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順天堂醫事雜誌

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(951st issue)

JUNTENDO MEDICAL JOURNAL

順天堂醫事雑誌

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* (順天堂醫事研究會報告) 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 intension, 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* (順天堂醫事研究會報告) 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會の雑誌『報告』（計39集）が発行されている．

その後『順天堂醫事研究會報告』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會の雑誌『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.
小川秀興：順天堂醫事雑誌　2013；59：6-10.

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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.

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The Juntendo Medical Society

From the illustrator: This summer is extremely hot. It's still July. So I'm worried about whether I'll survive this summer. Nevertheless, the summer reminds me of sunflowers, and I purchased blue delphinium flowers to match the yellow petals of sunflowers, seeking a short period of coolness.

Perspectives

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Visualization of Vulnerable Coronary Plaque and Prevention of Plaque Rupture

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In daily clinical practice, assessing anatomical findings and the presence or absence of ischemia is pivotal for determining the need for percutaneous coronary intervention. However, concurrently, comprehending vulnerability can greatly assist in predicting future cardiovascular events and formulating preventive strategies for individual patients. This review aims to describe the vulnerability of coronary artery plaques, primarily focusing on vulnerable plaques through pathological, morphological, and physiological viewpoints. Our review emphasizes the usefulness of coronary imaging modalities for the diagnosis of vulnerable plaques and the assessment of their rupture risk, as well as the possibility of percutaneous coronary intervention as a management strategy for plaque stabilization. Our findings show that there have been sporadic accounts of the potential of preventing cardiovascular events through early invasive treatments in patients with moderate or greater ischemia and utilizing new-generation stents to seal lipid core plaques. Thus, it is anticipated that direct intervention targeting coronary plaques, coupled with strict low-density lipoprotein-cholesterol lowering therapy, can play a vital role in suppressing future cardiovascular events and archiving zero perioperative myocardial infarction.

Key words: vulnerable plaques, plaque rupture, near-infrared spectroscopy, intravascular ultrasound, plaque sealing

Definition of vulnerable plaque

Vulnerable plaque refers to a vulnerable atheroma that has a risk of inducing cardiovascular events such as sudden cardiac death and acute coronary syndrome associated with thrombus formation. According to autopsy reports of sudden cardiac death and acute myocardial infarction, three main pathologies in coronary atherosclerotic plaque cause coronary thrombosis. "Plaque rupture" is the most frequent, accounting for 60–75%, followed by "plaque erosion" at 25–40%, and "calcified nodule" at approximately 5%[1–5]. In a recent study that performed analysis according to intravascular modality, the pathologies occurred at a similar ratio in ST-elevation myocardial infarction (STEMI). Although the ratio of plaque erosion and calcified nodules is slightly higher in non-ST-elevation coronary syndrome, plaque rupture remains the primary cause of acute coronary syndrome[6].

Since the first study of plaque rupture in an autopsy case of sudden cardiac death in 1844[7], there have been various discussions on the paradigm of plaque vulnerability from multiple viewpoints, such as pathological, morphological, and physiological approaches. Particularly, many studies have been conducted on pathological characteristics of plaque vulnerability since the first report. Plaque rupture is due to rupture of the fibrous cap covering the lipid core and tends to occur in vulnerable plaque with the following characteristics as shown in Figure 1: (1) large lipid core, (2) thin fibrous capsule, (3) strong infiltration of inflammatory cells such as macrophages and T lymphocytes,

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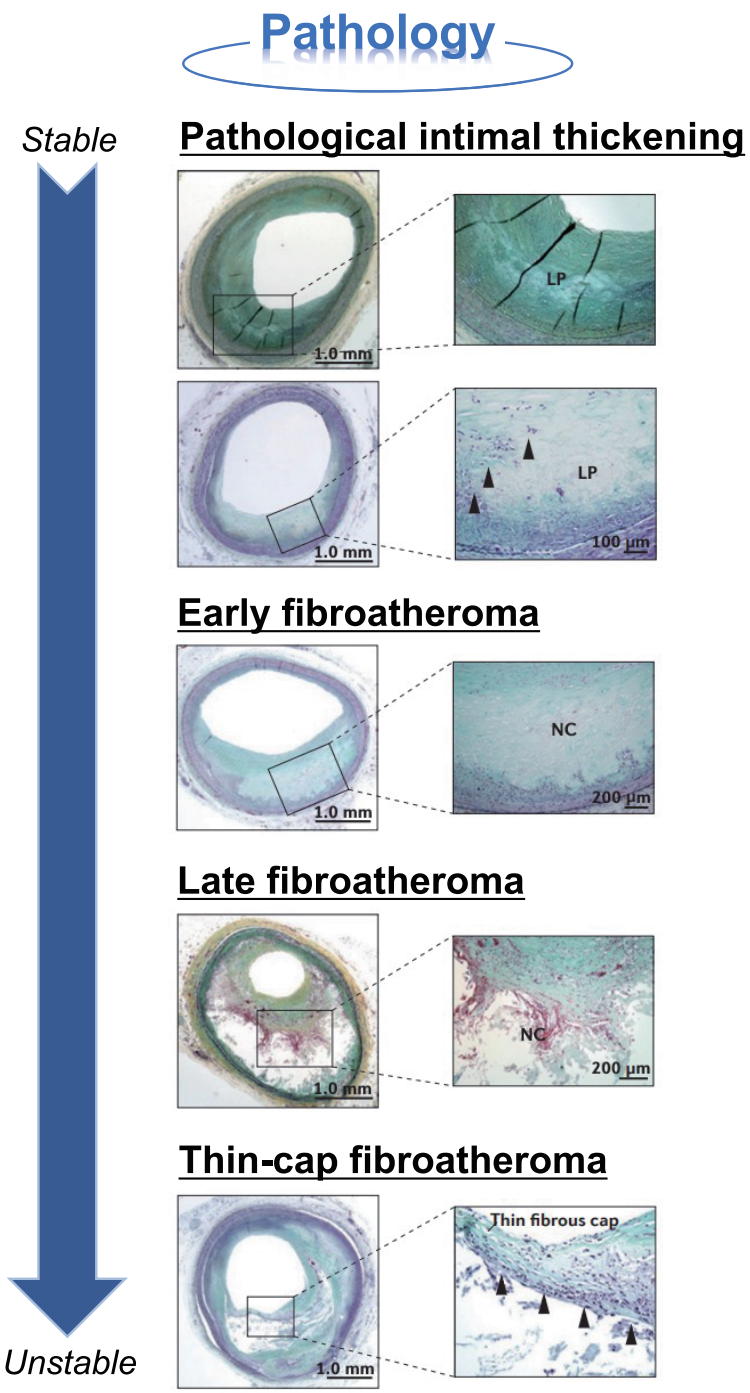

Figure 1 Progression to vulnerable plaque based on pathological findings
The early atherosclerotic plaque progression from pathologic intimal thickening to a fibroatheroma is due to macrophage filtration (shown as ▲). Pathologic intimal thickening is characterized by the presence of LP which consist of proteoglycan with lipid insudation. The fibroatheroma has a thick fibrous cap that begins to thin over time macrophage matrix metalloproteinase release and apoptotic death of smooth muscle cells converting the fibroatheroma into a thin-cap fibroatheroma.
NC, necrotic core; LP, lipid pool.
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(4) abundant neovascularization, (5) accompanied by calcification, and (6) accompanied by positive remodeling[4, 8].

Diagnosis and risk assessment of vulnerable plaque

Diagnostic imaging is crucial in understanding morphological plaque characteristics in coronary arteries. This is because approximately 70% of the

lesions responsible for myocardial infarction have <50% coronary artery stenosis[9]; identifying not only degree of coronary artery stenosis but also vulnerable plaque can lead to the prevention of future cardiovascular events.

Intravascular imaging modalities such as intravascular ultrasound (IVUS), optical coherence tomography (OCT), near-infrared spectroscopy (NIRS), and angioscopy are used in clinical practice. Pathological findings have emphasized the presence of a thin fibrous cap and an abundant lipid core as indicators of vulnerable plaques. To address the limitations of plaque tissue identification in grayscale IVUS, virtual histological IVUS (VH-IVUS), which classifies plaque properties into four types (fibrous, fibro-fatty, dense calcium, and necrotic core) and displays them using color mapping, was developed. VH-IVUS-derived thin-cap fibroatheroma (VH-TCFA) was defined according to the criteria of "atheroma volume ratio ≥40%", "necrotic core ≥10%", and "plaques in contact with the lumen in 3 or more sections" in the Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) study[10]. Its frequency was significantly higher in patients with acute coronary syndrome than in those with stable angina, and VH-TCFA was a significant predictor of cardiovascular events. Additionally, OCT has a high spatial resolution, enabling accurate measurement of fibrous cap thickness and more accurate identification of TCFAs. Notably, TCFA is defined as thin fibrous caps with a thickness of <65 μm, bearing large lipid cores and macrophage infiltration. This cutoff value is derived from the analysis of histopathological samples[1, 11]. The presence of TCFA detected using OCT increased perioperative myocardial infarction[12], and was a significant predictor of cardiovascular events in the CLIMA study[13]. This finding suggests that TCFA contributes to the development of acute coronary syndrome, concurrent perioperative myocardial infarction, and future cardiovascular event risk.

Furthermore, NIRS-IVUS, which uses NIRS for grayscale IVUS and can quantitatively evaluate the lipid core with an index called the lipid core burden index (LCBI), has been developed and applied in clinical practice. In both culprit and non-culprit lesions, lipid core plaques have been detected at a higher rate in patients with acute coronary syndrome than in those with stable angina[14]. Additionally, the maximum LCBI within any 4-mm long segment ($maxLCBI_{4mm}$) in culprit lesions for STEMI was 5.8 times higher than in non-culprit lesions. $MaxLCBI_{4mm}$ ≥400 was established as the cutoff value for predicting the development of STEMI[15]. Furthermore, in patients undergoing elective percutaneous coronary intervention (PCI) in the Coronary Assessment by Near-infrared of Atherosclerotic Rupture-prone Yellow (CANARY) trial, $maxLCBI_{4mm}$ was significantly higher in the perioperative myocardial infarction group; however, there was no significant difference in the frequency of perioperative myocardial infarction with or without distal embolic protection in patients with maxLCBI4mm ≥600[16].

Whereas, although numerous studies have been published on non-invasive examinations using coronary computed tomography angiography (CCTA), cardiac magnetic resonance (CMR), and positron emission tomography (PET), CCTA is the most practical in clinical practice. The distinctive features of vulnerable plaques identified using CCTA include (1) positive remodeling (≥1.1), (2) low-attenuated plaques (<30 Hounsfield Unit), (3) spotty calcification, and (4) napkin-ring signs. These characteristics have been reported to correlate with vulnerable plaque findings identified using VH-IVUS, OCT, and NIRS-IVUS[17, 18]. Regarding coronary plaque detected by CMR, to visualize coronary plaques, imaging is performed using black blood method which suppresses blood flow signal, in addition, the coronary artery walls and plaques can be visualized by suppressing the fat signal around the coronary arteries. Furthermore, the coronary atherosclerosis T1-weighted characterization (CATCH) method, which combines a black blood sequence that can visualize high-intensity plaque in the coronary arteries and a bright blood sequence that can visualize the coronary artery lumen with high-brightness, has recently been developed. Notably, high-intensity plaques identified using the CATCH method were significant predictors of $maxLCBI_{4mm}$ ≥400 and perioperative myocardial infarction, and the CATCH method was useful for vulnerable plaque detection and risk assessment of perioperative myocardial infarction before PCI[19]. Representative findings of vulnerable plaques on both invasive and non-invasive coro-

nary modalities were shown in Figure 2.

Onset of clinical events in functional ischemia and vulnerable plaque

One physiological evaluation of coronary arteries is fractional flow reserve (FFR), which is used as a functional evaluation for moderate stenotic lesions. The Fractional Flow Reserve Guided Percutaneous Coronary Intervention Plus Optimal Medical Therapy Versus Optimal Medical Therapy (FAME2) study compared the PCI + optimal medical therapy group and the optimal medical therapy alone group in patients with stable angina pectoris, and the cutoff value was set at FFR ≤0.80. When FFR-guided PCI was combined with optimal drug therapy, although there was no significant difference in all-cause mortality or the onset of myocardial infarction compared with the optimal drug therapy alone group, it was observed that emergency revascularization significantly decreased[20]. A study on the association between FFR and vulnerable plaque demonstrated that the lower FFR value, the more high-risk plaque (HRP) characteristics were identified in CCTA shown in Figure 3[21]. In addition, this study reported that the lesions with ≥3 HRP characteristics showed a significantly higher risk of vessel-orientated composite outcomes compared with those with <3 HRP characteristics in the FFR >0.80 group; however, there was no significant difference in the risk of vessel-orientated composite outcomes between ≥3 HRP characteristics versus <3 HRP characteristics in the FFR ≤0.80 group. Therefore, in FFR ischemia-positive patients, stent treatment with PCI had a certain effect in suppressing emergency revascularization and may have contributed to plaque stabilization. Furthermore, in the

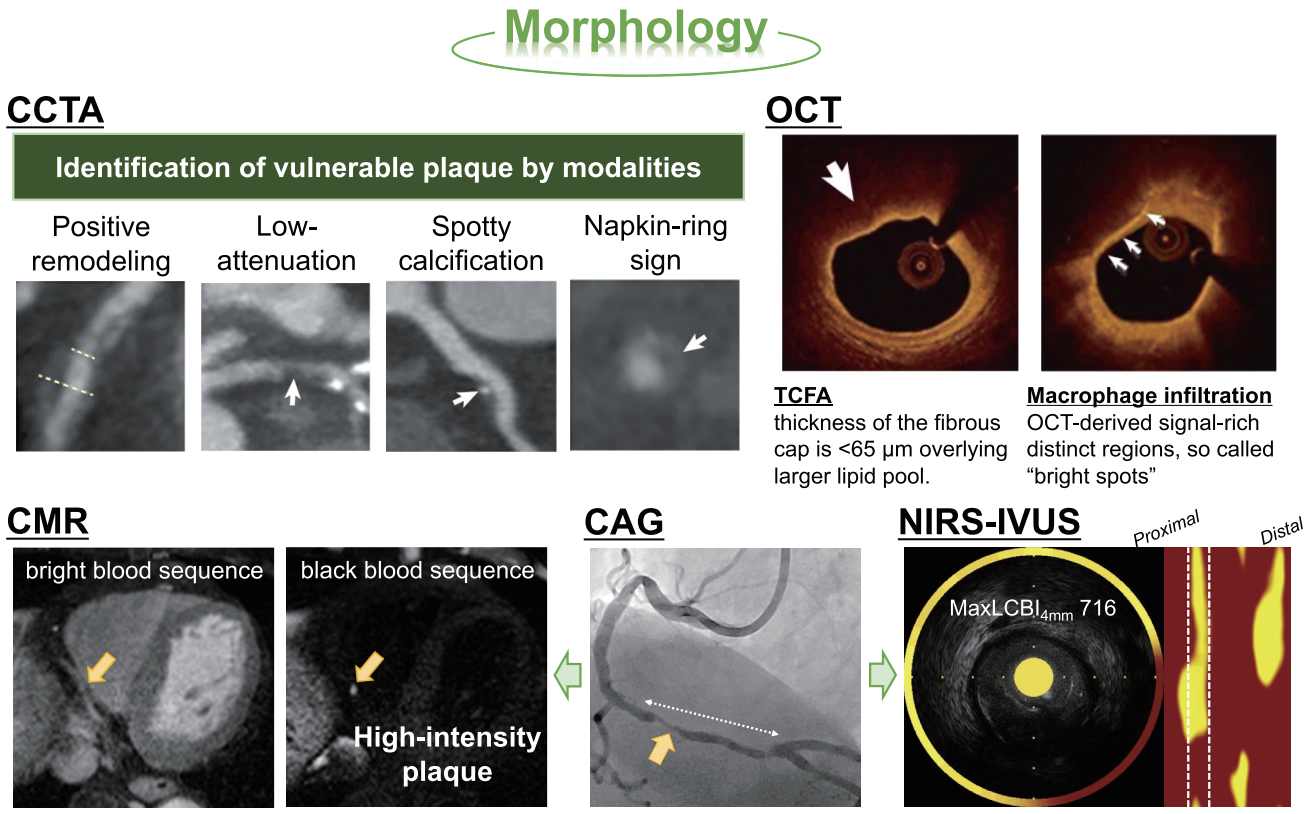

Figure 2 Morphological findings of vulnerable plaques on coronary modalities
The findings of vulnerable coronary plaque identified by both invasive and non-invasive modalities, such as CCTA, non-contrast CMR, OCT, and NIRS-IVUS, are shown. The upper panel shows the representative vulnerable characteristics detected by CCTA. The upper right panel shows the TCFA and macrophage filtration using OCT. The lower panel shows that CMR-derived high intensity plaque, IVUS-derived attenuated plaque, and NIRS-derived large lipid-rich plaque defines as maxLCBI4mm ≥400 are measured in culprit lesion site of segment 3 indicated by the yellow arrow on CAG imaging.
CAG, coronary angiography; CCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance; MaxLCBI4mm, maximum lipid core burden index within any 4-mm long segment; NIRS-IVUS, near-infrared spectroscopy and intravascular ultrasound; OCT, optical coherence tomography, TCFA, thin-cap fibroatheroma.
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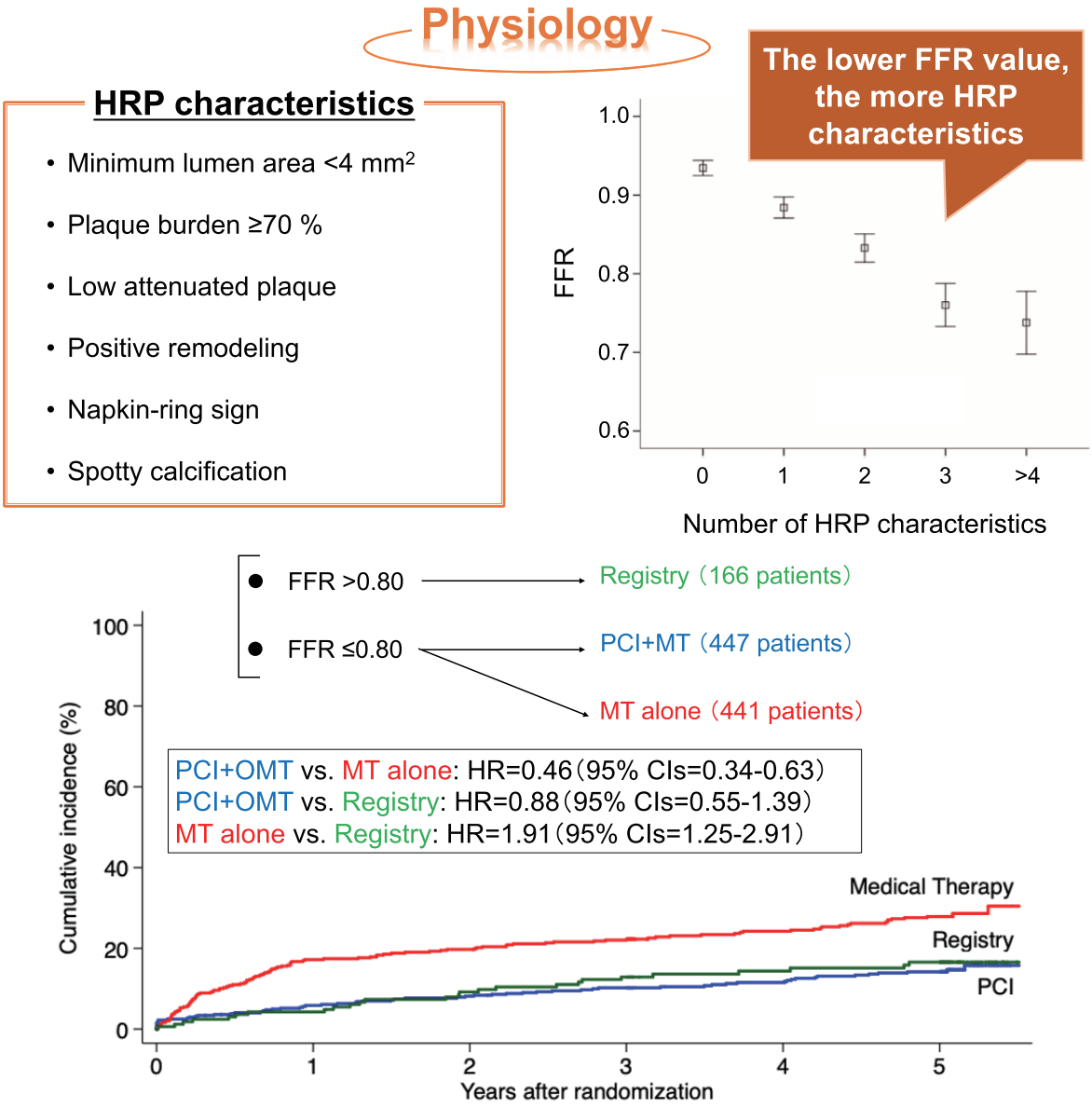

Figure 3 Association of physiological evaluation with vulnerable plaque characteristics and clinical outcomes
The upper right panel shows the HRP characteristics items detected by CCTA, and the upper left panel shows the association between FFR value and number of its HRP characteristics. The lower panel shows the results of FAME2 trial during the follow-up period of 5 years.
CCTA, coronary computed tomography angiography; FAME2, Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2; FFR, fractional floe reserve; HRP, high-risk plaque; MT, medical therapy; PCI, percutaneous coronary intervention.
Reorganized from the references of 21) and 22) with permission from the publisher.

population that led to a diagnosis of FFR ≤0.80 ischemia in the 5-year follow-up of the FAME2 trial, although the composite endpoint (all-cause mortality, myocardial infarction, and emergency revascularization) significantly decreased in the PCI + optimal medical therapy group compared to the optimal medical therapy alone group (13.9% vs. 27.0%, $p<0.05$), 15.7% of the patients without ischemia with FFR >0.80 developed the composite endpoint and its rate was higher than the PCI + optimal drug therapy group shown in Figure 3[22]. Even if optimal drug therapy is continued after the diagnosis of non-ischemia in FFR, the event will still occur; consequently, the presence of vulnerable plaque and residual risk in patients without ischemia is one of the challenges. Therefore, the early identification of vulnerable plaque and the reinforcement of its treatment, as well as the

setting of new FFR cutoff values in the era of next-generation drug-eluting stent (DES), may help reduce the risk of cardiovascular events in patients without ischemia.

Possibility of PCI for vulnerable plaque

Regarding PCI in patients with stable angina pectoris, many studies have indicated that PCI does not enhance prognosis, although it is expected to improve angina symptoms, and the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial is often regarded as a representative study[23]. The COURAGE trial compared the PCI + medical therapy group with a medical therapy group and defined a composite endpoint of all-cause mortality and nonfatal myocardial infarction. No significant difference was observed in the composite endpoint during the follow-up period of 4.6 years between the PCI + medical and medical therapy groups (18.5% vs. 19.0%, p=0.62). However, the COURAGE trial had limitations, including the fact that most of the stents used were bare-metal stent (BMS), and high-risk patients were excluded. Nevertheless, the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial published in 2020 eventually included 5,179 patients with stable angina with moderate or greater ischemia. A comparison was made between an early invasive strategy group (PCI [87% 2nd generation DES usage] or coronary artery bypass grafting) and a conservative strategy group[24]. During the median follow-up period of 3.2 years, no significant difference was observed between the two groups regarding the composite endpoint of cardiovascular mortality, myocardial infarction, unstable angina, heart failure, resuscitated cardiac arrest, or all-cause mortality. However, although the event risk was low in the conservative treatment strategy group in the first half, that tended to decrease gradually in the early invasive strategy group in the second half. In ISCHEMIA-EXTEND trial, which was started as an even longer-term prognostic evaluation, the cardiovascular mortality rate decreased in the early invasive strategy group during the follow-up period of 7 years[25]. The evolution of DES may also be cited as a factor contributing to the increasing disparity between the two groups.

DES enabled a notable reduction in restenosis compared to BMS. Nonetheless, certain problems emerged, including (1) thrombotic risk due to inadequate coverage of the neointima, (2) poor long-term results of stenting in lipid-rich lesions, and (3) late events due to chronic inflammation caused by polymers in 1st generation DES[26, 27]. Therefore, 2nd generation DES has improved design, drug concentration, and polymer to overcome such weaknesses, and are currently the most widely used devices. Several reports of stent performance for vulnerable plaque lesions with abundant lipid cores in such next-generation DES shall be presented.

The Chemometric Observations of Lipid Core Plaques of Interest in Native Coronary Arteries Registry) COLOR trial evaluated NIRS-detected lipid core plaques in culprit lesions and clinical outcomes (major cardiovascular events (MACEs): cardiovascular mortality, myocardial infarction, stent thrombosis, and unplanned revascularization or readmission for progressive or unstable angina) in patients with coronary artery disease treated with DES (approximately 80% are 2nd generation DES)[28]. MACEs accounted for 18.0% overall and 8.3% for the culprit lesion only. There was no significant difference in $maxLCBI_{4mm}$ using NIRS and minimum lumen area and plaque burden using IVUS with or without an event related to the culprit lesion. Moreover, no significant difference was observed in MACEs when $maxLCBI_{4mm}$ was divided into three groups and compared with each other ($maxLCBI_{4mm}$ = 0-196, 197-420, 421-1,000). Additionally, a Revelation of Pathophysiological Phenotypes of Vulnerable Lipid-Rich Plaque (REASSURE)-NIRS trial evaluated the effect of a residual maxLCBI4mm after stent placement on lesion-derived (cardiovascular mortality, nonfatal target lesion-related myocardial infarction, and target lesion revascularization) and patient-derived (all-cause mortality, nonfatal myocardial infarction, and unplanned revascularization) clinical outcomes[29]. The median residual $maxLCBI_{4mm}$ was 183, and 16% of all lesions had a residual $maxLCBI_{4mm}$ >400. The subjects were divided into three groups according to the tertile of residual $maxLCBI_{4mm}$ (residual $maxLCBI_{4mm}$ = 0-123, 124-270, 271-799). There was no significant difference in the occurrence of events among the three groups, and residual $maxLCBI_{4mm}$ did not emerge as a signifi-

cant predictor of those events. In short, no difference was observed in lesion-derived outcomes depending on the residual maxLCBI$_{4mm}$ value due to 2nd generation DES usage. Compared with the 1st generation DES, 2nd generation DES had a greater strut coverage with less inflammation, less fibrin deposition, and less late and very late stent thrombosis[30]. In addition, the 2nd generation DES was associated with a significantly reduced risk of long-term target lesion failure than the 1st generation DES, although there were no significant differences in cardiac death and myocardial infarction[31]. Thus, 2nd generation DES could suppress arteriosclerosis and contribute to reducing events only in stented lesion site. These findings at least suggest that the lipid core in the culprit lesion might be sealed.

A study on the sealing effect of stents demonstrated that everolimus-eluting stent placement significantly reduced the number of macrophages involved in vulnerable plaque formation in an animal study[32]. Recently, the PROSPECT ABSORB trial was reported, which evaluated the effect of bioabsorbable vascular scaffold (BVS) for non-stenotic lesions (moderate stenosis and functional ischemia negative) with plaque burden ≥65 % assessed using IVUS, and the subjects were divided into two groups (BVS + guideline-directed medical therapy [GDMT] and GDMT alone)[33]. This study evaluated IVUS-derived minimum lumen area at the follow-up period, the primary safety endpoint was target lesion failure (cardiovascular death, target vessel-related myocardial infarction, or clinically driven target lesion revascularization), and secondary clinical effectiveness endpoint was lesion-related MACEs (cardiovascular death, myocardial infarction, unstable angina, or progressive angina). During the median follow-up period of 4.1 years, the minimum lumen area was 6.9 ± 2.6 mm^2 vs. 3.0 ± 1.0 mm^2 in the BVS + GDMT and GDMT alone groups, respectively (least square means difference: 3.9 mm^2, p<0.05). Although no significant differences were observed in primary and secondary endpoints between the two groups, secondary endpoint rate tended to be lower in the BVS + GDMT group (4.3% vs. 10.7%, p=0.12). Thus, prophylactic plaque stabilization of BVS against high-risk plaques with non-ischemic moderate stenosis was confirmed. However, prophylactic PCI for FFR-negative vulnerable plaque relies on very small effects, and there are certain limitations due to the enormous sample size required[34].

Achieving zero perioperative myocardial infarction

As stated above, the characteristic finding of vulnerable plaque identified using preoperative and intraoperative modalities is a strong predictor of perioperative myocardial infarction. Plaque stabilization is considered the most critical factor in preventing perioperative myocardial infarction, and expectations are high for plaque sealing with stents. However, preventing iatrogenic perioperative myocardial infarction is considered a prerequisite for plaque-sealing treatment, even though plaque rupture has not occurred. Moreover, statin, ezetimibe, or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor combination therapy has been reported to stabilize and regress coronary artery plaques, and low-density lipoprotein-cholesterol (LDL-C) lowering therapy is essential for the prevention of perioperative myocardial infarction[35–37]. The Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging (PRADIGM) trial reported that statins contributed to increased plaque calcification and decreased characteristic findings of high-risk plaques, slowing the progression of overall coronary atherosclerosis[38]. Although the period of plaque stabilization has not been clarified, a case report has reported changes over time in LDL-C levels due to strict LDL-C lowering therapy and maxLCBI$_{4mm}$ at non-culprit lesion segment using NIRS[39]. In addition to statin, a PCSK9 inhibitor was used in combination, and LDL-C decreased rapidly over several months and remained at the 10 mg/dL level. Meanwhile, the maxLCBI$_{4mm}$ at the non-culprit lesion site of left main tract gradually decreased from 422 to 109 over 2 years, quantitatively demonstrating favorable results for lipid core plaques. Therefore, based on the target LDL-C levels for primary and secondary prevention of coronary artery disease in Japanese guidelines[40], aggressive lipid management from an early stage expecting long-term benefits may contribute to the suppression of perioperative complications. Prevention and treatment of comorbidities such as hypertension, diabetes, and chronic kidney disease, as well as guidance on diet, exercise, and smoking cessation, are equally crucial.

Conclusion

In this article, we described the vulnerability of coronary artery plaques (mainly vulnerable plaque) from pathological, morphological, and physiological viewpoints. In our daily clinical practice, it is crucial to evaluate anatomical findings and the presence or absence of ischemia in determining the indication for PCI. Simultaneously, understanding and grasping plaque vulnerability will be of great help in predicting future cardiovascular events and in developing preventive strategies in individual patients. Recently, there have been sporadic reports on myocardial infarction prevention using early invasive treatment and the sealing effect of lipid core plaques by the deployment of new-generation stents. In the future, it is expected that direct plaque intervention, in addition to strict LDL-C lowering therapy, may lead to prevention of plaque rapture and suppression of cardiovascular event, not only by identifying vulnerable plaques but also by considering active therapeutic intervention.

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Author contributions

TF and TD wrote and reviewed the manuscript. All authors read and approved the final manuscript.

Conflicts of interest statement

The authors report no relationships that could be construed as a conflict of interest.

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Perspectives

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Mitochondrial Damage in Sepsis

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Mitochondria not only generate adenosine triphosphate (ATP) and act as the powerhouse of the cell but also contribute to host defense by producing reactive oxygen species. Therefore, mitochondrial damage in sepsis directly results in a shortage of energy currency and dysregulation of the immune system. Other than those, mitochondrial damage results in the release of highly dangerous mitochondrial DNA, facilitating acidosis by modulating the metabolism and inducing programmed cell death, thereby facilitating disease progression in sepsis. Various forms of cell death are induced by mitochondrial damage. Aponecrosis is a secondary conversion from apoptosis to necrosis. Although apoptosis is initially intended, it cannot be completed due to ATP depletion from mitochondrial damage, ultimately leading to inflammatory necrosis. Besides such accidental cell death, programmed inflammation–inducing cell deaths such as necroptosis, ferroptosis, and pyroptosis are induced by mitochondrial damage in sepsis. Based on these findings, the regulation of mitochondrial damage holds promise for the development of new therapeutic approaches for sepsis.

Key words: sepsis, mitochondria, programmed cell death, organ dysfunction, oxidative stress

Introduction

Mitochondria are essential components of living cells that generate energy currency, control metabolic pathways, regulate intracellular calcium levels, produce reactive oxygen species, and modulate programmed cell death[1)]. Mitochondrial function is readily compromised in sepsis and significantly contributes to the worsening of the disease condition. In this perspective, we briefly overview recent advances in mitochondrial research related to sepsis.

Impaired cellular respiration

Mitochondria is responsible for producing adenosine triphosphate (ATP) via oxidative phosphorylation and functioning as the powerhouse of the cell (Figure 1). Damage to mitochondria impairs ATP production, leading to energy deficits in cells, particularly in high-energy-demanding organs such as the heart, kidneys, and liver. The count of mitochondria is considerably different between the cell types, and the mean volume for mitochondria from the rat was reportedly 0 60 μ^3 in the heart, 0.42 μ^3 in the liver, and 0.23 μ^3 in the kidney cortex[2)]. Disrupted mitochondrial function is considered the fundamental mechanism of organ dysfunction, such as myocardial dysfunction and acute kidney injury in sepsis, and avoiding the decrease in the number and impaired function of mitochondria is crucial for maintaining cellular and organ functions[3, 4)].

Increase in oxidative stress

Reactive oxygen species (ROS) is a physiological byproduct of metabolism and is essential to the functions of immune systems. However, damaged mitochondria are known to produce excessive ROS,

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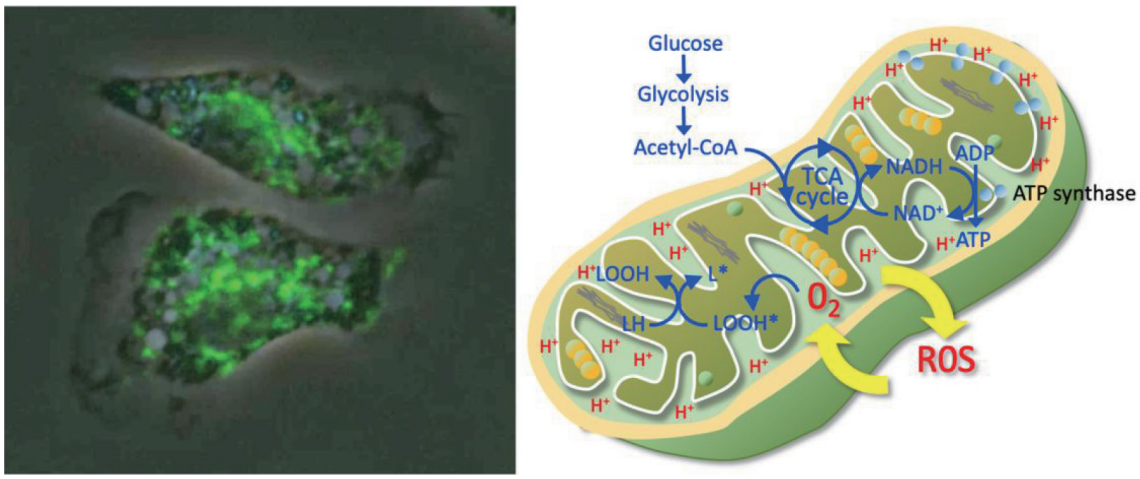

Figure 1 Immunofluorescent staining of mitochondria of the leukocytes and their functions
Immunofluorescence of the leukocytes from rats displaying a mitochondrial fluorescein isothiocyanate (FITC) staining pattern of cellular distribution (left). Mitochondria are most densely distributed around the nucleus. The function of mitochondria is summarized in the right panel.

and overproduced ROS under pathophysiological conditions like sepsis are involved in the progression of the diseases. ROS can harm cellular components, including organelles, lipids, proteins, and DNA. Subsequent ROS-induced impaired cellular functions and inflammatory responses may result in organ damage. A complex system of interacting physiological antioxidant defenses normally diminishes oxidative stress and prevents damage to the mitochondria[5]. However, since oxidative stress-mediated injury increases in sepsis, overwhelming the antioxidant defenses and facilitating the development of cellular damage and organ failure, antioxidant supplementation has been considered a potentially beneficial treatment for sepsis. The effects of multiple agents, including vitamins E and C, melatonin, N-acetylcysteine, selenium, carnosine, fish oil, and glutathione, have been examined[6]. Nevertheless, the efficacy of these substances has not yet been established.

Release of mitochondrial DNA

Mitochondrial damage can trigger the release of mitochondrial DNA (mtDNA) and other mitochondrial components into the cytoplasm and extracellular space, which act as a damage-associated molecular pattern (DAMP), inducing systemic toxicity and damage to multiple organs[7]. Since mitochondria are suggested to originate from gram-negative bacteria and coexist in the cell (endosymbiotic theory), this endogenous 'enemy' acts as a pathogen-associated molecular pattern (PAMP) to induce hyper-proinflammatory reactions[8]. It was reported that plasma levels of mtDNA are associated with the clinical outcome of septic shock and were suggested to be a better biomarker than lactate in predicting mortality in severe sepsis[9]. Recently, mitochondrial dysfunction and the release of mtDNA have attracted attention due to their relevance to skeletal muscle weakness, known as ICU-acquired weakness[10].

Metabolic dysfunction

Mitochondrial dysfunction disrupts cellular metabolism, leading to metabolic imbalances. First, glycolysis is intensified in carbohydrate metabolism; the failure to enter pyruvate into the tricarboxylic acid (TCA) cycle increases lactate generation. Second, mitochondrial dysfunction also affects lipid metabolism, and lipolysis is upregulated, increasing fatty acids and triglycerides. Impaired fatty acid oxidation and shifting towards anaerobic glycolysis result in further accumulation of lactate and metabolic acidosis. Third, changes in lipid metabolism also affect the levels of ketone bodies and amino acids[11]. Other than the above, mitochondrial damage also affects calcium metabolism. Since mitochondria store a large amount of calcium, mitochondrial damage affects cellular signaling pathways, leading to increased cytosolic calcium levels. Elevated cytosolic calcium can activate various calcium-dependent enzymes, inducing cell death pathways and

leading to reduced ATP production and further cellular stress[12]. These metabolic changes are an important area of research for developing novel therapies for sepsis.

Regulation of programmed cell death

Mitochondria can pursue programmed apoptosis, which can convert secondary to necrosis (aponecrosis), a form of uncontrolled cell death that further promotes inflammation and tissue damage. The mechanisms of apoptosis are explained as follows: first, in response to pro-apoptotic signals, mitochondria release cytochrome c from the intermembrane space into the cytosol. Cytochrome c binds to apoptotic protease activating factor-1 in the cytosol, leading to the formation of the apoptosome[13]. This complex then recruits and activates procaspase-9, which initiates a cascade of downstream caspase activations, including caspase-3, -6, and -7. These executioner caspases dismantle the cell by cleaving various structural and regulatory proteins. Apoptosis is a silent form of cell death that does not impair organ function. However, since the apoptotic process requires sufficient ATP, a lack of ATP production by the mitochondrial damage causes apoptosis to transition into necrosis[14]. In other words, apoptosis and necrosis partially share the same pathway, and apoptosis relies on adequate intracellular ATP levels. Meanwhile, when ATP is depleted, the cell death mechanism shifts to necrosis. Ultimately, mitochondrial damage in sepsis leads to an increase in necrotic cell death.

Mitochondrial damage can contribute to the initiation of necroptosis, a form of regulated inflammatory cell death that shares features with both apoptosis and necrosis. Increased production of ROS, the release of DAMPs, such as mtDNA and other mitochondrial components, and receptor-interacting protein kinases (RIPK) 1 and RIPK3 are involved in the induction of necroptosis[15]. Necroptotic cells release DAMPs, triggering a robust inflammatory response similar to necrosis.

Mitochondrial damage also can contribute to the induction of ferroptosis, a form of regulated cell death distinct from apoptosis, necrosis, and necroptosis. Ferroptosis is characterized by iron-dependent lipid peroxidation. ROS produced by the damaged mitochondria promotes lipid peroxidation, a key feature of ferroptosis. Mitochondria play a crucial role in iron metabolism, including the storage and utilization of iron. Mitochondrial damage can disrupt iron homeostasis, leading to increased free iron within the cell. This free iron can catalyze the formation of highly reactive hydroxyl radicals via the Fenton reaction and induce ferroptosis[16].

Mitochondrial damage contributes to the induction of pyroptosis, which is characterized by the activation of inflammatory caspases. This leads to the cleavage of gasdermin D (GSDMD) and the subsequent formation of pores in the cell membrane. Increased ROS and DAMPs activate the NLRP3 (NACHT, LRR, and PYD domains-containing protein 3) inflammasome, which plays a critical role in the initiation of pyroptosis. mtDNA is recognized by NLRP3, leading to the activation of the inflammasome and subsequent pyroptosis[17].

Organ dysfunction

The combined effects of energy deficits, increased oxidative stress, upregulated inflammation, and cell death induction contribute to the dysfunction of vital organs such as the heart, kidneys, lungs, and liver, a hallmark of severe sepsis and septic shock. Therefore, protecting and maintaining mitochondrial function is a promising strategy to improve organ damage in sepsis.

Conclusion

In these two decades, the effects of impaired cellular function due to mitochondrial dysfunction on the development of organ dysfunction in sepsis have been unveiled. Impaired cellular respiration, increase in oxidative stress, release of mitochondrial DNA, metabolic dysfunction, and altered cell death mechanisms are the fundamental mechanisms of mitochondrial damage-induced cellular injury. Mitochondrial damage should be paid more attention to as a critical factor in the progression of sepsis. New research targeting the maintenance of mitochondrial function is warranted to pave the way for improved sepsis management.

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Author contributions

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

Conflicts of interest statement

The authors declare that they have no conflict of interest.

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Original Articles

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Association of Neural Activities in Language Processing and Memory with Rapid Reading

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Objectives: To elucidate physiological changes in the brain caused by rapid reading, we herein focused on brain areas related to language processing and reading comprehension and memory processes and evaluated changes in neural activities associated with reading speed and comprehension using functional magnetic resonance imaging (fMRI).
Materials: This study included 23 nonrapid and 23 rapid readers matched for age, gender, and handedness. T1 weighted image and fMRI were acquired using 3T MRI.
Methods: The neural activity was compared between nonrapid and rapid readers using fMRI. The correlation between neural activity and reading speed and comprehension was also determined.
Results: The neural activities of rapid readers were significantly lower in Wernicke's and Broca's areas, left angular and supramarginal gyri, and hippocampus. Furthermore, reading speed was negatively correlated with neural activities in these areas. Conversely, reading comprehension was negatively correlated with the neural activities in the left angular gyrus.
Conclusions: Rapid readers exhibited reduced language processing, including phonological transformation, analysis, inner speech, semantic and syntactic processes, and constant reading comprehension during rapid reading.

Key words: memory, MRI, neural activity, language processing, rapid reading

Introduction

Rapid reading is a way of efficiently obtaining information or knowledge by reading something quickly and is considered beneficial[1)]. Although it is believed that rapid reading worsens reading comprehension, a previous study showed that rapid readers had superior reading comprehension than nonrapid readers[2)]. Williams et al.[3)] also found that students with faster reading skills had higher university grades than those with slower reading skills. Moreover, a study comparing rapid and nonrapid readers reported that the faster the reading speed, the better the reading comprehension[4)]. Furthermore, a study evaluating reading comprehension after rapid reading training revealed that reading comprehension did not decline compared with that before the training. However, the participants could read the sentences rapidly after the training[5)], highlighting the advantages of rapid reading.

Despite the benefits of rapid reading, it is associated with distrust, which might be a major factor limiting its practice[6)]. According to Morita et al.[7)], the phenomenon or mechanism underlying rapid reading is not well understood. Kurita[8–10)] proposed the "super reading system (SRS)," which enables 80%–90% of the participants to improve their reading speed 10 times after approximately 50 h of training.

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However, the mechanism of acquiring rapid reading skills and the difference between normal and rapid reading have not been elucidated from the neuroscience perspective. To encourage rapid reading and derive benefits from it, establishing the scientific basis of physiological changes in the brain during rapid reading is necessary.

Although investigating physiological changes in the brain during rapid reading is challenging because of the scarcity of rapid readers, Fujimaki et al.[11,12] explored these changes using functional magnetic resonance imaging (fMRI), which reflects neural activities indirectly using blood oxygenation level-dependent (BOLD) imaging. Rapid readers showed lower neural activities than nonrapid readers in Wernicke's and Broca's areas, which are associated with internal speech of articulation processes. This finding implies that rapid reading decreases or cuts the linguistic processes compared with ordinary reading. However, it remains unclear whether rapid readers understand the sentences they read or whether they exhibit improved reading comprehension[1-5]. Moreover, previous studies had small sample sizes (rapid readers, n = 4 [1 male and 3 females][11]; n = 8 [1 male and 7 females][12]) and did not match age and sex between nonrapid and rapid readers. Therefore, to elucidate physiological changes in the brain caused by rapid reading, this study focused on brain areas related to language processing, such as Wernicke's and Broca's areas, supramarginal gyrus, and angular gyrus[11,12], and reading comprehension and memory processes, such as the hippocampus[13-17], and evaluated changes in neural activities during rapid reading and comprehension in nonrapid and rapid readers using fMRI.

Materials and Methods

Participants

The study was approved by the Ethics Committee and Research and Development Department of Tokyo Metropolitan University (approval number: 22022). All participants provided written informed consent before participating in the study. Table 1 shows the participants' demographic data obtained at Tokyo Metropolitan University. This study included 23 nonrapid readers (age, 26.2 ± 9.5 years; male/female, 14/9; handedness, all right) and 23 rapid readers (age, 28.6 ± 7.8 years; male/female, 14/9; handedness, all right). To avoid the effect of age, sex, and handedness on the results, these parameters were matched between nonrapid and rapid readers.

MRI acquisition

All MRI data were acquired using a 3-T scanner (Signa Premier; GE Healthcare, Chicago, IL, USA) with a 48-channel head coil. Whole-brain 3D magnetization prepared rapid gradient echo (MP-RAGE) T1-weighted imaging and T2*-weighted echo planar imaging, which are sensitive to the BOLD contrast and can reflect neural activities, were conducted in all participants. Whole-brain 3D MP-RAGE T1-weighted images were acquired using the following parameters: repetition time, 2210 ms; echo time, 3.24 ms; inversion time, 1000 ms; field of view, 220 × 220 mm; matrix size, 512 × 512; resolution, 0.43 × 0.43 mm; slice thickness, 1.0 mm; and acquisition time, 5 min 30 s. For the fMRI protocol, T2*-weighted echo planar diffusion-weighted images were acquired using spin-echo planar imaging with the following parameters: repetition time, 1000 ms; echo time, 30 ms; flip angle, 60°; field of view, 220 × 220 mm; matrix size, 64 × 64; resolution,

Table 1 Participants' demographic data

	Nonrapid reader	Rapid reader	*P*
N	23	23	—
Age at baseline MRI, y	26.2 ± 9.5	28.6 ± 7.8	0.34
Sex, male/female	14/9	14/9	1.00
Handedness, L/R	0/23	0/23	1.00
Reading speed, characters per minute	720 ± 202	4191 ± 254	<.001
Reading comprehension score	27.8 ± 13.2	46.8 ± 7.1	<.05

Abbreviations: MRI, magnetic resonance imaging.

3.44 × 3.44 mm; slice thickness, 3.0 mm; and acquisition time, 9 min 40 s.

fMRI tasks

fMRI was conducted according to previously published methods (Figure 1)[11,12]. The fMRI protocol consisted of a block design that alternated the task block in 60 s and the control block in 30 s. In the task block of the fMRI session, several novels written by Natsume Soseki, a well-known Japanese novelist, were used: Kokoro (Heart), Higansugi-made (To the spring equinox and beyond), Michi-kusa (Grass on the wayside), and Nowaki (Autumn wind) (Aozora-bunko; https://www.aozora.gr.jp/). In the task block, the participants were instructed to covertly read the sentences. In the rest block, a white cross was shown on a black background. The participants were instructed to look at the white cross without thinking to record only neural activities related to visual processes. Neural activities under the control conditions were subtracted from those under the test conditions to exclude visual-related activities.

Each participant was given a different novel to read, which the participant had either not read or had read it several years before the experiment. The novels were written in a mixture of kanji, hiragana, and katakana characters (three Japanese writing systems: morphograms [first] and syllabograms [last two]), where the characters were arranged in 12 rows and 27 columns (approximately 300 characters), from top to bottom and from right to left, which is the usual style for Japanese novels printed in paperback.

The characters were presented on a screen, which was placed 1.6 m away from the participants. Their size represented a visual angle of 0.46 × 0.46°, which was slightly larger than the typical size when books are physically read in a hardcopy form. The luminance was 0.75 cd/m^2 for the characters and 160 cd/m^2 for the background.

Other data

Reading speed was calculated as characters per minute (cpm) in the 30-min session outside MRI and just before MRI. The reading comprehension

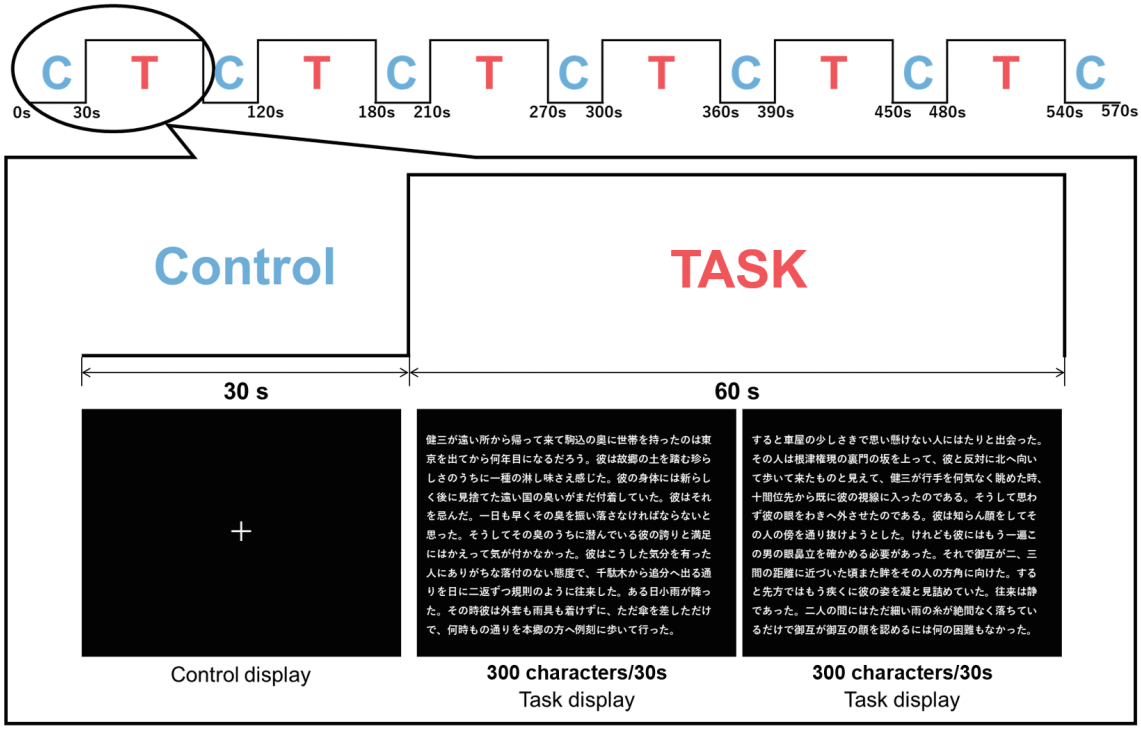

Figure 1 Task design in the fMRI session
The protocol consisted of a block design that alternated the task block in 60 s and the control block in 30 s. In the task block of the fMRI session, several novels written by Natsume Soseki, a well-known Japanese novelist, were shown. In the task block, the participants were instructed to covertly read the sentences. In the rest block, a white cross was shown on a black background. The participants were instructed to look at the white cross without thinking to record only neural activities related to visual processes.

score in the fMRI task was calculated as the cosine similarity between the original sentence shown in the task session and the sentence written by the participant 30 min right after MRI acquisition. The cosine similarity was calculated using Python version 3.7.0 (https://www.python.org/) with the MeCab (http://taku910.github.io/mecab/) and scikit-learn (https://scikit-learn.org/stable/) libraries.

MRI preprocessing

fMRI image preprocessing was performed using the CONN toolbox v.21.a (Functional Connectivity SPM Toolbox 2021, McGovern Institute for Brain Research, Massachusetts Institute of Technology, http://ww.nitrc.org/projects/conn) relying on the SPM 12 software package (Wellcome Trust Centre for Neuroimaging, University College London, United Kingdom, http://www.fil.ion.ucl.ac.uk/spm/software) implemented in MATLAB 2019b (MathWorks, Natick, MA). All preprocessing steps were performed following the default preprocessing pipeline for volume-based analyses[18]. Preprocessing included the following steps: (1) realignment and unwarping, (2) slice-timing correction, (3) structural segmentation and normalization, and (4) outlier identification.

In brief, all volumes of an fMR image were realigned with the first volume to correct for motion. The realigned fMR images were slice time-corrected, followed by tissue segmentation (i.e., gray matter-/white matter-/cerebrospinal fluid-normalized masks were determined) and coregistration to a T1-weighted image. Outlier identification was performed using artifact detection tools, which compute regressors for outliers and movements (i.e., resulting in scrubbing parameters). Participant movement realignment and scrubbing parameters (using conservative settings for functional outlier detection settings, global signal z-value threshold, and subject motion of 0.5 mm) were regarded as first-level covariates. Quality assurance (QA) plots were visually inspected to detect other possible outliers (i.e., "QA_ValidScans," "QA_MaxMotion," and "QA_InvalidScans") and an adequate match with Montreal Neurological Institute space and proper coregistration across participants. After anatomical and functional preprocessing, denoising was performed to define, explore, and remove possible confounders in the BOLD signal. In denoising, linear regression and band-pass (i.e., 0.01–0.1 Hz) filtering were used to remove unwanted motion, white matter, cerebrospinal fluid noise components, and physiological noise sources, thereby reducing spurious sources of variance in fMRI.

After separating the preprocessed fMR images into task and rest sessions and averaging each volume using automated anatomical labeling atlas 3[19] in Wernicke's area (i.e., superior and posterior temporal gyri), Broca's area (i.e., angular gyrus), supramarginal gyrus, angular gyrus, and left hippocampus, the relative change in signal intensity was calculated as follows:

$$\textit{Relative change in signal intensity} = \frac{\textit{mean signal intensity}_{Task} - \textit{mean signal intensity}_{Rest}}{\textit{mean signal intensity}_{Rest}}$$

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Continuous data, such as reading speed, reading comprehension, and relative change in signal intensity, between nonrapid and rapid readers were compared using the Mann-Whitney U-test. In addition, to evaluate the relationship between neural activities associated with reading and reading skills (i.e., reading speed and comprehension), partial Spearman's rank correlation (r_s) was calculated between them, with age and sex as the covariates. In all statistical analyses, false discovery rate (FDR) correction was used for multiple comparisons. A P-value of <.05 was considered statistically significant.

Results

Reading speed and comprehension

Table 1 shows the reading speed and comprehension scores of the nonrapid and rapid readers. Both the reading speed and comprehension scores were significantly higher among rapid readers than nonrapid readers ($P < .001$ and $P < .05$, respectively). Compared with nonrapid readers, the reading speed was higher by approximately 6.0 in rapid readers, whereas the reading comprehension score was higher by approximately 1.7 times.

Comparison of neural activities

Table 2 and Figure 2 show the comparison of

Table 2 Comparison of neural activities

	Nonrapid reader	Rapid reader	*FDR-corrected P*
Wernicke area	0.718 ± 0.003	0.714 ± 0.003	<0.001
Broca's area	0.716 ± 0.002	0.712 ± 0.002	<0.001
Angular gyrus	0.714 ± 0.002	0.711 ± 0.002	<0.001
Supramarginal gyrus	0.715 ± 0.004	0.710 ± 0.003	<0.001
Hippocampus	0.717 ± 0.003	0.714 ± 0.003	<0.01

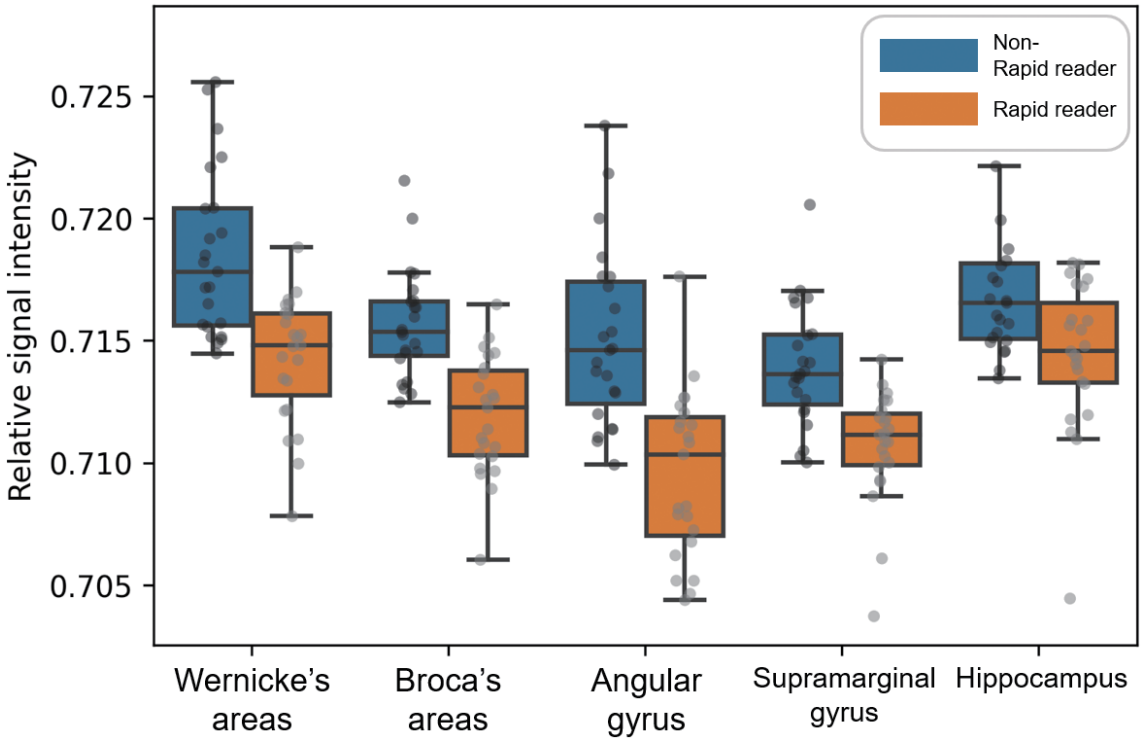

Figure 2 Comparison of neural activities
Boxplots indicate the difference in relative signal intensity (i.e., neural activity) between nonrapid (blue) and rapid readers (red). The boxplots represent interquartile ranges, which contain 50% of the values of the participants. The whiskers are lines that extend from the box to the highest and lowest values. Neural activities of rapid readers were significantly lower in Wernicke's (FDR-corrected $P < .001$) and Broca's (FDR-corrected $P < .001$) areas, left angular (FDR-corrected $P < .001$) and supramarginal gyri (FDR-corrected $P < .001$), and hippocampus (FDR-corrected $P < .01$).

neural activities in each brain region between nonrapid and rapid readers. The neural activities of rapid readers were significantly lower in Wernicke's (FDR-corrected $P < .001$) and Broca's areas (FDR-corrected $P < .001$), left angular (FDR-corrected $P < .001$) and supramarginal (FDR-corrected $P < .001$) gyri, and hippocampus (FDR-corrected $P < .01$).

Correlation between the change in neural activities and reading skills

Table 3 and Figure 3 show the correlation between neural activities in each brain region and reading skills, such as reading speed and comprehension. The reading speed was negatively correlated with neural activities in Wernicke's ($r_s = -0.48$, FDR-corrected $P < .05$) and Broca's areas ($r_s = -0.68$, FDR-corrected $P < .001$), left angular ($r_s = -0.52$, FDR-corrected $P < .001$) and supramarginal gyri ($r_s = -0.53$, FDR-corrected $P < -.001$), and hippocampus ($r_s = -0.40$, FDR-corrected $P < .05$). In contrast, reading comprehension was negatively correlated with neural activities in the left angular gyrus ($r_s = -0.50$, FDR-corrected $P < .05$).

Table 3 Correlation between neural activities and reading skills

	Neural activity vs. Reading speed		Neural activity vs. Reading comprehension score	
	r_s	*FDR-corrected P*	r_s	*FDR-corrected P*
Wernicke area	−0.48	<0.05	−0.18	0.55
Broca's area	−0.60	<0.001	0.04	0.97
Angular gyrus	−0.52	<0.001	−0.50	<0.05
Supramarginal gyrus	−0.53	<0.001	0.01	0.97
Hippocampus	−0.40	<0.05	−0.01	0.97

Discussion

To elucidate physiological changes in the brain during rapid reading, we herein focused on brain areas related to language processing, such as Wernicke's and Broca's areas, supramarginal gyrus, and angular gyrus, and reading comprehension and memory processes, such as the hippocampus, and evaluated changes in neural activities associated with reading speed and comprehension in nonrapid and rapid readers using fMRI. The results revealed that both the reading speed and comprehension scores were significantly higher in rapid readers than in nonrapid readers. Moreover, the neural activities of rapid readers were significantly lower in Wernicke's and Broca's areas, left angular and supramarginal gyri, and hippocampus. Furthermore, the reading speed was negatively correlated with neural activities in Wernicke's and Broca's area, left angular and supramarginal gyri, and hippocampus. Conversely, reading comprehension was negatively correlated with neural activities in the left angular gyrus.

Fujimaki et al.[11, 12] reported that neural activation in Wernicke's and Broca's areas decreased during rapid reading. This result was consistent with that of our study. Previous character and word experiments have demonstrated that neural activation in Wernicke's and Broca's areas was related to phonological processes, including phonological transformation, analysis, and inner speech[20, 21] and that activation of these areas depended on the task that demands inner speech[22, 23]. Furthermore, experimental evidence supported a connectionist model in which these areas constitute a neural network for a phonological loop of working memory[24]. Thus, the result obtained in the present study that neural activities were significantly lower in rapid readers and negatively correlated with reading speed suggests that phonological processes, such as phonological transformation and accompanying inner speech, were reduced during rapid reading.

Since the early 20th century, damage to the left angular gyrus[25] and both the left angular and supramarginal gyrus[26], is associated with language comprehension deficits. Recently, fMRI studies have shown that these regions together with the left inferior parietal lobe are activated in language comprehension through semantic and syntactic processes[27–31]. In the present study, neural activities in the left angular and supramarginal gyri were significantly lower in rapid readers and negatively correlated with reading speed, indicating that rapid readers had reduced semantic and syntactic processes while maintaining reading comprehension during rapid reading.

Regarding neural activities in the hippocampus, research on brain regions of humans and experimental animals has identified a system of hippocampal structures essential for the formation of learning and memory (e.g., reading contents)[32]. Neuroimaging techniques, such as fMRI and positron emission tomography (PET), have provided additional evidence for the importance of the hippocampus in learning and memory[33, 34]. Moreover, in a recognition memory study, Stark and Squire[35] found increased hippocampal activities during the retrieval of previously presented words or objects. Eldridge et al.[36] also reported that hippocampal activities during recognition memory for words are selective for episodic rather than nonepisodic retrieval. Interestingly, against all expectations, the present study indicated that neural activities in the left hippocampus significantly decreased in rapid readers and negatively correlated with the reading speed. Thus, a rapid reader exhibited reduced

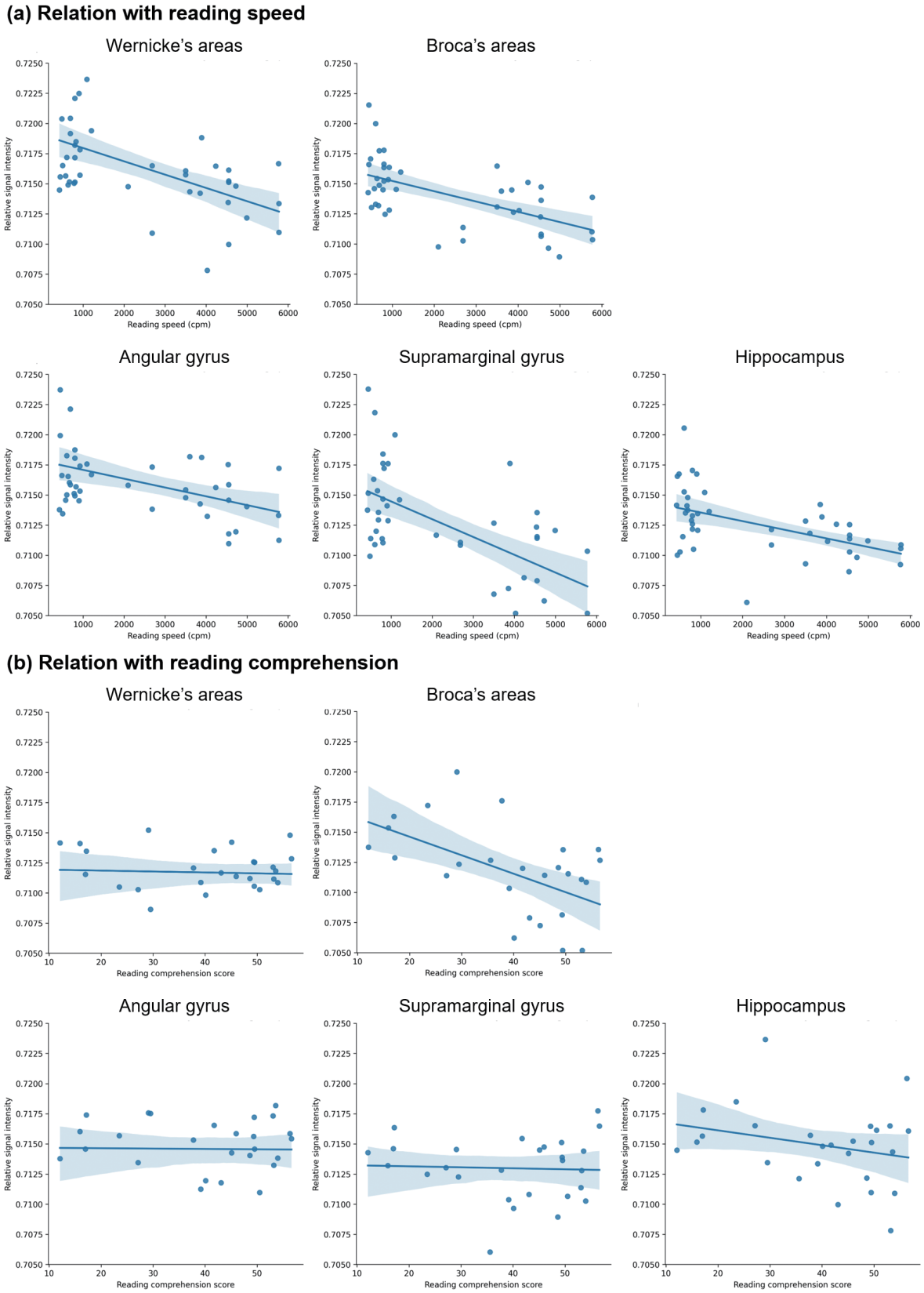

Figure 3 Scatter plot of the relationship between neural activities and reading skills

Lines are estimated using linear regression, and error bar indicates 95% confidence interval. (a) Reading speed negatively correlated with neural activities in Wernicke's (r_s = −0.48, FDR-corrected P < .05) and Broca's (r_s = −0.68, FDR-corrected P < .001) areas, left angular (r_s = −0.52, FDR-corrected P < .001) and supramarginal (r_s = −0.53, FDR-corrected P < .001) gyri, and hippocampus (r_s = −0.40, FDR-corrected P < .05). (b) On the contrary, reading comprehension negatively correlated with neural activities in the left angular gyrus (r_s = −0.50, FDR-corrected P < .05).

retrieval of previously presented words or objects while maintaining reading comprehension. This finding suggests that nonrapid and rapid readers have different reading strategies. Indeed, Douglas et al. reported that reading speed was more related to visual acuity during rapid reading[37]. In addition, a study using fMRI showed increased neural activities with increasing reading speed in the right intraparietal sulcus, which is considered to reflect visuospatial processes[12]. However, our study did not measure visual activity during reading, nor did it prove that rapid readers in this research exhibited better visual acuity. Therefore, further study including measurement of visual activity during reading is required.

In the present study, both reading speed and comprehension were significantly higher in rapid readers than in nonrapid readers. Stevens et al.[37] investigated reading speed and comprehension in college freshmen with nonrapid and rapid reading skills and reported that rapid readers read sentences with higher reading comprehension and speed. Our result was consistent with that of the abovementioned study by Stevens et al. in terms of the relationship between reading speed and comprehension. On the contrary, studies have reported that the activity level in the left hippocampus during learning positively correlated with subsequent recognition memory accuracy[38–40]. The reading comprehension score did not significantly correlate with neural activities in the left hippocampus, whereas a significant negative correlation was observed between reading comprehension score and neural activities in the left angular gyrus. The aforementioned studies targeted nonrapid readers, whereas the present study included both rapid and nonrapid readers. Considering that the reading strategy might be different between nonrapid and rapid readers as mentioned above, an inconsistency in the correlation between neural activities in the left hippocampus and memory may arise between our results and those of previous studies. To elucidate this mechanism, further studies including brain network analysis are warranted to consider microstructural and structural connectivities using diffusion-weighted MRI and functional connectivity using fMRI.

This study had some limitations. First, the sample size was small. To improve the statistical power and reliability of the results, a larger sample size is required. However, collecting data on rapid readers is challenging because only a few individuals have rapid reading skills. Second, MRI data were obtained using a single scanner in a single institution. Further longitudinal and multicenter studies incorporating scanners from different sites with different field strengths and manufacturers would be beneficial for robust results that do not depend on the institution and scanner. Third, the fMRI task included only Japanese tasks. Therefore, it remains unclear whether our results make sense for other language or not, although language differs. Fourth, this was a cross-sectional study. Longitudinal studies are necessary to clarify physiological changes in the brain during rapid reading.

This study evaluated neural activities associated with reading speed and reading comprehension during rapid reading, which were not evaluated in previous studies. In addition, this study showed great consistency with previous studies, and rapid readers read sentences while maintaining reading comprehension.

In conclusion, neural activities of rapid readers were significantly lower in Wernicke's and Broca's areas, left angular and supramarginal gyri, and hippocampus. Furthermore, reading speed was negatively correlated with neural activities in Wernicke's and Broca's area, left angular and supramarginal gyri, and hippocampus. On the contrary, reading comprehension was negatively correlated with neural activities in the left angular gyrus. These results suggest that rapid readers have reduced language processes, such as phonological processes (e.g., phonological transformation, analysis, and inner speech) and semantic and syntactic processes, and constant reading comprehension during rapid reading. The findings of this study could deepen our understanding of the mechanism of rapid reading and provide a scientific basis for physiological changes in the brain during rapid reading, thereby reducing distrust toward rapid reading and promoting benefit from it.

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Author contributions

YS, SY, and AS conceived the presented idea. YS developed the theory and investigated the report on this research. AS and RU encouraged YS to investigate this work. All authors discussed the results and contributed to the final manuscript.

Conflicts of interest statement

All authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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Original Articles

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Effects of Different Intensities of Repetitive Peripheral Magnetic Stimulation on Spinal Reciprocal Inhibition in Healthy Persons

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Objectives: This study aimed to assess the effect of the spinal circuit of repetitive magnetic stimulation (rPMS) on the soleus muscle among healthy subjects.

Methods: Nineteen healthy adults were included in this study. Intermittent rPMS was applied to the left soleus muscle for 20 minutes. We applied different intensity rPMS (high-intensity, low-intensity, and non-stimulation) in different three days. RI (reciprocal inhibition) from the tibialis anterior to the soleus muscle with an inter-stimulus interval (ISI) of 2ms and 20ms was assessed before, immediately after and 30 minutes at each session.

Results: Two factor repeated measure ANOVA test showed a significant interaction ($F_{2,33} = 9.688$, $p < 0.001$) between tasks and time in the RI ratio 2ms. Post-hoc analysis showed that RI ratio 2ms significantly differed from those immediately after, and 30 min after high-intensity rPMS ($p = 0.001$ and $p = 0.003$, respectively). A significant difference was observed between high-intensity rPMS and non-stimulation immediately after the stimulation ($p = 0.003$). However, no significant difference was found in the RI ratio 20ms between all the intensities ($p > 0.05$).

Conclusion: This study demonstrates that high-intensity rPMS can effectively modulate spinal circuits, as evidenced by the decreased RI in healthy individuals. This suggests the potential use of rPMS as a therapeutic intervention for patients with muscle weakness. Disinhibition of the RI may lead to a more effective contraction of the target muscle. This effect could be expected to strengthen the muscles and alleviate paralysis, making it a promising avenue for future research and clinical applications in the field of rehabilitation. Further investigation is warranted to explore the precise mechanisms underlying the observed effects and to optimize the parameters of rPMS for specific clinical populations.

Key words: repetitive peripheral magnetic stimulation, reciprocal Inhibition, spinal circuits, h-reflex

Introduction

Repetitive peripheral magnetic stimulation (rPMS) and peripheral nerve electrical stimulation are known to induce muscle contraction. Notably, magnetic stimulation is considered less painful than electrical stimulation, as the induced electrical current can directly target deep tissues without penetrating the skin[1)]. This characteristic makes rPMS particularly well-suited for application in patients with chronic pain and muscle weakness. The effectiveness of rPMS extends beyond its application in healthy subjects, where it enhances motor performance[2)], to benefiting patients experiencing central hemiparesis[3)]. Previous research has also highlighted the therapeutic potential of rPMS in addressing musculoskeletal pain[4, 5)] and reducing lumbar radiculopathy pain[6)].

In a comprehensive analysis conducted in 2022, Pan et al. analyzed eight randomized controlled trials

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(RCTs) involving 170 patients with stroke or other neurological disorders, revealing that rPMS can effectively reduce spasticity in both upper and lower limbs[7]. Despite these positive findings, the impact of rPMS on spinal circuit remains unclear. While existing evidence suggests the potential of rPMS as a valuable treatment for promoting motor performance, further exploration is needed to elucidate its effects on spinal circuitry.

Reciprocal inhibition (RI) between agonist and antagonist muscle is mediated by the Ia inhibitory interneurons[8–10], which are responsible for the achievement of smooth movement between these muscles[10, 11]. RI plays a crucial role in modifying aspects of locomotor and other functional abnormalities associated with conditions such as stroke, spinal cord injuries, and other chronic disorders of motor control, ultimately contributing to more effective function[12]. For instance, spinal cord injuries in humans are characterized by heightened stretch reflexes and flexor afferent reflexes, coupled with a reduction in RI. These anomalies are believed to contribute to spasticity[13]. Conditioning the RI pathway holds potential for enhancing spinal cord function in individuals with incomplete spinal cord injuries or other neurological disorders.

Therefore, our study aims to investigate the effects of repetitive peripheral magnetic stimulation (rPMS) on spinal RI using the H-reflex. This exploration seeks to advance our understanding of how rPMS may modulate spinal circuitry and potentially offer therapeutic benefits for individuals with incomplete spinal cord injuries or other neurological disorders.

Materials and Methods

Participants

19 healthy volunteers (8 females and 11 males, with a mean age of 27.79 ± 5.27 years) participated in this single-blind crossover study. All of them met the following inclusion criteria: (1) age between 20–50 years; (2) no history of orthopedic surgery in the lower limb; (3) no medical history of nervous system disease (including epilepsy); (4) not using drugs affecting the central nervous system; (5) without pacemaker or other metallic orthopedic implants in the body. All subjects provided written informed consent before participating in the study. The experiment commenced on July 5, 2022, and concluded on August 30, 2023.

Repetitive peripheral magnetic stimulation (rPMS)

RPMS was delivered using a coil connected to a Salus Talent Pro (REMED, Korea). Subjects were instructed to sit in a relaxed position, and the stimulation coil was positioned on the calf of the left limb, targeting the top of the Achilles tendon to stimulate the soleus muscle belly. Stimulation parameters were a frequency of 50Hz, a 3-second stimulation (10 biphasic pulses, each pulse width 0.02 seconds) with a 6-second interval, and a total stimulation duration of 20 minutes (Figure 1). Notable side effects, such as pain and a burning sensation were carefully managed by adjusting the stimulation intensity according to the subject's pain threshold. Electrodes were removed as a precautionary measure to prevent potential skin burns caused by the heat generated during stimulation.

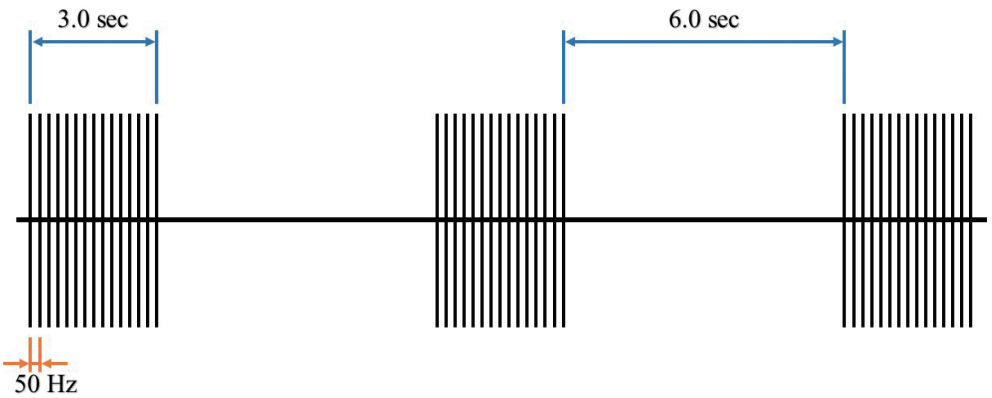

Figure 1 Illustration of the stimulation frequency. The stimulation frequency is set at 50Hz, and each train consists of 10 pulses delivered 3 seconds, followed by a 6-second interval, the stimulation will last for 20 mins.

H-reflex

The H-reflex was elicited by stimulating the tibial nerve at the popliteal fossa using 1ms rectangular pulse. Conditioning stimulation to the common peroneal nerve (CPN) was delivered below the fibular head, with a stimulus intensity of 1.0×motor threshold (MT). MT was defined as a 100μV response of the tibialis anterior (TA). The reflexes were recorded by disc electrodes placed over the soleus muscle. The sensitivity of the H-reflex to facilitatory and inhibitory conditioning effects has been shown to depend crucially on its size[14]. Hence, when measuring the effects of conditioning stimuli, the size of the test soleus H-reflex (testH) amplitude maintained at 20-25% of the maximum M amplitude (Mmax) for each block of trials. The amplitude of Mmax before and 30min after the stimulation was measured to ensure there was no displacement of stimulating electrodes during movement.

Reciprocal inhibition (RI)

RI was assessed using a soleus H-reflex conditioning-test paradigm[15]. Ten conditioned and ten test H-reflexes were measured, and the mean value of the ten measures was calculated. The amount of RI was defined as mean conditioned H-reflex amplitude divided by mean test H-reflex amplitude. To confirm optimal disynaptic RI, we checked the H-reflex at a conditioning-test interstimulus interval (ISI) of 0, 1, and 2ms at the beginning of each session. The ISI were set at 2ms and 20ms to trigger inhibition through separate mechanisms[16]. Inhibition at an ISI of 2ms is called disynaptic RI (RI2ms) and is mediated by a spinal glycinergic disynaptic inhibitory pathway[17,18]. Inhibition at an ISI of 20ms (RI20ms) is called short-latency presynaptic inhibition, which is thought to result from presynaptic Ia inhibition of afferent fibers that mediate the H-reflex[16]. We assessed RI before, immediately after, and 30 minutes after each stimulation.

Experimental Procedure

Three types of rPMS (high-intensity stimulation, low-intensity stimulation and non-stimulation) were randomly applied on separate days. High-intensity was defined as the maximal intensity the participants can tolerate without pain and induce muscle contraction. The low-intensity is the motor threshold of soleus muscle, with intensity stimulation evoking minimum muscle twitch. For the non-stimulation, coil was placed in the same position as high and low-intensity stimulation, but stimulus intensity was set at 0. We assessed RI before, immediately after rPMS (post) and 30 minutes after rPMS (post 30) (Figure 2).

Statistical analyses

The Kolmogorov-Smirnov test was utilized to assess the normal distribution of all data, and no significant deviation from normality was observed. Two-factor repeated measures ANOVA was used to analyze the effects of types of rPMS (high-inten-

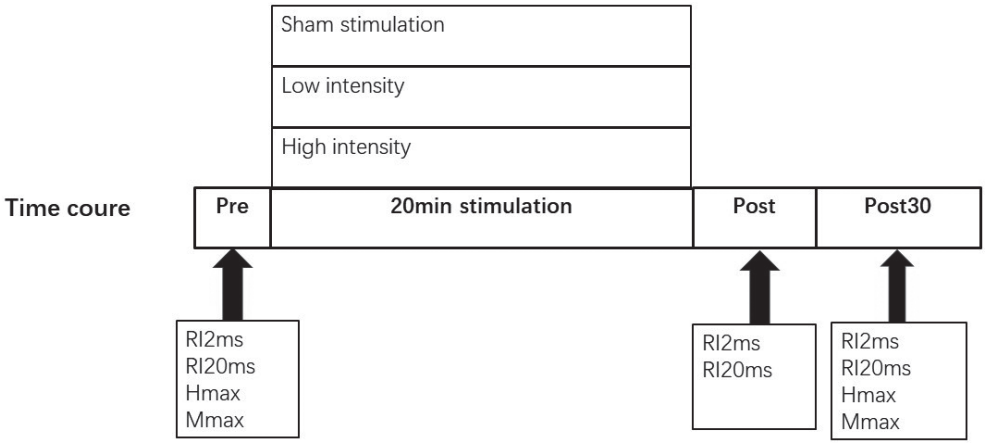

Figure 2 Experimental procedure. Nineteen subjects participated in three sessions: (1) non-stimulation; (2) low-intensity; (3) high-intensity. All three sessions are delivered in 20 minutes. Measurements of reciprocal inhibition at ISI 2ms and 20ms were taken before, immediately after (post), and 30 minutes after (post30) each stimulation session.

sity stimulation, low-intensity stimulation, and non-stimulation) and time points (before, immediately after and post30) of the differences in RI ratio. The changes of testH and Mmax amplitudes of each stimulation were analyzed with one-factor repeated measure ANOVA with main factor of time.

For post hoc comparisons, Scheffe's test for multiple comparisons was employed to analyze the results of all data. Results with P values < 0.05 were considered statistically for all analyses. Statistical analyses were conducted using SPSS 29.0 (IBM Corp, Armonk, NY, USA) for Windows.

Results

The mean testH amplitude was 3.54 ± 1.49 mV before high-intensity stimulation, 3.19 ± 1.55 mV before low-intensity stimulation, 3.70 ± 1.63 mV before non-stimulation. There were no significant differences in the baseline of the testH amplitudes among different paradigms ($F = 0.510$, $p = 0.603$). One-way repeated measure ANOVA showed no significant main effect of time (before, immediately after, 30min after) on the testH amplitudes in high-intensity stimulation ($F = 0.053$, $p = 0.948$), low-intensity stimulation ($F = 0.154$, $p = 0.858$), and non-stimulation ($F = 0.063$, $p = 0.939$).

The mean Mmax amplitude was 18.25 ± 4.76 mV before high-intensity stimulation, 18.41 ± 4.52 mV before low-intensity stimulation, 18.83 ± 5.00 mV before non-stimulation. There were no significant differences in the baseline of the Mmax amplitudes among different paradigms ($F = 0.185$, $p = 0.981$). One-way repeated measure ANOVA showed no significant main effect of time (before and 30min after) on the Mmax amplitudes in high-intensity stimulation ($F = 3.888$, $p = 0.058$), low-intensity stimulation ($F = 0.528$, $p = 0.473$), and non-stimulation ($F = 0.819$, $p = 0.373$).

Furthermore, at baseline, the amount of RI ratio did not exhibit a significant difference between different stimulation types. However the analysis (ANOVA) revealed a significant interaction ($F_{2,33} = 9.688$, $p < 0.001$) between tasks and time in the RI ratio at 2ms. Post-hoc testing indicated that high-intensity rPMS significantly increased RI ratio 2ms post and post30 compared to pre ($p = 0.001$ and $p = 0.003$, respectively). Additionally, a significant difference of RI ratio 2ms was observed between the value of high-intensity and non-stimulation rPMS immediately after the stimulation ($p = 0.003$) (Figure 3A).

The RI ratio is calculated by dividing conditioned H-reflex amplitude by test H-reflex amplitude, an increase in the RI ratio represents a decrease in inhibition, while a decrease in the RI ratio represents

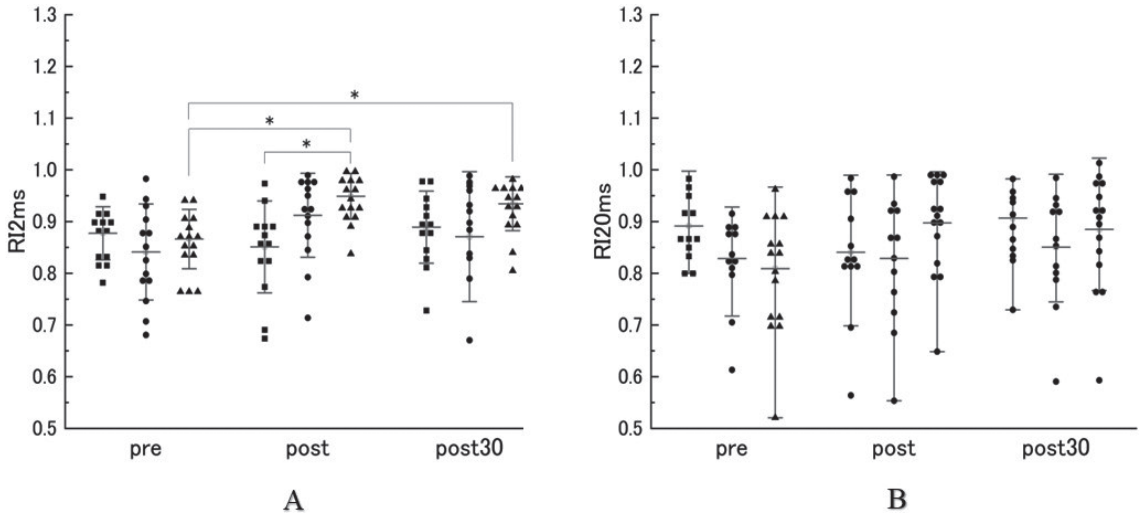

Figure 3 Changes in reciprocal inhibition (RI) with an ISI of 2ms (RI ratio 2ms) and 20ms (RI ratio 20ms) under different stimulation intensities. Asterisks indicate significant differences. Filled square represents non-stimulation intensity; filled circle represents low-intensity; filled triangle represents high-intensity. Significant difference was observed between pre RI ratio 2ms and post RI ratio 2ms ($p = 0.001$) as well as pre RI ratio2ms and post 30 RI ratio 2ms ($p = 0.003$) following the high-intensity rPMS intervention. There is also a significant difference between the non-stimulation post RI ratio 2ms and high-intensity post RI ratio 2ms ($p = 0.003$) (Figure 3A). However, no significant difference was found in the RI ratio 20ms between all the intensities (Figure 3B).

an increase in inhibition. We also found no significant difference in the RI ratio 20ms between all the intensities ($p > 0.05$) (Figure 3B).

Discussion

In this experiment, we applied 3 intensities of rPMS to the soleus muscle and utilized RI to access the effect of the spinal circuit. We observed that high-intensity rPMS led to disinhibition with an ISI of 2ms. RPMS on the soleus muscle induced a visible, strong plantar flexion of the ankle, forcing the soleus muscle to contract, similar to voluntary plantar flexion. Higher intensity rPMS can activate more muscle spindles; the activated Ia afferent neuron can fire more alpha motor units which can generate stronger contraction of the soleus muscle. The contraction of the soleus muscle generates stronger inhibition to the tibial anterior (TA), and weaker activity of the TA can also explain the disinhibition effects of RI from TA to soleus found under high-intensity stimulation. And we also considered the reason why only RI2ms is disinhibited. In this experiment, all subjects are healthy people with normal RI, making interference of RI20ms more challenging than in patients with impaired RI. The simplest explanation for this result is that modulation of the interneurons mediating short-latency presynaptic inhibitions might be weak compared to the effects on the circuit responsible for disynaptic RI. Applying high-intensity rPMS to patients with neurological disease or paralysis, who may struggle with voluntary contraction to control the target muscle, could potentially induce disinhibition of the RI. This could also result in more effective contraction to the target muscle, offering the potential to strengthen muscle and alleviate paralysis, making it a promising avenue for future research and clinical applications in the field of rehabilitation. The non-invasive nature of rPMS, along with its capacity to induce plasticity in spinal circuits, highlights its potential for future research and clinical applications in neuromodulation. Further investigations are needed to elucidate the underlying mechanisms and optimize rPMS parameters for specific clinical populations.

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Author contributions

All authors read and approved the final manuscript.

Conflicts of interest statement

The authors declare that there are no conflicts of interest.

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Original Articles

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An Investigation into the Prevention of Turnover of Medical Interpreters

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Objective: Since there have been no studies for the prevention of job turnover among medical interpreters, this study examined the effects of social support, professional career maturity and stress coping on their attitudes toward job continuity intentions.
Design: A cross-sectional study was conducted to examine the relationships between social support, professional career maturity, stress coping and job continuity intentions.
Methods: Stress coping was measured by using a simplified stress coping scale (with 9 items and 1 factor structure). Social support was measured by defining the interpreters who answered "Yes" for "I have someone to talk to when I feel emotional stress". Professional carrier maturity was assessed by using, 12 career-related items. We defined those interpreters who responded "No" to "Have you ever wanted to quit medical interpreting due to emotional stress?" were to have job continuity intentions.
Results: The present study indicated that 14 (25.5%) of the interpreters did not intend to continue their occupation because of their psychological stresses. Compared to interpreters without social support, the odds ratio of job continuity intentions was 4.39 (95% confidence interval [CI] : 1.13–18.3) for those with social support. Moreover, in comparison with the interpreters with low professional career maturity, the odds ratio of job continuity intentions was significantly higher for those with high professional career maturity (odds ratio [OR] = 4.35; 95%CI: 1.12–21.8). However, there was an association found for stress coping.
Conclusions: Strengthening social support and helping professional career development were the important factors for medical interpreters to be able to continue their careers.

Key words: stress coping, mental stress, social support, professional carrier maturity, job continuity intentions

Introduction

As medical tourism and inbound activities (i.e., tourism, travel, and business) are likely to increase rapidly when normality is restored with regards to COVID-19[1], the demand for medical interpreters is also expected to rise[2]. For instance, approximately 2.88 million foreigners (2.2% of the total population at the end of FY2020) live in Japan[3]. The demand for medical interpreters has been increasing[4]. And due to language barriers and differences in culture, religion, and lifestyle, only 2.2% of the medical institutions were able to provide services to the required department for foreign patients[5]. This reality implies that there is virtually no medical support system for non-Japanese residents. Moreover, benefits in relation to improved health habits from continuous usage of medical interpreters is estimated to be worth roughly 5.8 billion yen by the MHLW[6]. Yet, the reality is that the medical

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interpretation field in our country is very much behind compared to Western countries[7, 8]. As a result, a shortage of professional medical interpreters seems to be nearing reality[9].

Since the medical interpreting system is not standardized in Japan[10–12] various organizations and institutions have developed their own systems, yet the recognition of medical interpreters is still low[13]. Moreover, the salary of a medical interpreter is often said to be at volunteer level and is not sufficient to make a decent living[7, 14]. For example, a reward, 3,000 Japanese yen (including transportation and income tax) per 3-hour session is paid to medical interpreters by Multicultural Center Kyoto, which is hardly to say an adequate livelihood guarantee. The study also has been pointed out that medical interpreters tended to quit their jobs within five years[15].

The current situation clearly highlights the unstable social status of medical interpreters[16]. In comparison with other conference interpreters, Mizuno and Naito (2015) pointed out the large emotional burden of medical interpreters[17]. Medical interpreters work in stressful medical-specific situations such as illness, death, injuries, treatments, and lab examinations. However, their duties cannot be fulfilled if they are upset by surgery, emergency care, or the mere sight of blood. In addition, if they empathize too much with the patient, they will experience a lot of mental suffering[17, 18]. Torikai[19] asserts that "Even if the world becomes a multilingual society, medical interpretation will not be handled by automatic interpretation machines". The rationale for this is that empathy, which medical interpreters can provide, is a function of the mind[20]. In other words, verbal communication between patients and health care professionals (HCPs) in the clinical environment is extremely delicate and requires a high level of sensitivity, as well as a variety of non-verbal communications[21]. For medical interpreters to function as professionals while maintaining a certain level of quality, mental and physical health management is considered to be essential. However, there have been no studies on the prevention of turnover as well as stress coping among medical interpreters in Japan[22], while there is a report[23] of 200 workers who developed mental illnesses and left their jobs due to workplace stress in 2021.

Therefore, it is crucial to investigate how medical interpreters avoid burnout through stress coping and/or social support to prevent them from leaving their jobs to continue their careers.

Methods

Subjects

Medical interpreters that were registered with MediPhone (248 interpreters) − a telephone medical interpreter dispatch organization − or the National Association of Medical Interpreters (NAMI; 305 interpreters) were targeted for this study. A total of 55 medical interpreters were enrolled in the present study.

A "Request for Research, Purpose and Significance of the Study" was sent via email to the responsible person at the targeted organization. After obtaining permission, we sent an anonymous questionnaire survey via Google Forms to active medical interpreters registered with the organizations. The explanatory document also included information on the "purpose of the research", "withdrawal after consent to conduct research", "handling of personal information" and "consultation service for research subjects", and checking the consent box was considered to agree with informed consent.

This study was approved by the Juntendo University Graduate School of Medicine Ethics Committee for Medical Research (approval number: Juntendo University Medical Ethics No. E21-0235-M01) and conducted from January 12, 2022, to February 28, 2022 and the questionnaire was conducted in Japanese.

Measures

The survey took approximately 5 minutes to complete and interpreters were asked stress coping, social support, professional carrier maturity, job continuity intentions and the basic information including age (years), sex (male vs. female), salary (adequate vs. insufficient), native language, and interpreting language. Stress coping was calculated using a simplified (factor-structured) stress coping scale with nine items (Appendix 1)[24]. And the following four-point scale was used: "1: not at all", "2: hardly at all", "3: sometimes", and "4: often." Interpreters with a median value of ≥ 27 out of 36 points were defined as having stress coping. Stressful medical interpreting environment was also investi-

gated with the question "In which situation did you feel stressed?" and interpreters responded from answers including "in medical environments", "psychological problems (anxiety, shock, pressure)", "responsibility/confidentiality", and "human relations". Social support was measured by defining the interpreters who answered "Yes" for "I have someone to talk to when I feel emotional stress" as having social support. For those who answered "Yes" to the above, the following question was also asked: "Who (where) do you consult when you feel emotionally stressed?" This question was asked to induce specific social support by providing multiple answers from nine choices that were categorized into four segments: "1: fellow interpreters", "2: psychological counseling or others", "3: family/friends (patients, family, friends)", and "4: medical personnel (doctors, nurses, clerks)". To assess professional carrier maturity in the present study, 12 career-related items were taken from the Occupational Career Maturity Measurement Scale (Appendix 2), which was developed by Karino et al.[25], with permission of the first author. Occupational career maturity was calculated using the following five-point scale out of 60 points: "1: not applicable", "2: not very applicable", "3: undecided", "4: somewhat applicable", and "5: very applicable. We used a median value of ≥ 49 to signify a high level of professional carrier maturity. The professional carrier maturity was consisted of three types of questions with three reverse questions (i.e., interest, autonomy, and planning and analysis). Questions 1 to 4 related to interest, 5 to 8 related to autonomy, and 9 to 12 related to planning and analysis. Higher total scores indicated greater professional carrier maturity[26].

Measurement of medical interpreters' willingness for job continuity intentions

Interpreters who responded "No" to "Have you ever wanted to quit medical interpreting due to emotional stress?" were defined to have job continuity intentions. Interpreters who answered that they have never wanted to quit interpreting due to mental stress were considered to have an awareness of continuity in the profession. We used a question from a previous study[27] to confirm their intention to continue in the profession (Appendix 2). The interpreters who answered that they have wanted to quit their job as a medical interpreter were asked in which situations they felt like quitting, with four categories of multiple choice: "1: in the medical environment (consultation room, shock by seeing wounds, anxiety by contacting COVID-19 patients, PTSD)", "2: psychological problems (mental illness, cancer, emergency, operation, DV and crime victims, death of the patients who interpreted)", "3: high responsibility and low pay, confidentiality stress", and "4: human relations with HCPs, with medical interpreters)".

Statistical analysis

The difference of proportions and means according to stress coping, social support, and professional carrier maturity categories were tested by Chi-square and T-test. Multivariate logistic regression analysis was used to examine the relationships between job continuity intentions, stress coping, social support, and professional carrier maturity, with adjustments for sex and age. All statistical analyses were performed using the SAS software package (version 9.4, SAS Institute, Cary, NC, USA). All p-values for statistical tests were two-tailed, and values of $p < 0.05$ were denoted as statistically significant differences.

Results

The basic characteristics of the interpreters are shown in Appendix 3. The study population consisted of 55 interpreters (7 males and 48 females) registered with a medical interpreting company, with a response rate of 9.9%. The minimum and maximum ages were 32 and 68, respectively, with a mean age of 50.2 years old (SD = 8.76). Most interpreters (36.4%) had been interpreting medical information for "5-10 years", while 14.5% had been interpreting for "10 years or longer" and 5.5% had been interpreting for "less than 1 year". Moreover, 60% in interpreters indicated that the salary was insufficient.

Most (80%) of were the native Japanese interpreters, while 20.0% were native speakers of a foreign language. Of the 11 native speakers of foreign languages, 27.3% were native speakers of Chinese and 27.3% were native speakers of Vietnamese, accounting for more than half of the interpreters. There was a total of 16 interpreting languages, with English and Japanese being the most common (31.0%), followed by Chinese and

Japanese (16.4%).

In terms of job continuity intentions (JCIs), 25.5% (14 interpreters) answered "I have wanted to quit my job as a medical interpreter due to emotional stress". The specific situations cited by those who wanted to quit medical interpreting were medical practices (35.7%), psychological problems such as anxiety, shock, and pressure (28.7%), responsibility/confidentiality (21.4%), and human relationships (14.2%).

The highest response regards to social support was from fellows (31%) or psychological counselors or others (31.0%), followed by family and/or friends (28.0%), and medical professionals (10.0%). On the other hand, more than one fourth (27.3%) responded that they have no person or place to consult with when they have psychological stress.

Table 1 shows that the interpreters with social support had high professional carrier maturity ($p = 0.02$). And among the 15 interpreters without social support, the percentage of the high professional carrier maturity was 62%. It was apparent that the interpreters with social support also had stress coping (92%) and the interpreters without social support were likely to have stress coping ($p = 0.007$). In terms of professional carrier maturity, interpreters with stress coping seems to have higher professional career maturity ($p = 0.05$). And the percentage of without stress coping and low professional carrier maturity was the highest (69%) while the percentage of without social support and low professional carrier maturity was 38.0%.

There were significant associations found between job continuity intentions and social support (OR = 4.39; 95%CI: = 1.13–18.31) and job continuity intentions and professional carrier maturity (OR = 4.35; 95%CI: = 1.12–21.85), respectively (Table 2). However, similar results were not observed for stress coping.

Table 1 Background of the medical interpreters

		n	Mean Age (SD)	p value	Medical interpretation history, %		p value	Sex, %		p value	Salary, %		p value	Social support, %		p value	Stress coping, %		p value	Professional carrier maturity, %		p value
					< 5 years	≥ 5 years		Male	Female		Adequate	Insufficient		With	Without		With	Without		High	Low	
Social support	With	40	50.9 (8.96)	0.33	45.0	55.0	0.38	10.0	90.0	0.38	37.5	62.5	0.7				45.0	55.0	0.007	88.0	12.0	0.02
	Without	15	48.3 (8.11)		60.0	40.0		20.0	80.0		46.7	53.3					87.0	13.0		62.0	38.0	
Stress coping	With	24	48.9 (8.56)	0.34	37.5	62.5	0.13	17.0	83.0	0.44	42.0	58.0	0.88	92.0	8.0	0.007				62.5	37.5	0.06
	Without	31	51.2 (8.92)		58.1	42.9		9.7	90.3		38.7	61.3		58.0	42.0					35.5	64.5	
Professional carrier maturity	High	26	51.0 (8.40)	0.52	54.0	46.0	0.59	15.0	85.0	0.58	38.0	62.0	0.96	85.0	15.0	0.06	58.0	42.0	0.05			
	Low	29	49.5 (9.15)		45.0	55.0		10.0	90.0		41.0	59.0		62.0	38.0		31.0	69.0				

Discussion

Recently, surveys of medical interpreters in a wide variety of languages have revealed a variety of conditions involving psychological distress, burden, and stress[28–30]. For example, a study of interpreters working in the field of refugee care in Germany (164 interpreters) reported significantly higher psychological distress in terms of anxiety and depression, and approximately 7% of those surveyed were positive for post-traumatic stress

Table 2 Relationship between social supports, stress coping, professional carrier maturity, and job continuity intentions

		Odds ratio	95% Confidence Interval	R^2	p-value
Social support	Crude	4.13	1.13–15.73	4.55	0.03
	Multivariable*	4.39	1.13–18.31	4.46	0.03
Stress coping	Crude	1.04	0.31–3.68	0.005	0.95
	Multivariable*	1.11	0.31–4.13	0.02	0.88
Professional career maturity	Crude	4.69	1.25–23.05	4.56	0.03
	Multivariable*	4.35	1.12–21.85	3.98	0.05

*Adjusted for age and sex.

disorder (PTSD)[31]. Moreover, Loutan et al. (1999) conducted an anonymous survey of 22 interpreters registered as volunteers with the Red Cross in Geneva[32]. Five of these interpreters (28%) frequently experienced psychologically difficult emotions while interpreting, while 12 (66%) reported recalling painful memories frequently. According to the Report of the Survey of the Dispatched Medical Interpreters' Performance in Japan[33], the most common stress experienced by medical interpreters is "emotional involvement with the patient" (31%), followed by "stressful due to confidentiality" (22%). In response to this mental stress, strengthening the self-management of medical interpreters has been proposed in recent years[34].

Most of the previous studies on stress coping among medical interpreters have been qualitative studies[18, 26, 29]; instead, this cross-sectional study was a quantitative study based on an online survey. Our study found that interpreters with social support or professional carrier maturity had higher odds of having job continuity intentions. However, we did not find a similar association for stress coping.

Previous studies have shown that many medical interpreters leave the profession due to low pay, high emotional strain, and volunteer status, in contrast to the high levels of skill and responsibility required[35].

The results of this study were consistent with previous studies, with more than half (60.0%) reporting that their salary is low[36], and more than a quarter (25.5%) stating that they have wanted to quit the medical interpreting profession due to emotional stress[14]. The results of the survey also agreed with those of previous studies, in that the medical environment was the most common situation in which the interpreters cited wanting to leave their jobs, followed by psychological pressure[32–33, 37].

Social support seems to be a crucial element for the prevention of turnover of medical interpreters. Our results showed that medical interpreters with higher stress coping had a higher percentage of social support (92.0%) compared to those with low stress coping (58.0%), which are consistent with the results of previous studies[16, 18]. Interpreters with higher professional carrier maturity were more likely to have stress coping. Folkman and Lazarus (1986) examined cognitive appraisal and coping processes in stressful situations and found that coping was strongly related to cognitive appraisal and that forms of coping differed depending on coping options[38]. This suggests that medical interpreters with high professional carrier maturity and job continuity intentions may have high autonomy[39] and are less likely to leave their jobs even if their stress coping is low because of their psychological burdens[40]. Furthermore, the simplified stress coping scale used in this study contained only item that was classified as cognitive (automatic thinking) coping; all other items were classified as behavioral coping. Although cognitive (automatic thinking) and behavioral coping are considered to be the only effective stress reactions, behavioral coping items such as "enjoyed time with family and friends" and "talked to someone" may not be recognized as coping by certain individuals because these items are not regarded as skills obtained by learning[41]. Since stress coping is also regarded as self-care[42], there may be a need for improved structural regulation of the professional occupation of medical interpreter[6].

The results from our study potentially suggest the need for improved social support and working conditions for interpreters. While some studies have

focused on stress coping and stress reduction[43-44], Nakajima (2006) revealed that social welfare workers who have high social support from supervisors, colleagues, and family and friends are less likely to suffer depression[45] and may have a decreased turnover rate. Having high social support can bring a sense of controlling stress[46] and intention to work[47].

Hence, social support helps to alleviate stress because it may provide instant emotional releases and solutions to problems[48].

There were few limitations of this study. Firstly, selection bias may have occurred when selecting the two organizations to be surveyed. The survey was conducted for medical interpreters in Tokyo; therefore, the generalization of our study may be limited. Secondly, this study did not obtain interpreters' educational background and marital status, which have been shown to be related to stress and professional career maturity in the previous studies[29, 40]. The results could be confounded by these unmeasured variables. Thirdly, since this is cross-sectional study, causality cannot be shown clearly. Fourthly, interpreters without job continuity intentions were defined as those that answered "Yes" to a single question "I have wanted to quit my job as a medical interpreter due to mental stress." However, this cannot exclude contradictory human emotion and cognition. In addition, since this survey was conducted during the COVID-19 pandemic, the lower response rate could be due to a reduced demand for medical interpreters because of a burden on medical facilities with policies such as stay homes and avoid the "Three Cs[49] (i.e. closed spaces, crowded places, and close-contact settings)". With regard to this survey, we only know the attributes of the respondents, therefore, the difference in attributes between those who responded to this survey and those who did not cannot be considered. Finally, since this study had a small sample, further research is necessary for more detailed results.

Nonetheless, this is the first quantitative study that examined the impact of social support, stress coping, and professional carrier maturity on job continuity intentions in Japan, as the only a quantitative study has been conducted in Germany[29]. The results corroborated that professional carrier maturity is related to job continuity intentions of medical interpreters and showed the importance of social support for daily mental stress.

In summary, social support and professional carrier maturity seem to play important roles in the continuity of medical interpreters' careers. The results of our study suggested that it is important to strengthen social support for mental stress in medical interpreters. In the future, it will be necessary to increase the number of survey participants and conduct a longitudinal study to examine any causal associations between social support and professional carrier maturity. In order to prevent medical interpreters from leaving the profession, it is important to develop a system to enhance their social support and therefore reduce mental stress.

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Author contributions

JH, SS, and JY contributed in discussion for the preparation of the questionnaire and collecting raw data. FN and NO examined the research process and provided various comments on the research. AI analyzed the statistical data and a major contributor in the statistical interpretation. All authors read and approved the final manuscript.

Conflicts of interest statement

The authors declare that there are no conflicts of interest.

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Appendix 1　Stress coping scale (9 items)

1　Laughing and having a good time
2　Enjoyed time with family and friends
3　Tried to relax
4　Tried to change my mood (hobbies, travel, etc.)
5　Tried to be physically active as much as possible
6　Tried to reduce stress
7　Talked to someone about it
8　Talked to someone about something
9　Tried to sleep well

Appendix 2　Professional carrier maturity (12 items) and job continuity intentions (1 item) scales

Interest
1　I actively try to collect information that is useful for my professional life and work
2　I give serious thought to designing my professional life because it is an important issue for me
3* I do not care much about how I should work
4　I have thought about how I can improve my professional life

Autonomy
5　I am proactive in my professional life
6* Often find working boring
7　I have voluntarily decided what kind of professional life I want to lead
8　I want to further develop and improve myself through my professional life

Planning and analysis
9　I have my own outlook on my future professional life
10　I have a number of things I would like to work on in my future professional life
11* I do not know what my goals should be in my professional life
12　I think I will be able to achieve the kind of professional life I expect in the future

Professional continuity consciousness
13　Questions about attitudes towards continuing in the profession
Do you want to continue in your current profession (medical interpreting)?

*Reverse questions.

Appendix 3　Basic characteristics of the medical interpreters

		n	%
Sex			
	Female	48	87.2
	Male	7	12.8
Age	Mean age (SD)	50.2 (8.76)	
	40s and under	26	47.3
	50s	19	34.5
	60s and over	10	18.2
Length of medical interpretation experience			
	Less than 1 year	3	5.5
	1 year – less than 3 years	7	12.7
	3 years – less than 5 years	17	30.9
	5 years – less than 10 years	20	36.4
	More than 10 years	8	14.5
Native speakers of Japanese		44	80.0
Native speakers of foreign languages		11	20.0
	Chinese	3	27.3
	Vietnamese	3	27.3
	Portuguese	1	9.1
	Russian	1	9.1
	Burmese	1	9.1
	Indonesian	1	9.1
	Tagalog	1	9.1
Language of interpretation			
	English⇔Japanese	17	31.0
	Chinese⇔Japanese	9	16.4
	Spanish⇔Japanese	7	12.7
	Portuguese⇔Japanese	5	9.1
Other languages between Japanese and (Korean, Thai, Indonesian, Mongolian, Nepalese, Russian, French, Sinhalese, Burmese, Vietnamese, Tagalog)		17	30.8
Salary			
	Adequate	22	40.0
	Insufficient	33	60.0
Have you ever wanted to stop working as a medical interpreter due to emotional stress? (JCIs)			
	Yes (Without JCIs)	14	25.5
	No (With JCIs)	41	74.5
In what situations have you wanted to quit your job as a medical interpreter?			
	In the medical environment such as consultation room	5	35.7
	Psychological problems (anxiety, shock, pressure)	4	28.7
	Responsibility/confidentiality	3	21.4
	Human relations	2	14.2
Do you have people (or places) to talk about mental stress? (SS)			
	Yes (With SS)	40	72.7
	No (Without SS)	15	27.3

	n	%
If you answered “Yes”, who (where) do you consult when you feel emotionally stressed? (SS)		
Fellow interpreters	13	31.0
Psychological counseling or others	13	31.0
Family/friends	11	28.0
Medical personnel	2	10.0
Stress coping (9 items)		
Total score 9–26: (Without SC)	31	56.0
Total score 27–36: (With SC)	24	44.0
Professional career maturity (13 items)		
Total score 12–48: Low (Without JCIs)	29	52.7
Total score 49–60: High (With JCIs)	26	47.3

JCIs indicated job continuity intentions; SS indicated social support; SC indicated stress coping

Reviews

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Effect and Concern of Breastfeeding in Infants

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Human breast milk is considered the optimal source of nutrition for infants and is recommended as the exclusive nutrient source for term infants during the first six months of life. Existing evidence strongly supports the direct benefits of breastfeeding, encompassing benefits for nutrition, gastrointestinal function, and protection against acute illness in both term and preterm infants. Previously, we demonstrated a notable reduction in a urinary marker of oxidative DNA damage in breastfed term and preterm infants compared to formula-fed infants. While long-term benefits of breastfeeding on neurodevelopmental outcomes and adult health have been reported, the effects may be relatively modest and limited.

Key words: human milk, oxidative stress, infants

Introduction

Breastfeeding provides optimum support for infant and maternal health, and is recommended in both industrialized and developing countries as the exclusive nutrient source for term infants during the first six months of life[1]. In the Global Nutrition Targets for 2025, the World Health Organization recommends increasing the rate of exclusive breastfeeding up to at least 50% among infants less than six months[2]. Human breast milk offers nutrients with high bioavailability and in sufficient qualities to support infant growth, and this practice is recommended to be continued alongside the introduction of complementary foods after the initial six months[1]. Various factors, such as the duration of lactation, gestational length, maternal health, genotype, and diet, influence the composition of milk and the production of colostrum, transitional, and mature milk[3]. Colostrum contains a high concentration of whey proteins and exhibits lower levels of lactose and fat compared to mature milk[3,4]. Colostrum includes high concentrations of bioactive compounds, including secretory immunoglobulin A (sIgA) and lactoferrin[5]. sIgA plays a crucial role in protecting the intestinal epithelium from enteric toxins and pathogenic microorganisms. Through a process known as immune exclusion, sIgA facilitates the clearance of antigens and pathogenic microorganisms from the intestinal lumen by blocking their access to epithelial receptors and entrapping them in mucus[6]. This review aimed to summarize the existing literature on the health benefits of breastfeeding in term and preterm infants.

Macronutrients in human milk

The macronutrients of human milk and their contributions to the total energy intake of breastfed infants are derived from carbohydrates (45%), fats (44%) and proteins (8%) at one month of age[7].

Proteins and nonprotein nitrogen

The protein content of human milk is at its peak during the production of colostrum (approximately

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15 to 20 g/L) and gradually decreases in mature milk from the second to the sixth or seventh month of lactation, reaching approximately 10 g/dL[3,4]. Human milk contains a heterogeneous mixture of over 400 casein, whey, and mucin proteins and peptides that provide nutrition, antimicrobial and immunomodulatory activities, and stimulate nutrient absorption[8]. Proteins are essential for infant growth, with specific proteins (e.g., lactoferrin and α-lactalbumin) acting as carriers of nutrients, promoting gut development (e.g., growth factors and insulin), aiding nutrient absorption (e.g., bile salt-stimulated lipase, amylase, and α-antitrypsin), or exhibiting immune and antimicrobial activity (e.g., lactoferrin and sIgA)[9]. Colostrum has a whey-predominant composition (90:10 whey/casein ratio) and elevated concentrations of growth factors, sIgA, lactoferrin, and lysozyme compared to mature milk. The quantity and quality of milk proteins exert a significant influence on infant growth and body composition. High protein intake during infancy activates the insulin-like growth factor-I axis and has been associated with increased weight gain and a higher risk of obesity later in life[10]. The total nitrogen content in human milk follows a similar pattern, being highest in colostrum (3.0 g/L) and decreasing in mature milk (1.9 g/dL)[3,4]. Nonprotein nitrogen, encompassing urea, creatinine, nucleotides, free amino acids, and peptides comprise 25% of the total nitrogen in human milk. Nucleotides, considered conditionally essential nutrients, modulate enzyme activities and promote the development and maturation of the gastrointestinal and immunological systems[3].

Carbohydrates

The principal sugar in human milk is lactose, a disaccharide with a concentration of approximately 6.7 g/dL. This concentration surpasses that found in the milk of other species and underscores its significance in meeting the nutritional requirements of the brain[3]. Lactose serves as an important source of galactose, essential for the development of the central nervous system. Other major carbohydrates found in human milk are oligosaccharides, ranging from 2.1 g/dL in colostrum to 1.3 g/dL in mature milk[11]. Over 200 acidic or natural oligosaccharides have been identified in human milk, with their composition influenced by maternal genetics[12,13]. While oligosaccharides are not digestible, they function as prebiotics that serve as metabolic substrates for beneficial bacteria, including *Bifidobacteria* and *Bacteroides* species. Additionally, oligosaccharides modulate infant mucosal and systemic immune functions[14].

Lipids

Lipids, present as an emulsion, contribute 40–50% of the total energy of human milk[7]. Colostrum contains lipid concentrations of 1.5–2.0 g/dL, while mature milk exhibits 3.5–4.8 g/dL. Approximately 98% of milk lipids are secreted as triglycerides, serving as a crucial source of essential nutrients such as polyunsaturated fatty acids (PUFAs), lipid-soluble vitamins, complex lipids, and bioactive compounds. The remaining lipid content consists of diglycerides, monoglycerides, free fatty acids, phospholipids, and cholesterol[7]. The properties of triglycerides are determined by their fatty acid composition, with minimal non-estrified fatty acids present in human milk. Triglycerides account for 88% of the fat, with approximately 43% saturated fatty acids, 35% cis-monosaturated, 1% to 7% trans-monounsaturated, and 20% PUFAs (19% n-6 and 1% n-3)[15]. Although the lipid content is influenced by the mother's diet, palmitic acid is the most predominant saturated fatty acid, commonly found in the sn-2 position. This positioning enhances absorption and improves calcium absorption. Most infant formulas contain triglycerides with palmitic acid in the sn-1 and sn-3 positions. Pancreatic lipase selectively hydrolyzes triglycerides in these positions, producing two free fatty acids and a monoglyceride. The 2-monopalmitin produced during the digestion of human milk fat is readily absorbed, while the free palmitate formed during the digestion of formula milk may combine with calcium to form soaps and be lost in the feces[16].

The long-chain polyunsaturated fatty acids (LCPUFAs) in human milk are influenced by the mother's diet, with those possessing more than 20 carbons and 2 or more double bounds comprise only about 2% of the total fatty acids in breast milk[17]. Human milk contains n-3 and n-6 LCPUFAs, such as arachidonic acid (AA, 20:4, n-6) and docosahexaenoic acid (DHA, 20:4 n-3). A systematic review reported worldwide concentrations (by weight) of 0.47 ± 0.13% for AA and 0.32 ± 0.22% for

DHA. The DHA content tends to be lower and more variable based on the mother's diet[18, 19]. The importance of dietary intake of AA and DHA for visual and cognitive development, particularly in preterm infants[20]. Consequently, LCPUFAs are now routinely supplemented in preterm and term infant formulas.

Benefits of breastfeeding

Direct effects

The antimicrobial and immunomodulatory properties of human milk support the immature neonatal immune system and inhibit the movement of pathogens across the gastrointestinal barrier[21]. Notably, breastfed infants exhibit a more stable and less variable intestinal microbiota compared to formula-fed infants, with over twice the number of bacterial cells[22]. Human milk contains various factors that inhibit inflammation or stimulate antibody production, including platelet-activating factor acetylhydrolase (PAF-AH), interleukins, and transforming growth factor[21]. Colostrum contains high concentrations of bioactive compounds such as sIgA, lactoferrin, and leukocytes[5]. Moreover, specific components of human milk, such as insulin-like growth factor, insulin, and epidermal growth factor, actively promote gastrointestinal growth, motility, and maturation, and may be protective against disease[23].

Antioxidant properties

Human milk is rich in various antioxidant enzymes, including catalase, glutathione peroxidase, and superoxide dismutase. Additionally, it contains essential cofactors such as copper (Cu) and zinc (Zn); vitamins A, C, and E; and binding proteins such as lactoferrin[24]. In contrast, infant formulas lack antioxidative enzymes[25], but compensate with the inclusion of higher amounts of vitamin supplements compared to human milk to compensate for the reduced bioavailability. Therefore, evaluating the overall antioxidant capacities of human milk versus infant formulas is challenging; however, it is likely that human milk is favorable in this regard[26]. A previous study reported significantly lower urinary excretion of 8-hydroxy-2′-deoxyguanosine, a marker of oxidative DNA damage, in breastfed term infants compared to formula-fed term infants (Figure 1)[27]. This difference may be attributed to the presence of antioxidants in human milk, which are effectively transferred through the relatively porous neonatal intestine.

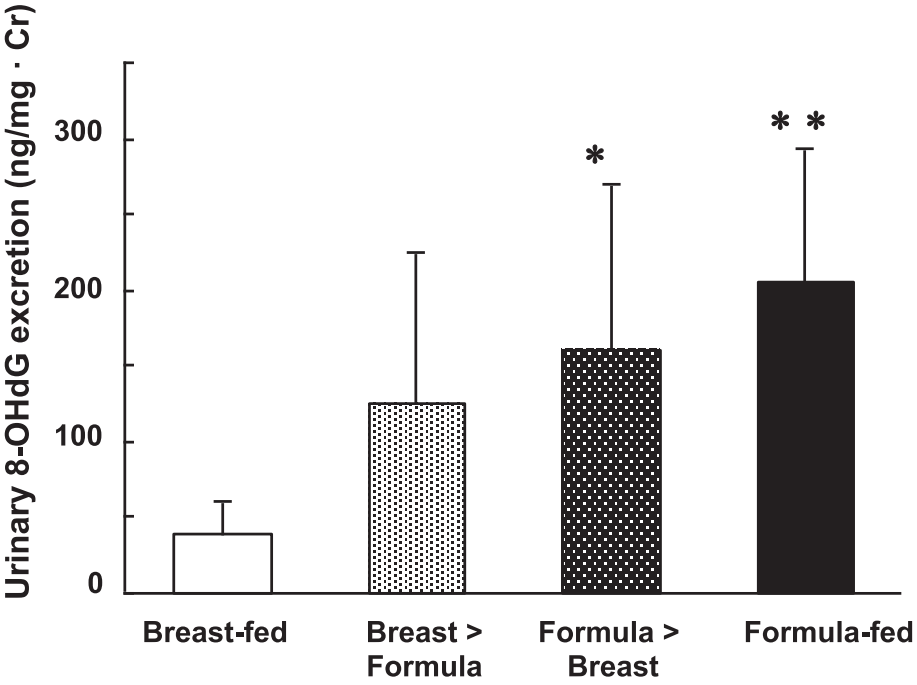

Figure 1 Urinary 8-hydroxydeoxyguanosine (8-OHdG) in one-month-old term infants
Values are expressed as mean ± SD
*$p < 0.05$, **$p < 0.01$ compared with values of the breastfed group

Breastfeeding and associated outcomes

Short-term health outcomes

Human milk provides direct benefits that include supporting gastrointestinal function, enhancing host defense, and preventing acute illnesses such as acute otitis media during breastfeeding. The protective role of breastfeeding against infections is considered one of its most important health benefits[1, 28]. A review by Kramer and Kakuma supported exclusive breastfeeding for six months to prevent infection[29]. The Promotion of Breastfeeding Intervention Trial (PROBIT) reported relative risks of 0.67 (95% confidence interval [CI]: 0.46–0.97) for acute gastroenteritis episodes and 0.75 (95% CI: 0.60–0.94) at 12 months of age, comparing 6–7 months to 3–4 months of exclusive breastfeeding. Systematic reviews from 2016 emphasized a strong protective effect of exclusive breastfeeding for the first six months of life, resulting in an 88% reduction in infectious disease mortality compared to non-breastfed infants[30, 31]. Three studies conducted in low- and medium-income countries found that the absence of breastfeeding was associated with an increased risk of mortality. The protective effect of breastfeeding demonstrated a dose-dependent relationship, with a 78% reduction in the risk of death associated to predominant breastfeeding and a 48% reduction associated with partial breastfeeding[31]. In resource-rich countries, breastfed infants exhibit a lower attack rate of acute illnesses compared to formula-fed infants[32]. In addition, a meta-analysis found that exclusive breastfeeding has been associated with a 36% (95% CI: 19–49) reduction in incidence of sudden infant death syndrome[33]. However, the evidence of a protective effect of breastfeeding against eczema or food allergy was found to be less strong[30]. In 2020, Sakihara, et al. reported on the results of the Strategy for Prevention of Milk Allergy by Daily Ingestion of Infants Formula in Early Infancy (SPADE) study, which demonstrated that the continuous daily ingestion of about 20 mL of formula milk between 1 and 2 months of age prevented the development of cow's milk allergy[34]. Meanwhile, another study found a modest inverse association between breastfeeding and circulating insulin levels in infancy[35]. Moreover, human milk contains hormones such as leptin, adiponectin, resistin, and ghrelin, actively contributing to the regulation of energy balance and glucose homeostasis[36].

Long-term health outcomes

Breastfeeding has been associated with a reduction in the risk of hypertension[37, 38], obesity[39, 40], and insulin resistance[41, 42] during adulthood, all of which contribute to metabolic syndrome (MS). While a definitive long-term benefit of human milk versus formula milk in reducing the incidence of MS remains unclear, recent findings from a meta-analysis found that longer exposure to breastfeeding was associated to a 35% (95% CI: 14–51) reduction in the risk of developing type II diabetes[43]. However, a protective effect of breastfeeding against hypertension and/or hypercholesterolemia was not observed[43]. A nationwide longitudinal survey conducted in Japan between 2001 and 2009 found that exclusive breastfeeding decreased the risk of overweight (adjusted odds ratio [OR]: 0.85, 95% CI: 0.69–1.05) and obesity (adjusted OR: 0.55, 95% CI: 0.39–0.78)[44]. Moreover, a previous meta-analysis indicated that increased breastfeeding duration was associated with a 26% reduction in the odds of overweight or obesity, and this effect was consistent across income levels[30]. However, not all studies have consistently found an association between breastfeeding and a lower risk of overweight or obesity[45, 46]. In terms of childhood leukemia, a meta-analysis of 18 case-control studies revealed that breastfeeding reduced the overall risk by 20% (OR: 0.80, 95% CI: 0.82–0.90)[47]. Breastfeeding has consistently demonstrated positive effects on cognitive outcomes. A previous study indicated that exclusively and more breastfed infants had a mean intelligence quotient 3.4 points higher (95% CI 2.3–4.6) than that of never or less breastfed infants[48]. Another meta-analysis confirmed higher cognitive function (3.2 points) in exclusively and partially breastfed infants compared to formula-fed infants, with improved scores persisting throughout childhood and adolescence. The benefit was particularly pronounced in low birth weight infants compared to those with normal birth weight[49]. However, when controlling for maternal IQ and other confounders, the effect was small (0.52 points) and not significant[50]. In the PROBIT, the only prospective randomized study, the intervention group exhibited significantly higher intelligence scores and

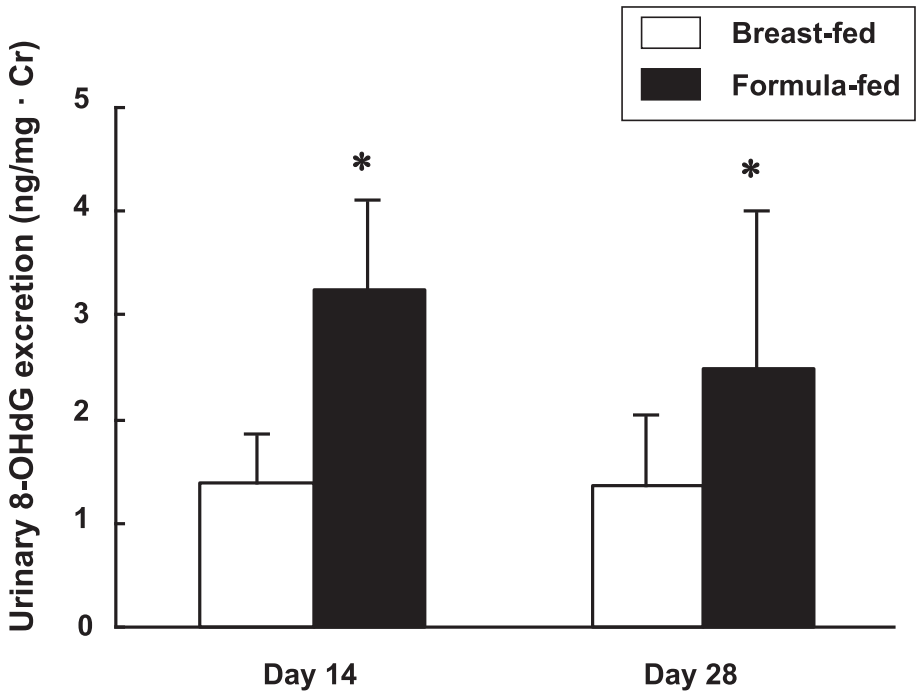

Figure 2 Change in urinary 8-hydroxydeoxyguanosine (8-OHdG) excretion at 14 and 28 days of age in breastfed and formula-fed very low birthweight infants
Values are expressed as mean ± SD
*$p < 0.01$ compared with breastfed infants

Thatcher's rating[51].

Benefits for preterm infants

Human milk is recommended for preterm infants because of its association with a reduced incidence of necrotizing enterocolitis (NEC)[52] and improved IQ scores[53]. Breastfed preterm infants exhibit a 6- to 10-fold lower risk of NEC compared to formula-fed infants[54]. While the exact cause is yet to be determined, factors such as immunoglobulins, PAF-AH, PUFAs, epidermal growth factors, or interleukin-10 (IL-10) in human milk[55], and the colonization of the intestine with *Bifidobacteria* and *Lactobacilli* species may have been involved. Breastfeeding is also associated with a decreased incidence of oxidative stress-related illnesses in preterm infants, including respiratory disease[56] and retinopathy of prematurity[57]. A previous study demonstrated that urinary 8-OHdG excretion at 14 and 28 days of age was significantly lower in breastfed preterm infants compared to formula-fed preterm infants (Figure 2)[58]. However, the nutrient content of both term and preterm breast milk is insufficient to meet the needs of infants weighing less than 1,500 g, necessitating supplementation with a human milk fortifier[52]. The benefits of breastfeeding for preterm infants extend beyond the neonatal intensive care unit (NICU), with fewer hospital readmissions for illnesses in the year following NICU discharge[59, 60]. Extremely preterm infants receiving a higher proportion of human milk in the NICU demonstrated significantly increased mental, motor, and behavior rating scores at 18 and 30 months of age[59, 60].

Conclusions

Breastfeeding is unequivocally endorsed by all medical professional organizations and public health authorities. Current evidence strongly supports the direct benefits of breastfeeding across various dimensions, encompassing nutrition, gastrointestinal function, and protection against acute illness, both in term and preterm infants. Long-term benefits of breastfeeding on neurodevelopmental outcomes and adult health have been reported; however, the magnitude of these effects may be modest and limited.

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Author contributions

The author read and approved the final manuscript.

Conflicts of interest statement

The author declares that there are no conflicts of interest.

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(Updated: May 27, 2024)

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Manuscripts should be arranged in the following order: 1.

Title page; 2. Abstract and keywords; 3. main text; 4. Acknowledgements, Funding, Author Contributions, Conflict of interest statements; 5. tables together with any accompanying legends; 6. figure legends; 7. other as required. Each of the numbered items should begin on a separate page.

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2. Materials (or "Design")
3. Methods (or "Interventions")
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5. Conclusions

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Discussion

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Acknowledgments

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Journal article

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.

Book

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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編 集 後 記

The best teacher in my life

小学校から大学まで、多くの先生方から指導を受けた。どの先生も素晴らしい方たちだったが、私にとって最高の先生は、米国留学中に受講したライティング・コースの先生 Mimi Zeiger である。留学先の UCSF Cardiovascular Research Institute では、留学生やポスドク向けに、論文執筆のためのライティング・コースを無料で提供していた。この講座は、人気のコースで希望者が多いと抽選となる。日常生活にも慣れた頃に申し込んだところ、10 数名の受講者で日本人は私だけで、ほとんどが英語のネイティブ・スピーカーだった。授業は 1 回 2 時間で週 2 回、全部で 12 回あった。受講者には、予習のために毎回 20 から 30 ページの資料が渡される。学術論文で用いる英単語の選択の仕方から、論文の各セクションの書き方、結果を効果的に示す図表の作り方や図の説明、表の脚注の書き方、パラグラフ・ライティングの方法などを学んだ。資料には、実際の論文から引用した「わかりにくい文章」とその添削例が載っていた。「わかりにくい文章」は、アメリカ人のポスドクでさえ正確に理解できないという事実に驚いた。講義後には、毎回復習用の課題が出される。「わかりにくい文章」の一部を、授業で習ったことを参考に書き直すのだ。Mimi は、提出された課題をチェックして次回の講義で返却する。書き直し方が不十分な時にコメントがあるのは予想通りだったが、Mimi は私が修正した英文一つ一つの出来ばえにより、good try, nice, excellent, yes, right などレポート用紙が真っ赤になるほど沢山のコメントを書き込んでくれた。授業も残り少なくなったある日、Mimi は私の提出した課題をみんなに披露し、良い例としてほめてくれた。これが大きな自信となり、帰国後も論文執筆を続けることができた。私が定年退職を迎えるにあたり、帰国後に執筆した英文論文のリストを送って Mimi に感謝の気持ちを伝えた。メールを "From your permanent student in your temporary class" で締めくくったところ、Mimi はこう返信してくれた。"You have a way with words!"

三井田　孝
順天堂大学医療科学部臨床検査学科

イラスト作者より

今年の夏は異常な暑さです。まだ 7 月というのに。無事に乗り切ることができるか心配なくらい。それでも夏というと向日葵が浮かびます。黄色の花弁にあわせてブルーのデルフィニウムを買ってきました。しばしの涼を求めて。（宮道明子）

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抄　録

順天堂醫事雑誌
2024. 70(4), 319

脆弱な冠動脈プラークの可視化とプラーク破綻の予防

深瀬達也，土肥智貴

順天堂大学・大学院医学部研究科　循環器内科講座学

日常の臨床診療において，冠動脈の解剖学的所見と虚血の有無を評価することは，経皮的冠動脈形成術の必要性を判断する上で極めて重要である．しかしながら同時に，冠動脈プラークの脆弱性・不安定性を理解することは，将来の心血管イベントを予測し，患者個々の予防戦略を立てるのに大いに役立つ．本レビューは，冠動脈プラークの脆弱性・不安定性について説明することを目的としており，主に病理学的，形態学的，生理学的な観点から不安定プラークに焦点を当てている．不安定性プラークの診断とその破綻リスクの評価のための冠動脈画像診断法の有用性と，プラーク安定化の管理戦略としての薬物治療や経皮的冠動脈形成術の可能性を強調している．さらに，中等度以上の虚血を有する患者に対する早期侵襲的治療，および脂質コアプラークをシーリングするための新世代ステントの利用によって，心血管イベントを予防できる可能性についての報告が散発的に存在することも記した．したがって，LDL- コレステロールを主な標的とする厳格な脂質低下療法，ならびにそれに組みわせた冠動脈プラークを標的とした直接的介入は，将来の心血管イベントを抑制し，周術期心筋梗塞をゼロにする上で重要な役割を果たすことができると考えている．

キーワード：不安定プラーク，プラーク破綻，近赤外線分光法，血管内超音波，プラークシーリング

この抄録は，順天堂醫事雑誌 70 巻 4 号，p260–268，2024 掲載の『Visualization of Vulnerable Coronary Plaque and Prevention of Plaque Rupture』の和文抄録です．

抄　録

順天堂醫事雑誌
2024. 70(4), 320

Mitochondrial Damage in Sepsis

Ricard FERRER[1)]，射場敏明[2)]

[1)]Intensive Care Department, Hospital Universitari Vall d'Hebron Universitat Autònoma de Barcelona, Barcelona, Spain
[2)]順天堂大学救急・災害医学

ミトコンドリアはアデノシン三リン酸(ATP)を生成し，細胞の恒常性維持に機能するだけでなく，活性酸素種を産生することで生体防御にも貢献している．したがって敗血症におけるミトコンドリアの損傷は，エネルギー不足と免疫系の調節不全をもたらし，他にも障害性の高いミトコンドリア DNA を放出することで細胞障害を惹起し，代謝異常によるアシドーシスを促進させ，またプログラムされた細胞死を誘導することで敗血症の重症化を促進している．このうち細胞死については，ミトコンドリア障害は様々な形態の細胞死を誘導し，病態の複雑化に関与していることが知られている．アポネクローシスはアポトーシスからネクローシスへの二次的転換であり，ネクローシス同様の向炎症性細胞死である．ここでは当初アポトーシスが誘導されていても，ミトコンドリア障害による ATP の枯渇によりそれが完結できず，最終的にネクローシスに至る．他にもネクロトーシス，フェロトーシス，パイロトーシスなどのプログラムされた炎症誘発性細胞死が，敗血症におけるミトコンドリア障害よって誘導され，病態の重症化に関与している．このようなミトコンドリア損傷を制御することにより，敗血症に対する新しい治療法が開発されることを期待する．

キーワード：敗血症，ミトコンドリア，プログラム細胞死，臓器障害，酸化ストレス

この抄録は，順天堂醫事雑誌 70 巻 4 号，p269–272，2024 掲載の『Mitochondrial Damage in Sepsis』の和文抄録です．

抄　録

順天堂醫事雑誌
2024. 70(4), 321

母乳栄養の利点と留意点

東　海　林　宏　道

順天堂大学医学部小児科学講座

母乳が新生児，乳児にとって最適な栄養源であることに疑問の余地はなく，国際的にも離乳食開始前の正期産児における唯一の栄養源として推奨されている．これまでの大規模な検討で，母乳育児は正期産児，早産児の双方で栄養学的利点や消化管機能改善，急性感染症防止などの直接的な効果を有することが報告されている．以前当研究室では，母乳栄養の正期産児および早産児において，人工乳栄養児と比較して酸化ストレスの指標である尿中 8-OHdG 排泄が有意に減少していることを明らかにした．母乳育児による神経発達や成人期の生活習慣病といった長期予後に関する効果が報告されているが，有意差がないとする報告もあり，その影響は限定的である可能性がある．本稿では大学院特別講義の内容を基に，母乳栄養の基礎知識と短期的，長期的効果について概説する．

キーワード： 母乳育児，抗酸化作用，生活習慣病，壊死性腸炎

この抄録は，順天堂醫事雑誌 70 巻 4 号，p300–306，2024 掲載の『Effect and Concern of Breastfeeding in Infants』の和文抄録です．

順天堂医学会 会員の皆様

順天堂医学会海外留学時助成金給付制度

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下記すべての要件を満たす者

(1) 医学会会員で1か月以上の海外留学をする者

(2) 留学先の研究機関からの給与の支払いがない者

(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

(4) 学部学生、大学院生、臨床研究医あるいは博士の学位取得後8年未満の者

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(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
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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
12か月以上	50万円

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：順天堂医学会海外留学時助成金選考委員会

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7. 本件の照会先

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