APR 10, 2024

Heart Rate Variability Parameters for Assessing Autonomic Responses to Brief Rectal Distention in Patients with Irritable Bowel Syndrome

M Khawar Ali[1], Shiyuan Gong[1], Jiande Chen[1], Borko Nojkov[1], Colin Burnett[1]

[1]University of Michigan

M Khawar Ali
University of Michigan

OPEN ACCESS

DOI:
dx.doi.org/10.17504/protocols.io.j8nlko3x1v5r/v1

External link:
https://doi.org/10.3390/s23198128

Protocol Citation: M Khawar Ali, Shiyuan Gong, Jiande Chen, Borko Nojkov, Colin Burnett 2024. Heart Rate Variability Parameters for Assessing Autonomic Responses to Brief Rectal Distention in Patients with Irritable Bowel Syndrome. **protocols.io** https://dx.doi.org/10.17504/protocols.io.j8nlko3x1v5r/v1

MANUSCRIPT CITATION:
Ali, M.K.; Gong, S.; Nojkov, B.; Burnett, C.; Chen, J.D.Z. Best Parameters of Heart Rate Variability for Assessing Autonomic Responses to Brief Rectal Distention in Patients with Irritable Bowel Syndrome. *Sensors* **2023**, *23*, 8128. https://doi.org/10.3390/s23198128

Protocol status: Working
We use this protocol and it's working

Created: Oct 12, 2023

Last Modified: Apr 10, 2024

PROTOCOL integer ID: 89225

Keywords: HRV, IBS, rectal distension, signal processing, habituation, adaptation

Funders Acknowledgement:
National Institute of Neurological Diseases and Stroke
Grant ID: UG3NS115108

ABSTRACT

Heart rate variability (HRV) has been used to measure autonomic nervous system (ANS) activity noninvasively. The purpose of this study was to identify the most suitable HRV parameters for ANS activity in response to brief rectal distension (RD) in patients with Irritable Bowel Syndrome (IBS). IBS patients participated in a five-session study. During each visit, an ECG was recorded for 15 min for baseline values and during rectal distension. For rectal distension, a balloon was inflated in the rectum and the pressure was increased in steps of 5 mmHg for 30 s; each distension was followed by a 30 s rest period when the balloon was fully deflated (0 mmHg) until either the maximum tolerance of each patient was reached or up to 60 mmHg. The time-domain, frequency-domain and nonlinear HRV parameters were calculated to assess the ANS activity. The values of each HRV parameter were compared between baseline and RD for each of the five visits as well as for all five visits combined. The sensitivity and robustness/reproducibility of each HRV parameter were also assessed. The parameters included the Sympathetic Index (SI); Root Mean Square of Successive Differences (RMSSD); High-Frequency Power (HF); Low-Frequency Power (LF); Normalized HF Power (HFn);
Normalized LF Power (LFn); LF/HF; Respiratory Sinus Arrhythmia (RSA); the Poincare Plot's SD1, SD2 and their ratio;
and the pNN50, SDSD, SDNN and SDNN Index. Data from 17 patients were analyzed and compared between baseline and FD and among five sessions. The SI was found to be the most sensitive and robust HRV parameter in detecting the ANS response to RD. Out of nine parasympathetic parameters, only the SDNN and SDNN Index were sensitive enough to detect the parasympathetic modulation to RD during the first visit. The frequency-domain parameters did not show any change in response to RD. It was also observed that the repetitive RD in IBS patients resulted in a decreased autonomic response due to habituation because the amount of change in the HRV parameters was the highest during the first visit but diminished during subsequent visits. In conclusion, the SI and SDNN/SDNN Index are most sensitive at assessing the autonomic response to rectal distention. The autonomic response to rectal distention diminishes in repetitive sessions, demonstrating the necessity of randomization for repetitive tests

PROTOCOL REFERENCES

Akbar, A.; Walters, J.R.F.; Ghosh, S. Review Article: Visceral Hypersensitivity in Irritable Bowel Syndrome: Molecular Mechanisms and Therapeutic Agents. *Aliment. Pharmacol. Ther.* **2009**, *30*, 423–435. https://doi.org/10.1111/j.1365-2036.2009.04056.x.

Ali, M.K.; Chen, J.D. Roles of Heart Rate Variability in Assessing Autonomic Nervous System in Functional Gastrointestinal Disorders: A Systematic Review. *Diagnostics* **2023**, *13*, 293. https://doi.org/10.3390/diagnostics13020293.

Ali, M.K.; Liu, L.; Chen, J.H.; Huizinga, J.D. Optimizing Autonomic Function Analysis via Heart Rate Variability Associated With Motor Activity of the Human Colon. *Front. Physiol.* **2021**, *12*, 619722. https://doi.org/10.3389/fphys.2021.619722.

Ali, M.K.; Liu, L.; Hussain, A.; Zheng, D.; Alam, M.; Chen, J.H.; Huizinga, J.D. Root Mean Square of Successive Differences Is Nota Valid Measure of Parasympathetic Reactivity during Slow Deep Breathing. *Am. J. Physiol.-Regul. Integr. Comp. Physiol.* **2023**, *324*, R446–R456. https://doi.org/10.1152/ajpregu.00272.2022.

Bouin, M.; Plourde, V.; Boivin, M.; Riberdy, M.; Lupien, F.; Laganière, M.; Poitras, P. Rectal Distention Testing in Patients with Irritable Bowel Syndrome: Sensitivity, Specificity, and Predictive Values of Pain Sensory Thresholds. *Gastroenterology* **2002**, *122*, 1771–1777. https://doi.org/10.1053/gast.2002.33601.

Farzaei, M.H.; Bahramsoltani, R.; Abdollahi, M.; Rahimi, R. The Role of Visceral Hypersensitivity in Irritable Bowel Syndrome: Pharmacological Targets and Novel Treatments. *J. Neurogastroenterol. Motil.* **2016**, *22*, 558–574. https://doi.org/10.5056/jnm16001.

Fichna, J.; Storr, M.A. Storr. Brain-Gut Interactions inIBS. *Front. Pharmacol.* **2012**, *3*, 127. https://doi.org/10.3389/fphar.2012.00127.

Grissom, N.; Bhatnagar, S. Habituation to Repeated Stress: Get Used tolt. *Neurobiol. Learn. Mem.* **2009**, *92*, 215–224. https://doi.org/10.1016/j.nlm.2008.07.001.

Kano, M.; Yoshizawa, M.; Kono, K.; Muratsubaki, T.; Morishita, J.; Van Oudenhove, L.; Fukudo, S.; Yagihashi, M.; Mugikura, S.; Dupont, P.; et al. Parasympathetic Activity

Correlates with Subjective and Brain Responses to Rectal Distension in Healthy Subjects but Not in Non-Constipated Patients with Irritable Bowel Syndrome. *Sci. Rep.* **2019**, *9*, 7358. https://doi.org/10.1038/s41598-019-43455-5.

Mertz, H.; Naliboff, B.; Munakata, J.; Niazi, N.; Mayer, E.A. Altered Rectal Perception Isa Biological Marker of Patients with Irritable Bowel Syndrome. *Gastroenterology* **1995**, *109*, 40–52. https://doi.org/10.1016/0016-5085(95)90267-8.

Nakata, R.; Tanaka, F.; Sugawara, N.; Kojima, Y.; Takeuchi, T.; Shiba, M.; Fujiwara, Y. Analysis of Autonomic Function during Natural Defecation in Patients with Irritable Bowel Syndrome Using Real-Time Recording with a Wearable Device. Edited by Gopal Krishna Dhali. *PLoS ONE* **2022**, *17*, e0278922. https://doi.org/10.1371/journal.pone.0278922.

Ng, C.; Malcolm, A.; Hansen, R.; Kellow, J. Feeding and Colonic Distension Provoke Altered Autonomic Responses in Irritable Bowel Syndrome. *Scand. J. Gastroenterol.* **2007**, *42*, 441–446. https://doi.org/10.1080/00365520600965749.

Spaziani, R.; Bayati, A.; Redmond, K.; Bajaj, H.; Bienenstock, J.; Collins, S.M.; Kamath, M.V. Vagal Dysfunction in Irritable Bowel Syndrome Assessed by Rectal Distension and Baroreceptor Sensitivity. *Neurogastroenterol. Motil.* **2008**, *20*, 336–342. https://doi.org/10.1111/j.1365-2982.2007.01042.x.

Tanaka, Y.; Kanazawa, M.; Palsson, O.S.; Van Tilburg, M.A.; Gangarosa, L.M.; Fukudo, S.; Whitehead, W.E. Increased Postprandial Colonic Motility and Autonomic Nervous System Activity in Patients With Irritable Bowel Syndrome: A Prospective Study. *J. Neurogastroenterol. Motil.* **2018**, *24*, 87–95. https://doi.org/10.5056/jnm16216.

Thompson, R.F.; Spencer, W.A. Habituation: A Model Phenomenon for the Study of Neuronal Substrates of Behavior. *Psychol. Rev.* **1966**, *73*, 16–43. https://doi.org/10.1037/h0022681.

Uribe-Bahamonde, Y.E.; Becerra, S.A.; Ponce, F.P.; Vogel, E.H. A Quantitative Account of the Behavioral Characteristics of Habituation: The Sometimes Opponent Processes Model of Stimulus Processing. *Front. Psychol.* **2019**, *10*, 504. https://doi.org/10.3389/fpsyg.2019.00504.

Whitehead, W.E.; Holtkotter, B.; Enck, P.; Hoelzl, R.; Holmes, K.D.; Anthony, J.; Schuster, M.M. Tolerance for Rectosigmoid Distention in Irritable Bowel Syndrome. *Gastroenterology* **1990**, *98*, 1187–1192. https://doi.org/10.1016/0016-5085(90)90332-U.

Yuan, Y.; Ali, M.K.; Mathewson, K.J.; Sharma, K.; Faiyaz, M.; Tan, W.; Huizinga, J.D.

Associations Between Colonic Motor Patterns and Autonomic Nervous System Activity Assessed by High-Resolution Manometry and Concurrent Heart Rate Variability. *Front. Neurosci.* **2020**, *13*, 1447. https://doi.org/10.3389/fnins.2019.01447.

MATERIALS

The barostat is a FDA approved device (K99 1288)used in clinical practice and research to study the function and activity of the motor and sensory functions of the gastrointestinal tract. This is a common method used to measure gastric motility (or the movement of food from the mouth through the pharynx(throat), esophagus, stomach, small and large intestines and out of the body). It can monitor volume changes while maintaining a set constant pressure and deliver controlled distensions of gastrointestinal organs. The controlled distension is completed by the device's ability to inflate at the tip of the catheter. In this study, the device was used in the rectum. This device does not use electricity to stimulate the rectum.

- This device is not being studied. Rather it is used to collect measurements. In this case, we used the barostat device to monitor the activity in the rectum. The rectum of the GI tract is thought to have abnormal activity in study participants with IBS-C, contributing to their symptoms.

Three ECG electrodes connected to the ECG machine were placed on the study participant's skin, one on the manubrium of the sternum, one above the breast bone, and one on the study participant's right chest. These three electrodes were used for recording the ECG.

The author-developed MATLAB code was used to detect R peaks from the recorded ECG and an HRV signal (RR intervals) was generated during baseline and rectal distension. This HRV signal was then used to calculate the HRV parameters. Sympathetic Index, Root Mean Square of Successive Differences (RMSSD), RSA, SD1, SD2, SD2/SD1.

HRV software named "HRV Analyzer" was used to calculate the other HRV parameters. SDNN, SDNN Index, HF, HFn, LF, LFn, LF/HF etc.

Both the MATLAB Code and HRV analyzer software are shared in the repository.
https://doi.org/10.26275/nung-b9bm

SAFETY WARNINGS

The immediate risks involved with barostat inflation and subsequent rectal distension include:

- Discomfort during the balloon insertion.
- Sensation (discomfort) with the balloon inflation which is a variable of the study. The likelihood of this risk is common, up to 100% of participants will experience discomfort. The study team will make the study participant aware of this before consenting to the procedure. The study participant has the right to stop the procedure at any time.
- Bleeding at the site of balloon inflation (in the rectum).

The likelihood of this risk is rare, approximate incidence of <1%. However, the duration of rectal distention is brief and the distention can be immediately terminated upon intolerable pain or discomfort.

The long range risk of barostat inflation is:

- Perforation of the rectum into the peritoneal space, the likelihood of this risk is rare, approximate incidence of <1%.

The risk involved with the ECG recording:

- Allergic reaction of ECG electrodes.The likelihood of this risk is rare, approximate incidence of<1%

ETHICS STATEMENT

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Study participants of Research, as drafted by the US National Commission for the Protection of Human Study participants of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46; 62 Federal Regulations 25691 (1997) and the Declaration of Helsinki and Good Clinical Practice (GCP).

Methods

2d

1 Twenty-two patients with IBS (constipation-dominant or IBS-C) were recruited initially. Nineteen patients had completed all five visits and recordings throughout the study. Out of the nineteen patients, two patients were excluded because of their HRV data were considered outliers.

- Since each patient will serve as his/her own control, the actual proportion of IBS subtypes in recruited patients should not affect the study outcomes.
- Each participant came to the clinic five time throughout the study.

2 All medications known to affect the gut will be discontinued 48 h before each session.

3 The patients were fasted overnight and given arectal enema (250ml) to clean the rectum. After a 30-min rest, a polyvinyl catheter attached with a non-compliance polyethylene bag (500ml capacity and 10cm long) will be inserted and placed 5-15cm from the anal verge.

4 An electrocardiogram (ECG) was recorded for 15 min at baseline to assess their autonomic function (through analyzing the HRV data, described below).

- Placement of the electrodes: place the RA electrode under the right clavical within the rib cage frame; place the LA

electrode under the left clavicle within the rib cage frame; place the LL electrode on the lower left abdomen within the rib cage frame).

5 After the 15 min rest("baseline"), the bag will be distended using an FDA-approved barostat device at 60 ml/min until the maximum tolerance.
Rectal distention was performed at different pressures from 5 mmHg to the maximum tolerable pressure with an increment of 5 mmHg.

- Each distension lasted for 30s and was followed by a 30s rest period when the balloon was deflated.

6 During the distention period ("Rectal Distention"), the patient will be asked to circle the following sensations:1) first sensation,2) urge to defecate, 3) discomfort or pain and 4) maximal tolerance.

- electrocardiogram (ECG) was recorded at the rectal distention period for each individual to assess their autonomic function.

7 The interbeat interval (RR interval) signal was calculated from the recorded and refined (after removing the segments of the ECG signal with noise, removing ectopic beats, and inserting interbeat wherever the peak was missed) ECG signal to calculate the HRV parameters; the Sympathetic Index (SI), Root Mean Square of Successive Differences (RMSSD), Respiratory Sinus Arrythmia (RSA) and SD1and SD2 of the Poincare Plot and their ratio (SD2/SD1) were calculated by using MATLAB code developed by the authors. The frequency-domain parameters of the SDSD, SDNN, and SDNN Index and HF, LF, HFn, LFn and LF/HF were calculated by using previously validated software developed in the lab.
The robustness/reproducibility of each HRV parameter was evaluated by comparing their values among each visit as described below.

Statistical analysis

8 A Shapiro–Wilk normality test was performed on each HRV parameter before each comparison. If the parameter was normally distributed, the paired t-test was applied to investigate the difference between the baseline and rectal distension. Otherwise, if not normally distributed, a Wilcoxon test was performed to investigate the differences. To test the reproducibility of the HRV parameters, the baseline and RD values of each visit were compared. The baseline values of all the five visits were compared by using a one-way ANOVA for the normally distributed data and a Kruskal–Wallis test for the data that were not normally distributed, followed by a Dunn's multiple comparison test. The procedure was repeated by using HRV values during rectal distension and compared among 5 visits.