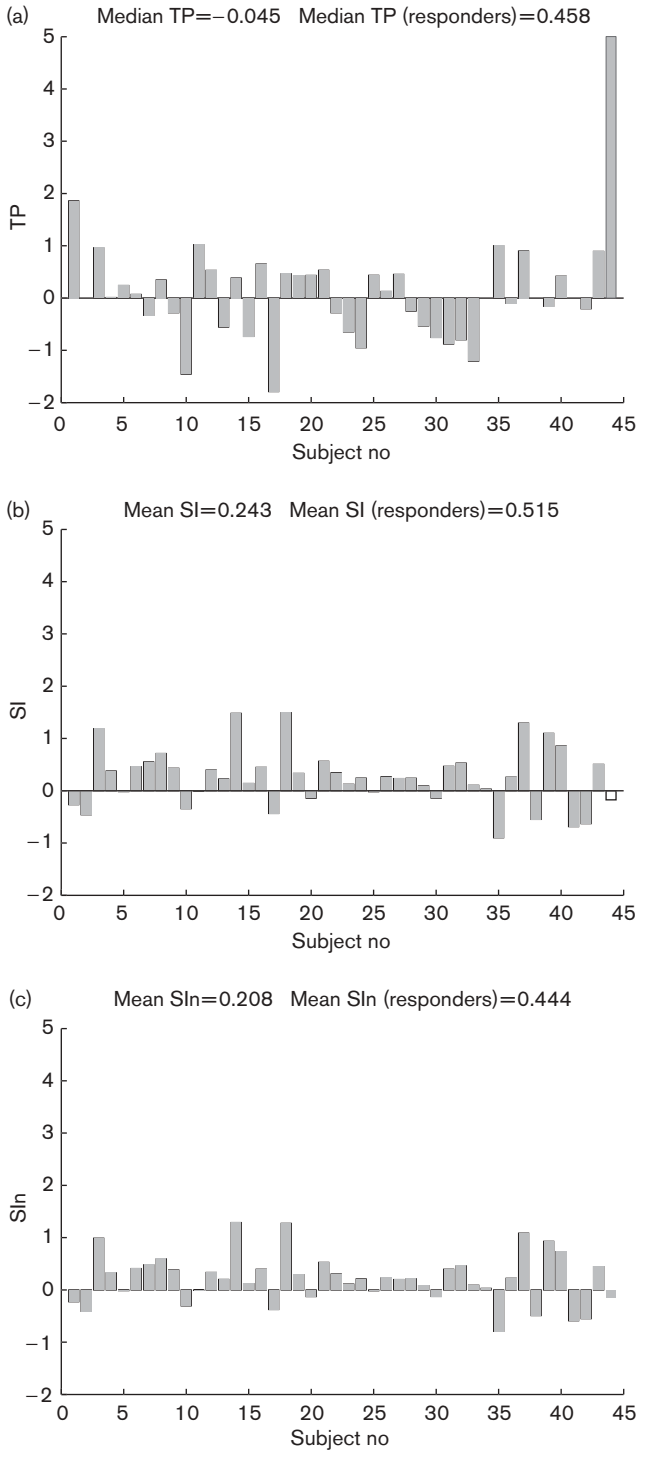
(2) *Normotensive individuals*: We studied 44 (22 men and 22 women) diurnally active and nocturnally resting healthy normotensive young Spanish adults, aged 22.43 ± 1.66 years. These patients did not take any antihypertensive

Fig. 1



Evaluation of conventional indices on 59 hypertensive subjects (treated group). (a) trough–peak (TP) ratio, (b) smoothness index (SI), (c) normalized smoothness index (SIn). Analysis based on systolic blood pressure.

Fig. 2



Evaluation of conventional indices on 44 normotensive subjects not taking any antihypertensive medication (nontreated group). (a) Trough–peak (TP) ratio, (b) smoothness index (SI), (c) normalized smoothness index (SIn). Analysis based on systolic blood pressure SBP.

medication. Inclusion criteria were absence of hypertension by medical history and casual BP measurements. Exclusion criteria were, among others, chronic hypertension and any condition requiring the use of antihypertensive medication, any disease requiring the use of anti-inflammatory medication, chronic liver disease, endocrine diseases such as diabetes and hyperthyroidism, or intolerance to ABPM. Participants who were not adhering to a usual diurnal activity and nocturnal resting routine were also excluded from the study. All volunteers signed consent forms before entering the study.

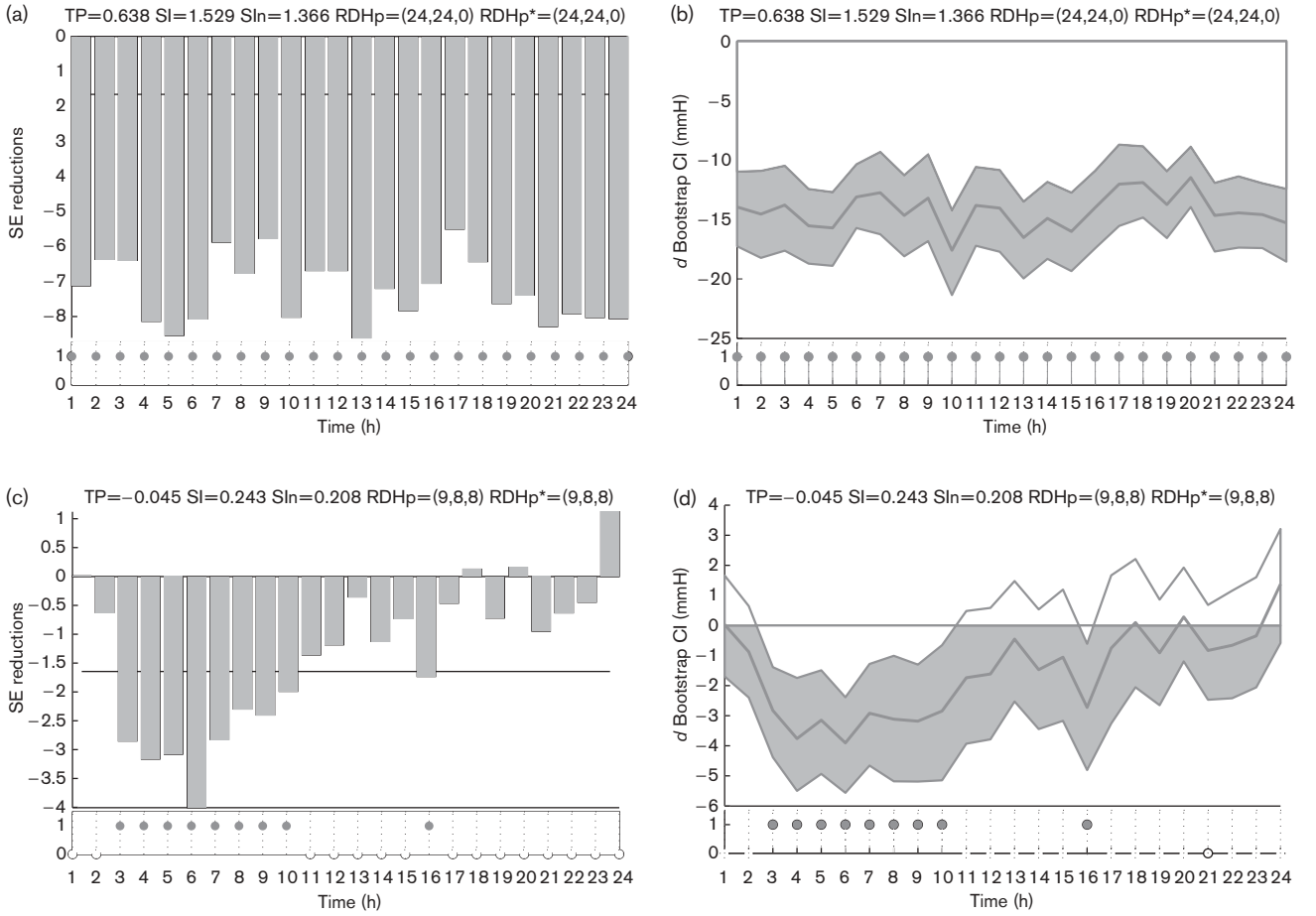
The SBP and DBP, and HR of each participant were automatically measured every 20 min from 0700 to 2300 h and every 30 min during the night for 48 consecutive hours with a validated SpaceLabs 90207 device (SpaceLabs Inc.) [24] on two occasions 3 months apart. The participants did not take any medication. The actigraphy data were used to determine the onset and offset times of diurnal activity and nocturnal sleep so as to accurately determine the diurnal and nocturnal BP means of each participant. Each individual's clock hour BP and HR values were first re-referenced from clock time to hours after awakening from nocturnal sleep, according to the information obtained from wrist actigraphy.

Results and discussion

Figures 1 and 2 show the TP, SI, and SIn calculated on the SBP for each of the 59 hypertensive individuals (treated group), and for each of the 44 normotensive individuals not taking any antihypertensive medication (nontreated group), respectively. As expected, the TP, SI, and SIn are higher in the treated group.

Figure 3 shows a comparison of the treated group and the nontreated group based on the population RDH (RDHp) described in this paper. In Fig. 3, the RDH index was computed from the analysis of the SBP population data. These figures show the results using the parametric (Fig. 3a,c) and the nonparametric (Fig. 3b,d) versions of the RDH index. Note that both tests lead to the same results. In Fig. 3(a,c), the top plot shows the BP reductions normalized in units of standard errors, and the bottom plot shows the statistical (grey) and nonstatistical (white) reductions. In Fig. 3(b,d), the top shows the mean BP reduction and the Bootstrap confidence intervals for each time category. In the case of the treated group, RDHp = (24, 24, 0), which indicates that there were statistically significant reductions in all the 24 time categories. On the basis of this RDHp value, we can conclude that treatment is a drug with a 24-h duration of action. Furthermore, the RDHp plot shows the estimated confidence intervals and the estimated mean BP reduction. On the basis of the RDHp plot, we can also state that the treatment (i.e. valsartan) induced a mean BP reduction of 15 mmHg approximately. The confidence intervals indicate that the reduction is

Fig. 3



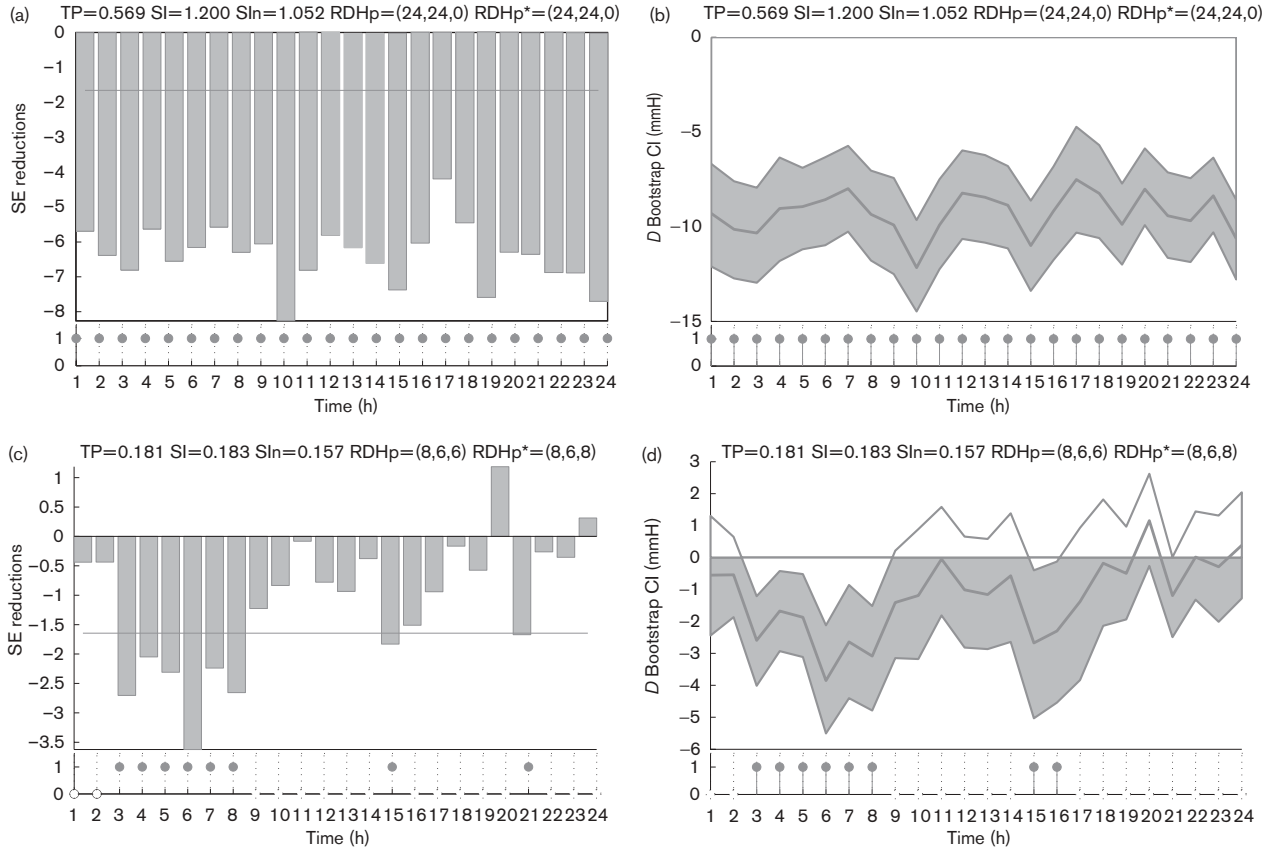
Comparison of the population reduction, duration, and homogeneity (RDHp) in the treated (a) and (b) versus nontreated (c) and (d) groups. (a) Parametric RDHp, (b) nonparametric RDHp, (c) parametric RDHp, (d) nonparametric RDHp. Analysis based on systolic blood pressure. TP, trough–peak ratio; SI, smoothness index; SIn, normalized smoothness index.

homogeneous across the 24-h period. On the other hand, we see that in the case of the nontreated participants, RHDp = (9, 8, 8); that is, there were nine statistically significant reductions, eight consecutive statistically significant reductions, and eight consecutive nonsignificant reductions. Note that the graph of the RDH index clearly shows that all the statistically significant reductions occurred between hour 3 and hour 10 after waking up. This result suggests that there is an 'ABPM effect' in the first 10 h of ABPM [29]. The RDHp plot indicates that the mean reduction due to this ABPM effect is approximately 3 mmHg.

Additionally, the RDHp can be used to test the effectiveness of a given antihypertensive treatment on a specific population by comparing the upper confidence interval against a threshold different from zero. For instance, the RDHp can be used to test the number of statistically significant and effective reductions by comparing the confidence interval against a 5 mmHg threshold. Even without performing the statistical test, the current nonparametric RDHp graph showing the confidence intervals can be used for this purpose. In Fig. 3b, for instance, we can see that if the test threshold was changed from 0 to −7 mmHg, all the reductions would still be statistically significant. Thus, we can conclude that this treatment not only induces statistically significant reductions across the 24 h period, but also that these reductions are all effective against a −7 mmHg threshold. Note that if we were to apply the same criteria to the nontreated group (Fig. 3d), none of the reductions would come out statistically significant, indicating noneffectiveness.

Figure 4 shows a comparison of the treated and the nontreated groups based on the RDHp computed from analysis of the DBP population data. In the treated group, RDHp = (24, 24, 0), which indicates that there were

Fig. 4



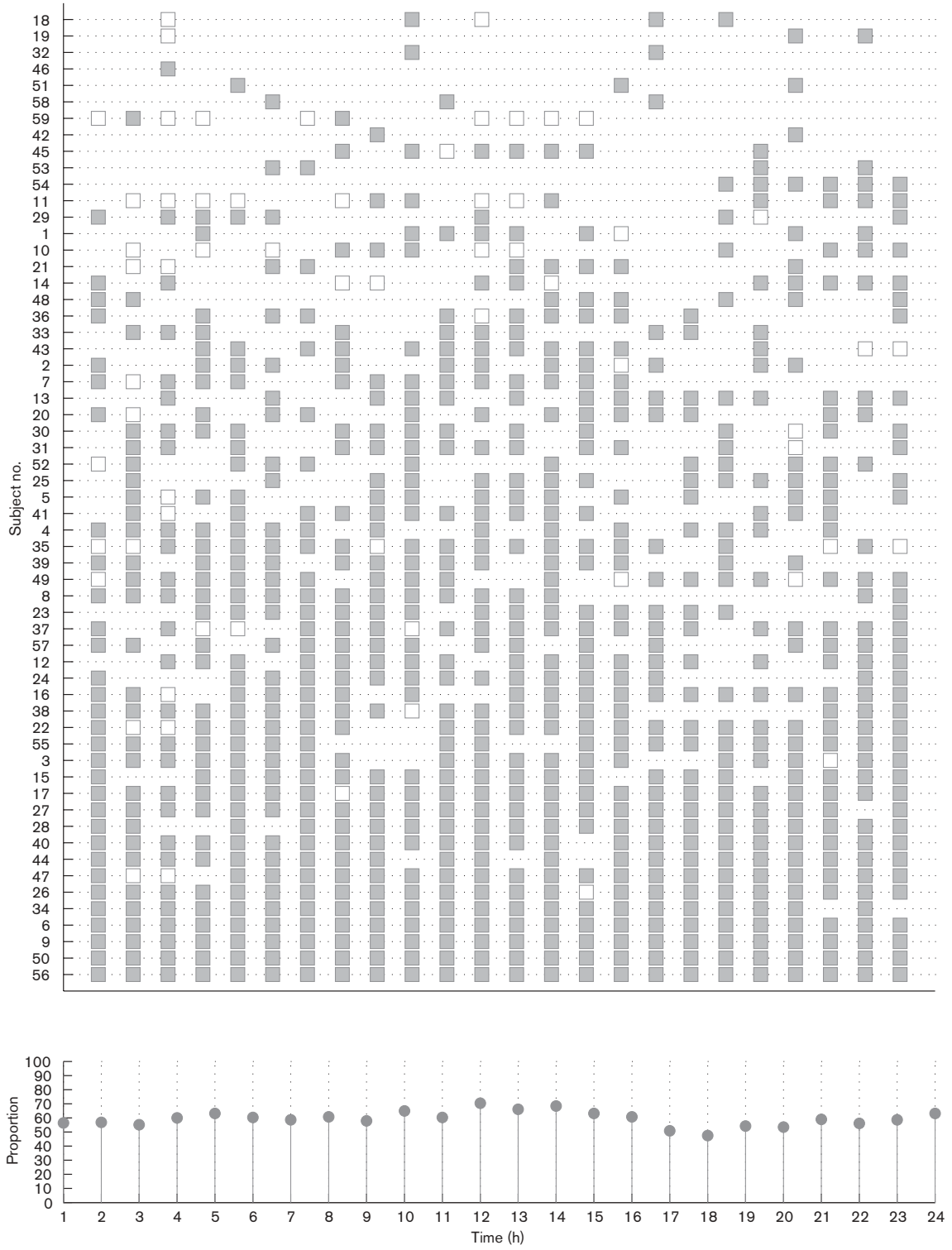
Comparison of the population reduction, duration, and homogeneity (RDHp) in the treated (a) and (b) versus nontreated (c) and (d) groups. (a) Parametric RDHp, (b) nonparametric RDHp, (c) parametric RDHp, (d) nonparametric RDHp. Analysis based on diastolic blood pressure. TP, trough–peak ratio; SI, smoothness index; SIn, normalized smoothness index.

statistically significant reductions in all the 24 time categories. On the basis of this RDHp value, we can conclude that treatment also induces a statistically significant reduction on the DBP of 24-h duration. In the case of the nontreated group, RHDp = (8, 6, 8). From the RDHp graph we can see that the mean BP reduction is lower in the DBP than in the SBP. This difference is approximately 5 mmHg in the treated group (15 versus 10 mmHg approximately).

Figures 5 and 6 show a graphical representation of the individual RDHs, and a comparison between the treated and the nontreated groups on SBP using the nonparametric RDH. The top plot shows the individual RDH sequence for each participant. In this plot, a gray square indicates a statistically significant reduction, the absence of a square corresponds to a nonsignificant BP reduction, and a white square denotes a time category in which no data were available to perform the statistical test. This graph complements the RDHp plot by displaying the RDH corresponding to each individual participant in the population under study. The bottom plot in this graph shows the proportion of statistically significant reductions in each category, and whether the population RDH resulted in a statistically significant reduction (gray circle) or in a nonsignificant reduction (white circle). This graphical representation enables researchers to immediately identify the nonresponder participants (i.e. participants for whom the antihypertensive treatment did not induce statistically significant reductions across the 24-h period).

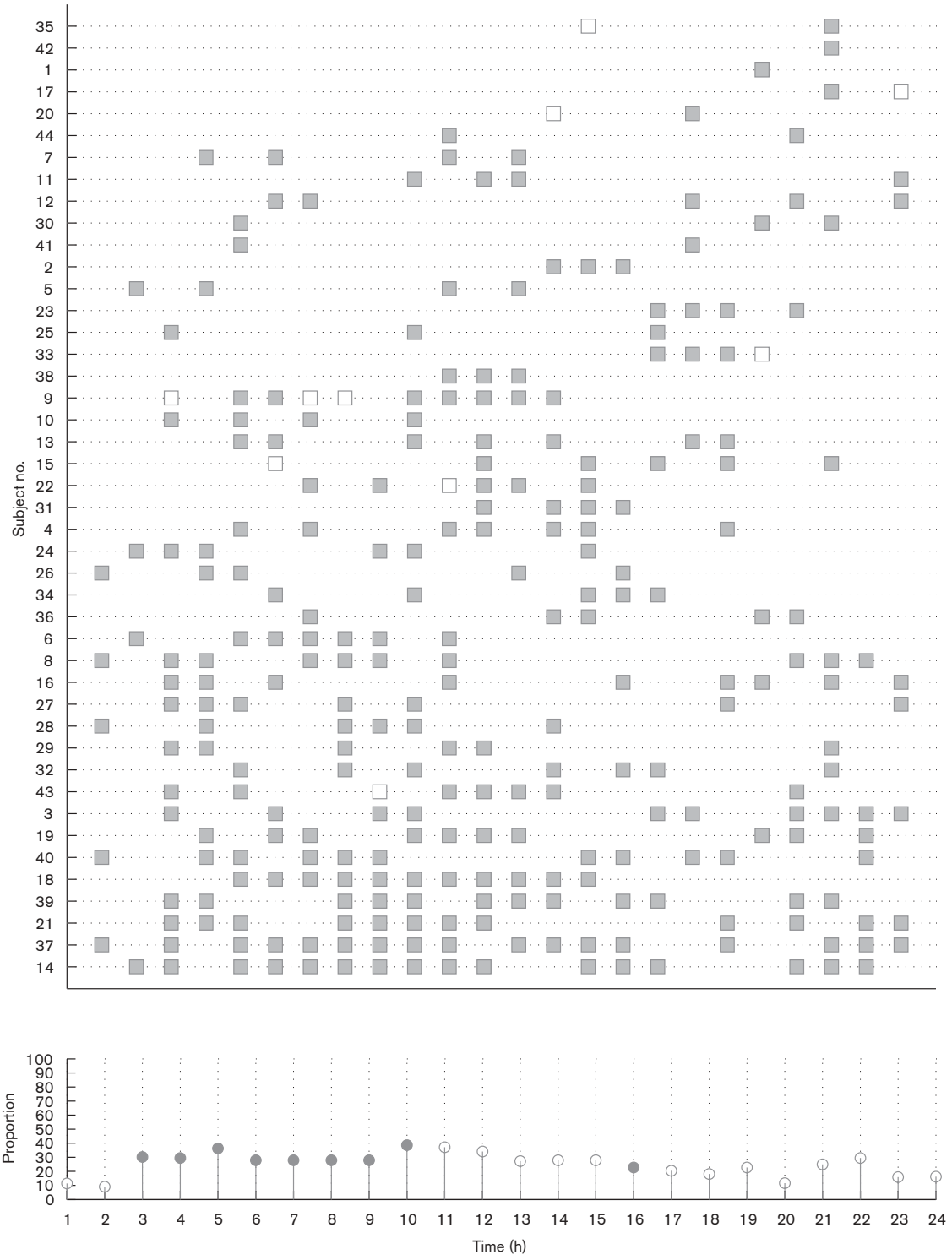
Figure 7 shows scatter plots of each of the three RDHp components versus the TP and SIn, scatter plots of the SIn versus the SI, and scatter plots of SIn versus the TP on the treated groups. Figure 8 shows the same scatter plots on the nontreated group. Both graphs were generated by analysis of the SBP. Note that the SIn has a positive correlation with the first two RDH components, RDH(c1) and RDH(c2), and a negative correlation with the third RDH component, RDH(c3). As expected, the SIn is positively correlated with the total number of

Fig. 5



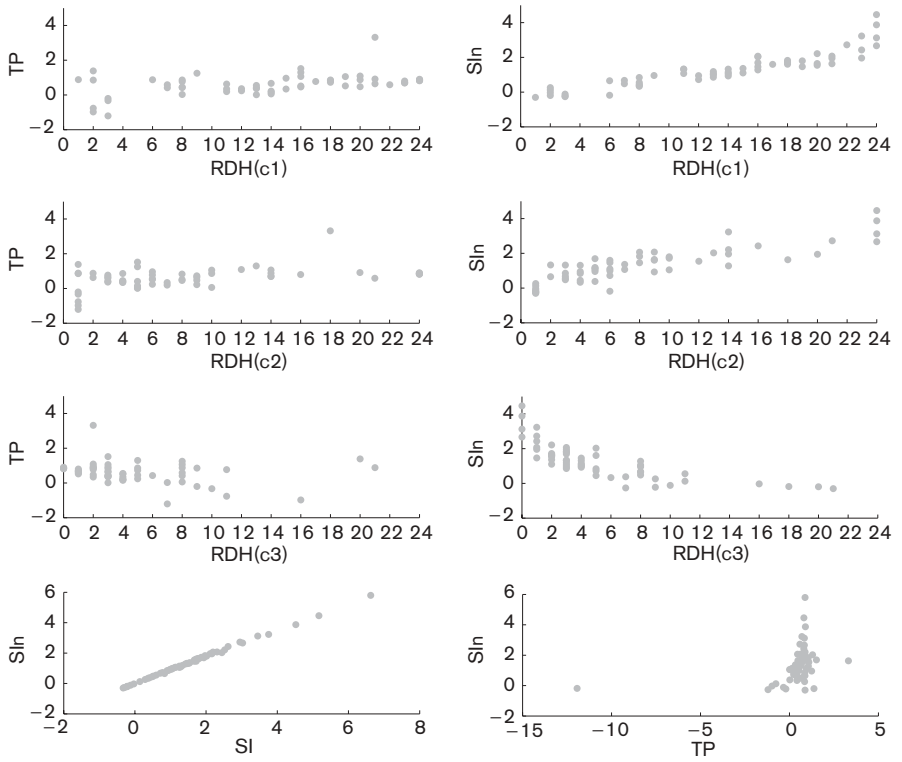
Nonparametric reduction, duration, and homogeneity (RDH) population plot for the treated group (analysis based on systolic blood pressure). The top plot shows the individual RDH sequence for each participant. In this plot, a gray square indicates a statistically signicant reduction, the absence of a square corresponds to a nonsignicant blood pressure reduction, and a white square denotes a time category when no data were available to perform the statistical test. This graph complements the RDH population plot by displaying the RDH corresponding to each individual participant in the population under study. The bottom plot in this graph shows the proportion of statistically significant reductions in each category, and whether the population RDH resulted in a statistically significant reduction (gray circle) or in a nonsignificant reduction (white circle).

Fig. 6



Nonparametric reduction, duration, and homogeneity population (RDHp) plot for nontreated group (analysis based on systolic blood pressure). The top plot shows the individual RDH sequence for each participant. In this plot, a gray square indicates a statistically significant reduction, the absence of a square corresponds to a nonsignificant blood pressure reduction, and a white square denotes a time category when no data were available to perform the statistical test. This graph complements the RDHp plot by displaying the RDH corresponding to each individual participant in the population under study. The bottom plot in this graph shows the proportion of statistically significant reductions in each category, and whether the population RDH resulted in a statistically significant reduction (gray circle) or in a nonsignificant reduction (white circle). This visualization tool enables researchers to quickly compare treatment or populations. As expected, the number of statistical significant reductions is much lower in the nontreated group than in the treated group.

Fig. 7

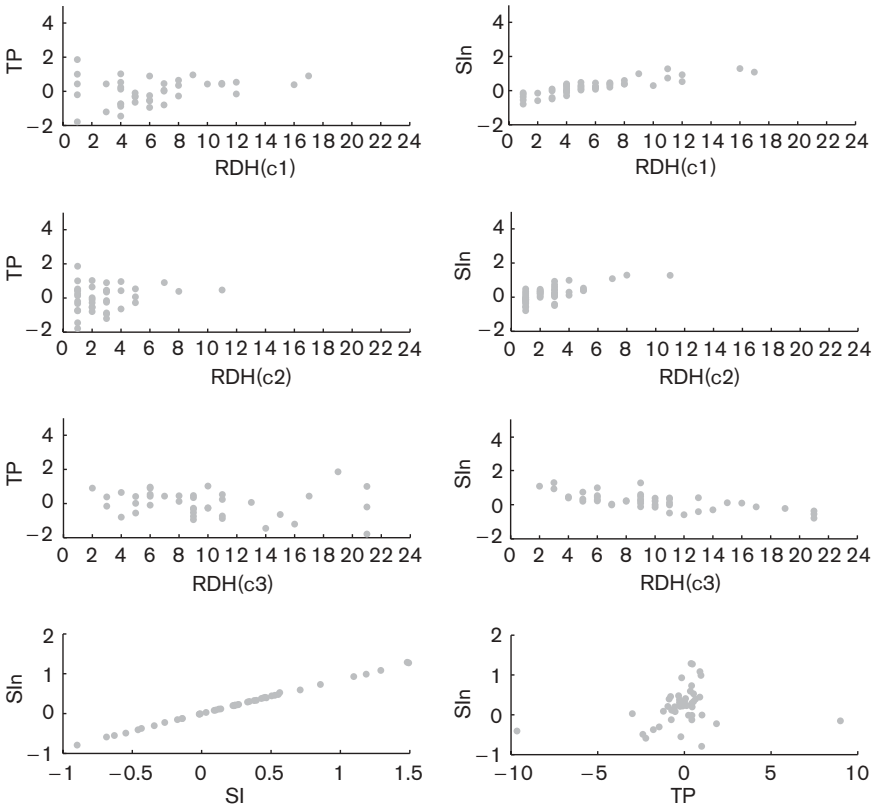


Correlation between nonparametric reduction, duration, and homogeneity (RDH) components versus trough–peak ratio (TP) and normalized smoothness index (SIn) (treated group). SI, smoothness index

statistically significant reductions and with the number of consecutive statistically significant reductions across the 24-h period, and negatively correlated with the number of consecutive nonsignificant reductions. This conclusion also applies to the SI, as the SI and SIn are highly correlated as shown in the corresponding scatter plot shown in Fig. 7. Interestingly, the TP does not correlate with the total number of statistically significant reductions, the SI, or the SIn. The fact that the TP does not correlate with the total number of time categories when the treatment induced a statistically significant reduction is especially troublesome. This result provides further evidence to conclude that the use of the TP as an index for the assessment of antihypertensive treatment duration and homogeneity should be abandoned as suggested by other researchers [30].

It is important to emphasize the importance of the graphical representations of the RDH index. Although a well-designed statistical vector index such as the RDH can provide much more and better information to characterize the antihypertensive drug effect in individuals and populations than the indices currently used for this purpose, this limitation also applies to any three-component vector index. From a statistical point of view, this can be more formally stated by saying that there is no three-component vector that is a sufficient statistic of the before and post-treatment ABPM data records, and their difference. A graph can be used to convey significantly more quantitative and statistical information than any three numbers. It is important for the ABPM research community to develop standardized statistical graphical methods specifically designed to convey all the clinically significant information concerning the specific antihypertensive treatment or treatments under study and report reproducible results. The availability of standardized plots to accurately and statistically describe the effect of antihypertensive drugs for specific individuals and populations will enable the research community to report more and better information than by using numerical indices. Standardized graphical representations of the antihypertensive drug effect will also improve comparability and reproducibility of results. In this paper, we proposed a statistical graph designed to report the results of the population RDH (e.g. Fig. 3b), and a new visualization technique that enables researchers to visualize each of the individual RDH indices calculated on the population compactly (e.g. Fig. 5).

Fig. 8



Correlation between nonparametric reduction, duration, and homogeneity (RDH) components versus trough–peak ratio (TP) and normalized smoothness index (SIn) (nontreated group). SI, smoothness index

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