



# Heart rate variability is reduced during acute uncomplicated diverticulitis



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## ABSTRACT

**Background:** The aim of the present study was to report the trajectory of heart rate variability (HRV) indices during a low-grade acute inflammation and their associations to biomarkers for infection.

**Methods:** Twelve patients with uncomplicated acute diverticulitis completed this observational study, which composed of 3 sessions of continuous HRV recording from 9 PM to 8 AM during ongoing diverticulitis and at complete remission (baseline). The blood samples were collected at each study session measuring C-reactive protein (CRP) and leukocytes.

**Results:** This study showed that the trajectories of the HRV indices were decreased both in time and frequency domains during acute diverticulitis compared to baseline. In particular, the indices reflecting the balance of sympathetic and parasympathetic activities were affected: standard deviation of normal-to-normal beats ( $P = .003$ ), low-frequency power ( $P < .001$ ), and total power ( $P = .001$ ). These HRV changes indicate alterations in the autonomic nervous system during acute inflammation. All reductions of mean HRV indices had significant ( $P < .001$ ) correlations to increased CRP correlations to increased CRP levels during diverticulitis suggesting inflammatory involvement in the observed HRV alterations.

**Conclusion:** We found substantial HRV depression in relation to acute uncomplicated diverticulitis, and this was associated with the elevated CRP levels.

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## 1. Introduction

Despite the modern advancement in medicine, sepsis and septic shock still account for many intensive care unit (ICU) admissions and causing almost 50% mortality among these patients [1]. In United States, the incidence of sepsis is estimated to be increased to more than 1 million cases per year by 2020 [2]. The sepsis is characterized by inflammation-induced organ dysfunction and associated with changes in functions of immune, endocrine, and autonomic nervous systems [3].

The sinus node of our heart is under constant modulation by the sympathetic and the parasympathetic branches of the autonomic nervous system (ANS) [4]. Heart rate variability (HRV), the alteration in the time between successive heart beats, is believed to represent the dynamic balance of this system [4]. Clinical studies have shown that reduced variability in physiological parameter, notably reduced HRV, is associated with poor outcomes and death [5] and serves as an independent predictor of mortality in patients with sepsis [6–13]. Heart rate variability is measured non-invasively using continuous

electrocardiographic recordings [14]. There are different statistical methods for determining HRV, all representing the modulation of heart rate (HR) by the sympathetic and the parasympathetic outflow (see reference [4] for extended review). Because pathophysiology of infections and sepsis involve disruption of ANS [3], changes in HRV may precede alterations in biochemical markers, thus allowing early recognition of a poor prognosis and giving the possibility for early intervention of septic shock [15].

To our knowledge, much work has already been done to characterize HRV in patients with sepsis and in healthy subjects during endotoxemia [6–13]. However, no prior clinical studies have investigated HRV in patients with abdominal (intra-abdominal) infection, which is one of the major causes of sepsis [16]. Our aim was to characterize the trajectory of HRV during acute uncomplicated diverticulitis, an infection involving the colonic wall that can lead to complications such as complicated diverticulitis and sepsis [17,18], and to investigate the relationship between HRV changes and inflammation severity.

## 2. Materials and methods

Patients were enrolled after given written informed consent, and the study was approved by the Research Ethics Committees of the Capital Region of Denmark (reference, H-1-2012-155) and the Danish Data Protection Agency. The study was registered on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) before enrollment of the first patient (reference, NCT01840917).

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## 2.1. Patients

We included patients between 18 and 75 years, with the American Society of Anesthesiologists physical status classification I to III and with a computed tomographic scan confirming acute uncomplicated diverticulitis (Hansen and Stock stage I). The Hansen and Stock staging of diverticulitis is a clinical classification that also accounts for asymptomatic diverticulosis (stage 0). Stages I to III refer to increasing severity of diverticulitis. Stage I refers to acute uncomplicated diverticulitis, stage II refers to acute complicated diverticulitis, and stage III refers to chronic recurrent diverticulitis [18]. Finally, the onset of lower abdominal pain and fever had to be within 72 hours before admission.

The exclusion criteria were patients with diverticulitis requiring surgical intervention, complicated diverticular disease (fistula or abscess), onset of symptoms more than 3 days from inclusion, previous history of diverticulitis within the past year, recent history (up to 3 months) of surgical intervention, myocardial infarction or arrhythmia, autoimmune diseases (inflammatory bowel disease, lupus, multiple sclerosis), sleep disorders including obstructive sleep apnea, night shift professions, daily use of opioids, psychoactive drugs or hypnotics, psychiatry disorders, daily consumption of more than 50 g of alcohol, diabetes mellitus, predicted bad compliance (language difficulties, etc), pregnancy or nursing, urinary or fecal incontinence, severe kidney disease, or current cancer.

## 2.2. Study setup

The study was composed of 3 sessions of HRV monitoring in 3 separate days while the patients were admitted to the hospital, all from 9 PM to 8 AM in a private room. The first study session (S1) was conducted at admission day, whereas the second study session (S2) was conducted at the following day. After these 2 successive sessions of HRV monitoring, the patients continued their treatment according to standard treatment guidelines for the department. The patients were readmitted at 30 days after S1 to attend the last study session (S3), also regarded as baseline session, as the patients were recovered from their episode of colonic inflammation at that time. Before the readmission, we performed a focused clinical examination and a blood sampling of C-reactive protein (CRP) on the patients to confirm that they no longer suffered from active clinically detectable infections. In case of relapse or failure of treatment, the patient was excluded.

The patients were prohibited from intake of stimulating beverages or alcohol during the day of the study nights. In each session, blood samples were collected at 10:30 PM followed by lights out at 11 PM. The patients agreed to stay in bed between 11 PM and 7 AM, except for toilet visits.

## 2.3. Heart rate variability monitoring

Heart rate variability monitoring was performed with a portable recording unit (Medilog AR12 Holter Recorder; Schiller AG, Baar, Switzerland). Continuous recording from 9 PM to 8 AM was made by using 3-channel, 5-lead electrocardiographic electrodes. All electrodes were placed in accordance to the user's manual. The HRV data were

analyzed and extracted using the bundle software (Medilog Darwin full version; Schiller AG). Both frequency and time domain analyses were based on 5-minutes recording epochs according to recommendation by the Task Force in 1996 [19]. Before HRV analysis, the authors reviewed all the QRS complexes in the recordings manually to only tabulate normal-to-normal beat intervals (normal R-R intervals). Abnormal R-R intervals (due to artifacts, ectopic beats, or arrhythmic events) and R-R intervals before and after an abnormal R-R interval were not tabulated. Any recording epoch with abnormal R-R intervals comprising 10% or more of the total of the epoch was excluded from the analysis. The interpretations of HRV indices in relation to ANS are further explained in Table 1.

## 2.4. Blood sampling

Blood samples collected at each study session were analyzed within few hours. Standard hospital assays were used to measure plasma concentrations of biomarkers for bacterial infection: C-reactive protein, total leukocytes, and its subpopulations (neutrophil granulocytes, lymphocytes, and monocytes). The levels of plasma CRP and white blood cells (WBCs) are expressed as medians (interquartile range).

## 2.5. Statistics

This is a proof-of-concept study, and no previous HRV study exists in this patient group. Therefore, the included number of patients was set on empirical basis. Unless specified otherwise, the data are presented as medians (interquartile range) or means  $\pm$  SEM according to their distribution. All data were tested for normality using Shapiro-Wilk test. Non-normally disturbed HRV data were log transformed and thereby met normal distribution. Two-way repeated analysis of variance (ANOVA) was performed to analyze the alterations of log HRV and HR in respect to the study sessions, the time course of individual study session, and their interactions. Due to the values of biomarkers (CRP and WBC) were not normal distributed, Wilcoxon signed rank test was performed to contrast the values between study sessions during diverticulitis and baseline (S1 vs S3 and S2 vs S3) for these data. Pearson correlation was used to analyze the correlations between changes in mean HRV, HR, and biomarkers, and the changes were calculated by subtracting corresponding baseline values (S3) from S1 and S2, before pooling both subtracted values into the analysis. To meet the normality for Pearson correlation, values of CRP, WBC, and HRV were log transformed before the subtraction. IBM SPSS Statistics for Windows, version 20.0 (IBM Corp, Armonk, NY) was used to carry out the calculations. The level of statistical significance was set to 0.05.

## 3. Results

Thirteen patients were enrolled, 12 completed the study, and 1 was excluded due to recurrence of diverticulitis within 30 days. Characteristics of patients are presented in Table 2. All 12 patients (American Society of Anesthesiologists I) with uncomplicated diverticulitis (Hansen and Stock stage I) were treated with oral or intravenous antibiotics

**Table 1**  
Description of HRV indices and their interpretations

Indices		Description	Interpretations
SDNN	Time domain	Standard deviation of normal-to-normal beats (milliseconds)	Sympathetic and parasympathetic activity
rMSSD		Square root of the mean of the sum of the square of differences between consecutive normal beats (milliseconds)	Parasympathetic activity
pNN50		Percentage of difference between consecutive normal beats that is greater than 50 milliseconds	Parasympathetic activity
LF	Frequency domain	Low-frequency power (0.04–0.15 Hz)	Sympathetic and parasympathetic activity
HF		High-frequency power (0.15–0.40 Hz)	Parasympathetic activity
LF/HF ratio		Ratio between LF and HF	Sympathetic activity
TP		Total power, variance of all NN intervals (<0.40 Hz)	Sympathetic and parasympathetic activity

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