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Time domain baroreflex sensitivity assessment by joint analysis of spontaneous SBP and RR series

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ABSTRACT

The sequences technique is frequently used for time domain assessment of the arterial-cardiac baroreceptor reflex sensitivity (BRS). The BRS is estimated by the slope between systolic blood pressure and RR interval values in baroreflex sequences (BSs) and an overall estimate is obtained by slope averaging. However, only 25% of all beats are in BSs with 60% of those located in 3-beat length segments. Also, in cases of BSs absence (usually associated with poor BRS function), the BRS cannot be quantified.

Here, baroreflex events (BEs) are introduced and used with global/total slope estimators to improve BRS assessment. The performance of the novel method is evaluated using the EuroBaVar dataset. The events technique benefits from a higher number of beats: 50% of all beats are in BEs with more than 70% exceeding 3-beat length. It always provides a BRS estimate, even when BSs cannot be identified. When BSs are available, estimates from BEs and BSs are highly correlated. The estimates from BEs for the cases without BSs are lower than the estimates for the remaining cases, indicating poorer BRS function. The events technique also offers superior ability to discriminate lying from standing position in the EuroBaVar dataset (23/23 versus 18/23 for the sequences technique).

1. Introduction

It is currently accepted that the joint analysis of systolic blood pressure (SBP) and RR interval series allows the assessment of the arterial-cardiac baroreceptor reflex sensitivity (BRS), either using time or frequency domain methods [1]. The sequences technique is a frequently used time domain method for spontaneous BRS estimation, thanks to its ease of implementation [2]. This method is based on the identification of baroreflex sequences (BSs) and linear regression over the corresponding SBP and RR values. An overall estimate is obtained by averaging the slope estimates from all BSs identified in a record. In spite of its simplicity, this technique sometimes fails to provide an estimate for low BRS patients, depending of the parameters used. As a result, this method is considered by some authors to have limited value for the BRS evaluation/quantification in autonomic dysfunction cases [3], which are the crucial cases to identify. Therefore, performance improvements that preserve simplicity are needed.

The sequences technique was first used in sino-aortic denervated cats [4,5]. The spontaneous BSs appeared to reflect baroreflex mechanisms as their number (and mean slope) was drastically reduced after denervation. Studies in humans confirmed the existence of such BSs and reported similar results in subjects with poor BRS function [6]. In practice, several thresholds are imposed for BSs identification and no consensual opinion about their values can be found in the literature; slight modifications in threshold values can change the number of BSs and the BRS estimate [7]. The values derived for cats are most likely non-optimal for humans. Moreover, the elimination of certain thresholds has also been suggested [7,8].

In normal cases, the overall number of beats in BSs is approximately one fourth of the total number of beats [5] and, consequently, a large part of the data is discarded from BRS analysis. More than half of the BSs have 3-beat length [9], implying that the BRS estimate is more likely to be influenced by outlier values. In cases of BRS dysfunction, the number of BSs is further reduced so that the slope estimate will exhibit higher variance. In cases of BSs being unavailable, the BRS cannot be quantified. The validity of BRS estimates obtained from short and few SBP–RR segments remains to be addressed [10].

Improvements on time domain BRS assessment have been proposed with the 'xBRS' estimate [8]. Briefly, the regression is

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performed over 10 s windows of the SBP and RR series resampled at 1 Hz, considering the SBP–RR delay that maximizes their cross-correlation (up to 5 s). The BRS estimates are accepted if positive valued and statistically significant at the probability 0.01. Finally, the BRS estimate from an entire recording is obtained by geometric averaging of the local estimates. As pointed out in [11], this method provides more BRS estimates than the sequences technique because it allows a non-constant SBP–RR delay. However, as the BRS is estimated in relatively long time windows, different effects such as arterial baroreceptor stimulation and deactivation can occur and, therefore, cannot be separated.

In this work, a new criterion for beat-to-beat SBP–RR segmentation is introduced. It consists of the identification of high SBP–RR correlation segments, here referred as baroreflex events (BEs), which are not constrained to be of constant length. Alternative BRS estimators combined with BEs are proposed to improve time domain BRS assessment in normal conditions and to allow its quantification in cases of BS absence.

The methods for time domain BRS estimation are described in Section 2. The experimental data used in this work is described in Section 3. The results are presented in Section 4 and discussed in Section 5.

2. Methods

BRS analysis is performed over SBP and RR series, denoted $x_{\mathrm{SBP}}(n)$ and $x_{\mathrm{RR}}(n)$ respectively, with $n = 1, 2, \ldots, N_{\max}$ indicating beat number. The analysis is considered with a beat lag of $\tau = 1$, i.e., $x_{\mathrm{SBP}}(n-1)$ is paired with $x_{\mathrm{RR}}(n)$ [5].

The methods are based on 2 steps: first the identification of baroreflex related segments (sequences or events) and then BRS estimation from SBP–RR slope. The sequences technique is based on BSs identification and on the average of the slopes computed at each BS [2,5], here referred as local approach for slope estimation. The events technique, proposed in this work to improve BRS assessment, makes use of baroreflex events (BEs) and global/total slope estimators.

2.1. The sequences technique

The threshold values used for BSs identification are summarized in Table 1. The kth BS must have a minimum length in beats ($N_k \geq N_{\min}$), a minimum x_{SBP} and x_{RR} beat-to-beat changes in the same direction ($\Delta_k^{\mathrm{SBP}} \geq \Delta_{\min}^{\mathrm{SBP}}$ and $\Delta_k^{\mathrm{RR}} \geq \Delta_{\min}^{\mathrm{RR}}$) and a minimum correlation between the x_{SBP} and x_{RR} values in BSs ($r_k \geq r_{\min}$). Each identified BS$_k$, $k = 1, 2, \ldots, K$ is characterized by N_k pairs of values $(\mathbf{x}_{\mathrm{SBP}}^k, \mathbf{x}_{\mathrm{RR}}^k)$ beginning at index n_k, that is,

$$\mathbf{x}_{\mathrm{SBP}}^k = [x_{\mathrm{SBP}}(n_k - 1)\, x_{\mathrm{SBP}}(n_k) \cdots x_{\mathrm{SBP}}(n_k + N_k - 2)]$$
$$\mathbf{x}_{\mathrm{RR}}^k = [x_{\mathrm{RR}}(n_k) x_{\mathrm{RR}}(n_k + 1) \cdots x_{\mathrm{RR}}(n_k + N_k - 1)].$$

The local approach provides one BRS estimate (slope) from each baroreflex related segment. Formally, the BRS measure b_k, associated to the kth segment, is estimated assuming the linear regression between $\mathbf{x}_{\mathrm{SBP}}^k$ and $\mathbf{x}_{\mathrm{SBP}}^k$, i.e.,

$$\mathbf{x}_{\mathrm{RR}}^k = b_k \mathbf{x}_{\mathrm{SBP}}^k + c_k \mathbf{1}_{N_k} + \boldsymbol{\epsilon}_k, \quad k = 1, 2, \ldots, K \tag{1}$$

Table 1
Lower thresholds values for BS and BE identification.

Threshold (units)	BS	BE
$N_{\min}$ (beats)	3	3
$\Delta_{\min}^{\mathrm{SBP}}$ (mmHg)	1	–
$\Delta_{\min}^{\mathrm{RR}}$ (ms)	5	–
$r_{\min}$	0.8	0.8

where $\boldsymbol{\epsilon}_k$ is a vector of residuals and $\mathbf{1}_{N_k}$ is a vector of ones with length N_k. The parameters b_k and c_k are estimated by ordinary least squares (OLS) minimization. Finally, an overall estimator is obtained from the mean of the K local slopes

$$\mathcal{B}_{\mathrm{L,O}} = \frac{1}{K} \sum_{k=1}^{K} b_k. \tag{2}$$

2.2. The events technique

The new criterion for SBP–RR segmentation consists of the identification of segments that exhibit positive and high correlation between the x_{SBP} and x_{RR} values. That is, for the identification of each baroreflex event BE$_k$ only the thresholds $N_{\min}$ and $r_{\min}$ are enforced, as pointed out in Table 1. Since no minimum values for Δ_k^{SBP} and Δ_k^{RR} are required, x_{SBP} and x_{RR} may not be consecutively increasing or decreasing on a beat-to-beat basis as in BSs. Fig. 1 displays x_{SBP} and x_{RR} in BSs and BEs identified in a record, illustrating that BEs are not necessarily simultaneous x_{SBP} and x_{RR} ramps over time as BSs. Also, it can be observed that BEs can achieve a longer length than BSs and that x_{SBP} and x_{RR} in BEs exhibit more variability as a consequence of less restrictive identification thresholds.

2.2.1. Global approach for slope estimation

The global approach is based on a global regression slope over the local mean detrended baroreflex related segments [12]. The kth local mean detrended segment $(\mathbf{d}_{\mathrm{SBP}}^k, \mathbf{d}_{\mathrm{RR}}^k)$ is obtained from the original segment $(\mathbf{x}_{\mathrm{SBP}}^k, \mathbf{x}_{\mathrm{RR}}^k)$ by

$$\mathbf{d}_{\mathrm{SBP}}^k = \mathbf{x}_{\mathrm{SBP}}^k - \bar{x}_{\mathrm{SBP}}^k \mathbf{1}_{N_k} \quad \text{and} \quad \mathbf{d}_{\mathrm{RR}}^k = \mathbf{x}_{\mathrm{RR}}^k - \bar{x}_{\mathrm{RR}}^k \mathbf{1}_{N_k}, \tag{3}$$

where $\bar{x}_{\mathrm{SBP}}^k$ and $\bar{x}_{\mathrm{RR}}^k$ represent the mean value of $\mathbf{x}_{\mathrm{SBP}}^k$ and $\mathbf{x}_{\mathrm{SBP}}^k$, respectively, i.e,

$$\bar{x}_{\mathrm{SBP}}^k = \frac{1}{N_k} \sum_{i=1}^{N_k} \mathbf{x}_{\mathrm{SBP}}^k(i) \quad \text{and} \quad \bar{x}_{\mathrm{RR}}^k = \frac{1}{N_k} \sum_{i=1}^{N_k} \mathbf{x}_{\mathrm{RR}}^k(i). \tag{4}$$

Local mean detrending allows the correction of the differences in $\mathbf{x}_{\mathrm{SBP}}^k$ and $\mathbf{x}_{\mathrm{RR}}^k$ baselines, emphasizing their fluctuations around their local mean value. The detrended pairs of values can be represented in a dispersion diagram with $\mathbf{d}_{\mathrm{SBP}}^k$ displayed against $\mathbf{d}_{\mathrm{RR}}^k$ as in Fig. 2(a) and (b).

A global BRS measure $\mathcal{B}_{\mathrm{G,O}}$ can be considered as the slope obtained from the mean detrended values,

$$\mathbf{d}_{\mathrm{RR}} = \mathcal{B}_{\mathrm{G,O}} \mathbf{d}_{\mathrm{SBP}} + \boldsymbol{\epsilon}, \tag{5}$$

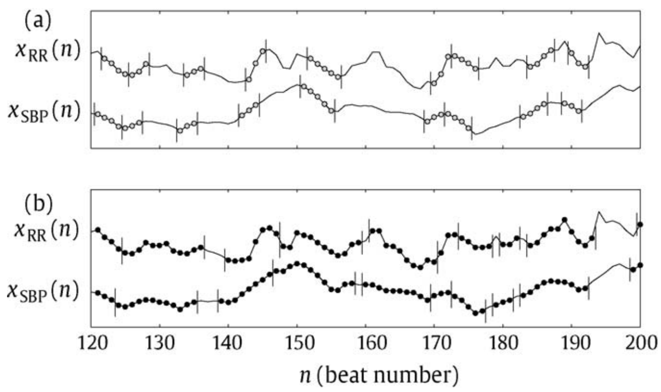

Fig. 1. Values of x_{SBP} and x_{RR} for the identified (a) BS and (b) BE in "A001LB" file of the EuroBavar Dataset [10]. There are 171 beats in 52 BSs and 448 beats in 57 BEs, in the first 512 beats of the record. Thresholds for BS/BE identification are given in Table 1.

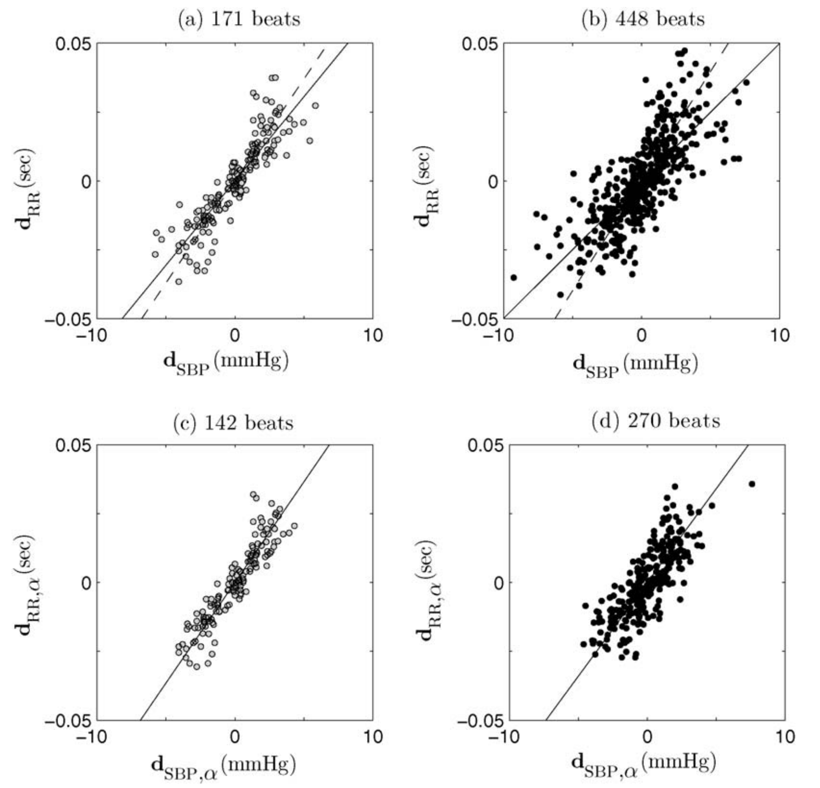

Fig. 2. Dispersion diagram of $\mathbf{d}_{SBP}$ and $\mathbf{d}_{RR}$ for the identified (a and c) BS and (b and d) BE. In figures (a) and (b), the dashed line has slope $\hat{\mathcal{B}}_{L,O}$ and passes through the origin. The solid line is the global regression line with slope $\hat{\mathcal{B}}_{G,O}$, estimated by OLS minimization. In figures (c) and (d), the solid line is the total regression line with slope $\hat{\mathcal{B}}_{G,T}$, estimated by TLS minimization. Same data as in Fig. 1.

where $\mathbf{d}_{SBP} = [\mathbf{d}^1_{SBP} \cdots \mathbf{d}^K_{SBP}]$, $\mathbf{d}_{RR} = [\mathbf{d}^1_{RR} \cdots \mathbf{d}^K_{RR}]$ and $\boldsymbol{\epsilon}$ is a vector of residuals. The parameter $\mathcal{B}_{G,O}$ is estimated by OLS minimization.

2.2.2. Total approach for slope estimation

The total approach is a robust version of the global approach, consisting of an outlier rejection rule combined with the slope estimation in (5) using total least squares (TLS) minimization [13]. In linear regression, the OLS method attributes all errors to the dependent variable and the solution minimizes the sum of squared vertical direction errors. On the other hand, the TLS method minimizes the sum of squared orthogonal direction errors, accounting for errors in both the dependent and the independent variables [14].

Before TLS slope estimation, outlier segments are removed from BRS analysis. The influence of the kth segment is evaluated by f_k, this being the ratio between the *TLS slope estimated when the kth segment is omitted from BRS analysis* and the *TLS slope estimated when all segments are used for BRS analysis*. A value of f_k near 1 indicates no excessive influence of that segment in the BRS estimation. The kth segment is an outlier if f_k exceeds the median value more than twice the median absolute deviation (MAD) divided by 0.6745 [15].

After the removal of outlier segments, the total slope $\mathcal{B}_{G,T}$ is estimated with the remaining pairs $(\mathbf{d}_{SBP,\alpha}, \mathbf{d}_{RR,\alpha})$. The TLS approach is sensitive to scale changes in the data [14], meaning that a multiplicative factor in one of the variables will not produce a proportional slope. To deal with this shortcoming, $\mathbf{d}_{SBP,\alpha}$ and $\mathbf{d}_{RR,\alpha}$ must be normalized and to guarantee the same order of magnitude in $\mathbf{d}_{SBP,\alpha}$ and $\mathbf{d}_{RR,\alpha}$ errors, the correction factors are defined by the corresponding MAD values. The slope α is estimated using TLS minimization over the normalized values from

$$\frac{\mathbf{d}_{RR,\alpha}}{\mathrm{MAD}(\mathbf{d}_{RR,\alpha})} = \alpha \frac{\mathbf{d}_{SBP,\alpha}}{\mathrm{MAD}(\mathbf{d}_{SBP,\alpha})} + \boldsymbol{\epsilon}_\alpha, \tag{6}$$

where $\boldsymbol{\epsilon}_\alpha$ is a vector of residuals and the total approach estimator is

$$\mathcal{B}_{G,T} = \frac{\mathrm{MAD}(\mathbf{d}_{RR,\alpha})}{\mathrm{MAD}(\mathbf{d}_{SBP,\alpha})}\alpha. \tag{7}$$

Fig. 2(c) and (d) illustrate the dispersion of $\mathbf{d}_{SBP,\alpha}$ and $\mathbf{d}_{RR,\alpha}$ together with the corresponding total regression line. Comparing to Fig. 2(a) and (b), it can be observed that the identified outlier segments have their extreme points outside the mass center of the data.

3. Experimental data

The performance of the methods is evaluated using the EuroBaVar dataset, available for the comparison of BRS estimation procedures [10]. This dataset has 46 paired records of spontaneous x_{SBP} and x_{RR} series, acquired from 21 subjects in lying (L) and standing (S) positions. The record lengths range from 553 to 1218 beats. Therefore, in order to set comparable results for all records, the BRS analysis was based on the first $N_{max} = 512$ beats.

The dataset is non-homogenous: one subject is diabetic with evident cardiac autonomic neuropathy and another is recently heart transplanted, both classified as cardiac baroreflex failure patients by the Ewing score [10]. The remaining 19 subjects are 12 normotensive outpatients, 1 untreated hypertensive, 2 treated hypertensive and 4 healthy volunteers. In addition, replica records of two subjects were incorporated to test reproducibility. There is no information about the match of each subject to its corresponding records.

4. Results

The methods were compared with respect to the variables given in Table 2 and their ability to discriminate L and S positions for each record. The upper index S or E was added to each variable according to its evaluation in BSs or BEs, e.g., N^S and N^E indicate the number of beats available for BRS analysis using BSs and BEs.

Table 2
Summary of BRS variables evaluated for each record.

Variable	Description
N	# of beats
K	# of segments
N/K	segments mean length
r	$\mathbf{d}_{SBP} - \mathbf{d}_{RR}$ correlation
$\hat{\mathcal{B}}_{L,O}$	local BRS estimate
$\hat{\mathcal{B}}_{G,O}$	global BRS estimate
$\hat{\mathcal{B}}_{G,T}$	total BRS estimate

4.1. Sensitivity analysis of r_{min}

Fig. 3 presents the distribution of the variables in Table 2, as a function of r_{min}. For BSs, all variables are constant for $r_{min} < 0.8$, because the identified BSs are the same. This result indicates that the x_{SBP} and x_{RR} values in BSs present $r_{min} > 0.8$. In median, N^S is close to 128 of the 512 beats and N^S/K^S is lower than 4 beats/segment. The r^S is very high, probably due to the small values of N^S and N^S/K^S. For $r_{min} > 0.8$, N^S and K^S decrease in the same proportion so that N^S/K^S is kept constant for all r_{min} values. The BSs that exhibit lower correlation are rejected for $r_{min} > 0.8$, leading to higher r^S values. For BEs, N^E decreases and K^E increases with increasing r_{min}. The ratio N^E/K^E decreases and tends to $N_{min} = 3$, with r_{min} increasing to 1. Regarding the BRS estimates, $\hat{\mathcal{B}}^E_{L,O}$ and $\hat{\mathcal{B}}^E_{G,O}$ increase with increasing r_{min}, because BEs with lower $x_{SBP} - x_{RR}$ correlation and slope are identified for lower r_{min} values. When r_{min} increases, these segments are more unlikely to be identified and $\hat{\mathcal{B}}^E_{G,O}$ tends to $\hat{\mathcal{B}}^S_{G,O}$. As previously indicated, N^E/K^E decreases when r_{min} increases. The mean of the local slopes $\hat{\mathcal{B}}^E_{L,O}$ is calculated from more segments of shorter length (and higher slope) and, therefore $\hat{\mathcal{B}}^E_{L,O}$ increases for increasing r_{min}. The robust estimates $\hat{\mathcal{B}}^E_{G,T}$ do not seem to be much affected by r_{min}, mainly due to the outlier rejection rule. Finally, as illustrated in Fig. 3(c), r^E increases linearly with r_{min}, being approximately r_{min} for $0.2 < r_{min} < 0.8$. The four files without BSs (circles in Fig. 3) present the same trend in N^E, N^E/K^E and $\hat{\mathcal{B}}^E$ as for the remaining files, although presenting lower values.

Fig. 3(d) and (e) suggest that $r_{min} = 0.8$ for BEs identification is an optimum trade-off between N^E and r^E. Since N^E decreases and r^E increases when r_{min} increases, r_{min} can be set to a value that maximizes the product $N^E r^E$. Alternatively, the product $N^E(r^E)^2$ can be considered, once the squared correlation coefficient r^2

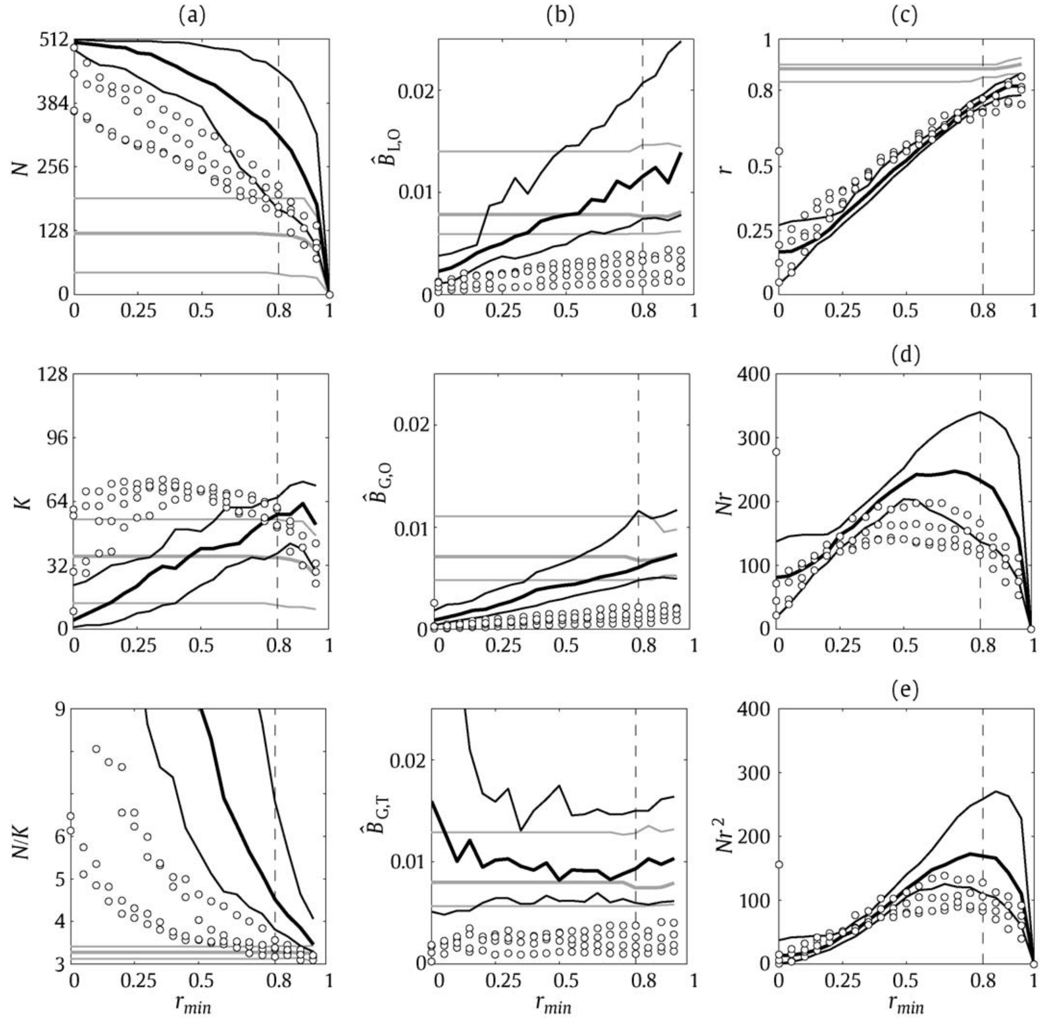

Fig. 3. Distribution of BRS variables as a function of r_{min} (from 0 to 1 by steps of 0.05) showing lower quartile, median and upper quartile values. Values obtained from BS (grey) and BE (black). The circles localize the files without BSs and with BEs.

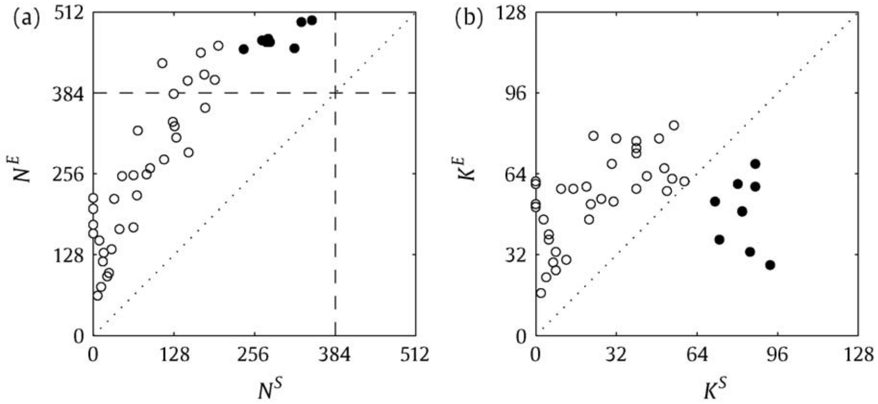

Fig. 4. Dispersion diagrams comparing N and K produced by BS and BE. Values equal to 0 correspond to the files without BSs and with BEs. The filled circles localize the files that satisfy $K^S > K^E$. The dotted line is the identity line.

corresponds to the fraction of $\mathbf{d}_{RR}$ variance accounted for the $\mathbf{d}_{SBP} - \mathbf{d}_{RR}$ linear regression.

4.2. Number of beats/segments in BRS analysis

Fig. 4 shows that N^E is highly correlated with N^S and is always higher than N^S (Fig. 4(a)), because BEs are in larger numbers for most of the files (open circles in Fig. 4(b)) and BEs are longer segments segments than BSs. The files that present $K^S > K^E$ (filled circles) are the files that present the highest N^E and N^S values and still satisfy $N^E > N^S$, because in these cases BEs are much longer than BSs.

Fig. 5 shows the distribution of the median of K and the number of EuroBaVar records (out of 46) as a function of N_k (the segments length), evidencing that BEs are longer segments than BSs. For BSs, 12 records have one 6-beat BS and none present BSs longer than 8 beats, whereas 24 records have one 10-beat BE and 21 records one 15-beat BE.

4.3. BRS estimates and L from S discrimination

Fig. 6(a) shows the empirical distribution of $\hat{B}$. The $\hat{B}^E_{L,O}$ values are higher than $\hat{B}^S_{L,O}$ and show larger interindividual differences. With the use of the global/total approaches, $\hat{B}^S$ and $\hat{B}^E$ have similar distributions. The pairwise comparison between estimates from BSs corroborates that $\hat{B}^S_{L,O} > \hat{B}^S_{G,O}$ [12], mainly due to the fact that the global approach emphasizes BSs with lower slopes. There are no significant statistical differences between the mean of paired $\hat{B}^S_{L,O} - \hat{B}^S_{G,T}$ values and zero ($p > 0.7$). The comparison between $\hat{B}^E_{G,O}$ and $\hat{B}^E_{G,T}$ with the traditional $\hat{B}^S_{L,O}$ evidences that $\hat{B}^S_{L,O} > \hat{B}^E_{G,O}$ in 34/42 of the files, $\hat{B}^E_{G,T} > \hat{B}^S_{L,O}$ in 25/42 of the files and $\hat{B}^E_{G,T} > \hat{B}^S_{L,O} > \hat{B}^E_{G,O}$ in 17/42 of the files. All approaches produce $\hat{B}^S$ with pairwise correlations exceeding 0.97 and $\hat{B}^E$ with pairwise correlations exceeding 0.8. The estimates $\hat{B}^S_{G,T}$ and $\hat{B}^E_{G,T}$ attained

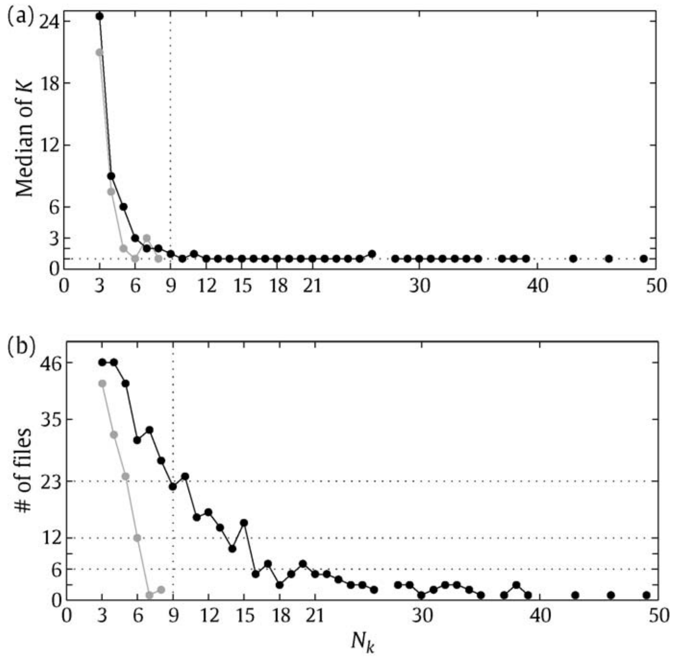

Fig. 5. Distribution of (a) the median of K and (b) the number of EuroBaVar files (out of the 46 records with 512 beats) a function of N_k (segment length). Values obtained from BS/BE (●/●). There were also found 5 files with BEs longer than 50 beats.

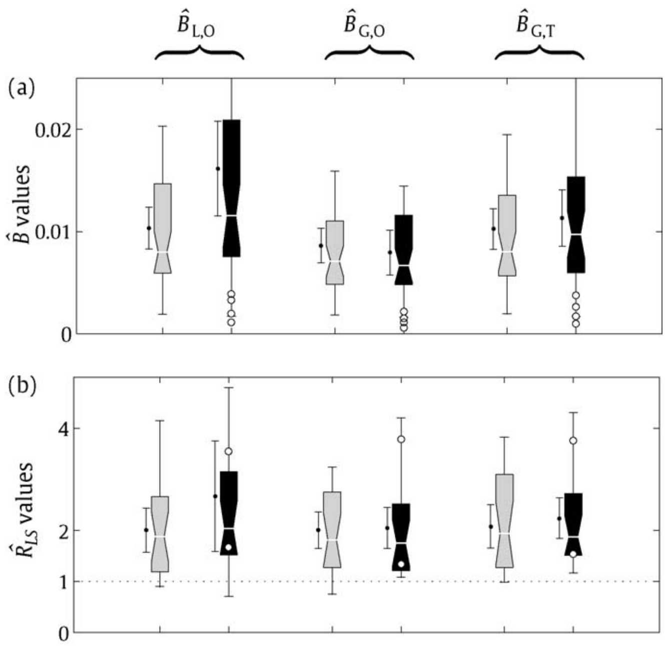

Fig. 6. Boxplots of (a) $\hat{B}$ in s/mmHg and (b) L to S ratio of $\hat{B}$ ($\hat{R}_{LS}$). Median and mean 95% confidence intervals represented by the notch and by the interval displayed at the left of each boxplot. Values obtained from BS (grey) and BE (black). The circles localize the files without BSs and with BEs.

the highest correlation between estimates using BSs and BEs (0.94).

BRS analysis based on BEs has also the capability of providing a BRS estimate when BSs cannot be identified. The 4 files without BSs correspond to the paired L and S evaluations of the 2 subjects (B005 and B010), in which neuropathy was evidenced by inadequate Heart Rate response to Ewing's test. For these files, identified in Fig. 6(a) with the open circles, the $\hat{\mathcal{B}}^{\mathrm{E}}$ values are lower than the 5th percentile of the BRS estimates empirical distribution of the remaining files.

For the discrimination between L and S, it is expected that the L to S ratio of $\hat{\mathcal{B}}$ ($\hat{R}_{LS}$) is above 1 [10]. As shown in Fig. 6(b) there is strong evidence that both the mean and median of $\hat{R}_{LS}$ are above 1 for all approaches combined with BSs or BEs, being approximatly two times greater in L than in S. Of the 23 pairs of records, 21 present BSs in both positions and $\hat{R}_{LS}$ from local/global/total approach is above 1 in 18/20/20 of the pairs, respectively. All 23 pairs present BEs, and $\hat{R}_{LS}$ is above 1 in 20/23/23 of the pairs, respectively. The use of global/total approach combined with BEs is able to distinguish L from S also for the files without BSs, but not able to differentiate them from the remaining files.

The results of the events technique are compared to those of the 'xBRS' estimate [8] in Table 3. All techniques are able to differenciate L from S positions ($\hat{R}_{LS} > 1$), with the $\hat{\mathcal{B}}^{\mathrm{E}}_{\mathrm{G,T}}$ estimates achieving a higher $\hat{R}_{LS}$ mean (better discrimination), with similar variability and lower amplitude range. Both $\hat{\mathcal{B}}^{\mathrm{E}}_{\mathrm{G,O}}$ and $\hat{\mathcal{B}}^{\mathrm{E}}_{\mathrm{G,T}}$ are able to distinguish L and S conditions for all subjects.

5. Discussion

The thresholds minimum beat-to-beat changes ($\Delta^{\mathrm{SBP}}_{\min}$ and $\Delta^{\mathrm{RR}}_{\min}$) and minimum correlation ($r_{\min}$) required for x_{SBP} and x_{RR} segmentation are set to increase the reliability of the identified BS being a segment clearly baroreflex related. In this way, there is an increased assurance that the corresponding slope is quantifying a real baroreflex effect. However, their use may also reduce the ability of providing an individual estimate, particularly if the thresholds values are very restrictive and/or the analyzed subject has poor BRS function.

The simultaneous use of $\Delta^{\mathrm{SBP}}_{\min}$, $\Delta^{\mathrm{RR}}_{\min}$ and $r_{\min}$ can be avoided [16]. In fact, $x_{\mathrm{SBP}} - x_{\mathrm{RR}}$ segments satisfying restrictive $\Delta^{\mathrm{SBP}}_{\min}$ and $\Delta^{\mathrm{RR}}_{\min}$ values present high $x_{\mathrm{SBP}} - x_{\mathrm{RR}}$ correlation. The correlation is usually higher than $r_{\min}$, suggesting that these 3 thresholds are redundant. This fact is in accordance with results in cats data [5], where it is reported that the correlation between x_{SBP} and x_{RR} value that fulfill $\Delta^{\mathrm{SBP}}_{\min} = 1$ mmHg and $\Delta^{\mathrm{RR}}_{\min} = 4$ ms exceeds 0.92; the authors state that this high correlation supports a true baroreflex nature of BSs rather than random coupling. The high correlation is clearly a consequence of BSs being chosen as to satisfy restrictive values on $\Delta^{\mathrm{SBP}}_{\min}$ and $\Delta^{\mathrm{RR}}_{\min}$. In the EuroBaVar data, 85% of the $x_{\mathrm{SBP}} - x_{\mathrm{RR}}$ segments that fulfill $N_{\min} = 3$, $\Delta^{\mathrm{SBP}}_{\min} = 1$ and $\Delta^{\mathrm{RR}}_{\min} = 4$ also satisfy $r_{\min} = 0.92$. This percentage increases to 99% for $r_{\min} = 0.8$, either setting $\Delta^{\mathrm{RR}}_{\min} = 4$ or $\Delta^{\mathrm{RR}}_{\min} = 5$ ms.

Removing $\Delta^{\mathrm{SBP}}_{\min}$ and $\Delta^{\mathrm{RR}}_{\min}$ for x_{SBP} and x_{RR} segmentation (as in BEs), there are more beats available for the slope estimation in the files that present BSs. Also it enables to identify segments in cases of BSs absence and, therefore, it is possible to provide a BRS estimate. Consequently, it would be more adequate to remove $\Delta^{\mathrm{SBP}}_{\min}$ and $\Delta^{\mathrm{RR}}_{\min}$ thresholds and only impose the $r_{\min}$ threshold. The results of the $r_{\min}$ sensitivity analysis show that $r_{\min} = 0.8$ is an adequate value for BEs identification, achieving a trade-off between N^{E} and r^{E} and maximizing r^{E} (see Fig. 3(c)–(e)).

It is important to point out that both BSs and BEs are identified by imposing a $r_{\min}$ value, regardless of its statistical significance (p_r as the p-value for the null hypothesis of no correlation). If such a criterion was to be additionally considered, 60% of the BSs identified in the EuroBaVar files (representing 54% of the BSs beats) would not present statistically significant x_{SBP} and x_{RR} correlation (i.e., $p_r > 0.05$). For BEs, the corresponding proportions would be 61% and 38%. The inclusion of non-significant segments can turn into a disadvantage if $\mathcal{B}_{\mathrm{L,O}}$ is used (either combined with BSs or BEs), but not if the events technique estimators ($\mathcal{B}^{\mathrm{E}}_{\mathrm{G,O}}$ and $\mathcal{B}^{\mathrm{E}}_{\mathrm{G,T}}$) are used. With that inclusion, $\hat{\mathcal{B}}_{\mathrm{L,O}}$ considers slopes estimated from non-significant segments to compute the average slope, whereas the events technique estimates are still based on data that presents r^{E} close to 0.8 and, due to the large N^{E} value, it is obviously statistically significant (see Fig. 3). The non-significant BEs are typically 3-beat segments that are located around the origin of the $\mathbf{d}_{\mathrm{SBP}}$ and $\mathbf{d}_{\mathrm{RR}}$ dispersion diagrams (as the ones in Fig. 2(b) and (d)). Therefore, these short segments have small weight in the global/total slope estimation: the correlation between the $\hat{\mathcal{B}}^{\mathrm{E}}_{\mathrm{G,O}}$ and the $\hat{\mathcal{B}}_{\mathrm{G,O}}$ computed from the segments identified by imposing $r_{\min} = 0.8$ and $p_r \leq 0.05$ is 0.98 and their median paired differences is not significantly different from zero ($p > 0.35$). Patients with a weak baroreflex response can be expected to present x_{SBP} and x_{RR} correlation lower than 0.8, although statistically significant. If the segments identification would be performed with $r_{\min} = 0$ and $p_r \leq 0.05$, r and N would be much lower than with BEs (for both dysfunction and normal cases) and, therefore, the ability of such method to provide an adequate BRS estimate would be diminished. As for the normal, the dysfunction cases present r^{E} close to 0.8 (also statistically significant due to large N^{E}) and the expected lower x_{SBP} and x_{RR} correlation is reflected in shorter $N^{\mathrm{E}}/K^{\mathrm{E}}$, i.e., shorter segments of high correlation (see Fig. 3).

A shorter length of BSs leads to a higher variance in the BRS estimate when the sequences technique is used (local approach with BSs), since each slope is typically estimated from 3 points. BRS estimation based on the local approach with BEs reduces the accuracy problem, because BEs are longer segments than BSs. This shortcoming can be further reduced if BEs are used together with global/total approach. First, with the global/total approach the slope is estimated from the overall number of $x_{\mathrm{SBP}} - x_{\mathrm{RR}}$ pairs in all of the identified segments. Second, as BEs are longer segments and usually in higher number than BSs, the overall number of beats in BEs is higher than in BSs. Also, the stationarity of BRS over segments in this dataset (a priori setting of $r_{\min} = 0.8$ leading to r close to 0.8) supports the use of global/total approach for BRS estimation, which implicitly assume stationarity.

Table 3
BRS assessment compared with time domain BRS estimate xBRS [8](in ms/mmHg).

	xBRS [7]	$\hat{\mathcal{B}}^{\mathrm{E}}_{\mathrm{G,O}}$	$\hat{\mathcal{B}}^{\mathrm{E}}_{\mathrm{G,T}}$
Lying			
Mean	12.4	10.5	15.3
SD	12.1	9.4	11.1
Range	2.0–60.0	1.4–49.8	2.6–55.4
Standing			
Mean	6.2	5.4	7.3
SD	3.9	3.1	4.3
Range	0.8–16.3	0.57–11.8	0.99–15.8
$\hat{R}_{LS}$			
Mean	1.96	2.05	2.24
SD	0.92	0.94	0.92
Range	0.85–4.20	1.08–4.20	1.17–4.31

The mean, SD (standard deviation) and range were computed over the non-repeated 21 EuroBaVar files and compared with the values in [8](Table 2). Comparisons with BRS estimates from other classes of methods can be depicted from [10,8].

Regarding the BRS values, it was shown that local estimates from BEs are higher and present higher dispersion than local estimates from BSs. The higher dispersion in BEs estimates simply indicates that, in the EuroBaVar dataset (a heterogenous dataset), the inter-subject variability measured by BEs analysis is greater than the inter-subject variability measured by BSs analysis. These results can be explained by the weight of 3-beat BEs in the slopes averaging, once they present higher slopes than the 3-beat BSs (as a result of avoiding $\Delta_{\min}^{\mathrm{SBP}}$ and $\Delta_{\min}^{\mathrm{RR}}$ thresholds). This was corroborated by recalculating local estimates from BEs considering $N_{\min}=4$ and observing that the differences both in median and dispersion disappear. Concerning the global/total approach with $N_{\min}=3$, the median and dispersion differences in the BSs/BEs estimates are smaller (see Fig. 6(a)).

In general, local estimates are higher than global estimates (both with BSs and BEs) and there are no significant statistical differences between local and total estimates. All estimates present pairwise correlation with the sequences technique estimates exceeding 0.8. With the use of the global/total approaches, BRS estimates from BSs and BEs have similar distributions and the total approach presents the highest correlation between BSs and BEs estimates with no significant statistical differences.

The fact that BRS estimates from BSs and BEs are correlated, though in the latter case obtained from a higher number of beats, indicates that both are measuring the same phenomenon but with a more visible expression in BEs. The absence of BSs in a record, and the impossibility to assess the BRS, is not synonymous to an absent BRS function, but rather a shortcoming of the sequences technique to provide a BRS estimate. In EuroBaVar recordings without BSs, the number of beats in BEs is around 200 out of 512 beats with r^{E} exceeding 0.75. The corresponding BRS estimates are lower than the 5th percentile of the BRS estimates empirical distribution for the remaining files, therefore indicating a poorer BRS function of these subjects.

The ratio $\hat{R}_{LS}$ obtained from BEs allows the discrimination of L and S positions in all subjects, whether obtained with the global or the total approach. However, the median of the ratios is higher when the total approach is used. In general, the total approach is preferred since it is more robust than the global approach and can handle nonstationary data. It should be noticed that for the single purpose of L and S discrimination, simpler statistical measures over the whole x_{RR} series can be considered. For example, the L to S ratio of x_{RR} mean value (or any quartile) discriminates 22/23 of the cases and the L to S ratio of x_{RR} maximum value (or minimum) discriminates 21/23 of the cases.

The use of BEs in BRS analysis also allows L and S discrimination for the subjects without BSs and it is not possible to differentiate these cases from the remaining ones. The location of the ratio $\hat{R}_{LS}$ for these files in separate tails of the overall distribution could be explained by the fact that the ratio of two small values is more sensitive to a small variation in one of the values. Another explanation could be the different origins of the baroreflex failure (one diabetic with cardiac neuropathy and another after heart transplantation). From this work, clinical interpretation studies facing pathological/control cases should be carried out in order to further investigate this behaviour.

There has been debate about the meaning of BSs and the reasons why the SBP–RR analysis based on BSs reflects the BRS function [5,9]. It is reported that the parasympathetic modulation may be already active on the same RR interval or on the one immediately following a blood pressure change, while sympathetic modulation usually becomes apparent after 5–6 beats [9]. As displayed in Fig. 5, BSs are typically of 3-beat length, 12/46 of the records have 6-beat BSs and none present BSs longer than 8 beats. Therefore, BRS analysis from BSs mostly reflects the autonomic control of the heart through parasympathetic neural afferents [9]. The sympathetic arm of the ANS presents typically oscillations of lower frequency than the parasympathetic [9] and, therefore, longer x_{SBP} and x_{RR} data segments are needed to detect and quantify this modulation. As the events technique is able to provide long data segments, besides the short segments already identified by the sequences technique, BEs are more likely to capture the sympathetic modulation than BSs. Also, as BEs are not constrained to be of constant length (as in [8]), arterial baroreceptors stimulation and deactivation effects can be separable. Experimental studies making use of manoeuvers for the activation or inhibition parasympathetic/sympathetic modulations are now needed to clarify the physiological meaning of baroreflex events.

6. Conclusions

In this work, the events technique is proposed to improve time domain BRS assessment. This novel technique consists of the joint use of baroreflex events (BEs) and global/total slope estimators. With the use of BEs instead of BSs, the BRS analysis benefits from more and longer segments of data, leading to a higher number of beats available for the slope estimation (more than 50% of all beats in BEs against 25% in BSs). Also, the use of BEs provides a BRS estimate for all subjects. If BSs are identified, BRS estimates from BEs and BSs are highly correlated. For the cases of BSs absence (usually associated with poor BRS function), BRS estimates based on BEs are lower than the 5th percentile of the remaining BRS estimates empirical distribution. Finally, the events technique provides a higher BRS estimates inter-subject variability, which allows to distinguish lying from standing positions in all subjects, including those without BSs (23/23 against 18/23 for the sequences technique).

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