Lower ultra-short-term heart rate variability is a risk factor for worse mucosal healing in ulcerative colitis

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Research Article

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Abstract

Background

Psychological stress has been proved to be a risk factor for exacerbation for ulcerative colitis (UC). However, traditional approaches of quantifying psychological stress using psychological scales are time-consuming and the results may not be comparable among patients with different educational levels and cultural backgrounds. Alternatively, heart rate variability (HRV) is an indicator for psychological stress and not biased by educational and cultural backgrounds.

Aims

In this study, we try to explore the relationship between psychological stress and UC by analyzing the effect of ultra-short-term HRV on mucosal and histological remission status of UC.

Methods

This is a retrospective case-control study on UC inpatients from 2018 through 2020. Ultra-short-term HRV were calculated using baseline electrocardiography. Patients were divided into case and control groups according to their Mayo endoscopic scores or histological Geboes scores. Three variables of ultra-short-term HRV (SDNN, SDSD and RMSSD) were compared between different groups. And for those variables with significant differences, we built univariate and multivariate logistic regressions to depict the relationship between HRV variables and remission status of UC.

Results

All three HRV variables showed significant differences between the mucosal groups. However, none of them showed significant difference between the histological groups. In further logistic regression analyses, smaller RMSSD was detected as a risk factor for severe mucosal healing status (OR = 5.21).

Conclusions

Lower ultra-short-term HRV (i.e. smaller RMSSD) is shown to correlate with worse mucosal healing status. However, ultra-short-term HRV cannot predict histological healing status according to our data.

Highlights

- Desiccation caused zone-specific elevation of ROS in radicles of germinated seeds.
- Non-enzymatic ROS bursting was responsible for loss of desiccation tolerance.
• ROS induced the activity of antioxidants during the desiccation of germinated seeds.
• PEG treatment re-induced the expression of antioxidative enzymes.
• Antioxidants and ROS have a key role in the re-induction of DT in germinated seeds.

Introduction

Ulcerative colitis (UC) is a chronic disease with remitting and relapse that brings heavy burden both physically and psychologically to patients. Psychological stress is considered a risk factor for UC exacerbation. The association between heart rate variability (HRV) and psychological stress has been widely accepted[1]. Significant correlation has been observed between long-term HRV and stress in UC patients in a pilot study[2], while short-term HRV is also considered an objective biomarker for psychological stress both consciously recognized or subconsciously existed[3].

Ultra-short term HRV is calculated using data from an electrocardiograph (ECG) that is shorter than five minutes. Compared with long-term HRV, it is more feasible in daily clinical practice, with high reliability and acceptably low bias[4], especially when the ECG data is collected under static conditions[5]. Meanwhile, ultra-short-term HRV is shown to be sensitive in detecting psychological stress in real life[6, 7]. Based on those merits, ultra-short-term HRV is a reasonable biomarker for quantifying psychological stress among UC patients.

However, the relationship between the ultra-short-term HRV and the severity of UC has not been directly demonstrated yet. This study is designed to use ultra-short-term HRV as a metric to explore the relationship between psychological stress and the severity of UC. This is a retrospective case-control study using baseline ultra-short-term HRV as an objective measurement of psychological stress in UC patients. The case and control groups were naturally divided by their mucosal or histological inflammatory status. In this study we characterize the relationship between the baseline ultra-short-term HRV and the inflammatory status of UC patient, and develop a predictive model of mucosal or histological remission status of UC.

Methods

In this retrospective case-control study, we analyzed the clinical data from patients with a primary diagnosis of ulcerative colitis and who were admitted in the First Affiliated Hospital of Zhejiang University between January 1st, 2018 and December 31st, 2020 (including both days). The diagnosis of UC in all participants included was confirmed by both colonoscopy and pathology of biopsy. Detailed inclusion and exclusion criteria are listed in Table1. The two key criteria to evaluate the disease activity is the Mayo endoscopic score (MES) and the histological Geboes Score (GS), which reflect the baseline mucosal and the histological inflammatory status, respectively. Colonoscopy images before treatment adjustment were reviewed by a senior gastroenterologist and their MES was recorded. Histological images of colonic biopsy were reviewed by a senior pathologist and their GS was recorded. Patients were divided into different groups according to the MES and the GS. Specifically, in the evaluation of the mucosal
inflammatory status, patients with a MES of 2 or 3 were defined as “severe”, while patients with a MES of 0 or 1 were defined as “mild-moderate”. In terms of the histological inflammatory status, a GS less than 2 was defined as mucosal healing, while a GS less than 3.1 was defined as mucosal remission. The baseline demographic information, the disease duration, the treatment adjustment, and the baseline inflammation status of the participants were also collected. Here the baseline inflammation status includes the white cell count, the C-reactive protein (CRP) and the erythrocyte sedimentation rate (ESR). The three variables used to evaluate the ultra-short-term HRV in this study include: the standard deviation of normal to normal R-R intervals (SDNN), the root mean square of successive differences of normal to normal R-R intervals (RMSSD), and the standard deviation of successive differences between adjacent normal to normal R-R intervals (SDSD). They were calculated based on the time-domain methods using the baseline 10-seconds electrocardiography at patient admission.

Statistics:

The categorical variables in this study were analyzed by the Pearson χ² test while the quantitative variables were analyzed using Student’s t test. The association between HRV and severity of UC was evaluated via univariate and multivariable logistic regression models and odds ratio (OR) with 95% confidence intervals (CI). Univariate logistic regression was applied to detect possible association between the variables and the outcomes of interest. Multivariate logistic regression was applied to differentiate the real predictor out of potential confounders. All data were analyzed by the software SPSS (version 26.0, Chicago, IL, USA). A p-value less than 0.05 was considered statistically significant.

Ethical approval:

This study was approved by the Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (Prot No 2022086).

Results

Baseline demographic information and inflammatory status:

We finally included 91 patients in this study. Detailed information about the inclusion and exclusion criteria were listed in Flowchart 1. The included patients had a mean age of 47.89±13.44 years, a mean disease duration of 4.64±6.23 years, and a mean hospital stay length of 11.94±10.77 days. Based on the MES, 59 patients (with MES 2 or 3) were assigned to the “Severe group” while 32 patients (with MES 0 or 1) were assigned to the “Mild-Moderate group”. Similarly, based on the Geboes Scores (GS) calculated from their histological images, 70 patients with GS ≥ 2 were considered not achieve histological healing while 21 patients with GS < 2 were considered histological healed. When an alternative GS cut-off of 3.1 was used, 65 patients (with GS ≥ 3.1) were considered histological active while the other 26 patients (with GS < 3.1) were considered histological inactive.
Baseline demographic distributions and basic disease characteristics (including age, gender, disease duration, and therapy categories) and D-dimer level analysis did not show statistically different between the two MES groups. Fecal calprotectin level was not statistically different between the two MES groups either. However, it is noteworthy that fecal calprotectin was not commonly tested in 2018 in this hospital, and the lack of this data could lead to bias in the results. Detailed information is listed in Table 2.

According to histological remission using GS score 2 as a cut-off point, age, gender distribution, disease duration, therapy distribution and D-dimer level were not statistically different between the two groups. These were consistent to endoscopic remission evaluation using MES. However, when switch the cut-off point of GS score to 3.1 in differentiate histological active and inactive, variate differences were similar except that D-dimer was statistically different between the two groups. Detailed information is listed in Table 3.

**The relationship between ECG-based ultra-short-term HRV and mucosal and histological remission status:**

Ultra-short-term HRV was calculated based on each patient’s 10-second-ECG in the first 24 hours upon admission using time-domain analysis. HRV variables including SDNN, SDSD, RMSSD and the heart rate (HR) were compared among different groups. All HRV variables showed significant differences between the “Severe group” and the “Mild-Moderate group” based on MES. The “Severe group” has lower SDNN, SDSD and RMSSD and higher HR compared with the “Mild-Moderate group”. However, when evaluating the histological status using GS, no HRV variables showed significant difference either between groups with a GS cut-off of 2 nor 3.1. Detailed information is listed in Table 4.

Receiver operating curves (ROC) were made to decide the optimal cut-off to transfer quantitative variables into categorical. According to the calculated maximum Youden index, the cut-offs for SDNN, SDSD and RMSSD should be 16.807ms, 14.721ms, 15.516ms and 77.5beats/min, respectively. Cut-offs for other quantitative variables were decided using either commonly used or previously published clinical references [8, 9]. The accuracy, sensitivity and specificity for our model was 89.0%, 84.4% and 91.5%, respectively. We have included all significant variables under MES group into univariate analysis. Finally, RMSSD, hemoglobulin, CRP and ESR were variables screened by multivariate logistic regression analysis. Detailed information is listed in Table 5. Despite different distributions were observed among all of the HRV parameters include SDNN, SDSD and RMSSD between severe and mild-moderate UC patients, multivariate regression analysis included only lower RMSSD (RMSSD<15.516ms) as a risk factor for severe mucosal inflammation of UC (OR=5.21).

**Discussion**

**Ultra-short-term HRV can predict mucosal remission status:**

Psychological stress can trigger the symptomatic flare in IBD patients though the mechanism is not yet clear[10]. Psychological assessment through questionnaires or interviews can be used to measure
psychological stress in real life, however, the results can be subjective and should be cautiously interpreted due to the huge heterogeneity of cultural and educational backgrounds among patients. On the other hand, HRV is deeply studied in previous research and has been proved to be an objective indicator of psychological stress level. It is quantitative and not biased by different cultural and educational backgrounds, which makes it an ideal marker for psychological stress.

Specifically, ultra-short-term HRV is consistent with long-term HRV and can be used as a surrogate for long-term HRV in previous clinical research[6]. In this retrospective case-control study, we try to explore the potential relationship between ultra-short-term HRV and the severity of UC. We use both mucosal and histological scores to evaluate UC severity.

Significant differences in SDNN, SDSD and RMSSD were observed between the mucosal “severe” and “mild-moderate” groups. In further univariate and multivariate logistic regression model, lower RMSSD was detected as a risk factor for severe mucosal status (OR=5.21). These results provided evidence that low ultra-short-term HRV may be a risk factor for mucosal flare in UC. Notably, these results indicate that RMSSD may be used to predict the mucosal severity in UC, which provides a potentially non-invasive method for UC mucosal healing surveillance or even suggests new target for UC treatment.

**Discrepancy in that ultra-short-term HRV predicts mucosal remission but not histological remission:**

Since psychological stress is a risk factor for UC exacerbation, we have hypothesized that lower ultra-short-term HRV is a risk factor for poorer mucosal healing status however, we did not observe significant differences between different histological groups in our study, which suggests that ultra-short-term HRV is not a useful metric to predict the histological severity or remission status of UC. However, our results also indicate discrepancy in that ultra-short-term HRV predicts the mucosal remission but not the histological remission.

One possible explanation for this discrepancy is the latency between histological healing and mucosal healing. Endoscopically quiescent UC may still be histological active according to a previous clinical study[11]. Patients with a MES of 0 may still have a high risk of relapse if they have histological basal plasmacytosis[12]. Our rationale is that during mucosal healing, patients may realize the improvement of the symptoms and this subjective cognition of improvement may bring positive feedback on their HRV. On the other hand, patients cannot “feel” the histological remission and therefore it doesn’t directly correlate with the HRV.

Though histological remission is widely accepted as a sensitive way in evaluating UC, the clinical application of histological healing as a treatment target is still controversial[13] and no clear criterion for histological remission has been consensually defined or validated. Moreover, in a prospective multi-center cohort study, the correlation between UC mucosal healing and histological healing is low[14]. These previous studies suggest that it is probably not necessary or feasible to expect consistent prediction of the two healing standards in one clinical model, which mitigates the concerns of the discrepancy observed in our study.
Psychological stress is developing under the background of COVID-19 pandemic. Lower ultra-short-term HRV, a measure of psychological stress, was found to be a risk factor for poor mucosal healing in ulcerative colitis patients in this study. Our work provides insight for non-invasive evaluation for the mucosal remission status of UC. Furthermore, bioelectronic medicine treatment like vagal nerve stimulation is considered has therapeutic potential in UC treatment[15]. These findings may give support for future treatment like vagal nerve stimulation. Due to the limitation of retrospective observational study with limited sample size, a prospective clinical trial exploring the relationship of UC and HRV with larger sample size may provide more evidence.

**Abbreviations**

HRV: heart rate variability, UC: Ulcerative Colitis, MES: Mayo endoscopic score , SDNN: the standard deviation of normal to normal, SDSD: the standard deviation of successive differences, RMSSD: the root mean square of successive differences, HR: heart rate, GS: Geboes Score, ECG: electrocardiograph, CRP : the C-reactive protein, ESR : erythrocyte sedimentation rate, OR: odds ratio, CI: confidence intervals

**Declarations**

**Ethics approval and consent to participate:** This study was approved by the Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (Prot No 20220086). The consent form was waived and approved by the Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine according to the International Ethical Guidelines for Health-related Research Involving Humans. Approval of using recorded data in this retrospective study was achieved from the Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine.

**Consent for publication:** Not applicable.

**Availability of data and materials:** The datasets used in the current study are available from the corresponding author on reasonable request.

**Competing interests:** None declared.

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**Authors’ contributions:** Jianan Guo and Guoqiang Xu designed the study. Jianan Guo and Huatuo Zhu collected the clinical data. Wenguo Chen and Hongtan Chen reviewed the colonoscopy images and re-evaluated the Mayo endoscopic scores. Xiaodong Teng reviewed the colon histological images and evaluated the Geboes scores. Jianan Guo finished the statistical calculations and wrote the manuscript.

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References


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**Tables**

Table 1 To 5 is available in Supplementary Files section.

**Figures**

**Flowchart 1**

98 patients were initially screened

- 4 cases were excluded due to unavailable ECG image
- 1 case was excluded due to low quality of ECG image for HRV analysis
- 1 case was excluded due to ventricular pre-excitation syndrome
- 1 case was excluded because the case was finally pathologically confirmed as Crohn disease

Mucosal score : MES
- Severe group (MES≥2): n=59
- Mild-moderate group (MES<2): n=32

Histological score : GS
- Not Histological healing (GS≥2): n=70
- Histological healing (GS<2): n=21
- Histological active: (GS≥3.1): n=65
- Histological remission(GS<3.1): n=26

**Figure 1**

Flowchart 1

**Supplementary Files**
This is a list of supplementary files associated with this preprint. Click to download.

- Table1.png
- Table2.png
- Table3.png
- Table4.png
- Table5.png