Hualien Tzu Chi Hospital
Medical TechnologyResearch Project Proposal In the hospital

A. Basic information

Application number：_____

Project Category (Single choice)	■Individual Research Project: The principal investigator of this project is a senior member of our institution. ■Experimental Research (up to 800,000 NT Dollars) □ Non-experimental Research (up to 400,000 NT Dollars) □Integrated Care Department Project (Maximum Budget: 800,000 NT Dollars) (Restricted to Department Heads for Application) □New Staff Research Project (Up to 200,000 NT Dollars) □School-Industry Collaboration Research Project (Up to 400,000 NT Dollars) □Transfer In-House Project of the Ministry of Science and Technology (Maximum Funding: 800,000 NT Dollars) □Medical Education Research Project (Up to 400,000 NT Dollars)
人員類別 (單選)	■Physician □Non-Physician
The Project Name	Application of diaphragmatic breathing in patients with disorders of gut-brain interaction: impact on gastrointestinal and psychological symptoms as well as autonomic nervous system

Principal Investigator Name	Wong, Ming-Wun	Job Title	Attending Physician	Applicant Department or Division	Gastroenterology

Project Execution Deadline	From September 1, 2023 to December 31, 2024, a total of 1 year.
Nature and Classification of Research	□Fundamental Research ■Applied Research □Technological Development **(Note: Innovators engaged in applied research and technological development should select the category of innovative research and development)** Innovation and Research & Development Classification：■(1) Clinical Research □(2) Translational Research □(3)Medical Engineering and Materials □(4) Information □(5) Medical Assistance Operations □(6) Other, please specify _____。
Holistic Care (Please refer to the noun explanations, multiple selections allowed)	Holistic Care Classification： (1) Patient-Centered（■physiological ■psychological ■environmental □spiritual） (2) Health Education（■behavior change□health promotion■Disease Prevention■early diagnosis ■Early Treatment) (3) Other, please specify _____。

Has the current in-house project ever applied for the 112th-year Ministry of Science and Technology Special Research Project? ■No □Yes

Has any application been made for government grants for various research projects in the current year? □No ■Yes, Total 1 items.

This year, PI have applied to host a total of 1 research project within the institute. (Projects co-led with others will not be counted.)

The priority order of this project is 1 .

Does this project require ☐No ■Human experiments/human specimens (including human embryos/human embryonic stem cells)☐Animal Experimentation ☐Biosafety (including recombinant DNA experiments/genetically modified field trials/second-level or higher infectious biological materials) ?【Please check】	
Project Contact Person	Name：Wong, Ming-Wun Telephone：(03)8561825#13224 / 0982-098812 E-MAIL：hypertr42@gmail.com

B. Apply for Financial Assistance（Budget allocation will be included in the review scoring criteria; please do not inflate the budget.）

In accordance with the actual needs of the research project, subsidies can be applied for the following items: For individual research projects, the upper limit for experimental researchers is 800,000 NT dollars, and for non-experimental researchers, the principle upper limit is 400,000 NT dollars. For newly recruited personnel research projects, the total research budget is capped at 200,000 NT dollars. For university-industry collaborative research projects, the total research budget is capped at 400,000 NT dollars. For projects under the Department of Whole Person Care, the budget ceiling is 800,000 NT dollars. Technology transfer projects within the Ministry of Science and Technology have a maximum budget limit of 800,000 NT dollars.

Subsidy Programs		Requested Amount
Business expenses	1. Research personnel expenses	83,016
	2. Animal testing expenses	
	3. Consumables, Supplies, Books, and Miscellaneous expenses	716,984
Research equipment expenses		
Total		800,000

C. Equipment configuration

The principal instruments required for this project, their respective locations, and the signatures of the individuals authorized to use them.。

Instrument Name	Location Setup (Department)	Signature of the Unit Supervisor/Manager agreeing to the use of the equipment

D. Personnel involved in the project

1. Mainly researching human resources

Category (Host, co-host, co-presenter, research assistant, etc.)	Name	Current position	Nature, projects, and scope of work involved in this research project.
Host	Wong, Ming-Wun	Attending Physician of Gastroenterology	Project schedule supervision, research progress tracking and plan development, data analysis and report writing.
Co-host	Chen, Chien-Lin	Director of Gastroenterology	Actual case handling procedures, such as inspection operations, in the planned project.
Co-host	Yi, Chih-Hsun	Attending Physician of Gastroenterology	Actual case handling procedures, such as inspection operations, in the planned project.
Co-host	Liu, Tso-Tsai	Director of Endoscopy Department	Actual case handling procedures, such as inspection operations, in the planned project.
Co-host	Lei, Wei-Yi	Attending Physician of Gastroenterology	Actual case handling procedures, such as inspection operations, in the planned project.
Co-host	Hung, Jui-Sheng	Attending Physician of Gastroenterology	Actual case handling procedures, such as inspection operations, in the planned project.
Research assistant	Chen, Yan-Zhu	Research assistant	Organize data, data analysis and statistics and handle administrative affairs.
Research assistant	Jian,Yu-xuan	Research assistant	Organize data, data analysis and statistics and handle administrative affairs.

2. Research projects that the host, co-hosts, and co-researchers have participated in in the past three years.

Surname name	Count painting name say	Jobs within the plan	From year to month	Grant agencies
Wong, Ming-Wun	Antireflux mucosal ablation for the treatment of PPI-dependent gastroesophageal reflux disease: treatment efficacy and physiological alteration	Host	2023/01/01~ 2023/12/31	Hualien Tzu Chi Hospital
Wong, Ming-Wun	Exploring pathophysiological mechanisms of laryngopharyngeal reflux: utilization with artificial intelligence and clinical implication for precision diagnosis and personalized treatment strategies	Host	2022/8/1~ 2025/07/31	Ministry of Science and Technology
Wong, Ming-Wun	Supervised Learning Artificial Intelligence in 24-h Impedance-pH: Technique Performance and Clinical Implications for Diagnosing GERD	Host	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital
Wong, Ming-Wun	Jing Si Herbal Tea in the treatment of dyspeptic symptoms and psychophysical burden in patients with disorders of long COVID gut brain interaction a doub le blind, randomized,placebo controlled study	Co-host	2023/01/01~ 2023/12/31	Tzu Chi Medical Corporation
Wong, Ming-Wun	Interaction among supragastric belching, psychologic distress and esophageal acid reflux: Implications for optimal management of GERD	Co-host	2023/01/01~ 2023/12/31	Hualien Tzu Chi Hospital
Wong, Ming-Wun	Relevance of esophageal hypervigilance, functional gastrointestinal disorders, and psychological distress as pathophysiological	Co-host	2023/01/01~ 2023/12/31	Hualien Tzu Chi Hospital

	mechanisms to esophageal symptoms			
Wong, Ming-Wun	Oropharyngeal swallowing physiology in patients with esophageal hypomotility: Studies with HRPM	Co-host	2023/01/01~ 2023/12/31	Hualien Tzu Chi Hospital
Wong, Ming-Wun	Exploring capsaicin sensitization, sensorimotor function, psychophyiological reflux characteristics in human esophagus: therapeutic implications for esophageal dysfunction and gastroesophageal reflux disease	Co-host	2023/8/1~ 2026/07/31	Ministry of Science and Technology
Wong, Ming-Wun	Utility of high resolution pharyngeal manometry and Sydney Swallow Questionnaire for evaluation of oropharyngeal dysphagia and voice disorder	Co-host	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital
Wong, Ming-Wun	Application of Artificial Intelligence in High-resolution Esophageal Function Testing: A Study on Unsupervised Deep Learning Algorithms	Co-host	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital
Wong, Ming-Wun	Impact of regulating diet and exercise on clinical characteristics and intestinal microbiota in patients with metabolic-related fatty liver	Co-host	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital
Wong, Ming-Wun	Jing Si Herbal Tea in the treatment of dyspeptic symptoms and psychophysical burden	Co-host	2022/1/1~ 2022/12/31	Tzu Chi Medical Corporation
Wong, Ming-Wun	Diagnosis and establishment of indications for proton pump inhibitors in the improvement of laryngopharyngeal reflux based on nighttime average basal impedance values of the proximal esophagus	Host	2020/8/1~ 2022/07/31	Ministry of Science and Technology
Wong, Ming-Wun	Interrelationships among esophageal peristalsis, mucosa integrity, and mucosa afferent innervation: mechanisms for esophageal dysfunction and gastroesophageal reflux	Co-host	2020/8/1~ 2023/07/31	Ministry of Science and Technology
Wong, Ming-Wun	Exploring the role of esophageal microbiome in the novel impedance parameters, clinical classification, and hypersensitivity in gastroesophageal reflux disease	Co-host	2021/1/1~ 2021/12/31	Hualien Tzu Chi Hospital
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Wong, Ming-Wun	Clinical application of high-resolution impedance pharyngeal function examination in the study of pharyngeal swallowing difficulties and drug response	Co-host	2021/1/1~ 2021/12/31	Hualien Tzu Chi Hospital
Chen, Chien-Lin	Jing Si Herbal Tea in the treatment of dyspeptic symptoms and psychophysical burden in patients with disorders of long COVID gut brain interaction a doub le blind, randomized,placebo controlled study	Host	2023/01/01~ 2023/12/31	Tzu Chi Medical Corporation
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Chen, Chien-Lin	Exploring capsaicin sensitization, sensorimotor function, psychophyiological reflux characteristics in human esophagus: therapeutic	Host	2023/8/1~ 2026/07/31	Ministry of Science and Technology

	implications for esophageal dysfunction and gastroesophageal reflux disease			
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E. Research-related expenses

Project Name		Explanation	Unit price	Quantity	Total Price	Notes
i. Business expenses	1.Research manpower costs (please consult the Human Resources Department for related insurance expenses)	(1) Dedicated Personnel (Limited to Individual Project Applications)： Remuneration for work (including year-end bonus) is the responsibility of the employer for labor insurance and health insurance. The employer is also responsible for labor retirement benefits (insured at 6% of salary)				
		(2) "Part-time staff (must be current students)： Work remuneration ☐College graduates ☐Master's students ☐Other：_____ Labor and health insurance borne by the employer Employer's contribution to labor retirement (insured salary 6%)				
		(3) Temporary worker： Remuneration for work Labor and health insurance borne by the employer Employer's contribution to labor retirement (insured salary 6%)	4,400 936 26 1,286 270	12 12 12 12 12	52,800 11,232 312 15,432 3,240	Hourly wage $176 25 hours per month. Subtotal: 83,016 NTD
				Subtotal：	83,016	
	2. Animal testing expenses					
				Subtotal：		
	3. Consumables, Supplies, Books, and Miscellaneous expenses	Participant Allowance Heart rate variability rental expenses for equipment Computer peripheral consumables expenses: Toner cartridge, ink cartridge, printer photosensitive drum/photoreceptor, special printing paper, etc. Miscellaneous: Postage and telecommunication expenses, printing expenses, photocopy paper expenses, photocopying expenses, binding expenses, stationery expenses, poster production expenses, computer data	1,000 9,000 5,000 3,984	600 12 1 1	600,000 108,000 5,000 3,984	

		statistical expenses, computer data analysis expenses, thesis submission fees, thesis publication fees, slicing, embedding, and immunostaining expenses				
				Subtotal：	716,984	
ii. Research equipment expenses (According to regulations, books, computers, and peripheral equipment are not eligible for subsidies. The necessity of medium and large-sized instruments will be determined by the Research Department, and applications for their unified use will be submitted)						
				Subtotal：	0	
Total					800,000	

F. Project Abstract

Please provide a brief overview of the key points of this project within 500 words and customize keywords based on the nature of the project.

Patients with disorders of gut-brain interaction (DGBI) often present gastrointestinal symptoms that do not show noticeable irregularities in standard examinations. However, due to unclear causes and a high prevalence rate, this condition often exerts a profound impact on the physical and mental health of patients. The scope of DGBI encompasses conditions such as laryngopharyngeal reflux, functional dyspepsia, and irritable bowel syndrome. Previous research has confirmed that in patients with DGBI, their autonomic nervous system exhibits an imbalance, characterized by decreased parasympathetic activity and dominant sympathetic activity. Diaphragmatic breathing helps reduce the respiratory rate and can stimulate parasympathetic activity while suppressing sympathetic activity. Hence, it is now officially recommended as an effective adjunct therapy for relieving symptoms of gastroesophageal reflux. Accordingly, this study plans to implement a randomized controlled trial, introducing diaphragmatic breathing to patients with DGBI who exhibit normal results in objective examinations. This work allows evaluate changes in their psychophysical symptoms before and after treatment, as well as alterations in the autonomic nervous system.

Key words: disorders of gut-brain interaction, psychophysical symptoms, diaphragmatic breathing, autonomic nervous system

G. Background and Objectives of the Research Project

Please elaborate on the background, objectives, significance, as well as the domestic and international research status related to this research project. Provide a review of the important references and literature relevant to this project.

Research Background

Disorders of gut-brain interaction, DGBI

Functional GI Disorders, currently referred to as Disorders of gut-brain interaction (DGBI), encompass gastrointestinal symptoms for which, upon objective examination, no organic cause can be identified. Nevertheless, patients still endure the distressing symptoms related to the gastrointestinal tract.[1] The symptoms of gastrointestinal disorders are diverse, encompassing the esophagus, stomach, small intestine, and large intestine. The origin of these symptoms is complex and includes factors such as imbalance in the intestinal microbiota, changes in mucosal immune function, alterations in signaling around the intestinal area, and dysregulation of central nervous system control over intestinal signaling and motor function (Figure 1).[2] If it affects the upper digestive tract, it may lead to symptoms such as upper abdominal pain and bloating; these symptoms are referred to as Functional Dyspepsia (FD). If it affects the lower digestive tract, there may be issues such as abdominal pain, diarrhea, and constipation; this condition is classified as Irritable Bowel Syndrome (IBS).[2] The recent research we have conducted indicates that among patients with symptoms of gastroesophageal reflux disease (GERD), only about 20% show pathological evidence of reflux. However, among those with throat reflux symptoms (such as hoarseness, sensation of a lump in the throat, chronic cough, and frequent throat clearing), their Esophageal Hypervigilance and Anxiety Scale (EHAS) scores are higher compared to individuals without throat reflux symptoms, even in the absence of pathological reflux evidence.[3] These DGBIs (Functional Gastrointestinal Disorders) do not respond well to conventional gastrointestinal medications, so sometimes it is necessary to supplement treatment with neuromodulators from the field of psychosomatic medicine.[4]

The Relationship Between the Autonomic Nervous System and the Disorders of gut-brain interaction

The gastrointestinal tract is governed by the intrinsic Enteric nervous system (ENS) and the extrinsic Autonomic nervous system (ANS).[5, 6] ENS can automatically regulate the gastrointestinal tract, while the Central Nervous System (CNS) interacts with the Enteric Nervous System (ENS) through the Autonomic Nervous System (ANS), providing external neural input to regulate and control gastrointestinal functions (Figure 1).[7-9] The Parasympathetic Nervous System (PNS) or Sympathetic Nervous System (SNS), either singly or both, may encounter disruptions, leading to impaired communication between the gastrointestinal tract and the brain, subsequently resulting in Functional Gastrointestinal Disorders (FGID).[5, 10] The upper gastrointestinal tract (esophagus, stomach, small intestine, ascending colon) is innervated by the parasympathetic nervous system, with the main source being the Vagus nerve. In contrast, the lower gastrointestinal tract (transverse colon, descending colon, sigmoid colon, external anal sphincter muscles) receives parasympathetic innervation from the Lumbosacral spinal cord's pre-ganglionic neurons, primarily originating from the S1–S4 segments.[11-13] Most research reports consistently find that patients with Functional Gastrointestinal Disorders (DGBI) exhibit reduced parasympathetic nervous system activity and an increased dominance of sympathetic nervous system activity. These findings align with the autonomic control of gastrointestinal motility: activation of the parasympathetic nervous system enhances

gastrointestinal motility, while activation of the sympathetic nervous system inhibits gastrointestinal motility.[14]

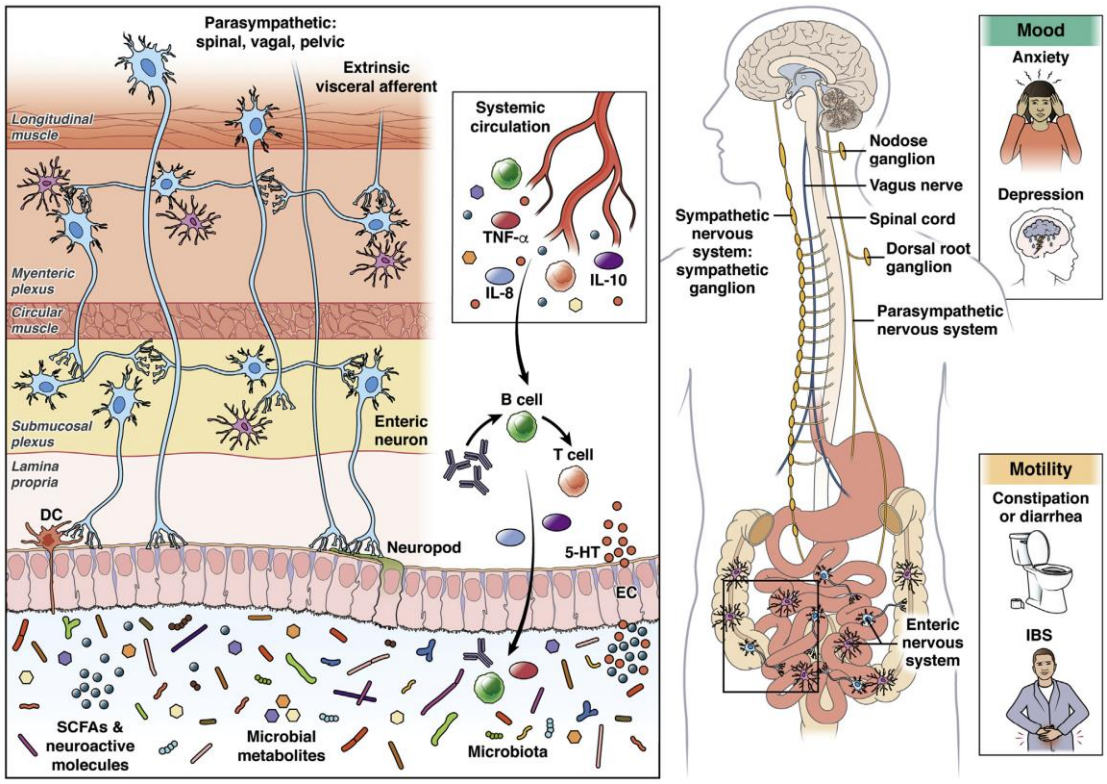


Figure 1. The possible etiology of DGBI includes microbial imbalance in the intestinal tract, changes in mucosal immune function, alterations in peripheral signaling around the intestines, and dysregulation of central nervous system control over intestinal signaling and motor function. Among these factors, the autonomic nervous system plays a crucial role as a communication bridge between the brain (central) and the gastrointestinal tract (peripheral).[1]

Heart rate variability

Early studies have shown that through Heart Rate Variability (HRV), the autonomic nervous system (ANS) can be assessed to evaluate the functional status of the gastrointestinal system.[15, 16] The reason is that the autonomic nervous system (ANS) includes both the parasympathetic and sympathetic nervous systems, which regulate the outgoing and incoming fibers of the gastrointestinal tract through the nucleus tractus solitarius (NTS). The NTS also contains other autonomic neural control over organs whose functions are regulated by the central nervous system (CNS) through the ANS, such as cardiovascular functions.[13, 15] Therefore, the central nervous system (CNS) also influences cardiovascular function through the autonomous regulation of sensory inputs from the gastrointestinal tract. This is because there is interaction between subnuclei in the nucleus tractus solitarius (NTS), regulating the rhythm or variability of the heart, known as heart rate variability (HRV).[13] In addition to assessing the autonomic nervous system (ANS), the analysis of heart rate variability (HRV) has also been found to be clinically effective in evaluating the therapeutic efficacy of the autonomic nervous system for disorders of gut-brain interaction (DGBI). HRV parameters can be used as biological markers for assessing treatment outcomes.[14] For example, electrical stimulation therapy is an emerging treatment method for these diseases.[17] Numerous studies consistently demonstrate that neurostimulation therapy improves symptoms of DGBI by enhancing autonomic nervous system dysfunction assessed through HRV.[18-20]

HRV is influenced by two main physiological mechanisms: the first originates from the complex and dynamic interplay between the sympathetic and parasympathetic nervous systems; the second arises from regulatory mechanisms controlling heart rate, including RSA, blood pressure reflexes, and rhythmic variations in vascular tone. HRV is primarily applied in the assessment of the autonomic nervous system (ANS). As follows：[21]

1. **Time Domain Indicator**

- ✧ Root mean square of successive differences (RMSSD): RMSSD reflects the variability between heartbeats and is primarily used to estimate the changes in parasympathetic nervous system activity, especially the vagus nerve, in Heart Rate Variability (HRV).[22] RMSSD is considered to be an important indicator of HRV.[23] The RMSSD values over a 24-hour period are highly correlated with the difference in adjacent normal heartbeat intervals exceeding pNN50 and high-frequency (HF) power.[24] The lower RMSSD values are positively correlated with the risk assessment of sudden unexplained death in epilepsy.[25]
- ✧ Adjacent normal heartbeat interval differences exceeding pNN50: The deviation of adjacent normal heartbeat interval differences beyond pNN50 is closely associated with parasympathetic nervous system activity[26] and is related to RMSSD and HF power. However, RMSSD typically provides a better assessment of parasympathetic nervous system activity (especially in the elderly). Therefore, most researchers tend to choose RMSSD over the adjacent normal-to-normal heartbeat interval differences exceeding pNN50.[27]

2. **Frequency Domain Indices**

- ✧ Low frequency (LF)：The low frequency (LF: 0.04-0.15 Hz) reflects the mixed activity of the sympathetic and parasympathetic nervous systems. In certain situations, LF can be used to assess the influence of the sympathetic nervous system, but this requires consideration of respiratory and other physiological influencing factors.
- ✧ High frequency (HF)：The high frequency (HF: 0.15-0.4 Hz) primarily reflects parasympathetic nervous system activity, especially vagal nerve activity. This can be observed through Respiratory Sinus Arrhythmia (RSA).[28]
- ✧ LF/HF ratio：The LF/HF ratio is used to assess the balance between the sympathetic nervous system and the parasympathetic nervous system.

Diaphragmatic breathing

The relationship between respiration and the autonomic nervous system (ANS) is closely intertwined, as the phrenic nerve, responsible for controlling the movement of the diaphragm, is connected to the vagus nerve of the parasympathetic nervous system.[29] The respiratory cycle reflects the balance between the parasympathetic and sympathetic nervous systems in the Autonomic Nervous System (ANS), which can be observed through Heart Rate Variability (HRV). The ANS state shifts from the parasympathetic nervous system to the sympathetic nervous system during inhalation, while it transitions from the sympathetic nervous system to the parasympathetic nervous system during exhalation. In HRV, an increase in heart rate indicates enhanced sympathetic nervous system activity during inhalation, whereas a decrease in heart rate signifies increased parasympathetic nervous system activity during exhalation.[30]

Diaphragmatic breathing can be achieved by reducing the respiratory rate, promoting parasympathetic nervous system activity, and concurrently inhibiting sympathetic nervous system activity.[31, 32] Due to the increase in tidal volume during diaphragmatic breathing, the Hering-Breuer reflex is activated. This reflex reduces chemoreflex sensitivity and enhances baroreflex, further lowering sympathetic nervous system activity.[33] The rhythm of diaphragmatic breathing is as follows: Step 1: Inhale through the nose for about 4 seconds, feeling the expansion of the abdomen; Step 2: Hold the breath for 2 seconds; Step 3: Exhale slowly and steadily through the mouth for about 6 seconds (see Figure 2). (Diaphragmatic Breathing for GI Patients - Michigan Medicine) Currently, diaphragmatic breathing is formally recommended for alleviating symptoms of gastroesophageal reflux disease (GERD) and is proven effective in reducing the frequency of reflux occurrences in randomized controlled trials. It is now recognized as an effective adjunctive therapy.[34, 35] However, currently, there is still no randomized controlled experiment confirming the effects of abdominal breathing on other functional gastrointestinal disorders (DGBI issues).

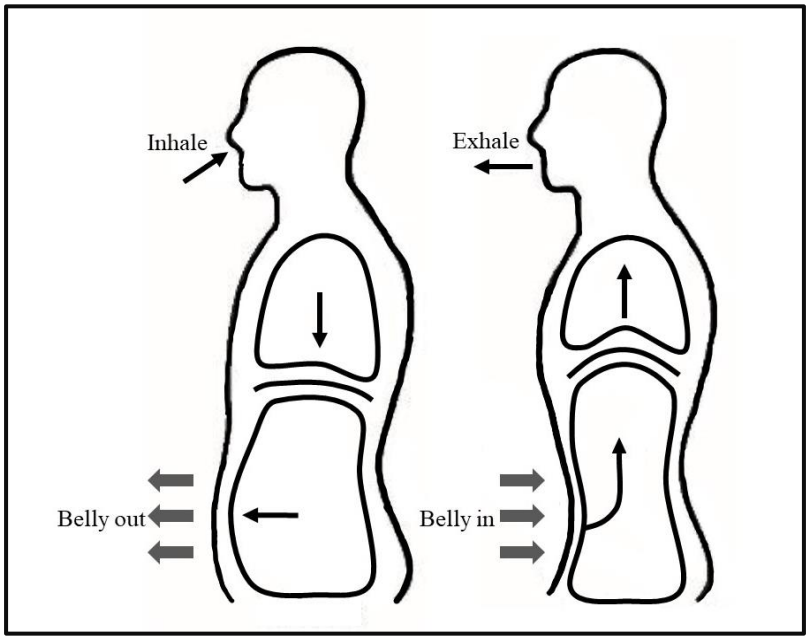


Figure 2. Diaphragmatic breathing：When inhaling in the left image, the diaphragm descends, causing the abdomen to protrude. In the right image, during exhalation, the diaphragm ascends, and the abdomen returns to a flat state.

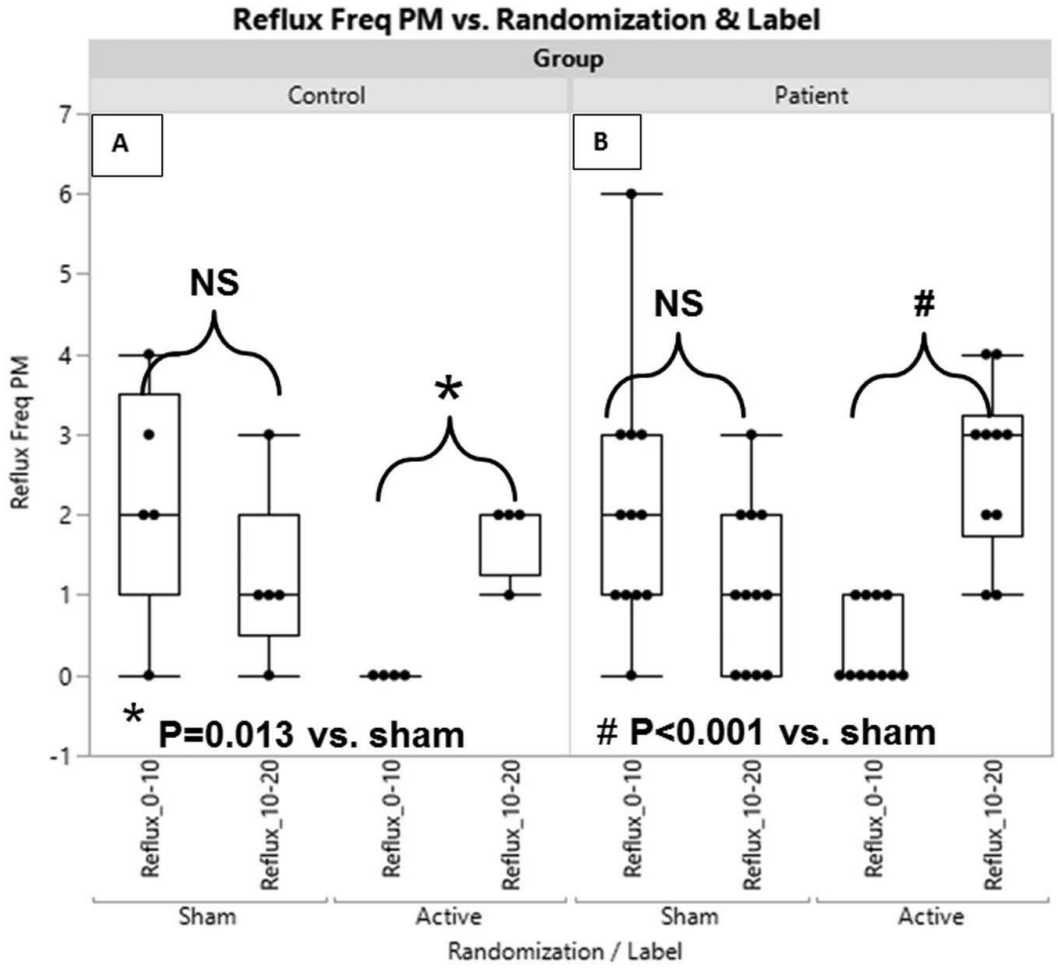
Figure 3. During the high-resolution esophageal impedance measurement period after a 20-minute meal, under random allocation, both the healthy control group (a) and the patient group (b) demonstrated a significant reduction in the number of reflux events with diaphragmatic breathing. In contrast, the sham (normal) breathing group showed no significant difference in reflux events.[35]

Research Purpose

For patients with DGBI (Functional Gastrointestinal Disorders) who exhibit gastrointestinal symptoms that cannot identify organic causes after objective examinations, current treatment options are significantly limited. Dysregulation of the autonomic nervous system is one contributing factor. Abdominal breathing, by reducing respiratory frequency, promotes parasympathetic nervous system activity while inhibiting sympathetic nervous system activity. It is now officially recommended by

international consensus conferences as an adjunctive therapy to alleviate symptoms of gastroesophageal reflux.

The purpose of this study is to investigate the autonomic nervous system responses through standardized autonomic nervous system monitoring, focusing on the impact of diaphragmatic breathing on the autonomic nervous system in both healthy subjects and patients with Functional Gastrointestinal Disorders (DGBI). Additionally, the study aims to confirm whether the implementation of diaphragmatic breathing can improve symptoms in DGBI patients, providing a basis for future reference in the treatment of DGBI patients.



Research hypothesis

Hypothesis 1：Diaphragmatic breathing can change Autonomic nervous system

Hypothesis 1-1：Diaphragmatic breathing can increase the activity of the parasympathetic nervous system and decrease the activity of the sympathetic nervous system in healthy subjects.

Hypothesis 1-2：Diaphragmatic breathing can increase parasympathetic nervous system activity and decrease sympathetic nervous system activity in patients with DGBI.

Hypothesis 2：Diaphragmatic breathing can improve symptoms in patients with DGBI.

Hypothesis 2-1：Introducing diaphragmatic breathing can improve symptoms in patients with Laryngopharyngeal Reflux Disease (LPR).

Hypothesis 2-2：Introducing diaphragmatic breathing can improve symptoms in patients with Functional Dyspepsia (FD).

Hypothesis 2-3：Introducing diaphragmatic breathing can improve symptoms in patients with Irritable Bowel Syndrome (IBS).

H. Research methods, procedures, and execution progress.

1. Please elaborate on the research methods adopted in this project and the reasons behind their selection.
2. Anticipated difficulties and possible solutions.
3. If it is a consecutive project, please also attach the annual research progress report or primary data for the corresponding year.

Research Methods

Participant

The trial is expected to last for 1 year, with a research period ending on December 31, 2024. It aims to recruit 600 participants, including 150 healthy volunteers to be solicited through advertisements. Additionally, 150 participants with Laryngopharyngeal Reflux (LPR) will be recruited from the Gastroenterology Outpatient Department, along with 150 participants with Functional Dyspepsia (FD) and 150 participants with Irritable Bowel Syndrome (IBS). The inclusion and exclusion criteria for participants are as follows：

Inclusion Criteria for Participants：

Inclusion criteria for healthy subjects：

1. Aged between 18 and 70 years old, clear consciousness, and willing to sign the informed consent form for the study.
2. Without any gastrointestinal symptoms or the use of gastrointestinal medications.

Inclusion criteria for Laryngopharyngeal reflux disease subject：

1. Aged between 18 and 70 years old, clear consciousness, and willing to sign the informed consent form for the study.
2. The definition of Laryngopharyngeal Reflux (LPR) is characterized by the presence of symptoms lasting for more than three months, including hoarseness, a sensation of a lump in the throat, chronic cough, and frequent throat clearing. These symptoms occur at least once a week. Diagnosis is confirmed through a standardized LPR assessment questionnaire (Reflux Symptom Index - RSI), which consists of nine reflux-related symptoms. Each symptom is rated on a severity scale from 0 (asymptomatic) to 5 (most severe). If the total score exceeds 13 points, the patient meets the criteria for Laryngopharyngeal Reflux.

Inclusion criteria for Functional dyspepsia subject：

1. Aged between 18 and 70 years old, clear consciousness, and willing to sign the informed consent form for the study.
2. Those who meet the FD definition Functional dyspepsia is characterized by chronic (occurring at least once a week, lasting for a minimum of three months, with the first symptoms manifesting at least six months ago) upper gastrointestinal symptoms (any of the following): postprandial bloating, a tendency to feel full easily, upper abdominal pain or a burning sensation, without symptoms of gastrointestinal bleeding or significant weight loss, and with no abnormalities found upon upper gastrointestinal endoscopic examination.

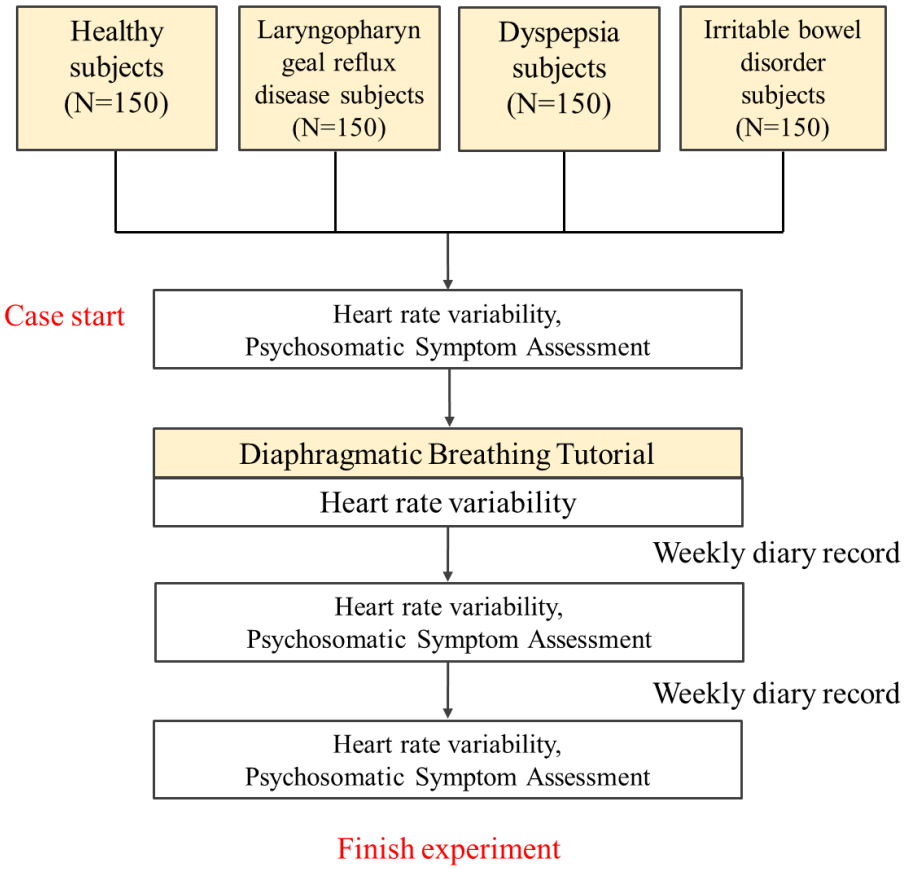
Inclusion criteria for Irritable bowel syndrome subject：

1. Aged between 18 and 70 years old, clear consciousness, and willing to sign the informed consent form for the study.
2. Those who meet the definition of IBS. Irritable bowel syndrome (IBS) is a chronic condition characterized by lower gastrointestinal symptoms occurring at least once a week and lasting for a minimum of three months. These symptoms include abdominal pain accompanied by either diarrhea or constipation, without any signs of gastrointestinal bleeding or significant weight loss. Individuals with IBS exhibit no abnormalities upon examination through colonoscopy.

Exclusion Criteria for Participants：

1. Pregnant or lactating women.
2. Infection currently undergoing antibiotic treatment.
3. In the past two months, underwent tracheal intubation.
4. Those with myocardial hypoxia or who have recently experienced a myocardial infarction.
5. Unable to collaborate.

Research Process Diagram



Research Steps

The subjects who meet the inclusion criteria of this study will undergo an initial assessment of heart rate variability and psychosomatic symptoms after enrollment. Subsequently, a two-week

experiment will be conducted, during which the subjects will receive one session of diaphragmatic breathing training by the researchers. After the guided training, the subjects will undergo another assessment of heart rate variability. In the first week, participants will engage in self-practice of the instructed content twice daily, each session lasting 5 minutes, and will record a weekly diaphragmatic breathing diary.

After the first week, subjects will undergo another assessment of heart rate variability and psychosomatic symptoms. In the second week, participants will continue daily self-practice with two sessions of instructed content, each lasting 5 minutes, and will maintain a diaphragmatic breathing diary. Following the second week, subjects will undergo a final assessment of heart rate variability and psychosomatic symptoms, completing the experiment.

Researchers recommend spending approximately 15 minutes on diaphragmatic breathing training, 15 minutes on measuring heart rate variability, and approximately 20 minutes for questionnaire completion. The measurement of heart rate variability utilizes a non-invasive device called "LEADTEK" portable electrocardiogram recorder (Ministry of Health and Welfare Medical Device Manufacturing License No. 006972). If participants have any questions or concerns during the abdominal breathing training process, they are encouraged to contact the researchers.

Diaphragmatic Breathing (It takes about 15 minutes)

1. Sit in a comfortable place and close your eyes.
2. Place one hand on the chest and the other hand on the abdomen to practice diaphragmatic breathing: During diaphragmatic breathing exercises, the hand on the abdomen will rise with inhalation and fall with exhalation, while the hand on the chest remains stationary.
3. Inhale through the nose for about 4 seconds, feeling the expansion of the abdomen. (Upon the first inhalation, there may be a slight sense of tension.)
4. Hold your breath for 2 seconds.
5. Exhale slowly and steadily through the mouth for approximately 6 seconds, keeping the mouth relaxed throughout the process.
6. Repeat this breathing cycle for 5 minutes.

ANS Protocol (It takes about 15 minutes)

The ANS Protocol is a standardized and validated method used to assess the autonomic nervous system's (ANS) responses to baseline conditions and stress stimuli. It consists of three stages: a resting phase (5 minutes), a mental arithmetic test under stress conditions (3 minutes), and a recovery period (5 minutes) during which heart rate variability (HRV) is measured. The mental arithmetic test involves subjects performing continuous subtraction of 7 from a randomly generated four-digit number using mental calculation only. If an error occurs, the process is restarted, and the entire procedure lasts for 3 minutes.[36]

ANS Detection Steps：

1. Confirm that the status indicator light is in a measurable state (LED color: green), and then attach the electrode patches. ◦
2. R (Red dot): Please paste on the inner side of the right wrist.
3. L (Yellow dot): Please paste on the inner side of the left wrist.
4. F (Green Marking): Please paste on the inside of the left wrist.
5. Press the measurement button on the device to initiate the measurement.
6. Before the formal commencement of measurements, the device will conduct a preliminary signal quality check. Participants are advised to remain still and refrain from engaging in conversation during this process.
7. The measurement officially begins at 7: Please instruct the subjects to remain still and refrain from talking, waiting quietly for 3 to 5 minutes until the measurement is completed. ◦
8. Measurement Completed: Display Measurement Results.

The HRV indicators for assessing the ANS are as follows：[21]

1. **Time Domain Indicators**
   - ✧ The square root of the mean of the sum of the squares of the Successive differences (RMSSD)：Assessing Parasympathetic Nervous System Activity
2. **Frequency Domain Indicators**
   - ✧ Low frequency power (LF)：Assessing Sympathetic Nervous System Activity
   - ✧ High frequency power (HF)：Assessing Parasympathetic Nervous System Activity
   - ✧ Low-frequency/High-frequency Power Ratio (LF/HF ratio)：Assessing the balance of the sympathetic and parasympathetic nervous systems.

Questionnaire Evaluation Tool (It takes about 20 minutes)

Disease Questionnaire Assessment：

- Gastroesophageal Reflux Disease Questionnaire (GERDQ)[37] The questionnaire score exceeding 12 points indicates a high likelihood of having GERD.
- Reflux Symptom Index (RSI) [38] The nine reflux-related symptoms are graded on a severity scale from 0 (no symptoms) to 5 (most severe), and a total score exceeding 13 indicates a higher probability of suffering from laryngopharyngeal reflux.
- Functional Dyspepsia (FD)[39] The subjective assessment revolves around symptoms and quality of life, primarily including postprandial fullness, early satiety, and upper abdominal bloating as digestive discomfort symptoms. Each item is scored from 0 to 6 points, with 0 points indicating no symptoms and 6 points indicating extremely severe symptoms. The total score ranges from 0 to 52 points, with higher scores indicating more severe symptoms.
- Irritable Bowel Syndrome (IBS)[39] Diagnostic criteria reference Rome IV, The main symptoms began at least 6 months ago, with recurrent abdominal pain occurring at least once a week on average in the past three months. Additionally, at least two of the following symptoms are present: abdominal pain related to bowel movements, changes in bowel frequency, and alterations in the appearance of stool.
- Gastrointestinal Symptom Rating Scale (GSRS)[40] Applicable to the general population with gastrointestinal symptoms for measurement and evaluation of treatment effectiveness, using a Likert 4-point scoring system. Positive scoring is employed, where higher scores indicate greater severity of symptoms, and lower scores represent higher levels of health.

- Pittsburgh Sleep Quality Index (PSQI) 41 is not only suitable for evaluating sleep quality of patients with sleep disorders and mental disorders, but also suitable for the evaluation of sleep quality of ordinary people. 18 items are composed of 7 components, each component is scored on a scale of 0-3 , and the total score ranges from 0-21 points. The higher the score, the worse the sleep quality .
- Taiwanese Depression Scale (TDQ) 42 includes three parts: emotion, cognition and body, with a total of 18 questions, and the scale is scored on a four-point scale. Each question is scored on a scale from 0 to 3 , and the total score ranges from 0 to 54 points. Those with a score greater than 18 indicate depressive symptoms.
- State-Trait Anxiety. Inventory (STAI) 43 includes two subscales, the Situational and Trait Anxiety Scale, with a minimum score of 20 and a maximum score of 80 , with higher scores representing anxiety symptoms.
- The Perceived Stress Scale (PSS-10) 44 is to evaluate the degree of stress in personal life situations, and the higher the score, the greater the stress.
- Esophageal Hypervigilance and Anxiety Scale (EHAS) 41 Esophageal hypervigilance and anxiety can cause symptoms in patients with chronic esophageal diseases, including gastroesophageal reflux, esophageal atlasia and functional esophageal diseases. The questionnaire contains 15 items and can be divided into two main categories . Section: Symptoms of Esophageal Hypervigilance and Symptoms of Esophageal Anxiety. This questionnaire can not only assess the sensory system symptoms of any esophagus-related diseases, but also assist in the diagnosis of functional esophageal diseases.
- Laryngeal Hypervigilance and Anxiety Scale (LHAS) 41 Throat hypervigilance and anxiety can trigger symptoms in patients with chronic esophageal disease. The questionnaire contains 15 items and can be divided into two main parts: throat hypervigilance symptoms and throat anxiety symptoms. This questionnaire can not only assess the sensory system symptoms of any esophagus-related diseases, but also assist in the diagnosis of functional esophageal diseases.
- Visceral Sensitivity Index (VSI) 45 measures anxiety specific to the gastrointestinal tract. It includes 15 items, with a minimum score of 0 and a maximum of 5 points for each item, and a minimum score of 0 and a maximum score of 75 points for the total score.

Statistical Analysis

If a continuous variable follows a normal distribution, it is represented by the mean and standard deviation; if it does not follow a normal distribution, it is represented by the median and interquartile range. The treatment effectiveness is presented as the improvement percentage based on the pre- and post-treatment sleep habit questionnaire, depression questionnaire, anxiety questionnaire, stress questionnaire, digestive symptom questionnaire, and irritable bowel syndrome questionnaire. The efficacy of diaphragmatic breathing was assessed using a Chi-squared test to compare percentages. A P-value less than 0.05 was considered statistically significant. The statistical analysis software used is SPSS 19 (SPSS, Inc, Chicago, IL, USA).

The clinical significance and originality of this study

This study will be the first to extensively apply diaphragmatic breathing to the management of functional gastrointestinal disorders (FGIDs). In addition to assessing gastrointestinal symptoms, it will also evaluate physical and mental symptoms, sleep quality, stress indicators, and visceral sensitivity. Further understanding of autonomic nervous system changes through heart rate variability (HRV). This study aims to investigate the efficacy and mechanism of non-invasive, non-pharmacological diaphragmatic breathing on patients with disorders of the gut-brain axis (DGBI).

I. Expected deliverables and specific outcomes of the planned tasks

1.Please list the work items expected to be completed within the implementation period.
2.Anticipated contributions to academic research and other applications.
3.For participating staff, the training expected to be available.

1. Expected tasks to be completed

This study expects that diaphragmatic breathing may potentially improve the psychosomatic symptoms of Disorders of Gut-Brain Interaction (DGBI), and it may be achieved by altering autonomic nervous system regulation.

2. Expected contributions to academic research, national development, and other applications

The results of this study will provide empirical evidence for the use of diaphragmatic breathing in the treatment of disorders of the gut-brain axis (DGBI). In the future, we hope to participate in the evaluation of the National Healthcare Quality Awards by the Taiwan Medical Association to help a large number of DGBI patients.

3. Expected training for participating staff

Participants will receive not only general research training, such as experimental design and execution, result analysis and statistics, data visualization, oral presentations, paper writing, and manuscript submission process, but also have the opportunity to gain exposure to various experimental techniques and skills due to the diversity of their tasks.

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