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# Association between Short Term and Long Term Communication in Pathological Autonomic Control

D. Hoyer, B. Frank, Ch. Götze, R. Baranowski, J. J. Żebrowski, M. Vallverdú, M. Palacios, P. Caminal, A. Bayés de Luna, P. K. Stein, G. Schmidt, and H. Schmidt

*Abstract*- **Autonomic Information Flow (AIF) reflects the time scale dependence of autonomic communications such as vagal, sympathetic, and slower rhythms and their complex interplay.**

**We investigated the hypothesis that pathologically disturbed short term control is associated with simplified complex long term control. This particular characteristic of altered autonomic communication was evaluated in different medical patient groups.**

**Holter recordings were assessed in patients with multiple organ dysfunction (MODS) (26 survivors, 10 non-survivors); with heart failure (14 low risk-without history of aborted cardiac arrest (CA), 13 high risk – with history of CA); with idiopathic dilated cardiomyopathy (IDC) (26 low risk, 11 high risk of CA), after myocardial infarction (MI) (1221 low risk - survivors, 55 high risk - non-survivors); after abdominal aorta surgery (AAS, 32 length of stay in hospital LOS > 7 days, 62 LOS ≤ 7 days). AIF of short and long time scales was investigated.**

**We found a fundamental association of increased short term randomness and decreased long term randomness due to pathology. Concerning risk, high risk patients were characterized by increased short term complexity and decreased long term complexity in all patients groups with the exception of the IDC patients.**

**We conclude that different time scales of AIF represent specific pathophysiological aspects of altered autonomic communication and control. The association of altered short term control with simplified long term behavior might be a pathophysiologically relevant compensation mechanism in the case of a disturbed fastest actuator. This knowledge might be useful for the development of comprehensive therapeutic strategies besides the predictive implications.**

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D. Hoyer, B. Frank and Ch. Götze are with the Biomagnetic Center, Department of Neurology, Friedrich Schiller University, Jena, Germany (corresponding author: dirk.hoyer@biomag.uni-jena.de).

R. Baranowski is with the National Institute of Cardiology, Warsaw, Poland. J. J. Żebrowski is with the Faculty of Physics, Warsaw University of Technology, Poland.

M. Vallverdú, M. Palacios, and P. Caminal are with the Centre for Biomedical Engineering Research, Technical University of Catalonia, Barcelona, Spain. A. Bayés de Luna is with the Hospital de la Santa Creu i Sant Pau, Barcelona, Spain.

P. K. Stein is with the Washington University School of Medicine, St. Louis, MO, 63110, USA.

G. Schmidt is with Medizinische Klinik der Technischen Universität München, Germany.

H. Schmidt is with the University Department of Medicine III, Martin Luther University, Halle-Wittenberg, Germany.

## I. INTRODUCTION

Every control system must guarantee the stability of the closed-loop behavior. This theory is well established in the design of linear control systems. The theory fails in the case of complex and non-linear control systems. Instead, Lyapunov stability is usually used to study the behavior of those systems. The underlying hypothesis is that the system behaves within an attractor. In the case of the organism that attractor incorporates the multiple-organ object function of staying alive.

Recently it was shown that specific prediction time intervals of the attractor are associated with specific mechanisms of the cardiovascular control system. The cardiovascular controller incorporates mechanisms at different time scales, such as the heart period (around 0.5-1 s), vagal (around 1-2 s), sympathetic (around 10 s), renin-angiotensin-aldosterone system (scale of minutes), renal volume pressure regulation (scale of hours), and circadian rhythm (which is present in all autonomic and humoral activities). Information flow measures, treated as functions of the time horizon of prediction (time scale of communication), can improve the assessment of particular aspects of complex cardiovascular mechanisms which themselves operate over different scales [1].

In clinical studies it was confirmed that AIF of different time scales identifies pathophysiologically disturbed autonomic function in several patient groups. Furthermore, the outcome of these patients was related to particular AIF measures. This result holds for Multiple Organ Dysfunction Syndrome (MODS) patients [2], patients with heart failure [3], myocardial infarction (MI) [4], Idiopathic Dilated Cardiomyopathy (IDC) [5], and length of stay in hospital (LOS) after abdominal aortic surgery (AAS) [6].

The objective of the present work was an evaluation of the association of AIF between different time scales. We investigated the hypothesis that there is a fundamental inverse relationship between alterations of the short term heart rate pattern and long term behavior.

## II. MATERIALS AND METHODS

The present study is based on the results of [2-6] where the details are outlined.

*Patients*

36 patients with MODS (26 survivors, 10 non-survivors, 28 day mortality [2]),

27 patients with heart failure (14 low risk-without history of aborted cardiac arrest (CA), 13 high risk – with history of CA) [3]),

36 patients with IDC (11 high risk patients with aborted cardiac arrest after the ECG recording or who died during follow-up, 26 low risk, patients without cardiac arrest) [5]),

94 patients after AAS (32 length of stay (LOS) > 7 days, 62 LOS ≤ 7 days) [6]),

1276 patients after MI (1221 low risk - survivors, 55 high risk - non-survivors [4]),

In all groups 24 h Holter recordings were analyzed using AIF methodology according to the HRV Task Force guidelines [2,3,7].

*Autonomic Information Flow*

Information flow characterizes communication within a time series in terms of information transfer over a prediction time horizon $\tau$. It measures the average information of the time shifted signal $X(t+\tau)$ which is already contained in the signal $X(t)$.

This autonomic information flow (AIF) function is assessed based on the Shannon entropy

$$H_x = -\sum_i p_i \log_2 p_i \qquad (1)$$

applied to the original time series $X(t)$, leading to $H_{X(t)}$; the part $X(t+\tau)$ shifted by time lag $\tau$, leading to $H_{X(t+\tau)}$; and a bivariate presentation, leading to $H_{[X(t), X(t+\tau)]}$, as

$$\mathrm{AIF}_{[x(t),x(t+\tau)]} = H_{x(t)} + H_{x(t+\tau)} - H_{[x(t),x(t+\tau)]} \qquad (2).$$

The information flow over particular time horizons $\tau$ allows the identification of particular physiological oscillators [1]. The information loss is related to complexity measures [1]. We developed AIF measures based on NN interval series from resampled time series, corresponding to conventional HRV the Task Force guidelines [7], completely introduced in [2,3]

*AIF Measures*

AIF functions were estimated according to the short and long term approaches of the linear measures of Task Force HRV [2,3,7]. HRV at short time scales has been clearly related to autonomic mechanisms as follows: HF (high frequency power) mainly reflects vagal modulation of HR; LF (low frequency power) reflects sympathetic and parasympathetic modulation; the physiological basis of VLF (very low frequency power) is inconsistently reported, but a clear parasympathetic influence has been confirmed [8]; long term communication reflects slower fluctuations with high amplitudes mainly circadian rhythm. Communication over one heart beat period might additionally indicate inherent cardiac behavior.

Typical measures of the AIF are their respective decays (DEC*) over prominent prediction time horizons (see figure 1). Those measures were assessed as short term measures, based on the average of short data windows as well as long term measures based on the entire data set as follows:

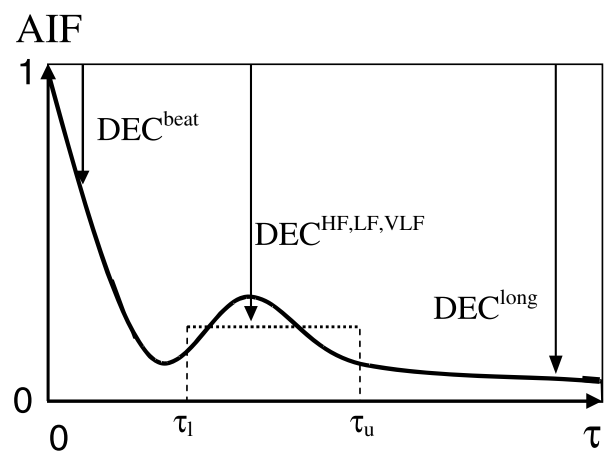


Fig. 1. Sketch of Autonomic Information Flow (AIF) functions. This function describes the information loss (decay) over the prediction horizon $\tau$. AIF is normalized to AIF=1 at $\tau$=0. In the case of frequency band filtered signals $\tau_l$ and $\tau_u$ indicate the corresponding boundary periods. Take care that decay measures DEC* of different AIF functions (non-filtered, filtered, short term, long term) are sketched together. The decay measures over different time scales are indicated by respective arrows.

*Short Term Measures*

$DEC^{R1}$:

AIF decay over $\tau$=0.6 s ($\tau$ standard beat period in all studies presented here, in bit/s, normalized).

This measure is the mean of all 30 min segments based on non-filtered time series resampled at 5 Hz.

$DEC^{HF}$, $DEC^{LF}$, $DEC^{VLF}$:

AIF decay over periods related to the standard frequency band boundaries (HF: $\tau$=1.25-3.33 s, LF: $\tau$=3.33-12.5s, VLF: $\tau$=12.5-166.7 s) (in bit/s normalized).

These measures are the mean of all 5 min (HF), 5 min (LF), 30 min (VLF) segments, respectively, based on filtered (HF, LF, VLF, respectively) time series.

*Long Term Measures*

$DEC^{long}$ :

AIF decay over $\tau$=100 s.

This measure reflects the complex communication involving long term mechanisms based on the non-filtered entire data set.

*Statistical Analysis*

The comparison between patients and controls, as well as between high risk and low risk groups, were done by means of the receiver operating curve (ROC) characteristics; pairs of true and false positives for the prediction of prognosis group were estimated over the full range of possible cut-off values. The area under the ROC curve (AUC) of 1 is associated with perfect classification, and AUC of 0.5 corresponds to a random assignment of patients by prognosis group. Significantly discrimination was considered to exist if the lower bound of the two-sided 95%-confidence interval of the respective AUC was >0.5.

## III. Results

The results obtained in different clinical studies are reviewed in Table I. Both, in the comparison of patients versus controls, and in the higher risk patients a predominant result was a increased AIF decay measure of a shorter time scale (cardiac: $DEC^{R1}$, vagal: $DEC^{HF}$) associated with a decreased AIF decay measure of a longer time scale ($DEC^{VLF}$, $DEC^{long}$).

TABLE I

SIGNIFICANT CHANGES OF AIF DECAY MEASURES.

| | short | | | | long |
|---|---|---|---|---|---|
| **Patients vs. Controls** | **$DEC^{R1}$** | **$DEC^{HF}$** | **$DEC^{LF}$** | **$DEC^{VLF}$** | **$DEC^{long}$** |
| **Multiple Organ Dysfunction Syndrome (MODS) [2]** | ↑ | -↓↑* | ↑ | - | ↓ |
| **After Myocardial Infarction (MI) [3]** | ↑ | ↑ | - | - | ↓ |
| **Idiopathic Dilated Cardiomyopathy (IDC) [5]** | ↓ | ↑ | ↓ | ↓ | ↓ |
| **Abdominal Aorta Surgery (AAS) [6]** | - | ↑ | - | ↓ | ↓ |
| **High risk vs. Low Risk** | **$DEC^{R1}$** | **$DEC^{HF}$** | **$DEC^{LF}$** | **$DEC^{VLF}$** | **$DEC^{long}$** |
| **MODS: LET<28 vs. LET ≥ 28 days [2]** | - | ↑ | ↑ | - | - |
| **Risk of cardiac arrest after MI [3]** | ↑ | - | - | - | - |
| **Mortality after MI [4]** | ↑ | | | | ↓ |
| **Risk of cardiac arrest in IDC patients [5]** | - | ↑ | - | - | - |
| **AAS: LOS>7 vs. LOS≤ 7 days [6]** | - | - | - | ↓ | ↓ |

*: different results of data sets from 24h -, 6h daytime ↓, 6h nighttime ↑

## IV. Discussion

The stable behavior of the organism requires the adjustment between multiple physiological control mechanisms acting at similar and different time horizons. The identification of particular mechanisms and their interrelationships is limited due to their non-linearity and complexity. Established approaches of nonlinear dynamics and statistics are Lyapunov stability and entropy measures, focused on source behavior characteristics. Phase synchronization statistics allow the assessment of couplings between rhythms with different frequencies, an important characteristic of coupled physiological oscillators. Information flow characterizes the information transfer of a representative state variable as well as between different variables. We investigated the systems theoretical hypothesis, that the prediction time horizons of the information flow function are associated with time horizons of particular physiological controllers and therefore allow the assessment of interrelationships between mechanisms with different inherent time scales.

In the present work the time horizon of autonomic information flow function was used to emphasize the contribution of particular control mechanisms within the cardiovascular system, essentially mediated by the autonomic nervous system, because of their inherent time scale.

The heart acts as common actuator of different control loops and therefore reflects their complex contribution. Pathophysiological disturbances can be situated within cardiac processes and/or within particular control mechanisms such as vagally and sympathetically mediated feedback loops and further slower mechanisms of homeostasis.

In MODS sepsis mediators and toxins disturb the cardiac cellular signal transduction leading to attenuated cellular responses reflected in the increased randomness (=complexity) of the heart beat period reflected as the cardiac cycle time scale (increased $DEC^{R1}$).

After MI the cardiac excitation cycle is altered leading to a similar destabilisation of information flow (increased $DEC^{R1}$). In both diseases the disturbance of cardiac horizon (attractor divergence over 0.6 s) was associated with a reduced complex control (simplification) of the long term behavior (reduced $DEC^{long}$, attractor with reduced divergence over 100 s).

In IDC patients the heart muscle becomes enlarged and ineffective. In that case we found reduced randomness in the cardiac cycle (reduced $DEC^{R1}$), however increased randomness of in vagal time scale (increased $DEC^{HF}$) associated with simplified long term control (reduced $DEC^{long}$).

After AAS (where the heart is not affected) the cardiac cycle information flow is not altered. But at least in the comparison of patients with normal and prolonged recoveries the short term vagal time scale behavior became more stochastic (increased $DEC^{HF}$) which was associated with simplified long term control (reduced $DEC^{long}$).

These indications of a fundamental type of associations (coordination) between short term and long term control holds for both, the pathophysiological dysfunction and stratification of risk such as stay in ICU of hospital or mortality. The discriminatory advantages of the AIF measures over the Task Force HRV measures were shown in all patients groups elsewhere [2,3,4,5,6,]. Another perspective of application is based on the comprehensive knowledge of complex autonomic control, namely the participating subsystems and their interplay, such as identified concerning the adjustment between short and long term control as one predominant phenomenon. Therapeutic consequences such confirming the vagal anti-inflammatory reflex in MODS by AIF measures reflecting vagal activity [2,9,10,11] will be verified in future studies.

The behavior of selected mechanisms cannot represent the complex organism. Therefore, the current approach of assessing the interplay between mechanisms acting on different time scales might significantly improve the comprehensive understanding and description of the complete organism.

## V. Conclusion

The adjustment of different physiological controllers acting at different time scales has implications with regard to understanding pathophysiologic function, risk stratification, and developing therapeutic interventions. AIF functions of heart rate data enable the identification of underlying controllers and their complex coordinations.

The approach presented is to be discussed in the Minisymposium “Coordinations of Physiological Rhythms”

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