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Factors influencing differences between invasive and spontaneous baroreflex estimates: distinct methods or different data?

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Abstract— **Currently invasive BRS estimates are obtained with drug-induced data assuming a sigmoidal SBP–RR relationship, while spontaneous BRS estimates are obtained with non-sigmoidal estimators. In particular, the events (sequences) technique provides a spontaneous BRS estimate based on baroreflex events, BEs (baroreflex sequences, BSs). In this work, BRS estimates are compared considering that can be obtained with different estimators and evaluated in different conditions.**

All BRS estimates were found to be significantly correlated. In comparison with BS estimates, BE estimates from spontaneous data exhibited higher correlation with sigmoidal estimates and their differences were associated with differences in SBP levels from invasive to spontaneous condition. BE estimator evaluated in different conditions decreased the differences between BRS estimates, pointing out differences due to the use of distinct methods, and such differences were correlated with differences in SBP and RR levels from invasive to spontaneous conditions. Finally, sigmoid estimates were more correlated with BE estimates in invasive data in comparison with those evaluated from BS. In conclusion, BRS analysis from BEs provides an estimate that exhibits higher correlation and lower differences between BRS estimates from different conditions, and reflects properly the BRS physiology.

I. INTRODUCTION

Time domain baroreflex sensitivity (BRS) is usually quantified from systolic blood pressure (SBP) and RR series, using either drug induced or spontaneous data [1]. In comparison with the spontaneous methods, drug induced techniques stimulate a larger and clearer SBP change in order to force a pronounced RR response (i.e., clearer baroreflex activation). Therefore, pharmacological protocols explore the baroreflex function over a wider SBP range, while spontaneous methods allow the BRS assessment near the subject's operating point.

The sequences technique is based on a regression analysis over the SBP and RR values occurring during short segments called "baroreflex sequences" (BSs). The events technique provides a BRS estimate as the global slope computed from the SBP and the RR values in identified "baroreflex events" (BEs), that can be both of short or long length [2], [3]. The use of BEs is introduced as an alternative to BSs, to improve time domain BRS assessment, allowing its quantification in cases of BS absence [2]. Also, global slope estimators combined with BEs are proposed to increase robustness, to increase reproducibility and to decrease dispersion in the BRS estimation [4]. Finally, the events technique captures better BRS changes due to sympathetic low-frequency modulation, as BEs can be of longer length than BSs [3].

Time domain spontaneous techniques were introduced after pharmacological methods, e.g. the (Modified) Oxford protocols [1]. Despite their obvious advantages, the wide spread use of those methods has been limited because of their poor agreement with the invasive ones [5]. Several comparisons between spontaneous and invasive BRS estimates report significant differences and poor significant correlation [6], [7], [8]. On the contrary, a comparison between BRS estimates from the sequences technique and the slope of the SBP–RR sigmoidal tangent line at the SBP rest level reported no significant differences and high correlation between estimates [9]. The comparisons between spontaneous/invasive BRS methods have been focused on differences that spontaneous/invasive data carry out. Obviously, it is possible that the reported differences between spontaneous and invasive BRS estimates are due to both physiological and methodological differences between the methods. Consequently, the comparison between spontaneous/invasive BRS methods must consider these two aspects.

In this work, BRS methods are compared and existing differences are further explored: (1) different BRS estimators are evaluated on the same condition and (2) a BRS estimator is evaluated on different conditions. Additionally, BRS estimation from BS and from BE are further compared on spontaneous and drug-induced data.

II. METHODS

A. Experimental protocol and Data

The experiments were carried out in the Erasme University Hospital, Belgium, approved by the Ethics Committee and with written consent of the participants. Thirty sets of SBP and RR beat-to-beat series were collected from 15 healthy male subjects (20–36 years) in supine rest condition [10], [4]. Each subject was monitored 5 min in spontaneous condition (SP) and 3 min during the Modified Oxford protocol (OX): 1 min of baseline acquisition (BAS) followed by consecutive boluses of 150 μg sodium nitroprusside (NT) and of 150 μg phenylephrine hydrochloride (PH). Figure 1 presents the SBP and RR data from one subject (respectively x_{SBP} and x_{RR}), illustrating that the NT (vasodilator) bolus acutely

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decreases x_{SBP} and produces a baroreflex mediated shortening of the x_{RR} interval. On the contrary, the PH (vasoconstrictor) bolus acutely increases x_{SBP} and x_{RR} values. Figure 1 also illustrates the short time gap between the successive NT and PH injections, leading to a mixture of effects.

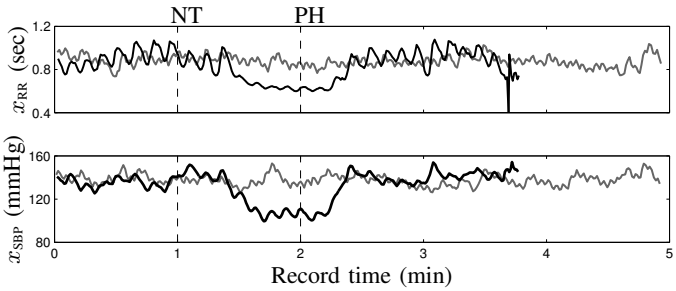

Fig. 1. SBP and RR data from a representative subject in SP condition (grey) and during the OX protocol (black), superimposed to facilitate comparison. The dashed lines identify the timing of NT and PH boluses during the OX protocol.

The OX protocol is generally described in the literature as the administration of successive injections of NT and PH (or vice versa). However, OX data can exhibit different characteristics depending of, e.g., the time between NT and PH injections. For example, in [9] PH bolus was administrated after at least 5 minutes from NT bolus, which allowed the x_{SBP} and x_{RR} values to lower and raise with respect to the baseline of the subject. In this way, the entire sigmoidal function that characterizes the BRS function could be obtained while, for the OX protocol used in this work, only the downpart of that sigmoidal curve could be assessed.

B. Invasive time domain BRS evaluation

The invasive BRS estimate $\hat{\mathcal{B}}^{\text{I}}$ was obtained as the slope of the tangent line to the SBP–RR sigmoidal curve [9]. Figure 2(a) shows the same data as in Fig. 1, where it is possible to observe high dispersion in the data, in particular around the operating point of the subject, denoted as $(\bar{x}_{\text{SBP}}[\text{BAS}],\bar{x}_{\text{RR}}[\text{BAS}])$ and defined as the SBP and RR averaged values in the first minute of the OX protocol, just before the NT bolus (see Fig. 1). This high variability can lead to difficulties in the estimation of the sigmoidal parameters, which were overcome in two different ways. First, only the data in the time window from the NT bolus to the maximal effect of the bolus, i.e., the minimum $x_{\text{SBP}}(n-1)$ value was considered (Fig. 2(b)). Second, as proposed in [11], $x_{\text{SBP}}(n-1)$ and $x_{\text{RR}}(n)$ values were averaged across bins of 2 mmHg increments in the $x_{\text{SBP}}(n-1)$ values (Fig. 2(c)). The sigmoidal parameters were estimated from the averages $\bar{\mathbf{x}}_{\text{SBP}}$ and $\bar{\mathbf{x}}_{\text{RR}}$ considering $(\bar{x}_{\text{SBP}}[\text{BAS}],\bar{x}_{\text{RR}}[\text{BAS}])$ as the sigmoid inflection point [12]. The model was estimated using nonlinear least-squares Levenberg-Marquardt optimization with line-search [13], and $\hat{\mathcal{B}}^{\text{I}}$ was obtained as the slope of the tangent line at the operating point (Fig. 2(d)).

C. Time domain BRS evaluation from BS or BE

Time domain methods for spontaneous BRS estimation use BSs or BEs, identified from $x_{\text{SBP}}(n-1)$ and $x_{\text{RR}}(n)$ where

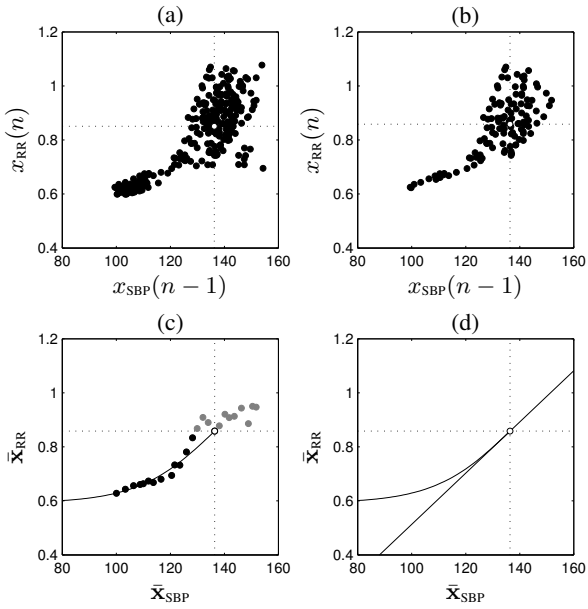

Fig. 2. Plot of SBP and RR from (a) the entire OX protocol and in (b) the time window between the NT bolus and the minimum $x_{\text{SBP}}(n-1)$ value, before PH bolus. Plot of $\bar{\mathbf{x}}_{\text{SBP}}$ and $\bar{\mathbf{x}}_{\text{RR}}$, superimposing (c) the estimated sigmoidal function and (d) the tangent line to the curve at the operating point of the subject $(\bar{x}_{\text{SBP}}[\text{BAS}],\bar{x}_{\text{RR}}[\text{BAS}])$, denoted by the white circle. The black circles in (c) identify the points used for the estimation of the sigmoidal parameters. Same data as in Fig. 1.

n is the beat number (Figs. 3(a–b)). BSs and BEs require at least 3 consecutive beats exhibiting SBP–RR correlation higher than 0.8 and BSs additionally require minimum SBP and RR beat-to-beat changes of 1 mmHg and 5 ms, respectively [2]. After identification, the mean is removed from x_{SBP} and x_{RR} at each segment and the mean detrended values are concatenated in $\mathbf{d}_{\text{SBP}}$ and $\mathbf{d}_{\text{RR}}$ vectors, respectively. Finally, the global slope $\mathcal{B}$ is estimated by ordinary least squares minimization following $\mathbf{d}_{\text{RR}} = \mathcal{B}\,\mathbf{d}_{\text{SBP}} + \boldsymbol{\epsilon}$, where $\boldsymbol{\epsilon}$ is a noise vector (Fig. 3(c–d)). Estimates $\hat{\mathcal{B}}^{\text{S}}$ and $\hat{\mathcal{B}}^{\text{E}}$ were obtained for each subject.

III. Results

Estimates $\hat{\mathcal{B}}^{\text{I}}$ were compared to $\hat{\mathcal{B}}^{\text{S}}$ and $\hat{\mathcal{B}}^{\text{E}}$, either evaluated in 5 min SP and 3 min OX conditions. An index was added to each estimate according to the condition, e.g., $\hat{\mathcal{B}}^{\text{E}}[\text{SP}]$ denoting the BRS estimate evaluated from BEs in SP condition. The $\mathcal{B}^{\text{I}}$ estimator was not evaluated in SP condition, because $\mathcal{B}^{\text{I}}$ assumes that the data follows a sigmoidal model, which is not a valid assumption in SP condition.

Figure 4 shows that $\hat{\mathcal{B}}^{\text{I}}$ and spontaneous BRS estimates, either $\hat{\mathcal{B}}^{\text{S}}[\text{SP}]$ or $\hat{\mathcal{B}}^{\text{E}}[\text{SP}]$, are moderately correlated. The observed differences between invasive and spontaneous estimates can be due to existing differences among invasive and spontaneous data, as the mean SBP value at baseline condition $\bar{x}_{\text{SBP}}[\text{BAS}]$ and the spontaneous mean SBP value $\bar{x}_{\text{SBP}}[\text{SP}]$ exhibited statistically significant differences (paired t-test $\text{H}_0 : \bar{x}_{\text{SBP}}[\text{BAS}] = \bar{x}_{\text{SBP}}[\text{SP}]$, $\text{p} < 0.01$).

Figure 5 compares $\hat{\mathcal{B}}^{\text{I}} - \hat{\mathcal{B}}[\text{SP}]$ with the differences in $\bar{x}[\text{BAS}] - \bar{x}[\text{SP}]$. By one hand, $\hat{\mathcal{B}}^{\text{I}} - \hat{\mathcal{B}}^{\text{S}}[\text{SP}]$ do not exhibit significant

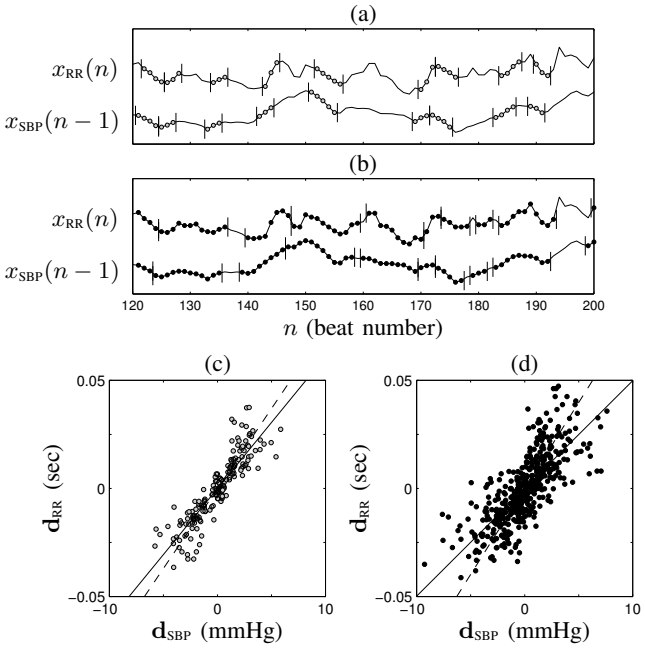

Fig. 3. Values of $x_{SBP}(n-1)$ and $x_{RR}(n)$ for the identified (a) BS and (b) BE in a spontaneous recording. Corresponding dispersion diagrams of $\mathbf{d}_{SBP}$ and $\mathbf{d}_{RR}$ for (c) BS and (d) BE, respectively, superimposing the global regression lines with slope $\hat{\mathcal{B}}$ (full line).

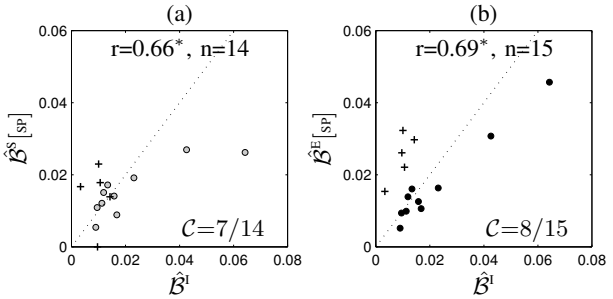

Fig. 4. Diagrams comparing $\hat{\mathcal{B}}^{I}$ with $\hat{\mathcal{B}}^{S}[SP]$ and $\hat{\mathcal{B}}^{E}[SP]$, evaluated for all subjects of the dataset. Subjects with largest $\hat{\mathcal{B}}^{I} - \hat{\mathcal{B}}^{E}[SP]$ absolute values are identified by '+'. In the x versus y diagram, $\mathcal{C}$ is the ratio $\#(x > y)/\#x$, where $\#$ stands for the counting numbers, r is the correlation between x and y, n is the sample size and symbol * denotes $p < 0.05$ for $H_0 : \rho = 0$.

correlation with differences of the operating point from BAS to SP condition (Fig. 5(a–b)). By the other hand, $\hat{\mathcal{B}}^{I} - \hat{\mathcal{B}}^{E}[SP]$ exhibit significant correlation with $\bar{x}_{SBP}[BAS] - \bar{x}_{SBP}[SP]$ (Fig. 5(c)) but not with $\bar{x}_{RR}[BAS] - \bar{x}_{RR}[SP]$ (Fig. 5(d)). As illustrated in Fig. 5(c), the lowest $\hat{\mathcal{B}}^{I} - \hat{\mathcal{B}}^{E}[SP]$ values hold the highest $\bar{x}_{SBP}[BAS] - \bar{x}_{SBP}[SP]$ differences. Regression analysis provided the linear model

$$\hat{\mathcal{B}}^{I} - \hat{\mathcal{B}}^{E}[SP] = -0.0009(\bar{x}_{SBP}[BAS] - \bar{x}_{SBP}[SP]) + 0.0041. \quad (1)$$

Parametric statistical inference could be carried out as the Kolmogorov-Smirnov test did not reject normal distribution for the regression residuals (p=0.83). The intercept of the model is not significant, with 95% confidence interval $[-0.0031, 0.0113]$. This result indicates that with no differences of the mean SBP values from BAS to SP conditions (i.e., $\bar{x}_{SBP}[BAS] - \bar{x}_{SBP}[SP] = 0$) it is not possible to reject the hypothesis that $\mathcal{B}^{I} - \mathcal{B}^{E}[SP] = 0$, i.e. that $\mathcal{B}^{I}$ and $\mathcal{B}^{E}[SP]$ are equal. This result is in accordance with [9], that reported no significant differences between spontaneous BRS estimates and the slope of the SBP–RR sigmoidal tangent line at the SBP rest level.

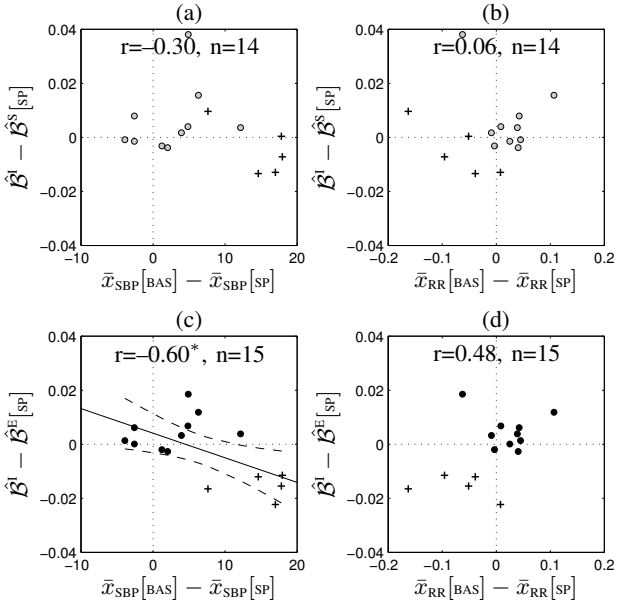

Fig. 5. Dispersion diagrams comparing $\hat{\mathcal{B}}^{I} - \hat{\mathcal{B}}[SP]$ with $\bar{x}[BAS] - \bar{x}[SP]$. Same caption as in Fig. 4. The solid and dashed lines in (c) represent the regression line and its 95% confidence intervals.

The results point out that differences between invasive and spontaneous BRS estimates are associated with differences in OX and SP operating points. However, the explained variance of 36% indicates that other factors besides these data dissimilarities, might explain the differences between these estimates.

A. Evaluation of different BRS estimators in OX condition

Figure 6 compares the different BRS estimators evaluated in OX condition, evidencing that $\hat{\mathcal{B}}^{I}$ values are correlated with both $\hat{\mathcal{B}}^{S}[OX]$ and $\hat{\mathcal{B}}^{E}[OX]$. In comparison with Fig. 4, pairwise sample correlations between different BRS estimates in OX condition are higher than those evaluated in different conditions (althought the increase of correlation was not statistically significant, probably due to the small sample size). This result suggests that some of the dissimilarities between the invasive and the spontaneous BRS estimates are due to methodological differences between the corresponding BRS estimators.

B. Evaluation of a BRS estimator in OX and SP conditions

The same BRS estimators were also compared in different conditions. As illustrated in Fig. 7, $\hat{\mathcal{B}}[OX]$ and $\hat{\mathcal{B}}[SP]$ values are highly correlated, with the highest sample correlation being obtained for $\hat{\mathcal{B}}^{E}$. In comparison with Fig. 6, the pairwise sample correlation between the same BRS estimator evaluated in different conditions is higher than that evaluated for different BRS estimators evaluated in the same condition.

Figure 8 shows that $\hat{\mathcal{B}}^{E}[OX] - \hat{\mathcal{B}}^{E}[SP]$ values exhibit significant correlation with SBP and RR differences from OX to SP

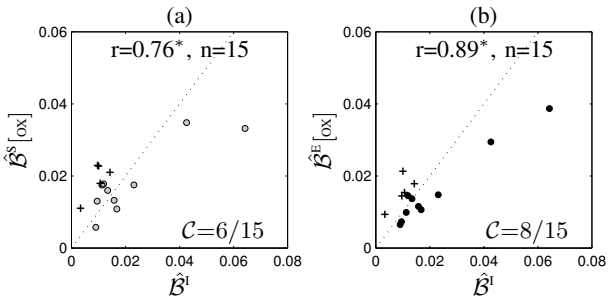

Fig. 6. Dispersion diagrams comparing $\hat{\mathcal{B}}^{\mathrm{I}}$ with $\hat{\mathcal{B}}^{\mathrm{S}}[\mathrm{OX}]$ and $\hat{\mathcal{B}}^{\mathrm{E}}[\mathrm{OX}]$. Same caption as in Fig. 4.

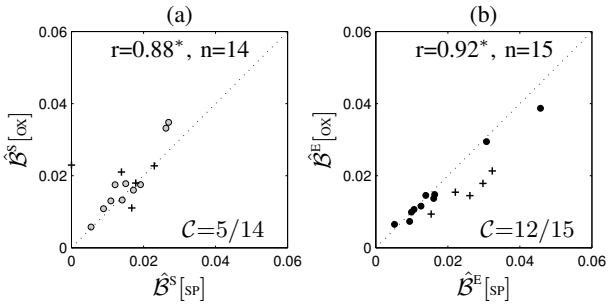

Fig. 7. Dispersion diagrams comparing $\hat{\mathcal{B}}^{\mathrm{S}}$ and $\hat{\mathcal{B}}^{\mathrm{E}}$ evaluated in OX and SP condition. Same caption as in Fig. 4.

conditions. Multiple linear regression estimated the model $\hat{\mathcal{B}}^{\mathrm{E}}[\mathrm{OX}] - \hat{\mathcal{B}}^{\mathrm{E}}[\mathrm{SP}] = a(\bar{x}_{\mathrm{SBP}}[\mathrm{BAS}] - \bar{x}_{\mathrm{SBP}}[\mathrm{SP}]) + b(\bar{x}_{\mathrm{RR}}[\mathrm{BAS}] - \bar{x}_{\mathrm{RR}}[\mathrm{SP}]) + c$, with $a = -0.0003$, $b = 0.0361$ and $c = -0.002$. Parametric statistical inference indicated that only the intercept of the model is not significant, with 95% confidence interval $[-0.0043, 0.0003]$. This result indicates that with no differences of the mean SBP and RR values from BAS to SP conditions it is not possible to reject the hypothesis that $\mathcal{B}^{\mathrm{E}}[\mathrm{OX}]$ and $\mathcal{B}^{\mathrm{E}}[\mathrm{SP}]$ are equal. This multiple regression model was found to explain only 66% of the $\hat{\mathcal{B}}^{\mathrm{E}}[\mathrm{OX}] - \hat{\mathcal{B}}^{\mathrm{E}}[\mathrm{SP}]$ variability, indicating other factors to explain differences in BRS estimates rather than differences in SBP and RR levels.

IV. CONCLUSIONS

In this work, different BRS estimators are evaluated in drug-induced (OX) and spontaneous (SP) data in order to study the factors influencing existing differences between BRS estimates. Spontaneous BRS estimates from BE are more correlated with $\hat{\mathcal{B}}^{\mathrm{I}}$ than BRS from BS. Also, BRS analysis from BE exhibits higher correlation between OX and SP than BRS from BS. Moreover, the differences $\hat{\mathcal{B}}^{\mathrm{I}} - \hat{\mathcal{B}}^{\mathrm{E}}[\mathrm{SP}]$ and $\hat{\mathcal{B}}^{\mathrm{E}}[\mathrm{OX}] - \hat{\mathcal{B}}^{\mathrm{E}}[\mathrm{SP}]$ were both found to be significantly correlated with differences in mean SBP and in mean RR from OX to SP condition, thus pointing out that BRS analysis from BE properly reflects the BRS physiology. Finally, regression analysis indicated that an important amount of the variability of the differences between BRS estimates is explained by both methodological and data differences.

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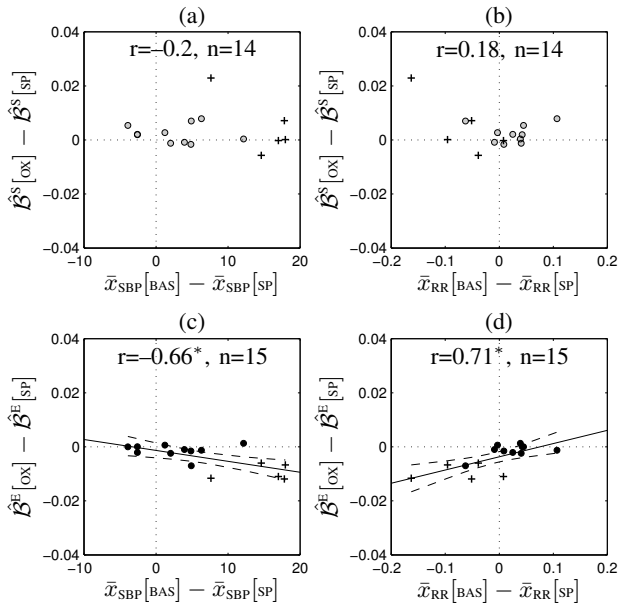

Fig. 8. Dispersion diagrams comparing $\hat{\mathcal{B}}[\mathrm{OX}] - \hat{\mathcal{B}}[\mathrm{SP}]$ with $\bar{x}[\mathrm{BAS}] - \bar{x}[\mathrm{SP}]$. Same caption as in Fig. 4. The solid and dashed lines in (c) represent the regression line and its 95% confidence intervals.

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