

JUNTENDO MEDICAL JOURNAL

順 天 堂 醫 事 雜 誌

December 2023

Career Perspectives

358th Triannual Meeting of the Juntendo Medical Society

“Farewell Lectures of Retiring Professors” [2]

My History in Juntendo University

..... Yasuyuki Okuma

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Publication List

Publications from Juntendo University Graduate School of Medicine, 2021 [4/6]

Instructions to Authors

JUNTENDO MEDICAL JOURNAL

順天堂醫事雑誌

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The History of *Juntendo Medical Journal*

This *Juntendo Medical Journal* has been published under the Japanese name *Juntendo Igaku* (順天堂医学) from 1964 to 2012. However, the origin of *Juntendo Medical Journal* dates back to the oldest medical journal in Japan, *Juntendo Iji Zasshi* (順天堂醫事雑誌), which had been published between 1875 and 1877 (total of 8 issues). Between 1885 and 1886, Juntendo issued a limited release of a research journal titled *Houkoku* [*Juntendo Iji Kenkyukai*] (報告) for a total of 39 issues.

In 1887, *Juntendo Iji Kenkyukai Houkoku* (順天堂醫事研究会報告) was published with the government's approval and we used to regard this as the first issue of *Juntendo Medical Journal*. Since then, *Juntendo Medical Journal* has undergone a series of name changes: *Juntendo Iji Kenkyukai Zasshi* (順天堂醫事研究会雑誌), *Juntendo Igaku Zasshi* (順天堂医学雑誌), and *Juntendo Igaku* (順天堂医学).

Now in commemoration of the 175th anniversary of Juntendo University, starting with the first volume issued in 2013 (Volume 59 Number 1), we return to *Juntendo Medical Journal*'s original Japanese title in 1875-*Juntendo Iji Zasshi* (順天堂醫事雑誌). We also reconsidered the numbering of the journal and set the first issue in 1875 as the initial publication of *Juntendo Medical Journal*. The Volume-Number counting system and the English name *Juntendo Medical Journal* started in 1955 from the January 10 issue. Although this is not our intention, we will retain the Volume-Number counting system to avoid confusion. However, Volume 59 Number 1 will be the 882nd issue, reflecting the sum of all issues to date: 8 issues of *Juntendo Iji Zasshi* (順天堂醫事雑誌), 39 issues of *Houkoku* [*Juntendo Iji Kenkyukai*] (報告) (47 issues combined), and 834 issues from *Juntendo Iji Kenkyukai Houkoku* (順天堂醫事研究会報告) in 1887 to the present.

出典：小川秀興 (OGAWA Hideoki, M.D., Ph.D.) : 順天堂醫事雑誌 (Juntendo Medical Journal) 2013 : 59 : 6-10.

本誌は昭和39年(1964年)から平成24年(2012年)末まで『順天堂医学』として刊行されてきた。しかし、その起源は明治8年(1875年)から10年(1877年)にかけて発刊された日本最古の医学誌『順天堂醫事雑誌』(計8巻)にある。さらに明治18年(1885年)から19年(1886年)まで、会員限定配本として順天堂醫事研究会の雑誌『報告』(計39集)が発行されている。

その後『順天堂醫事研究会報告』が明治20年(1887年)に官許を受けて公刊されたので、順天堂ではこれを通刊1号としてきた。以来、『順天堂醫事研究会雑誌』、『順天堂医学雑誌』、『順天堂医学』と名称を変更して刊行されてきた。

今般、順天堂が創立175周年を迎える平成25年(2013年)の59巻1号を期して、本来の名称である『順天堂醫事雑誌』と復刻し、その起源である明治8年(1875年)第1巻をもって創刊号(通刊第1号)とすることとした。従来の巻号と欧文誌名は、昭和30年(1955年)1月10日発行のものを1巻1号としており、欧文誌名もこれより付け始めたもので不本意であるが、混乱を避けるためにこれらを継承する。ただし、通刊数は明治8年(1875年)から19年(1886年)にかけて刊行された『順天堂醫事雑誌』8巻分と順天堂醫事研究会の雑誌『報告』39集、計47巻分を通巻834号に加え、59巻1号を通刊882号とした。

出典：小川鼎三、酒井シヅ：順天堂医学 1980 ; 26 : 414-418.
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The Juntendo Medical Society

From the illustrator: Every November I visit a doll specialty shop “Kyugetsu” with a history going back to 1835 in the Edo Era, in Tokyo Asakusabashi, and purchase a figurine of Japanese zodiac animal for the next year. Since next year (2024) is the year of the dragon, I got a dragon figurine. I am using this as a motif for new year’s greeting cards, and also the object to be drawn in my painting class.



My History in Juntendo University

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With my retirement as a professor, I would like to review my 47-year history of studying and working at Juntendo University. I was admitted to Juntendo University School of Medicine in 1976, and after graduation I joined the Department of Neurology in 1982, where Professor Hirotaro Narabayashi was the founding chairman. I became particularly interested in movement disorders and neurophysiology. The second chairman, Professor Yoshikuni Mizuno, established an American-style neurology training system. From 1992 to 1994, I studied electrophysiology at the University of Calgary in Canada, and my family and I enjoyed life in Canada very much. In 2000, I moved to Juntendo Izu-Nagaoka Hospital, now renamed Juntendo Shizuoka Hospital. I instructed young neurologists to write case reports in English. Owing to this achievement, the third chairman, Professor Nobutaka Hattori, recommended me to be a recipient of Alumni Scientific Award and to become a professor of neurology in 2009. I also became an executive officer of the Asian and Oceanian Section of the International Parkinson and Movement Disorders Society from 2015 to 2019. In 2017, I was appointed as the dean of the Faculty of Health Science and Nursing. I devoted myself to improving the nursing education and then I received the Best Professor Award twice. The level of the faculty improved, so that all the students were able to pass the National Nursing Examination consistently. In conclusion, I thank all my colleagues, faculty members, and family for letting me have valuable experiences and memories in Juntendo University.

Key words: neurologist, neurophysiology, Parkinson's disease, education, faculty development

Introduction

About 47 years have passed since I was admitted to Juntendo University School of Medicine in 1976. After graduation, I started my career as a neurologist in Juntendo University. Here, I would like to review my history as an undergraduate medical student, a neurologist, and as the dean of the Faculty of Health Science and Nursing until my retirement in March 2023.

As a medical student

From 1976 to 1982, I spent my student days both studying medicine and playing baseball in the medical school. I enjoyed living in the dormitory,

where students of medicine and physical education lived in the same room, in the first year of liberal education. We were very happy because our professors and other faculty members were all excellent and the staff members were so kind. As for baseball, when I was in my 6th year, our baseball team won the gold medal in the Eastern Medical Students Games for the first time. The baseball practice was very hard for me because I had no experience playing baseball competitively. However, I was lucky that the curriculum for medical education was not so tight then.

My early years as a neurologist

I started my neurology residency at the Depart-

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A



B

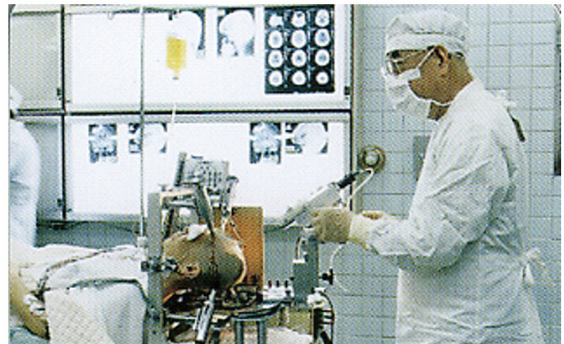


Figure 1

A. Case conference in the Department of Neurology in 1986

From left to right, Associate Professor Takeshi Sato, Professor Hirotaro Narabayashi, Lecturer Hisamasa Imai, Dr. Akito Hayashi, and me

B. Professor Narabayashi performing stereotaxic brain surgery at his private clinic

ment of Neurology, Juntendo University in 1982, where the late Professor Hirotaro Narabayashi was the founding chairman of the department. As he was an expert on Parkinson's disease, I became interested in movement disorders such as Parkinson's disease. Figure 1-A shows a picture of a case conference held in 1986. Professor Narabayashi also ran his private clinic for stereotaxic brain surgery, and once a week, I saw patients there before and after operation for 13 years (Figure 1-B). I joined the neurophysiology study group, which consisted of Drs. Masanori Nagaoka, Yasochi Nakajima, Yasuhiro Kagamihara, and Akito Hayashi, and we used electrophysiological techniques such as the Hoffmann reflex (H-reflex) technique to study motor control. The mentor of this group was the late Professor Reisaku Tanaka (Figure 2), who was working at the Tokyo Metropolitan Institute for Neuroscience. He emphasized eliminating ambiguity and recommended us to read "Scientists must write"¹⁾, which immensely influenced me. Since then, I wrote down all my ideas for planning or conducting experimental research.

In 1989, Professor Yoshikuni Mizuno became the second chairman of the Department of Neurology (Figure 3-A). Professor Mizuno completed his residency in Chicago, so we were able to learn American-style neurology. Figure 3-B shows a picture of a conference held every morning. Young



Figure 2 Professor Reisaku Tanaka (left) and Professor Hirotaro Narabayashi (right)

physicians worked till midnight to prepare for the next day's morning conference. Two years later, I was appointed as a chief physician of the neurology ward, and the Chief Resident System started. Initially it was difficult for us to get used to the new system, but upon seeing that the chief residents develop their skills of management, education, and mentorship after the completion of those terms, the system became established.

Study abroad in Canada

I had a chance to study abroad at the University of Calgary, Alberta, Canada from October 1992 to December 1994 with the recommendation by

A



B



Figure 3

A. Professor Yoshikuni Mizuno
B. Conference held every morning



Figure 4 Professor Robert G. Lee and me in his office at the University of Calgary during Christmas season

Professor Mizuno. My mentor was Professor Robert Lee, a neurologist in the Department of Clinical Neurosciences (Figure 4). Because both of us were neurologists, we got along very well. I studied reciprocal inhibition in hemiplegia and paraplegia using the H-reflex technique. Figure 5 shows the experimental setting in the laboratory and H-reflex recordings. Because Professor Reisaku Tanaka went to Calgary several years before and he established the laboratory to study the spasticity of patients with spinal cord injury, it was not difficult to start my experiments. My first project was

analyzing the reciprocal inhibition in hemiplegic patients following a stroke²). We found that the amount of Ia inhibition from peroneal nerve afferents to soleus motoneurons was increased in patients who were showing good recovery with mild spasticity; however, it did not change or even sometimes diminished in patients who made a poor recovery with marked extensor spasticity (Figure 5-C). The increased amount of Ia inhibition during recovery may be a mechanism to compensate for the loss of descending motor commands. The second project was on the search for the reciprocal Ia inhibition in patients with asymmetric spinal spasticity³). The Ia inhibition to the soleus motoneurons in the legs with good recovery and less spasticity was pronounced, but the Ia inhibition in more spastic legs was small or absent (Figure 5-C). Again, the increased amount of Ia inhibition may be a plastic change to compensate for the less descending motor commands³).

Aside from my research, I enjoyed attending the Clinical Neurosciences Grand Rounds every Friday morning. The rounds took place mainly at Foothills Hospital and they started with two case presentations on either neurology, neurosurgery, or pediatric neurology, followed by the guest speaker's presentation. One day, a girl showing paraparesis that worsened in the afternoon but improved after

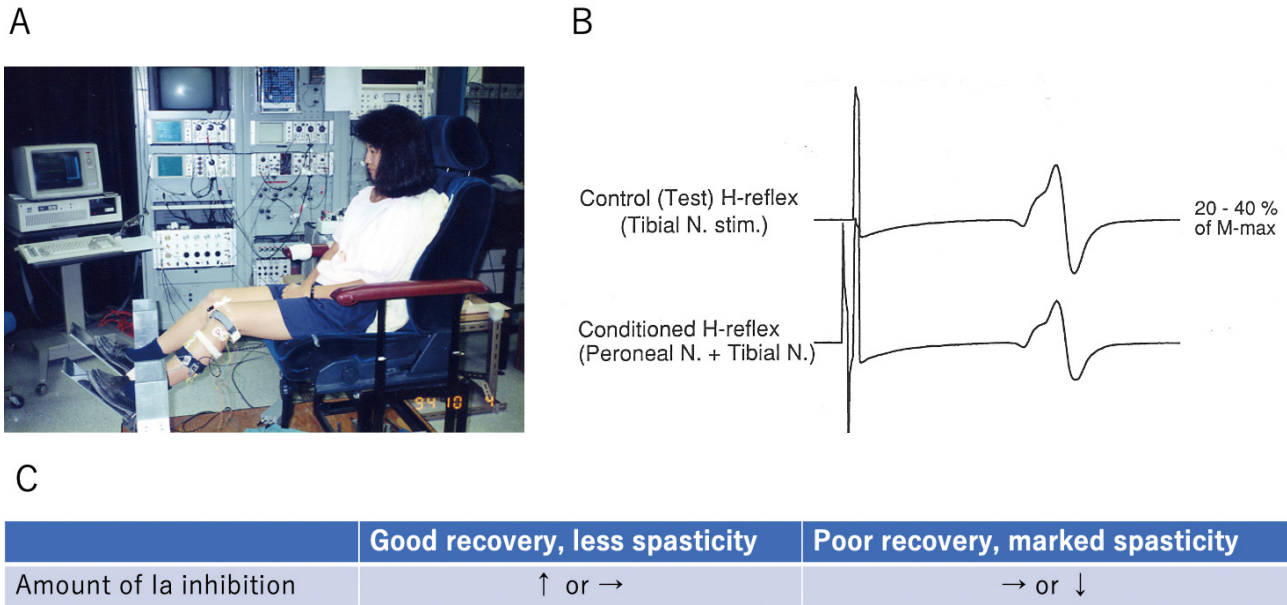


Figure 5

A. Experimental setting to record H-reflex: the posterior tibial nerve is stimulated and H-reflexes are recorded from the soleus muscle.

B. Upper wave: the test H-reflex

Lower wave: peroneal nerve conditioned H-reflex is slightly depressed. The decrement indicates reciprocal Ia inhibition from ankle flexors to extensors.

C. Amount of reciprocal Ia inhibition in the legs with good recovery or poor recovery

sleep was presented in the clinical round. I pointed out that she might have Segawa's disease (hereditary progressive dystonia with marked diurnal fluctuation)⁴⁾, which was discovered by the late Professor Masaya Segawa and is well known in Japan. I was very proud to make a diagnosis of this Japanese-discovered disease. Just before returning to Japan, I presented the results of my two-year

research work that I performed in Calgary at the Grand Round. At that time, my English has improved enough for the scientific presentation and question-and-answer sessions.

My family and I enjoyed life in Calgary very much. We went skiing in the Canadian Rockies in the winter and hiking in the summer (Figure 6). The people in the neighborhood were kind to us,

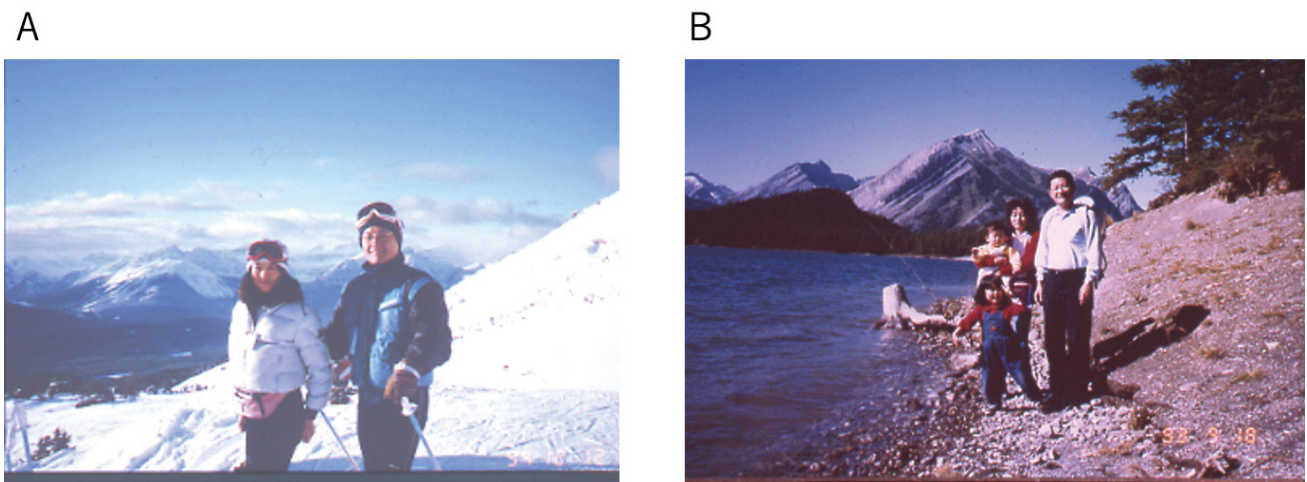


Figure 6

A. Skiing at Lake Louise resort in Canadian Rockies with my wife

B. Hiking in the Canadian Rockies with my family

perhaps because most of them were immigrants. A description of my life in Calgary was partly published in “Sagai”, the alumni magazine of the Faculty of Medicine, Juntendo University, in January 1994.

Returning to Japan

After returning to Japan, I worked in the Department of Neurology, Juntendo Urayasu Hospital for two years. I continued performing electrophysiological studies of patients with the encouragement from the director, Professor Shigeki Tanaka. We published two articles on “Familial cortical tremor with epilepsy”^{5,6}, that is now widely known as benign adult familial myoclonic epilepsy (BAFME). I thank Professor Yoichiro Kamiyama for allowing us to use a room that belongs to the Department of Anesthesiology for electrophysiological studies. Since we did not have any rooms specialized for such studies, it was very helpful.

In 1997, I returned to Hongo-Ochanomizu Campus, and served as the senior neurologist to manage human resources of the Department of Neurology as direction of the medical office under the guidance of Professor Mizuno. It was hard work, but I learned how to manage things in the department, and this experience later helped me when I became the director of the Department of Neurology, Juntendo Izu-Nagaoka Hospital and the dean of the Faculty of Health Science and Nursing. I therefore thank Professor Mizuno very much for this appointment. Together with administrative works, I continued trying to elucidate the pathophysiology of movement disorders using electrophysiological methods⁷⁻¹⁰.



Figure 7 Certificate for Alumni Scientific Award received in 2008

From Hongo to Izu-Nagaoka

In 2000, I was asked by Professor Mizuno to work in Juntendo University Izu-Nagaoka Hospital as the director of the Department of Neurology. The hospital is very active, and I saw many patients suitable for the education of young neurologists. I instructed them to present these cases at the Kanto regional meetings of the Japanese Society for Neurology and to write and submit articles to international academic journals. The first case report was on Neuro-Sweet disease¹¹ presented by Dr. Kazuyuki Noda, the present director of our department. Since then, more than 30 case reports have been published in international journals during my time as the director until 2017¹²⁻⁴⁴. The number of neurologists in our department increased from four to six; thus, we were able to work more actively. Owing to these achievements and faculty development, I received the Alumni Scientific Award in 2008, which was a great honor for me (Figure 7). Professor Nobutaka Hattori (Figure 8), who was the successor of Professor Mizuno, strongly recommended me for the award; thereafter, I was promoted to be a professor of neurology at Juntendo University Shizuoka Hospital in 2009.

As Izu-Nagaoka Hospital, later renamed Juntendo University Shizuoka Hospital, was the core hospital in the eastern part of Shizuoka Prefecture, I aimed to promote the medical care of patients with intractable neurological diseases such as Parkinson's



Figure 8 Professor Nobutaka Hattori (center) and associates at the Department of Neurology Alumni Association party in 2008. From left to right, Professor Hisamasa Imai, Professor Masanori Nagaoka, Professor Nobutaka Hattori, the author (Yasuyuki Okuma), and Professor Shigeki Tanaka

disease and to educate patients. In cooperation with the Shizuoka branch of the Japanese Parkinson's Disease Association (JPDA-Shizuoka) and health care centers, we held annual lecture meetings and consultation events for the patients and their family members in Mishima City, Numazu City, and Shimoda City. I also submitted educational articles to the bulletin of JPDA-Shizuoka. As for exercise for the parkinsonian patients, I started to play table tennis with the patients, which I found to be one of the most suitable sports for Parkinson's disease.

As for research on Parkinson's disease, I conducted many clinical studies with colleagues of Kanto Parkinson's Disease Study Group (KPDSG). KPDSG was established in 2004 by Professor Hattori (Juntendo University) and Professor Koichi Hirata (Dokkyo Medical University) to study clinical problems and unmet needs in Parkinson's disease. The topics included sleep problems, fatigue, postural abnormalities, and body weight loss in Parkinson's disease. Most research findings have been published in prestigious international journals⁴⁵⁻⁵¹.

Since I was particularly interested in gait disturbance in Parkinson's disease, I collected data from patients with freezing of gait (FOG) and falls after arriving at Izu-Nagaoka Hospital. I applied neurophysiological methods such as the use of a 3D accelerometer. We found that high-frequency oscillation of accelerations appeared during freezing, and the "freezing index" increased according to freezing episode. We also calculated the body angle so that we could detect falls⁵². Figure 9 shows the

3D accelerometer and the acceleration with walking steps and freezing episodes occurring while turning in a patient with advanced-stage Parkinson's disease. In addition to the accelerometric study, I studied the relationships among falls, motor fluctuation, and FOG using a questionnaire. We found that slightly more than half of the patients predominantly fell in the ON-state (patients' movement is relatively good) among 36 patients⁵³ (Figure 10-A). This may be explained by the fact that the patients' mobility partially improves but postural instability is generally not adequately improved even at the ON-state in advanced-stage Parkinson's disease. Only six patients predominantly fell at the OFF-state (patients' mobility is poor), and the main cause was FOG. These results reflected the fact that our patients were mostly in advanced stages of Parkinson's disease⁵³. Statistical analyses revealed that a higher number of FOG-related falls occurred in the OFF-state than in the transition and ON-states. In contrast, a higher number of FOG-unrelated falls happened in the ON-state than in the transition and OFF-states (Figure 10-B).

Through these research studies, I became well known as a specialist of gait in Parkinson's disease among Asian countries. I was then selected as Treasurer-Elect (2015-2017) and Treasurer (2017-2019) of the Asian and Oceanian Section of the International Parkinson and Movement Disorders Society (MDS-AOS), which was a great privilege for me. Figure 11 shows the members of the section during my terms. Please note that Professor Hattori was the Chairman of the MDS-AOS leaders. I thank

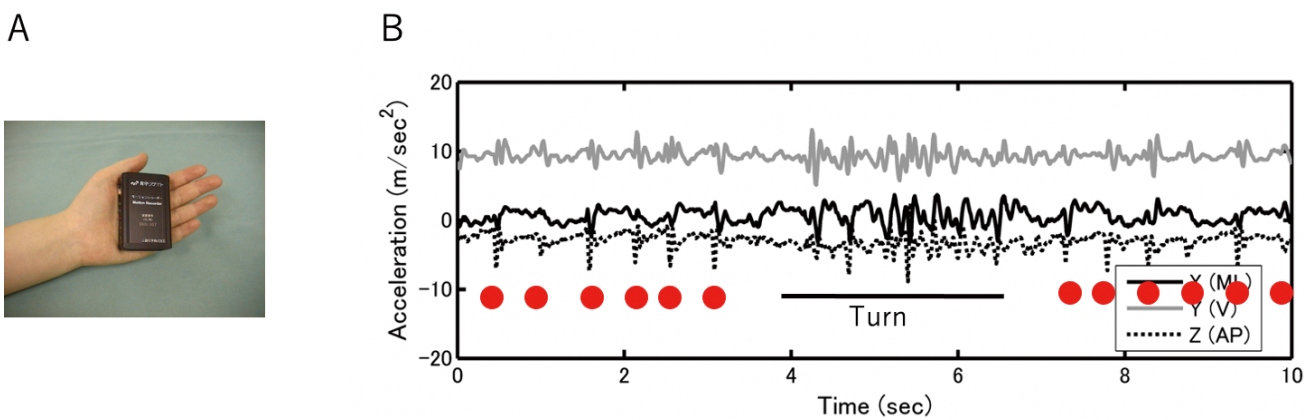


Figure 9

A. 3D accelerometer

B. Acceleration recordings during walking and turning in a patient with advanced-stage Parkinson's disease. Red circles show the step rhythm. During turning, high-frequency oscillations corresponding to the freezing of gait were observed.

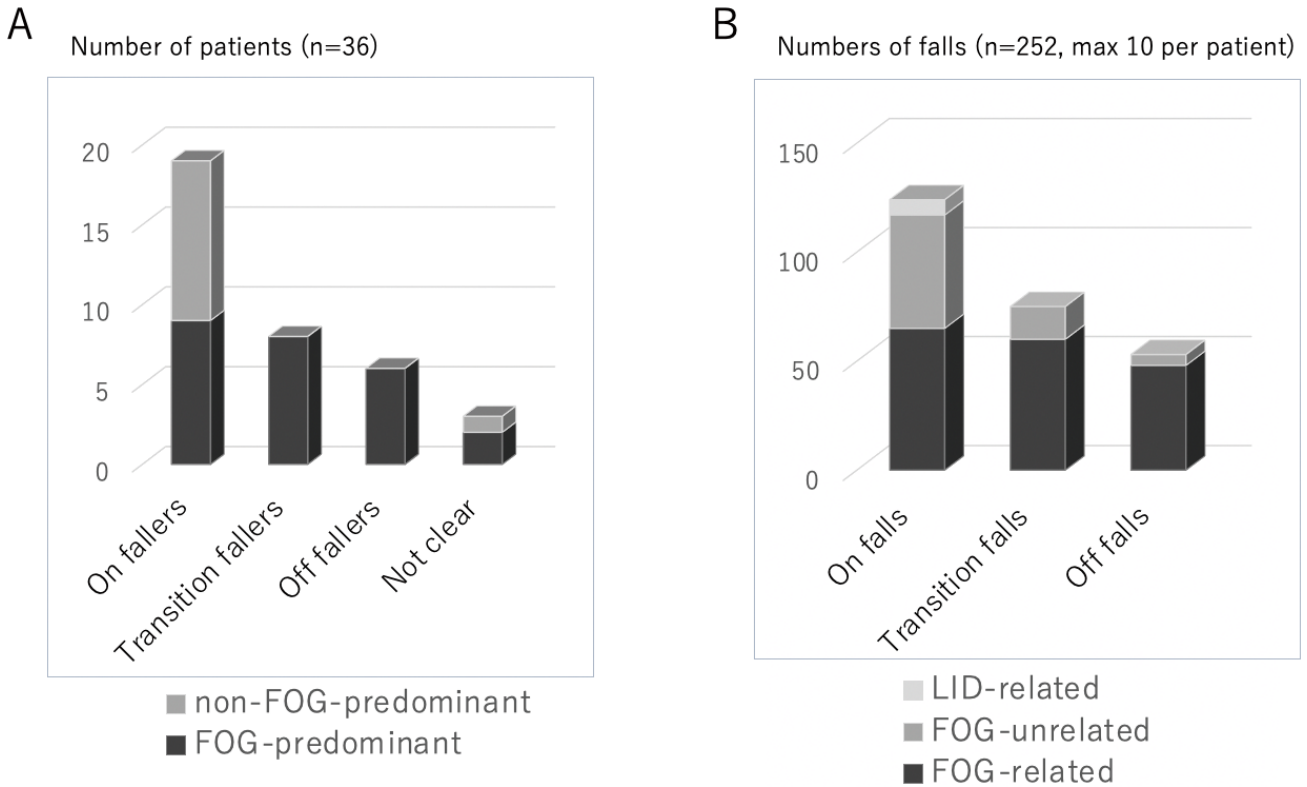


Figure 10 Results of prospective study of falls in Parkinson's disease

A. Number of patients for each faller category. Slightly more than half patients (19 patients) are categorized as On-faller. For the Transition-state fallers and Off-fallers, the main cause of falls was freezing of gait.
 B. Number of falls for each fall category. Only three falls were attributed to severe dyskinesia. The tendency was as the same as Figure 10-A.

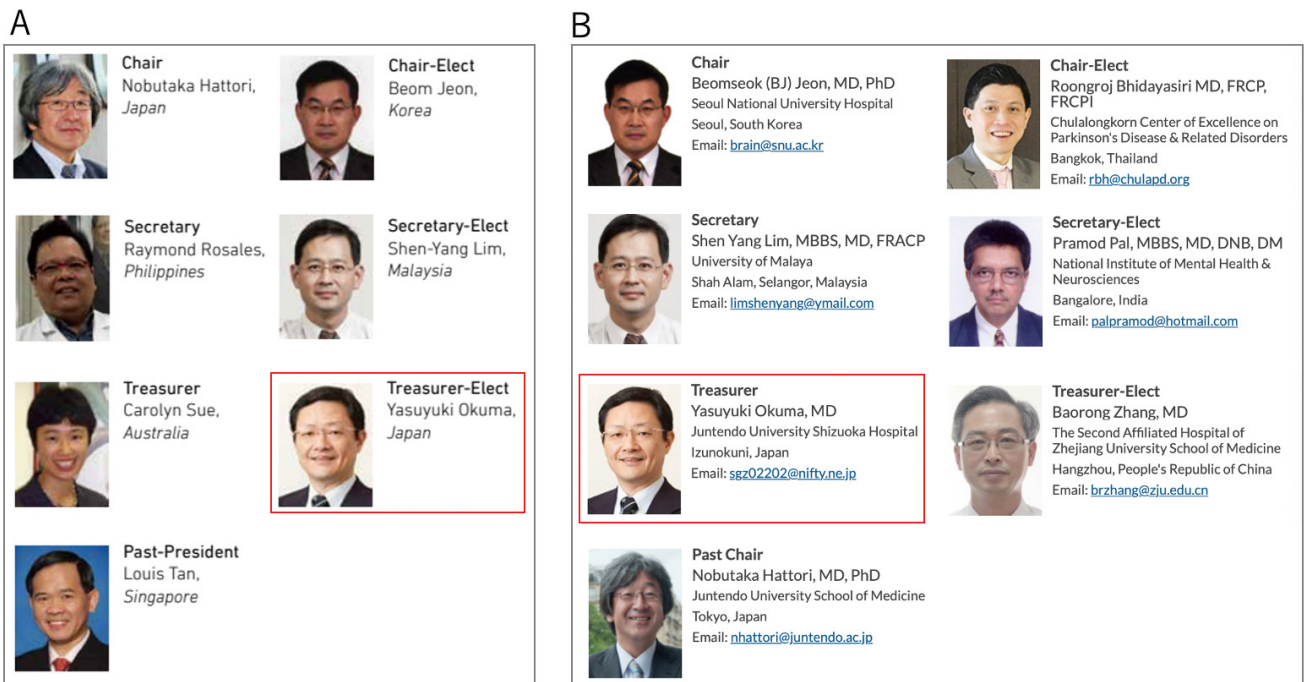


Figure 11

A. Officers of the Asian and Oceanian Section of the International Parkinson and Movement Disorders Society (MDS-AOS) from 2015 to 2017. I served as Treasurer-Elect. Note that Professor Hattori was the Chairman of MDS-AOS.
 B. Officers of MDS-AOS from 2017 to 2019. I served as Treasurer.

Professor Hattori and Professor Mitsutoshi Yamamoto of Takamatsu City for recommending me for an officer of MDS-AOS. It was a precious occasion to work with leaders of neurology in Asian countries.

Dean of Faculty of Health Science and Nursing

I was appointed as the dean of the Faculty of Health Science and Nursing in April 2017. This faculty was established in 2010 in Mishima City to produce nurses working in the Juntendo university hospitals. The founding dean was Professor Keiko Inatomi, who was followed by Professor Takao Okada; both previously worked as deans of the Faculty of Health Care and Nursing in the Urayasu Campus. In contrast to those former deans, I had no experience in nursing education. What I could do was only to brush up my lectures to attract nursing students' interest. Fortunately, since I had many videos of my patients, I used them frequently in my lecture slides, which made my lectures interesting. As a result, I received the Best Professor Award in March 2018 (Figure 12-A). I received the Best Professor Award again in 2021, feeling very proud that I was selected by students, 100% of whom passed the National Examination for Nurses despite the COVID-19 pandemic (Figure 12-B). During my term as the dean, the level of nursing students gradually improved. This was accomplished by recruiting excellent faculty members

and faculty development to provide better education, recruiting good students through PR activities, and administering appropriate entrance examinations. Eventually, I was able to complete my term as the dean with the exceptional support and guidance of CEO Hideoki Ogawa, President Hajime Arai, and Executive Advisor to President Eiki Kominami, and I heartfully thank these leaders of Juntendo University (Figure 13). I am very pleased to see the increase in admission capacity and the construction of the new education building in the Mishima Campus, which will be completed in 2024.

Finally, maybe this is not so important, but I would like to mention Hakone Ekiden, which is one of Juntendo University's popular sporting events. As I used to play the trumpet in junior and senior high schools, I joined the cheering squad in 2020. Juntendo cheering squad, initially organized by Professor Okada, is quite unique in that most of the members are nursing students. We were allowed to perform cheering for the first time in three years in January 2023 after the long COVID-19 pandemic (Figure 14). Cheering along the roadside gave us much excitement, and we were so moved that our Juntendo Ekiden team won fifth place in the 2023 race.

Acknowledgements

I thank all my colleagues, faculty members, and

A



B



Figure 12

A. Best Professor Prize awarded by CEO Hideoki Ogawa in the thank-you party after the graduation ceremony in March 2018.
 B. Best Professor Prize in March 2021.



Figure 13 Executive officers of Juntendo University

- A. CEO, Hideoki Ogawa
- B. President, Hajime Arai
- C. Executive Advisor to the President, Eiki Kominami



Figure 14 Cheering near the goal of Hakone Ekiden on Jan 2, 2023 at lakeside Ashinoko. The author is the third one from the left in the brass band team

family for supporting me and letting me experience valuable opportunities in Juntendo University.

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Author contributions

YO wrote the whole manuscript, read and approved the final manuscript.

Conflicts of interest statement

The author declares that there are no conflicts of interest.

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A Surgeon Involved in Basic Research - on the Occasion of Studying Abroad

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I, the author, expressed gratitude for receiving the 45th Juntendo Medical School Alumni Association Academic Encouragement Award in May 2023. After completing medical school and surgical training at Juntendo University, I embarked on a new challenge by pursuing a Ph.D. in basic clinical research, with a focus on gastric cancer, the third leading cause of cancer related death in Japan. Collaborating with various experts, I obtained a Ph.D. in cancer research studies in 2014. Subsequently, I pursued further research opportunities in the United States, where I undertook multiple projects focusing on cancer and maternal stress. I would like to present several studies, ERC/mesothelin, fatty acid synthase, and maternal stress in this manuscript.

On returning to clinical practice at Juntendo University Shizuoka Hospital in 2019, I developed an interest in various clinical issues and decided to address these through experiments. In collaborating with several researchers at the Shizuoka Medical Research Center for Disasters, our ongoing research aims to answer several clinical questions.

Furthermore, I aspire to guide junior staff in the future and am grateful for the invaluable connections and opportunities provided by Juntendo University.

Key words: ERC/mesothelin, fatty acid synthase, gastric cancer, maternal stress, lung tumor

Introduction

I (the author) received the 45th Juntendo Medical School Alumni Association Academic Encouragement Award in May 2023. I would like to thank all concerned persons. After graduating from Juntendo University School of Medicine in 2000, I trained in the Department of Surgery at Juntendo University, led by Professor Masahiko Tsurumaru, until 2008. In 2009, I was transferred to the Department of Surgery, led by Professor Koichi Sato, at Juntendo University Shizuoka Hospital, where I currently work. At the time of my transfer to Juntendo Shizuoka Hospital, I had been a surgeon for 10 years, so I decided to take on a new challenge and began my path to obtain a Ph.D. degree in basic

research in addition to my clinical work.

Malignant tumors are the leading cause of death in Japan. The second most common is heart disease, followed by senility. Among the malignant tumors, gastric cancer is the third leading cause of death in Japan.

Although the incidence of gastric cancer has decreased due to the decrease of *Helicobacter pylori* infection and improvement of dietary habits, I have researched gastric cancer. I was introduced to Dr. Kazunori Kajino and Dr. Masaaki Abe under the supervision of Professor Okio Hino of the Department of Pathology and Oncology. In 2011, I began my research while attending the main hospital once a week. They taught me how to conduct the experiments and helped me a lot.

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ERC/mesothelin is expressed in human gastric cancer tissues and cell lines¹⁾

ERC/mesothelin, a protein found in mesothelioma and other malignancies, is encoded by the ERC/mesothelin gene (*MSLN*), which produces a 71-kDa precursor protein. This precursor protein undergoes cleavage, resulting in the formation of a 31-kDa N-terminal protein (N-ERC/mesothelin) and a 40-kDa C-terminal protein (C-ERC/mesothelin). N-ERC/mesothelin is a soluble protein that has been identified as a diagnostic serum marker for mesothelioma and ovarian cancer. Although C-ERC/mesothelin is expressed in gastric cancer tissues, the diagnostic significance of serum N-ERC levels in gastric cancer remains unexplored. This study aimed to address this knowledge gap by investigating the importance of serum N-ERC levels in the diagnosis of gastric cancer and exploring C-ERC/mesothelin expression in human gastric cancer tissues and cell lines. C-ERC/mesothelin

expression was examined through immunohistochemistry in tissue samples from 50 gastric cancer patients, and C-ERC/mesothelin expression in six gastric cancer cell lines (MKN-1, MKN-7, MKN-74, NUGC-3, NUGC-4, and TMK-1) was assessed using various techniques such as reverse transcription-polymerase chain reaction (RT-PCR), flow cytometry, immunohistochemistry, and immunoblotting. Additionally, N-ERC/mesothelin concentrations in cultured cell supernatants and sera from patients with gastric cancer were measured using an enzyme-linked immunosorbent assay (ELISA). RT-PCR, flow cytometry, and immunohistochemistry confirmed the presence of ERC/mesothelin mRNA and C-ERC protein in five of the six gastric cancer cell lines investigated (MKN-1, MKN-7, MKN-74, NUGC-4, and TMK-1) (Figure 1A-C). ELISA detected N-ERC/mesothelin in the supernatants of the three gastric cancer cell lines (MKN-1, NUGC-4, and TMK-1) (Figure 1D). However, the concentration of N-ERC/mesothelin

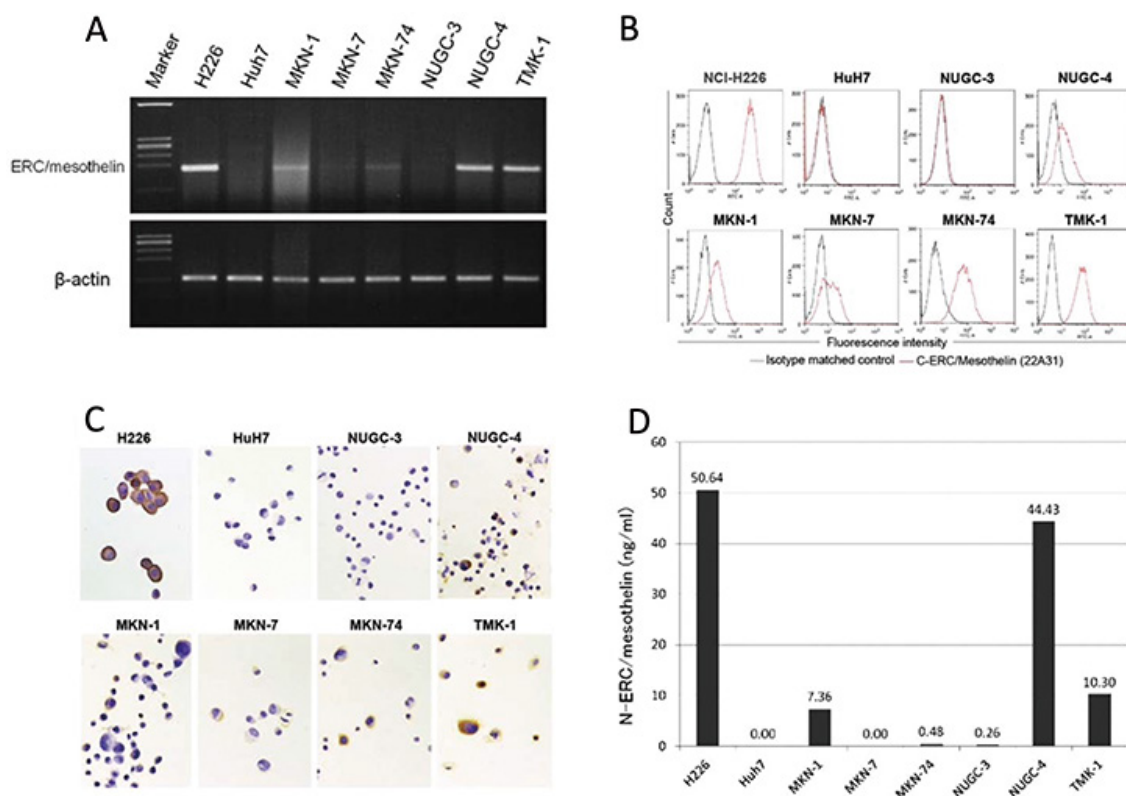


Figure 1 ERC expression¹⁾. (A) ERC/mesothelin transcript was detected in human gastric cancer cell lines by RT-PCR. H226 cells were used as a positive control. Huh7 cells were used as a negative control. The other cell lines are derived from human gastric cancer. (B) Cell surface C-ERC/mesothelin expression in the human gastric cancer cell lines as determined by flow cytometry. (C) Immunohistochemical staining of C-ERC/mesothelin in the human gastric cancer cell lines using 22A31 antibody. Magnification, x400. (D) ELISA detected N-ERC/mesothelin that had been secreted into the cell culture media of human gastric cancer cell lines.

in the sera of gastric cancer patients was comparable to that observed in the sera of normal controls (data not shown). Furthermore, C-ERC/mesothelin expression is associated with the lymphatic invasion of gastric cancer tissues. Although N-ERC/mesothelin is secreted by gastric cancer cell lines, it does not appear to be a useful serum marker for gastric cancer.

Elevated levels of serum fatty acid synthase in patients with gastric carcinoma²⁾

In order to facilitate optimal treatment strategies, the development of biomarkers for early detection and timely intervention of new cancers, as well as for recurrent cases, is crucial. Fatty acid synthase (FAS) is highly expressed in various human cancers, and is a potential biomarker. However, the applicability of FAS for the detection of gastric cancer remains unexplored. In this study, we conducted an initial evaluation of serum FAS levels as markers of gastric carcinoma. This study included 47 patients diagnosed with gastric cancer and 150 healthy individuals as controls. Blood samples were collected from each patient prior to treatment, and serum FAS levels were quantified using an ELISA, allowing for a comparison between the two groups. The analysis revealed significantly higher serum FAS levels in patients with gastric cancer (95% confidence interval [CI]: 30.37–52.46) compared to the healthy controls (95% CI: 1.331–2.131) (Figure 2A). Importantly, elevated FAS levels were observed in patients with early stage tumors (Figure 2B). These findings highlighted the potential of serum FAS as

a biomarker for sensitive and specific detection of gastric cancer.

Research in the USA

I received my Ph.D. in Research Studies in 2014. As I became involved in these basic studies, coupled with my long-held desire to study, I met Professor Malcolm Brock and Dr. Kathleen Gabrielson at Johns Hopkins University, United States. I told them that I wanted to conduct research in the United States, and they accepted my request. In February 2016, I began my long-term study abroad experience. In the United States, there are very few patients with gastric cancer, and it is no exaggeration to say that none of them are interested in gastric cancer. Therefore, I began several research projects simultaneously instead of focusing on only one project. One was on maternal stress, funded by the MEXT*-Supported Program for the Strategic Research Foundation at Private Universities (*Ministry of Education, Culture, Sports, Science, and Technology), 2015–2019 at Shizuoka Medical Research Center for Disaster.

Prenatal stress enhances NNK-induced lung tumors in A/J mice³⁾

Offspring born to mothers who experience stress during pregnancy have an elevated risk of cancer later in life. However, to the best of our knowledge, no animal studies have investigated this association. In this study, we examined whether prenatal stress (PS) in A/J mice influences the development of lung tumors following exposure to tobac-

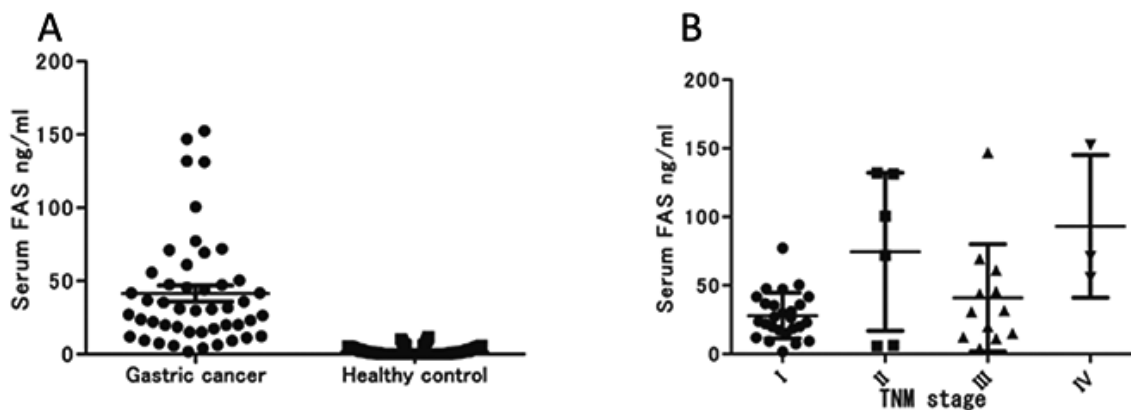


Figure 2 FAS levels²⁾. (A) Serum FAS levels of gastric cancer patients were significantly higher than healthy controls ($P < 0.0001$; Mann-Whitney U test). (B) When the TNM staging was analyzed, there was no significance in serum FAS concentration ($P = 0.0603$; Kruskal-Wallis test). TNM, tumor-node-metastasis; FAS, fatty acid synthase.

co-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). Timed-bred A/J mice were randomly assigned on gestation day 12.5 to either PS, achieved through restraint for five consecutive days, or a control group without restraint. Adult offspring from both control and stressed pregnancies were administered three injections of NNK (50 mg/kg every other day) and euthanized 16 weeks later for lung examination. Compared to the control group, dams subjected to PS exhibited significantly elevated levels of plasma corticosterone, increased adrenal weights, and reduced fetal weights without any fetal loss. Prenatally stressed litters experienced a notably higher neonatal mortality rate within the first week of life, and the surviving male and female offspring demonstrated increased lung epithelial proliferation (Figure 3), as well as increased tumor multiplicity, larger tumor area, and more aggressive tumor morphology. PS also resulted in the presence of advanced atypical adenomatous hyperplastic lesions. While we observed no difference in NNK-derived methyl DNA adducts in the lungs, PS treatment led to a significant increase in the infiltration of CD3⁺ and Foxp3⁺ T cells into lung

tumors. PS significantly enhanced tumor multiplicity, tumor area, and tumor morphology in NNK-induced lung tumors. PS did not affect the production of NNK-derived methyl DNA adducts but increased lymphocytic infiltration into lung tumors. To the best of our knowledge, this is the first animal model of PS that is used to assess the development of cancer in offspring. This novel mouse model holds potential for further elucidation of the mechanisms underlying the enhancement of carcinogenesis by PS.

PS enhances atherosclerosis and telomere shortening in ApoE knockout mouse offspring⁴⁾

Offspring born to mothers experiencing stress during pregnancy face an elevated risk of atherosclerosis later in life; however, only a limited number of animal models have explored the underlying mechanisms of this phenomenon. In the present study, time-bred ApoE-knockout mice were used to investigate this phenomenon. Pregnancy in mice was confirmed via ultrasound, and on gestation day 8.5, mice were randomly assigned to either a control group (no stress) or a PS group, which involved subjecting the mice to 2 h of restraint

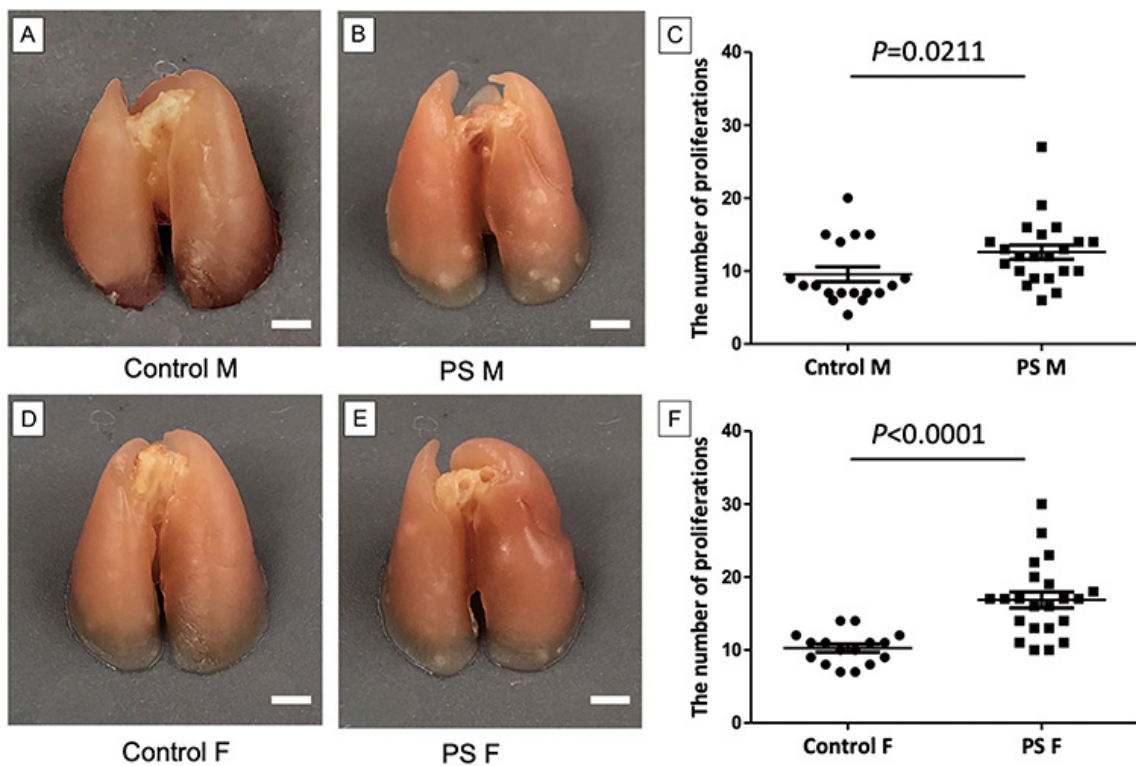


Figure 3 Macroscopic comparison of control and PS group lungs³⁾. PS group had significantly more proliferations than control group (males and females). M, Male; F, Female; PS, Prenatal stress.

for five consecutive days. The PS group showed a significant increase in plasma corticosterone levels during pregnancy. Neonatal mortality within the first week of life was higher in the litters of PS mice. After euthanasia, adult offspring from the PS group at 25 weeks of age had significantly higher body weights than those from the control group. Adult offspring were serially imaged using ultrasound to measure plaque thickness and were subjected to macroscopic and microscopic examinations of plaque pathology. The PS group displayed increased plaque thickness, as determined using ultrasonography, gross evaluation (Figure 4), and histological analysis, along with heightened infiltration of macrophages into the aortic root and valve at 25 weeks. At 5 weeks of age, mice in the PS group exhibited a significant decrease in mean arterial pressure, but blood pressure levels normalized by 10 weeks. Considering that the PS-induced increases in apoptosis and telomere shortening are stress-sensitive, telomere lengths were compared in the aorta of 10-week-old mice. The telomeres were significantly shorter in the PS group than in the control group. These findings encourage further exploration of how stress affects telomere shortening in animal models and the human aorta. Moreover, this model provides a valuable platform for

investigating the roles of PS, telomere biology, and the pathogenesis of atherosclerosis in adults.

Perspectives and Significance

The physical and mental health consequences of stress in adults are well-recognized; however, the impact of stress on unborn children during pregnancy is more challenging to comprehend. However, recent epidemiological investigations have documented detrimental health effects in populations exposed to PS caused by genocides, natural disasters, pandemics, and wars. The mechanisms underlying these effects, which likely persist across generations, remain largely unexplored. This study aimed to investigate the acceleration of atherosclerosis and lung tumors due to PS, with a focus on understanding the associated mechanisms. Animal models offer a valuable approach for examining these mechanisms, providing insights that can be extrapolated to human populations to develop preventive or mitigating strategies⁴.

After returning to Japan

I started my practical work at Juntendo University Shizuoka Hospital in May 2019, after returning from the United States. This marked the 20th year since I became a doctor. Although my clinical

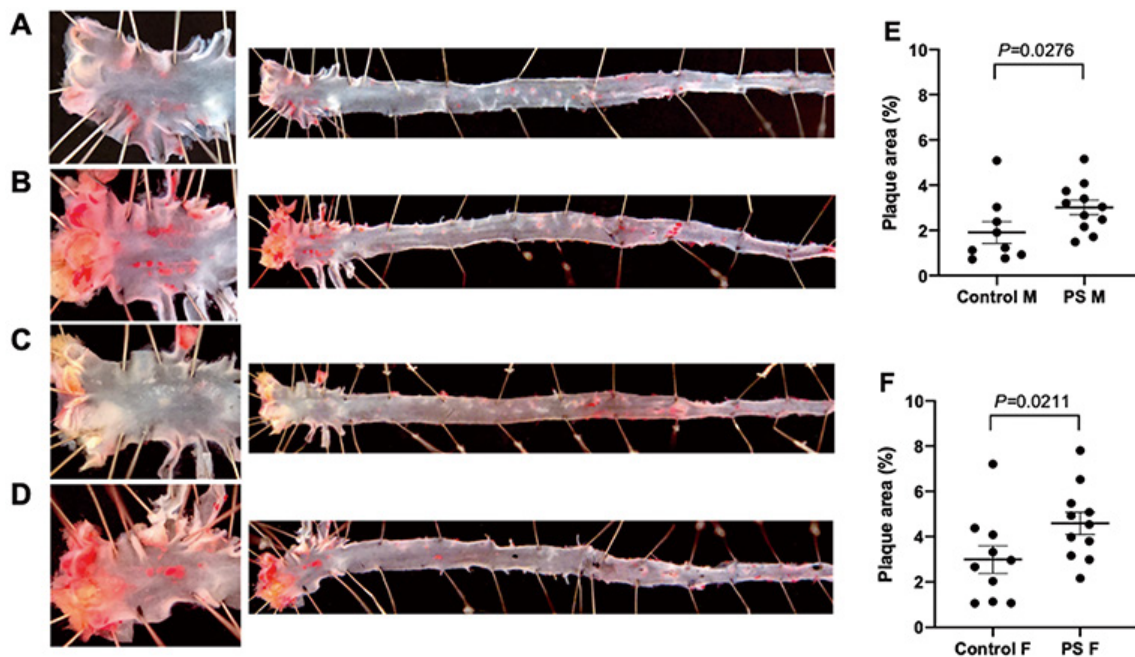


Figure 4 Comparison between plaque area in the whole aorta of the control group and prenatal stress group who were euthanized at 25 wk⁴. PS group had significantly more plaques than the control group in both of male and female. M, Male; F, Female; PS, Prenatal stress.

specialty is the gastrointestinal tract, I received a grant from KAKENHI and I am currently continuing my research.

When I returned to clinical practice, I became interested in the various clinical issues that I faced and wondered whether I could clarify them through experiments.

With the cooperation of several researchers at the Shizuoka Medical Research Center for Disasters, our ongoing research aims to answer several clinical questions.

In the future, I would like to guide junior staff so that they can understand the enjoyment of basic research. I can also reaffirm that this is because of the solid and broad connections I have established at Juntendo during my research. I would like to thank you for the 45th Juntendo Medical School Alumni Association Academic Encouragement Award.

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I would like to thank Prof. Koichi Sato for his leading, and Dr. Hajime Orita for his management of the studies.

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Author contributions

Not applicable.

Conflicts of interest statement

The author declare that there are no conflicts of interest.

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Designing the Diagnostic Criteria for Disseminated Intravascular Coagulation (DIC)

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Disseminated intravascular coagulation (DIC) is a common and critical complication in various diseases. There are several diagnostic criteria, such as the International Society on Thrombosis and Haemostasis (ISTH) criteria, the Japanese Society on Thrombosis and Hemostasis (JSTH) criteria, and the Japanese Association for Acute Medicine (JAAM) criteria. Due to the strengths and drawbacks inherent in each diagnostic criterion, it has the potential to cause confusion in clinical settings. It is possible to increase the specificity by making a complex criterion but simple and easy-to-use criteria are demanded in practice. To establish pragmatic criteria using readily available biomarkers, the ISTH focused on DIC arising from sepsis and released sepsis-induced coagulopathy criteria (SIC). A similar approach will aid in constructing a practical diagnostic criterion tailored to each specific background.

Key words: disseminated intravascular coagulation, coagulopathy, diagnostic criteria, sepsis, anticoagulation

Disseminated intravascular coagulation (DIC) was defined as “an acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different causes...” by the Scientific Subcommittee (SSC) on DIC of the International Society on Thrombosis and Haemostasis (ISTH) in 2001¹⁾. The essence of this definition was that despite DIC occurring from various backgrounds, it shows a similar hemostatic phenotype which is systemic activation in coagulation that can lead to hemostatic impairment and organ dysfunction. Therefore, the same diagnostic criteria should be applied for the diagnosis regardless of the underlying diseases. This concept has been widely accepted since then, but it is changing along with the significant advances in the management of DIC. For example, anticoagulant therapy using antithrombin or recombinant thrombomodulin was actively initiated at the early stage of DIC in Japan, and the Japanese Association for Acute

Medicine (JAAM) established the diagnostic criteria that diagnose the early phase DIC possible²⁾ (Table 1). The pathogenic role of disseminated thrombosis was also explored, and it has been accepted that systemic activation in coagulation and inflammation was elicited for the sake of host defense in sepsis³⁾. On the contrary, the temporal hyper-fibrinolysis in trauma-induced coagulopathy has been perceived as the counter-reaction to the massive thrombin generation (thrombin burst) and the effectiveness of anti-fibrinolytic therapy was proven if it was administered at the appropriate time⁴⁾. Similarly, the understanding of the pathophysiology of coagulation disorder arising from different backgrounds such as Coronavirus disease 2019-associated coagulopathy and heat-stroke-induced coagulopathy has been paid attention in these years. Subsequently, an individual diagnostic criterion for each underlying condition was proposed.

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Table 1 Comparison of ISTH overt DIC, JAAM DIC, and SIC scoring systems

Item	ISTH overt DIC		JAAM DIC	ISTH SIC
	Score	Range	Range	Range
Platelet count ($\times 10^9/L$)	3	–	< 80 or $\geq 50\%$ decrease within 24h	–
	2	< 50	–	< 100
	1	≥ 50 , < 100	120 >, 80 \leq or $\geq 30\%$ decrease within 24h	≥ 100 , < 150
FDP (D-dimer)	3	strong increase	$\geq 25 \mu g/mL$ (use convert chart)	–
	2	moderate increase	–	–
	1	–	≥ 10 , < 25 $\mu g/mL$ (use convert chart)	–
Prothrombin time	2	≥ 6 sec	–	> 1.4
	1	≥ 3 sec, < 6 sec	≥ 1.2 (PT ratio)	> 1.2, ≤ 1.4 (PT-INR)
Fibrinogen (g/mL)	1	< 100	–	–
SIRS score	1	–	> 3	–
SOFA score	2	–	–	≥ 2
	1	–	–	1
Total score for DIC or SIC		≥ 5	≥ 4	≥ 4

ISTH, International Society on Thrombosis and Haemostasis; DIC, disseminated intravascular coagulation; JAAM, Japanese Society for Acute Medicine; SIC, Sepsis-induced coagulopathy; SIRS, Systemic Inflammatory Response Syndrome; SOFA, sequential organ failure assessment

Total SOFA score is the sum of 4 items (respiratory SOFA, cardiovascular SOFA, hepatic SOFA, and renal SOFA).

Here is a first question. Is it prudent to formulate distinct diagnostic criteria tailored to each background? Along with the advances in pathogenic research, it has become difficult to apply the same diagnostic criteria to all types of DIC. Accordingly, the Japanese Society on Thrombosis and Hemostasis (JSTH) launched a new diagnostic criterion that was divided into three parts depending on the basal conditions; basic type, hematopoietic-disorder type, and infectious type⁵. In the JSTH criteria, the platelet count was removed for diagnosing the hematopoietic type, and fibrinogen was excluded from the infectious type of DIC. However, these modifications deviate from the original concept of DIC. Besides, the ISTH released new diagnostic criteria which are specifically designed to detect the early phase DIC in sepsis, per se, sepsis-induced coagulopathy (SIC) criteria⁶. The fault of SIC is the low specificity, requiring the differential diagnosis of the diseases that mimic DIC. On the contrary, the drawbacks of JSTH criteria are the complexity and the costs involved performing

molecular markers such as thrombin-antithrombin complex, soluble fibrin, prothrombin fragment₁₊₂, and antithrombin activity to make a more accurate diagnosis. Then, the second question arises: whether it is the right direction to make more 'accurate' diagnostic criteria.

Prior to delving into the aforementioned arguments, it is necessary to explore the meaning of an 'accurate' diagnosis of DIC. DIC is a conceptual idea, and recent research has elucidated the molecular pathogenic mechanisms of this condition⁷. Nevertheless, there still exists a wide gap between the pathological findings and the clinical diagnosis based on the laboratory data. Though the sensitive markers, such as molecular markers, endothelial damage markers, microparticles, and damage-associated molecular markers, may be helpful in diagnosing DIC more sensitively, the benefit will be limited in the clinical practice⁸. We think the ultimate value of diagnostic criteria should be defined from the viewpoint of clinical usefulness. In other words, how much does making a DIC diagnosis

impact on the clinical course of the patient is important. For example, the JAAM DIC criteria were designed to determine the timing of anticoagulant therapy²⁾, and its clinical usefulness was shown repeatedly in clinical studies^{9,10)}. Regarding the concept of diagnostic criteria, Gando et al.¹¹⁾ mentioned that they should be composed of readily available markers and easy to use; (2) they should have diagnostic accuracy; and (3) they should display prognostic value, meaning that the diagnostic criteria should be precise and practical.

Currently, there are two options, to make comprehensive or individual, and precise but complex or simple but less accurate, and we still don't know which way to go. As for simplification, we recently proposed the potential usefulness of the modified version of JAAM DIC diagnostic criteria¹²⁾ and a simplified version of JSTH DIC diagnostic criteria¹³⁾. Utmost, what could be the simplest version? In the case of infection-based coagulopathy, we have established the category named 'SIC'¹⁴⁾ using only three items, Sepsis-3 (infection with organ dysfunction)¹⁵⁾, platelet count, and prothrombin time. We hope this type of new category can identify the patients with a high risk of death and the cases that benefit from anticoagulant therapy. Certainly, SIC was specifically designed for sepsis-associated DIC and adopted only a minimal number of items, but its performance is considered to be practically sufficient¹⁶⁾.

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Author contributions

JT and TI wrote and reviewed the manuscript. Both authors read and approved the final manuscript.

Conflicts of the interest statement

The authors declare that they have not conflict of interest.

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Totally Laparoscopic Pylorus-Preserving Gastrectomy (TLPPG) is Safe and Effective for Early Gastric Cancer Treatment

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Background: Compared to distal gastrectomy (DG), pylorus-preserving gastrectomy (PPG), a peristaltic function-preserving surgery for early gastric cancer (EGC), is advantageous as it leads to a more improved nutritional status and quality of life (QOL) of patients. In recent years, total laparoscopic PPG (TLPPG), an anastomosis which is performed intracorporeally, has increasingly replaced laparoscopic-assisted PPG (LAPPG) due to its minimal invasiveness.

Aim: To evaluate the safety and feasibility of TLPPG in terms of perioperative efficacy.

Patients: Three patients underwent TLPPG in the Affiliated Hospital of Changzhi Medical College from September 2021 to March 2022.

Methods: Surgical safety analysis: Our three cases (TLPPG group) were compared to data from the CLASS-02 study, which collected data from multiple centers across China for the laparoscopic total gastrectomy (LTG group). The CLASS-02 study provides data from the most invasive type of gastric surgery, providing solid comparative data to our own.

Postoperative short-term efficacy analysis: Patient questionnaire responses provided data on postoperative nutritional and QOL status. Results from our three cases were compared to the Japanese multicenter data PGSAS-37 (PGSAS group).

Results: There were no complications or deaths occurred during or after operation in our cases. Compared to the PGSAS group, our cases scored lower for abdominal pain, dyspepsia, and weight loss.

Conclusion: Although more case information is needed, our findings demonstrate that TLPPG may be a possible and effective treatment for EGC in China, similar to that in Japan.

Key words: laparoscopic pylorus-preserving gastrectomy, post-gastrectomy syndrome, post-gastrectomy syndrome assessment scale-37, early gastric cancer

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Introduction

Early gastric cancer (EGC) has been able to achieve extremely high cure rates through the use of minimally invasive (MI) and function-preserving (FP) surgeries in east Asian countries¹⁾. Most notably, pylorus-preserving gastrectomy (PPG) aims to prevent dumping syndrome and maintains the nutritional status of patients being treated for EGC located in the middle third of the stomach^{1,2)}. Specifically, laparoscopic assisted PPG (LAPPG) has been used in recent years to perform anastomosis intracorporeally. With current advances in technology, LAPPG has gradually been replaced by total laparoscopic PPG (TLPPG), a procedure that produces more cosmetically desirable results, less patient pain and risk of infection, and better post-operative quality of life (QOL). TLPPG has become the standard in Japan and Korea^{3,4)}.

However, unlike Japan and Korea, China has not yet adopted TLPPG, perhaps due to the low EGC diagnosis rate and the technical complexity of the procedure. None-the-less, China still has a number of gastric cancer diagnoses every year that require optimal treatment. In 2022 alone, about 500,000 new cases presented⁵⁾, of which EGC was as great as 20%⁶⁾.

In order to initiate the use of TLPPG in China, it is necessary to ensure that newly learned TLPPG procedures are done properly and can yield similar results to procedures done regularly. Therefore, we performed TLPPG on three Chinese patients (TLPPG group) and quantitatively observed their postoperative conditions and QOL status to see if we could produce similar results to the CLASS-02 study⁷⁾ (LTG group) in China⁸⁾ the multicenter data PGSAS-37 (PGSAS group) in Japan.

Materials and methods

Patients

Three EGC patients underwent TLPPG at the Affiliated Heji Hospital of Changzhi Medical College from September 2021 to March 2022. All patients completed the PGSAS-37 questionnaire after the operation. The clinical, perioperative, pathological, and PGSAS-37 questionnaire data were retrospectively analyzed. Clinical data included time after surgery, age, gender, preoperative body mass index (BMI), pathological stage, surgical approach,

extent of lymph node dissection, and combined resection. The gastric tumors were pathologically staged according to Japanese guidelines of gastric cancer treatment. The study protocol was approved by the Ethics Committee of the Affiliated Heji Hospital of Changzhi Medical College (Approval No.202005). The need for informed consent was waived in view of the retrospective and observational nature of the study.

Surgical procedure

Our TLPPG operation focused on the upper and lower incisional margins, the protection of nerves and blood vessels, and the resection and reconstruction of the stomach, which we elaborate in the following three parts:

1. At the beginning of the operation, the tumor was accurately located using laparoscopy and endoscopy. The upper and lower boundaries that were identified before operation, were marked with sutures (Figure 1).
2. The hepatic branch of the vagus nerve and the pyloric branch needed to be preserved during the operation. First, the assistant held up the visceral surface of the liver, exposed the lesser omentum, and cut off the right gastric artery. The second branch of the right gastric artery was protected to preserve the blood supply to the lesser curvature of the antrum and the innervation of the pyloric branch of the vagus nerve. We cut the omentum along the right gastric vessel, hepatoduodenal ligament, and hepatic branch of the vagus nerve, and then cut off the anterior gastric branch at the distal end of the hepatic branch of the vagus nerve. In

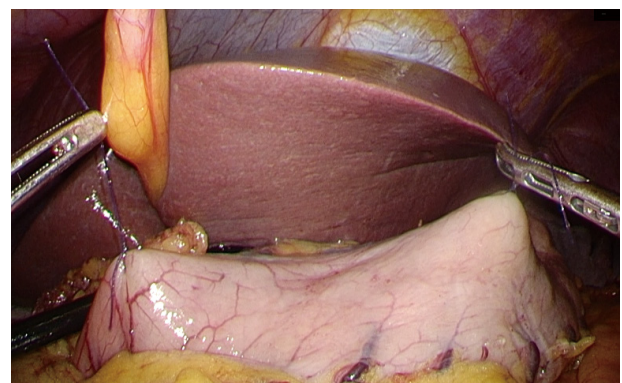


Figure 1 The upper and lower margins of the tumor were located by endoscopy and laparoscopy during the operation, and marked with suture.

order to avoid thermal injury, the distance between the head of the ultrasonic scalpel and the vagus nerve was more than 5 mm (Figure 2A). The inferior pyloric vessels also need to be protected to preserve the blood supply to the pylorus. Along the fusion fascia, the pancreatic head, duodenal bulb, and right gastroepiploic vessels were separated and exposed layer by layer, and the No.6v and No.6a lymph nodes were cleared near the pancreas. Then, the gastroduodenal artery was dissected by tracing the right gastroepiploic artery and the inferior pyloric artery along the GDA to identify positional relationships. Following this, the right gastroepiploic vessel was cut, and the inferior pyloric artery was retained (Figure 2B).

3. The middle part of the stomach was removed with two straight-line cutting closers from the

upper and lower boundaries at the marked site, thus preserving the pylorus and cardia. To reduce the risk of postoperative gastric emptying disorder, a sufficient antrum length was maintained. If conditions permitted, more than 3 cm of the antrum was kept, and the specimen was transected more than 2 cm from the distal edge of the tumor. After resection, the distal and proximal ends of the stomach were obtained (Figure 3). The lateral stapler was used to anastomose the posterior wall of the proximal stomach with the anterior wall of the distal stomach (Figure 4). A 3-0 barbed thread was used to suture the common opening to achieve full-thickness suture (Figure 5).

CLASS-02 study

The Chinese Laparoscopic Gastrointestinal Surgery

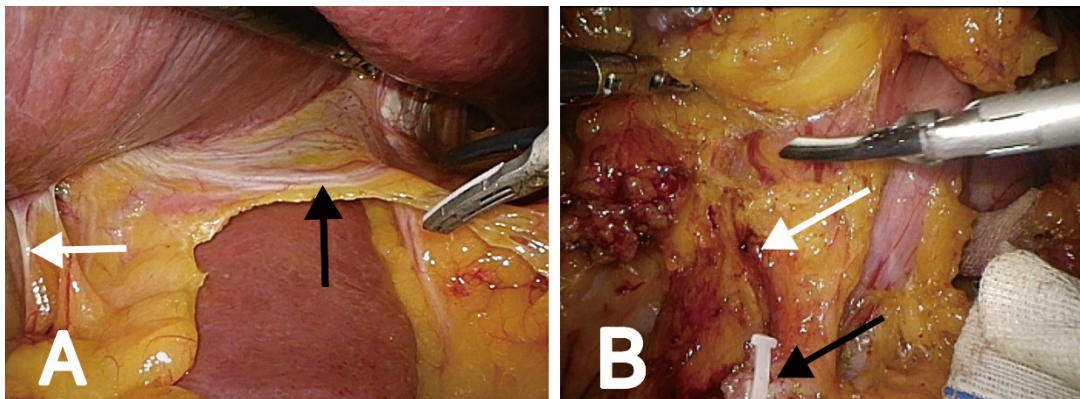


Figure 2 Preservation of the vagus nerve and inferior pyloric vessels. (A) The hepatic branch of vagus nerve (black arrowhead) is located at the omentum near the liver and the pyloric branch (black arrowhead) in the middle of the hepatoduodenal ligament. (B) The severed right gastroepiploic vessels (black arrowhead) at the beginning of the vessels and the preserved inferior pyloric vessels (white arrowhead).

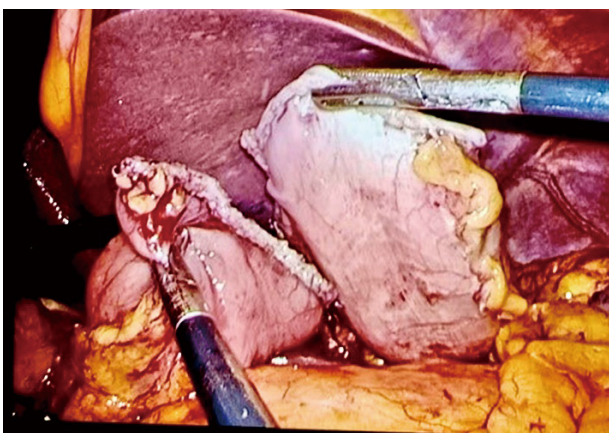


Figure 3 Straight-line cutting closers were used to remove the middle part of the stomach from the upper and lower edges at the marked site (A). The specimen removed through assisted small incision is shown in (B).

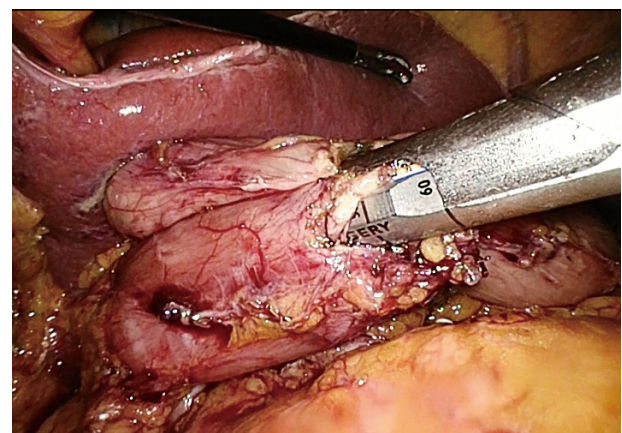


Figure 4 Anastomosis was performed by an endoscopic linear stapler.

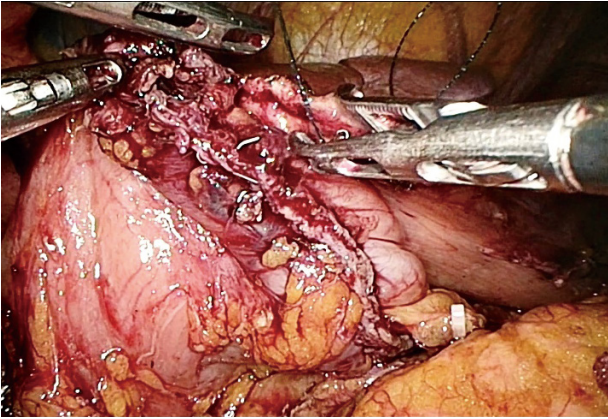


Figure 5 The anterior wall of the proximal and distal residual stomach was sutured and the common opening was closed.

Study (CLASS-02) was a prospective, multicenter, randomized clinical trial that compared the safety of laparoscopic total gastrectomy (LTG) versus open total gastrectomy (OTG) with D1+/D2 lymphadenectomy for patients with clinical stage I (T1N0M0, T1N1M0, T2N0M0) gastric cancer in the upper or middle third of the stomach. From January 2017 to September 2018, a total of 227 patients were enrolled. The primary outcome was the morbidity and mortality within 30 days following surgery. The secondary outcomes were the recovery courses and the postoperative hospital stays. We used the LTG group data of the CLASS-02 trial as the control group and compared perioperative data from the TLPPG and LTG groups.

PGS & QOL assessment

The PGSAS-37^{9,10)} questionnaire consists of 37 questions, of which 15 are from the Gastrointestinal Symptom Assessment Scale and 22 are clinically relevant questions that have been proposed by the Japanese Postgastrectomy Syndrome Working Party (JPGSWP) (supplemental Table 1) (https://www.jsqp.jp/index.php?page=about_pgsas). These questions are summarized into nine subscales with a total of 17 primary outcomes, including assessment of esophageal reflux, abdominal pain, diet-related discomfort, dyspepsia, diarrhea, constipation, dumping syndrome, food quality, and dissatisfaction with daily life. The main findings consist of three categories: symptoms, life status, and QOL (supplemental Table 2). Higher scores for food intake per meal, daily food intake, appetite, hunger, satiety, food quality, and body weight change indi-

cated better results, while lower scores for all other aspects indicated better results. The questionnaires were distributed by the physician at the time of the follow-up.

The PGSAS-37 questionnaire was completed by the three TLPPG patients in our center and by 313 PPG patients from the PGSAS group. The two groups were compared in terms of PGS symptoms and QOL scores.

Results

Three cases performed successfully based on perioperative status.

We counted and described the preoperative and postoperative data of three patients, including 2 males and 1 female. The average age was 60 ± 3.6 years old, and the average BMI was 24.3 ± 1.8 . The clinical stage was T1. The operation was completed under total laparoscopy, and the lymph node dissection was D1+. We followed up 3 patients after operation and filled in the PGSAS-37 questionnaire. Table 1 is the original data of 17 subscales, which provides evidence for our data comparison.

The PPG group in China compared the safety of LTG and OTG for EGC using the perioperative data of 214 patients (105 cases for LTG and 109 cases for OTG). In order to demonstrate the short-term safety of TLPPG, we utilized the LTG arm of CLASS-02 trial as the control group and compared the perioperative data of the TLPPG and LTG groups. As shown in Table 2, the number of retrieved lymph nodes in the TLPPG group (17 ± 2.2) was less than that in the LTG group (35 ± 12.7). The surgery time, estimated blood loss, time to first flatus, etc. were similar between the TLPPG and LTG groups. Furthermore, no complications or deaths occurred among our patients during or after operation (Table 3). The overall complication and mortality rates were similar between the two groups. In terms of intraoperative and postoperative complications, including surgery-related and system-related complications, no difference was noted between the two groups. These results indicated that TLPPG is a safe option.

The PGS and QOL are similar between PGSAS and TLPPG groups.

The clinicopathological features of the patients were summarized in Table 4. Because TLPPG is a

Table 1 Original data of 17 subscales

		Case 1	Case 2	Case 3	Mean	SD
Symptom	Esophageal reflux scale	2.25	1.75	1.89	1.88	0.21
	Abdominal pain scale	1.25	1.67	1.33	1.42	0.18
	Diet related discomfort scale	2.33	1.67	2.67	2.22	0.42
	Dyspepsia scale	1.67	1.75	2.00	1.81	0.14
	Diarrhea scale	2.33	1.00	2.00	1.78	0.57
	Constipation scale	1.33	2.33	2.33	2.00	0.47
	Dumping syndrome scale	2.33	2.00	1.00	1.78	0.57
	Overall symptom score	1.93	1.74	1.89	1.85	0.08
Living status	Body weight change rate (%)	-3.6%	-7.1%	-3.2%	-4.7%	1.8%
	Amount of food eaten at a time	8.00	5.00	6.00	6.33	1.25
	The need for extra meals	1.00	2.00	1.00	1.33	0.47
	Food intake quality scale	3.00	4.67	4.67	4.11	0.79
	service ability	1.00	4.00	2.00	2.33	1.25
QOL	Symptom dissatisfaction	2.00	1.00	1.00	1.33	0.47
	Dietary dissatisfaction	4.00	1.00	3.00	2.67	1.25
	Job dissatisfaction	2.00	1.00	2.00	1.67	0.47
	Dissatisfaction with daily life subscale	2.67	1.00	2.00	1.89	0.68

Table 2 Surgical results & outcome

	TLPPG group (<i>n</i> = 3)	LTG group (<i>n</i> = 105)
Surgical time (min)	193 ± 12	230 ± 67.3
Estimated blood loss (ml)	60 ± 8	92 ± 109.6
Time to first flatus (d)	3.3 ± 0.5	3.1 ± 0.9
Open conversion	0 (0%)	2 (1.9%)
No. of retrieved lymph nodes	17 ± 2.2	35 ± 12.7
Time to ambulation (d)	24.3 ± 1.2	40.6 ± 20.6
Postoperative hospital stay	10 ± 0.8	10.9 ± 5.1

Table 3 Morbidity and mortality

Morbidity type/mortality	TLPPG group (<i>n</i> = 3)		LTG group (<i>n</i> = 105)	
	No.	Rate, % (95% CI)	No.	Rate, % (95% CI)
All complications	0	0	24	22.9 (0.15~0.3)
Mortality	0	0	1	1.0 (0~2.8)

less invasive procedure, the observation period after surgery was shorter than that in the PGSAS group (6.7 ± 4.1 months vs 38.4 ± 27.7 months). The preservation of the celiac branch of vagal nerve and combined organ resection in TLPPG group were less than the PGSAS group. The average age of the TLPPG group was 60.0 ± 3.6 years and that of the PGSAS group was 61.5 ± 8.7 years. There were no differences between the two groups in terms of gender, preoperative body mass index, surgical

method, and lymph node dissection method.

The PGSAS-37 scores for 17 symptoms were summarized in Table 5. The abdominal pain (1.42 ± 0.18 vs 1.64 ± 0.73) and dyspepsia (2.83 ± 0.47 vs 2.01 ± 0.88) scores were higher in the TLPPG group compared to the PGSAS group. Furthermore, the percentage body weight loss was lower in the TLPPG group than in the PGSAS group (4.7% vs 6.9%). There were no differences in the amount of food taken per meal, the need for additional meals,

Table 4 Clinical and pathological characteristics results

	TLPPG group (<i>n</i> = 3)	PGSAS group (<i>n</i> = 313)
Postoperative time (month)	6.7 ± 4.1	38.4 ± 27.7
Age	60 ± 3.6	61.5 ± 8.7
Gender		
Male	2	183
Female	1	126
Preoperative BMI	24.3 ± 1.8	22.7 ± 3.0
Stages		
I	3	313
II	0	0
III	0	0
IV	0	0
Surgical approach		
peritoneoscope	3	136
open abdomen	0	173
Degree of lymph node dissection		
D1+	3	252
D1	0	6
D2	0	8
The celiac branch reservation (absence/presence)		
Absence	1	213
Presence	2	87
Combined resection (absence/presence)		
absence	1	12
presence	2	279

and the quality of intake between the TLPPG and PGSAS groups. Finally, the scores of QOL subscales, including dissatisfaction with symptoms, diet, work, and daily life, were also similar in both groups.

The self-nutrition indices also performed well.

We also compared the pre-operative and post-operative nutritional status of our three patients. As shown in Table 6, the BMI, albumin (ALB), and hemoglobin (HGB) level three months after operation were similar to the respective pre-operative values.

Discussion

Intracorporeal and robotic surgery for resections and anastomosis has become popular in GI surgery around the world due to recent technological advancements¹¹. Operation with good EGC prognosis requires highly skilled MI and FP methods.

However, full total operations have been increasing in Asia.

Total laparoscopic PPG (TLPPG) is one of many typical examples. This procedure prevents dumping syndrome, maintains the nutritional status, and requires a cosmetically small incision which is less painful and has a quicker recover time³. Because of these benefits, we introduced TLPPG, a technique not extensively used in China, to our clinic with the anticipation of increasing EGC diagnoses and the aim of offering better postoperative outcomes to Chinese patients with this disease.

To successfully perform the procedure and obtain ideal results, there are two major challenges that physicians must overcome. First, the operator needs to develop a scientific system for diagnosis and treatment of gastric cancer, such as preoperative positioning, intraoperative positioning, frozen section analysis of the cutting edge in the perioperative.

Table 5 PGSAS-37 main symptom scores

		TLPPG group (<i>n</i> = 3)		PGSAS group (<i>n</i> = 313)	
		Mean	SD	Mean	SD
Symptom	Esophageal reflux scale	1.88	0.21	1.70	0.82
	Abdominal pain scale	1.42	0.18	1.64	0.73
	Diet related discomfort scale	2.22	0.42	2.11	0.87
	Dyspepsia scale	1.81	0.14	2.01	0.88
	Diarrhea scale	1.78	0.57	1.84	0.97
	Constipation scale	2.00	0.47	2.24	1.08
	Dumping syndrome scale	1.78	0.57	1.75	0.94
	Overall symptom score	2.00	0.14	1.89	0.67
Living status	Body weight change rate (%)	-4.7%	1.8%	-6.9%	7.0%
	Amount of food eaten at a time	6.33	1.25	7.02	1.87
	The need for extra meals	1.33	0.47	1.75	0.75
	Food intake quality scale	4.11	0.79	3.76	0.93
	Service ability	2.33	1.25	1.77	0.95
QOL	Symptom dissatisfaction	1.33	0.47	1.80	0.94
	Dietary dissatisfaction	2.67	1.25	2.23	1.11
	Job dissatisfaction	1.67	0.47	1.67	0.91
	Dissatisfaction with daily life subscale	1.89	0.68	1.90	0.83

Table 6 Self-nutrition indices results

	Preoperative	3 months after surgery
BMI	24.3 ± 1.8	23.3 ± 1.1
ALB(g/L)	44.4 ± 2.8	45.4 ± 2.1
HGB	144.3 ± 9.0	142.3 ± 9.2

Second, the operator needs to protect the hepatic branch and pyloric branch of the vagus nerve, as well as protect the blood vessels under the pylorus, and clean up the No.6a and No.6v lymph nodes.

Furthermore, it is worth emphasizing that: 1. A scientific diagnosis and treatment system for gastric cancer should be developed in conjunction with relevant departments, such as the Endoscopy Department, Pathology Department and other relevant disciplines. 2. The operator should be familiar with the vagus nerve and its branches. The distance between the ultrasonic scalpel head and the vagus nerve should be more than 5 mm to avoid thermal injury. 3. The operator should dissect along GDA to reveal the position relationship between the right gastroepiploic artery and the inferior pyloric artery, and then disconnect and retain these vessels.

To estimate the quality of our three TLPPG cases, we were required to measure the MI and

FP. We used the CLASS-02 study (LTG) in China to estimate MI and evaluate surgical safety because LTG is the most difficult full total operation in China for EGC. There were no differences regarding blood loss, surgical time, hospital stay, and the incidence of complications compared with LTG in China. These results indicated that our initial TLPPG procedures were a safe option in our center. As for FP, we used PGSAS-37, the Japanese standard post operative score, which discusses post gastrectomy status.

Compared with other indicators, the postoperative efficacy of patients is difficult to evaluate since many symptoms cannot be quantified. In order to better quantify the postoperative state of our patients, we assessed the PGS score and QOL using the PGSAS-37 questionnaire by the Japanese national database that has been designed to evaluate functional parameters after gastrectomy. When comparing postoperative short-term efficacy, most symptom subscales and overall symptom scores were similar in both groups, with the most similar results between postoperative QOL scores. The abdominal pain, dyspepsia, and body weight loss in the PPG group yielded better results than that of the PGSAS group. Data from the PGSAS

group were obtained from open and laparoscopic surgeries in multiple centers across Japan beginning in 2015.

In our center, we adopted the latest TLPPG technique, allowing us to obtain desirable patient outcomes for EGC. Abdominal pain was reduced by TLPPG since it was less invasive (Table 4), it's mainly manifested in stomach ache. The smaller incision led to less tissue damage compared to conventional laparotomy and laparoscopic-assisted surgery¹²⁾, this will reduce the obstruction caused by adhesion of the stomach or intestines and reduce abdominal pains. As compared to LAPPG, the small incisions required for TLPPG remained uniform in size between patients and were independent of patient factors, leading to a potential advantage for using the technique¹³⁻¹⁵⁾. The score of the dyspepsia subscale was also lower than that of the PGSAS group. Studies have shown that, delayed gastric emptying (DGE)^{16,17)} and decreased receptive relaxation function¹⁸⁾ can cause dyspepsia. DGE is the most common and prominent complication after PPG, which may be related to factors such as blood supply to the gastric antrum¹⁹⁾ and the retention length of gastric antrum²⁰⁾. According to Fukunaga¹⁹⁻²¹⁾, preserving the infrapyloric vessel and the first branch of the right gastric vessel can greatly reduce DGE. The initial cases of PPG involved maintaining the length of the gastric antrum at 1.5 cm. With this antral length, the incidence of postoperative DGE ranged from 23% to 40%¹⁹⁻²¹⁾. Multiple retrospective studies have shown that in order to exert the functions of the preserved gastric antrum and pylorus and to reduce DGE, the reserved length of the gastric antrum above the pyloric canal should be at least 2.5-3 cm^{2,22-24)}. Some centers even require the preserved length of gastric antrum to be more than 4 cm^{25,26)}.

During operation in our center, we performed nerve protection and preserved a sufficient length of gastric antrum (3-4 cm) as well as the blood vessel under the pylorus and the first branch of the right gastric vessel. Gastrointestinal contrast examination during the perioperative period and three months post-surgery showed patency, and the incidence of DGE was 0. Sufficient antrum preservation ensured a large residual gastric cavity, maximal preservation of the receptive relaxation function of the stomach, and minimal risk of dyspepsia. In

addition, the rate of body weight loss was also better than the PGSAS group, primarily due to the reduction in DGE and dyspepsia, along with good nutrition absorption without obvious diet-related discomfort.

Despite observing the benefits of TLPPG in our cases, it is important to note that a weakness of this study was the extremely low number of our cases in comparison to that of previously collected data in the CLASS-02 and PGSAS-37 studies.

Conclusion

Having learned TLPPG from Professor Fukunaga, our clinic has been introduced to this innovative surgical technique and has observed its advantages. Although this method was only tested on three patients in our clinic thus far, our cases produced similar postoperative outcomes to those in Japan, suggesting that if done in larger number, more robust conclusions may be made. Nevertheless, our findings provide beginning evidence that this technique will be safe and effective for use in clinics across China.

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Author contributions

GW, HZP and HO designed the study; GW, HZP, MXH and WYY treated patients and collected material and clinical data from the patients; HZP, ZK and GXQ analyzed data; GW wrote the paper; All authors read and approved the final manuscript. MV and CF, native speaker, corrected English.

Conflicts of interest statement

The authors declare that there are no conflicts of interest.

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Supplemental Table 1 PGSAS-37 evaluation items

	Item	Subscales
Symptom	1 Abdominal pain*	Esophageal reflux sub-scale (Items 2, 3, 5 and 16)
	2 Heartburn	Abdominal pain sub-scale (Items 1, 4 and 20)
	3 Trans-acid	Sub-scale of diet-related irritability (Items 17-19)
	4 Fasting stomachache	Sub-scale for dyspepsia (Items 6-9)
	5 Nausea and vomiting	Diarrhea sub-scale (Items 11, 12 and 14)
	6 Borborygmus	Constipation sub-scale (Items 10, 13 and 15)
	7 Stomach distension	Dumping syndrome subscale (Items 22, 23 and 25)
	8 hiccups	
	9 Increased flatus	Total symptom score (over 7 subscales)
	10 Constipation	
	11 Diarrhea	
	12 Soft stool	
	13 Hard stool	
	14 Urgent need to defecate	
	15 Incomplete defecation	
	16 Bile reflux	
	17 Dysphagia	
	18 Postprandial stagflation	
	19 Early satiety	
	20 Lower abdominal pain	
	21 Number and type of early dumping syndrome	
	22 Early dumping, general symptoms	
	23 Early dumping, abdominal symptoms	
	24 Number and type of late dumping syndrome	
	25 Advanced dumping syndrome	
Living status	26 Amount of food consumed per meal	
	27 Daily food intake	
	28 Staple food frequency	
	29 Supplemental frequency	Intake quality subscale (Items 30-32)
	30 Appetite	
	31 Starvation	
	32 Feeling of satiety	
	33 The need for a meal	
	34 Working capacity	
QOL	35 Symptom dissatisfaction	
	36 Dissatisfaction with diet	Dissatisfaction with life sub-scale (Items 35-37)
	37 Dissatisfaction with one's work	

*: Abdominal pain mainly refers to stomach ache

Supplemental Table 2 Main results in the three categories

Category	Key findings
Symptoms	Esophageal reflux scale
	Abdominal pain scale
	Sub-scale of diet-related discomfort
	Dyspepsia sub-scale
	Diarrhea subset scale
	Constipation subscale
	Dumping syndrome subscale
	Total symptom score
Living conditions	
Weight	Weight change (%)
Diet (quantity)	Amount of food taken in per meal (%)
	The need for extra food
Diet (quality)	Intake quality sub-scale
Work	Service ability
QOL	Dissatisfaction with symptoms
Dissatisfaction	Dissatisfaction with one's diet
	Dissatisfaction with one's job
	Dissatisfaction with daily life subscale



Effect of Isokinetic Training with Blood Flow Restriction During Rest Interval Versus Exercise on Muscle Strength, Hypertrophy, and Perception: A Pilot Study

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Objectives: This study aimed to determine the effects of high-intensity isokinetic training with blood flow restriction during rest interval between set (rBFR) versus during exercise (eBFR) on muscle hypertrophy and increasing muscle strength and determine whether BFR-induced exercise pain is suppressed by rBFR.

Materials and Methods: Fourteen arms (7 participants) were recruited for the study. We conducted the following interventions for each arm: eBFR (n=4), rBFR (n=5), and exercise only (CON, n=5). The participants performed elbow flexion training with a BIODEX device twice weekly for 8 weeks. This study training consisted of total four sets; each was performed until <50% peak torque was achieved twice consecutively. BFR pressure was set at 120 mmHg. Elbow flexor peak torque during concentric contraction (CC), isometric contraction (IM), and muscle cross-sectional area (CSA) were measured before and after the intervention. Numerical rating scale scores used to assess pain during exercise were determined during training.

Results: Peak torque at the CC increased in the rBFR ($p<0.05$) and IM increased in the rBFR and CON ($p<0.05$), while CSA increased in the rBFR and CON ($p<0.001$). The pain during exercise was severe in the eBFR and moderate in the rBFR and CON.

Conclusions: This study's showed that high-intensity isokinetic training with rBFR did not have a synergistic effect on increasing muscle strength and muscle size. Additionally, high-intensity isokinetic training with BFR when it may be best not to perform it during exercise, because it induces severe pain and may inhibit increases in muscle strength.

Key words: vascular occlusion, ischemic, blood flow restriction, pain, discomfort

Introduction

Isokinetic training has the advantage of being able to measure muscle strength at any angle of the range of motion and has been used primarily in rehabilitation^{1,2)}. Therefore, isokinetic training can be performed at maximum effort in participants who have difficulty performing high-intensity exercise (e.g., postoperative patients and the elderly),

and can improve muscle strength and muscle size^{3,4)}. However, there are many cases of muscle weakness and persistent pain in the affected area due to muscle atrophy. In such cases, low-intensity exercise was chosen because maximal effort exercise is difficult.

Many recent studies have shown that blood flow restriction training (BFRT) is useful for rehabilitation^{5,6)}. BFRT is highly effective for muscle hyper-

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trophy and increasing muscle strength, even using low-intensity exercises, and useful for many people^{7,8}. BFRT is a simple method in which blood flow is restricted by a cuff attached to a limb. However, BFRT induces severe pain and discomfort during exercise than traditional training without it⁹. This problem negatively impacts participant motivation; thus, better options are needed.

Previous studies, pain during exercise with BFRT was due to excessive pressure caused by muscle contraction and cuff placement^{9,10}. Therefore, an alternative to BFR during exercise (eBFR) is required. The effects of exercise and BFR (e.g., interval rest) on pain during exercise, muscle hypertrophy, and increased muscle strength were recently investigated. The rating of perceived exertion and pain were lower for BFR performed during rest interval between set (rBFR) than those during eBFR, and muscle size and muscle function were comparable to eBFR and rBFR¹¹⁻¹³. High-intensity exercise with eBFR has no training effects¹⁴, but high-intensity exercise with rBFR increases metabolic stress¹⁵. In brief, training with rBFR may increase muscle hypertrophy and function while reducing pain.

Previous study combined rBFR with high-intensity exercise have shown no synergistic effects on increasing muscle strength or muscle size¹². However, the exercise task used leg curls, and the effect of combining rBFR with isokinetic training with maximal effort is unknown. We expected that isokinetic training with maximal effort combining rBFR would be more effective than eBFR and non-BFR at improving muscle hypertrophy and increasing muscle strength. Furthermore, the usefulness of rBFR has only recently been reported, and consensus is lacking about the most effective timing for BFR. This study aimed to determine the effects of high-intensity isokinetic training with rBFR and eBFR on muscle hypertrophy, muscle strength, and exercise pain caused by BFR was suppressed by rBFR.

Materials and Methods

Participants

This study assessed seven healthy men (mean \pm standard deviation [SD]: age, 23.6 \pm 1.0 years; height, 173.5 \pm 5.5 cm; weight, 66.4 \pm 4.7 kg). The exclusion criteria were a history of injury to the upper arm

and habitual training. The participants were instructed not to perform upper-arm training until after the study. The purpose, methods, procedures, risks, and compensation for this study were explained to the participants verbally and in writing, and all participants gave informed consent. The study was conducted in accordance with the guidelines of the Declaration of Helsinki and approved by the Ethics Committee for Human Experiments of Juntendo University, Japan (no. 30-28).

Design

Figure 1 showed an overview of the study design. The participants visited the laboratory 3-5 times for pre-measurement of elbow flexor strength and cross-sectional area (CSA) before the start of training. After the pre-measurement is completed, we conducted the following interventions to each arm (n = 14) subjected to the following interventions: eBFR (n = 4); rBFR (n = 5); and training only (CON; n = 5). The assignment of each condition was determined randomly that not both arms of the same participant would have the same condition. The training involved elbow flexor exercises twice weekly for 8 weeks. Pain during exercise was assessed using the numerical rating scale (NRS). Elbow flexor strength and CSA were measured before and after 8 weeks of training.

Training protocol

Figure 1 showed an overview of the training protocol. The training included elbow flexor exercises using a BIODEX device (BIODEX medical system, Shirley, NY, USA). The participants performed an elbow flexion exercise at 60°/sec under concentric contraction (CC) with a ROM of 120° (full extension = 0°). Training repetitions were performed at maximal effort. Training consisted of four sets with a 3-min rest interval between sets. This rest time was determined from the previous study¹⁶ on training rest time and our preliminary experiment. The standard for the end of each set were defined as until the participant could not achieve >50% of the peak torque of the CC pre-measurement twice consecutive (= one set). This was based on previous study that evaluated muscle fatigue after exercise with BFR training¹⁷. The training was performed twice weekly for 8 weeks.

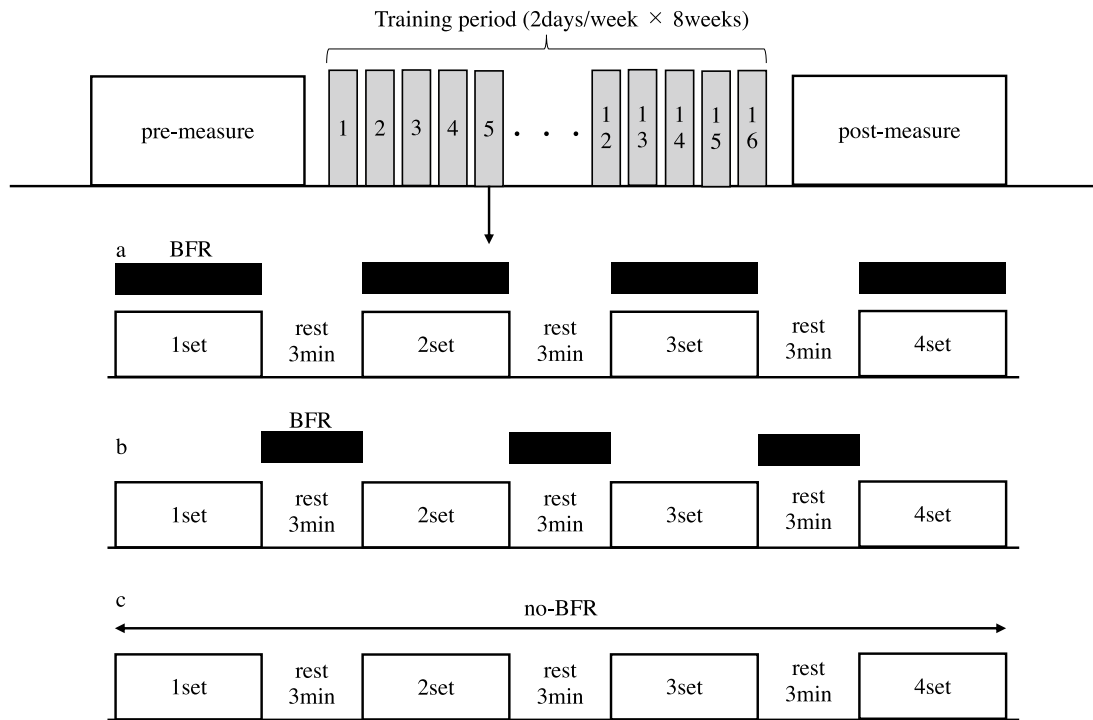


Figure 1 Overview of study design and training protocol. a: blood flow restriction during exercise (eBFR), b: blood flow restriction during rest interval between set (rBFR), c: Training only (CON). The black squares is blood flow restriction (BFR).

Blood flow restriction

BFR was induced on the proximal upper arm using a cuff (width, 77 mm; length, 770 mm; MIZUHO, Tokyo, Japan) at a pressure of 120 mmHg. This pressure volume was 100% of the systolic blood pressure in Japanese individuals determined based on previous study results¹⁸. The rBFR group underwent BFR training at rest, whereas the eBFR group underwent BFR training during exercise.

Muscle strength

Before and after training, changes in elbow flexor strength were measured using CC and isometric contraction (IM) with a BIODEX device. The measurements were performed with the participants in a sitting position with two belts fixed on the shoulder and one on the abdomen. IM contraction measurements were made with the elbow in a 90° flexed position. The participants performed 3-5 reps warm up at sub maximum before the true measurement.

Cross-sectional area

Before and after training, changes in the CSA of the biceps were measured on magnetic resonance

imaging (E-scan XQ; 0.2T, ESAOTE, Genoa, Italy). Measurements were made at 60% distally between the lateral epicondyle and the acromial process using T1-weighted magnetic resonance imaging with the spin-echo method (slice number, 28; slice width, 5 mm). Osirix open software (version 10.0.0; Pixmeo Sàrl, Bernex, Switzerland) was used to calculate muscle CSA. The measurements were performed twice before the training session, and the coefficient of variation was confirmed as being within 2%.

NRS scores

NRS score is a subjective score on an 11-point scale from 0 to 10. This study, subjective pain during exercise were used to assess using the NRS and the degree of arm pain was as follows; (0 = no pain; 1-3 = mild pain; 4-6 = moderate pain; 7-9 = severe pain; and 10 = extreme pain). The NRS scores were evaluated immediately after each set.

Statistical analysis

All data are shown as median (min-max). The analysis of muscle strength and CSA before and after training was performed using the Wilcoxon

signed-rank test (pre-post), while the intergroup analysis was performed using the Kruskal-Wallis test. NRS and exercise repetition results were analyzed using Friedman's test for each set, and the NRS and exercise repetitions of the intergroup analysis were examined using the Kruskal-Wallis test. Effect sizes were calculated from the $[r = Z/\sqrt{N}]$ formula. Effect sizes were rated as follows: <0.1 small, <0.3 medium, <0.50 large. The statistical analyses were performed using SPSS Statistics (version 22.0; IBM, Armonk, NY, USA), and the significance level was set at $p < 0.05$.

Results

Figure 2 shows the changes in CC after training. The peak torque at the CC increased after the intervention in the rBFR (pre: 40.6 N·m [34.3-48.1], post: 44.8 N·m [37.1-74.0]; $p = 0.043$; $r = 0.64$) while a marginally significant increase was noted in the CON (pre: 42.5 N·m [35.7-47.3], post: 45.5 N·m [42.2-62.2]; $p < 0.10$; $r = 0.64$) versus no increase after the intervention in the eBFR (pre: 41.7 N·m [34.0-46.3], post: 40.3 N·m [34.3-47.2]; $r = 0.00$). Figure 3 shows the changes in IM after training. The peak

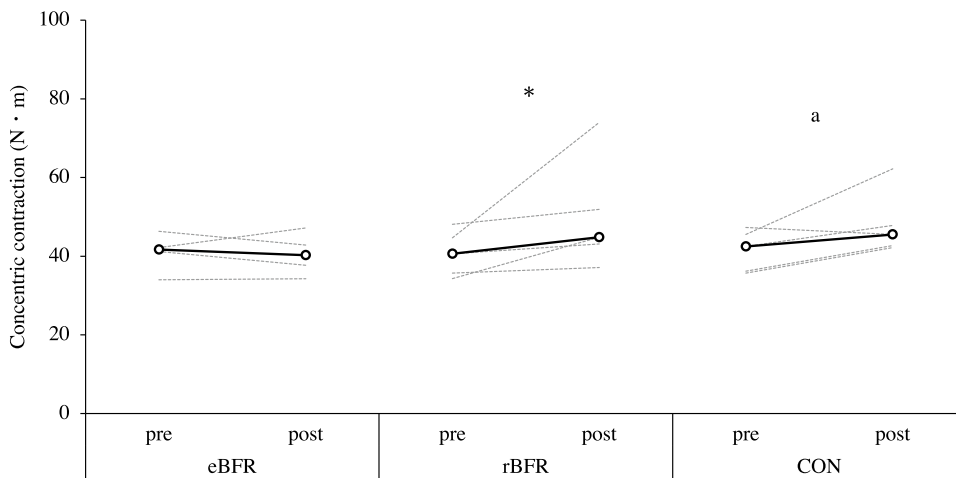


Figure 2 Elbow flexor isometric contraction strength after training to 8 weeks. eBFR: blood flow restriction during exercise, rBFR: blood flow restriction during rest interval between set, CON: training only. Black line shows the median value, and gray line showed the personal values. * = $p < 0.05$, a = $p < 0.10$.

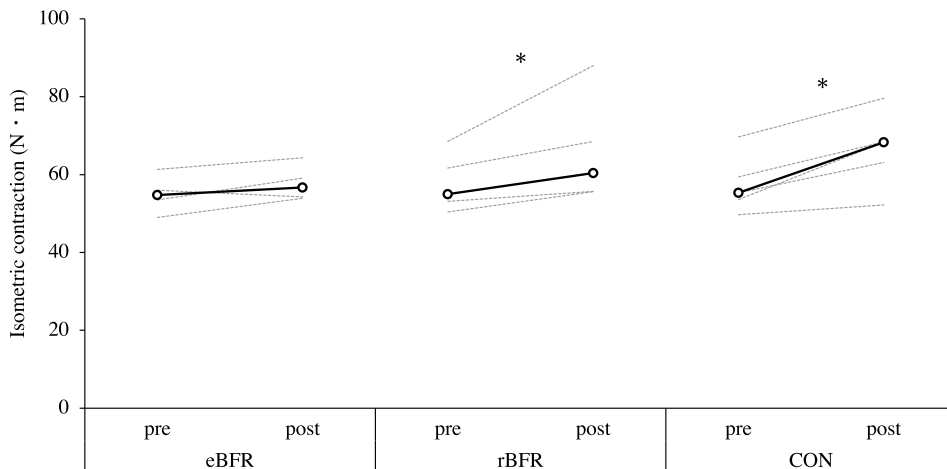


Figure 3 Elbow flexor concentric contraction strength after training to 8 weeks. eBFR: blood flow restriction during exercise, rBFR: blood flow restriction during rest interval between set, CON: training only. Black line shows the median value, and gray line showed the personal values. * = $p < 0.05$.

torque at the IM increased after the intervention in the rBFR (pre: 55.0 N·m [50.4-68.5], post: 60.4 N·m [55.6-88.0]; $p = 0.043$; $r = 0.64$) and CON (pre: 55.3 N·m [49.7-69.7], post: 68.3 N·m [52.2-79.6]; $p = 0.011$; $r = 0.64$) groups but did not increase after the intervention in the eBFR (pre: 54.8 N·m [49.4-64.3], post: 56.7 N·m [53.9-64.3]; $r = 0.52$). Figure 4 shows the changes in CSA after training. The CSA increased after the intervention in the rBFR (pre: 14.2 cm² [12.2-16.1], post: 15.2 cm² [14.1-18.0]; $p = 0.005$; $r = 0.64$) and CON (pre: 13.9 cm² [11.5-14.8], post: 15.6 cm² [12.9-17.0]; $p = 0.002$; $r = 0.64$) but did not increase after the intervention in the eBFR (pre: 14.6 cm² [11.0-17.0], post: 16.2 cm² [12.3-18.3]; $r = 0.65$). All measurement items did not differ significantly among the conditions.

Table 1 shows the changes in exercise repetition, torque, and pain during exercise. The exercise repetitions decreased in three sets for eBFR and CON and in 4 set for rBFR and CON versus 1 set ($p < 0.05$). The exercise repetitions were lower for the eBFR than CON for all sets ($p < 0.05$), while the rBFR was marginally lower in 1 set ($p = 0.67$). The torque during exercise decreased after three sets in the rBFR (vs. 1 set; $p = 0.042$) and CON (vs. 2 set; $p = 0.029$). Also, there were no significant differences between conditions in the total repetitions for all training sessions (eBFR: 1016 rep [779-1233], rBFR: 1130 rep [960-2213], CON: 2014 rep [1233-3326]).

Pain during exercise was not significantly different among the conditions for all sets. However, pain

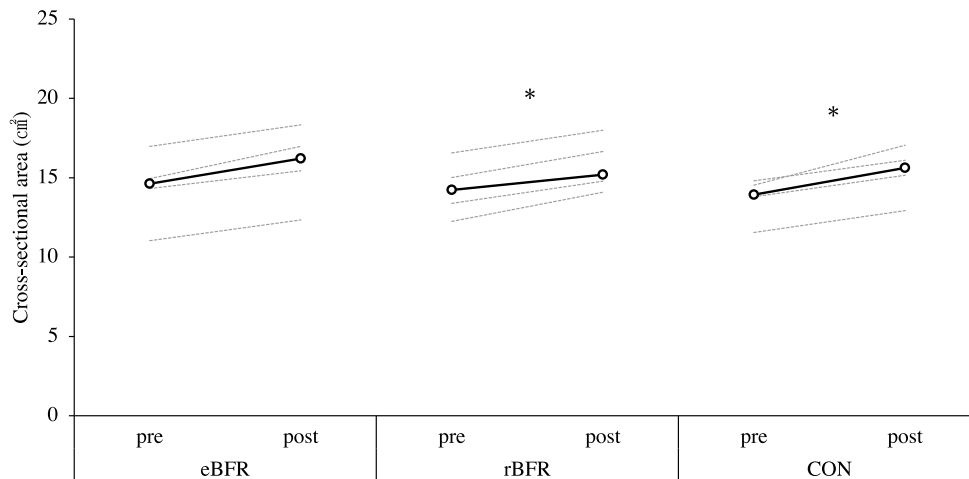


Figure 4 Cross-sectional area of the biceps after training to 8 weeks. eBFR: blood flow restriction during exercise, rBFR: blood flow restriction during rest interval between set, CON: training only. Black line shows the median value, and gray line showed the personal values. * = $p < 0.05$.

Table 1 Exercise repetitions, Torque, pain during exercise

		1set	2set	3set	4set
Repetition	eBFR (n=4)	14 (10-21)	12 (9-18)	11 (9-17)*	11 (9-18)
	rBFR (n=5)	27 (22-61) ^b	19 (12-31)	18 (11-29)	16 (11-26)*
	CON (n=5)	35 (22-63) [#]	30 (20-59) [#]	29 (17-47) ^{**}	30 (17-37) ^{**}
Torque (N·m)	eBFR	31.5 (29.8-33.3)	33.0 (32.8-33.3)	32.6 (31.3-33.0)	31.6 (30.3-32.3)
	rBFR	41.0 (31.0-45.0)	32.8 (25.5-42.0)	31.5 (25.0-39.8)*	30.3 (25.5-44.5)
	CON	39.0 (36.0-41.5)	38.3 (36.3-40.3)	36.5 (33.5-38.5) [†]	37.0 (33.8-40.0)
Pain	eBFR	6.6 (5.3-8.4)	7.4 (5.4-9.0)	7.9 (5.8-8.6)	7.8 (5.7-8.4)
	rBFR	5.6 (3.0-7.0)	5.9 (3.6-6.8)	6.3 (3.9-7.3)	6.5 (4.0-7.9)
	CON	5.4 (3.0-6.8)	5.8 (3.1-6.9)	6.4 (3.1-7.1)	6.7 (3.3-7.1)*

Data were median (min-max). Blood flow restriction during exercise (eBFR), Blood flow restriction during rest interval between set (rBFR), Training only (CON). * = $p < 0.05$ (vs. pre), † = $p < 0.05$ (vs. 2set), b = $p < 0.10$, # = $p < 0.05$ (vs. eBFR).

during exercise was increased for 4 set versus 1 set in the CON group ($p = 0.004$). Table 2 shows the number of respondents in pain intensity at the final training session.

Discussion

The study investigated isokinetic training with maximum effort for 8 weeks in eBFR, rBFR, and CON. These results showed that elbow flexor strength and muscle CSA increased with rBFR and CON. However, there were no statistically significant in elbow flexor strength and muscle CSA between the conditions, and the pain intensity was “severe pain” in eBFR, and “moderate pain” in rBFR and CON between the conditions. Our findings suggest that maximal effort of isokinetic training with eBFR inhibits hypertrophy and increase muscle strength. In contrast, rBFR suggested equally effects for CON, and does not exacerbate pain during exercise.

This study found no significant differences in the increase in muscle strength among the conditions. However, increasing CC was induced in the rBFR and CON, and rBFR may be more effective than eBFR as the effect size was higher in the rBFR (< 0.50 large) and CON (< 0.50 large) than the eBFR (< 0.10 small). In a previous study, training volume was important for muscle hypertrophy¹⁹, and muscle size and neuromuscular activation improved muscle strength²⁰. Therefore, high-intensity isokinetic training with the eBFR does not provide the required training volume or intensity. Muscle strength should decrease with accumulated fatigue, but only eBFR did not decrease. Therefore, we speculated that eBFR did not have a

training effect because it did not provide the required torque or training volume during exercise. Furthermore, a previous study used resistance training, which offered varied results as a result of the different exercise methods. A previous study that combined BIODEx exercises with BFR reported increased muscle strength²¹. However, the participants were athletes and the effect greater, with a relatively high-speed CC of 300°/sec. Consequently, varied results might be attributed to changes in the participants examined as well as the use of a CC of 60°/sec, a slower contraction speed than those in previous studies. Additionally, BFR alone effectively prevented disuse muscular atrophy and muscle weakness^{22,23}. Therefore, rBFR may be even more effective in postoperative patients with muscle atrophy who require muscle function recovery.

Muscle perception did not differ significantly among conditions; however, moderate pain was reported for rBFR and CON, whereas severe pain was reported for eBFR. In addition, table 2 also shows that the number of participants who complained of severe pain was 2 to 3, but only 1-participant each complained of rBFR and CON. This indicates that the pain was not excessive in the rBFR group. In addition, ischemia-reperfusion numbness is caused by stimulation of the sensitization of transient receptor potential ankyrin 1 with active oxygen generated by reperfusion²⁴. Therefore, if there is an effect of ischemia-reperfusion, rBFR is expected to be more painful during exercise. Furthermore, BFR during exercise and rest (continue BFR [cBFR]) reportedly increases pain, in which cases intermittent BFR has been recom-

Table 2 Number of Numerical Rating Scale respondents

		Numerical Rating Scale score										
		0	1	2	3	4	5	6	7	8	9	10
1set	eBFR (n=4)	-	-	-	-	1	1	-	-	-	2	-
	rBFR (n=5)	-	-	-	-	2	-	3	-	-	-	-
	CON (n=5)	-	-	-	1	-	3	-	1	-	-	-
4set	eBFR	-	-	-	-	1	-	-	2	-	-	1
	rBFR	-	-	-	1	-	2	1	-	1	-	-
	CON	-	-	-	-	1	1	2	-	-	-	1

The numbers in the table show the number of respondents, and this data were the final training session. eBFR: Blood flow restriction during exercise, rBFR: Blood flow restriction during rest interval between set, CON: training only. Scale were follows: 0; no pain, 1-3; mild pain, 4-6; moderate pain, 7-9; severe pain, 10; extreme pain.

mended²⁵). However, previous studies of rBFR versus cBFR (345 sec/session) with rBFR (30 sec/session)¹¹). However, this study considered that BFR did not induce excessive pain because it was performed for a short time of 60–180 sec/session. In addition, blood flow is inhibited by intramuscular pressure, even at a low muscle contraction of 20–30% of one repetition maximum²⁶), and the perception of pressure pain is influenced by the external stimulus intensity and stimulation area^{27,28}). Based on these results, muscle contraction and cuff pressure overlapped, thereby contributing to the increased pain. Accordingly, the method of separating exercise from BFR is expected to effectively improve pain.

The present study has some limitations. First, the BFR pressure used was 120 mmHg, and different BFR pressures may have produced different results. Previous studies reported that the training effects of BFR are equal regardless of the use of high or low pressure^{29,30}), however, these results are for eBFR. In the future, the effect of different volumes of pressure on rBFR should be examined. Second, the training in this experiment involved isokinetic resistance training using a BIODEX device, and each repetition was performed at the maximum output, representing high-intensity training. In previous study, BFR was not useful in high-intensity training¹⁴). However, studies of athletes indicated that BFR is more effective, particularly during intense training^{21,31}). Furthermore, there are several components of the training impact, and the current study focused on the influence on muscular hypertrophy and strength. Future studies of rBFR that evaluate items and training intensities may be useful. Third, this was a pilot study with a small number of participants. Future studies with larger groups of people are needed to determine the usefulness of rBFR. However, few studies have investigated the long-term interventions for rBFR. In particular, this is the first study to examine it in isokinetic training. We believe that these results will inform future studies of the usefulness of rBFR.

In conclusion, this study's showed that high-intensity isokinetic training with rBFR did not have a synergistic effect on increasing muscle strength and muscle size. Additionally, high-intensity isokinetic training combined with BFR when it may be best not to perform it during exercise, because it induces severe pain and may inhibit

increases in muscle strength.

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Author contributions

TT, AK and HO conceived of and designed the study. TT conducted the experiments and drafted the manuscript. AK, HO, HN, SN, and YT revised the manuscript and contributed to the data interpretation. All authors approved the version to be published.

Conflicts of interest statement

The authors have no competing interests to declare that are relevant to the content of this article and did not receive support from any organization for the submitted work.

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Environmental Factors Influencing Help-seeking Behavior Among Japanese Adolescents

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Objectives: Previous studies have demonstrated that adolescents do not tend to actively engage in help-seeking behaviors. Therefore, it is imperative to create an environment where adolescents can seek assistance on their own. However, no concrete method to create such environments has been established.

Design: We studied adolescents' help-seeking behaviors by administering a questionnaire that collected information on who offer help ("helpers"), how help is offered ("methods of help"), and where these interactions occur ("places of help").

Methods: We asked college students to recall their thoughts related to seeking help when they were 10-15 years old.

Results: Our results indicated that adolescents require trustworthy helpers who respect and understand them, face-to-face interactions, peer helpers of a similar age, mental health dialog, and safe and secure location outside of school for seeking help.

Conclusions: This study suggested a method to provide assistance in the field of child mental health, which is crucial for the development of the adolescents' ability to seek help and resolve mental health problems on their own.

Key words: help-seeking, adolescent, mental health, original questionnaire survey

Introduction

Adolescents do not tend to actively engage in help-seeking behaviors¹⁾. A study on middle and high school students reported that 38% of students did not seek help from others even when they were troubled²⁾. Another study on junior high school students revealed that >50% of students did not seek assistance in cases of trouble; moreover, it indicated that help-seeking behaviors varied depending on the type of concern, with >90% of students seeking assistance for some concerns³⁾. A 2019 survey⁴⁾ conducted by the Japan Cabinet Office reported that >40% of participants aged 15-29 years answered "somewhat disagree" or "disagree" to the question "Is there someone in your family you can talk to about any problems?"

Numerous studies have identified factors that discourage help-seeking behaviors. For instance, a

literature review identified four factors: (1) demographic factors, such as sex, age, education, and income; (2) network variables, such as social support; (3) personality variables, such as self-esteem and self-disclosure; and (4) severity of the problem and symptoms caused by the problem⁵⁾. Another study identified (1) sex-based differences, (2) availability and number of helpers, (3) mental health status, and (4) professional involvement⁶⁾ as factors that influenced adolescents' help-seeking behaviors.

Other studies have examined the decision-making process of seeking help⁷⁻⁹⁾. To seek help, an individual must pass through various stages, including "awareness of the problem," "recognition of the need for assistance from others," and "decision-making for requesting assistance." Instead of identifying psychological factors that prevent individuals from seeking help, some studies focused on

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educating individuals on how to request help, including how to communicate extreme distress (i.e., “SOS”)¹⁰ and gain literacy education^{11,12}. All these approaches focused on adolescents.

Some studies have identified helper-specific (i.e., those who help) factors that affect help-seeking behaviors of individuals. Helpers should have the skills to address adolescents’ wide spectrum of needs by offering new or expanded services and collaborating with other service providers if necessary. Researchers have discovered that many adolescents lack trustworthy and reliable confidants even when they are willing to interact with an adult close to them. These responses reflected a shortage of comfortable help-seeking environments for adolescents. Other factors such as the availability of physical facilities and equipment were also identified as influencing factors. Researchers have recommended training the staff to tend to various needs of the youth, offer new or expanded services, and establish appropriate collaborations with other service providers¹³. Many adolescents felt that attitudes of the staff affected their access to social support. Other adolescents reported feeling unwelcomed in such spaces¹³. Furthermore, a lack of staff who can empathize with adolescents, are sensitive to their needs and realities, and know how to listen and talk to them hinders the usage of existing healthcare services by adolescents¹⁴.

These studies suggest that solely approaching adolescents and offering help do not necessarily create a desire to seek help. Therefore, it is crucial to create comfortable environments for adolescents to ask for help. Although the need for such spaces has been identified, specific measures necessary for creating such spaces have not been established. To counteract this issue, three environmental factors must be considered: helpers, methods of helping, and places of helping. Each factor must meet the specific conditions desired by adolescents, and these conditions should be urgently identified.

This study aimed to clarify the conditions required to encourage adolescents to seek help. To accomplish this, we administered a questionnaire to college students that focused on helpers’ attitudes, methods of helping (e.g., remote or face-to-face), and places where an adolescent is more likely to seek help. College students enrolled in this study were asked to recall their experiences when they were 10–15

years old and describe their current conception regarding this.

Materials and Methods

Participants

The principal investigator conducted this study in June 2021. The study participants were second- and third-year university students enrolled in the B and C Faculties of the University of A. No exclusion criteria were applied. All participants were explained the purpose, method, and ethical implication of this study, and receiving a duly filled questionnaire from participants was considered their consent to participate in the study.

Questionnaire

The questionnaire used in this study enquired the views of the participants at the time of the survey by asking them to recall their feelings regarding help-seeking behavior when they were 10–15 years old. The questionnaire comprised questions about the following items: 1. gender, 2. experience of seeking help, 3. potential helpers, 4. ideal helpers, 5. ideal counseling place, 6. counseling methods (face-to-face and online), 7. peer support, and 8. support they wish they had received. Responses were given in a yes-or-no response format and free-text answers. For the yes-or-no type questions, respondents were asked to provide reasons for their answers in the form of open-ended questions. Since this was a self-administered questionnaire, a preliminary survey was conducted to ensure that respondents understood the questions as intended in the questionnaire design. Multiple open-ended items were added to gain a more specific understanding of what adolescents sought for when they wanted help.

There were three main reasons for selecting university students as the research subjects: they can objectively verbalize their feelings, they are considered to have relatively vivid memories of the time when they were 10–15 years old, and they can decide whether to participate in the research of their own volition.

The survey responses were recorded using a combination of written and Google forms.

Statistical analysis

The responses to the selected items and reasons

for the responses were tabulated, and responses to the open-ended questions were classified and categorized by question item per the KJ method¹⁵⁾. The specific procedures used in the KJ method are described below. (1) Label creation: For the data obtained from free descriptions, a response with one sentence was entered on a card as one item. For responses with multiple sentences, the sentences were separated to ensure the intended meaning was retained, and each sentence was entered on a single card. (2) Cards that were qualitatively similar were grouped together. Each group was given a name that could be expressed in simple words. (3) Group formation (large category): The groups created in (2) were further grouped together with other related groups to form a large group. Each group was given a new name that succinctly expressed the image of the group. In this process, all inappropriate responses were excluded.

Ethical considerations

The purpose and content of the study were verbally explained to the participants, and they were informed that participation in the study was voluntary and that questionnaire responses were anonymized. Questionnaire completion was regarded as consent for study participation. This study was conducted after obtaining approval from the Research Ethics Committee of the Juntendo University Graduate School of Health and Sports Sciences

(2021-14).

Results

Participant

This study included 211 university students (58 men and 153 women).

Helper characteristics

The labels were grouped into 7 major categories: “a person who listens to me,” “a person who respects me,” “a person I trust,” “a person who offers me affirmation,” “a person who helps me sort out my feelings,” “a person who understands me,” and “a person who can keep a secret” (Table 1).

For the category of “a person who listens to me,” the responses were “till the end,” “without interrupting,” “just listens,” “carefully,” and “properly,” which indicated the individual’s willingness to listen to the client.

For the category of “a person who respects me,” available responses reflected a sincere attitude toward the client (e.g., “kind,” “serious,” and “not mocking”), predisposition to consider the client’s viewpoint (e.g., “being an ally” or “being there for me”), and tolerance (e.g., “not judging” and “looking out for me”).

For the category of “a person I trust,” we noted expressions such as “someone you can trust” or “relax one’s guard (around).” These responses indicate the potential for building a trustworthy rela-

Table 1 Conditions of the person you wish to consult (help-giver)

Broad category	Medium category	Labels (Typical/excerpt)
A person with listens to me	listen to me	to the end, without interrupting, just (listen), carefully, properly
	sincere attitude	kind, serious, not mocking
A person with respects the me	a predisposition to take the client point of view	being an ally, being there for me, looking out for me, they worry about me
	open-mindedness	not judging, do not impose values
A person with relationship of trust	someone you can trust	we can trust each other, credible, be reliable
	relax one’s guard (around)	expose yourself, I can tell you anything
A person with affirm the me	not to deny	not to deny, affirmation
	to accept what I have to say	to accept what I have to say, empathy
A person with help me sort out my feeling	someone to think with me	someone to think with me, they think of me
	objective advice	advice after listening to you, they say all my good and bad points right
A person with who understands me	accepts me	accepts me, they recognize me
	understands me	he understands how i feel. they understand me
A person with can keep secre	be able to maintain a secret	tight-lipped, I will keep it to myself. I do not tell other people

tionship.

For the category of “a person who offers me affirmation,” the desired attitude was “not to deny” and “to accept what I have to say.” In other words, this indicated the acceptance of the client’s perspective.

For the category of “a person who helps me sort out my feelings,” the respondents desired for “someone to think with me” and “provide objective advice,” considering their position as a third party consultant.

For the category of “a person who understands me,” the respondents expressed a desire for someone who “accepts,” “understands,” or “grasps” the request for help. The respondents also desired someone who would try to understand them, rather than just focus on what they discussed.

Characteristics of places of help

The respondents classified places where they could seek help into two broad categories: “assurance of safety” (e.g., assurances of confidentiality and no “leaks”) and “assurance of security” (e.g., environment for one-on-one consultations where individuals can calmly confide in each other) (Table 2).

Upon being asked “do you think it would be good if there were places outside of school where students could feel free to seek advice or have a place to stay after school?,” 204 respondents (96.7%) answered “yes,” whereas 7 (3.3%) answered “no.” Most respondents confirmed (responded “yes”) the existence of a place outside of school where they could seek advice. The respondents who answered “yes” were asked to further classify their responses into four major categories: “Having a place to stay makes me feel safe,” “Nonschool locations are better locations for talking,” “More people and opportunities to talk,” and “Expanded relationships and sense of values.”

Most respondents believed that university students should volunteer in schools to build relationships with students, with 169 (80.1%) responding “yes.” The reasons for responding “yes” included “Close in age and easy to discuss,” “Easy to talk to as a third party,” “Important to be able to discuss,” “Can talk about own experiences,” and “Was meaningful to me.” We did not obtain sufficient negative responses for further analysis.

Characteristics of methods of help

Ease of consultation: Upon being asked “Which is easier: seeking help using a smartphone or tablet (i.e., internet or remote consultation) or through face-to-face communication?,” 82 (38.9%) participants responded “internet consultation” and 120 (56.9%) responded “face-to-face communication.” Thus, direct communication was preferred over indirect communication as a method of consultation.

Expectations for resolution: Upon being asked “Do you think it is easier to solve a problem through online or face-to-face consulting?,” 22 respondents (10.4%) answered “online,” whereas 172 (81.5%) answered “face-to-face.” One major category was obtained for why a respondent believed “internet consultation” was more likely to solve a problem: (It is) easy to say.

Other respondents believed that solving problems “face-to-face” was easier because this method made it “easier to convey feelings and facial expressions,” “easier to feel safe and talk to others,” and “easier to read others’ facial expressions.” Thus, they preferred face-to-face communication.

Desired supports: The following open-ended question was asked: “What kind of support would you have liked to have received?” The answers to this question were categorized under the broad category of “an environment which made it easier to ask for help.” Looking at the middle categories and labels, the results for “attitude of the helper,” such

Table 2 Conditions of the place you want to consult

Broad category	Medium category	Labels (Typical/excerpt)
Assurance of safety	Other people will not know that you are consulting	be able to maintain a secret, no information leakage, content is not leaked,
	The content of the consultation will not be leaked	no one else can hear you, nobody is here, no one will see it, no one else will know, one by one
Assurance of Security	One-on-one consultation	one-to-one, peace of mind
	Calmly confide in each other	everyone can enter without discrimination, quiet and relaxing

as “listening,” were similar to those for “characteristics of the helper,” as described above. In the “mental care” category, “cognitive-behavioral therapy-type involvement” was preferred, such as “changing the way they think” and “how to deal with problems.” The respondents also desired “meeting with everyone,” “one-on-one,” and “regular meetings,” among other forms of involvement that valued each individual (Table 3).

Discussion

This study aimed to clarify factors related to helpers, methods of helping, and places of help to promote help-seeking behavior among adolescents. The original questionnaire used in this study included questions about helpers’ attitudes, preferred mode of seeking help (remote or face-to-face setting), and the type of needed help. This study included college students who were asked to recall their own help-seeking experiences when they were 10–15 years old and describe their current thoughts regarding the same.

Previous studies¹⁶⁻¹⁸⁾ have revealed that “Confidentiality is guaranteed by helpers,” “I am treated with respect by helpers,” “I talk to helpers I trust,” “I talk to helpers who have had the same experience,” “I have helpers who listen to me when I ask for help,” “I have helpers who accept me,” and “I have helpers who respect me” promoted help-seeking behaviors in adolescents. This finding is generally consistent with the current study findings regarding the desired characteristics of helpers. These findings suggest that these seven factors also promote help-seeking behaviors in Japanese adolescents, thus strengthening the validity of the research methods used in this study.

The current and previous studies¹⁹⁾ have indicated that “trust” plays a particularly important role in the helper-help recipient relationship. “Trust” in this context implies that when the recipient requests assistance, the helper will understand the problem they are facing, provide useful assistance, and maintain the confidentiality of the consultation. This finding is also consistent with the seven aforementioned factors. Furthermore, the responses to the open-ended questions provided insight into what these participants wanted from helpers, and it was found that they did not want helpers to solve their problems but rather to have positive acceptance of them and understand to their feelings of pain, anger, and anxiety.

Objective advice was also assessed. This did not include preachy imposition of adult values, such as “this is the way to do it.” Instead, it included helping recipients seeking advice from people who accepted them and experienced similar feelings themselves. Ideally, helpers shared their experiences and accurately conveyed the points that were good or should be changed to ensure the best possible outcome. Thus, a mechanism is needed that encourages helpers and help recipients to think together.

Most respondents preferred face-to-face interactions and believed that these were more likely to provide actual solutions as it is “easy to convey feelings and facial expressions,” “reassuring and easy to talk to,” and “easy to read the other person’s facial expression.” Despite these advantages, many respondents reported that remote or internet-based consultations would be “easy.”

Our results demonstrated the effectiveness of peer support received from university students (support from close helpers who have similar prob-

Table 3 Desired support

Broad category	Medium category	Labels (Typical/excerpt)
An environment where you want to consult	Prepare the attitude of the person you are helping	listen to me, sincere attitude
	Peer supporter	listening to experiences, consulting with older adults close to your age, adult opinions, broad perspective
	Value each individual	noticing changes, talking to them, regular interviews, one-on-one meetings,
	Mental health care	dealing with stress, knowing how to change your thinking, correcting cognitive distortions, accepting emotions, accepting hard times, and recovering from them, consultation with specialists, cognitive-behavioral therapy involvement

lems or have experienced similar problems in the past) was high due to the following factors: “easy to talk to because of their close age,” “easy to talk to as a third party,” “important to be able to ask for help,” and “able to talk about their own experiences.”

When we asked what kind of support respondents wished they had received, they mentioned the following factors: “mental health care,” “creating an environment in which it was easy to ask for help,” “regular meetings,” “one-on-one meetings,” and “improving the attitude of those providing assistance.”

Before the survey began, we predicted that most respondents would prefer remote or phone- or internet-based consultations, because these technologies are commonly used by the current youth population; however, the actual responses indicated that face-to-face consultations were preferred by them. Most respondents also believed that “face-to-face meetings were more likely to provide solutions.” Therefore, many young individuals feel that their problems can only be truly understood in a face-to-face setting. In other studies^{20, 21}, young individuals expressed awareness of the risks of online help, including privacy concerns. Additionally, some individuals expressed concern over the impersonal nature of telecommunication tools, and some believed that the help they received in such settings is unreliable or untrustworthy. This concern may have contributed to our results regarding the places of help.

Furthermore, “regular meetings” and “one-on-one meetings” were desired by respondents in our study; however, prior research²² has shown that the presence of a caring adult is important. Thus, we believe that it is necessary to watch over each individual, regardless of whether they have problems. Care should be taken to monitor their growth and efforts and recognize and respect them.

Moreover, we observed a desire for “mental health care” among youth. Importantly, this was not a request for knowledge regarding mental health but for dialog using methods such as cognitive-behavioral therapy to correct cognitive distortions (which have a therapeutic aspect) and stress management. The respondents expected that these activities will lead to self-reflection, changed perspectives, and psychoemotional growth with a broader perspective and healthier mindset. Social skills training,

assertion training, and stress management are forms of mental health care that have been introduced in school settings and reported to be effective²³. However, rather than teaching “the correct way” to do something, helpers should incorporate these methods into their counseling and dialog with young individuals. This approach allows young individuals to directly experience the benefits of help-seeking.

Regarding places of help, most respondents sought “assurance of safety” and “assurance of security.” Approximately all respondents (96.7%) requested a nonschool location for the following reasons: “having a place to stay makes me feel safe,” “it is easier to talk outside of school,” “more people and opportunities to talk to,” “more people to talk to,” and “more human relationships and values.” Maximizing the abovementioned factors may help promote help-seeking behaviors. Prior research²⁴ has indicated lack of trust to be a major barrier to seeking help, in addition to concerns about confidentiality and trust²⁵, which may be related to stigma. The fear of broken confidentiality is rooted in the fear of stigma and embarrassment when peers or family members discover that a young person has sought help for a mental health problem. Thus, we believe that creating “consultation places outside of school where safety and security are guaranteed” is necessary for adolescents. Importantly, such spaces should be staffed by trusted helpers.

This study suggested a method to provide assistance in the field of child mental health, which is crucial for the development of the adolescents’ ability to express SOS and resolve mental health problems on their own.

Limitations of the study

In this study, college students were asked to reflect on their experiences at ages 10–15 years; thus, the study results are subject to recall bias from a convenience sample of college students. Future studies should focus on directly studying adolescents’ responses following the implementation of appropriate processes for parental or caregiver consent.

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Author contributions

EI contributed to drafting, planning, data collection, analysis, and manuscript writing.

Conflicts of interest statement

The author declares that there are no conflicts of interest.

Availability of data and materials

The data supporting the findings of this study are available from the corresponding author EI upon reasonable request.

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Hepato-Biliary-Pancreatic Surgery

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General Thoracic Surgery

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Neurosurgery

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Aims and Scope

Juntendo Medical Journal (JMJ) is the official peer-reviewed journal of the Juntendo Medical Society. JMJ aims to introduce achievements in the fields of basic and clinical medicine, sportology (a novel scientific field integrating sports and medicine), nursing, preventive medicine, and public health. JMJ is dedicated to the international exchange of knowledge to understand, treat and control diseases. The journal provides a platform for researchers to introduce, discuss and exchange novel achievements in biomedical science. JMJ invites original articles, review articles, case reports and other articles containing new insights into any aspect of biomedical sciences and health sciences that are not published or being considered for publication elsewhere. The journal, which is freely available online at J-STAGE (<https://www.jstage.jst.go.jp/browse/jmj>), publishes articles continuously online and collates them into issues six times per year.

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General:

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- Have the authors cited the data described in the manuscript adequately?
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3. Methods (or "Interventions")
4. Results
5. Conclusions

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Acknowledgments

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- 1) You WC, Blot WJ, Li JY, et al: Precancerous gastric lesions in a population at high risk of stomach cancer. *Cancer Res*, 1993; 53: 1317- 1321.

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- 2) Matsumoto A, Arai Y: Hypothalamus. In: Matsumoto A, Ishii S, eds. *Atlas of Endocrine Organs*. Berlin: Springer-Verlag, 1992: 25-38.

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Call for feature article proposals

To introduce the latest medical findings, Juntendo Medical Journal features a specific focus area for each issue. We would like to request all our readers to address any suggestions or proposals for suitable focus areas to our editorial office.

編集後記

先月、久しぶりに海外の学会にオンラインで参加しました。4年に一度開催されるアジア・オセアニア生理学会（FAOPS2023、韓国大邱にて開催）です。運動生理学に関するセッションのなかで、かなり衝撃的な報告がありました。“運動中は心臓迷走神経の活動が亢進する”という発表でした。古くから、「運動開始に伴い副交感神経活動は低下し、交感神経活動は亢進する。これにより心拍数が増加する。」といわれており、勿論今でも教科書にそう記載されています。交感神経とは異なり、技術的に電極法による副交感神経活動の直接記録は困難で、運動中のデータを記録した例は（私が知る限り）ありませんでした。副交感神経心臓枝の活動増加は冠状動脈を拡張させる働きがあり、運動中の心筋血流量の維持に重要であると考察されております。羊で得られたデータではありますが、これまでの常識を覆す、画期的な報告でした。運動生理学の分野においては、他にもここ数年の間で、大きく覆った定説があります。乳酸=疲労物質説です。解糖系により産生された乳酸は筋細胞内で乳酸イオン（ lactate^- ）+水素イオン（ H^+ ）となるため、 H^+ の蓄積（pHの低下）により筋疲労が起こります。しかし、乳酸イオン自体は心臓や骨格筋の逞筋線維内でエネルギー基質として利用されております。また最近では、 H^+ の蓄積が主な疲労要因ではなく、ATPやクレアチンリン酸の分解によってできる無機リン酸や筋細胞外 K^+ の蓄積などが、筋疲労の主役である可能性も報告されております。つまり、乳酸=疲労物質・老廃物とはなりません。いうまでもなく、最先端の技術を駆使して新規分子を発見したり、新しい機序を発見したりするのが、生命科学研究の主流ですが、実験手法がいささか古くても、常識や定説を覆すような研究成果はより大きなインパクトをもたらします。私がかかなり昔に取得した実験データの中には、（当時の）仮説と異なっていたり、解釈が困難であったりしてお蔵入りしてしまったものがあります。いつの日か過去のデータをじっくり見直してみたいと思います。破棄寸前のフロッピーディスクやMOディスクからお宝データが見つかるかもしれません。もし見つければ、論文としてまとめて本雑誌へ投稿したいと思います。

和氣 秀文
大学院スポーツ健康科学研究科

イラスト作者より

毎年11月になると、浅草橋の久月という江戸時代からの人形専門店に行き、来年の干支の人形を買ってきます。2024年は辰年ですので、こんな龍の置き物を買ってきました。年賀状のモチーフにしたり教室で描いたりします。（宮道明子）

順天堂醫事雑誌の記事については既に明治8年の創刊号から電子化されており、J-STAGE（科学技術情報発信・流通総合システム）の電子ジャーナル公開システムにおいて閲覧することができます。順天堂医学会のホームページからもご覧いただけますので、ご活用頂ければ幸いです（<https://www.juntendo.ac.jp/journal/>）。

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順天堂大学における私の歩み

大 熊 泰 之^{1,2)}¹⁾順天堂大学医学部神経学講座 (静岡病院)²⁾順天堂大学保健看護学部

この度2023年3月末日に定年を迎えるにあたり、小川秀興理事長、新井一学長、木南英紀学長特別補佐、服部信孝医学部長をはじめ、これまでご指導いただいた先生方に心より感謝申し上げます。私は1976年に順天堂大学に入学し、寮生活や硬式野球部の活動を通して順天堂スピリットを磨きました。1982年に卒業し、直ちに榎林博太郎教授の主宰する神経学教室(脳神経内科)に入局いたしました。研究では神経生理グループに所属しました。1989年に水野美邦教授が着任され、米国式診療・教育を徹底的に叩き込まれ、病棟医長も任されました。1992年から1994年までカナダのカルガリー大学に留学する機会をいただき、ヒトの脊髄反射(H反射)の研究を行い、これが後に学位論文となりました。家族でカナディアンロッキーにスキーに出かけるなど留学生生活をエンジョイしました。帰国後は水野教授のもとで医局長を務め、2000年からは伊豆長岡病院(現静岡病院)脳神経内科に赴任し、若手医師に論文作成指導を積極的に行いました。服部信孝教授の推薦により、2008年に「医学部同窓会学術奨励賞」を受賞、2009年には教授に昇任いたしました。また順大脳神経内科といえばパーキンソン病(PD)といわれるように、PDの臨床研究や神経難病診療に尽力いたしました。国際PD運動障害学会の役員を服部信孝教授と4年間務めたことも貴重な経験でした。2017年4月からは三島キャンパス保健看護学部の学部長に就任しました。看護学生の教育に情熱を注ぎ、ベストプロフェッサー賞に2度選出されました。看護師国試100%合格も達成し、学部のレベルアップに多少なりとも貢献できたと思います。また箱根駅伝の応援隊に加わり、大手町と芦ノ湖で両看護学部生と一緒に演奏(トランペット)し、感動を分かち合いました。私は順天堂大学に入学、奉職したおかげでこのように充実した順天堂ライフを歩むことができ、お世話になった全ての方々に心より感謝しております。

キーワード：脳神経内科医、神経生理学、パーキンソン病、教育、Faculty development



外科医が基礎研究に携わって －留学を機に－

伊 藤 智 彰

順天堂静岡病院外科, 順天堂大学医学部上部消化管外科学講座

私(筆者)は、2023年5月に第45回順天堂大学医学部同窓会学術奨励賞を受賞し、多くの関係した方々に感謝いたします。私は、2000年に順天堂大学卒業後、上部消化管外科の鶴丸昌彦教授の元で修練し、2009年に佐藤浩一教授率いる順天堂静岡病院の外科に配属された。その頃から病理腫瘍学の樋野興夫教授のもとで臨床の傍らであったが基礎研究を行うという新たな挑戦を始めました。日本人の死因の第3位を占める胃がんに焦点を当てて研究を行った。樋野教授の見出したERC/mesothelinと胃癌の関係を研究し、6種類の胃癌細胞株のうち5種でPCRとフローサイトメトリーでERCの発現を認め、その細胞株の上清中にもN-ERCを認め、ERC/mesothelinがタンパク分解酵素で分解されたN-ERC/mesothelin分泌していることを証明し、胃癌バイオマーカーとしての可能性を見いだした。この研究により2014年に医学博士を取得することに成功した。

これらの基礎研究の経験がきっかけで、2016年より2019年の3年間、米国のJohns Hopkins UniversityのMalcolm Brock教授、Kathleen Gabrielson先生の元にポスドクとして研究留学をした。そこでは、災害やストレスと癌に関する研究をすることとなり、妊娠中に地震が起きた場合の胎児期環境と生後成人期発症癌との関連についての解明を動物実験で行った。我々は、肺腫瘍発症モデルであるA/Jマウスを用いて、妊娠中期に5日間母体拘束ストレスを行い、生後ニトロソアミンを投与した後に27週齢でコントロールと比較した。胎児期ストレス群の肺腫瘍がマウス成熟期で増加していることを証明した。さらには、胎児期ストレスにより、動脈硬化が多く発症することも証明できた。

2019年に順天堂大学医学部附属静岡病院で臨床に復帰した後は、実験や研究を通して臨床の課題に取り組むことに興味を持つようになった。現在は、科研費や静岡災害医療研究センターとの連携によりいろいろな研究に取り組んでいる。今後の展望は、臨床の中での疑問や課題を基礎実験、動物実験などで一つでも多く解明し、後輩たちへ還元していきたい。

キーワード：ERC/mesothelin, 脂肪酸合成酵素, 胃癌, 胎児期ストレス, 肺腫瘍



播種性血管内凝固の診断基準

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敗血症性血管内凝固 (DIC) は種々の疾患に合併してみられる, 頻度が高く, かつ重症度の高い疾患である. これまでに複数の診断基準が公開されており, 国際血栓止血学会 (ISTH) 基準, 日本血栓止血学会基準, 急性期 DIC 診断基準などが知られている. いずれの診断基準においても長所と欠点があり, 臨床で使用する際に混乱を招いている. すなわち, 診断の特異度を上げるためには診断項目を増やし, 複雑な基準を作ることになるが, 臨床的にはより簡便な基準が求められている. 実用的な診断基準を作成する試みとして, ISTH は敗血症に合併する DIC に限定した診断基準を提唱し, sepsis-induced coagulopathy (SIC) 基準として発表している. このように基礎疾患別に簡便な診断基準を作る試みが, 他の疾患においても有用かもしれない.

キーワード: 播種性血管内凝固, 凝固異常症, 診断基準, 敗血症, 抗凝固療法

順天堂医学会短期海外留学時助成金給付制度

順天堂医学会では短期海外留学時助成金給付制度を開始いたしました。

1. 要件

下記すべての要件を満たす者

- (1) 順天堂大学（大学院を含む）の学生で1か月以上12か月未満の海外留学をする者
- (2) 留学先の研究機関または財団などからの援助がない者
- (3) 医学会の正会員として1年以上の経歴を有し、医学会費を完納している者

2. 申請書類

- (1) 順天堂医学会短期海外留学時助成金申込書
- (2) 所属長の推薦書
- (3) 申請者の主な研究テーマ・研究業績
- (4) 留学受け入れ機関の指導者からの推薦状

3. 助成金の給付金額

留学期間	助成金額
1か月以上4か月未満	10万円
4か月以上7か月未満	20万円
7か月以上12か月未満	30万円

4. 申請スケジュール（年2回）

申請期限	助成決定時期
6月末	8月
12月末	2月

5. 選考機関：順天堂医学会短期海外留学時助成金選考委員会

6. 助成後の義務

- (1) 帰国後直近の順天堂医学会学術集会において研究成果の発表および、その内容を「順天堂醫事雑誌」に報告する。
- (2) 帰国後は、順天堂大学またはその関連機関に原則として3年以上勤務する。

7. 本件の照会先

HP：https://www.juntendo.ac.jp/journal/membership/benefit_plan.html

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以上

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