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Clinical Studies

Relation of impaired interorgan communication and parasympathetic activity in chronic heart failure and multiple-organ dysfunction syndrome

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ABSTRACT

Background: We investigated the relationship of impaired autonomic function and severity of illness in chronic heart failure (CHF) and multiple-organ dysfunction syndrome (MODS) as an end stage of CHF. Furthermore, we assessed the link of parasympathetic modulation of the heart rate and inflammatory activation in CHF and MODS.

Methods: Sixty-five patients admitted for worsening of CHF were retrospectively enrolled in this study. In addition, 65 age- and sex-matched patients with pronounced MODS were assigned for comparison of autonomic function and C-reactive protein in patients with CHF or MODS, respectively. Heart rate variability (HRV) parameters of the time and frequency domain as markers of autonomic function were analyzed from 24-hour Holter electrocardiograms.

Results: The more pronounced the severity of illness as expressed by the Acute Physiology and Chronic Health Evaluation score, the more the HRV was impaired. This effect was particularly seen for overall variability (SD of RR intervals) and HRV parameters characterizing the parasympathetic modulations of the heart rate (high, very low frequency power). C-reactive protein levels as markers of inflammation were inversely related to high and very low frequencies.

Conclusion: Our results allow for speculation that autonomic dysfunction in CHF indicates a beginning of uncoupled interorgan communication potentially leading to MODS as characterized by disruption of communication between the organs.

1. Introduction

An extremely worsening of chronic heart failure (CHF) is able to trigger a sequential failure of several organs resulting in a multiple-organ dysfunction syndrome (MODS). Despite advances in the treatment of MODS, the mortality remains high even today, achieving up to 40% to 60%, and the treatment at the intensive care unit (ICU) is still cost-intensive [1,2].

Development of MODS is characterized by an overwhelming activation of the innate immunity resulting in an inappropriate release of inflammatory mediators associated with subsequent cell damage of parenchymatous organs and with inflammatory, metabolic, and neuroendocrine disorders [3]. Autonomic dysfunction reflects the "uncoupling" of neurally mediated organ interactions in MODS: bacterial toxins and sepsis mediators can potentially alter neural reflexes and cytokine pathways and thus cause a defect in interorgan communication, thereby advancing single-organ dysfunction into MODS. A disruption of interorgan communication can be characterized by several variables of autonomic function such as heart rate variability (HRV) and baroreflex (BRS) and chemoreflex sensitivities (CRS) [4]. Attenuated HRV is a strong predictor of mortality in MODS [5,6].

The aforementioned variables of autonomic function (HRV, BRS, and CRS) are also applicable to characterize autonomic function in CHF [7,8]. Consequently, the UK Heart trial revealed higher all-cause mortality for patients with CHF having reduced HRV and identified this variable as a better predictor of death due to progressive heart failure than other conventional clinical parameters [9].

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Chronic heart failure is, similarly to MODS, characterized by a clear activation of the innate immunity as characterized by elevated cytokine levels, which are of prognostic significance [10].

Taken all these data together, we hypothesize that a slight uncoupling of interorgan communication, which is not as pronounced as in MODS, already occurs in patients admitted for worsening CHF. This feature can be characterized by HRV, BRS, and CRS. The severity of illness can be precisely described by scoring (Acute Physiology and Chronic Health Evaluation [APACHE] score) [11]. This score evaluates not only pathological variables concerning cardiac function such as the New York Heart Association (NYHA) classification but also incorporates information concerning abnormal renal, pulmonary, and gastrointestinal function, as well as age and preexisting condition, and is therefore utmost appropriate to assess interorgan communication and inflammatory activation.

Therefore, the aim of the present study was to investigate

1. whether a deterioration of autonomic function is related to the severity of illness, starting with worsening CHF as a potentially nonfatal stage and finishing with MODS as the final state, and
2. whether parasympathetic modulation of heart rate is blunted in CHF and even more in MODS as well as whether there is a correlation between parasympathetic activity and activation of immunity in CHF and MODS.

2. Materials and methods

This noninterventional study was approved by the local ethics committee of the Medical Faculty of the Martin-Luther-University Halle-Wittenberg. The need for written informed consent for unconscious patients with MODS was waived, but all conscious patients gave their written informed consent prior to the study.

2.1. Patients

We retrospectively enrolled 70 consecutive patients who were admitted to the emergency department of the Department of Medicine III of Martin-Luther-University Halle-Wittenberg for acute worsening of CHF with left ventricular ejection fraction less than 39%, as reported previously [12], within 4 days of admission. Consequently, after administration of loop diuretics, very few patients (n = 3) initially showing a higher NYHA functional class were in NYHA class I at the time point of data collection. Those patients with CHF having an intermittent loss of sinus rhythm, pacemaker beats or episodes of atrioventricular blocks II° or III° were excluded from the study because these conditions do not allow a proper assessment of autonomic function. Thus, all together, the data of 65 patients with CHF were used for analysis, and 65 age- and sex-matched patients with pronounced MODS were assigned to be compared with the patients with CHF for autonomic function. These patients with MODS were consecutively recruited in the course of a prospective clinical trial [5]. *Multiple-organ dysfunction syndrome* was defined by an APACHE II score of 20 or above [5,6].

Multiple-organ dysfunction syndrome was triggered by an initial cardiac event (n = 37; decompensated CHF, cardiogenic shock, cardiac arrest, endocarditis, valvular heart disease), respiratory failure (n = 14; pneumonia, acute respiratory distress syndrome, exacerbated chronic obstructive pulmonary disease), hepatic/gastrointestinal failure (n = 3; decompensated liver failure, pancreatitis), hematologic disease (n = 1), acute renal failure (n = 1), and sepsis of unknown origin (n = 7).

2.2. Calculation of APACHE II score

The APACHE II score [11] is used for the determination of severity of illness in various cohorts of patients such as medical, preoperative and postoperative surgical, and neurologic patients. It is based on the calculation of an acute physiological score with 12 routinely assessed variables, an age assessment, and an evaluation of the chronic health status.

All data for calculation of the score were available in the group of patients with MODS. Nevertheless, there were some data missing for the CHF group on account of the retrospective design of the study. These data were assumed to be normal. Thus, the severity of illness might be slightly underestimated in the CHF group.

2.3. Technical and laboratory measurements

2.3.1. Heart rate variability

Twenty-four-hour continuous electrocardiogram (ECG) recordings were obtained using Holter recorders (DMS, Stateline, Nev; USA/MTM multitechmed GmbH, Huenfelden-Dauborn, Germany; and Ela Med, Munich, Germany). Recordings were analyzed by a blinded research Holter technician using a standard software package (DMS) and standard Holter analysis techniques for labeling beats and artifacts. All artifacts and ectopic beats were removed, and the resulting missing data were replaced by interpolation between the 3 preceding and the 3 succeeding intervals. A second independent observer (ICU-experienced cardiologist) edited and double-checked the recordings, reanalyzed the data, and compared the results with those of the research Holter technician. Only recordings with at least 20 hours of usable data were included in the analysis. The sampling rate of the ECG acquisition was 256 Hz. The HRV analysis was done according to the taskforce guidelines [13].

The standard time domain indices of HRV, which are depicted in the Appendix, were calculated from the entire 24-hour ECG recordings [13]. The parameters percentage of differences of successive RR intervals differing more than 50 milliseconds (pNN50) and root mean square of successive differences of N-N intervals (rMSSD) primarily reflect parasympathetically mediated changes in heart rate; the other variables represent a mixture of sympathetic, parasympathetic, and other physiological influences on heart rate [14].

The frequency domain indices were calculated from the power spectra for heart periods time series (by Fast Fourier Transformation) expressed in milliseconds squared per hertz according to the standards [13,14] as follows (please refer also to Appendix 2): (*a*) very-low-frequency (VLF; 0.003-0.04 Hz) power may represent physiological influences such as hormones, chemoreflexes, thermoregulation, and parasympathetic modulations of heart rate; (*b*) low-frequency (LF; 0.04-0.15 Hz) power, which reflects sympathetic and parasympathetic modulation of heart rate [17]; and (*c*) high-frequency (HF; 0.15-0.4 Hz) power, mainly reflecting vagal modulation [16]. The ratio of LF to HF power (LF/HF ratio) was calculated as a marker of sympathetic-parasympathetic balance.

2.3.2. C-reactive protein

C-reactive protein (CRP) was measured as an indicator of the inflammatory status using routine laboratory analysis at admission to hospital, thereby measuring the basic inflammation level of patients with CHF. Patients with CHF presenting with a predominant infection, especially of the lungs, per se leading to a highly activated general inflammation, were not taken into consideration for the present study.

2.4. Statistical analysis

Continuous data are given as mean values ± SD, except when indicated otherwise. The Kolmogorov-Smirnov test was used to test for normal distribution, and, if required, data were log transformed. One-way analysis of variance with Scheffé post hoc procedure was used for intergroup comparisons. Pearson correlation analysis and simple linear and stepwise backward regression models were performed. *P* values less than .05 were considered significant. All