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Information Flow to Assess Cardiorespiratory Interactions in Patients on Weaning Trials

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***Abstract*—. Nonlinear processes of the autonomic nervous system (ANS) can produce breath-to-breath variability in the pattern of breathing. In order to provide assess to these nonlinear processes, nonlinear statistical dependencies between heart rate variability and respiratory pattern variability are analyzed. In this way, auto-mutual information and cross-mutual information concepts are applied. This information flow analysis is presented as a short-term non-linear analysis method to investigate the information flow interactions in patients on weaning trials. 78 patients from mechanical ventilation were studied: Group A of 28 patients that failed to maintain spontaneous breathing and were reconnected; Group B of 50 patients with successful trials. The results show lower complexity with an increase of information flow in group A than in group B. Furthermore, a more (weakly) coupled nonlinear oscillator behavior is observed in the series of group A than in B.**

I. Introduction

The possible causes of breath-to-breath variability in the pattern of breathing have been discussed [1,2]. Nonlinear dynamic processes of the autonomic nervous system (ANS) can produce this variability [3,4]. Analysis of respiratory variability (RV) and heart rate variability (HRV) can provide a new tool to study the action of chemoreflexes without the application of external stimuli [5]. It has been described that respiratory variability was reduced in patients with restrictive lung disease, compared with that of healthy subjects [4]. One of the most challenging problems in intensive care [6] is the process of discontinuing mechanical ventilation, termed weaning. In this way, the weaning trial protocols are very important in patients under mechanical ventilation. A failed weaning trial is discomforting for the patient and may induce significant cardiopulmonary distress. When mechanical ventilation is discontinued, up to 25 percent of patients have respiratory distress severe enough to require reinstitution of ventilation support [6]. It has been hypothesized that the variability of the respiratory volume could be convenient weaning criteria to reduce the number of patients not successfully weaned [7]. Furthermore, it is known that the complexity of heart rate fluctuations can reflect the interrelationships between different control systems and intrinsic mechanisms, such as sympathetic and vagal influences, respiration, thermoregulation and peripheral vasomotor tone.

Various attempts have been reported to apply the concepts of nonlinear dynamics to the analysis of complex physiological systems [8-11]. Correlation dimension, Lyapunov exponents, and Kolmogorov entropy have improved the assessment of complex autonomic coordinations in several cases as risk stratification of sudden cardiac death, after myocardial infarction, multiple organ dysfunction, or particular autonomic dysfunction and blockades [12-15]. However, all these complexity measures need long time series. The application of information flow (*IF*) concepts to physiological systems has been recently performed [11,16,17] to assess the complex multimatched control loops acting on different time horizons within the ANS.

The aim of the present study is the development and evaluation of the *IF* with regard to the assessment of the different rhythmic dynamics of the cardiorespiratory system. Auto-Mutual Information Function (*AMIF*) and Cross-Mutual Information Function (*CMIF*) are applied in order to assess these different nonlinear rhythms. Also the linear concepts as auto-correlation function (*ACF*) and cross-correlation function (*CCF*) are applied in this analysis.

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II. Methodology

A. Analyzed Data

Electrocardiographic (ECG) signal and respiratory flow were measured in 78 patients on weaning trials from mechanical ventilation (WEANDB data base). The analyzed patients were recorded in the Departments of Intensive Care Medicine at Santa Creu i Sant Pau Hospital and at Getafe Hospital, according to a protocol approved by the local ethic committees. Using clinical criteria, the patients were classified into two groups: Group A, 28 patients that failed to maintain spontaneous breathing and were reconnected after 30 minutes of weaning trials, and Group B, 50 patients with successful trials after 30 minutes. The mean age of the subjects was 63.2±19.1 year old. This study contains 50 males and 28 females.

Respiratory flow was obtained using a pneumotachograph connected to an endotraqueal tube. The pneumotach consists in a Datex-Ohmeda monitor with a Validyne Model MP45-1-871 Variable-Reluctance Transducer. The ECG signal was obtained using a SpaceLabs Medical monitor. Both signals were recorded at a sampling frequency of 250 Hz during 30 minutes. The analyzed series in this study were the cardiac interbeat durations (*NN*) and the breath durations (T_{Tot}), respectively. Table I shows the mean and standard deviation of both series in group A and B.

TABLE I
MEAN AND STANDARD DEVIATION OF *NN* AND T_{Tot} SERIES

mean±sd	Group A	Group B
NN (ms)		
mean	647.9±109.2	702.2±111.6
SD	54.7±37.2	60.1±44.3
T_{Tot} (s)		
mean	2.23±0.833	2.93±0.792
SD	0.580±0.458	0.778±0.661

For the present study, *NN* and T_{Tot} series were transformed to time series, linearly interpolated and resampled at 4 Hz. The data were ranked with an independent scale and equally distributed.

B. Information Flow

Information Flow (*IF*) function provides complexity characteristics and allows physiological interpretations based on the relationship of physiological mechanisms [11, 16]. Those dependencies, which are non-linear and complex, can adequately be assessed by information theoretical methods such as *AMIF* and *CMIF*. Information flow functions are independent of signal amplitudes and describe the predictability and regularity of a signal.

The *IF* depending on a time lag τ can be assessed by the Shannon entropy

$$H(x) = -\sum_m p_m \log p_m \qquad (1)$$

applied to the original time series *x(n)* leading to *H(x)*, by time lag τ shifted on *y(n)* leading to *H(y)*, and the bivariate presentation leading to *H(x,y)*, namely by

$$IF(x,y) = H(x) + H(y) - H(x,y) \qquad (2)$$

It describes the amount of information with regard to the time shifted quantity *y(n)* if the original quantity *x(n)* is known. Whereby *H(y)* is the a-priori uncertainty with regard to *y,* and [*H(x,y)–H(x)*] is the remaining a-posteriori uncertainty, thus symmetric, namely *IF(x,y)=IF(y,x).*

In the case of two statistically independent quantities, such as in the case of a non-predictable time series, *IF(x,y)* is zero, otherwise it is positive.

Fig. 1 shows the evolution of *AMIF* on time lags τ of a Henon map and a random series. These deterministic nonlinear and random behaviors, respectively, can be compared with the graphics in Fig 2, where Henon map and random series are represented by a linear autocorrelation function (*ACF*).

In order to characterize *IF* using *AMIF* and *CMIF*, different representative measures are considered:

- *dec*, decay from τ=0 to τ=100 samples.
- *diff,* slope of the curve calculated by differences on consecutive τ samples.
- *grad*, slope of the curve calculated by the gradient function on consecutive τ samples.
- *int*, integral under de curve from τ=0 to τ=100 samples.

All these measures have been calculated for distinct histogram bins *b*={8,16,32,64}: *dec_b*, *diff_b*, *grad_b*, *int_b*.

The results are statistically classified using the Mann-Whitney test and validated constructing a discriminant function on each measure, using the leaving-one-out method. A statistical significance level p_{value}<0.05 is considered for the analysis. Under these criteria a measure is statistically accepted if p_{value}<0.05 and the discriminant function, constructed on that measure, can well classify the patients with a percentage higher or equal to 60%.

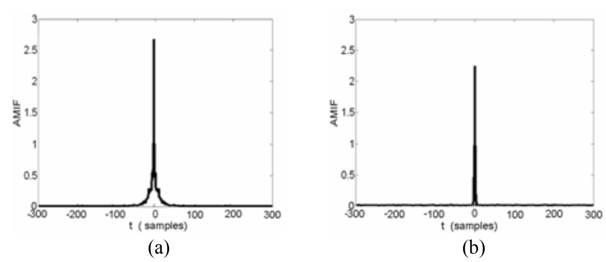

Fig. 1. Auto-mutual information function (*AMIF*): (a) Henon map; (b) Random data.

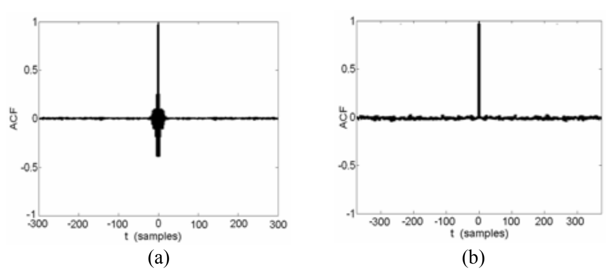

Fig. 2. Auto-correlation function (*ACF*): (a) Henon map; (b) Random data.

III. Results

NN and T_{Tot} time series are differently represented when nonlinear functions, *AMIF* and *CMIF*, are applied compared with linear functions, *ACF* and *CCF*. Fig. 3

contains these linear and no linear representations of *NN* and T_{Tot} series of a patient of group B.

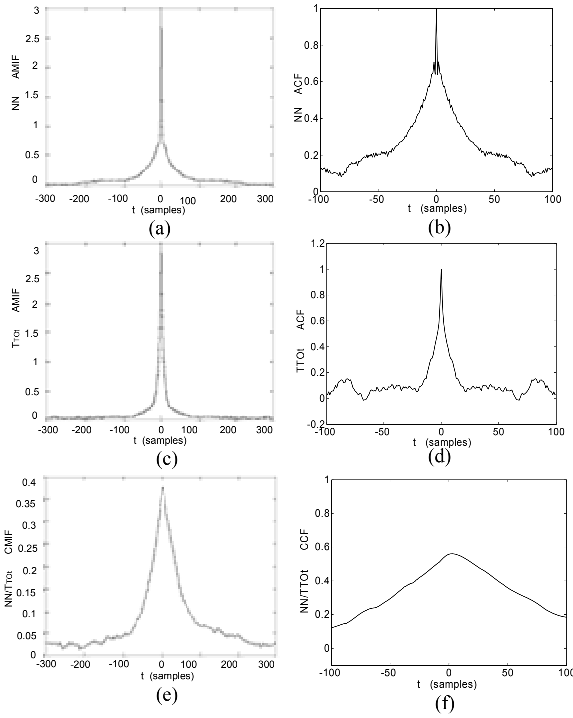

Fig. 3. Representation of *NN* series: (a) *AMIF*, (b) *ACF*; Representation of T_{Tot} series: (c) *AMIF*, (d) *ACF*; Representation of *NN* and T_{Tot} series: (e) C*MIF*, (f) *CCF*.

Table II summarizes the results of the analysis developed at time series *NN*. Only the measures *diff_b* and *grad_b* have been able to statistically classify A and B groups with $p_{value}<0.05$. Comparing groups A and B, measures in group A show low values of the slopes. In this way, *NN* series of group A present lower complexity and more *IF* than in group B. All these measures have been obtained on a low τ value (τ <10 samples). Moreover, it can be seen that these results do not depend on the number of histogram-bins considered for the analysis.

Studying T_{Tot} series, *dec_8*, *diff_b*, *grad_b* and *int*_8 have presented statistically significant differences as it can be observed in Table III. However, neither *dec_8* nor *int_8* have been able to stratify both groups with a discriminant function. As in NN series, group A shows low values of the slopes (*diff_b* and *grad_b*) compared with group B. In this sense, T_{Tot} series of group A also present lower complexity and more *IF* than in group B. This can be corroborated observing *dec_8* between A and B groups (A, mean±sd: 0.745±0.143; B, mean±sd: 0.782±0.179). All these results were obtained on a low τ value (τ <10 samples) and only *dec_b* and *int_b* seem to depend on the number of histogram-bins used in T_{Tot} series.

Results offering the quantification of the dependencies between *NN* and T_{Tot} series are presented in Table IV. These measures were obtained applying *CMIF*. Measures *dec_b, diff_b* and *grad_b* have statistically classified both groups. Independently of the number of bins *b* considered, values of *dec_b* are more negative in group A than in group B, $p_{value}<0.05$. These express a more (weakly) coupled nonlinear oscillator behavior of the series in A than in B. These results seem to be corroborated by the values of the slopes measured on *CMIF*, described by *diff_b* and *grad_b*, where the values of the slopes are higher in group A than in group B.

TABLE II
HEART RATE VARIABILITY: *NN* SERIES

AMIF	τ	Group A mean±sd	Group B mean±sd	p_{value}	A/B (%)
diff_8	5	0.003±0.065	-0.053±0.059	0.0004	67.8/60
diff_16	5	-0.006±0.069	-0.064±0.065	0.0005	67.8/60
diff_32	5	-0.019±0.072	-0.077±0.066	0.0007	64.3/66
diff_64	5	-0.030±0.073	-0.086±0.065	0.0011	64.3/68
grad_8	5	-0.025±0.059	-0.071±0.061	0.0059	64.3/62
grad_16	7	0.006±0.056	-0.022±0.056	0.01	71.4/60
grad_32	5	-0.051±0.063	-0.099±0.071	0.0032	67.8/62
grad_64	5	-0.064±0.062	-0.109±0.071	0.0089	71.4/60

dec_b: p_{value}(A,B) = n.s.; *int_b*: p_{value}(A,B) = n.s.
(%) well classified subjects in groups A and B: A/B

TABLE III
RESPIRATORY CYCLE VARIABILITY: T_{Tot} SERIES

AMIF	τ	Group A mean±sd	Group B mean±sd	p_{value}	A/B (%)
dec_8	1	0.745±0.143	0.782±0.179	0.0433	--
diff_8	6	-0.139±0.015	-0.153±0.013	0.0003	64.3/70
diff_16	6	-0.162±0.021	-0.178±0.015	0.0008	64.3/70
diff_32	10	-0.059±0.024	-0.079±0.019	0.0005	71.4/68
diff_64	9	-0.071±0.025	-0.092±0.018	0.0002	78.6/72
grad_8	7	-0.124±0.017	-0.139±0.013	0.0004	64/70
grad_16	7	-0.143±0.022	-0.160±0.016	0.0005	67/70
grad_32	10	-0.068±0.025	-0.089±0.019	0.0004	75/70
grad_64	10	-0.062±0.024	-0.081±0.018	0.0004	78.6/68
int_8	2	5.15±0.217	5.26 ±0.143	0.0433	--

(%) well classified subjects in groups A and B: A/B

The measures *diff_b* and *grad-b* do not differ excessively when their values are compared along the Tables II to IV, however, *grad_b* presents some better results compared with *diff_b*. Moreover, histograms of 32-bins and 64-bins seem to better represent the time series under analysis.

Tables V and VI present the values of the proposed measures when *ACF* is applied to *NN* and T_{Tot} series, respectively. Only *grad* was able to discriminate both groups, presenting a lower value in group A than in B.

No statistically significant differences have been found when CCF was applied, emphasizing these results the nonlinear dynamic behavior of the system under study.

IV. Conclusion

An approach based on Information Flow (*IF*) analysis has been introduced for the study of the cardiorespiratory interactions in patients on weaning trials. *IF* was used to identify essential aspects of the complex autonomic communication in the cardiorespiratory system when comparing patients that failed to maintain spontaneous breathing and patients with successful trials. Complexity and information flow, respectively, are independent on the signal amplitude. Therefore, the relationship between amplitude and information of a measured signal is an open question.

TABLE IV
DEPENDENCIES BETWEEN *NN* AND T_{Tot} SERIES

CMIF	τ	Group A mean±sd	Group B mean±sd	p_{value}	A/B (%)
dec_8	6	-0.004±0.011	-0.000±0.011	0.0422	64.3/66
dec_16	5	-0.005±0.009	-0.0005±0.011	0.0372	--
dec_32	4	-0.007±0.008	0.001±0.012	0.0014	67.8/68
dec_64	4	-0.006±0.011	0.003±0.013	0.0205	67.8/64
diff_8	4	0.001±0.002	-0.0003±0.002	0.0110	--
diff_16	5	0.001±0.003	-0.0005±0.003	0.0124	67.9/66
diff_32	4	0.003±0.006	0.0002±0.005	0.0031	71.4/66
diff_64	46	0.005±0.012	-0.001±0.011	0.0213	64.2/66
grad_8	5	0.001±0.002	-0.0002±0.002	0.0219	60.7/64
grad_16	5	0.001±0.002	-0.0004±0.002	0.0031	64.3/60
grad_32	4	0.003±0.004	-0.0004±0.004	0.0012	75/64
grad_64	58	0.003±0.004	-0.0007±0.006	0.0270	60/82.3

int_b: $p_{value}(A,B)$ = n.s.
(%) well classified subjects in groups A and B: A/B

TABLE V
HEART RATE VARIABILITY: *NN* SERIES

ACF	τ	Group A mean±sd	Group B mean±sd	p_{value}	A/B (%)
dec	16	0.039±0.018	0.047±0.016	0.0412	--
diff	16	0.008±0.045	0.000±0.043	0.0372	--
grad	33	0.001±0.010	0.000±0.016	0.0466	--
int	57	20.1±16.6	12.9±12.6	0.0455	--

(%) well classified subjects in groups A and B: A/B

TABLE VI
RESPIRATORY CYCLE VARIABILITY: T_{Tot} SERIES

ACF	τ	Group A mean±sd	Group B mean±sd	p_{value}	A/B (%)
dec	15	0.000±0.033	0.007±0.081	0.0455	--
diff	16	0.003±0.029	0.000±0.044	0.0335	--
grad	29	0.000±0.017	0.006±0.021	0.0066	64.3/60

int_b: $p_{value}(A,B)$ = n.s.
(%) well classified subjects in groups A and B: A/B

Both, the complexity of the signal itself *dec_b* and the related parameters *diff_b* and *grad_b* indicated that higher amplitudes are related to higher complexity in the investigated signal. The *IF* enables a quantitative assessment of short-term non-linear analysis of cardiorespiratory interactions. The *IF* seems to show the presence of non deterministic structures, expressing a lower complexity of the series in group A than in B, and a more coupled nonlinear oscillator behavior in group A than in B. This is corroborated with a less discriminatory power of *ACF* which supports the assumption of nonlinear processes in those statistical dependencies.

IF approach seems to be well founded to identify the some relevant interactions of information transfers within the ANS. These complex communications within the associated system seem to be expressed in the *NN* and T_{Tot} series under study.

The clinical relevance of discriminating heart rate variability and respiratory volume variability is related with the study of patients to control the mean tidal volume in response to alterations in respiratory demand. In this way, the proposed method could be a convenient weaning criteria to reduce the number of patients not successfully weaned. However, this study belongs to a preliminary analysis of the phenomena.

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