Autonomic Neuroscience: Basic and Clinical 178 (2013) 1–3

Contents lists available at ScienceDirect

Autonomic Neuroscience: Basic and Clinical

journal homepage: www.elsevier.com/locate/autneu

Editorial

Inferring cardiovascular control from spontaneous variability

Keywords:
Heart rate variability
Multivariate analysis
Complexity
Biomedical signal processing
Autonomic nervous system
Cardiovascular control

When observed on a beat-to-beat basis cardiovascular variables exhibit spontaneous rhythmical fluctuations about their mean values even in the absence of any external stimulus and under well-controlled experimental conditions (e.g. in resting supine state in quiet environment). A constantly growing amount of literature suggests that these beat-to-beat variations are the result of reflex and non-reflex (i.e. autonomous) control mechanisms operating over different time scales aiming at the maintenance of cardiovascular variables within safe intervals of values while guaranteeing a rapid adaptation to fulfill the variable demands of the organism. One of the peculiar features of cardiovascular variabilities is its partial predictability suggesting an underlying determinism and prompting for the search of rules governing these variations and the cardiovascular control underpinning them. Since the early recognition of the importance of the analysis of cardiovascular variabilities (Akselrod et al., 1983), it has appeared clear that inferring cardiovascular regulatory mechanisms from spontaneous variability would have been a complex task requiring the contemporaneous application of several techniques (Porta et al., 2009). The complexity of the task raises from the multiplicity of mechanisms contemporaneously active to maintain homeostasis, the vague nature of the relationships among cardiovascular variables, the variable strength of the interactions, the relatively large amount of temporal scales involved in short-term regulation even when restricting the analysis over recordings of few minutes, the presence of nonlinearities capable of generating completely different behaviors in response to the same input in the presence of small changes of system parameters, the distributed nature of some mechanisms (e.g. vasomotion) leading to independent or weakly dependent activities that can be easily synchronized or entrained by common triggering inputs (e.g. sympathetic drive), and the incidence of non-stationarities resulting from the variety of interacting subsystems capable of imposing its own specific dynamics when one component takes priority over the others.

Given the difficulty of the task a multidisciplinary approach involving bioengineers, physicists, mathematicians, computer scientists, biologists, physiologists, clinicians and physicians has been advocated (Di Rienzo and Porta, 2009; Porta et al., 2009; Wessel and van Leeuwen, 2012). This approach should favor the development of feasible and effective signal processing techniques overcoming limitations, caveats and pitfalls of traditional tools and the design of experimental protocols useful to separate the overall cardiovascular regulatory system into individual subunits. This multidisciplinary approach should definitely prove the additional, clinically relevant, information provided by the tools exploiting spontaneous cardiovascular variabilities with respect to more standard procedures or techniques and facilitate comparison among signal processing strategies over bigger and bigger databases.

The present issue of *Autonomic Neuroscience: Basic and Clinical* is designed to stimulate this joint effort. It collects together a set of contributions presented at the 7th meeting of the European Study Group on Cardiovascular Oscillations (ESGCO), which was held in Kazimierz Dolny, Poland in 2012 and featured as Honorary Chairman, Prof. Andrzej Trzebski, a well known physiologist belonging to the ESGCO community since its foundation. The 7th ESGCO meeting was especially focused on the dynamical interactions among several, simultaneously recorded, cardiovascular variables, and on the effects of pharmacological challenges and experimental maneuvers on cardiovascular and cerebrovascular regulation in both physiological and pathological conditions. The best presentations were selected for this issue and the authors were encouraged to enhance the scope of their contribution as well as, in a few cases, to merge some of them. The meeting held in Kazimierz Dolny, Poland was the last of a series of ESGCO meetings started in Cardiff, Wales in 2000 and followed by Siena, Italy in 2002, Leuven, Belgium in 2004, Jena, Germany in 2006, Parma, Italy in 2008 and Berlin, Germany in 2010. Since its foundation in 1998 the ESGCO promotes collaborations among specialists from several disciplines and cross-fertilization among different fields to address the complexity of cardiovascular control through the analysis of the oscillatory patterns of physiological variables monitored as a function of time. This issue includes a tribute to Tudor Griffith (Edwards, 2013–in this issue), one of the four founders of the group with Alberto Malliani, Pontus Persson and Bernard Swynghedauw. Tudor Griffith was a pioneer in applying nonlinear signal processing tools, devised according to the chaos theory, to study integrated vascular control and peripheral vasomotion. His approach, matching a strong technical background on modeling and signal processing with a deep knowledge about the biological problem and a strong attitude to experimental research (Griffith and Edwards, 1994), can be taken as a manifesto of the ESGCO. The rest of the contributions listed in this issue can be roughly grouped in two categories: i) studies inferring cardiovascular control based on univariate techniques assessing the magnitude of the changes of a single variable in time and frequency domains and/or the complexity of the fluctuations in the information domain; ii) studies exploiting bivariate, and more generally multivariate, methods to disentangle specific mechanisms through the estimation of the magnitude of the relation between interacting variability series and/or of the information transferred from one beat-to-beat series to another. The immediate final, very practical, aim of all the contributions is to provide indexes helpful to separate experimental conditions within the same population and/or differentiate groups within the same experimental condition, thus exploring the pathophysiology of the cardiovascular control, improving classification,

1566-0702/$ – see front matter
http://dx.doi.org/10.1016/j.autneu.2013.05.006

and favoring more tailored treatments, more precise diagnosis and more accurate prognosis. The long term final aim is to promote the exploitation of indexes derived from spontaneous cardiovascular variabilities outside the well controlled conditions of the research laboratories in ambulant subjects during daily activities to continuously typify over time the pathophysiological state of an individual.

Among the contributions using univariate approaches Schulz et al. (2013–in this issue) assessed the vascular control through the analysis of blood pressure variability using traditional time and frequency domain tools and methods for the quantification of complexity based on entropy and symbolic dynamics, and showed that these tools were able to detect the impairment of the vascular regulation in patients suffering for idiopathic sudden sensorineural hearing loss, Voss et al. (2013–in this issue) investigated the cutaneous microcirculation in schizophrenic patients by means of a spectral approach applied to laser Doppler blood flow signals reflecting vasomotion of tissue layers at different depths, Van Leeuwen et al. (2013–in this issue) monitored the individual degree of maturation of the autonomic nervous system through the complexity analysis of heart rate variability based on entropy in fetuses as a function of the gestational age, Gieraltowski et al. (2013–in this issue) showed that multiscale and multifractal analyses of heart rate variability provide additional information to traditional monoscale and monofractal analyses in monitoring the progression of the development of autonomic nervous system in fetuses during the course of gestation, Cysarz et al. (2013–in this issue) tracked changes of cardiac autonomic modulation during childhood and adolescence via complexity analysis of heart rate variability based on symbolic dynamics, Castiglioni et al. (2013–in this issue) assessed the role played by sympathetic control in determining frequency content and fractal properties of heart rate and blood pressure variabilities in rats, Di Rienzo et al. (2013–in this issue) developed and tested a smart garment capable of monitoring ECG and seismocardiogram, thus continuously assessing over time heart period, time intervals between cardiac mechanical events and indexes of respiratory activity in ambulant subjects, and Graff et al. (2013–in this issue) studied the autonomic nervous system response to hyperoxia in healthy subjects via the analysis of heart rate variability and compared it to the observed changes of blood pressure and arterial wall properties.

Among the contributions using multivariate approaches Porta et al. (2013–in this issue) typified baroreflex control through the calculation of cross-conditional entropy of heart period given systolic arterial pressure in a healthy population during pharmacological challenges and assessed the complementary information provided by this approach with respect to traditional bivariate methods in the frequency domain, Faes et al. (2013a–in this issue) explored the cerebrovascular and baroreflex controls in subjects developing orthostatic syncope in response to prolonged head-up tilt using a tool assessing information transferred from the variability series of the mean arterial pressure to mean cerebral blood flow velocity and from the variability series of the systolic arterial pressure to heart rate respectively, Bassani et al. (2013–in this issue) assessed the involvement of baroreflex in governing the dynamical interactions between heart period and systolic arterial pressure via a model-based time domain Granger causality approach accounting for mechanical ventilation under different anesthesiological treatments in humans (i.e. intravenous versus volatile administration of anesthetic) and under different mechanical ventilation strategies in animals (pressure controlled versus pressure support mechanical ventilation modes), Fonseca et al. (2013–in this issue) investigated the mechanisms of cardiorespiratory coupling using a bivariate model-based causal coherence approach in young healthy subjects as a function of the breathing phase (inspiration versus expiration periods), Faes et al. (2013b–in this issue) studied baroreflex regulation in healthy subjects after sustained water immersion using causal and non-causal bivariate methods for the assessment of the transfer function from systolic arterial pressure variability to heart period variability, and Ramírez Ávila et al. (2013–in this issue) proposed a recurrence analysis in a multidimensional embedding space formed by heart rate, diastolic and systolic arterial pressure values and demonstrated its usefulness for the early detection of pregnancies at risk to develop life-threatening preeclampsia.

We hope that the reading of this issue could promote methodological advancements in the field of the analysis of cardiovascular oscillations by favoring the development of new signal processing tools, by stimulating more lively debates on existing methods and their real potential, by suggesting new ideas on how to overcome experimental and methodological limitations and by encouraging the integration among different signals to make more comprehensive the description of the cardiovascular control system. We hope also that this issue could stimulate the application of the proposed signal processing tools to previously collected databases, inspire experimental protocols designed to test new working hypotheses and trigger applications focused on the monitoring of the cardiovascular control during daily activities. Finally, we advocate applications testing the additional diagnostic and prognostic value of cardiovascular control indexes in terms of ability to track the progression of a chronic disease, to monitor the recovery from an adverse event and to predict unfavorable outcomes of a treatment or surgery.

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9 May 2013