Relation of Body Mass Index to Adverse Right Ventricular Mechanics

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Although higher body mass index (BMI) is associated with adverse left ventricular morphology and functional remodeling, its possible association with right ventricular (RV) dysfunction has not been extensively evaluated. RV free wall longitudinal strain (RVLS) is emerging as an important tool to detect early RV dysfunction. This study aimed to investigate the independent effect of increased BMI on RVLS in a large sample of the general population without overt cardiac disease. We examined 1,085 participants (603 men, mean age 62 years) who voluntarily underwent an extensive cardiovascular health check-up. This included laboratory tests and speckle-tracking echocardiography to assess RVLS. The association between BMI and RVLS was determined by logistic regression analyses. The prevalence of abnormal RVLS (>−19.2%) was greatest in obese individuals (29.7%), followed by overweight (16.3%), and normal weight (10.6%, p <0.001). In multivariable analyses, BMI was significantly associated with abnormal RVLS (adjusted odds ratio [OR] = 1.07 per 1 kg/m^2, p = 0.033) independent of traditional cardiovascular risk factors, pertinent laboratory and echocardiographic parameters including RV size and pulmonary artery systolic pressure. In subgroup analyses, BMI was significantly associated with abnormal RVLS in men (adjusted OR 1.10 per 1 kg/m^2, p = 0.032) and younger (<65 years) participants (adjusted OR 1.13 per 1 kg/m^2, p = 0.011), but not in women and the elderly. In a sample of the general population, higher BMI was independently associated with subclinical RV dysfunction. Furthermore, an increased BMI may carry different risk for impaired RVLS depending on the age and sex. **(Am J Cardiol 2021;144:137−142)**

Obesity and overweight are significant and growing epidemics impacting nearly three-fourths of US adults. The most commonly used criteria for classifying obesity is the body mass index (BMI) and a higher BMI is associated with left ventricular (LV) hypertrophy and diastolic dysfunction, both precursors of heart failure (HF). Recently, particular attention has been given to right ventricular (RV) dysfunction in HF patients because of its deleterious impact on functional capacity[1,2] as well as prognosis.[3,4] Myocardial systolic strain quantification, an indicator of cardiac function, is now feasible with speckle-tracking echocardiography. Longitudinal strain (LS), a measure of the myocardial systolic deformation over the longitudinal axis, is emerging as an important tool to detect early RV, as well as LV dysfunction, and is more sensitive than conventional parameters.[5,6] However, the possible association between BMI and subclinical RV dysfunction assessed by RV strain has not been extensively evaluated. The aim of the present study was to investigate whether higher BMI is associated with impaired RV free wall LS (RVLS) independent of LV morphology and function in a community-based cohort without overt cardiac disease, and investigate possible age and gender differences.

Methods

The study population was derived from the Subclinical Cardiac Dysfunction in General Population (SCADGP) study, which was designed to assess the prevalence and determinants of subclinical cardiac dysfunction in a community-based cohort who voluntarily underwent extensive cardiovascular health check at the University of Tokyo.[7] The Institutional Review Boards of the University of Tokyo approved the study. In a total of 1,243 SCADGP participants, 1,241 underwent laboratory testing, transthoracic echocardiographic examination, and pulmonary functional testing. Participants with a history of atrial fibrillation or atrial flutter (n = 15), coronary artery disease (n = 29), decreased LV systolic fraction (LV ejection fraction <50%; n = 17), significant tricuspid regurgitation (n = 3), and suboptimal image quality or incomplete echocardiographic examination (n = 92) were excluded from the study. None of the participants had significant mitral and/or aortic valvular disease, or pulmonary hypertension defined as tricuspid

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regurgitation velocity >3.4 m/s.[8] Thus, the final study group comprised 1,085 participants without overt cardiac disease.

BMI was calculated as the ratio of weight (in kilograms) to height (in meters) squared (kg/m^2). According to the World Health Organization, overweight was defined as a BMI between 25.0 and 29.9 kg/m^2 and obesity was defined as a BMI ≥30 kg/m.[9] Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, or by the use of antihypertensive medication. Diabetes mellitus was defined by a fasting blood glucose of ≥126 mg/dl or by the current use of insulin or hypoglycemic agents. Hyperlipidemia was defined as total serum cholesterol >240 mg/dl, or by the use of lipid-lowering medications. Finally, chronic obstructive pulmonary disease (COPD) was defined as the ratio of forced expiratory volume in the first second to forced vital capacity: FEV_1/FVC of <0.7.[10,11] Venous blood samples were collected under fasting conditions on the same day as echocardiographic examination. Blood samples were used to evaluate serum levels of C-reactive protein (CRP) and B-type natriuretic peptide (BNP).

Echocardiographic examination was performed using a commercially available system (Aplio 300, Toshiba Medical Systems, Tokyo, Japan) by trained and registered cardiac sonographers that were blinded to the participant's clinical information in accordance with a standardized protocol. The dimensions of the cardiac chambers were measured in the standard manner.[12] LV mass was calculated with a validated formula[13]: LV mass = 0.8(1.04[(SWT + LVEDD + PWT)^3 − LVEDD^3]) + 0.6, where SWT = LV end-diastolic septal wall thickness, LVEDD = LV end-diastolic diameter, and PWT = LV end-diastolic posterior wall thickness. Left atrial (LA) volume was measured using the biplane Simpson's rule.[12] LV mass and LA volume were indexed for body surface area. LV hypertrophy was defined as LV mass index >115 g/m^2 for men and >95 g/m^2 for women.[12] RV end-diastolic area and end-systolic area were also obtained from apical 4-chamber view and RV fractional area change (FAC) was calculated utilizing the following formula: (RV end-diastolic area − RV end-systolic area)/RV end-diastolic area × 100.[12] The peak systolic velocity of RV lateral wall at tricuspid annulus (RV-S') by tissue Doppler imaging in the apical 4-chamber view was also measured. RVFAC <35% and RV-S' <9.5 cm/s was defined as impaired RV function.[12] LV diastolic parameters were assessed in accordance with current guidelines.[14] Briefly, transmitral diastolic flow was obtained from an apical 4-chamber view. Pulsed-wave Doppler examination of mitral inflow was performed to measure early (E) and late peak velocity (A), and the ratio between the 2 (E/A) was calculated. Peak early diastolic mitral annular velocity (e') was also measured from tissue Doppler imaging in the lateral and septal mitral annulus, and the average value was used. Diastolic dysfunction was defined as the presence of ≥3 of the following parameters: (1) average E/e' >14, (2) septal e' velocity <7 cm/s or lateral e' velocity <10 cm/s, (3) maximum velocity of tricuspid regurgitation >2.8 m/s, and (4) LA volume index >34 ml/m^2.

Speckle-tracking analysis was performed off-line using vendor-independent commercially available software (2D Cardiac Performance Analysis; Tomtec Imaging System, Germany). Semiautomated border detection was performed using the software and RV borders were tracked throughout the entire cardiac cycle. Manual correction was performed in case of inaccurate endocardial detection. RV strain was evaluated by longitudinal peak systolic strain of the RV free wall from apical 4-chamber view (Figure 1). Impaired RVLS was defined as a RVLS >−19.2%, which is the 90th percentile of the strain value distribution in the SCADGP participants without any conditions associated with RV remodeling, including hypertension, diabetes mellitus, coronary artery disease, BMI >25 kg/m^2, significant valvular disease, arrhythmias and COPD. This cut-off value was consistent with previous studies exploring normal RVLS.[6,12] LVGLS was also calculated by averaging the negative peak of LS from all 3 apical

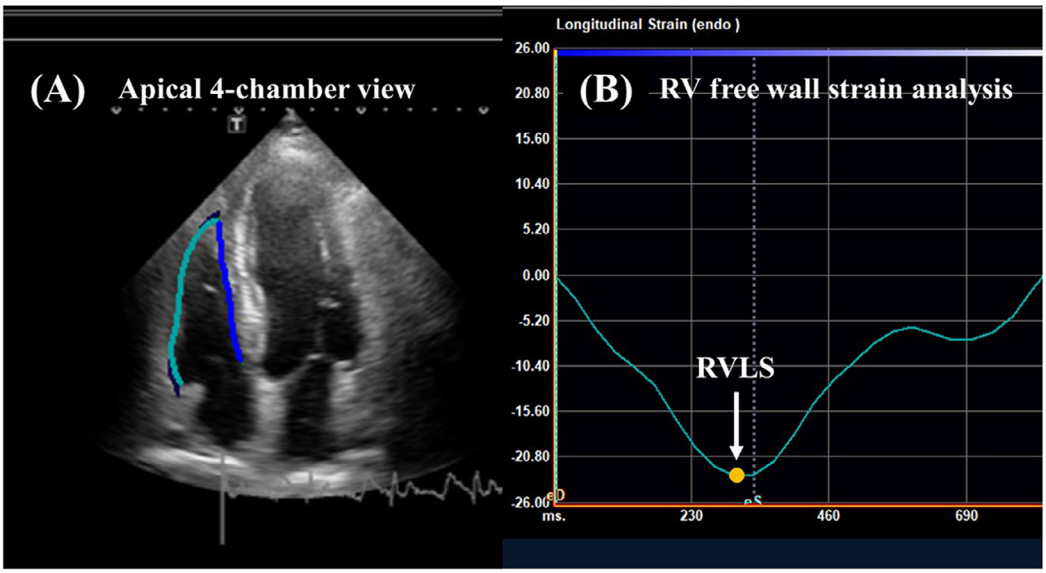

Figure 1. Measurement of free wall RVLS. Apical 4-chamber view used for the measurement of RV strain (*A*). RVLS was defined as the peak negative value of the strain curve during the entire cardiac cycle (white arrow; *B*). RVLS = right ventricular longitudinal strain.

views, including 4-chamber, 2-chamber, and long-axis views. We have reported the excellent reproducibility for strain measurements.[7]

Categorical variables are presented as numbers and percentages and were compared using chi-square test. Continuous variables are expressed as means ± standard deviations or median (interquartile range) and were compared using analysis of variance with Tukey-Kramer post hoc analysis or a Kruskal-Wallis test with the post-test Dunn correction, as appropriate. Univariable and multivariable logistic regression analyses were conducted to evaluate the association between BMI and RV dysfunction in a stepwise fashion in 5 models: Model 1: adjustment for age and sex; Model 2: adjustment for age, sex, hypertension, diabetes mellitus, hyperlipidemia, smoking status, and COPD; Model 3: adjustment as in Model 2 plus LV parameters including LV ejection fraction, LV hypertrophy and diastolic dysfunction; Model 4: adjustment as in Model 3 plus RV parameters including RV end-diastolic area and pulmonary artery systolic pressure; Model 5: adjustment as in Model 4 plus serum CRP and BNP levels. Adjusted odds ratios (ORs) with their 95% confidence interval were calculated in the entire study group and in sex and age subgroups. A value of $p < 0.05$ was considered significant. Statistical analyses were performed using JMP 10 software (SAS Institute, Cary, NC, USA).

Results

Clinical characteristics and echocardiographic data of the study population are also shown in Table 1. In the 1,085 participants, 766 (70.6%) were classified as having normal weight, 282 (26.0%) overweight, and 37 (3.4%) obesity. The prevalence of abnormal RVLS (>−19.2%) was greatest in obese participants (29.7%) followed by overweight (16.3%) and normal weight participants (10.6%, $p < 0.001$; Figure 2), whereas no significant differences were observed in abnormal RVFAC ($p = 0.185$) and RV-S' ($p = 0.795$) among the 3 groups. Increased BMI was associated with abnormal RVLS in the age- and sex-adjusted model (Table 2, Model 1). In the multivariable analyses adjusted for age, sex, hypertension, diabetes mellitus, hyperlipidemia, smoking status, and COPD, this association persisted (Table 2, Model 2). After further adjustment for

Table 1
Characteristics of the study population

	Normal weight (N = 766)	Overweight (N = 282)	Obese (N = 37)	p value
Age (years)	63±12	62±11	55±11*,†	<0.001
Men	369 (48.2%)	206 (73.1%)	28 (75.7%)	<0.001
Hypertension	216 (28.2%)	130 (46.1%)	26 (70.3%)	<0.001
Diabetes mellitus	64 (8.4%)	39 (13.8%)	7 (18.9%)	0.007
Hyperlipidemia	283 (36.9%)	97 (34.4%)	16 (43.2%)	0.514
Body mass index (kg/m^2)	21.7±2.1	26.7±1.4*	32.6±2.6*,†	<0.001
Smoker				0.012
Never	512 (66.8%)	159 (56.4%)	23 (62.2%)	
Former	195 (25.5%)	86 (30.5%)	9 (24.3%)	
Current	59 (7.7%)	37 (13.1%)	5 (13.5%)	
Chronic obstructive pulmonary disease	69 (9.0%)	30 (10.6%)	3 (8.1%)	0.698
Glucose (mg/dl)	97±17	105±23*	107±16*	<0.001
Total cholesterol (mg/dl)	207±34	203±33	202±42	0.100
C-reactive protein (mg/dl)	0.04 (0.02-0.08)	0.07 (0.04-0.12)*	0.09 (0.06-0.24)*	<0.001
B-type natriuretic peptide (pg/ml)	18 (10-30)	15 (8-25)*	11 (6-20)*	<0.001
Echocardiography				
LV end-diastolic diameter (mm)	44.2±4.2	46.5±4.5*	48.5±4.0*,†	<0.001
LV end-systolic diameter (mm)	27.2±3.6	28.0±3.8*	28.8±3.7	0.003
LV ejection fraction (%)	63.7±5.6	63.3±5.9	60.6±4.7*†	0.002
LV mass index (g/m^2)	68.0±14.3	77.5±18.0*	80.8±21.2*	<0.001
LA volume index (ml/m^2)	24.4±7.1	26.2±8.1*	27.1±6.3*	<0.001
E wave (cm/s)	70.7±15.4	68.8±14.3	65.9±10.4	0.023
A wave (cm/s)	66.8±19.8	71.6±19.9*	73.6±18.2	<0.001
E/A ratio	1.15±0.44	1.03±0.35*	0.94±0.27*	<0.001
e' (cm/s)	8.4±2.4	7.7±1.9*	7.8±1.6	<0.001
E/e' ratio	9.0±2.8	9.4±2.8	8.8±1.9	0.066
RV end-diastolic area (cm^2)	13.9±3.4	15.4±4.5*	16.6±4.9*	<0.001
RV end-systolic area (cm^2)	7.7±2.3	8.6±2.9*	9.7±3.4*	<0.001
RV systolic pressure (mm Hg)	25.9±5.3	27.4±5.8*	27.4±5.0	0.002
RV fractional area change (%)	44.8±7.6	44.5±6.8	41.9±8.0*	0.048
Peak systolic velocity of RV lateral wall at tricuspid annulus (cm/s)	12.5±2.1	12.4±2.3	13.0±2.6	0.408
RV free wall longitudinal strain (%)	-25.6±5.3	-24.2±5.2*	-22.7±5.2*	<0.001
LV global longitudinal strain (%)	-21.6±2.8	-20.6±2.4*	-20.2±2.5*	<0.001

* $p < 0.05$ compared with normal weight.
† $p < 0.05$ compared with overweight.
Values are mean ± standard deviation, n (percentage), or median (25th to 75th percentile).

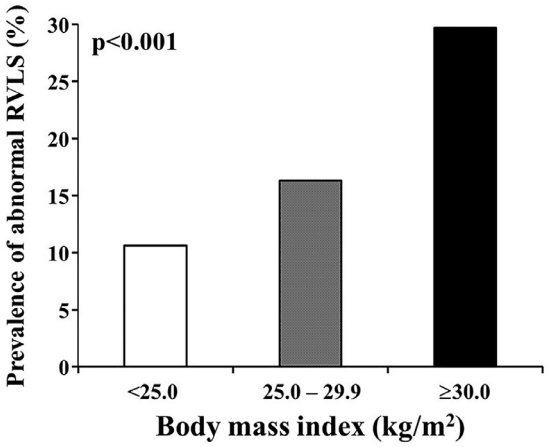

Figure 2. Prevalence of abnormal RVLS according to BMI level. BMI = body mass index; RVLS = right ventricular longitudinal strain.

echocardiographic parameters including LV ejection fraction, LV hypertrophy, and diastolic dysfunction, increased BMI remained significantly associated with abnormal RVLS (Table 2, Model 3). This finding persisted after further adjustment for RV size and pulmonary artery systolic pressure (Table 2, Model 4). Finally, even after controlling for BNP and CRP levels, BMI was still independently associated with abnormal RVLS (adjusted OR 1.07 per 1 kg/m^2, p = 0.033, Table 2, Model 5). Overall, in all 5 models, there was a strong correlation between increased BMI and abnormal RVLS. On the other hand, there was no independent association of BMI with RVFAC and RV-S' (also Table 2). Furthermore, when BMI was examined as a categorical variable, obesity was independently associated with abnormal RVLS in a fully adjusted model (adjusted OR 3.83, p = 0.007). A similar trend was observed in overweight participants, but it was not statistically significant in the fully adjusted model (adjusted OR 1.54, p = 0.065). In the sex and age subgroups analyses, BMI was significantly associated with abnormal RVLS both in men (adjusted OR 1.10 per 1 kg/m^2, p = 0.032) and in younger (<65 years) participants (adjusted OR 1.13 per 1 kg/m^2, p = 0.011) in a fully adjusted model. However, no significant association was observed in women (adjusted OR 1.05 per 1 kg/m^2, p = 0.394), as well as in elderly participants (adjusted OR 1.02 per 1 kg/m^2, p = 0.708).

Discussion

We demonstrated for the first time that higher BMI is associated with impaired RVLS in a large sample of the general population without overt cardiac disease. The association was independent of traditional cardiovascular risk factors, as well as pertinent laboratory and echocardiographic parameters including LV morphology and function. Furthermore, sex- and age-specific differences existed in the association between BMI and RVLS.

RV dysfunction is recognized as a major prognostic factor in HF patients.[3,4] Mohammed et al demonstrated that RV dysfunction was common and associated with poor outcome in 562 HF patients.[3] Bosch et al showed that RV dysfunction was related to all-cause death and HF hospitalization in both HF with and without preserved LV ejection fraction.[4] Furthermore, recent study has demonstrated that impaired RV contractility predicted the incident HF, independent of LV ejection fraction.[15] These observations underline the importance of an accurate assessment of RV function. Speckle-tracking echocardiography is a novel and feasible method for objective quantification of myocardial deformation, which allows for a more accurate evaluation of RV performance. Clinical studies have demonstrated that RVLS was the best predictor of RV contractility assessed by cardiac magnetic resonance imaging as the reference compared with other conventional measures.[5,6] Despite the impact of obesity on incident HF and the relevance of assessing RV function in HF patients, very few studies have assessed the impact of BMI on RV function. Wong et al demonstrated that obesity was strongly associated with impaired RV function using tissue-Doppler imaging in 148 subjects without overt cardiac disease.[16] Another study by Tadic et al also showed that obesity was inversely associated with RVLS in 127 untreated hypertensive patients.[17] Although the findings from the above studies were consistent, they were mostly obtained in small cohorts of significantly younger participants compared with the present study. We demonstrated that higher BMI was significantly associated with abnormal RVLS, independent of traditional

Table 2
Relation between BMI and impaired RV contractility

	RVFAC <35%		RV-S' <9.5 cm/s		RVLS >−19.2%	
Model	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
1	1.05 (0.96-1.15)	0.239	1.03 (0.95-1.10)	0.507	1.09 (1.03-1.15)	0.002
2	1.04 (0.95-1.13)	0.416	1.01 (0.93-1.09)	0.769	1.09 (1.03-1.16)	0.003
3	1.04 (0.95-1.13)	0.442	1.01 (0.93-1.09)	0.774	1.08 (1.02-1.14)	0.013
4	1.05 (0.95-1.16)	0.337	1.05 (0.97-1.14)	0.240	1.08 (1.01-1.15)	0.027
5	1.04 (0.95-1.15)	0.393	1.06 (0.97-1.15)	0.214	1.07 (1.01-1.15)	0.033

1: Adjustment for age and sex.
2: Adjusted for age, sex, hypertension, diabetes mellitus, hyperlipidemia, smoking and COPD.
3: Adjusted for variables as in Model 2 plus LVEF, LV hypertrophy, and diastolic dysfunction.
4: Adjusted for variables as in Model 3 plus RV end-diastolic area and pulmonary artery systolic pressure.
5: Adjusted for variables as in Model 4 plus serum CRP and BNP levels.

cardiovascular risk factors and pertinent laboratory and echocardiographic parameters.

The underlying mechanisms by which increased BMI is associated with lower RVLS are not entirely clear, but we hypothesize several potential explanations. First, sleep disorders, common in obese patients that may be involved in the development of RV dysfunction in obese subjects.[18] However, the impact of sleep disorders on our observations could not be assessed, because the information was not uniformly available in our study. Second, obesity induces chronic inflammation and alters adipokine levels, which may have an effect on RV function.[19,20] Third, clinical and experimental studies have identified the common occurrence of fatty infiltration into the RV wall, especially the free wall, which may directly affect RV contractility.[21,22] Finally, the positional change of the heart in obesity (more horizontal in position) might affect RVLS. Sex-specific patterns of ventricular remodeling have been shown in obese patients.[23–25] In the present study, we found that increased BMI carried an independent risk for subclinical RV dysfunction in men, whereas no significant association was observed in women. Furthermore, we demonstrated the independent association between BMI and RVLS in younger participants, but not in older participants. A possible explanation is that older individuals undergo a progressive loss of lean mass and BMI does not give sufficient indication on the body composition, which may have attenuated the association between increased BMI and impaired RVLS. Our findings provide valuable information to elucidate the pathophysiological mechanism underlying the obesity-related HF. In addition, they may emphasize the importance of early detection of RV remodeling for possible preventive strategies in individuals with overweight/obesity. Serrano-Ferrer et al reported a significant improvement of RV function through 3-month lifestyle changes in patients with metabolic syndrome.[26] Furthermore, although obesity significantly increases risk for HF, the condition is associated with a more favorable prognosis in the established HF setting (i.e., obesity paradox). Recent studies identified cardiorespiratory fitness as a potential modifier of this inverse association.[27,28] Future studies are warranted to investigate the role of cardiorespiratory fitness in the observed association between obesity and RV dysfunction.

Several limitations of this study should be noted. First, due to the cross-sectional nature of our study, we cannot establish a cause-effect relation between BMI and RVLS. In addition, the number of obese participants is somewhat small in the present study because Asians tended to have smaller BMI compared with Westerns, which might not allow generalization of the results to cohorts with different demographic composition. Second, although RVLS shows promise in various clinical settings,[15] normal value for RVLS is not yet established. Therefore, we used the internally obtained cut-off value, although the cut-off value of RVLS in the present study is consistent with those observed in previous studies.[6,12] Third, BMI has been a simple and convenient index for overweight/obesity, but it is difficult to define these conditions by BMI alone because they are remarkably heterogeneous, with varying cardiovascular manifestations across individuals. Recent studies demonstrated the clinical importance of body fat distribution on LV dysfunction and subsequent HF development.[29,30] Future studies are warranted to investigate the association between regional adiposity accumulation (i.e., epicardial fat and liver fat) and RV functional alteration. Fourth, we cannot estimate the impact of RVLS on working capacity, although previous studies demonstrated the close association between RV functional alteration and reduced working capacity.[1,2] Finally, although no participants had pulmonary hypertension assessed by echocardiography (tricuspid regurgitation velocity >3.4 m/s) in the entire study population,[8] the definitive diagnosis should be based on invasive hemodynamic examination, which was not performed.

In conclusion, this study demonstrated a significant association between higher BMI and impaired RVLS in a sample of the general population without overt cardiac disease. The association was independent of traditional cardiovascular risk factors, as well as serum biomarkers, and LV morphology and function. Our findings suggest that increased cardiovascular risk related to obesity might be mediated at least in part by RV dysfunction.

Authors' Contributions

Koki Nakanishi: Conceptualization, Methodology, Investigation, Formal analysis and Writing - Original Draft; Masao Daimon: Methodology, Writing - Review & Editing and Supervision; Yuriko Yoshida: Methodology, Data Curation, Validation and Writing - Review & Editing; Jumpei Ishiwata: Writing - Review & Editing; Naoko Sawada: Writing - Review & Editing; Megumi Hirokawa: Writing - Review & Editing; Hidehiro Kaneko: Writing - Review & Editing; Tomoko Nakao: Methodology and Writing - Review & Editing; Yoshiko Mizuno: Methodology and Writing - Review & Editing; Hiroyuki Morita: Methodology and Writing - Review & Editing; Marco R. Di Tullio: Writing - Review & Editing and Supervision; Shunichi Homma: Writing - Review & Editing and Supervision; Issei Komuro: Writing - Review & Editing and Supervision.

Disclosures

The authors report no disclosures pertinent to the content of the manuscript.

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