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Investigating the mechanisms of cardiovascular and cerebrovascular regulation in orthostatic syncope through an information decomposition strategy

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ABSTRACT

Some previous evidence suggests that postural related syncope is associated with defective mechanisms of cerebrovascular (CB) and cardiovascular (CV) control. We characterized the information processing in short-term CB regulation, from the variability of mean cerebral blood flow velocity (CBFV) and mean arterial pressure (AP), and in CV regulation, from the variability of heart period (HP) and systolic AP (SAP), in ten young subjects developing orthostatic syncope in response to prolonged head-up tilt testing. We exploited a novel information-theoretic approach that decomposes the information associated with a variability series into three amounts: the information stored in the series, the information transferred to the series from another series, and the information unexplained by the knowledge of both series. With this approach we were able to show that, compared with the first minutes after head-up tilt, in the period preceding the syncope event (i) the information stored in CBFV variability decreased significantly while the information transferred to CBFV from AP variability increased significantly; (ii) the information storage of HP was kept high but the information transferred to HP from SAP variability decreased significantly. These patterns of information processing suggest that presyncope occurs with a loss both of CB regulation, described by the reduced ability of CBFV of buffering AP fluctuations, and of CV regulation, described by the reduced baroreflex modulation from SAP to HP. We believe that the utilization of tools from the field of information dynamics may give an integrated view of the mechanisms of CB and CV regulation in normal and diseased states, and also provide a deeper understanding of findings revealed by more traditional techniques.

1. Introduction

The spontaneous oscillations observed in the physiological variables that reflect the activity of the heart and circulatory systems are focus of rich interdisciplinary research since more than two decades. In particular, fluctuations of the heart period (RR interval of the ECG) and systolic arterial pressure (SAP) measured over temporal scales up to few hundred heart beats are commonly studied as descriptors of the short-term cardiovascular regulation (Cohen and Taylor, 2002), while changes of the cerebral blood flow velocity (CBFV) associated with corresponding changes of the mean arterial pressure (AP) are supposed to reflect the mechanisms of dynamic cerebral autoregulation (Zhang et al., 1998). Most of these mechanisms can be probed noninvasively studying the relevant variables measured under different conditions. For instance, a perturbation like orthostatic stress that profoundly affects autonomic regulation is commonly used to evoke and study postural related syncope in a clinical setting (Brignole et al., 2001). Orthostatic syncope, which is defined as a transient loss of consciousness and postural tone with spontaneous recovery, has been associated with the failure of some physiological mechanisms of cardiovascular and cerebrovascular regulation, such as baroreflex dysfunction (Bechir et al., 2003) and cerebral hypoperfusion (Toyry et al., 1997). According to recent studies, the impairment of these mechanisms may be detected and characterized in advance of the fainting event through the analysis of spontaneous cardiovascular or cerebrovascular variability (Dan et al., 2002; Julu et al., 2003; Faes et al., 2006; Ocon et al., 2009).

Several time series analysis approaches have been proposed in the past to characterize cardiovascular and cerebrovascular regulations in normal and diseased physiological states, including linear/nonlinear methods to assess the oscillatory content and the complexity of individual variables, and causal/non-causal methods to characterize the

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coupling between different variables (Porta et al., 2000; Giller and Mueller, 2003; Faes and Nollo, 2006; Nollo et al., 2009; Voss et al., 2009). Despite their demonstrated usefulness, these approaches typically describe single aspects of the variability measured in the observed time series (e.g., how regular is heart rate variability or how it is coupled with AP variability), without considering how these aspects contribute in a synergic or redundant way in determining the variability itself. This intriguing possibility can be explored inside the framework of information theory (Cover and Thomas, 2006), where the observed time series are seen as realizations of stochastic processes and dynamical properties like complexity and coupling are quantified in terms of information amounts carried by a single process and shared between processes. Recent advances in the development of information-theoretic measures have indeed made it possible to quantify, starting from a short and noisy realization of a given process, how much information is generated by the process and, most important, how this information is actively stored in the process, flows into the process from other coupled processes, or remains unexplained given the observed set of processes (Lizier et al., 2011, 2012). Therefore, looking at the spontaneous cardiovascular and cerebrovascular variability in such an integrated way would give a new perspective in the analysis of the underlying physiological mechanisms in both normal and impaired conditions.

The present study proposes an integrated approach, defined in the information domain, to characterize the mechanisms of short-term cardiovascular and cerebrovascular regulations during the development of postural related syncope. The approach is based on decomposing the information carried by a time series into three basic elements: the information actively stored in the series (intended as the information "self-contained" in the series), the information transferred to the series from another time series, and the residual information not explained by the knowledge of the dynamics of the two series. It is applied to the RR and SAP series for the study of cardiovascular regulation, and to the mean AP and mean CBFV series for the study of cerebrovascular regulation, in a group of subjects with recurrent syncope studied during head-up tilt testing. We hypothesize that utilization of this novel approach would provide further clarification of the physiological mechanisms underlying the impairment of cardiovascular and cerebrovascular control systems occurring with orthostatic syncope.

2. Methods

2.1. Patients and experimental protocol

We studied ten young subjects (3 males, 22.4 ± 9.5 years old) admitted to the Neurology Division of the Sacro Cuore Hospital of Negrar, Italy, for the evaluation of recurrent unexplained syncope (i.e., more than three events during the foregoing year).

Before participating to the experiment, subjects refrained from the intake of caffeine or alcohol-beverage for 24 h. Each subject provided informed consent to the experimental protocol, which conformed to the principles of the Declaration of Helsinki and was approved by the Ethical Committee of the hospital. Head-up tilt test was performed in a maximally controlled environment, with subjects laying on a tilt table supported by two belts at the level of thigh and waist, and with both feet in contact with the footrest of the table. After a period allowed for stabilization, signal acquisition was performed for 10 min in the resting supine position, followed by passive transition to 60° upright position and prolongation of the postural stress. All subjects had a positive response to head-up tilt test, consisting in the occurrence of a vasovagal episode characterized by progressive hypotension and reflex bradycardia leading to partial loss of consciousness. All exhibited spontaneous recovery with return to the supine position.

2.2. Variability series measurement and pre-processing

The analyzed signals were the surface ECG (lead II), the continuous photoplethysmographic AP measured in the finger (Finapres, Ohmeda), and the blood flow velocity of the middle cerebral artery acquired by transcranial Doppler ultrasonography (Multi-Dop T2, Dwl). Signals were synchronously acquired with 1 KHz sampling rate and stored for offline analysis. Cardiovascular and cerebrovascular variability series were measured from the signals as follows (see Fig. 1). For the analysis of cardiovascular variability, the RR interval was measured as the temporal distance between two consecutive R peaks of the ECG, which were identified by detecting the QRS complex and then locating the R apex through template matching. The corresponding SAP was taken as the local maximum of the AP signal measured inside the detected RR interval. For the analysis of cerebrovascular variability, values of mean AP and CBFV were calculated through waveform integration of the sampled pressure and velocity signals within each detected diastolic pulse interval, divided by the duration of the interval itself. The beat-to-beat variability series of RR interval, SAP, mean AP, and mean CBFV, denoted respectively as $R(n)$, $S(n)$, $P(n)$, and $F(n)$, $n = 1,\ldots, N$, were then measured as the sequences of consecutive values collected during three stationary time windows, each lasting $N = 300$ beats: supine position (*su*); upright position at ~2 min from the tilt transition (early tilt, *et*); and upright position just before the decrease in AP associated with presyncope (late tilt, *lt*; start at 16 ± 8 min after the tilting transition). For each window, the occurrences of QRS and SAP were carefully inspected to avoid erroneous detections or missed beats. Erroneous SAP values due to drifts in the AP signal caused by the automatic calibration of the Finapres device were corrected by applying spline interpolation. Spline interpolation was used also to remove narrow spikes, when present, from the raw blood flow velocity signal before calculating the relevant CBFV time series value. Moreover each time series was detrended using a zero-phase high pass filter (with cutoff at 0.01 Hz)

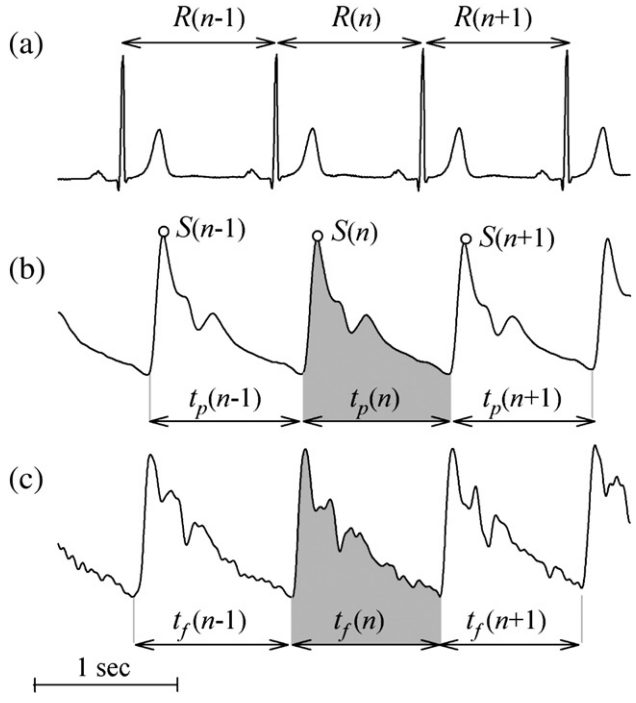

Fig. 1. Measurement of the beat-to-beat variability of RR interval, SAP, mean AP and mean CBFV from the ECG signal (a), the arterial pressure signal (b) and the cerebral blood flow velocity signal (c). At the n-th cardiac beat, the RR interval $R(n)$ is measured as the ECG interbeat interval, the SAP $S(n)$ is measured as the maximum arterial pressure inside $R(n)$, the mean AP $P(n)$ is measured as the area under the arterial pressure signal (gray area in (b)) divided by the diastolic interval $t_p(n)$, and the mean CBFV $F(n)$ is measured as the area under the flow velocity signal (gray area in (c)) divided by the flow diastolic interval $t_f(n)$.

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