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Federico Lombardi, MD, Heikki Huikuri, MD, Georg Schmidt, MD, Marek Malik, PhD, MD, FHRS

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Short-term heart rate variability: easy to measure, difficult to interpret.

by

Federico Lombardi; MD[1], Heikki Huikuri, MD,[2], Georg Schmidt, MD,[3], Marek Malik, PhD, MD, FHRS[4], on behalf of e-Rhythm Study Group of EHRA.

[1]UOC Cardiologia, Fondazione IRCCS Ospedale Maggiore Policlinico, University of Milan, Italy; [2]University of Oulu, Oulu, Finland;[3] Technische Universitat Munchen, Munchen, Germany; [4]Imperial College, London, England.

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Corresponding author:
Federico Lombardi, MD, FESC
UOC Cardiologia, Fondazione IRCCS Ospedale Maggiore Policlinico.
University of Milan
Via F. Sforza 35, 20122 Milan, Italy
Email: federico.lombardi@unimi.it

Alkselroad et al (1) were the first to report that the analysis of spontaneous fluctuation of RR interval could provide direct insight into the physiology of the autonomic control branches. Since then, heart rate variability (HRV) analysis (2) has then become the most employed non-invasive tool to evaluate autonomic control mechanisms and to predict mortality risk in several clinical conditions. As explained (2) in the 1996 Task Force Document, the term of HRV analysis accommodates a number of methodologies despite their major computational and physiological interpretative differences. The length of the analysed RR interval time series and the computational algorithm are only two examples. The Task Force document also explains that information on autonomic control mechanisms derived from HRV analysis of short-term recording under controlled conditions is substantially different from that derived from 24-hour Holter recordings in unrestricted ambulatory subjects. The different computational algorithms ranging from simple mathematical or geometrical indices to complex non-linear parameters, generate a variety of parameters describing different HRV characteristics relevant to many physiological and pathophysiological conditions. However, the interpretation of these HRV parameters is complex and, in some cases, controversial compared to what is sometimes assumed (2,3). For example, in some published articles, there is a tendency to simplify the physiologic interpretation of HRV by assuming that HRV reduction might always be considered as reflecting autonomic control alteration with sympathetic activation and reduced parasympathetic modulations. HRV reduction, consistently observed in patients with increased mortality risk in several clinical conditions including coronary artery disease, heart failure, diabetes and hypertension is frequently considered to reflect a causative mechanism related to primary autonomic alteration. Nevertheless, autonomic changes secondary to the clinical condition need always be also considered (2-4).

Despite the overwhelming extent of data, the use of HRV has declined in clinical settings and the methodology is presently almost ignored in the risk stratification process of most of patients. At the same time, it is also presently clear that risk stratification based strictly on the assessment of ventricular

performance leads to disappointing results. Autonomic changes (regardless whether primary or secondary) might thus need to be carefully reconsidered in risk stratification strategies.

In this issue of the journal, Tegegne et al (5) report the results of evaluating the HRV determinants in the general population. From standard 10-second electrocardiographic recordings, they calculated a single time domain HRV parameter, namely the RMSSD, and correlated it with several demographic, lifestyle and psychosocial factors. They report that RMSSD strongly declined with age and was higher in women. Age and sex, in addition, could explain almost 20% of all inter-individual HRV differences, whereas the effects of lifestyle and psychosocial factors were negligible. In fact, the inclusion of the potential confounding effects of medication and disease status increased the amount of explained variance of less than 2% (5). Tegegne et al chosen RMSSD as the index parameter or after for instantaneous heart rate normalization based on the assumption it could reflect vagal control of the heart rhythm and that longevity was associated with preserved autonomic function.

The study by Tegegne et al needs to be commended for the number of enrolled patients and for collecting large sets of demographic and personal data. Nevertheless, their study also suffers from severe limitations that make the interpretation of results questionable.

Our first concern relates to HRV measurement. The authors computed HRV in a RR interval series derived from standard 10-second electrocardiograms recorded at rest in supine position without controlling respiratory frequency. The derived time series was excluded if the number of cardiac cycles was <5 or if there was an increased variability of the inter-beat intervals for presence of premature atrial or ventricular beats. As indicated by several studies employing spectral analysis of HRV, window of 256 inter-beat intervals (or 5 minutes) is the appropriate signal duration to safely compute high and low frequency HRV components, that reflect autonomic modulation of sinus nodal periodicity (2,3,6). Much less defined and largely unknown and unproven is the interpretation of 10-second RMSSD as an

index of vagal modulation. During a 10-second window, there might be only 2-3 fluctuations of sinus nodal periods related to respiration which might reflect vagal modulation (2,6).

Quite surprisingly, despite all available evidence, instantaneous heart rate was not considered in data analysis (7). When the authors corrected RMSSD for its dependency on heart rate, they were able to explain almost 5% more variance, thus confirming the critical importance of this parameter, so easily obtainable from a standard electrocardiogram.

The second point is the uncertainty of the reproducibility of 10-second HRV. This aspect, which caused extensive discussion in the past (2) requiring specific adjustments to recording protocols and data filtering, was not considered by Tegegne et al. No data are available on the temporal stability of RMSSD measured at the time of enrolment. Although the design of the study prevents the acquisition of repetitive recordings within the same subject, it is likely if not guaranteed that confounding factors such as disease progression or medicalization could affect resting heart rate and its variability. Even the very short-term reproducibility is questionable. If a subject suddenly remembers an uncomfortable situation, instantaneous heart rate increases markedly regardless of any arrangements of the recording protocol.

Thirdly, an even more intriguingly, neither cardiovascular disease nor psychosocial factors including social wellbeing, stressful life events and chronic stress, showed any significant association with RMSSD. We believe that these negative findings were mainly caused by the use of a single time domain HRV parameter measured on a very short-term basis rather than by a true lack of effects of these factors on HRV. It is self-evident that within a single 10-second recording at rest, most of information related to the influence of environmental factors and physiological activities and psych-social status are easily missed (2-4).

While more sophisticated and more advanced HRV methodologies have been repeatedly utilized in different clinical settings (2,4,8), the study by Tegegne et al confirms that HRV declines with increasing age. However, the interpretation of the causative mechanism of this phenomenon still remains to be fully understood.

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