ISSN 0030-6096

OSAKA CITY MEDICAL JOURNAL

Vol. 68
No. 2

2022

PUBLISHED BY
OSAKA CITY MEDICAL ASSOCIATION
OSAKA JAPAN

Osaka City Medical Journal
Vol. 68, No. 2, December 2022

CONTENTS

Osaka City Med. J. Vol. 68, 51-60, 2022

Establishment of a Long-term Survival Model after Extracorporeal Circulation in Rats

Ryoji Sada[1)], Yosuke Takahashi[1)], Toshihiko Shibata[1)], Tomohiro Nakano[2)], and Syuji Inamori[2)]

Department of Cardiovascular Surgery[1)], Osaka City University Graduate School of Medicine; and Department of Medical Engineering[2)], Junshin Gakuen University

Abstract

Background

The purpose of this study is to establish a long-term survival model in rats after extracorporeal circulation.

Methods

SD rats (male, 400-600g) were used. To establish an extracorporeal circulation without thoracotomy, an arterial cannula was inserted into the right common carotid artery with venous drainage from the right internal jugular vein. The heart was then allowed to beat for 1 hour, followed by forced ventilation during extracorporeal circulation. Hematocrit level was then examined between the thoracotomy (n=8) and non-thoracotomy groups (n=8). To examine how tidal volume affects the survival period and organ damage, the non-thoracotomy group was divided into two groups based on the tidal volume. The left ventricular diameter shortening rate was measured. After 30 days of survival, rats were examined the pathophysiology of the left ventricle, lungs, and kidneys.

Results

In the non-thoracotomy group, the minimum hematocrit level was higher (30.8% vs 21.7%, $p \leqq 0.05$) compared to the thoracotomy group. Postoperative left ventricular diameter shortening rate was significantly different between the low and normal tidal volume groups (47.3% vs 36.1%, $p \leqq 0.05$). Pathological examination revealed bleeding due to congestion in the lungs of rats that survived 30 days after extracorporeal circulation. On the other hand, the kidneys and left ventricular collagen fiber density did not differ significantly.

Conclusions

A tidal volume might affect systolic left ventricular function during extracorporeal circulation. Although pulmonary congestion was recognized on pathological findings, long-term survival was successfully achieved using the non-thoracotomy model with a low tidal volume during extracorporeal circulation.

Key Words: Cardiopulmonary bypass; Chronic experiment model; Rat model

Received October 21, 2021; accepted April 12, 2022.

Correspondence to: Yosuke Takahashi, MD.
Department of Cardiovascular Surgery, Osaka Metropolitan University Graduate School of Medicine,
1-4-3 Asahimachi, Abeno-ku, Osaka 545-8585, Japan
Tel: +81-6-6645-3840; Fax: +81-6-6646-6057
E-mail: takahashi.yosuke@omu.ac.jp

Introduction

Extracorporeal circulation (ECC) technology is essential for cardiovascular surgery and is now used worldwide as an established procedure. These advancements resulted from various studies and improvements by Dr. John Gibbon in 1953, who used the artificial heart-lung machine for cardiovascular surgery[1]. Research on ECC technology has been conducted using large animals such as goats and dogs because the devices used were so large that we could not perform this kind of study on small animals[2,3]. In recent years, however, experiments using large animals have become difficult to continue due to economic and ethical backgrounds. There is a growing need for experimental systems using small animals such as mice and rats that can be supplied at low cost[4,5].

Since 2005, we have been conducting experiments on rats using ECCs. In this experiment, ECC was established by inserting an arterial cannula from the right common carotid artery and venous cannula from the right atrium via median sternotomy. We found that pulsating perfusion for cerebral microcirculation during ECC and suppression of neutrophil activity prevents lung damage after ECC[6-10]. On the other hand, there was a problem of short survival in the rat ECC models. The reason for this was related to the invasiveness of ECC establishment[4,5]. The invasion of open chest surgery and artificial respiration may have caused heart failure and lung damage. We hypothesized that the introduction of ECC in a non-open chest setting, as well as low tidal volume during ventilation, would prolong survival in the rat model. The aim of this study was to create a long-term survival model using an ECC model with continuous cardiac contraction by making it less invasive. Furthermore, we investigated whether tidal volume during ECC affects cardiac function and survival. Lastly, organ damage was examined pathologically in surviving samples.

Methods

In all experiments, we used SD male rats (10-13 weeks old, 400-600g, Japan SLC Co., Ltd., Tokyo). Respiratory management was performed using a small animal ventilator (Respirator Model SN-48D-7, Shinano Seisakusho Co., Ltd., Tokyo). The rat ECC system consisted of a closed circuit, heat exchanger, artificial lung (membrane area: 0.03 m^2, filling volume: 2.0 mL manufactured by Senko Medical Instrument mfg. Co., Ltd., Tokyo) (Fig. 1), and a roller pump (PERISTA Mini-Pump SJ-1211; manufactured by ATTO Co., Ltd., Tokyo) (Fig. 1). The priming volume was summed up to 10 mL (Mannitol 2 mL, sodium bicarbonate 2 mL, and Ringer's solution 6 mL). The blood flow volume of the ECC was 90 mL/kg/min, and the ratio of oxygen to carbon dioxide sent to the artificial lung was set to 95: 5. Rectal temperature was controlled to be 37℃.

Experiment 1 (Establishment of non- thoracotomy rat model)

Anesthesia was induced by oxygen (1 L/min) and isoflurane (4.0%) using a dedicated box. A 14-gauge indwelling needle outer cylinder was inserted in the thoracotomy rat model (N=8) from the tracheostomy. The non-thoracotomy rat model (N=8) was subjected to endotracheal intubation using a 14-gauge indwelling needle outer cylinder. Monitoring was done using electrocardiography, arterial pressure (canulation site of the common carotid artery), and rectal temperature. In the thoracotomy rat model, the right common carotid artery was cut to insert the arterial cannula (outer diameter, 1.1 mm polyethylene tube). Systemic heparinization (1000 IU /kg) was performed from the arterial cannula. Eighteen-gauge needle outer tube was inserted from the right atrium for drainage after a median sternotomy. In the non-thoracotomy group, the venous cannula (18-gauge indwelling needle outer cylinder) was placed in the right atrium using a guidewire from the right internal jugular vein.

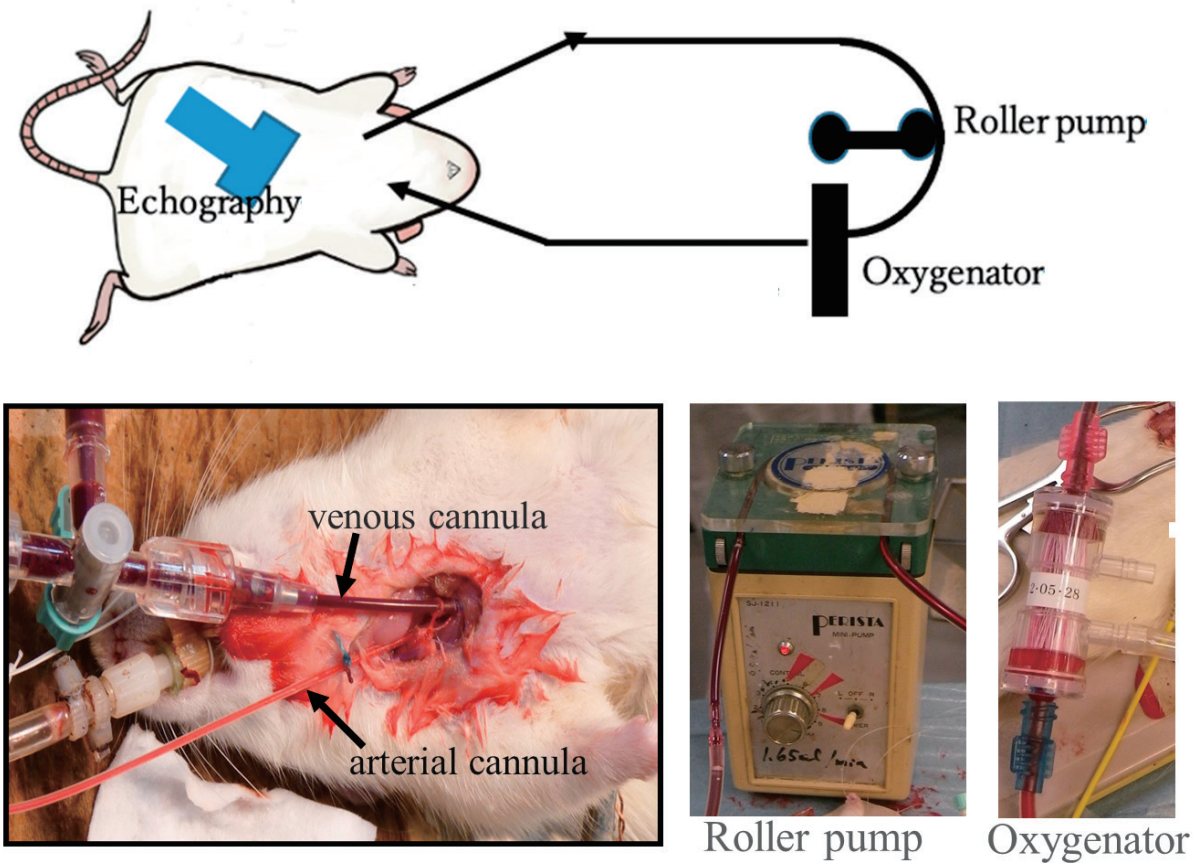

Figure 1. Layout of the experiment. After the right carotid artery and jugular vein were exposed, the arterial and venous cannulas were inserted using the cut down method in the non-thoracotomy group. The tip of the venous drainage tube was located in the right atrium. Venous drainage is sent to the artificial lung by a roller pump to oxygenize and subsequently sent to the right carotid artery.

Right common carotid artery was cut to insert the arterial cannula (outer diameter, 1.1 mm polyethylene tube). Forced ventilation without spontaneous respiration was continued during partial ECC in both groups. All data were measured just before cessation of ECC. The ventilator was set to have an oxygen concentration of 100%, 2% isoflurane, 1:1 to I:E ratio, 90 beats per minute, and a ventilation volume of 5 mL/kg to maintain arterial blood carbon dioxide pressure at approximately 40 mm Hg. To maintain acid-based equilibrium, sodium bicarbonate was administered as appropriate.

After continuing the ECC for one-hour, sufficient hemostasis was performed, and the arterial and venous cannula were removed. The cervical incision was then ligated and closed. Isoflurane administration was stopped, and sufficient spontaneous respiration was confirmed. Arterial blood gas analysis, rectal temperature, operation time, intraoperative bleeding volume, and minimum hematocrit level during ECC were compared between the two groups. The endotracheal tube was extuvated and observed under room air to check the survival time in both groups. The survival rats were euthanized 30 days after experiment.

Experiment 2

To study the effects of respiratory management during ECC on long-term survival, we performed Experiment 2. The protocols for anesthesia induction and ECC establishment were the same with the non-thoracotomy group in experiment 1. After induction of anesthesia, the rats were placed in

the lateral supine position. The diastolic left ventricle dimension and systolic left ventricle dimension during spontaneous breathing were measured using an ultrasonographic apparatus (Nemio TMXG SSA-580 A; Toshiba Medical Systems Co., Ltd., Tokyo). The fractional shortening rate (%FS) of the left ventricle was also calculated (Fig. 2A).

The rat groups comprised of group A (n=8; respiratory frequency, 90 bpm, single ventilation volume: 5 mL/kg), which is a low tidal volume group and group B (n=8; respiratory frequency, 60 bpm, single ventilation volume: 8 mL/kg), which is a normal range of tidal volume. The minute ventilation volumes of both groups were the same in both groups. After initiating ventilation, the %FS during positive pressure ventilation was measured. After weaning from ECC for one hour and extubating the endotracheal tube, %FS was measured again by echocardiography under spontaneous respiration at rates of 70 bpm or more. After the operation, the survival time was measured using a video camera under room air management in both groups. The rats were observed for 30 days, and experiment 3 was performed on the surviving rats.

Experiment 3

Organ damage was examined in rats that survived for a long period of 30 days after Experiment 2. We compared their rates with the control group. The rats in control group were also anesthetized with endotracheal intubation. We made cervical incision as the same manner as non-thoracotomy group, and the incision was closed immediately without applying ECC. Rats were euthanized by injecting an overdose of potassium. The heart, lungs, and kidneys were then removed to verify organ damage by pathological diagnosis. After collecting the samples, the tissues from both groups were fixed with 10% formalin, embedded in paraffin, and cut into 4 μm sections. After fixing the tissues, the lungs and kidneys were stained with hematoxylin and eosin while the left ventricle was stained with Asan stain.

Animal preparation

In this study, breeding, handling, and experimental planning of laboratory animals were carried out with the guidance and approval from Osaka City University Medical School Animal Experiment Committee based on animal experiment guidelines of Osaka City University (approval number 16016).

Statistical analysis

Data were expressed as median (25th-75th percentile). A Mann-Whitney U test was used for statistical analysis to compare the groups using IBM SPSS Statistics (IBM Co., Ltd., Tokyo). Statistical significance was set at p value <0.05.

Results

Experiment 1 (comparison between the thoracotomy group and the non-thoracotomy group regarding peri-operative data) (Table 1)

The survival time was 720 (527-720) hours in non-thoracotomy group. There were no significant differences in operating time, blood gas data just before end of the ECC, and central temperature between the thoracotomy and non-thoracotomy groups. In the non-thoracotomy group, bleeding quantity was lower [1.1 (0.9-1.4) mL) vs 5.9 (5.6-6.2) mL, $p \leqq 0.05$)] while minimum hematocrit level was higher [30.8 (28.9-32.2) % vs 21.7 (19.3-22.7) %, $p \leqq 0.05$] compared to the thoracotomy group.

Experiment 2 (the %FS measurement between group A and B) (Fig. 2)

Group A had a preserved %FS and a significantly higher %FS than group B after weaning from

Table 1. Data during experiment 1 between both groups

	Group	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Median (25th-75th percentile)
Operating time (min.)	Thoracotomy	99	87	82	84	90	95	86	83	87 (84-89)
	Non-thoracotomy	86	88	75	96	91	87	95	83	88 (85-93)
PO_2 (mmHg)	Thoracotomy	88	93	95	91	89	90	93	85	91 (89-93)
	Non-thoracotomy	87	88	94	86	90	93	92	80	89 (87-93)
PCO_2 (mmHg)	Thoracotomy	42	44	42	45	46	46	44	38	44 (42-46)
	Non-thoracotomy	44	46	47	48	39	40	44	48	45 (43-48)
Rectum temperature (℃)	Thoracotomy	33.3	30.4	32.1	29.9	31.7	33	32.5	31.8	32.0 (31.4-32.3)
	Non-thoracotomy	33.6	30.6	32.4	31.5	32.8	33	30.4	29.9	32.0 (30.6-32.6)
Bleeding volume (mL)	Thoracotomy	5.2	5.4	5.7	5.8	5.9	6	6.4	6.6	5.9 (5.6-6.2)
	Non-thoracotomy	0.8	0.8	0.9	1	1.2	1.3	1.4	1.4	1.1 (0.9-1.4)*
Survival time (hours)	Thoracotomy	4	7	11	8	6	5	5	7	7 (5-8)
	Non-thoracotomy	576	720	720	384	720	720	240	720	720 (527-720)
Minimum Hct level (%)	Thoracotomy	18.5	22	21.4	17.6	19.5	23.1	22.2	24.1	21.7 (19.3-22.7)
	Non-thoracotomy	31.6	33	28.6	31.4	34.3	30.2	28.7	29	30.8 (28.9-32.2)*

*$p \leqq 0.05$. Hct, hematocrit.

Table 2. Data during experiment 2 between both groups

	Group	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Median (25th-75th percentile)
Operating time (min.)	A	85	78	80	86	95	84	77	75	82 (78-85)
	B	83	88	86	75	74	86	82	82	83 (80-86)
PO_2 (mmHg)	A	111	104	92	88	117	99	91	110	102 (92-107)
	B	108	115	110	118	99	106	112	111	111 (108-114)
PCO_2 (mmHg)	A	46	41	39	38	40	42	45	42	42 (40-42)
	B	38	38	40	42	36	35	36	39	38 (36-40)
Rectum temperature (℃)	A	32.1	30.8	30.5	32.2	31.6	32.8	33	31.8	32.0 (31.4-32.5)
	B	32.4	33.1	31.5	32.8	31	30.8	31.5	30.4	31.5 (31.0-32.2)
Airway pressure (cmH_2O)	A	13	14	12	14	15	12	12	13	13 (12-14)
	B	15	17	13	14	15	15	16	14	15 (14-16)
Bleeding volume (mL)	A	1	1.4	0.8	1.1	1.5	1	0.8	1.3	1.1 (1.0-1.4)
	B	0.9	0.8	1.2	1.1	1.8	1.6	0.9	1.1	1.1 (0.9-1.4)
Survival time (hours)	A	720	720	528	720	439	720	720	720	720 (672-720)
	B	8	12	24	17	30	8	42	22	20 (11-27)*

*$p \leqq 0.05$.

ECC. The %FS under spontaneous respiration before ECC was 51.1 (49.4-51.9) % in group A and 50.1 (48.7-51.8) % in group B, showing no significant difference between groups. On the other hand, %FS was 47.3 (45.1-48.5) % in group A and 36.1 (35.1-36.3) in group B after ECC, which showed significantly lower %FS values in group B ($p \leqq 0.05$) (Fig. 2B). The survival time in group A was better than that in group B (720 (672-720) hours vs 20 (11-27) hours, $p \leqq 0.05$). In group A, six out of eight rats achieved 30-day survival after weaning from ECC (Table 2).

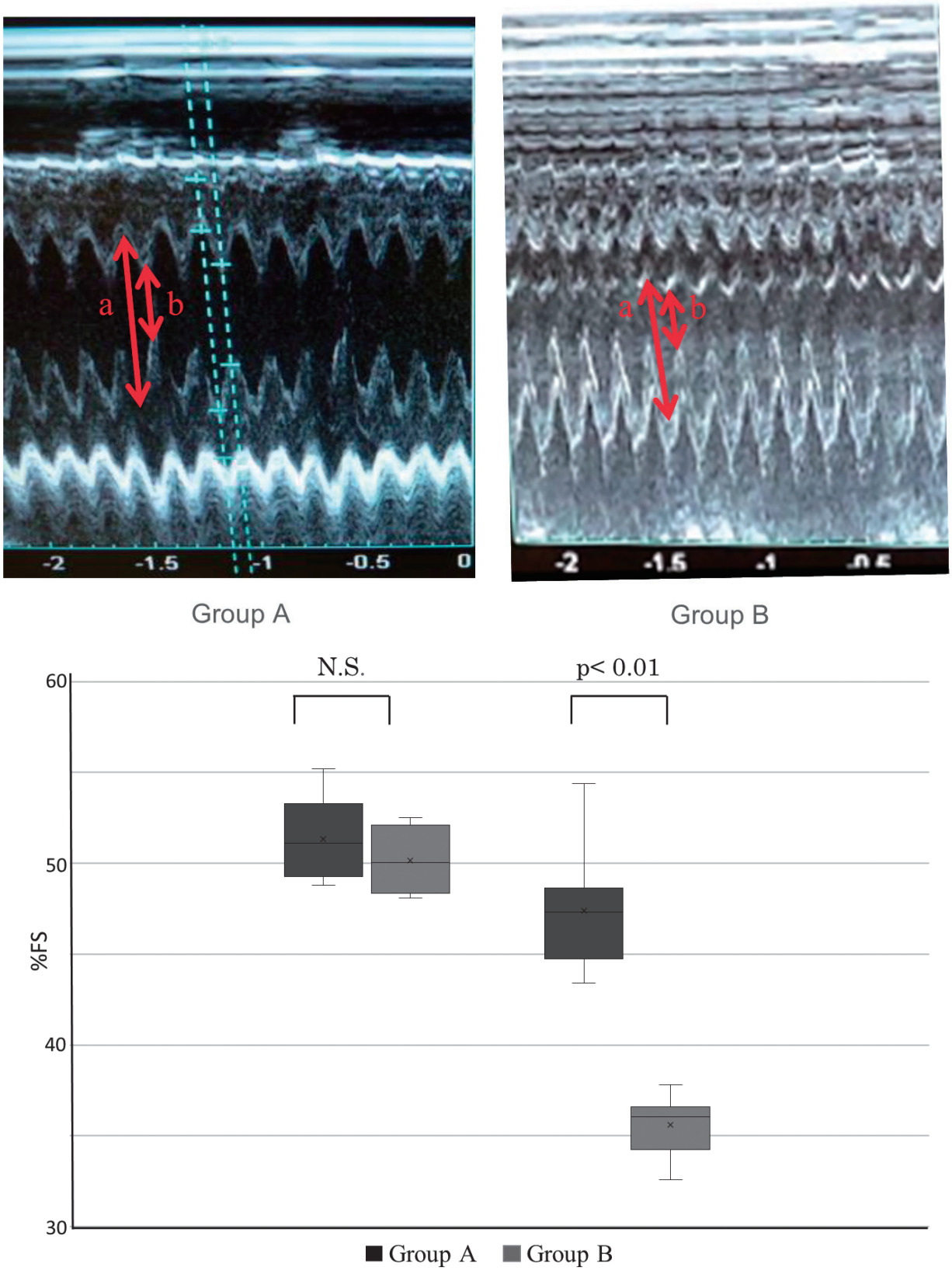

Figure 2. (A) M-mode imaging of echocardiogram. The image on the left is group A and the right is group B. diastolic dimension (a) and systolic dimension (b).
(B) Box plots showing %FS in both groups before ECC and just after ECC. Black box indicates the %FS in group A and grey box indicates the %FS in group B. The %FS just after surgery was worse than that before ECC in group B ($p< 0.05$). %FS is calculated by (LVDd-LVDs) / LVDd×100. FS, fractional shortening; and ECC, extracorporeal circulation.

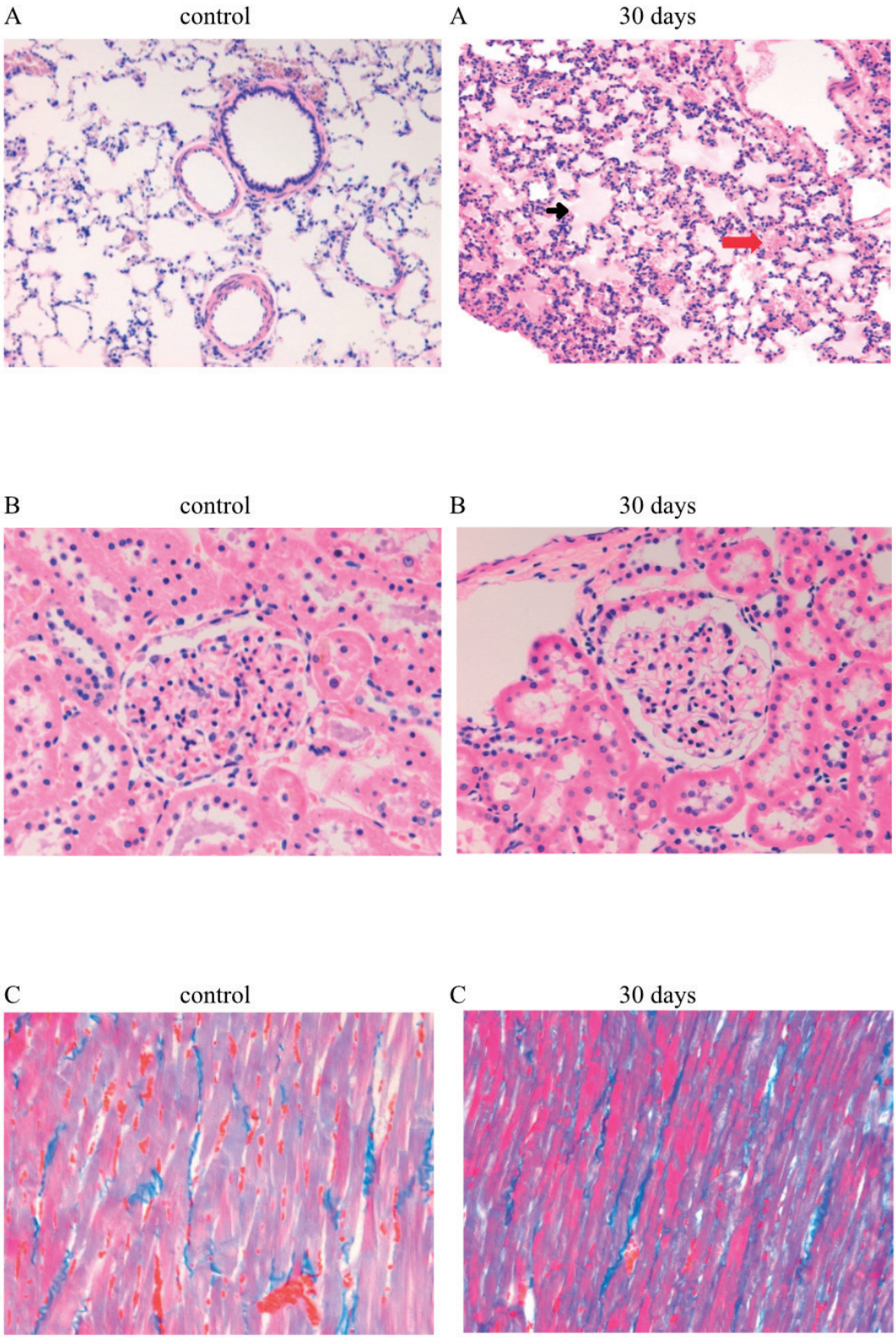

Figure 3. Photomicrophotograph of the left lung (A), left kidney (B) and left ventricle (C). The control group is depicted on the left and the group with 30 days survival on the right. The left lung and left kidney were stained by hematoxylin and eosin with original magnification×20. The heart section was stained by Asan stain with original magnification×40. Increased density of alveolar epithelium and multinucleated giant cell in the lung are shown in the group with 30 days survival. There is no pathologically difference in kidney between groups. There is no difference regarding collagen fiber in the left ventricle between groups. Black arrow shows plasma components lightly stained with eosin in the alveoli. Red arrow shows red blood cells in the alveoli, indicating bleeding.

Experiment 3 (pathological examination of rat organs) (Fig. 3)

Figure 3 compares the pathological images of the survival cases and the control group. In the survival cases, local emphysema, red blood cell infiltration, swelling of the pulmonary capillaries, and transudate bleeding in the alveoli were observed; these findings were not observed in the control group. Macrographic findings showed that dilatation of the left ventricular cavities and thinning of the left ventricular wall were observed in survival cases. On the other hand, there was no difference in the left ventricular wall's collagen fiber density between survival cases and the control group. There were also no significant differences in the kidneys of the two groups.

Discussion

In this experiment, 1) we established a rat model of long-term survival after weaning from ECC. 2) The %FS was maintained within the normal range in rats with reduced tidal volume during ECC. 3) Pathological findings showed pulmonary congestion and cardiac enlargement in a rat model of long-term survival.

We have been conducting experiments on ECC using rats since 2011, which is an acute experimental model[11-13]. Bleeding quantity in the non-thoracotomy model that did not require both tracheostomy and median sternotomy was significantly lower compared to the thoracotomy model. The cause of anemia in the thoracotomy model is bleeding from the sternum due to systemic heparinization. To establish a chronic model, it is necessary to maintain stable hemodynamics during and after ECC. Therefore, it is mandatory to establish an experimental model with less bleeding. By devising the cannulation method without thoracotomy, we were able to establish a less invasive chronic rat model.

Differences in respiratory management during ECC significantly affected postprocedural cardiac function. Our experiment involved ECC with assisted beating heart circulation under forced ventilation. After ECC, the %FS in group B, which had a higher tidal volume, was 36.1 (35.1-36.3) %. From this result, we considered that it is better to use a low tidal volume with increased respiratory rate while maintaining the minute volume, to prevent postoperative cardiac suppression. Conventionally, the effect of positive pressure ventilation in humans differs greatly between the right and left ventricles. Since increased intrathoracic pressure compresses the right ventricle, venous perfusion was suppressed, and the preload of the left ventricle decreased. The decrease of the preload of the left ventricle has little effect on left ventricular tension and afterload[14,15]. However, when a high intrathoracic pressure is continuously exposed to inappropriate respirator settings, there will be an increase in afterload of the left ventricle and a decrease in cardiac function[16]. In fact, even in humans, cardiac suppression is reported to range from 14.5% to 16.5% due to positive pressure ventilation using a respirator[17]. Based on these, it is necessary to consider appropriate tidal volume settings.

Injuries to vital organs caused by ECC and ventilator itself have been reported, including elevated levels of inflammatory cytokines and damage caused by reactive oxygen species[18-20]. Lung injury caused by ventilator is also considered to one of the reasons that affected survival[21,22]. We consider that lung injury via barotrauma, volutrauma and biotrauma due to positive pressure ventilation might affect the survival of the rat.

In this study, pathological findings showed no ischemic findings in the kidneys due to ECC. However, mild pulmonary congestion and left ventricular dilatation in long-term survival cases

showed that elevated afterload caused by ECC might affect the lungs and left ventricle. Persistently high intrathoracic pressure reduces venous return in the right heart system but increases pulmonary vascular resistance, which ultimately surpasses left atrial pressure[16]. As a result, venous return and cardiac output from the left ventricle is expected to increase. However, deformity of the interventricular septum due to increased right ventricular pressure and elevated afterload might worsen %FS, pulmonary congestion, and left ventricular function. This may be one of the reasons why long-term survival could not be obtained in the group where the tidal volume was larger. It was also suggested that the possible cause of pulmonary congestion and cardiac dilatation may include ECC invasion, ventilator-induced lung injury, and associated reactive oxygen species and inflammatory cytokines. A more stable rat model of long-term survival may be constructed by adjusting to the appropriate tidal volume or creating a less invasive ECC model that maintains spontaneous respiration regardless of the presence of a respirator synchronized with spontaneous respiration.

ECC applied to humans can now be performed safely. However, cerebral complications and organ damage, including the lung and heart associated with ECC, will likely develop. It is necessary to conduct further studies regarding the detailed pathophysiological organ damage caused by ECC. Establishing a long-term survival model of ECC by our research might be useful for a wide range of studies because various non-physiological conditions can be added during ECC in small animals that are inexpensive and easy to handle. In addition, circulatory dynamics management can be performed safely by considering the appropriate tidal volume setting on the respirator in clinical settings requiring percutaneous cardiopulmonary support.

Limitations

Since the number of cases is small, it is necessary to conduct further experiments in the future. Second, cardiac function was evaluated at two points only: before ECC and immediately after the end of ECC. Therefore, it is necessary to evaluate whether the decreased cardiac function is temporary or sustained by measuring several points after ECC. Thirdly, it would be very useful to quantify the tissue evaluation of the lungs and heart as an objective indicator. It would be easier to understand the results if we could quantify them, but we have not been able to do so in this experiment. We are planning to quantify the tissue evaluation in the next research. Lastly, although a successful long-term survival model after ECC was established, pathological myocardial and pulmonary damage occurred. We consider that there is room for further improvement, such as setting tidal volume and ECC management regarding volume support and blood pressure control.

Acknowledgement

All authors have no COI to declare regarding the present study. This work was supported by JSPS KAKENHI (Grant Number 17K11601).

References

1. Gibbon JH Jr. Application of a mechanical heart and lung apparatus to cardiac surgery. Minn Med 1954;37: 171-185.
2. Dreyer WJ, Michael LH, Millman EE, et al. Neutrophil sequestration and pulmonary dysfunction in a canine model of open heart surgery with cardiopulmonary bypass. Evidence for a CD18-dependent mechanism. Circulation 1995;92:2276-2283.
3. Gillinov AM, Davis EA, Curtis WE, et al. Cardiopulmonary bypass and the blood-brain barrier. An experimental study. J Thorac Cardiovasc Surg 1992;104:1110-1115.

4. de Lange F, Yoshitani K, Podgoreanu MV, et al. A novel survival model of cardioplegic arrest and cardiopulmonary bypass in rats: a methodology paper. J Cardiothorac Surg 2008;3:51.
5. Modine T, Azzaoui R, Fayad G, et al. A recovery model of minimally invasive cardiopulmonary bypass in the rat. Perfusion 2006;21:87-92.
6. Inamori S, Fujii Y, Oshita T, et al. Development of a pulsatile flow-generating circulatory-assist device. J Artif Organs 2010;13:67-70.
7. Inamori S, Shirai M, Yahagi N, et al. A comparative study of cerebral microcirculation during pulsatile and nonpulsatile selective cerebral perfusion: assessment by synchrotron radiation microangiography. ASAIO J 2013;59:374-379.
8. Hamamoto M, Suga M, Takahashi Y, et al. Suppressive effect of phosphodiesterase type 4 inhibition on systemic inflammatory responses after cardiopulmonary bypass. J Artif Organs 2006;9:144-148.
9. Hamamoto M, Suga M, Nakatani T, et al. Phosphodiesterase type 4 inhibitor prevents acute lung injury induced by cardiopulmonary bypass in a rat model. Eur J Cardiothorac Surg 2004;25:833-838.
10. Ohnisi Y, Inamori S, Suematu Y. Pial microcirculatory change in rat with a cardiopulmonary bypass (CPS) using fluorescence videomicroscopy. Effect of CPS floein 1997:305-310.
11. Fujii Y, Shirai M, Inamori S, et al. Insufflation of hydrogen gas restrains the inflammatory response of cardiopulmonary bypass in a rat model. Artif Organs 2013;37:136-141.
12. Fujii Y, Shirai M, Inamori S, et al. A novel small animal extracorporeal circulation model for studying pathophysiology of cardiopulmonary bypass. J Artif Organs 2015;18:35-39.
13. Fujii Y, Tanabe T, Yamashiro T, et al. Effect of hydroxyethyl starch priming on the systemic inflammatory response and lung edema after cardiopulmonary bypass in a rat model. ASAIO J 2017;63:618-623.
14. Pinsky MR, Summer WR. Cardiac augmentation by phasic high intrathoracic pressure support in man. Chest 1983;84:370-375.
15. Pinsky MR, Summer WR, Wise RA, et al. Augmentation of cardiac function by elevation of intrathoracic pressure. J Appl Physiol Respir Environ Exerc Physiol 1983;54:950-955.
16. Cheifetz IM. Cardiorespiratory interactions: the relationship between mechanical ventilation and hemodynamics. Respir Care 2014;59:1937-1945.
17. Cournand A, Motley HL. Physiological studies of the effects of intermittent positive pressure breathing on cardiac output in man. Am J Physiol 1948;152:162-174.
18. Orhan G, Yapici N, Yuksel M, et al. Effects of N-acetylcysteine on myocardial ischemia-reperfusion injury in bypass surgery. Heart Vessels 2006;21:42-47.
19. Fujii Y, Shirai M, Tsuchimochi H, et al. Hyperoxic condition promotes an inflammatory response during cardiopulmonary bypass in a rat model. Artif Organs 2013;37:1034-1040.
20. Zakkar M, Guida G, Suleiman M-S, et al. Cardiopulmonary bypass and oxidative stress. Oxid Med Cell Longev 2015;2015:189863.
21. Lentsch AB, Czermak BJ, Bless NM, et al. Essential role of alveolar macrophages in intrapulmonary activation of NF-kappaB. Am J Respir Cell Mol Biol 1999;20:692-698.
22. Papaiahgari S, Yerrapureddy A, Reddy SR, et al. Genetic and pharmacologic evidence links oxidative stress to ventilator-induced lung injury in mice. Am J Respir Crit Care Med 2007;176:1222-1235.

Osaka City Med. J. Vol. 68, 61-72, 2022

Correlation between Low Amount of Epicardial Adipose Tissue and the Severity of Right Ventricular Dysfunction in Patients with Nonischemic Heart Failure with Reduced Ejection Fraction

Akiko Tanihata[1)], Shoichi Ehara[2)], Ryoko Kitada[2)], Hirotoshi Ishikawa[2)], Toshitake Yoshida[1)], Hiroya Hayashi[1)], Yumi Yamaguchi[2)], Atsushi Shibata[2)], Yasuhiro Izumiya[2)], and Daiju Fukuda[2)]

Department of Cardiovascular Medicine[1)],
Osaka City University Graduate School of Medicine; and
Department of Cardiovascular Medicine[2)],
Osaka Metropolitan University Graduate School of Medicine

Abstract

Background

Although epicardial adipose tissue (EAT) volume is associated with coronary artery disease and atrial fibrillation, the clinical role of EAT in heart failure (HF) remains controversial. In patients with HF with reduced ejection fraction (HFrEF), right ventricular (RV) dysfunction is associated with impaired functional capacity. This study aimed to investigate the relationship between the EAT volume and RV systolic function in patients with HFrEF.

Methods and Results

A total of 100 consecutive patients with nonischemic HF who had undergone cardiac magnetic resonance imaging and computed tomography were enrolled. First, patients were categorized based on the left ventricular (LV) EF; patients with LVEF ≧50% and LVEF <50% were classified into the HF with preserved EF (HFpEF) (n=14) and HFrEF (n=86) groups, respectively. Then, the HFrEF group was further divided into the HFrEF with RV dysfunction (RVEF <45%, n=54) and HFrEF without RV dysfunction (RVEF ≧45%; n=32) groups. The EAT volume indexed to body surface area (BSA) in the HFrEF with RV dysfunction group was significantly lower than that in the other groups. In the HFrEF group, EAT volume indexed to BSA was positively correlated with RVEF ($r=0.28$, $p<0.01$) but not with LVEF. Multivariate analysis revealed that LVEF and EAT volume indexed to BSA were independent factors associated with HFrEF with RV dysfunction.

Conclusions

This study demonstrated that HFrEF patients with RV dysfunction had less EAT compared to HFpEF patients, and less amount of EAT was related to the severity of RV dysfunction in HFrEF.

Key Words: Epicardial adipose tissue, Heart failure, Right ventricular failure, Magnetic resonance imaging

Received February 21, 2022; accepted June 14, 2022.

Correspondence to: Shoichi Ehara, MD.
Department of Cardiovascular Medicine, Osaka Metropolitan University Graduate School of Medicine, 1-4-3 Asahimachi, Abeno-ku, Osaka 545-8585, Japan
Tel: +81-6-6645-3801; Fax: +81-6-6646-6808
E-mail: ehara@omu.ac.jp

Introduction

The concept of cardiac adiposity as a novel cardiovascular risk factor has recently received increasing attention. Epicardial adipose tissue (EAT) is a unique and multifaceted visceral fat depot and has anatomic and biomolecular relationship with the heart. The functional and anatomic proximity of EAT to the coronary artery and myocardium enables endocrine, paracrine, and vasocrine effects on the heart. Previous studies have shown that EAT volume is associated with obesity[1], metabolic syndrome[2,3], insulin resistance[4], atrial fibrillation[5,6], and coronary artery disease[7,8]. However, the clinical role of EAT in heart failure (HF) remains controversial[9]. This confusion may be attributed to the heterogeneity of HF in terms of classification, stage, and severity.

It has been proposed that left ventricular (LV) remodeling in HF with reduced ejection fraction (HFrEF) is driven by the progressive loss of cardiomyocytes, which results from ischemia, infection, or toxicity[10]. Although nonischemic HFrEF, especially dilated cardiomyopathy, is a primary heart muscle disease characterized by LV cavity enlargement and impaired contractility, right ventricular (RV) systolic dysfunction is frequently observed during the initial evaluation. In patients with HFrEF, RV systolic dysfunction is associated with impaired functional capacity and is a key factor in determining prognosis[11]. However, most EAT-related studies have analyzed only LV function and paid less attention to RV function[12-14]. One of the reasons is that the RV has a complex shape, and it is difficult to estimate RV volume and function.

Cardiac magnetic resonance (CMR) imaging is the most accurate method for evaluating RV volume and function[15]. Furthermore, multidetector computed tomography (MDCT) can provide a more accurate and volumetric measurement of EAT compared with echocardiography. This study aimed to compare the EAT volume among patients with nonischemic HFrEF, patients with preserved ejection fraction (HFpEF), and control subjects, and to investigate the relationship between the EAT volume and RV systolic function in patients with nonischemic HFrEF.

Methods

The study was approved by the hospital ethics committee, and informed consent of patients was obtained according to the institutional review board policies regarding hospital administration (approval no.3785).

Study population

This single-center retrospective observational study enrolled 100 consecutive patients with newly diagnosed nonischemic HF who visited our institution for the evaluation of cardiac dysfunction or management of HF and underwent CMR imaging and MDCT between September 2017 and April 2021. To be diagnosed with HF, all patients had to satisfy two major or one major and two minor Framingham criteria[16]. The exclusion criteria were as follows: i) significant coronary artery disease (defined as the presence of ≧70% luminal stenosis in an epicardial coronary artery or any history of myocardial infarction or coronary revascularization), ii) severe valvular heart disease, iii) infiltrative cardiomyopathy, iv) sarcoidosis, v) amyloidosis, vi) hypertrophic cardiomyopathy, vii) myocarditis, viii) permanent pacemaker, implantable cardiac defibrillator, or cardiac resynchronization therapy, ix) uncontrolled insulin dependent diabetes mellitus, x) severe renal dysfunction with estimated glomerular filtration rate <30 mL/min/1.73m^2. First, patients were categorized based on the LV ejection fraction (LVEF) measured by CMR; patients with LVEF ≧50% and LVEF <50% were classified into the HFpEF and HFrEF groups, respectively. The HFrEF group was then further

divided into the HFrEF with RV dysfunction (RVEF <45%) and HFrEF without RV dysfunction (RVEF ≧45%) groups[17]. The HFrEF group was treated with beta-blockers, angiotensin-converting enzyme inhibitors, or angiotensin Ⅱ receptor blockers unless contraindicated. Furthermore, we included 50 individuals matched for age, sex, and body mass index (BMI), including 35 men and 15 women with a mean age of 57±12 years and BMI of 23.3±4.0, as controls to evaluate EAT volume. The control group satisfied the following criteria: normal physical examination; normal electrocardiographic findings; no significant coronary stenosis on MDCT; no history of HF, myocardial infarction, or coronary revascularization; and normal 2D echocardiographic and Doppler examination results.

Data on age, sex, and the presence of risk factors (such as smoking and hypertension, as defined by the Joint National Committee Ⅶ; diabetes mellitus, as defined by the World Health Organization study group; or dyslipidemia, as defined by the Japan Atherosclerosis Society guidelines) were also collected.

CMR image acquisition and analysis

CMR images were acquired using a 1.5-T MR imager (Achieva, Philips Medical Systems, Best, the Netherlands) with a 32-element cardiac coil. Cine MR studies were conducted using steady-state free-precession sequence at the shortest possible repetition/echo time and at a flip angle of 55° or 60° along the LV vertical long-axis. By presenting a 4-chamber view and a sequential 10-mm short-axis (no gap) from the aortic valve ring to the apex, these studies allowed for the evaluation of structural and functional assessment.

LVEF and RVEF were calculated by short-axis cine MR imaging, performed under clinically stable conditions, using Simpson's method[15]. LV and RV volumes were quantified by planimetry of the end-diastolic and -systolic endocardial borders on short-axis cine CMR images acquired from base to apex, and were indexed to body surface area (BSA). EF was calculated as the difference between end-systolic volume and end-diastolic volume divided by end-diastolic volume. CMR analyses were performed by an experienced physician (R.K) who was blinded to the clinical information using an offline workstation (View Forum, Philips Medical Systems).

Acquisition of CT data for the assessment of EAT

All MDCT scans were performed using a 64-slice CT scanner (LightSpeed VCT VISION, GE Healthcare Japan Co, Tokyo, Japan). Images were acquired during a single breath hold using prospective ECG gating with imaging triggered at 75% of the R-R interval (collimation, 64×0.625 mm; tube voltage, 120 kV; gantry rotation time, 350 ms; tube current, 200 mA). Reconstructed axial images of 2.5-mm thickness were transferred to an offline workstation (Synapse Vincent, Fujifilm Medical Co, Tokyo, Japan) for image post-processing and analysis. The pericardium counter was manually traced on each transaxial CT slice, followed by automated processing of all continuous voxels with a density range of −200 to −30 Hounsfield units (HU) within the pericardial sac. The upper border and lower border of EAT were considered at the bifurcation of the pulmonary trunk and at the LV apex, respectively. A region of interest was placed within the visceral epicardium to determine EAT area, and the total EAT volume was calculated as the sum of the EAT area on each slice multiplied by the thickness and number of slices[5]. EAT volumes were indexed to BSA or BMI. EAT volumes were analyzed by an experienced physician blinded to other information (T.Y).

Clinical measurements

In patients with HF, baseline clinical parameters were obtained from hospital records, including

laboratory analyses [serum brain natriuretic peptide (BNP) and high sensitivity C-reactive protein levels] at hospital discharge. The LV diastolic function (mitral peak E and A velocities, E/A ratio, e', and E/e' ratio, and deceleration time) and left atrial volume were assessed by echocardiography performed under clinically stable conditions.

Statistical analyses

Continuous variables are presented as mean±standard deviation for normally distributed data and as median and interquartile range for non-normally distributed data. BNP level data were not normally distributed; therefore, log-transformed values of BNP level were used for all analyses. Continuous variables were compared among the three groups using one-way analysis of variance (ANOVA), followed by a multiple comparison using post-hoc Tukey test. Categorical variables were compared using Pearson's χ^2 test. Correlations among continuous variables were assessed using the Spearman rank-correlation coefficient. Multivariate logistic regression analyses were performed to identify independent factors associated with HFrEF with RV dysfunction. Univariate predictors with a p value <0.10 were included in the multivariate model. A two-tailed p value <0.05 was considered statistically significant. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (the R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R designed to add statistical functions frequently used in biostatics.

Results

A total of 100 patients were classified into the HFpEF (n=14, 14%) and HFrEF (n=86, 86%) groups. In the HFrEF group, there were 54 patients (63%) with RV dysfunction (RVEF <45%, HFrEF with RV dysfunction group) and 32 patients (37%) without RV dysfunction (RVEF ≧45%, HFrEF without RV dysfunction group). The interobserver variabilities for LVEF and RVEF measurements performed in a random sample of patients were 4.5±1.6% (r^2=0.995, p<0.0001) and 6.2±4.9% (r^2=0.995, p<0.001), respectively. The intraobserver variabilities were 2.8±2.2% (r^2=1, p< 0.0001) and 2.8±1.9% (r^2=0.997, p<0.0001), respectively. Table 1 shows the baseline clinical characteristics, echocardiographic data, and CMR data in the HFpEF, HFrEF with RV dysfunction, and HFrEF without RV dysfunction groups. There were no significant differences among the three groups regarding age, gender, BMI, and coronary risk factors except diabetes mellitus. The HFrEF with RV dysfunction group had significantly lower systolic blood pressure and higher heart rates than the HFrEF without RV dysfunction or the HFpEF group. Regarding echocardiographic parameters of LV diastolic function, the HFrEF with RV dysfunction group had significantly higher E/A ratio and lower peak A velocity and deceleration time than the HFrEF without RV dysfunction group. The HFrEF group showed significantly higher LV end-diastolic and LV end-systolic volume index and lower LVEF than the HFpEF group. The HFrEF with RV dysfunction group had significantly higher RV end-diastolic and RV end-systolic volume index and lower RVEF than the HFrEF without RV dysfunction group. Medications at discharge were significantly different among the three groups.

Figure 1 compares EAT volume and EAT volume indexed to BSA or BMI among the HFpEF, HFrEF, and control groups. The EAT volume in the HFrEF group was significantly lower than that in the HFpEF group (ANOVA: p<0.05; Fig 1A). The EAT volume indexed to BSA or BMI in the HFrEF group was also significantly lower than that in the HFpEF group (indexed to BSA, ANOVA: p

Table 1. Baseline characteristics

	HFpEF (n=14)	HFrEF without RV dysfunction (n=32)	HFrEF with RV dysfunction (n=54)	p
Age, years	63±18	60±16	57±14	0.37
Men, n (%)	9 (64%)	19 (59%)	35 (65%)	0.8
Body mass index, kg/m^2	24.6±3.5	23.2±4.1	22.2±4.3	0.25
Hypertension, n (%)	7 (50%)	15 (47%)	21 (39%)	0.66
Dyslipidemia, n (%)	5 (36%)	12 (38%)	11 (20%)	0.2
Diabetic mellitus, n (%)	0 (0%)	11 (34%)	10 (19%)	<0.05
Current Smoking, n (%)	6 (43%)	5 (16%)	14 (26%)	0.13
Systolic blood pressure, mm Hg	113.3±14.4	120.2±18.9	108.5±17.7	<0.05
Diastolic blood pressure, mm Hg	78.8±18.0	83.4±17.9	78.2±16.8	0.38
Heart rate, bpm	63.5±11.6	70.6±14.3	75.3±16.5	<0.05
Atrial fibrillation, n (%)	4 (29%)	3 (9%)	8 (15%)	0.28
Laboratory data				
Hemoglobin, g/dL	13.4±1.7	13.3±3.1	14.1±2.2	0.32
Hemoglobin A1c, mg/dL	5.7±0.4	6.0±0.6	6.2±1.6	0.4
BNP, pg/mL	180±211	160±184	249±235	0.16
Log BNP	1.93±0.60	1.96±0.49	2.18±0.47	0.07
C-reactive protein, mg/dL	0.16±0.18	0.17±0.30	0.13±0.17	0.75
Echocardiographic parameters				
Left atrial volume, mL	66.1±23.9	59.6±22.6	65.7±23.4	0.46
Peak E velocity, cm/s	74.6±20.1	63.1±23.4	75.5±24.6	0.06
Peak A velocity, cm/s	86.3±28.63	70.0±21.6	58.5±19.6	<0.001
E/A ratio	0.92±0.48	0.95±0.47	1.39±0.75	<0.05
è, cm/s	4.8±2.2	4.6±1.9	4.8±2.0	0.9
E/è ratio	19.1±12.9	14.8±4.8	18.1±9.7	0.19
Deceleration time, msec	245±98	197±76	160±60	<0.001
Moderate				
Mitral valve regurgitation	2 (14%)	6 (19%)	12 (22%)	0.83
Aortic valve regurgitation	0 (0%)	1 (3%)	0 (0%)	-
Tricuspid valve regurgitation	1 (7%)	0 (0%)	2 (4%)	-
CMR parameters				
LV ejection fraction, %	59.6±7.8	31.1±7.8	24.4±9.0	<0.001
LV EDVI, mL/m^2	78.7±20.1	124.9±32.9	135.9±45.4	<0.001
LV ESVI, mL/m^2	32.7±12.4	88.0±30.3	104.9±42.2	<0.001
RV ejection fraction, %	52.8±13.5	53.0±5.9	31.7±8.7	<0.001
RV EDVI, mL/m^2	89.6±35.7	68.7±14.3	101.7±38.3	<0.001
RV ESVI, mL/m^2	45.6±29.5	37.1±29.0	71.1±34.4	<0.001
Medication at discharge				
β blocker, n (%)	9 (64%)	28 (88%)	50 (93%)	<0.05
ACE inhibitors/ARB, n (%)	10 (71%)	25 (78%)	43 (80%)	0.75
MRB, n (%)	4 (29%)	18 (56%)	38 (70%)	<0.05
Tolvaptan, n (%)	2 (14%)	1 (3%)	4 (7%)	0.40
Loop diuretics, n (%)	8 (57%)	15 (47%)	38 (70%)	0.09

Values are mean±SD, n (%), or median (interquartile range). HFpEF indicates heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; RV, right ventricular; BNP, brain natriuretic peptide; CMR, cardiac magnetic resonance; LV, left ventricular; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; ACE, angiotensin converting enzyme; ARB, angiotensin Ⅱ type 1 receptor blockers; and MRB, mineralocorticoid receptor blocker.

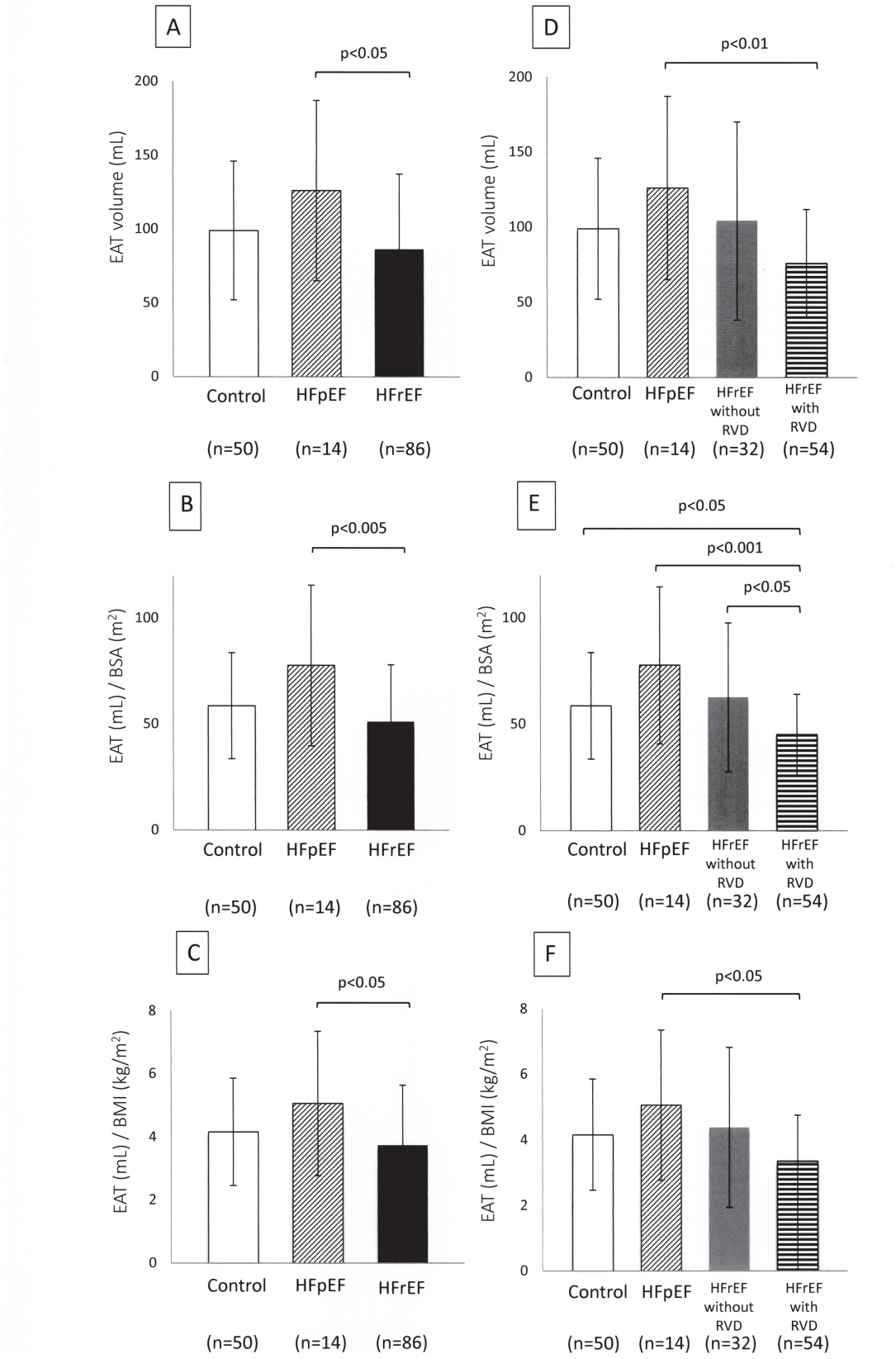

Figure 1. (A) EAT volume, (B) EAT volume indexed to BSA, and (C) EAT volume indexed to BMI in the HFpEF, HFrEF, and control groups. (D) EAT volume, (E) EAT volume indexed to BSA, and (F) EAT volume indexed to BMI in the HFpEF, HFrEF without RV dysfunction, HFrEF with RV dysfunction, and control groups. EAT, epicardial adipose tissue; BSA, body surface area; BMI, body mass index; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; and RVD, right ventricular dysfunction.

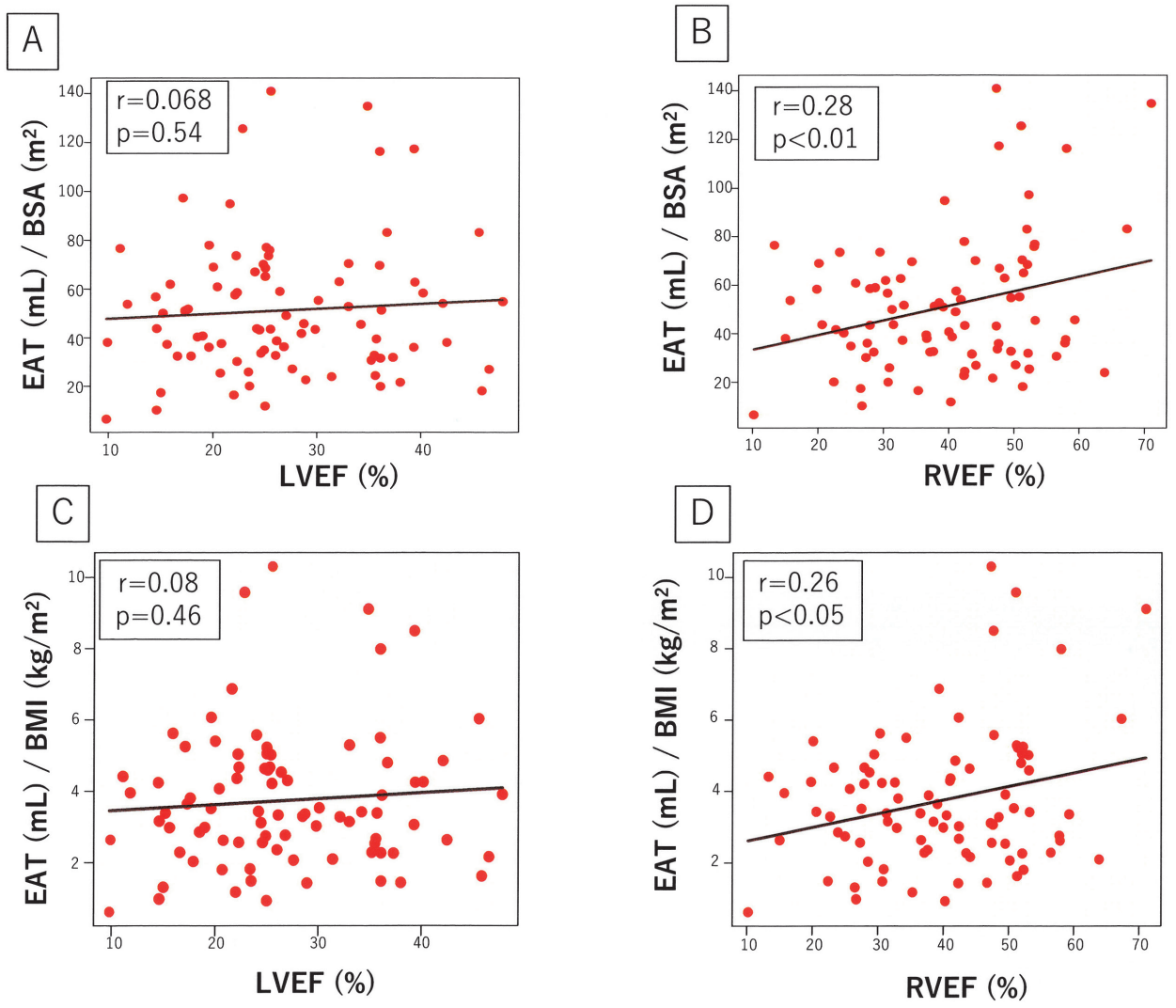

Figure 2. In the HFrEF group, the correlation of EAT volume indexed to BSA or BMI with LVEF or RVEF. (A) EAT volume indexed to BSA vs LVEF, (B) EAT volume indexed to BSA vs RVEF. (C) EAT volume indexed to BMI vs LVEF, (B) EAT volume indexed to BMI vs RVEF. HFrEF, heart failure with reduced ejection fraction; EAT, epicardial adipose tissue; BSA, body surface area; BMI, body mass index; LVEF, left ventricular ejection fraction; and RVEF, right ventricular ejection fraction.

Table 2. Univariate and multivariate analyses for association with HFrEF with RV dysfunction in patients with HF

	Univariate analysis			Multivariate analysis		
Factors	OR	95% CI	p-value	OR	95% CI	p-value
Systolic blood pressure	0.97	0.95-0.99	<0.05			
Log BNP	2.62	1.13-6.1	<0.05			
Deceleration time	0.99	0.98-1.00	<0.005			
LV ejection fraction	0.90	0.86-0.94	<0.001	0.90	0.84-0.95	<0.001
EAT volume indexed to BSA	0.97	0.96-0.99	<0.001	0.97	0.95-0.99	<0.01

HFrEF indicates heart failure with reduced ejection fraction; RV, right ventricular; HF, heart failure; BNP, brain natriuretic peptide; LV, left ventricular; EAT, epicardial adipose tissue; BSA, body surface area; OR, odds ratio; and CI, confidence interval.

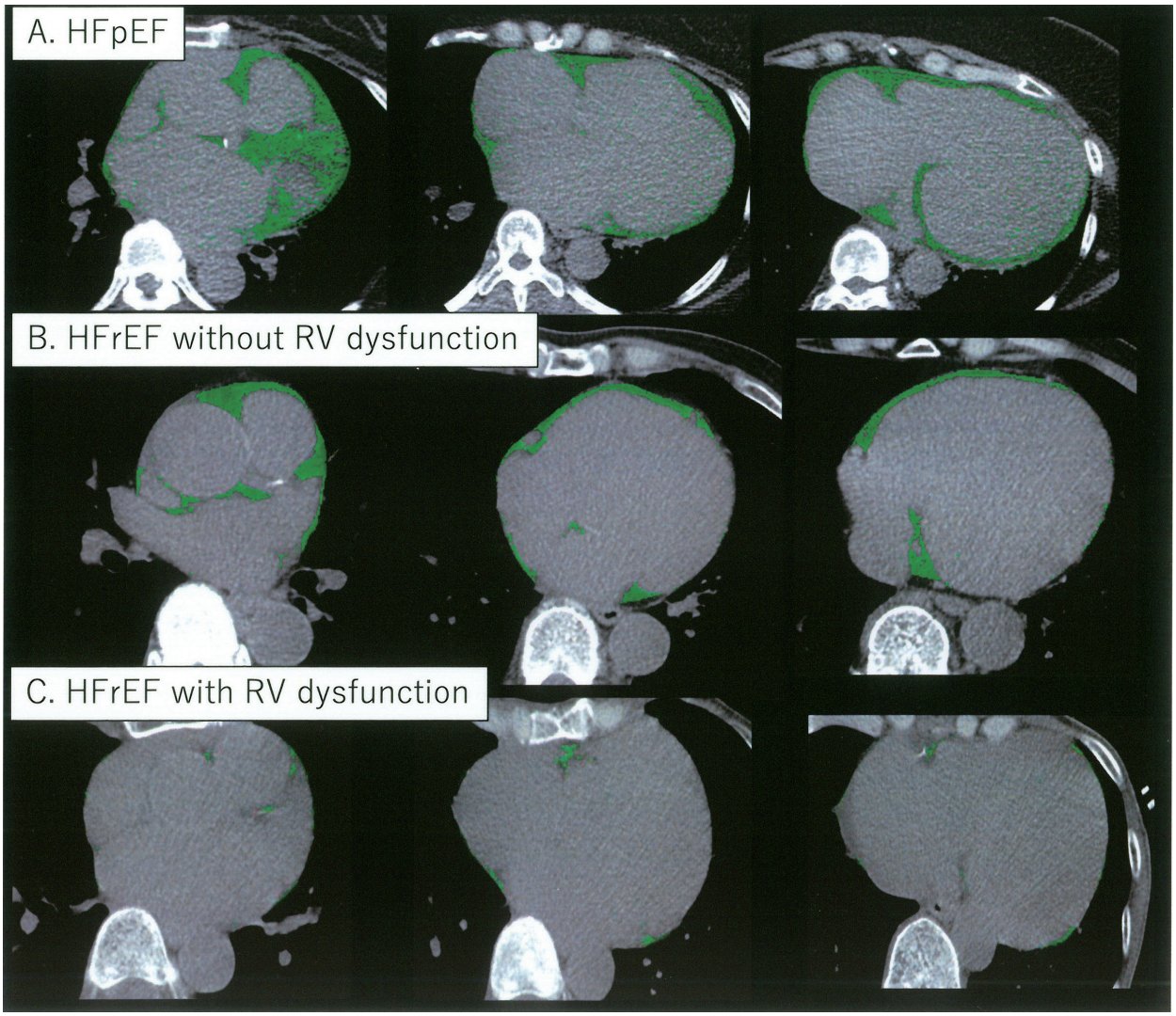

Figure 3. CT showing EAT in representative cases of HFpEF, HFrEF without RV dysfunction, and HFrEF with RVD. (A) CT showing abundant EAT surrounding the heart in a patient with HFpEF. (B) CT showing intermediate amount of EAT surrounding the heart in a patient with HFrEF without RVD. (C) CT showing very little EAT surrounding the heart in a patient with HFrEF with RVD. CT, computed tomography; EAT, epicardial adipose tissue; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; and RVD, right ventricular dysfunction.

<0.005; indexed to BMI, ANOVA: $p<0.05$, Fig 1B and C). Moreover, the EAT volume in the HFrEF with RV dysfunction group was significantly lower than in the HFpEF group (HFrEF with RV dysfunction, 75.57±35.7 mL; HFrEF without RV dysfunction, 104.1±66.1 mL, HFpEF, 126.0±61.4 mL; and controls, 99.0±47.2 mL; ANOVA: $p<0.005$; HFrEF with RV dysfunction vs HFpEF, $p<0.01$; Fig. 1D). The EAT volume indexed to BSA in the HFrEF with RV dysfunction group was significantly lower than that in the other groups (HFrEF with RV dysfunction, 44.70±19.2 mL/m^2; HFrEF without RV dysfunction, 62.0±35.2 mL/m^2, HFpEF, 77.9±38.0 mL/m^2; and controls, 58.6±25.0 mL/m^2; ANOVA: $p<0.001$; HFrEF with RV dysfunction vs HFrEF without RV dysfunction, $p<0.05$; and HFrEF with RV dysfunction vs HFpEF, $p<0.001$; Fig 1E). There was no significant difference in EAT volume and index between the HFpEF and control groups. As shown in Figure 2, the EAT volume indexed to BSA or BMI in the HFrEF group was positively correlated with RVEF (indexed to BSA, r=

0.28, $p<0.01$; indexed to BMI, $r=0.26$, $p<0.05$; Fig 2B and D), but not with LVEF (indexed to BSA, $r=0.068$, $p=0.54$; indexed to BMI, $r=0.08$, $p=0.46$; Fig 2A and C). In contrast, the EAT volume indexed to BSA or BMI in the HFpEF group was not significantly correlated with LVEF or RVEF. In patients with HF, univariable and multivariable analyses were performed to identify the independent factors associated with HFrEF with RV dysfunction (Table 2). Multivariable analysis revealed that LVEF and EAT volume indexed to BSA were independent factors associated with HFrEF with RV dysfunction. Figure 3 shows representative CT images assessing EAT in the HFpEF, HFrEF without RV dysfunction, and HFrEF with RV dysfunction groups. Figure 3-A shows abundant EAT surrounding the heart in a patient with HFpEF. In contrast, Figure 3-C and Figure 3-B show very little EAT in an HFrEF patient with RV dysfunction and intermediate amount of EAT in an HFrEF patient without RV dysfunction, respectively.

Discussion

To the best of our knowledge, this is the first study to investigate the correlation between the amount of EAT and RV function in patients with HFrEF. The major finding of this study was that HFrEF patients, especially those with RV dysfunction, had less EAT volume index compared to HFpEF patients or control patients despite similar BMI. Furthermore, the EAT volume index in the HFrEF group was positively correlated with RVEF but not LVEF. Multivariable analysis revealed that EAT volume index was an independent factor associated with HFrEF with RV dysfunction.

Some studies have shown that EAT is significantly reduced in patients with HFrEF compared to that in the healthy controls[12-14]. Our data support those findings. The association between EAT and mechanisms responsible for the progression of HFrEF remains unclear. González et al proposed that myocardial dysfunction and remodeling in patients with HFrEF were driven by the progressive loss of cardiomyocytes[22]. This loss of cardiomyocytes results from various modes of cell death, such as exaggerated autophagy, apoptosis, or necrosis, all of which are triggered by oxidative stress present within the cardiomyocytes because of ischemia, infection, or toxic agents. As the myocardium becomes more dysfunctional and develops abnormal metabolic needs, EAT satisfies its energy requirements. EAT exhibits a high lipolytic activity and might serve as a ready source of free fatty acids, leading to a decrease in EAT[23]. However, data regarding the correlation between LVEF and the amount of EAT are complicated and controversial. Some studies have reported the EAT volume measured by CT or echocardiography to be positively correlated with LVEF[12,13]. On the contrary, Doesch et al demonstrated a negative correlation between LVEF and EAT volume index, measured using CMR imaging[14]. This disagreement may reflect a difference in study population and the severity of HFrEF. In patients with HFrEF, RV systolic dysfunction is associated with impaired functional capacity and represents a more advanced stage[11]. However, RV function was not taken into account in previous EAT-related studies. Therefore, the current study considered RV function and observed that EAT volume index was positively correlated with RVEF (i.e., the worse the RV function was, the lower the EAT volumes were). A postmortem study by Schejbal showed that persistent RV failure was associated with thinning of the surrounding fatty layer[24]. At an early stage of HFrEF, preserved vascular distensibility maintains pulmonary vascular resistance within the normal ranges. However, as disease progresses, long-standing left atrial hypertension results in an increase in RV afterload, which intern leads to RV dysfunction[25]. Therefore, at a more advanced stage of HFrEF, the lipolytic activity of EAT increases with a diminished responsiveness to adjust to the

special energy demands of the heart, which may decrease EAT volumes.

On the contrary, several lines of evidence have suggested that an increase in EAT is significantly related to a proportional increase in LV mass[18]. A recent study by van Woerden et al revealed higher EAT volume in patients with HFpEF than in healthy controls[19]. Therefore, one can imagine that EAT is also involved in the pathophysiology of HFpEF. In patients with HFpEF, endothelial inflammation and oxidative stress induced by comorbidities, such as obesity, hypertension, diabetes mellitus, and chronic kidney disease, have recently been shown to drive myocardial dysfunction and remodeling[10]. In patients with visceral obesity, excessive fat cells tend to cause muscular hypertrophy and become dysfunctional due to surplus energy. Dysfunctional fat cells release pro-inflammatory adipokines into the bloodstream, possibly leading to chronic systemic inflammation associated with arterial stiffness, endothelial dysfunction in arterioles, and fibrosis, all of which have been implicated in the development of HFpEF[20,21]. Therefore, the new paradigm proposes that myocardial dysfunction and remodeling in HFpEF result from a series of bad flow caused by comorbidities, especially visceral obesity. This may explain a high EAT volume in patients with HFpEF although there was no significant difference in EAT volume between the HFpEF and control groups in the present study.

Recently, Pugliese et al showed the opposite association of EAT with cardiometabolic profile, haemodynamics and outcome in HF cohorts. In HFrEF, EAT accumulation is protective as a metabolic reservoir, therefore, EAT reduction is detrimental. In HFpEF, on the other hand, increased EAT plays an adverse role to promote haemodynamic derangements and alter adipogenesis by secretion of pro-inflammatory adipokines. Recent evidences suggest that natriuretic peptides activate lipolysis in adipose tissue in patients with HFrEF[24]. Consequently, increased BNP levels may contribute to the decrease in EAT in patients with HFrEF. A difference between the physiologic and pathophysiologic roles of EAT may reflect a difference in mechanisms responsible for the progression of cardiac dysfunction in patients with HFpEF and HFrEF. Such information on the difference in EAT volumes between the HFrEF and HFpEF groups may have a novel clinical implication in the therapy of HF. EAT may be a potential target for therapies using nutrient supply and drugs, such as glucagon peptide-like 1 analogs, sodium glucose transport 2 inhibitors, or ghrelin[26], to prevent the progression of HF. Further studies are needed to confirm the finding of this study.

This study has several limitations. First, due to the cross-sectional, retrospective nature of this study, we could not explore the direct causal relationships between EAT, comorbidities, and myocardial function and contractility. Therefore, it remains unclear whether EAT is a cause or a consequence of these diseases or merely an innocent bystander. Second, RV diastolic function was not taken into account in our study, although it may relate to EAT volume in patients with HF. Third, we did not measure various biological and metabolic markers such as pro-inflammatory adipokines and free fatty acids. Despite advances in the treatment of HF, our understanding of the energy metabolic mechanisms limiting cardiac pump function remains incomplete. In the future, the energy metabolism in the failing human heart needs to be elucidated. Finally, due to limited data in the HFpEF and control groups, only our primary question and not any additional questions could be answered.

In conclusion, this study demonstrated that HFrEF patients with RV dysfunction had less EAT compared to HFpEF patients, and less amount of EAT was related to the severity of RV dysfunction in HFrEF.

Acknowledgements

All authors have no COI to declare regarding the present study.

References

1. González N, Moreno-Villegas Z, González-Bris A, et al. Regulation of visceral and epicardial adipose tissue for preventing cardiovascular injuries associated to obesity and diabetes. Cardiovasc Diabetol 2017;16:44.
2. Iacobellis G, Ribaudo MC, Assael F, et al. Echocardiographic epicardial adipose tissue is related to anthropometric and clinical parameters of metabolic syndrome: a new indicator of cardiovascular risk. J Clin Endocrinol Metab 2003;88:5163-5168.
3. Pierdomenico SD, Pierdomenico AM, Cuccurullo F, et al. Meta-analysis of the relation of echocardiographic epicardial adipose tissue thickness and the metabolic syndrome. Am J Cardiol 2013;111:73-78.
4. Iacobellis G, Leonetti F. Epicardila adipose tissue and insulin resistance in obese subjects. J Clin Endocrinol Metab 2005;90:6300-6302.
5. Nakanishi K, Fukuda S, Tanaka A, et al. Peri-atrial epicardial adipose tissue is associated with new-onset nonvalvular atrial fibrillation. Circ J 2012;76:2748-2754.
6. Gaeta M, Bandera F, Tassinari F, et al. Is epicardial fat depot associated with atrial fibrillation? A systemic review and meta-analysis. Europace 2017;19:747-752.
7. Oka T, Yamamoto H, Ohashi N, et al. Association between epicardial adipose tissue volume and characteristics of non-calcified plaques assessed by coronary computed tomographic angiography. Int J Cardiol 2012;161:45-49.
8. Mancio J, Azevedo D, Saraiva F, et al. Epicardial adipose tissue volume assessed by computed tomography and coronary artery disease: a systematic review and meta-analysis. Eur Heart J Cardiovasc Imaging 2018;19:490-497.
9. Le Jemtel TH, Samson R, Ayinapudi K, et al. Epicardial adipose tissue and cardiovascular disease. Curr Hypertens Rep 2019;21:36.
10. Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol 2013;62:263-271.
11. Merlo M, Gobbo M, Stolfo D, et al. The prognostic impact of the evolution of RV function in idiopathic DCM. JACC Cardiovasc Imaging 2016;9:1034-1042.
12. Khawaja T, Greer C, Chokshi A, et al. Epicardial fat volume in patients with left ventricular systolic dysfunction. Am J Cardiol 2011;108:397-401.
13. Tabakci MM, Durmuş Hİ, Avci A, et al. Relation of epicardial fat thickness to the severity of heart failure in patients with nonischemic dilated cardiomyopathy. Echocardiography 2015;32:740-748.
14. Doesch C, Haghi D, Flüchter S, et al. Epicardial adipose tissue in patients with heart failure. J Cardiovasc Magn Reson 2010;12:40.
15. Schulz-Menger J, Bluemke DA, Bremerich J, et al. Standardized image interpretation and post-processing in cardiovascular magnetic resonance - 2020 update: Society for Cardiovascular Magnetic Resonance (SCMR): Board of Trustees Task Force on Standardized Post Processing. J Cardiovasc Magn Reson 2020;22:19.
16. McKee PA, Castelli WP, McNamara PM, et al. The natural history of congestive heart failure: the Framingham study. N Engl J Med 1971;285:1441-1446.
17. Aschauer S, Kammerlander AA, Zotter-Tufaro C, et al. The right heart in heart failure with preserved ejection fraction: insights from cardiac magnetic resonance imaging and invasive haemodynamics. Eur J Heart Fail 2016;18:71-80.
18. Iacobellis G, Ribaudo MC, Zappaterreno A, et al. Relation between epicardial adipose tissue and left ventricular mass. Am J Cardiol 2004;94:1084-1087.
19. van Woerden G, Gorter TM, Westenbrink BD, et al. Epicardial fat in heart failure patients with mid-range and preserved ejection fraction. Eur J Heart Fail 2018;20:1559-1566.
20. Jelic S, Lederer DJ, Adams T, et al. Vascular inflammation in obesity and sleep apnea. Circulation 2010;121:1014-1021.
21. Taube A, Schlich R, Sell H, et al. Inflammation and metabolic dysfunction: links to cardiovascular diseases. Am J Physiol Heart Circ Physiol 2012;302:H2148-2165.
22. González A, Ravassa S, Beaumont J, et al. New targets to treat the structural remodeling of the myocardium. J Am Coll Cardiol 2011;58:1833-1843.
23. Iacobellis G, Corradi D, Sharma AM. Epicardial adipose tissue: anatomic, biomolecular and clinical relationships with the heart. Nat Clin Pract Cardiovasc Med 2005;2:536-543.

24. Schejbal V. Epicardial fatty tissue of the right ventricle — morphology, morphometry and functional significance. Pneumologie 1989;43:490-499.
25. Haddad F, Doyle R, Murphy DJ, et al. Right ventricular function in cardiovascular disease, part Ⅱ: pathophysiology, clinical importance, and management of right ventricular failure. Circulation 2008;117:1717-1731.
26. Nagaya N, Moriya J, Yasumura Y, et al. Effects of ghrelin administration on left ventricular function, exercise capacity, and muscle wasting in patients with chronic heart failure. Circulation 2004;110:3674-3679.

Osaka City Med. J. Vol. 68, 73-80, 2022

Association between Receiving Feedback on the Results of an Automated Cognitive Function Test and Motivation for Dementia-preventive Behavior

Satoshi Akada[1)], Kentaro Uchida[2)], Jumpei Maruta[3)], Hideo Kurozumi[1)], Satoshi Nogi[1)], and Koki Inoue[1,4)]

Department of Neuropsychiatry[1)], Osaka City University Graduate School of Medicine; Department of Neuropsychiatry[2)], Osaka Metropolitan University Graduate School of Medicine; Department of Psychiatry[3)], Osaka City Kosaiin Hospital; and Center for Brain Science[4)], Osaka Metropolitan University Graduate School of Medicine

Abstract

Background

Receiving feedback on the results of cognitive function tests is an effective motivating factor for producing dementia-preventive behavior, but the association between receiving feedback on the results of automated cognitive function tests and motivation for dementia-preventive behavior is unclear. We investigated the association between receiving feedback on the results of the Cogstate Brief Battery and motivation for dementia-preventive behavior.

Methods

The participants were community-dwelling older adults aged ≧65 years without a diagnosis of dementia or mild cognitive impairment. They were divided into the Cogstate Brief Battery and control groups. They responded to a questionnaire twice, 3 months apart. We compare the percentage of participants who were more motivated regarding dementia-preventive behavior between the two groups. Multivariate logistic regression analysis was conducted on the association between being in the Cogstate Brief Battery group and a stronger motivation.

Results

The study included 222 participants (105 in the Cogstate Brief Battery group and 117 in control group). Being in the Cogstate Brief Battery group was significantly associated with a stronger motivation for dementia-preventive behavior, even after adjusting for sex, age, education, and contact with persons with dementia. Factors such as sex were not significantly associated with a stronger motivation.

Conclusions

This study found that receiving feedback automatically on the results of the Cogstate Brief

Received August 24, 2022; accepted October 31, 2022.
Correspondence to: Satoshi Akada, MD.
Department of Neuropsychiatry, Osaka Metropolitan University Graduate School of Medicine,
1-4-3 Asahimachi, Abeno-ku, Osaka 545-8585, Japan
Tel: +81-6-6645-3821; Fax: +81-6-6636-0439
E-mail: i21973f@omu.ac.jp

Battery was significantly associated with a stronger motivation for improved dementia-preventive behavior among community-dwelling older adults. This study may provide useful insights for interventions targeting dementia prevention among community-dwelling older adults.

Key Words: The Cogstate Brief Battery; Cognitive function test; Motivating factor; Behavior change; Older adults.

Introduction

Japan is a hyper-aged society with a declining birthrate and an aging population. According to the report by Ninomiya et al, 36.4 million people aged ≧65 years accounted for 29.1% of the total population in 2021, and this figure is estimated to reach 35.3% by 2040. Dementia is a major mental disorder among older adults, and its prevalence among those aged ≧65 years in Japan is estimated to reach 20.7% by 2040[1]. Dementia can lead to a variety of mental, physical, and social health problems that impair qualitative living. Inappropriate eating habits, lack of exercise, heavy alcohol consumption, and smoking are reported to be associated with the onset of dementia[2,3], and change in lifestyle involving diet and exercise is effective for preventing dementia. However, few people actually take action to prevent dementia, and Smith et al reported that less than 40% of people take action to forestall dementia[4]. Reports indicate that dementia-preventive behavior is associated with a higher level of knowledge about dementia[5,6] and awareness of cognitive decline[7]. Therefore, gaining knowledge about dementia and receiving feedback on the results of cognitive function tests should be effective in motivating behavior change for the prevention of dementia.

The usefulness of the Mini Mental State Examination (MMSE)[8] and the Montreal Cognitive Assessment (MoCA)[9] as simple bedside tests for screening mild cognitive impairment and dementia associated with Alzheimer's disease has been reported, but recently, automated cognitive function tests have begun to be widely used[10]. Tools such as the Cognitive Assessment for Dementia, iPad version 2 (CADi2)[11] and MSP-1100[12], which is produced by Nihon Kohden Corp (Tokyo, Japan), have also been developed for mass screening for the secondary prevention of dementia. Automated tools can be self-administered without the need for a specialist; they also take less time and are easier to administer than conventional cognitive function tests[13]. Among these, the Cogstate Brief Battery (CBB) has been shown to have validity as a cognitive function test[14] and has been reported to be effective in screening for mild cognitive impairment and dementia associated with Alzheimer's disease[15,16]. However, the association between receiving feedback on the results of CBB and the motivation for improved dementia-preventive behavior is unclear.

In this study, we investigated the association between receiving feedback on the results of CBB, which is an automated cognitive function test, and motivation for behavior change regarding the prevention of dementia among community-dwelling older adults. We compared the CBB group, which was administered CBB, received feedback automatically on the results, and was educated about dementia based on materials on important lifestyle changes for preventing dementia, with the non-CBB group, which was only educated about dementia.

Methods

Participants

Our co-researcher, Akakabe Co., Ltd. (Osaka, Japan), who operates drugstores nationwide, recruited participants for this study. Participants were recruited from January 2021 to May 2021

using personal information already held by Akakabe Co., Ltd. in its membership system. Our target participants were community-dwelling adults in Japan aged ≧65 years who had not been diagnosed with dementia or mild cognitive impairment. The required number of participants was set at 200 (100 in the CBB group and 100 in the non-CBB group) with a threshold response rate of 30%, expected response rate of 50%, power of 80%, and alpha of 0.05 (two-sided). The proportion of dropouts and ineligible participants was estimated at 50%, and 400 participants were required in the first step. Those who had been diagnosed with dementia or mild cognitive impairment or had visited a medical institution for cognitive dysfunction were excluded. This study was approved by the Ethical Committee of Osaka City University Graduate School of Medicine (approval number: 2020-238). This study was conducted in accordance with the Declaration of Helsinki and its future amendments. All participants were informed of the purpose and methods of the study, and they provided written consent.

Procedure

In the first step, 400 participants were randomly assigned to two groups (CBB and non-CBB groups) by a simple method, with 200 participants in each group. After gaining prior consent for mailing, CBB was mailed to the CBB group, and CBB was administered and the results were fed back automatically to the participants. All participants were educated on dementia and important lifestyle changes for preventing dementia using relevant materials. In addition, a questionnaire was mailed to all participants and their responses were obtained. For the CBB group, the questionnaire was provided before the CBB was administered. The questionnaire included five questions regarding sex, age, educational background, contact with dementia, and whether they were willing to change their lifestyle to prevent dementia. For education, we calculated the number of years of education. We defined "contact with dementia" as having a history of personal contact with people with dementia. In the second step (3 months after the first step), a questionnaire was mailed to all participants regarding whether they were willing to change lifestyle for the prevention of dementia, and their responses were recorded. Concerning the questionnaire on whether they were willing to change their lifestyle to prevent dementia, the respondents were asked to choose from five stages: "1: not planning to change within 6 months", "2: planning to change within 6 months", "3: planning to change within 1 month", and "4: have changed but for less than 6 months", "5: have changed for more than 6 months". Because the dropout rate from the non-CBB group was higher than expected, 150 additional non-CBB participants were added to this study, for a total of 550 participants who fully consented to the study.

The Cogstate Brief Battery

CBB which is produced by Cogstate, Ltd. (Melbourne, Australia) is an automated tool for cognitive self-assessment and consists of four cognitive tests that assess psychomotor function, attention, working memory, and visual learning[17]. CBB plays an important role in Alzheimer's disease research and clinical trials[18,19] and has been reported to be effective in screening for mild cognitive impairment and dementia associated with Alzheimer's disease[15,16]. Furthermore, because CBB is a computer-based tool, the administration, evaluation, and reporting of the test is automated and highly standardized. It can be administered in 10 minutes, making it easier to apply than conventional cognitive function tests. In addition, as CBB is not a medical device, it can be easily used at events for residents. In the US and Europe, Cognigram™, which is a medical version of CBB with a specialized feedback function for medical professionals, has been approved as a medical device and is used to assist medical professionals in examining and diagnosing mild cognitive impairment and

dementia[20,21]. The nouKNOW, developed by Eisai Co., Ltd. in Japan, was used in this study. It is the Japanese version of CBB, and the content of the nouKNOW test is the same as that of CBB, with additional advice on dementia prevention as feedback. The nouKNOW was developed as a digital tool (non-medical device) for self-checking brain performance. The results of nouKNOW are fed back to the participants with the Concentration score and the Memory score. These scores range from 0 to 50 (0-14.9: incorporate activities to maintain and improve, 15-19.9: border line, 20-50: normal). Furthermore, recommendations on lifestyle improvement such as habits of regular exercise, non-smoking, balanced diet intake, and moderate alcohol consumption as well as on physical and mental health management, such as on the management of blood pressure, blood sugar, body fat, mental health, and hearing consumption related to the test results is automatically fed back to participants.

Statistical analysis

Statistical analysis was performed using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (version 2.13.0; R Foundation for Statistical Computing, Vienna, Austria). We investigated the association between receiving feedback on the results of CBB, which is an automated cognitive function test, and motivation for dementia-preventive behavior. Regarding the questionnaire on whether they were willing to change their lifestyle to prevent dementia, the respondents whose stage of behavior changed from "1" to "2", "3", "4", or "5", from "2" to "3", "4", or "5", and from "3" to "4" or "5", from the first to the second step, were considered to be more motivated regarding dementia-preventive behavior; the rest were considered to be less motivated. Age was compared using a student's t-test. Sex and whether participants had contacted people with dementia were compared using Fisher's exact test. Education and whether participants were willing to change their lifestyle to prevent dementia was compared using the Mann-Whitney U test. After adjusting for factors such as sex, age, education, and contact with dementia, multivariate logistic regression analysis was conducted on the association between being in the CBB group and a stronger motivation for dementia-preventive behavior. Education[4,7] and contact with dementia[22-24] have been reported to be associated with dementia-preventive behavior; therefore, they were set as confounding factors. Student's t-test was used for intergroup comparison of the Concentration and Memory scores between the group that is motivated towards dementia-preventive behavior and the one that is not. P values <0.05 were considered statistically significant.

Results

This study included 550 (200 in the CBB group and 350 in the non-CBB group) community-dwelling older adults. After excluding 30 persons who did not respond in the first step (8 in the CBB group and 22 in the non-CBB group), 203 persons who responded in the first step but not in the second step (46 in the CBB group and 157 in the non-CBB group), and 95 persons whose questionnaires were invalid due to missing values (41 in the CBB group and 54 in the non-CBB group), 222 participants (105 in the CBB group and 117 in the non-CBB group) were included in the analysis.

Table 1 shows the characteristics of the participants assigned to the CBB and non-CBB groups. Significant differences were found in sex ($p=0.037$), age ($p=0.004$), and education ($p=0.049$).

Table 2 shows the odds ratios (ORs) and 95% confidence intervals (CIs) for the multivariate logistic regression analysis of the association between being in the CBB group and a stronger motivation for dementia-preventive behavior, after adjusting for factors such as sex, age, education,

and contact with dementia. Being in the CBB group was significantly associated with a stronger motivation for dementia-preventive behavior (OR=1.99; CI: 1.10-3.61; p=0.023). Sex, age, education, and contact with dementia were not significantly associated with a stronger motivation for dementia-preventive behavior.

Table 3 shows the association between the score of CBB and motivation for dementia-preventive behavior. Significant differences were not found in both Concentration (p=0.117) and Memory (p=0.189) scores.

Table 1. Characteristics of the participants

		CBB group	Non-CBB group	p-value
n		105	117	
Sex	Men	17 (16.2%)	33 (28.2%)	0.037
	Women	88 (83.8%)	84 (71.8%)	
Age, years (mean±SD)		71.70±4.67	73.81±6.05	0.004
Education, years (range)		12 (9-16)	12 (9-16)	0.049
Contact with dementia	No	55 (52.4%)	77 (65.8%)	0.055
	Yes	50 (47.6%)	40 (34.2%)	
Question about change	1	60	64	0.832
in lifestyle † (first step)	2	15	20	
	3	5	6	
	4	2	2	
	5	23	25	
Question about change	1	36	50	0.114
in lifestyle † (second step)	2	16	21	
	3	8	6	
	4	5	6	
	5	40	34	
Results of CBB	C-score	22.87±4.58		
(mean±SD)	M-score	24.08±5.45		

† 1: not planning to change within 6 months, 2: planning to change within 6 months, 3: planning to change within 1 month, 4: have changed but for less than 6 months, 5: have changed for more than 6 months. Abbreviations: CBB, Cogstate Brief Battery; SD, standard deviation; C-score, Concentration score; and M-score, Memory score.

Table 2. Influencing factors for improved dementia-preventive behavior

		All	N of participants with improved dementia-preventive behavior	OR † (95% CI)	p-value
Group	CBB	105	43 (41.0%)	1.99 (1.10-3.61)	0.023
	Non-CBB	117	32 (27.4%)		
Sex	Men	50	14 (28.0%)	0.81 (0.39-1.69)	0.57
	Women	172	61 (35.5%)		
Age, years				1.04 (0.99-1.10)	0.15
Education, years				0.97 (0.84-1.12)	0.67
Contact with dementia	No	132	42 (31.8%)	0.88 (0.48-1.59)	0.66
	Yes	90	33 (36.7%)		

† OR was adjusted for sex, age, education, and contact with dementia. Abbreviations: N, number; OR, odds ratio; CI, confidence interval; and CBB, Cogstate Brief Battery.

Table 3. Association between the scores of CBB and motivation towards dementia-preventive behavior

	Motivated to change lifestyle	Not motivated to change lifestyle	p-value
n	43	62	
C-score (mean±SD)	23.71±4.51	22.29±4.57	0.117
M-score (mean±SD)	23.24±5.63	24.66±5.28	0.189

Abbreviations: CBB, Cogstate Brief Battery; C-score, Concentration score; M-score, Memory score, and SD, standard deviation.

Discussion

This study aimed to determine whether there is an association between receiving feedback on the results of CBB, which is an automated cognitive function test, and motivation for dementia-preventive behavior among community-dwelling older adults. The study found two things. First, receiving feedback on results of CBB, not the score of CBB, was significantly associated with a stronger motivation. Second, factors such as sex, age, education, and contact with dementia were not significantly associated with a stronger motivation. These results suggest that receiving feedback on the results of CBB is effective in motivating community-dwelling older adults who have not been diagnosed with dementia or mild cognitive impairment to change their lifestyles for the prevention of dementia.

First, receiving feedback on the results of CBB motivated dementia-preventive behavior. Prochaska et al. identified dramatic relief as one of the 10 processes (Consciousness raising, Dramatic relief, Environmental reevaluation, Self-reevaluation, Self-liberation, Social liberation, Contingency management, Helping relationship, Counterconditioning, and Stimulus control) that produce behavior change[25]. Dramatic relief refers to the experience of various emotional reactions and feelings that motivate behavior change, and in this study, learning about one's own cognitive functioning by receiving feedback on the results of CBB, and the resulting emotional reactions, such as being happy or sad, were considered to fall under the category of dramatic relief. A report noted that awareness of the importance of actions for preventing dementia was associated with actual preventive actions[26], and in this study, the combination with dramatic relief seemed more effective. Among automated tools for self-checking cognitive function, CBB is sufficient to detect mild cognitive impairment related to Alzheimer's disease associated with Alzheimer's disease[15,16]. Therefore, it is considered that no ceiling effect occurred and the test was able to provide appropriate feedback, even when used for people who are generally considered cognitively normal, such as community-dwelling older adults.

Second, factors such as sex, age, education, and contact with dementia were not significantly associated with a stronger motivation for improved dementia-preventive behavior. Education[4,7] and contact with dementia[22-24] have been reported to be associated with dementia-preventive behavior. Although studies indicate that people who have contact with dementia are less likely to believe that dementia is preventable[27], in this study, contact with dementia was not a significant inhibitor of motivation for dementia-preventive behavior. These results suggest that CBB-based interventions are effective for a wide range of people with different backgrounds, and CBB may enable us to reach those who are less likely to take action to prevent dementia.

There are several limitations to this study. First, there were significant differences in sex, age, and education between CBB and non-CBB groups. This may have been due to participation bias, as

those who cooperated in the study, which was more time-consuming than the non-CBB group, participated in the CBB group. However, even after adjusting for known factors that influence dementia-preventive behavior, such as sex, age, education, and contact with dementia, receiving feedback on results of CBB was significantly associated with a stronger motivation for dementia-preventive behavior. Therefore, the bias in characteristics between CBB and non-CBB groups does not seem to weaken our argument. Second, the dropout rate was high between the first and second steps. Since many of the participants who dropped out were considered less likely to be motivated to change their lifestyle for the prevention of dementia, it is possible that the proportion of participants who became more motivated was actually higher than noted. However, the CBB group had a lower dropout rate than the non-CBB group. Therefore, this does not weaken our argument that the CBB group was more motivated. Third, 6 months is the standard definition of each stage in the behavior change stages proposed by Prochaska et al[25], but in this study, participants were asked in a questionnaire about their willingness to change their lifestyle for the prevention of dementia 3 months after the first step. Therefore, the long-term effects are not known. Fourth, although this study showed an association between receiving feedback on CBB results and motivation for dementia-preventive behavior, we were unable to follow the progress after that point. Therefore, we do not know whether the increased motivation actually led to the prevention of dementia. Future longitudinal studies on the development of dementia after receiving feedback on the results of CBB are awaited.

This study found that receiving feedback on results of CBB was significantly associated with a stronger motivation for dementia-preventive behavior among community-dwelling older adults aged ≧65 years who were undiagnosed with dementia or mild cognitive impairment. This study should provide useful insights regarding dementia prevention among community-dwelling older adults.

Acknowledgements

All authors have no COI to declare regarding the present study.

This study was conducted with the support of the Wellness Open Living Lab, which provided the nouKNOW and funds for this study, among other forms of support. We would like to thank Editage (https://www.editage.com) for the English language editing. The authors also acknowledge the role of Akakabe Co., Ltd. in conducting this study. We would also like to express our sincere gratitude to the associations in the target areas and to all the people who understood the purpose of this study and willingly cooperated.

References

1. Ninomiya K. Study on Future Estimates of the Elderly Population with Dementia in Japan. Ministry of Health, Labour and Welfare. 2015. (In Japanese) Available from: https://mhlw-grants.niph.go.jp/system/files/2014/141031/201405037A/201405037A0001.pdf
2. Parial LL, Lam SC, Ho JYS, et al. Public knowledge of the influence of modifiable cardiovascular risk factors on dementia: a systematic literature review and meta-analysis. Aging Ment Health 2021;25:1395-1409.
3. Hazar N, Seddigh L, Rampisheh Z, et al. Population attributable fraction of modifiable risk factors for Alzheimer disease: a systematic review of systematic reviews. Iran J Neurol 2016;15:164-172.
4. Smith BJ, Ali S, Quach H. The motivation and actions of Australians concerning brain health and dementia risk reduction. Health Promot J Austr 2015;26:115-121.
5. Lee J, Lim JM. Factors associated with the experience of cognitive training apps for the prevention of dementia: cross-sectional study using an extended health Belief model. J Med Internet Res 2022;24:e31664.

6. Kim S, Sargent-Cox KA, Anstey KJ. A qualitative study of older and middle-aged adults' perception and attitudes towards dementia and dementia risk reduction. J Adv Nurs 2015;71:1694-1703.
7. Akyol MA, Zehirlioğlu L, Erünal M, et al. Determining middle-aged and older adults' health beliefs to change lifestyle and health behavior for dementia risk reduction. Am J Alzheimers Dis Other Demen 2020;35: 1533317519898996.
8. Wild K, Howieson D, Webbe F, et al. Status of computerized cognitive testing in aging: a systematic review. Alzheimers Dement 2008;4:428-437.
9. Onoda K, Yamaguchi S. Revision of the Cognitive Assessment for Dementia, iPad version (CADi2). PLoS One 2014;9:e109931.
10. Inoue M, Jinbo D, Nakamura Y, et al. Development and evaluation of a computerized test battery for Alzheimer's disease screening in community-based settings. Am J Alzheimers Dis Other Demen 2009;24:129-135.
11. Wesnes KA. Moving beyond the pros and cons of automating cognitive testing in pathological aging and dementia: the case for equal opportunity. Alzheimers Res Ther 2014;6:58.
12. Sugishita M, Hemmi I. Validity and reliability of the Mini Mental State Examination-Japanese (MMSE-J): a preliminary report. Japanese Journal of Cognitive Neuroscience 2010;12:186-190. (In Japanese)
13. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53:695-699.
14. Maruff P, Thomas E, Cysique L, et al. Validity of the CogState brief battery: relationship to standardized tests and sensitivity to cognitive impairment in mild traumatic brain injury, schizophrenia, and AIDS dementia complex. Arch Clin Neuropsychol 2009;24:165-178.
15. Lim YY, Ellis KA, Harrington K, et al. Use of the CogState Brief Battery in the assessment of Alzheimer's disease related cognitive impairment in the Australian Imaging, Biomarkers and Lifestyle (AIBL) study. J Clin Exp Neuropsychol 2012;34:345-358.
16. Maruff P, Lim YY, Darby D, et al. Clinical utility of the cogstate brief battery in identifying cognitive impairment in mild cognitive impairment and Alzheimer's disease. BMC Psychol 2013;1:30.
17. Fredrickson J, Maruff P, Woodward M, et al. Evaluation of the usability of a brief computerized cognitive screening test in older people for epidemiological studies. Neuroepidemiology 2010;34:65-75.
18. Weiner MW, Veitch DP, Aisen PS, et al. The Alzheimer's Disease Neuroimaging Initiative 3: continued innovation for clinical trial improvement. Alzheimers Dement 2017;13:561-571.
19. Mackin RS, Insel PS, Truran D, et al. Unsupervised online neuropsychological test performance for individuals with mild cognitive impairment and dementia: results from the Brain Health Registry. Alzheimers Dement (Amst) 2018;10:573-582.
20. Stricker NH, Lundt ES, Albertson SM, et al. Diagnostic and prognostic accuracy of the Cogstate Brief Battery and Auditory Verbal Learning Test in preclinical Alzheimer's disease and incident mild cognitive impairment: implications for defining subtle objective cognitive impairment. J Alzheimers Dis 2020;76:261-274.
21. Alden EC, Pudumjee SB, Lundt ES, et al. Diagnostic accuracy of the Cogstate Brief Battery for prevalent MCI and prodromal AD (MCI $A^+ T^+$) in a population-based sample. Alzheimers Dement 2021;17:584-594.
22. Rosenberg A, Coley N, Soulier A, et al. Experiences of dementia and attitude towards prevention: a qualitative study among older adults participating in a prevention trial. BMC Geriatr 2020;20:99.
23. Oliveira D, Knight H, Jones KA, et al. Motivation and willingness to increase physical activity for dementia risk reduction: cross-sectional UK survey with people aged 50 and over. Aging Ment Health 2022;26:1899-1908.
24. Bosco A, Jones KA, Di Lorito C, et al. Changing lifestyle for dementia risk reduction: inductive content analysis of a national UK survey. PLoS One 2020;15:e0233039.
25. Prochaska JO, Velicer WF. The transtheoretical model of health behavior change. Am J Health Promot 1997; 12:38-48.
26. Werner P, AboJabel H. Perceptions about and engagement in behaviors to reduce the risk of dementia among adult persons in Israel. J Alzheimers Dis 2020;78:1011-1017.
27. Lee W, Gray SL, Zaslavsky O, et al. Association between having a family member with dementia and perceptions of dementia preventability. Aging Ment Health 2022;26:270-276.

Osaka City Med. J. Vol. 68, 81-90, 2022

A History of Obesity in Severe Anorexia Nervosa Predicts Outpatient Treatment Dropout

Mihoko Honda[1)], Tomoko Harada[2)], Tsuneo Yamauchi[2)], Saori Miyamoto[2)], Takumi Matsuzuka[1)], Akihiro Mui[1)], Naoki Ohara[1)], and Koki Inoue[2)]

Department of Neuropsychiatry[1)], Osaka City University Graduate School of Medicine; and Department of Neuropsychiatry[2)], Osaka Metropolitan University Graduate School of Medicine

Abstract

Background

Anorexia nervosa (AN) is a psychiatric disorder with a high mortality rate, and low body mass index (BMI), one of features of AN, is a poor prognostic factor. Treatment dropout is common in AN. Treatment dropout is related to the AN binge-eating/purging subtype, low BMI, and age. The relationship between a history of obesity or family involvement and treatment dropout is unknown. We investigated the relationship between treatment dropout in outpatients with AN with low BMI and a history of obesity or family involvement.

Methods

This retrospective study analyzed adult female patients with AN with BMI <16 kg/m^2. Age and BMI at the initial visit, marital status, AN subtype, maximum weight, a history of obesity, and accompanying persons at the initial visit as a family involvement were assessed. Factors associated with treatment dropout from the initial visit to 6 months were examined.

Results

The 6-month dropout rate was 33.1% (57 dropped out, 115 continued treatment). Treatment dropout was significantly associated with a history of obesity and low BMI at the initial visit. Treatment dropout was not significantly associated with the presence or absence of family members at the initial visit.

Conclusions

To prevent treatment dropout of physical high-risk patients with low BMI, clinicians need to recognize patients with a history of obesity and provide them with psychotherapy considering their perceptions and stigmas of obesity.

Key Words: Anorexia nervosa; Treatment dropout; Obesity; Outpatient

Received September 1, 2022; accepted October 31, 2022.

Correspondence to: Tomoko Harada, MD, PhD.
Department of Neuropsychiatry, Osaka Metropolitan University Graduate School of Medicine,
1-4-3 Asahimachi, Abeno-ku, Osaka 545-8585, Japan
Tel: +81-6-6645-3821; Fax: +81-6-6636-0439
E-mail: t-harada@omu.ac.jp

Introduction

Eating disorders (EDs) are psychiatric disorders characterized by abnormal eating behavior, excessive valuing of weight and shape, and cognitive deficits[1]. Anorexia nervosa (AN) is an ED characterized by low body weight and associated with high mortality[2]. Patients with AN are at high risk of early mortality[3], and factors that increase the risk of mortality in AN include low body mass index (BMI), long duration of disease, substance abuse, and poor psychosocial functioning[4,5]. The standardized mortality ratio for patients with AN was reported as 11.7 and that for patients with AN with BMI less than 11.5 kg/m^2 was over 30[6].

Dropout rates have been reported to be 31%-50% for inpatients and 23%-57% for outpatients[7]. As studies on treatment dropout differ in treatment methods, definition of dropout, and observation period, the dropout rates have been reported to range widely[7,8]. Treatment dropout had a severe impact on recovery, and patients who dropped out from treatment early were less likely to recover on their own and had a greater risk for relapse[9]. In a 10-year prognostic study using cognitive behavioral therapy (CBT), the treatment dropout group had a poorer prognosis than the treatment completion group[10]. In particular, treatment dropout among patients with AN with low BMI is a serious problem because of the high risk of mortality. Factors affecting dropout need to be examined to prevent treatment dropout. Previous studies have reported on various factors responsible for treatment dropout in patients with AN in hospitalization and outpatient settings[7,8]. Predictors of treatment dropout were reported to be the AN binge-eating/purging type (AN-BP), age, and BMI for inpatient treatment[11,12] and the AN-BP subtype, ED-related quality of life[13], and anxiety level[14] for outpatient treatment.

The association between premorbid overweight or obesity and the development of EDs has been established[15,16]. Patients with ED with a history of overweight or obesity have been reported to have a higher rate and speed of weight loss, higher physical risk[17], and greater severity of psychopathology related to EDs compared to patients with EDs without a history of obesity[18]. Therefore, patients with AN with a history of obesity are likely to be at high risk of treatment dropout, but this is not clear.

It is also known that family involvement in AN treatment is effective in children and adolescents[19]. Some reports of adults with AN have examined the association between caregiver interventions and patient treatment effects[20,21], but to our knowledge, it is not clear whether family involvement is related to the factors associated with treatment dropout in adults with AN. However, it is assumed that even in adults with AN undergoing treatment, caregiver, i.e., family and partner, cooperation and interest in treatment is associated with the continuation of patient visits to the hospital.

In this study, we examined the association between treatment dropout in the outpatient setting and a history of obesity and family involvement in adult female patients with AN with severe, low BMI.

Methods

Patients

This was a retrospective study based on the medical records of outpatients with AN who visited the Department of Neuropsychiatry at Osaka City University Hospital (now Osaka Metropolitan University Hospital) between January 1, 2014, and November 31, 2021. This institution is a large urban-type general hospital that provides specialized outpatient and inpatient treatment for patients

with EDs. AN was diagnosed by psychiatrists with extensive clinical experience in ED based on the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5)[22]. This study included patients with AN who were older than 18 years and had a BMI less than 16 kg/m^2, classified as severe and most severe based on the DSM-5 criteria. Patients who were aged less than 18 years or had a BMI of 16 kg/m^2 or higher were excluded. In addition, to investigate patient-initiated dropout, we excluded patients who dropped out for the following reasons: dropout due to not consenting to the treatment agreement at the initial visit, transferring to a different hospital, moving to a distant place, or pregnancy within 6 months from the initial visit. Those who received inpatient treatment within 6 months of the initial visit were also excluded, as inpatient hospitalization is a factor associated with dropout or continued treatment. A total of 172 patients were included in the study.

Procedure

Variables collected included age of onset, duration of illness, AN subtype, i.e., AN restricting type (AN-R) or AN-BP, career status, and marital status. We defined family involvement in treatment as family members accompanying the patients and collected data on accompanying persons at the initial visit. We also collected information on the patients' age, weight, height, and BMI at the time of the initial visit, as well as their lifetime maximum weight, height, and age at that time.

Patients with or without a history of obesity were classified based on maximum weight. If the patients were 18 years or older at their maximum weight, a BMI of 25 kg/m^2 or more was considered to indicate obesity according to the definition of the Japan Society for the Study of Obesity[23]. If the patients were under 18 years of age at their maximum weight, we calculated the standard weight and degree of obesity [degree of obesity=$\{$(actual weight−standard weight)/standard weight$\}$] from their age and height at that time, using the standard weight calculation formula of the Japanese Society for Pediatric Endocrinology[24], which was developed based on data from the 2000 Report of the School Health Statistics Survey (5-17 years) by the Ministry of Education, Culture, Sports, Science and Technology[25]. If the degree of obesity was greater than 20%, the patient was considered to have a history of obesity according to the definition of the Japanese Society for Pediatric Endocrinology[24]. Patients who dropped out of treatment on their own within 6 months from the initial visit were included in the "Dropout group" and those who continued treatment for more than 6 months from the initial visit were included in the "Continuation group". Censored patients who improved during the 6 months and completed treatment were included in the continuation group. This study was approved by the Ethics Committee of the Osaka City University Graduate School of Medicine (now Osaka Metropolitan University Graduate School of Medicine) (approval number: 2020-106).

Statistics analysis

We compared the sociodemographic and clinical characteristics of patients between the dropout and continuation groups using the chi-square test and the Mann-Whitney U-test. Kaplan-Meier survival analysis was performed to estimate the treatment continuation rate for the two groups according to whether the patients had a history of obesity. We used multivariate Cox regression analysis to calculate hazard ratios and 95% confidence intervals to examine factors associated with treatment dropout from the initial visit to 6 months. Data were analyzed using SPSS 26 for Mac OS X (SPSS Japan, Tokyo, Japan).

Results

The dropout group consisted of 57 patients, and the continuation group consisted of 115 patients.

The dropout rate for outpatient treatment during the 6-month period was 33.1%. Table 1 shows a comparison of sociodemographic and clinical background data of the patients in the dropout and continuation groups. There was no significant difference in age at the initial visit, duration of illness, or age of onset between the groups. In the AN subtype, the rates of AN-R and AN-BP were 58.7% (n=101) and 41.3% (n=71), respectively. The proportion of patients with AN-BP was higher in the dropout group (50.9%, 29/57) than in the continuation group (36.5%, 42/115), but the difference was not significant. There was a significant difference in marital status (p=0.015), with 28.1% (16/57) of the patients in the dropout group and 19.1% (22/115) of the patients in the continuation group being married. The presence or absence of accompanying persons at the initial visit and career status were not significantly different between the groups.

Table 2 shows a comparison of BMI and presence or absence of a history of obesity between the dropout and continuation groups. There were no significant differences in BMI at the initial visit, maximum BMI, age at maximum weight, or a history of obesity between the groups.

The difference in treatment dropout between patients with and without a history of obesity is shown in Figure 1. The x-axis represents the number of days in the first 6 months of treatment, and the y-axis corresponds to the percentage of patients who continued treatment. One patient was censored because she improved and no longer required to go to the hospital. Although the dropout rate tended to be higher in the group with a history of obesity, the log-rank test showed no significant difference between patients with and without a history of obesity.

Factors associated with treatment dropout were analyzed using Cox regression analysis (Table 3). Covariates included were a history of obesity and the presence of an accompanying person at the initial visit, which were adjusted for previously reported treatment dropout factors including age, AN subtype, and BMI at the initial visit. A history of obesity and low BMI were significantly associated

Table 1. Comparison of sociodemographics of patients at the initial visit between the dropout and continuation groups

		Dropout (n=57)	Continuation (n=115)	
		median [interquartile range]		p
age (years)		32.6 [23.3-40.3]	25.7 [20.8-37.2]	0.058
age of onset (years)		19.9 [17.8-30.4]	19.7 [17.7-23.1]	0.197
duration of illness (years)		5.1 [1.5-12.3]	3.7 [1.2-10.5]	0.206
		n	n	
type	AN-R	28 (49.1%)	73 (63.5%)	0.072
	AN-BP	29 (50.9%)	42 (36.5%)	
marital status	unmarried	32 (56.1%)	87 (75.7%)	0.015*
	married	16 (28.1%)	22 (19.1%)	
	divorce/bereavement	9 (15.8%)	6 (5.2%)	
career status	unemployed	27 (47.4%)	38 (33.0%)	0.183
	employed	18 (31.6%)	44 (38.3%)	
	student	12 (21.0%)	33 (28.7%)	
accompanying person	yes	43 (75.4%)	97 (84.3%)	0.158
	no	14 (24.6%)	18 (15.7%)	

*statistically significant. AN-R, anorexia nervosa-restricting type; and AN-BP, anorexia nervosa binge-eating/purging type.

with dropout from outpatient treatment from the initial visit to 6 months. Age, AN subtype, and the presence of an accompanying person at the initial visit were not significant predictors of treatment dropout.

Table 2. Comparison of body mass index and a history of obesity between the dropout and continuation groups

		Dropout (n=57)	Continuation (n=115)	
		median [interquartile range]		p
BMI at the initial visit (kg/m²)		13.2 [11.7-14.7]	13.7 [12.6-14.7]	0.097
maximum BMI (kg/m²)		21.5 [19.8-23.8]	21.2 [19.3-23.0]	0.342
age at maximum weight (years)		19.5 [16.8-21.9]	18.3 [16.7-22.3]	0.583
		n	n	
history of obesity	yes	14	16	0.083
	no	43	99	

BMI, body mass index.

Table 3. Variables predicting dropout from anorexia nervosa outpatient treatment

Variables at the initial visit	HR	95% CI	p
age	1.012	0.989-1.036	0.307
type: AN-R	1	(Reference)	-
type: AN-BP	1.602	0.946-2.713	0.08
BMI	0.851	0.727-0.996	0.045*
history of obesity	1.989	1.062-3.727	0.032*
accompanying person	0.696	0.368-1.318	0.266

*statistically significant. HR, hazard ratio; CI, confidence interval; AN-R, anorexia nervosa-restrictive type; AN-BP, anorexia nervosa binge-eating/purging type; and BMI, body mass index.

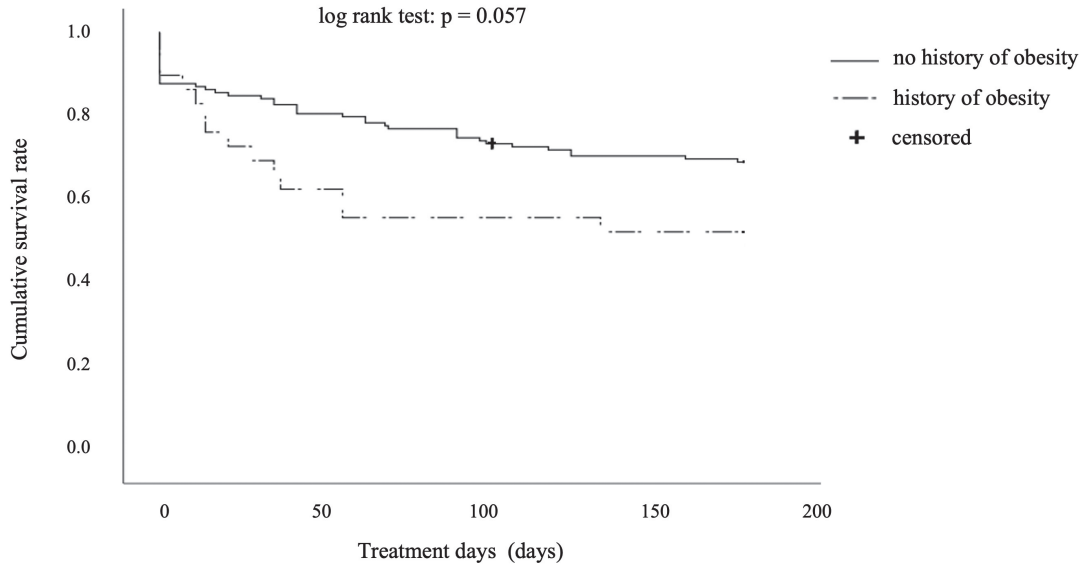

Figure 1. Cumulative survival rate of treatment dropout using the Kaplan-Meier method for patients with and without a history of obesity. One patient was censored because of improvement.

Discussion

We found that a history of obesity and low BMI at the initial visit were associated with dropout from outpatient treatment. The presence of an accompanying person at the initial visit was not significantly associated with treatment dropout. Low BMI has been reported to be a risk factor for early mortality[3] and a poor prognostic factor[26]; thus, prevention of treatment dropout is necessary, especially in outpatients with AN with low BMI. To the best of our knowledge, this was the first study to determine the relationship between a history of obesity and treatment dropout in female outpatients with AN with low BMI.

A history of obesity was a significant factor for treatment dropout in our study. The dropout rates tended to be higher among patients with a history of obesity, although the log-rank test showed no significant difference. When adjusted for factors previously reported to be associated with treatment dropout including age, AN subtype, and BMI at the initial visit, the multivariate Cox regression analysis showed that a history of obesity was significantly associated with treatment dropout. Body dissatisfaction was stronger in individuals who were overweight or obese[27-29], and stigma and body dissatisfaction in these individuals were risk factors for EDs[30-32]. Patients with AN with a history of obesity were shown to experience more weight-based teasing from peers and more frequent talks of their weight from their families compared to patients with AN without a history of obesity[33]. In addition, patients with AN with a history of obesity were also reported to have more severe ED symptoms such as weight and shape concerns and higher degrees of anxiety and depression[33]. Similar to the findings of previous reports, we assumed that the patients with AN with a history of obesity in our study had harbored body dissatisfaction and weight-related stigma due to uncomfortable comments regarding their weight in the past. They appeared to have also experienced anxiety and depression, which may have prevented them from continuing to be motivated to seek treatment. Furthermore, the difference between the adulthood maximum weight and current weight was reported to be associated with overeating[34,35] and with greater and faster weight gain in the treatment of AN[35]. It appears that the patients with a history of obesity in this study were also more likely to overeat and gain weight. As psychological improvement was shown to be slower than weight gain[36,37], patients in this study are assumed to have dropped out of treatment because of increased fear of obesity. Additionally, in our study, we used the Japanese criteria for obesity to consider the difference in body size from Westerners, and the proportion of individuals with a history of obesity in the total sample was 17.4%. Previous studies have indicated that lifetime obesity in patients with EDs was 28.8%[18] and the rate of premorbid overweight or obese in patients with AN was approximately 40%[33,38]. The proportions we reported were lower than those reported by previous studies. This result is thought to be related to the lower BMI of Asians than that of Westerners[39] and to the fact that there are fewer people with obesity in Japan[40]. In the Japanese culture where few people are obese, the experience of obesity may have caused more intense distress.

We also found that low BMI at the initial visit was associated with treatment dropout. Low BMI was similar to previous reports on dropout factors associated with inpatient treatment[11,12]. It has been suggested that patients with low weight have more severe psychopathology[7], which might have resulted in treatment dropout. In our study, the median BMI of the patients who dropped out was 12.9 kg/m^2, which was considered low. It is especially important to strive to prevent patients with severely low BMI from dropping out because these patients are exposed to the highest medical risk if they do not receive effective treatment[5,6].

We considered accompanying persons at the initial visit as a representative factor of family involvement in treatment. However, we found no significant difference between treatment dropout and the presence or absence of accompanying persons at the initial visit to the hospital. Dysfunction in a family with a patient with EDs was reported to related to worse ED psychopathology[41], which suggesting that therapeutic family intervention could be needed. It was also found that family members of patients with AN had a poor understanding of the disease, holding the patient responsible for the disease and regarding the disease as an issue of food[42]. A study that investigated a skill training intervention for caregivers during the treatment of inpatients with AN reported that patients in the intervention group had improved ED psychopathology and quality of life[20]. It is assumed that encouraging family involvement in inpatient and outpatient treatment settings helps families gain a better understanding of the disease, build trust between the patient and family members, and prevent treatment dropout. The rate of accompanying persons present at the initial visit was 75.4% in the dropout group and 84.3% in the continuation group. As is evident from this data, presence or absence of accompanying persons at the initial visit did not have any significant effect on the treatment dropout. Patient's lack of motivation and desire for treatment appears to be a predominant factor for treatment dropout rather than the influence of others, such as accompanying the patient to the hospital or encouraging the patient to visit the hospital. There could be association between the presence or absence of an accompanying person after the second visit and treatment dropout, which could not be investigated in this study.

The AN-BP subtype was not associated with treatment dropout in our study. The results of previous studies assessing whether AN-BP was associated with treatment dropout were not consistent, with some finding no association[43-45] and others finding an association[12,13,46]. AN-BP was strongly associated with impulsivity[47], and controlling impulsivity was more difficult in AN-BP than in AN-R[48]. Impulsivity was suggested as a reason that AN-BP was associated with treatment dropout[12]. Since our sample included patients with a low BMI, there may not have been such differences between AN-R and AN-BP.

The dropout rate within 6 months from the initial visit was found to be 33.1%. Previous meta-analyses have reported dropout rates of 23%-57% for outpatient treatment[7], and our findings were within this range. In the Japanese healthcare system, the treatment of EDs is generally based on patient education and supportive psychotherapy[49]. Institutions that can use specific treatment techniques such as CBT and family-based treatment are limited. Yamada and Motoyama[50] described that typical treatment for EDs in Japan is similar to specialist supportive clinical management (SSCM)[51]. Our unit provides treatment similar to SSCM once every few days to once every 2 weeks, depending on the patient's condition. A study on outpatient psychotherapy for outpatients with AN aged 17-40 years, which defined dropout as failure to attend at least 15 of 20 sessions over a 6-month period, reported a 37.5% dropout rate[43]. Another study with a longer observation period reported a 50% dropout rate for patients with AN over 16 years of age who continued treatment with enhanced CBT for 1 year[52]. The dropout rate in our study was comparable to that in the study with the same observation period. This indicates that our treatment was as effective as other treatments.

Although treatment dropout may be due to psychological factors such as unpreparedness for recovery on the part of the patient and considered to be unavoidable to some extent, the high rate of treatment dropout in a disease with high mortality, particularly for patients with low BMI, is a serious problem. For patients with AN, the therapist should be aware of whether or not the patient

has experienced obesity in the past. If so, special attention should be paid. 1. Psychotherapy should be provided after confirming the perceptions and stigma that the patient has regarding obesity. 2. Patients should receive psychoeducation that overeating symptoms are likely to occur after treatment begins and that the weight gain is a process of recovery. 3. The therapist should carefully monitor the weight progress.

There were several limitations to our study. First, the sample size was small. If the sample size had been larger, some results might have been statistically significant. Second, although each patient had different backgrounds, such as the circumstances leading to the visit to our hospital and the history of treatment for eating disorders, we did not assess these factors, which possibly created a selection bias in the patients. Third, self-reports by patients of their maximum weight and height at that time may have introduced recall bias. The World Health Organization definition[53] of obesity is a BMI of 30 kg/m^2 or higher, but this study used a BMI of 25 kg/m^2 or higher as defined by the Japan Society for the Study of Obesity[23]; therefore, BMI values cannot be simply compared with those in previous studies. Fourth, we could not follow up continuously on the presence or absence of an accompanying person, which was noted only at the time of the initial visit, and we could not conduct a qualitative study on their involvement in the treatment. Finally, our study is limited in its generalizability because it was conducted at a single institution, a university hospital with a high level of functionality.

In conclusion, factors contributing to treatment dropout in outpatients with AN were investigated in this study. We found that a history of obesity and low BMI were associated with treatment dropout among patients with AN with severe low BMI. Recognizing and addressing a history of obesity may improve treatment continuation rates for patients with AN with low BMI. An association between family members accompanying the patient to outpatient treatment and treatment dropout was not apparent; further research is needed.

Acknowledgements

All authors have no COI to declare regarding the present study.

We are grateful to the professors of the Department of Medical Statistics at Osaka Metropolitan University Graduate School of Medicine for their guidance and encouragement.

References

1. Treasure J, Duarte TA, Schmidt U. Eating disorders. Lancet 2020;395:899-911.
2. Zipfel S, Giel KE, Bulik CM, et al. Anorexia nervosa: aetiology, assessment, and treatment. Lancet Psychiatry 2015;2:1099-1111.
3. Button EJ, Chadalavada B, Palmer RL. Mortality and predictors of death in a cohort of patients presenting to an eating disorders service. Int J Eat Disord 2010;43:387-392.
4. Franko DL, Keshaviah A, Eddy KT, et al. A longitudinal investigation of mortality in anorexia nervosa and bulimia nervosa. Am J Psychiatry 2013;170:917-925.
5. Zipfel S, Löwe B, Reas DL, et al. Long-term prognosis in anorexia nervosa: lessons from a 21-year follow-up study. Lancet 2000;355:721-722.
6. Rosling AM, Sparén P, Norring C, et al. Mortality of eating disorders: a follow-up study of treatment in a specialist unit 1974-2000. Int J Eat Disord 2011;44:304-310.
7. Gregertsen EC, Mandy W, Kanakam N, et al. Pre-treatment patient characteristics as predictors of drop-out and treatment outcome in individual and family therapy for adolescents and adults with anorexia nervosa: a systematic review and meta-analysis. Psychiatry Res 2019;271:484-501.
8. Fassino S, Pierò A, Tomba E, et al. Factors associated with dropout from treatment for eating disorders: a

comprehensive literature review. BMC Psychiatry 2009;9:67.
9. Pike KM. Long-term course of anorexia nervosa: response, relapse, remission, and recovery. Clin Psychol Rev 1998;18:447-475.
10. Okamoto Y, Miyake Y, Nagasawa I, et al. A 10-year follow-up study of completers versus dropouts following treatment with an integrated cognitive-behavioral group therapy for eating disorders. J Eat Disord 2017;5:52.
11. Hubert T, Pioggiosi P, Huas C, et al. Drop-out from adolescent and young adult inpatient treatment for anorexia nervosa. Psychiatry Res 2013;209:632-637.
12. Surgenor LJ, Maguire S, Beaumont PJV. Drop-out from inpatient treatment for anorexia nervosa: can risk factors be identified at point of admission? Eur Eat Disord Rev 2004;12:94-100.
13. Abd Elbaky GB, Hay PJ, le Grange D, et al. Pre-treatment predictors of attrition in a randomised controlled trial of psychological therapy for severe and enduring anorexia nervosa. BMC Psychiatry 2014;14:69.
14. Lockwood R, Serpell L, Waller G. Moderators of weight gain in the early stages of outpatient cognitive behavioral therapy for adults with anorexia nervosa. Int J Eat Disord 2012;45:51-56.
15. Zachrisson HD, Vedul-Kjelsås E, Götestam KG, et al. Time trends in obesity and eating disorders. Int J Eat Disord 2008;41:673-680.
16. Berkowitz SA, Witt AA, Gillberg C, et al. Childhood body mass index in adolescent-onset anorexia nervosa. Int J Eat Disord 2016;49:1002-1009.
17. Meierer K, Hudon A, Sznajder M, et al. Anorexia nervosa in adolescents: evolution of weight history and impact of excess premorbid weight. Eur J Pediatr 2019;178:213-219.
18. Villarejo C, Fernández-Aranda F, Jiménez-Muricia S, et al. Lifetime obesity in patients with eating disorders: increasing prevalence, clinical and personality correlates. Eur Eat Disord Rev 2012;20:250-254.
19. National Guideline Alliance (UK). Eating disorders: recognition and treatment. London: National Institute for Health and Care Excellence (NICE) 2017.
20. Hibbs R, Magill N, Goddard E, et al. Clinical effectiveness of a skills training intervention for caregivers in improving patient and caregiver health following in-patient treatment for severe anorexia nervosa: pragmatic randomised controlled trial. BJPsych Open 2015;1:56-66.
21. Magill N, Rhind C, Hibbs R, et al. Two-year follow-up of a pragmatic randomised controlled trial examining the effect of adding a carer's skill training intervention in inpatients with anorexia nervosa. Eur Eat Disor Rev 2016;24:122-130.
22. American Psychiatric AFD. Diagnostic and statistical manual of mental disorders. 5th ed. Washington DC: American Psychiatric Association. 2013.
23. Japan Society for the Study of Obesity. Determination of obesity. Guidelines for the management of obesity disease 2016. Tokyo: Life Science Publication, 2016. pp. 4-5. (In Japanese)
24. The Japanese Society for Pediatric Endocrinology. Assessment of the physique of Japanese children [Internet]. Kyoto: The Japanese Society for Pediatric Endocrinology; [cited 2022 Aug 19]. Available from: http://jspe.umin.jp/medical/taikaku.html (In Japanese)
25. Ministry of Education, Culture, Sports, Science and Technology. Fiscal 2000 School Health Statistics Survey Ⅱ Summary of Survey Results [Internet]. Tokyo: Ministry of Education, Culture, Sports, Science and Technology; [cited 2022 Aug 19]. Available from: https://warp.ndl.go.jp/info:ndljp/pid/11293659/www.mext.go.jp/b_menu/toukei/001/h12/002.htm (In Japanese)
26. Löwe B, Zipfel S, Buchholz C, et al. Long-term outcome of anorexia nervosa in a prospective 21-year follow-up study. Psychol Med 2001;31:881-890.
27. Shin NY, Shin MS. Body dissatisfaction, self-esteem, and depression in obese Korean children. J Pediatr 2008;152:502-506.
28. Goldfield GS, Moore C, Henderson K, et al. Body dissatisfaction, dietary restraint, depression, and weight status in adolescents. J Sch Health 2010;80:186-192.
29. Weinberger NA, Kersting A, Riedel-Heller SG, et al. Body dissatisfaction in individuals with obesity compared to normal-weight individuals: a systematic review and meta-analysis. Obes Facts 2016;9:424-441.
30. Stice E. Risk and maintenance factors for eating pathology: a meta-analytic review. Psychol Bull 2002;128:825-848.
31. Almeida L, Savoy S, Boxer P. The role of weight stigmatization in cumulative risk for binge eating. J Clin Psychol 2011;67:278-292.
32. Gerke CK, Mazzeo SE, Stern M, et al. The stress process and eating pathology among racially diverse adolescents seeking treatment for obesity. J Pediatr Psychol 2013;38:785-793.
33. Matthews A, Kramer RA, Mitan L. Eating disorder severity and psychological morbidity in adolescents with anorexia nervosa or atypical anorexia nervosa and premorbid overweight/obesity. Eat Weight Disord 2022;27;

233-242.
34. Keel PK, Heatherton TF. Weight suppression predicts maintenance and onset of bulimic syndromes at 10-year follow-up. J Abnorm Psychol 2010;119:268-275.
35. Wildes JE, Marcus MD. Weight suppression as a predictor of weight gain and response to intensive behavioral treatment in patients with anorexia nervosa. Behav Res Ther 2012;50:266-274.
36. Couturier J, Lock J. What is recovery in adolescent anorexia nervosa? Int J Eat Disord 2006;39:550-555.
37. Accurso EC, Ciao AC, Fitzsimmons-Craft EE, et al. Is weight gain really a catalyst for broader recovery?: the impact of weight gain on psychological symptoms in the treatment of adolescent anorexia nervosa. Behav Res Ther 2014;56:1-6.
38. Lebow J, Sim LA, Kransdorf LN. Prevalence of a history of overweight and obesity in adolescents with restrictive eating disorders. J Adolesc Health 2015;56:19-24.
39. World Health Organization. THE GLOBAL HEALTH OBSERVATORY. Mean BMI (kg/m^2) (crude estimate) [Internet]. Geneva: World Health Organization; 2017 [cited 2022 Aug 19]. Available from: https://www.who.int/data/gho/data/indicators/indicator-details/GHO/mean-bmi-(kg-m-)-(crude-estimate).
40. Ministry of Health and Welfare. The National Health and Nutrition Survey in Japan, 2019 [Internet]. Tokyo: Ministry of Health and Welfare; 2020 [cited 2022 Aug 19]. Available from: https://www.mhlw.go.jp/content/000711007.pdf (In Japanese)
41. Rodríguez Martín A, Novalbos Ruiz JP, Martínez Nieto JM, et al. Epidemiological study of the influence of family and socioeconomic status in disorders of eating behaviour. Eur J Clin Nutr 2004;58:846-852.
42. Dimitropoulos G, Freeman VE. The perceptions of individuals with anorexia nervosa regarding their family's understanding of their illness, treatment, and recovery. Eat Disord 2016;24:375-382.
43. Jordan J, McIntosh VV, Carter FA, et al. Clinical characteristics associated with premature termination from outpatient psychotherapy for anorexia nervosa. Eur Eat Disord Rev 2014;22:278-284.
44. Godart NT, Rein Z, Perdereau F, et al. Predictors of premature termination of anorexia nervosa treatment. Am J Psychiatry 2005;162:2398-2399.
45. Huas C, Godart N, Foulon C, et al. Predictors of dropout from inpatient treatment for anorexia nervosa: data from a large French sample. Psychiatry Res 2011;185:421-426.
46. Bandini S, Antonelli G, Moretti P, et al. Factors affecting dropout in outpatient eating disorder treatment. Eat Weight Disord 2006;11:179-184.
47. Hoffman ER, Gagne DA, Thornton LM, et al. Understanding the association of impulsivity, obsessions, and compulsions with binge eating and purging behaviors in anorexia nervosa. Eur Eat Disord Rev 2012;20:e129-136.
48. Brockmeyer T, Skunde M, Wu M, et al. Difficulties in emotion regulation across the spectrum of eating disorders. Compr Psychiatry 2014;55:565-571.
49. Iguchi T, Miyawaki D, Harada T, et al. Introduction of family-based treatment to Japan with adaptations to optimize the cultural acceptability and advance current traditional treatments of adolescent anorexia nervosa. Int J Eat Disord 2021;54:117-119.
50. Yamada H, Motoyama M. Evidence-based clinical treatment guidelines of eating disorder. Japanese Journal of Clinical Psychiatry 2021;50:39-44. (In Japanese)
51. McIntosh VV, Jordan J, Luty SE, et al. Specialist supportive clinical management for anorexia nervosa. Int J Eat Disord 2006;39:625-632.
52. Frostad S, Danielsen YS, Rekkedal GÅ, et al. Implementation of enhanced cognitive behaviour therapy (CBT-E) for adults with anorexia nervosa in an outpatient eating-disorder unit at a public hospital. J Eat Disord 2018;6:12.
53. World Health Organization. Health topics. Obesity [Internet]. Geneva: World Health Organization; 2017 [cited 2022 Aug 19]. Available from: https://www.who.int/health-topics/obesity#tab=tab_1.

Osaka City Med. J. Vol. 68, 91-98, 2022

Strangulated Small-bowel Obstruction due to Transmesosigmoid Hernia Diagnosed with Multidetector Computed Tomography: A Case Report

Tohru Takeshita[1)], Hisakazu Matsushima[1)], Kimimasa Ikeda[2)], Toshiki Noma[2)], Takuya Goto[1)], and Daiju Ueda[3)]

Departments of Radiology[1)] and Gastrointestinal Surgery[2)], Osaka Habikino Medical Center; and Department of Diagnostic and Interventional Radiology[3)], Graduate School of Medicine, Osaka Metropolitan University

Abstract

Transmesosigmoid hernia (TMSH), an emergency abdominal condition, is a type of internal hernia (IH) that involves the sigmoid mesocolon; its clinical symptoms are non-specific, so clinically its preoperative diagnosis is usually difficult. Here, we report a case of TMSH in which multidetector computed tomography (MDCT) clearly showed penetration of the small-bowel with its mesenteric fat tissue and mesenteric vessels through a complete defect in the sigmoid mesocolon. These MDCT findings accurately reflected the direct findings of this rare type of IH, so we were confident in the preoperative diagnosis.

Key Words: Internal hernia; Transmesosigmoid hernia; Sigmoid mesocolon; Small-bowel obstruction; Multidetector computed tomography

Introduction

Internal hernia (IH) is a rare cause of small-bowel obstruction (SBO), accounting for ≦ 5.8% of all cases of SBO[1)]. IHs involving the sigmoid mesocolon account for approximately 6% of all IHs[1)]. Transmesosigmoid hernia (TMSH) is a type of IH involving the sigmoid mesocolon[2)]. A typical case of TMSH is a middle-aged man or woman in his or her 50s to 60s with no history of abdominal surgery and presenting with symptoms such as abdominal pain, abdominal distension, nausea, and vomiting[3-7)]. Because its clinical symptoms are non-specific, its clinical diagnosis is generally difficult[3-7)]. Currently, multidetector computed tomography (MDCT) has a central role in imaging diagnosis of IH[8)]. However, the computed tomography (CT) findings of TMSH have been reported only in a few cases in the radiologic literature[4,5)]. Here, we report a case of TMSH in which correct preoperative diagnosis was based on MDCT findings, which were confirmed by surgery.

Received April 11, 2022; accepted October 31, 2022.
Correspondence to: Tohru Takeshita, MD.
Department of Radiology, Osaka Habikino Medical Center,
3-7-1 Habikino, Habikino, Osaka 583-8588, Japan.
Tel: +81-072-957-2121; Fax: +81-072-958-3291
E-mail: ttakeshita@ra.opho.jp

Case Report

A 79-year-old woman with a history of appendectomy due to appendicitis in her 50s presented to the emergency room of our hospital with acute abdominal pain and nausea. She had been diagnosed with a squamous cell carcinoma of the uterine cervix, T3bN1M0, FIGO stage Ⅲ C1, according to the TNM classification and the FIGO system[9,10], at the age of 75 years. Consequently, she had been treated with external-beam radiation therapy with concurrent chemotherapy and brachytherapy. A follow-up examination at 42 months after the therapy revealed no evidence of locoregional recurrence or distant metastasis. Physical examination revealed tenderness in the left-lower quadrant. Blood testing findings (Table 1) were within normal limits except for a slightly increased white blood cell count (8800/μL) and elevated C-reactive protein level (17.01 mg/dL). An upright roentgenogram of the abdomen showed several dilated small-bowel loops with air-fluid levels (Fig. 1). The attending physician initially diagnosed an adhesive SBO and she was managed conservatively by the use of a long intestinal tube. After 5 days of conservative therapy, her clinical condition remained unchanged. Enterography with water-soluble iodinated contrast medium administered through the long intestinal

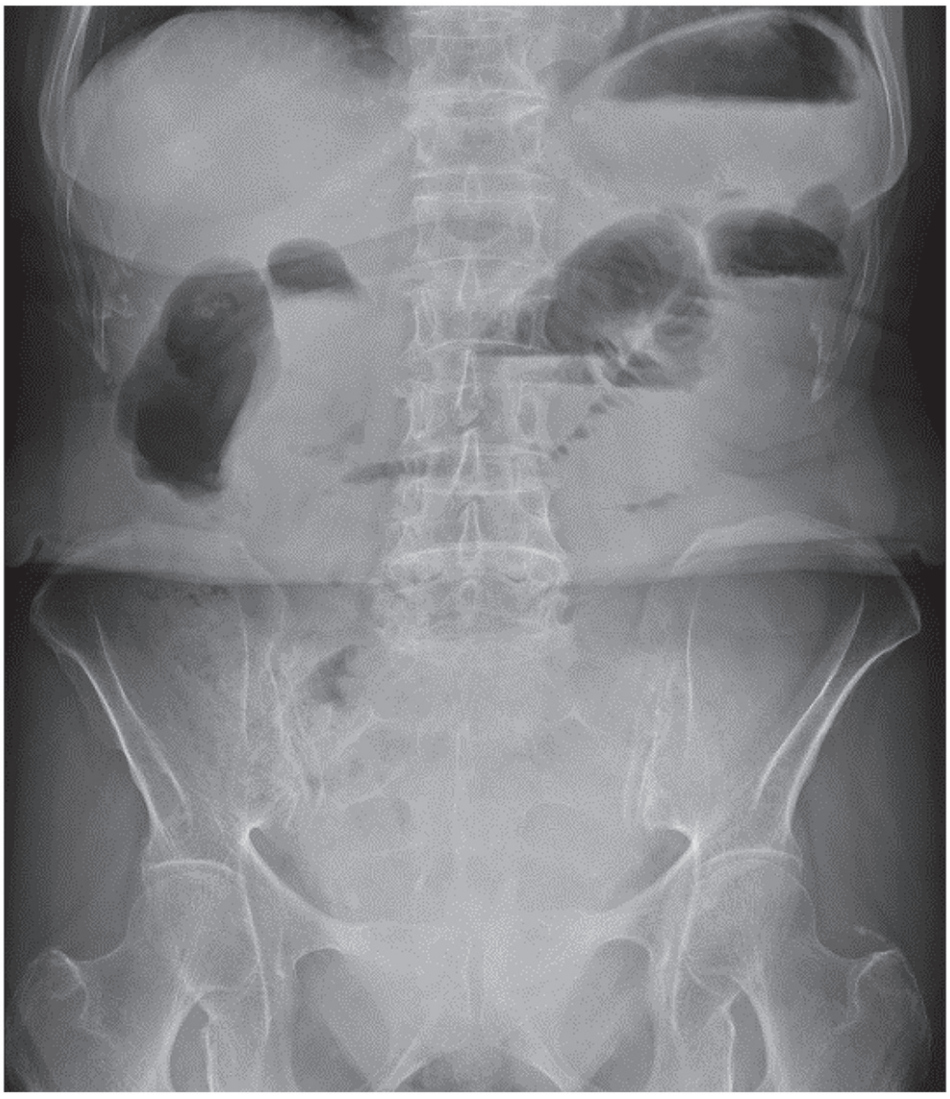

Figure 1. Abdominal roentgenogram showing several dilated small-bowel loops with air-fluid levels.

Table 1. Laboratory data on admission

【CBC】		【Biochemical】	
WBC	8,800/μL	ALB	4.5 g/dL
RBC	4.64×10^{6}/μL	T-BIL	1.4 mg/dL
Hb	14.4 g/dL	BUN	20 mg/dL
Ht	40.9%	CRE	1.17 mg/dL
PLT	20.3×10^{4}/μL	Na	138 mEq/L
		K	4.0 mEq/L
		CL	100 mEq/L
		AST	30 U/L
		ALT	18 U/L
		LDH	275 U/L
		CK	104 U/L
		AMY	53 U/L
		CRP	17.01 mg/dL

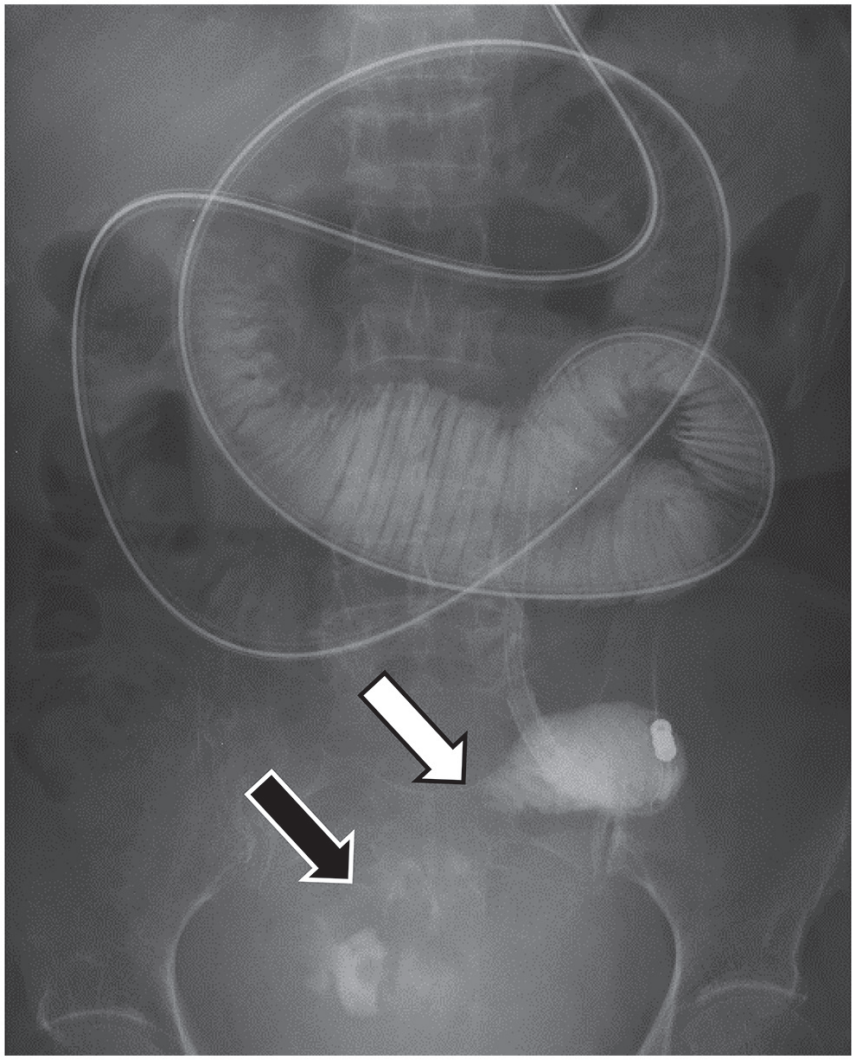

Figure 2. Enterography showing abrupt narrowing of the small-bowel at the upper-left pelvis level (white arrow). The contrast medium passed through the stricture site and slowly flowed into the small-bowel on the anal side (black arrow).

tube showed abrupt narrowing of the small-bowel in the left-upper pelvis. The contrast medium passed through the stricture site and slowly flowed into the small-bowel on the anal side (Fig. 2). Contrast-enhanced MDCT of the abdomen and pelvis was performed as further investigation. Axial MDCT images (Fig. 3) showed a fluid-filled, dilated, C-shaped small-bowel loop in the lower part of

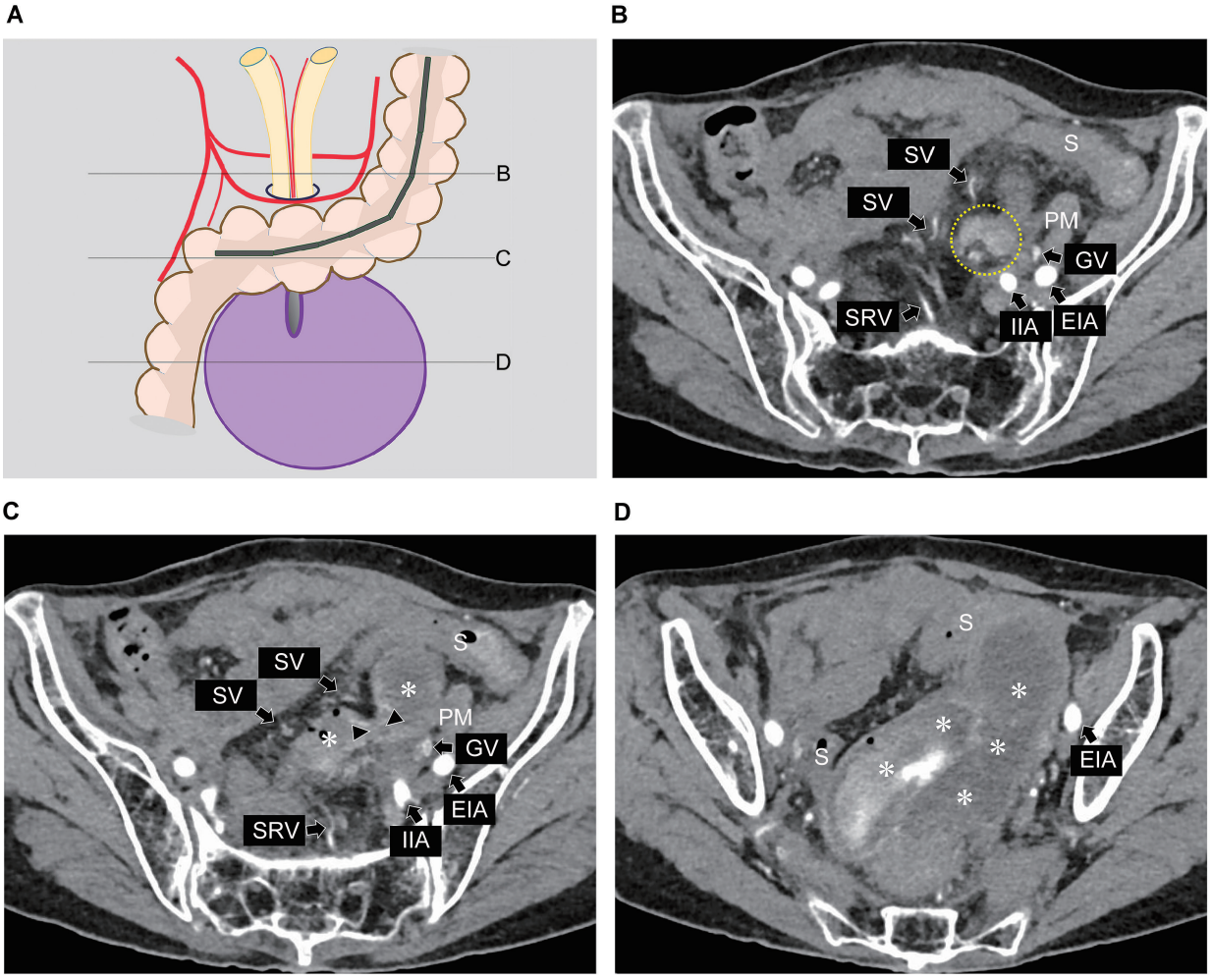

Figure 3. A) Drawing showing the strangulated small-bowel obstruction (SBO) due to transmesosigmoid hernia in our case. The horizontal lines B, C, and D correspond to subfigures B), C), and D) of the axial multidetector computed tomography (MDCT) images, respectively.
B) Contrast-enhanced axial MDCT image through the just proximal to the hernia gate in the sigmoid mesocolon. This axial MDCT image shows the afferent loop and efferent loop of the small-bowel and their mesenteric vessels are very close to each other and converge toward the hernia gate (yellow dot circle). Note that the sigmoid vessels and superior rectal vessels running along the margins of the hernia gate.
C) Contrast-enhanced axial MDCT image obtained at a 6-mm level caudal to B. This axial MDCT image is just distal to the hernia gate and shows a fluid-filled and dilated herniated small-bowel loop (white asterisks) and convergence toward the hernia gate (black arrowheads). Note that the sigmoid vessels and superior rectal vessels running along the margins of the hernia gate. Note also that displacement of the sigmoid colon anteriorly by the herniated small-bowel loop.
D) Contrast-enhanced axial MDCT image obtained at an 8-mm level caudal to C. This axial MDCT image shows a fluid-filled and dilated herniated small-bowel loop (white asterisks). Note the displacement of the sigmoid colon anteriorly and medially by the herniated dilated small-bowel loop. Note also the thickened intestinal wall of the dilated small-bowel loop and poor contrast enhancement of the intestinal wall. These findings suggest strangulation.
S=sigmoid colon, SV=sigmoid vessels, SRV=superior rectal vessels, PM=left psoas muscle, GV=left gonadal vessels, EIA=left external iliac artery, and IIA=left internal iliac artery.

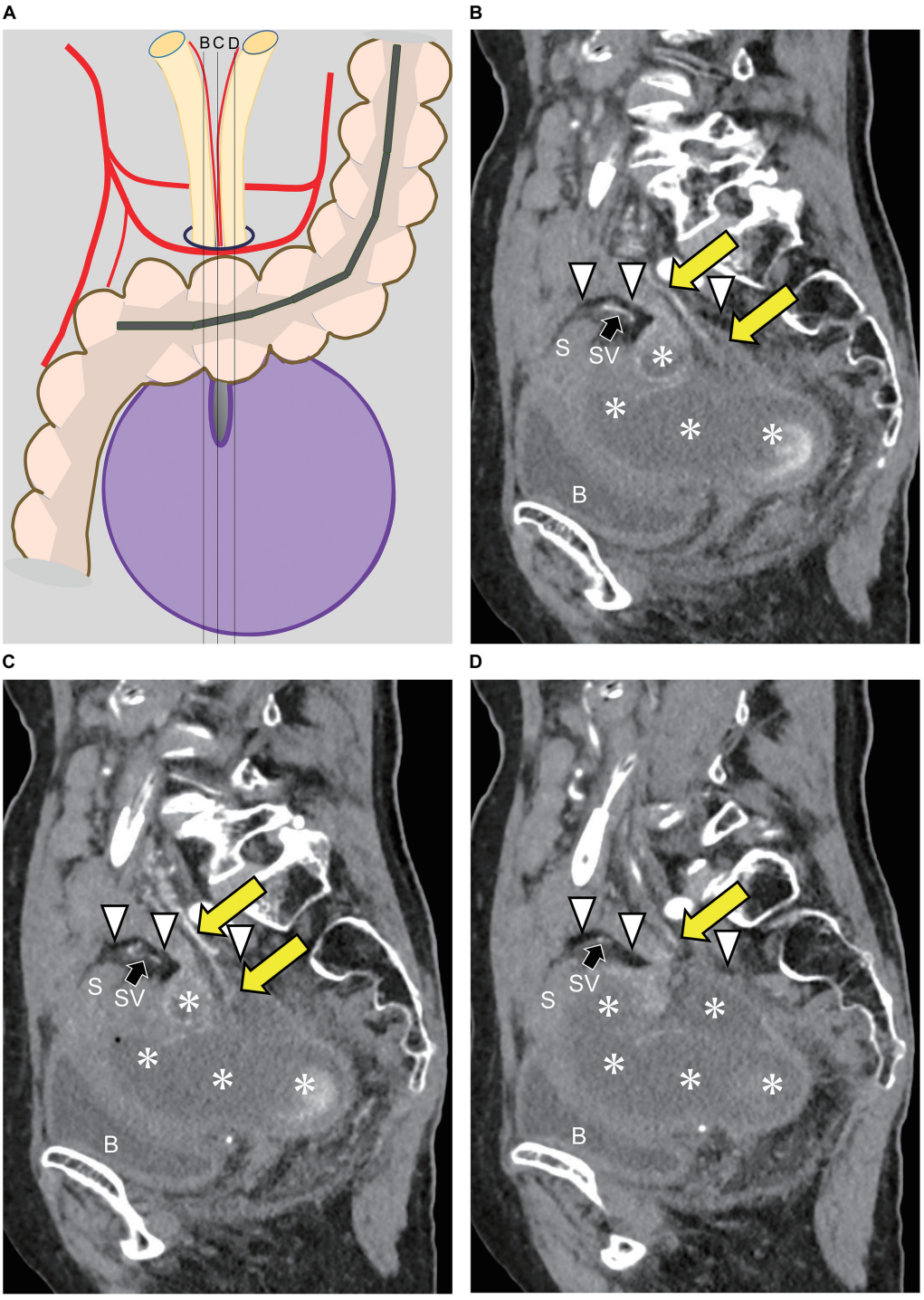

Figure 4. A) Drawing again showing the strangulated small-bowel obstruction (SBO) due to transmesosigmoid hernia in our case. The vertical lines B, C, and D correspond to subfigures B), C), and D) of the sagittal multidetector computed tomography (MDCT) images, respectively.
B) Contrast-enhanced sagittal MDCT image through the hernia gate in the sigmoid mesocolon.
C) Contrast-enhanced sagittal MDCT image obtained at a 2-mm level lateral to B.
D) Contrast-enhanced sagittal MDCT image obtained at a 4-mm level lateral to C.
These sagittal MDCT images clearly show the penetration of the small-bowel and its mesenteric fat tissue and mesenteric vessels through the defect in the sigmoid mesocolon (yellow arrows). Note that the sigmoid mesocolon (white arrowheads) is depicted as a thin sheet-like structure showing fat density and containing the sigmoid vessels. Also note the herniated small-bowel (white asterisks) tapers and narrows appearing like a bird's beak toward the hernia gate in the sigmoid mesocolon.
S=sigmoid colon, SV=sigmoid vessels, and B=urinary bladder.

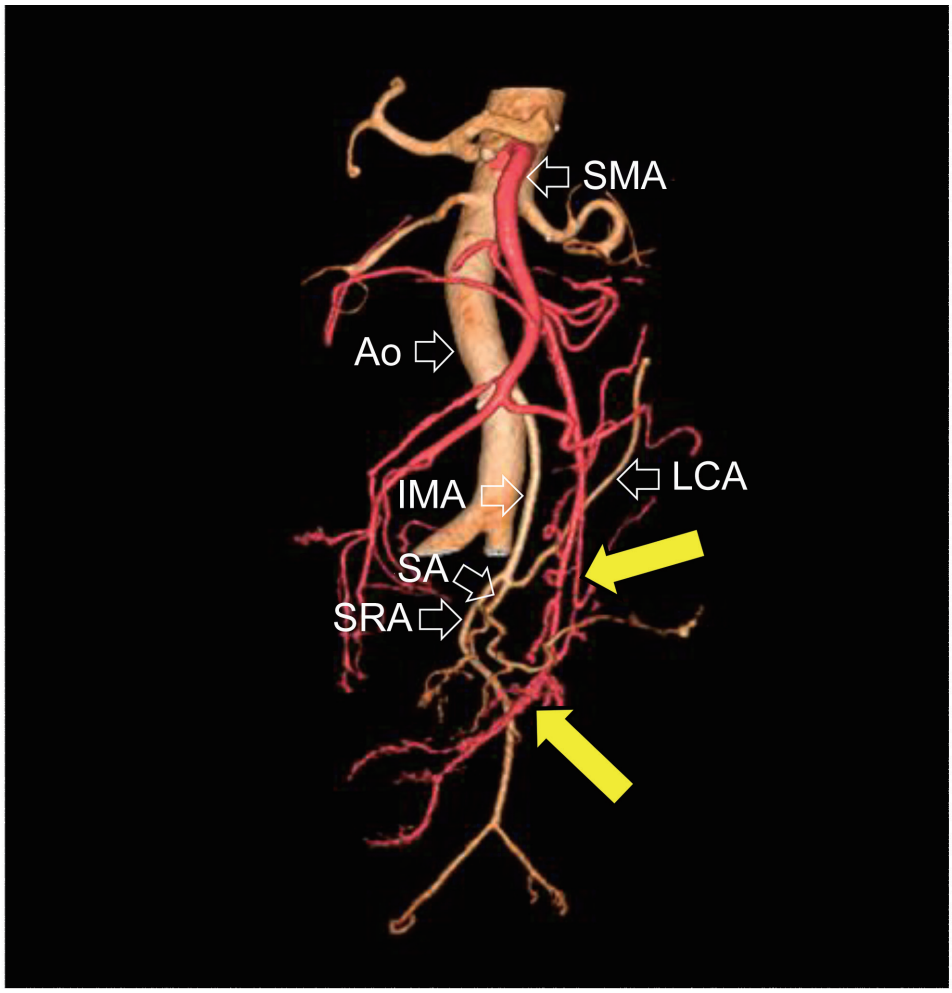

Figure 5. Selective volume-rendering three-dimensional computed tomography angiography image showing the mesenteric vessel of the herniated small-bowel running an abnormal course (yellow arrows). Notice that the mesenteric vessel of the herniated small-bowel runs dorsal to the sigmoid vessels.
AO=abdominal aorta, SMA=superior mesenteric artery, IMA=inferior mesenteric artery, LCA=left colic artery, SA=sigmoid artery, and SRA=superior rectal artery.

the pelvic cavity. Both ends of the C-shaped dilated small-bowel loop tapered toward the sigmoid mesocolon. Each transitional point of the afferent loop and efferent loop of the small-bowel were identified and very close together. This finding suggested a closed-loop SBO. The sigmoid colon was displaced anteriorly and medially by the C-shaped dilated small-bowel loop. In addition, a thickened intestinal wall of the dilated small-bowel loop, poor contrast enhancement of the intestinal wall, and mesenteric haziness were observed, which strongly suggested a strangulated SBO. The location of the obstruction site and its relationship with the surrounding structures suggested that the hernia gate was located in the sigmoid mesocolon and that the small intestine had penetrated the defect in the sigmoid mesocolon from cranial to caudal, thereby resulting in a strangulated SBO (i.e., a strangulated SBO due to TMSH, which is a type of IH). By combining the sagittal MDCT images (Fig. 4) with the volume-rendering three-dimensional CT angiography (3D-CTA) image (Fig. 5), the anatomical relationship of the sigmoid mesocolon, herniated small-bowel loop, and their mesenteric vessels could be better understood, and the diagnosis of TMSH could be made more efficiently. The patient underwent an emergency laparotomy. At surgery, a TMSH was confirmed. A small-bowel

segment, approximately 20-cm long and 60-cm distal to the ligament of Treitz was herniating through a complete defect in the sigmoid mesocolon. The incarcerated small-bowel was pulled out by gentle traction. The incarcerated small-bowel was severely discolored and did not return to its normal color. Thus, the necrotic segment of the small-bowel was resected, and end-to-end anastomosis was performed. The defect of the sigmoid mesocolon was closed by suture. The patient's postoperative course was uneventful. She was discharged on 09th hospital day after the operation.

Discussion

In 1964, Benson and Killen classified IHs involving the sigmoid mesocolon into three types: intersigmoid hernia, TMSH, and intramesosigmoid hernia[2]. TMSH is defined as herniation of the viscus (mostly the small intestine) through a full-thickness defect in the sigmoid mesocolon. The herniated small intestine passes through the hernia gate in the sigmoid mesocolon without having a hernia sac[2]. The etiology of the defect of the sigmoid mesocolon in TMSH is considered congenital or acquired (such as prior abdominal surgery, blunt trauma, and peritoneal inflammation)[3-7].

Since the report by Benson and Killen[2], nearly 20 cases of TMSH have been reported in the English literature[3-7]. Patients with TMSH present with non-specific abdominal symptoms, making its preoperative diagnosis usually difficult[3-7]. Recently, the utility of MDCT for the preoperative diagnosis of various types of IH has been apparent[8]. However, there are few reports showing the CT appearance of TMSH. In 2004, Yu CY et al reported a case of TMSH in which the preoperative diagnosis only was based on axial images on conventional CT[4]. Yu CY et al reported CT findings of TMSH as follows[4]: (1) closed-loop SBO, (2) a cluster of fluid-filled dilated small-bowel loops located in the left-upper pelvic cavity, (3) convergence of a herniated small-bowel toward the sigmoid mesocolon, and (4) displacement of the sigmoid colon anteriorly and medially caused by the herniated small-bowel. These findings were also identified in the present case except for the location of the herniated small-bowel. The location of a herniated small-bowel may depend on the direction of the herniation and/or the length of a herniated small-bowel. In 2020, Francis KC et al proposed the omega sign as a new CT sign for TMSH based on their case[5]. They stated that the omega sign was caused by an adhesive band between the surface of the sigmoid mesocolon and the pelvic sidewall, which caused the sigmoid colon to resemble the English letter omega. However, that omega sign does not represent a direct CT finding of TMSH, and it was not observed in our case. We believe that it is not a universal CT finding but rather a coincidental finding produced by the effect of the adhesive band between the surface of the sigmoid mesocolon and pelvic sidewall.

In the CT diagnosis of IH involving the sigmoid mesocolon, it is important to clarify the anatomical relationship between the hernia gate and mesenteric vessels of the sigmoid mesocolon[8]. On CT, both sigmoid vessels and superior rectal vessels are landmarks of the sigmoid mesocolon, and the attachment of the sigmoid mesocolon is close to both the left psoas muscle and left iliac vessels[11]. The most impressive findings on CT in our case were that combined sagittal MDCT images and 3D-CTA image could clearly visualize the small-bowel herniation with its mesenteric fat tissue and mesenteric vessels passing through the defect in the sigmoid mesocolon. These CT findings well reflected the pathophysiology of this rare type of IH, and we could make a preoperative diagnosis in confidence. To the best of our knowledge, this is the first case in which the preoperative diagnosis of TMSH was made by combining sagittal MDCT images and 3D-CTA image from MDCT data.

In an emergency setting, the radiologic aim is not simply to diagnose SBO caused by IH but

importantly, to then estimate the presence of intestinal and mesenteric ischemic changes associated with the SBO. It is worth noting that nearly half of the cases of TMSH have required resection of the herniated small-bowel[3-7]. Timely preoperative diagnosis and early surgical treatment will prevent extensive and irreparable damage to the small-bowel and reduce the rate of mortality associated with a strangulated SBO caused by IH.

In conclusion, we encountered a case of strangulated SBO due to TMSH. This case highlights the utility of MDCT for diagnosis of this rare type of IH. Detailed knowledge of the anatomy of the sigmoid mesocolon is the key to the diagnosis of TMSH.

Acknowledgement

All authors have no COI to declare regarding the present case report.

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

We thank Kentaro Nishimura and Shinichi Uga, Radiological Technologists (Department of Radiology, Osaka Habikino Medical Center) for preparing the MDCT images.

References

1. Martin LC, Merkle EM, Thompson WM. Review of internal hernias: radiographic and clinical findings. AJR Am J Roentgenol 2006;186:703-717.
2. Benson JR, Killen DA. Internal hernias involving the sigmoid mesocolon. Ann Surg 1964;159:382-384.
3. Kojima S, Sakamoto T, Honda M, et al. Strangulated transmesosigmoid hernia as a late complication of a fall from a height: a case report. Int J Surg Case Rep 2016;27:137-140.
4. Yu CY, Lin CC, Yu JC, et al. Strangulated transmesosigmoid hernia: CT diagnosis. Abdom Imaging 2004;29: 158-160.
5. Francis KC, Daley C, Williams BR, et al. The "Omega sign": a new radiological sign for a rare type of internal hernia involving the sigmoid mesocolon. BJR Case Rep 2020;6:20190127.
6. Li B, Assaf A, Gong YG, et al. Transmesosigmoid hernia: case report and review of literature. World J Gastroenterol 2014;20:5924-5929.
7. Van der Mieren G, de Gheldere C, Vanclooster P. Transmesosigmoid hernia: report of a case and review of the literature. Acta Chir Belg 2005;105:653-655.
8. Doishita S, Takeshita T, Uchima Y, et al. Internal hernias in the era of multidetector CT: correlation of imaging and surgical findings. Radiographics 2016;36:88-106.
9. Brierly JD, Gospodarowicz MK, Wittekind C, eds. TNM classification of Malignant Tumours (UICC), 8th ed. New York: Wiley-Blackwell, 2017. pp166-170.
10. Bhatla N, Aoki D, Sharma DN, et al. Cancer of the cervix uteri. Int J Gynaecol Obstet 2018;143 Suppl 2:22-36.
11. Charnsangavej C, DuBrow RA, Varma DG, et al. CT of the mesocolon. Part 1. Anatomic considerations. Radiographics 1993;13:1035-1345.

Instructions for Authors

The Osaka City Medical Journal will consider the publication of any original manuscript, review, case report, or short communication. Articles should be in English.

Manuscript submission. Manuscripts should be sent to the Editor, Osaka City Medical Journal, Osaka City Medical Association, Graduate School of Medicine, Osaka Metropolitan University, 1-4-3 Asahimachi, Abeno-ku, Osaka 545-8585, Japan; phone and fax 06-6645-3782; e-mail shiigakukai@med.osaka-cu.ac.jp

The Journal accepts only manuscripts that contain material that has not been and will not be published elsewhere. Duplicate publication of scientific data is not permitted. If closely related papers might be considered to be duplicate publications, the possible duplicate should be submitted with the manuscript and the authors should explain in their covering letter what is original in the submitted paper. Submit three copies of the manuscript (two of which may be photocopies) together with CD-R or DVD-R containing the body text, tables and figures. The manuscript should be prepared by Microsoft Word or its compatible software (doc or docx). Acceptable formats for figures are JPG or TIF. Use only 12-point font size and a standard serif font. Double-space throughout the manuscript and use standard-sized (ISO A4, 212×297 mm) white bond paper. Make margins at least 25 mm wide on all sides. Number pages consecutively starting with the title page and ending with the reference list. Begin each of these sections on a separate page: title page, abstract, text, acknowledgements, references, tables (each one separate), and figure legends. Do not use abbreviations in the title or abstract and limit their use in the text, defining each when it first appears. Manuscripts should meet the requirements outlined below to avoid delay in review and publication. Authors whose native language is not English must seek the assistance of a native English speaker who is familiar with medical sciences. Please attach the certificate from the person(s) who edit the manuscript. Some minor editorial revision of the manuscript will be made when the editorial committee considers it necessary.

Title page. All submissions must include a title page. The full title of the paper, should be concise, specific, and informative, and should contain the message of the paper without being in sentence form. Next, include the full names and academic affiliations of all authors, and indicate the corresponding author, address, phone, fax, and e-mail address. Give a running title (not to exceed 50 characters including spaces), and three to five key words. Last, give the word count for text only, exclusive of title, abstract, references, tables, and figure legends.

Structured abstract. The abstract of 250 words or less should consist of four paragraphs headed **Background, Methods, Results,** and **Conclusions.**

Text. Full papers about experiments or observations may be divided into sections headed **Introduction, Methods, Results,** and **Discussion.**

Tables. Each table should be typed on a separate sheet in characters of ordinary size, double-spaced (with at least 6 mm of white space between lines). Each table must have a title and should be assigned an Arabic numeral ('Table 3'). Vertical rules should not be used.

Figures. For black-and-white figures, submit three original glossy prints or laser-quality proofs and three photocopies of each. One transparency and three color prints should be submitted of each color figure. Label the front of figures with the figure number. Indicate on the back of each figure the first author, the first few words of the manuscript title, and the direction of the top of the figure (if needed). Photomicrographs should have scale markers that indicate the magnification. Provide figure legends on a separate page, double-spaced, immediately after the tables. All illustrations and graphs, to be referred to as figures, should be numbered in Arabic numerals ('Fig. 2' etc.). The approximate position of each figure in the text should be indicated in the right margin of the manuscript. Illustrations in full color are accepted for publication if the editors judge that color is necessary, with the cost paid by the author.

References. Reference must be double-spaced and numbered consecutively in the order cited in the text. When listing references, follow the style of the Uniform Requirements (http://www.icmje.org/) and abbreviate names of journals according to PubMed (http://www.ncbi.nlm.nih.gov/sites/netrez). List all authors up to three; when there are four or more, list the first three and use et al.

Examples of reference style

1. Priori SG, Schwartz PJ, Napolitano C, et al. Risk stratification in the long-QT syndrome. N Engl J Med 2003;348:1866-1874.
2. Schwartz PJ, Priori SG, Napolitano C. The long-QT syndrome. In: Zipes DP, Jalife J, editors. Cardiac electrophysiology: from cell to bedside. 3rd ed. Philadelphia: W.B. Saunders; 2000. pp. 597-615.

Proofs. One set of proofs together with the original manuscript will be sent to the author, to be carefully checked for any essential changes or printer's errors. The author is requested to return the corrected proofs within 48 h of their receipt.

Short communications and case reports.

1. A short communication should have between 1500 and 2000 words, including the abstract. This word count is equivalent to about four double-spaced manuscript pages.
2. The original and two copies including three sets of figures and tables should be sent to the Editorial Office.

Manuscript submission fee. A nonrefundable fee of 10,000 JPY is due on submission of original manuscripts, case reports, and short communications. A manuscript returned beyond six months of the date of the initial decision will be considered a new submission.

Page charges. A standard publication fee of 100,000 JPY will be applied for each accepted paper. Authors are also required to pay page charge of 10,000 JPY per printed page.
Ex) If your article has 10 pages, the amount of fee is 100,000 JPY+10 pages×10,000 JPY=200,000 JPY.

Reprints. If you were interested in ordering reprints of your article, we accept at least 50 full-color copies. Authors are required to pay page charge of 100 JPY per printed page. Ex) If you request 60 copies for 10-page article, the amount of fee is 100 JPY×10 pages×60 copies=60,000 JPY.

Studies of human subjects. It is the responsibility of the authors to ensure that any clinical investigation they did and report in manuscripts submitted to the Osaka City Medical Journal are in accordance with the Declaration of Helsinki (http://www.wma.net).

Animal studies. It is the responsibility of the authors to ensure that their experimental procedures are in compliance with the "Guiding Principles in the Care and Use of Animals" (http://www.the-aps.org/pub_affairs/humane/pa_aps_guiding.htm) published each month in the information for authors of the American Journal of Physiology.

Conflict of Interest (COI) Disclosure.

1. It is the responsibility of the authors to disclose any COI by signing the form.
2. If the authors have no conflicts, please state "All authors have no COI to declare regarding the present study" in the Acknowledgements.
   Authors are required to disclose any relationships with company or organization (such as funds, consultancy fee, grant, fee for speaking, stock or shares). At the time of initial submission, the corresponding author is responsible for obtaining conflict of interest information from all authors.

[Revised: June 8, 2021]

COPYRIGHT TRANSFER AND STATEMENT OF ORIGINALITY

We approve the submission of this paper to the Osaka City Medical Association for publication and have taken to ensure the integrity of this work. We confirm that the manuscript is original and does not in whole or part infringe any copyright, violate any right of privacy or other personal or priority right whatever, or falsely designate the source of authorship, and that it has not been published in whole or in part and is not being submitted or considered for publication in whole or in part elsewhere (abstracts excluded).
We agree to transfer copyright the manuscript entitled

_____

_____

to the Osaka City Medical Association upon its acceptance for publication.

Write clearly and signature

(Author: print or type)	(Signature)	(Date)
_____	_____	_____
(Author: print or type)	(Signature)	(Date)
_____	_____	_____
(Author: print or type)	(Signature)	(Date)
_____	_____	_____
(Author: print or type)	(Signature)	(Date)
_____	_____	_____
(Author: print or type)	(Signature)	(Date)
_____	_____	_____
(Author: print or type)	(Signature)	(Date)
_____	_____	_____
(Author: print or type)	(Signature)	(Date)
_____	_____	_____
(Author: print or type)	(Signature)	(Date)
_____	_____	_____
(Author: print or type)	(Signature)	(Date)
_____	_____	_____

OCMJ for Conflict of Interest (COI) Disclosure Statement

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed and stored electronically. Each author should submit this form and is responsible for the accuracy and completeness of the submitted information.

1. 1) Have you accepted from a sponsor or any company or organization (More than 1,000,000 JPY per year from a specific organization) ? (Please circle below)
   (1) Funds ? ····· Yes / No
   (2) Consultancy fee ? ····· Yes / No
   (3) Any grant ? ····· Yes / No
   (4) Fee for speaking ? ····· Yes / No

   2) Do you hold any stock or shares related to the manuscript ?
   (1) Directly ? ····· Yes / No
   (2) Indirectly, via family members or relatives ? ····· Yes / No

   3) If any of above items are “yes”, please provide detailed information below.

2. If none of the above apply and there is no COI please clearly state “All authors have no COI to declare regarding the present study”.

Manuscript Title:

Name / Signature_____ **Date**_____

Manuscript Identifying Number (if you know it):

Editorial Committee

The volumes and issues published in 1954-2018 were as follows: Vol 1 (one issue), Vols 2-5 (2 issues, each), Vols 6-7 (one issue, each), Vols 8-9 (2 issues, each), Vol 10 (one issue), Vol 11 (2 issues), Vol 12 (one issue), Vol 13 (2 issues), Vols 14-20 (one issue, each), Vol 21 (2 issues), Vol 22 (one issue), Vols 23-65 (2 issues, each), Vol 66 (one issue), Vol 67-68 (2 issues)

Publisher : Osaka City Medical Association,
Graduate School of Medicine, Osaka Metropolitan University
1-4-3 Asahimachi, Abeno-ku, Osaka 545-8585, Japan