

Cardiovascular and Respiratory Interactions in Idiopathic Pulmonary Fibrosis by Extended Partial Directed Coherence: Short-term Effects of Supplemental Oxygen

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Abstract— Idiopathic pulmonary fibrosis (IPF) is a progressive interstitial lung disease that can lead to chronic arterial hypoxemia, hypercapnia, and dyspnea. To improve clinical symptoms in IPF patients, supplemental oxygen (SupplO₂) has been prescribed with the aim to maintain SpO₂ level, and consequently to relieve dyspnea, increase physical activity and improve quality of life. In this study, we investigated the effect of disease and short-term SupplO₂ on cardiovascular and respiratory autonomic regulation. Linear and nonlinear indices were extracted from the beat-to-beat variability of heart rate (HR), systolic (SYS) blood pressure and respiration (RESP) in IPF patients and healthy subjects spontaneously breathing ambient air (AA) and during SupplO₂ at 3 L/min. It was found that the effects on autonomic nervous systems (ANS) regulation were better demonstrated by the Granger causality (GC) method. GC was significantly higher ($p < 0.01$) in patients compared to controls for the interactions RESP→SYS and BBI→SYS.

Clinical Relevance—Short-term SupplO₂ in IPF could adversely affect systolic blood pressure variability in particular. This study may help in the management of SupplO₂ administration.

I. INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic, restrictive, and progressive disease characterized by fibrosis and inflammatory changes in lung tissue. IPF also affects lung vasculature and prevents an adequate gas exchange leading to exertional chronic arterial hypoxemia and dyspnea. The disease has a poor prognosis since 50% of patients die within 3 to 5 years, after diagnosis [1]. IPF origin, treatment, and influences on quality of life, among others, have been investigated but the disease was considered to be limited to the lung. Recently, IPF has been hypothesized as a systemic disease but its influence on the autonomic nervous system (ANS) regulation has not been assessed as in other pulmonary diseases. For example, chronic obstructive pulmonary disease affects negatively the cardiovascular system and the ANS. The former conclusion has been mainly stated based on the analysis of heart rate variability [2,3]. However, studies about alterations of ANS regulation due to IPF are scarce. Furthermore, supplemental oxygen (SupplO₂) has been

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prescribed to IPF patients to improve clinical symptoms but its impact on ANS regulation of cardiovascular and respiratory systems has not been evaluated. A former effort by the authors analyzed the hemodynamic response to SupplO₂ in IPF in comparison with healthy subjects. The study demonstrated a potential detrimental effect on IPF hemodynamics, particularly on total peripheral resistance and cardiac output [4]. However, the analysis of cardiovascular times series of variability is relevant to count with a comprehensive picture of ANS regulation. In this study, linear and nonlinear techniques were used. In particular, interactions among the physiological systems were assessed by Granger causality (GC) method in IPF patients as compared to healthy subjects under the effect of short-term SupplO₂.

II. MATERIALS AND METHODS

A. Subjects, acquisition protocol, and preprocessing

The study protocol was approved by the Institutional Ethics Committee of the National Institute of Respiratory Diseases in Mexico City. All the enrolled subjects were medically evaluated and signed an informed consent according to the Declaration of Helsinki. This study includes 19 healthy subjects (CON) and 20 IPF patients with age of 67.79 ± 5.00 and 65.8 ± 6.48 years old, respectively. Table I displays parameters related to clinical measures and respiratory

Table I. Clinical and Functional Measures

Measure	Control (M 11/ W 8)	IPF (M 11/ W 9)
Hematocrit (%)	47.4 ± 4.9	51.6 ± 2.4
Hemoglobin(g/dL)	15.3 ± 1.4	15.0 ± 1.4
Respiratory rate	19 ± 6	$22 \pm 7^*$
FEV ₁ (% predicted)	98.63 ± 12.87	$78.15 \pm 30.27^*$
FVC(% predicted)	94.11 ± 12.72	$72.40 \pm 26.51^*$
FEV ₁ /FVC	77.69 ± 6.37	$88.08 \pm 9.54^*$
DL _{CO} (% predicted)	114.26 ± 20.85	$67.20 \pm 21.24^*$
PaO ₂ (mmHg)	-	61.92 ± 8.65
PaCO ₂ (mmHg)	-	34.76 ± 5.31

M, Men; W, women; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; DL_{CO}, diffusing capacity of the lungs for carbon monoxide; PaO₂, partial pressure of oxygen in arterial blood; PaCO₂, partial pressure of carbon dioxide; -, not registered. *Statistical difference with $p < 0.05$

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functional test of both groups. Signals acquisition was performed via a Biopac MP150 system during morning hours including ECG, continuous noninvasive arterial blood pressure, and peripheral blood oxygen saturation. In addition, a thoracic belt was used to acquire the respiratory signal. Raw signals were recorded in supine position for 10 min, with the subjects breathing ambient air (AA), and for another ten minutes breathing SupplO₂ at 3 L/min, to ensure an arterial oxygen saturation above 94%. In both phases, the subjects were breathing spontaneously [4], and all signals were digitized at sampling rate of 1000 Hz. Time series of successive beat-to-beat intervals (BBI), respiratory amplitude (RESP) at BBI onset as well as systolic (SYS) blood pressure (BP) were extracted from recorded signals. If necessary, all extracted time series were manually reviewed and corrected by interpolation of ventricular premature beats and artifacts. For GC analysis, time series were resampled at 2 Hz using spline interpolation and normalized to zero mean and unit variance. For dynamic data analysis, 5-minute sliding windows with 90% overlap were used. Therefore, there are 31 windows including different phases as indicated in Fig. 1. The transition phase (TPH) is characterized by windows sharing AA and Steady SupplO₂ conditions. In each window, univariate, and bivariate indices as well as the extended partial directed coherence (ePDC) were estimated.

B. Univariate and Bivariate Analysis

Linear indices from the time and frequency domains were extracted as the mean value, rmsd, and power of low (LF) and high-frequency (HF) bands, in absolute and normalized units. Nonlinear indices were also calculated by the symbolic dynamic technique as phvar5, an index of high variability, which provides the probability of occurrence of 6-length words of an alphabet of symbols “0” and “1”, with differences above 5 ms [5]. A bivariate approach, the dual sequence method (DSM), was applied to obtain the bslope and tslope indices, which are related to the baroreflex [6]. However, we avoided using the classical thresholds for SYS and BBI due to the criticisms about them [7]. Furthermore, SYS and BBI sequences with a length of one up to four samples were proved.

C. Multivariate Autoregressive Modeling, Extended Partial Coherence and Time-Frequency Analysis of Interactions

The ePDC is based on fitting the linear time-invariant parametric model of (1) to the observed set of M time series $\mathbf{Y}(n)$. The model coefficients $\mathbf{B}(k)$, $k=0, \dots, q$, are related to instantaneous and strictly causal effects, i.e.,

$$\mathbf{Y}(n) = \sum_{k=0}^q \mathbf{B}(k)\mathbf{Y}(n-k) + \mathbf{W}(n), \quad (1)$$

where q is the model order and $\mathbf{W}(n)$ is the innovation process formed by white and uncorrelated noises with diagonal covariance matrix $\mathbf{\Lambda} = \text{diag}(\lambda_i^2)$. To estimate $\mathbf{B}(k)$ is necessary to estimate first the coefficients of a strictly causal model [8, 9]. Afterward, to calculate $\mathbf{B}(0)$ and $\mathbf{B}(k)$ is necessary to perform a Cholesky decomposition of the covariance matrix of the strictly causal model to obtain a matrix \mathbf{L} . However, $\mathbf{B}(0)$ is a lower triangular matrix with a null diagonal requiring to order the time series $\mathbf{Y}(n)$ to define the direction of physiological influence among them. The model order q was obtained by the Akaike figure of merit defined as $AIC(q) =$

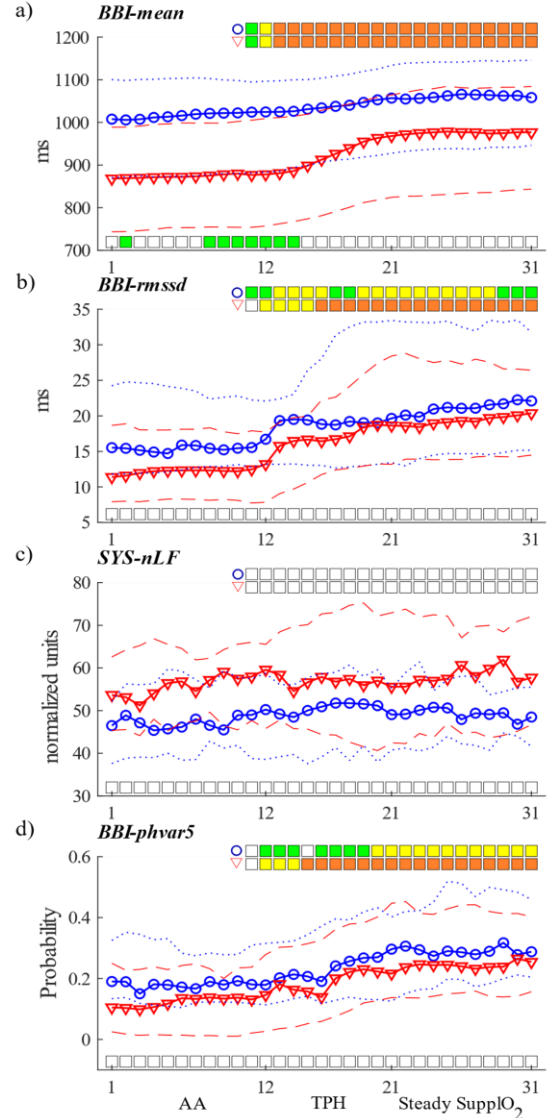


Fig. 1. Time course of median values of linear and nonlinear indices for BBI and SYS in AA (windows 1-11), TPH (windows 12-20) and Steady SupplO₂ (windows 21-31) conditions. Statistical significant differences are shown with a colored horizontal bar ($p < 0.05$ in green, $p < 0.01$ in yellow and $p < 0.001$ in orange). Significant differences between groups are displayed along the bottom of the graphs while differences within-group are at the top (IPF: red triangles, CON: blue circles). Interquartile range (25th -75th) in blue-dotted and red-dashed lines.

$N \log(\det \mathbf{\Sigma}) + M^2 q$, where $\mathbf{\Sigma}$ is the covariance matrix of the strictly causal model. Here, to achieve the former constrain $y_1 = \text{RESP}$, $y_2 = \text{SYS}$, and $y_3 = \text{BBI}$. From the frequency domain representation of (1) is possible to obtain the ePDC as:

$$\chi_{ij}(f) = \frac{\left(\frac{1}{\lambda_i}\right) \bar{B}_{ij}(f)}{\sqrt{\sum_{m=1}^M (1/\lambda_m^2) |\bar{B}_{mj}(f)|^2}} \quad (2)$$

Equation (2) provides a directional frequency-domain measure of connectivity quantifying the influence of the process y_i on the process y_j , removing the influence of other processes. ePDC is normalized with respect to the structure that sends the signal taking values between 0 (absence of causal coupling) and 1 (full causal coupling) at frequency f . Here, the coherence spectra were estimated using 512 bins. In

addition, the estimated ePDC values were corrected by statistical hypothesis testing with a threshold for significance via causal Fourier transform surrogates [8, 9]. An averaged time-frequency representation (TFR) for each group is shown since findings revealed certain variability for TFRs magnitude. The x -axis represents 31 windows while the y -axis refers to the frequency in Hz (range of 0.0-0.50 Hz). The magnitude of the information flow by ePDC (z -axis) ranges from 0 to 0.4.

C. Statistical Analysis

In each window, statistical significant differences between groups were established for univariate and bivariate indices while for ePDC, the comparison was performed tile by tile. The nonparametric Mann-Whitney-U-test was used, and the significance was set at three levels for descriptive purposes:

slightly significant for $p < 0.05$ (green), moderately significant for $p < 0.01$ (yellow), and highly significant for $p < 0.001$ (orange).

III. RESULTS AND DISCUSSION

According to Table I, the IPF group was characterized by a moderate reduction in vital capacity and FEV₁, mild reduction in diffusion capacity, hypoxemia, mild hypercapnia, and high respiratory rate. There were no statistical differences in age, anthropometric measures, hematocrit, or hemoglobin values.

A. Univariate Analysis in AA

Mean cardiac frequency was significantly higher in the patient group from windows 8 to 14, see Fig. 1. However, for mean SYS there were no group differences. For linear indices as BBI-rmssd there were no group differences, however the vagal activity in IPF has a tendency to be lower than in CON. In the case of spectral indices, BBI-LF and BBI-HF powers provided statistically significant differences ($p < 0.05$). Particularly, the BBI-HF power was significantly higher in CON than in IPF group, i.e., the vagal influence was increased in CON. Also, SYS-nLF power in IPF tends to higher values than in CON, reflecting an increased sympathetic influence to the vasculature. For nonlinear indices, BBI-phvar5 tends to show lower probability values in IPF, i.e., lower BBI variability. Based on univariate analysis, there were significant differences between groups, particularly for BBI indices.

B. Univariate Analysis in TPH and Steady SuppO₂

The expected effect of the oxygen upon the cardiac frequency was obtained during TPH and SuppO₂ conditions since the mean cardiac frequency decreased for both groups while the mean SYS was not different. Furthermore, linear and nonlinear indices did not provide statistical significant differences between groups. However, there were highly significant differences in the within-group analysis as AA condition was compared with TPH and Steady SuppO₂ for CON and IPF. Particularly, BBI-rmssd in IPF showed highly statistical differences against AA, i.e., it seems that the cardiac vagal modulation increased to a greater extent in IPF. This behavior was confirmed with the nonlinear index BBI-phvar5, see Fig. 1.

C. Bivariate Analysis

DSM did not show significant differences between groups in AA or TPH for any sequence length. However, bslope (ms/mmHg) was significant different ($p < 0.05 - 0.01$) in Steady SuppO₂ from window 21 with a sequence length of 2 samples. The index was higher in CON, i.e., CON increased their baroreflex in comparison with IPF.

D. Cardiovascular and Respiratory Interactions

GC method provided the TFRs for the RESP→SYS interaction for CON and IPF depicted in Fig. 2a. During AA condition, TFRs evidence differences between groups for the LF and HF bands with higher mean ePDC in IPF than in CON, Fig. 2b displays the corresponding time-frequency statistical values. LF band has been associated with the so-called Mayer waves, i.e., the IPF group shows an increased sympathetically mediated BP vasomotor modulation. For HF band, in particular for frequencies greater than 0.4 Hz, differences may

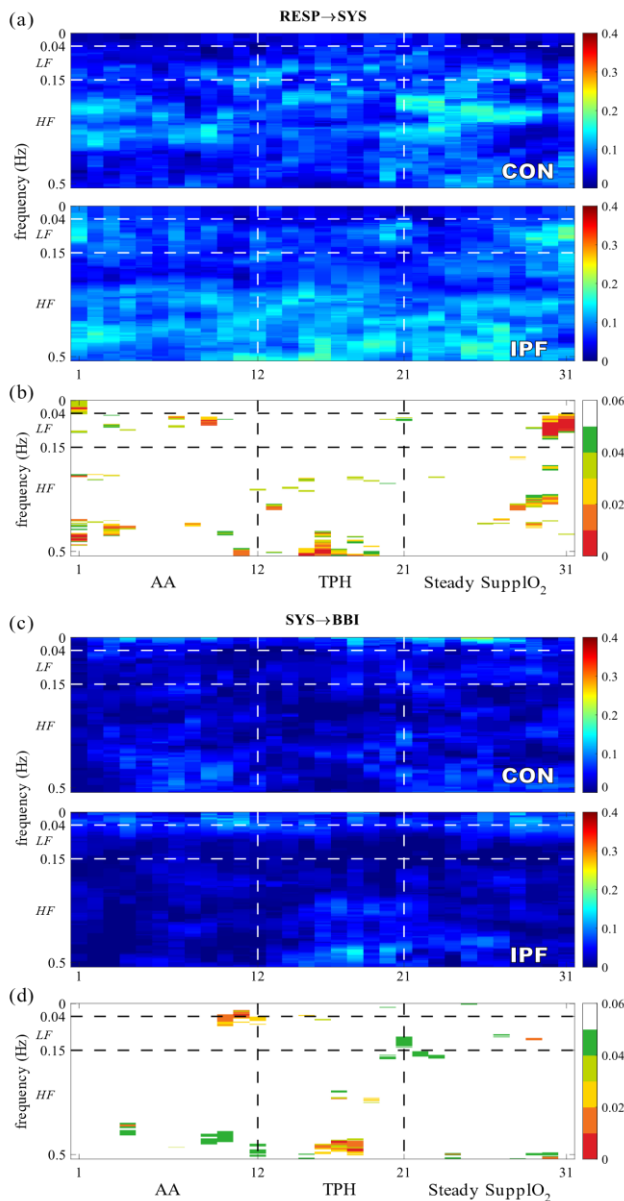


Fig. 2. Cardiorespiratory and cardiovascular interactions. (a) RESP→SYS and (b) statistical significant difference map between groups ($p < 0.05$ - green, $p < 0.03$ - yellow, $p < 0.01$ - red), (c) SYS→BBI and (d) its statistical difference map.

be produced partially by the higher respiratory frequency in IPF than in CON, leading to a different mechanical effect on central blood volumes. To analyze the mechanical change effect, a surrogate data was derived from the amplitude of the respiratory signal. However, no significant differences between groups along all the phases were found. The interaction SYS→BBI produced few statistical differences mainly for the highest part of the HF band. It is plausible that the baroreflex was blunted since the subjects were in supine position. The interaction RESP→BBI in the HF band showed highly statistical differences indicating a relevant respiratory sinus arrhythmia (RSA) for CON than for IPF, i.e., vagal influence was higher for CON group, but not for all AA windows, see Fig. 3a. Also, BBI→SYS interaction, the cardiac mechanical modulation, provided few significant differences in AA, see Fig. 3c. For TPH, RESP→SYS interaction

increased in the HF band in patients meaning that the influence of RESP increased when the oxygen begins to be delivered in IPF. Simultaneously, the SYS→BBI interaction, i.e., the baroreflex, increased only in IPF. Moreover, the RESP→BBI interaction pointed out an increased RSA for CON. Also, the BBI→SYS interaction increased for IPF, indicating a higher influence of the cardiac mechanical modulation. In the steady SupplO₂ phase, there were significant differences in the BBI→SYS interaction where IPF had higher mean ePDC in the LF band, associated with the sympathetic influence to the vasculature. Finally, SYS→BBI and RESP→BBI interactions showed few differences.

IV. CONCLUSION

The results of this study show that (a) ANS regulation is affected by the disease, which leads to a sympathetic predominance in AA; (b) a negative effect of short-term SupplO₂ occurs in IPF that is more evident by GC ($p < 0.01$), i.e., the oxygen increased the cardiac vagal activity but also the sympathetic modulation to the vasculature that leads to a decreased cardiac output, as we shown in a previous study [4]; and (c) with SupplO₂ the main differences are found in RESP→SYS interaction, particularly in LF band (sympathetic influence) and BBI→SYS. Since our previous studies pointed out a relevant increase of the total peripheral resistance (TPR) [4], the authors are currently analyzing other interactions including TPR.

REFERENCES

- [1] T. E. King, A. Pardo, and M. Selman, "Idiopathic pulmonary fibrosis," *The Lancet*, vol. 378, no. 9807, pp. 1949–1961, Dec. 2011.
- [2] J. Mohammed, M. Meeus, E. Derom, H. D. Silva, and P. Calders, "Evidence for Autonomic Function and Its Influencing Factors in Subjects with COPD: A Systematic Review," *Respiratory Care*, vol. 60, no. 12, pp. 1841–1851, Dec. 2015.
- [3] A. J. van Gestel and J. Steier, "Autonomic dysfunction in patients with chronic obstructive pulmonary disease (COPD)," *J Thorac Dis*, vol. 2, no. 4, pp. 215–222, Dec. 2010.
- [4] L. M. Santiago-Fuentes, R. González-Camarena, S. Charleston-Villalobos, M. E. Mejía-Ávila, S. Reulecke, I. Buendía-Roldán, M. J. Gaitán-González, G. Benítez-Valdez, T. Aljama-Corrales, "Hemodynamic response to low-flow acute supplemental oxygen in idiopathic pulmonary fibrosis and elderly healthy subjects," *Heart and Lung*, 50(1), pp. 197-205, 2021.
- [5] S. Schulz, A. Voss, *Symbolic dynamics, Poincaré plot analysis and compression entropy estimate complexity in biological time series*, In: Barbieri R., Scilingo E., Valenza G. (eds) *Complexity and Nonlinearity in Cardiovascular Signals*. Springer, pp. 45-85, 2017 – Springer.
- [6] H. Malberg, N. Wessel, A. Hasart, K. J. Osterziel, A. Voss, "Dual sequence method for analysis of spontaneous baroreceptor sensitivity," *Biomed Tech (Berl)*, 43 Suppl:532-3, 1998.
- [7] S. Gouveia, A. P. Rocha, P. Laguna, P. Lago, "Threshold Sensitivity in Time Domain BRS Estimation: Minimum Beat-to-Beat Changes and Minimum Correlation," *Computers in Cardiology* 34: 557-60, 2007.
- [8] L. Faes, A. Porta, G. Nollo, "Testing Frequency-Domain Causality in Multivariate Time Series," *IEEE T BioMed Eng*, 57, pp. 1897-1906, 2010.
- [9] S. Charleston-Villalobos, S. Reulecke, A. Voss, M.R. Azimi-Sadjadi, R. González-Camarena, M.J. Gaitán-González, J.A. González-Hermosillo, G. Hernández-Pacheco, S. Schulz, T. Aljama-Corrales, "Time-Frequency Analysis of Cardiovascular and Cardiorespiratory Interactions During Orthostatic Stress by Extended Partial Directed Coherence," *Entropy*, 21(5), pp. 468-482, 2019.

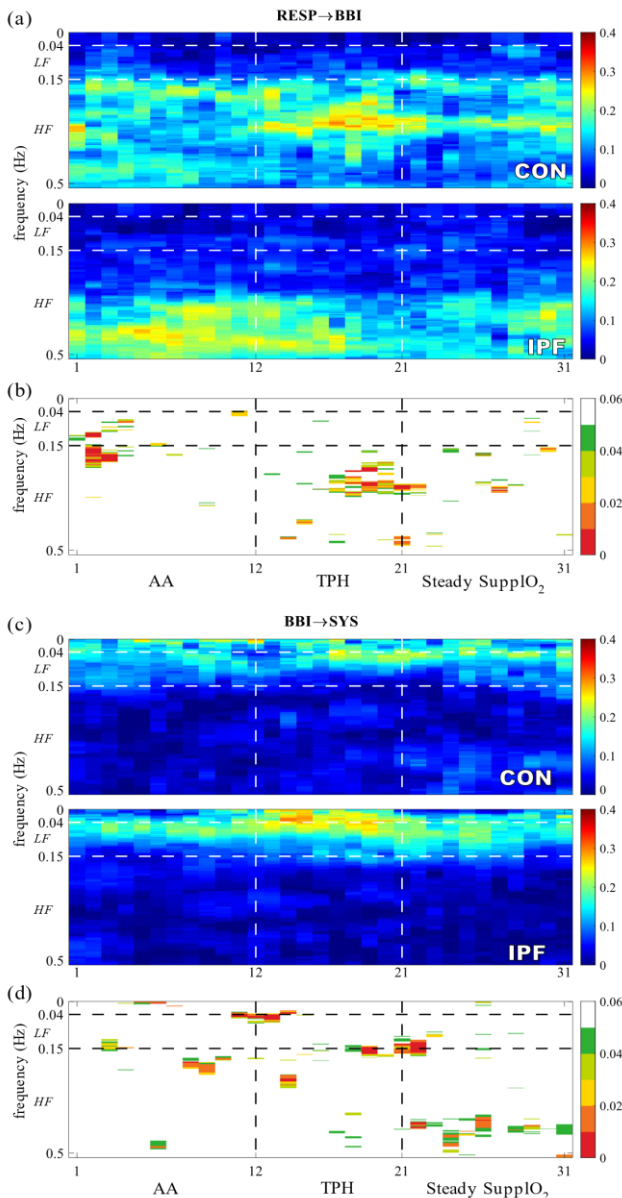


Figure 3. Cardiorespiratory and cardiovascular interactions. (a) RESP→BBI and (b) its statistical difference map, (c) BBI→SYS and (d) its statistical difference map.