ACKNOWLEDGEMENTS

1 Henon H, Godefroy O, Leys D, Mounier-Vehier F, Lucas C, Rondepierre P, Duhamel A, Pruvo JP. Early predictors of death and disability after acute cerebral ischemic event. *Stroke* 1995; **26**: 392–398.
2 Langhorne P, Stott DJ, Robertson L, MacDonald J, Jones L, McAlpine C, Dick F, Taylor GS, Murray G. Medical complications after stroke: a multicenter study. *Stroke* 2000; **31**: 1223–1229.
3 Katzan IL, Cebul RD, Husak SH, Dawson NV, Baker DW. The effect of pneumonia on mortality among patients hospitalized for acute stroke. *Neurology* 2003; **60**: 620–625.
4 Hilker R, Poetter C, Findeisen N, Sobesky J, Jacobs A, Neveling M, Heiss WD. Nosocomial pneumonia after acute stroke: Implication for neurological intensive care medicine. *Stroke* 2003; **34**: 975–981.
5 Hamidon BB, Raymond AA, Norlinah MI, Jefferelli SB. The predictors of early infection after an acute ischaemic stroke. *Singapore Med J* 2003; **44**: 344–346.
6 Upadya A, Thorevska N, Sena KN, Manthous C, Amoateng-Adjepong Y. Predictors and consequences of pneumonia in critically ill patients with stroke. *J Crit Care* 2004; **19**: 16–22.
7 Hinchey JA, Shephard T, Furie K, Smith D, Wang D, Tonn S. Formal dysphagia screening protocols prevent pneumonia. *Stroke* 2005; **36**: 1972–1976.
8 Walter U, Knoblich R, Steinhagen V, Donat M, Benecke R, Kloth A. Predictors of pneumonia in acute stroke patients admitted to a neurological intensive care unit. *J Neurol* 2007; **254**: 1323–1329.
9 Finlayson O, Kapral M, Hall R, Asllani E, Selchen D, Saposnik G. Risk factors, inpatient care, and outcomes of pneumonia after ischemic stroke. *Neurology* 2011; **77**: 1338–1345.
10 Aslanyan S, Weir CJ, Diener HC, Kaste M, Lees KR. Pneumonia and urinary tract infection after acute ischaemic stroke: a tertiary analysis of the GAIN International trial. *Eur J Neurol* 2004; **11**: 49–53.
11 Ovbiagele B, Hills NK, Saver JL, Johnston SC. Frequency and determinants of pneumonia and urinary tract infection during stroke hospitalization. *J Stroke Cerebrovasc Dis* 2006; **15**: 209–213.
12 Meyer J, Stoica E, Pascu I, Shimazu K, Hartmann A. Catecholamine concentrations in CSF and plasma of patients with cerebral infarction and haemorrhage. *Brain* 1973; **96**: 277–288.
13 Wallace JD, Levy LL. Blood pressure after stroke. *JAMA* 1981; **246**: 2177–2180.
14 Morfis L, Schwartz RS, Poulos R, Howes LG. Blood pressure changes in acute cerebral infarction and hemorrhage. *Stroke* 1997; **28**: 1401–1405.
15 Boreas AM, Lodder J, Kessels F, de Leeuw PW, Troost J. Predictors of poststroke blood pressure level and course. *J Stroke Cerebrovasc Dis* 2001; **10**: 85–91.
16 Weimar C, Roth MP, Zillessen G, Glahn J, Wimmer ML, Busse O, Haberl RL, Diener HC. Complications following acute ischemic stroke. *Eur Neurol* 2002; **48**: 133–140.
17 Britton M, Carlsson A, de Faire U. Blood pressure course stroke and matched controls. *Stroke* 1986; **17**: 861–864.
18 Chamorro A, Vila N, Asasco C, Elices E, Schonewille W, Blanc R. Blood pressure and functional recovery in acute ischemic stroke. *Stroke* 1998; **29**: 1850–1853.
19 Ahmed N. High initial blood pressure after stroke is associated with poor functional outcome. *J Intern Med* 2001; **249**: 467–473.
20 Ogata T, Yasaka M, Wakugawa Y, Ibayashi S, Okada Y. Predisposing factors for acute deterioration of minor ischemic stroke. *J Neurol Sci* 2009; **287**: 147–150.
21 Bath P, Chalmers J, Powers W, Beilin L, Davis S, Lenfant C, Mancia G, Neal B, Whitworth J, Zanchetti A. International Society of Hypertension (ISH): statement on the management of blood pressure in acute stroke. *J Hypertens* 2003; **21**: 665–672.
22 Vaughan CJ, Delanty N. Hypertensive emergencies. *Lancet* 2000; **356**: 411–417.
23 Collins MJ, Bakheit AM. Does pulse oximetry reliably detect aspiration in dysphagic stroke patients? *Stroke* 1997; **28**: 1773–1775.
24 Ogihara T, Kikuchi K, Matsuoka H, Fujita T, Higaki J, Horiuchi M, Imai Y, Imaizumi T, Ito S, Iwao H, Kario K, Kawano Y, Kim-Mitsuyama S, Kimura G, Matsubara H, Matsuura H, Naruse M, Saito I, Shimada K, Shimamoto K, Suzuki H, Takishita S, Tanahashi N, Tsuchihashi T, Uchiyama M, Ueda S, Ueshima H, Umemura S, Ishimitsu T, Rakugi H. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009). *Hypertens Res* 2009; **32**: 3–107.
25 Kang DW, Chalela JA, Ezzeddine MA, Warach S. Association of ischemic lesion patterns on early diffusion-weighted imaging with TOAST stroke subtypes. *Arch Neurol* 2003; **60**: 1730–1734.
26 Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009; **53**: 982–992.
27 Cibcati J, Feinstein AR, Holford TRE. The risk of determining risk with multivariable models. *Ann Intern Med* 1993; **118**: 201–210.
28 James MT, Quan H, Tonelli M, Manns BJ, Faris P, Laupland KB, Hemmelgarn BR. CKD and risk of hospitalization and death with pneumonia. *Am J Kidney Dis* 2009; **54**: 24–32.
29 Lim JS, Kwon HM. Risk of 'silent stroke' in patients older than 60 years: risk assessment and clinical perspectives. *Clin Interv Aging* 2010; **5**: 239–251.
30 Nakagawa T, Sekizawa K, Nakajoh K, Tanji H, Arai H, Sasaki H. Silent cerebral infarction: a potential risk for pneumonia in the elderly. *J Intern Med* 2000; **247**: 255–259.
31 Arai T, Yasuda Y, Toshima S, Yoshimi N, Kashiki Y. ACE inhibitors and pneumonia in elderly people. *Lancet* 1998; **352**: 1937–1938.
32 Okaishi K, Morimoto S, Fukuo K, Niinobu T, Hata S, Onishi T, Ogihara T. Reduction of risk of pneumonia associated with use of angiotensin I converting enzyme inhibitors in elderly inpatients. *Am J Hypertens* 1999; **12**: 778–783.
33 Mukamal KJ, Ghimire S, Pandey R, O'Meara ES, Gautam S. Antihypertensive medications and risk of community-acquired pneumonia. *J Hypertens* 2010; **28**: 401–405.
34 Jansen PAF, Themn TH, Gribnau FWJ, Schulte BP, Willemsen JJ, Lamers KJ, Poels EF. Blood pressure and both venous and urinary cathecholamines after cerebral infarction. *Clin Neurol Neurosurg* 1988; **90**: 41–45.
35 Perry L, Love CP. Screening for dysphagia and aspiration in acute stroke: a systematic review. *Dysphagia* 2001; **16**: 7–18.
36 Marik PE. Aspiration pneumonitis and aspiration pneumonia. *N Engl J Med* 2001; **344**: 665–671.
37 Prass K, Meisel C, Hoeflich C, Braun J, Halle E, Wolf T, Ruscher K, Victorov IV, Priller J, Dirnagl U, Volk H-D, Meisel A. Stroke-induced immunodeficiency promotes spontaneous bacterial infections and is mediated by sympathetic activation reversal by post-stroke T helper cell type 1-like immunostimulation. *J Exp Med* 2003; **198**: 725–736.
38 Prass K, Braun JS, Dirnagl U, Meisel C, Meisel A. Stroke propagates bacterial aspiration to pneumonia in a model of cerebral ischemia. *Stroke* 2006; **37**: 2607–2612.
39 Zeng L, Chen R, Ishigami K, Atsumi M, Koiszumi Y, Sato K, Iritani O, Okuro M, Morimoto S. Association between human metapneumovirus seroprevalence and hypertension in elderly subjects in a long-term care facility. *Hypertens Res* 2011; **34**: 474–478.

Sleep Apnoea Syndrome as a Risk for Mortality in Elderly Inpatients

S Morimoto[1], T Takahashi[5], K Okaishi[4], M Okuro[1], T Nakahashi[1],
D Sakamoto[2], T Mizuno[2], T Kanda[2], M Takahashi[2,3] and H Toga[3]

[1]Department of Geriatric Medicine, [2]Department of Rural Medicine, and [3]Department of Respiratory Medicine, Kanazawa Medical University, Kahoku-gun, Ishikawa, Japan; [4]Department of Internal Medicine, Sengi Hospital, Kanazawa, Ishikawa, Japan; [5]Laboratory of Infectious Diseases, Graduate School of Infection Control Sciences, Kitasato University, Tokyo, Japan

OBJECTIVE: The characteristics of sleep apnoea syndrome (SAS) in the elderly, including subtype classification and association with mortality, have not been fully elucidated. This study examined these factors in an elderly Japanese inpatient population. METHODS: Overnight polysomnography was used to diagnose and classify SAS in 145 elderly inpatients (mean ± age 81 ± 8 years). Clinical data, including brain computerized tomography findings, were recorded. The study population included nine inpatients with obstructive SAS, 12 with central SAS, 25 with mixed SAS and 99 controls (no SAS). RESULTS: Increased body mass index and grade of aortic arch calcification independently contributed to risk of all subtypes of SAS combined. There was an independent association between SAS and increased risk of mortality from all causes as well as from pneumonia and from cardiovascular disease. Only mixed SAS was independently and positively associated with increased risk of death from pneumonia. CONCLUSIONS: Obstructive, central and mixed SAS were associated with increased risk of cardiovascular-related and all-cause mortality. Mixed SAS was associated with an increase in mortality from pneumonia. There was no relationship between mortality and severity of SAS.

KEY WORDS: SLEEP APNOEA–HYPOPNOEA SYNDROME; CHEYNE–STOKES BREATHING SYNDROME; ELDERLY; MORTALITY; PNEUMONIA; CARDIOVASCULAR DISEASE

Introduction

Sleep apnoea syndrome (SAS) is estimated to affect 2 – 4% of middle-aged adults in the USA,[1] with a higher prevalence (7.5%) reported in Japanese industrial workers.[2] Obstructive SAS, the predominant subtype in middle-aged populations, is an independent risk factor for hypertension[3] and stroke,[4] and is associated with increased cardiovascular disease mortality.[5] Central SAS is often accompanied by congestive heart failure and is associated with increased mortality.[6] The clinical characteristics and mortality risks of other subtypes of SAS, such as mixed SAS,[7] have not, however, been studied.

Studies indicate a relatively high prevalence of SAS in the elderly,[8,9] and increased SAS-related mortality was reported

in a cohort of noninstitutionalized elderly individuals.[10] Detailed characteristics of SAS in the elderly, including subtype classification, clinical contributing factors for each subtype, and association with mortality (especially pneumonia and cardiovascular disease which are two major causes of death in disabled elderly subjects[11]) have not been fully elucidated. The present study examined these factors in an elderly inpatient population.

Patients and methods
STUDY POPULATION
This study was conducted at Sengi Hospital, Kanazawa, Japan – a 540-bed hospital and long-term care facility for elderly persons, which is a common combination in Japan of medical and care services.[12] Consecutive Japanese inpatients aged ≥ 65 years with an admission period of at least 6 months and who were hospital inpatients at the time of the study were enrolled. Exclusion criteria were: (i) immunocompromised state; (ii) hypothyroidism; (iii) receiving oxygen administration; (iv) pneumonia within the past 3 months; and (v) renal failure (serum creatinine > 265 μmol/l).

The research protocol was approved by the Ethics Committee of Sengi Hospital. All in patients who gave written informed consent (or whose family members gave consent) were enrolled.

OBSERVATION OF PATIENTS
Baseline data were collected between 1 January and 31 March 2003. Follow-up observation began on 1 April 2003 and ended on 31 March 2006. No distinct outbreaks of nosocomial pneumonia occurred during the observation period. Data on death due to acute stroke,[13] coronary artery disease,[13] deterioration of congestive heart failure, pneumonia and other causes

were collected daily. Pneumonia was not listed as a cause of death in patients with pneumonia who died during the acute or critical phase of any of the other listed illnesses; rather, the cause of death was determined to be the underlying disease. None of the inpatients received treatment for SAS.

Known contributing factors for SAS were recorded. These included: body mass index (BMI);[14] serum levels of albumin and total cholesterol; hypertension (systolic and/or diastolic blood pressure ≥ 140/90 mmHg, or drug treatment);[3] chronic cardiovascular disease (previous myocardial infarction or angina pectoris);[4] chronic heart failure (left ventricular ejection fraction < 40%); chronic phase of stroke (motor deficit and evidence of cerebral deficit on computerized tomography [CT]);[15] diabetes mellitus (fasting blood glucose ≥ 7 mmol/l, or drug treatment); dementia (Mini-Mental State Examination score ≤ 23);[16] past history of lung disease (chronic bronchitis, emphysema, bronchiectasis, interstitial lung disease or sequelae of tuberculosis); atrial fibrillation; and bedridden state. Severity of aortic arch calcification (AAC) on the chest X-ray was graded as previously determined:[17] grade 0, no visible calcification; grade 1, small spots of calcification or single thin calcification of the aortic bulb; grade 2, one or more areas of thick calcification; and grade 3, circumferential calcification of the aortic bulb. Data were retrieved from medical records before the start of the examination (i.e. before SAS screening and brain CT). Personal physicians made the diagnoses, which were further evaluated by a committee of expert physicians convened for the purposes of this study. Routinely collected medical information (patients' previous history of illnesses, current complications,

current medications, and the family histories of illnesses) was used to improve diagnostic accuracy.

DIAGNOSIS AND CLASSIFICATION OF SAS

Screening for SAS was performed using a pulse oximeter (Pulsox-24M; Teijin, Osaka, Japan) according to the method by Raymond *et al.*[18] Oximetric arterial oxygen saturation (SaO_2) was assessed from 21.00 h to 07.00 h whilst patients were in bed. Pulse oximetry was measured 12 times per minute, with each data point representing the lowest saturation level in a 5-s interval. Inpatients with at least five desaturation events per hour (defined as a $\geq$ 3% decrease in SaO_2) were selected as candidates for SAS. All patients underwent overnight poly-somnography with a cardiorespiratory monitoring device (Morpheus®; Teijin) to diagnose and classify SAS types.[19] Apnoea was defined as complete cessation of airflow for $\geq$ 10 s, and hypopnoea as a $\geq$ 50% reduction in oronasal airflow for $\geq$ 10 s or a decrease in SaO_2 of $\geq$ 3% for $\geq$ 10 s. The apnoea–hypopnoea index (AHI) was defined as the frequency of these events per hour during overnight recording.[19] SAS severity was classified as mild (AHI 5 – < 15 events/h), moderate (AHI 15 – < 30 events/h), or severe (AHI $\geq$ 30 events/h).[7] Apnoea events were classified as obstructive, central, or mixed SAS.[7] Obstructive SAS was defined as the need for thoracic effort for continued breathing following complete cessation of air flow. Central SAS was characterized as the complete cessation of both the respiratory system and air flow for $\geq$ 10 s. Mixed SAS was a mix of obstructive SAS and central SAS, defined as a pause of the respiratory system followed by obstruction of ventilation for a relatively short term.

BRAIN CT EXAMINATION

The CT images of the brain were obtained along the orbitomental line of a 0.5 cm thick slice using X-Force apparatus (Toshiba Electric Co., Tokyo, Japan). Leukoaraiosis (i.e. nonspecific changes in the cerebral white matter that can be detected with high frequency by CT and magnetic resonance imaging in aged individuals) was assessed in seven brain regions and recorded as: absent, 0; mild, 1; or severe, 2.[20] Mean scores across the seven regions were calculated. The presence (1) or absence (0) of lacunar infarctions in the basal ganglia, as well as cortical deficit due to previous cerebral haemorrhage or infarction, were noted.[21]

STATISTICAL ANALYSES

Data were analysed using SPSS® software package version 12.0 (SPSS Inc., Chicago, IL, USA) for Windows®. Data were expressed as mean ± SD for continuous variables and number (percentage) for categorical variables. Comparisons between two groups for association between SAS and clinical variables were examined by the χ^2-test for categorical variables and the Mann–Whitney U-test for continuous variables. Comparisons among three or more groups were analysed by the Kruskal–Wallis test and Mann–Whitney U-test with *post hoc* Bonferroni correction. Multiple logistic regression analysis was carried out to determine independent contributing factors for SAS using the confounding factors of age, male gender and potential factors (e.g. congestive heart failure) at P < 0.20.[22] Conditional multiple logistic regression analysis was performed to determine independently contributing factors between the control group and obstructive, central or mixed SAS.

Patients with no fatal events were censored at the end of the study period and

excluded from the analysis. Cumulative risks of fatal events in the control group and SAS subtypes were plotted using the life table method (Kaplan–Meier analyses). Unadjusted odds ratios (OR) and 95% confidence intervals (95% CI) of fatal events, according to age, gender and SAS risk factors, were estimated by the Cox proportional hazards model. Multivariate models were used to adjust for potential confounding factors at $P < 0.20$.[22] Cases of death due to underlying disease were not included in analysis of death from pneumonia or cardiovascular disease. A two-tailed value of $P < 0.05$ was considered to be statistically significant.

Results

The study recruited 151 elderly inpatients. Six patients (4%) who had no follow-up data because of discharge from hospital were excluded and so the final study population included 145 inpatients (38 males/107 females; mean ± SD age 81 ± 8 years; age range 66 – 96 years). The study population comprised 46 (32%) patients with SAS; nine (6%) with obstructive SAS; 12 (8%) with central SAS and 25 (17%) with mixed SAS.

Demographic and clinical data for the study population are given in Table 1. The prevalence of congestive heart failure was significantly higher in patients with central SAS than in controls (no SAS) ($P = 0.006$). Patients with SAS had a higher BMI than controls, but this did not reach statistical significance. Obstructive SAS was characterized by a significantly lower mean grade of leukoaraiosis compared with central SAS and mixed SAS ($P = 0.001$ for both), and a significantly lower prevalence of lacunar infarction than controls and central SAS ($P < 0.001$ for both). The aortic arch calcification (AAC) grade was significantly higher in patients with obstructive or central SAS

patients than in controls ($P < 0.001$ for both). There were no significant differences between the three SAS subtypes in SAS severity or AHI.

Multiple logistic regression analysis revealed that higher AAC grade (OR 2.11 [95% CI 1.48, 2.99]) and higher BMI (OR 1.18 [95% CI 1.03, 1.35]) were independent contributing factors for all subtypes of SAS combined. Conditional logistic regression analysis found that independently contributing factors for obstructive SAS were higher AAC grade (OR 4.43 [95% CI 1.54, 12.8]) and lower prevalence of lacunae (OR 0.12 [95% CI 0.02, 0.86]). Independently contributing factors for central SAS were higher AAC grade (OR 4.73 [95% CI 1.73, 12.9]) and higher leukoaraiosis grade (OR 2.65 [95% CI 1.19, 5.89]). The single independent contributing factor for mixed SAS was higher BMI (OR 1.18 [95% CI 1.01, 1.37]).

During 341 person-years of follow-up, 55 (38%) patients died. The incidence of fatal events was 12.6/100 person-years. Causes of death are given in Table 2. These 55 patients were followed-up for a mean ± SD of 15.4 ± 9.9 months (range 1 – 35 months). Overall mortality rate was significantly higher in patients with SAS than in controls ($P = 0.006$) and significantly more SAS patients than controls died of pneumonia ($P = 0.049$) or cardiovascular disease ($P < 0.001$).

Kaplan–Meier analyses of cumulative rates of mortality are shown in Fig. 1. Cox proportional hazards model analysis (using controls and each subtype of SAS as a categorical group) revealed that only mixed SAS was independently and positively associated with mortality from pneumonia ($P = 0.011$). Obstructive, central and mixed SAS were all significantly and positively associated with all-cause mortality ($P = 0.004$, $P = 0.004$ and $P = 0.005$, respectively) and mortality from cardiovascular disease ($P < 0.001$, $P < 0.001$ and $P = 0.037$,

TABLE 1:
Demographic and clinical characteristics of 145 elderly Japanese inpatients according to the absence or presence of different subtypes of sleep apnoea syndrome (SAS)

Characteristic	Control: no SAS ($n = 99$)	Obstructive SAS ($n = 9$)	Central SAS ($n = 12$)	Mixed SAS ($n = 25$)	Statistical significance[b]	Total SAS ($n = 46$)	Statistical significance[a]
Age, years	81 ± 8	79 ± 9	81 ± 11	82 ± 8	NS	81 ± 8	NS
Male/female	26/73	2/7	4/8	6/19	NS	12/34	NS
Body mass index, kg/m²	18.3 ± 3.7	21.4 ± 2.6	19.2 ± 2.4	19.3 ± 4.4	NS	19.7 ± 3.7	NS
Serum albumin, g/l	34.0 ± 4.4	32.6 ± 4.7	33.9 ± 1.8	33.4 ± 4.6	NS	33.4 ± 4.0	NS
Serum cholesterol, mM	4.3 ± 1.0	4.2 ± 1.2	4.2 ± 1.5	4.1 ± 0.7	NS	4.2 ± 0.8	NS
Major complications							
Hypertension	44 (44)	3 (33)	4 (33)	14 (56)	NS	21 (46)	NS
Ischaemic heart disease	5 (5)	1 (11)	3 (25)	1 (4)	NS	5 (11)	NS
Congestive heart failure	8 (8)	1 (11)	5 (42)[c]	2 (8)	$P = 0.006$	8 (17)	NS
Chronic phase of stroke	62 (63)	7 (78)	11 (92)	11 (44)	NS	29 (63)	NS
Diabetes mellitus	13 (13)	1 (11)	1 (8)	6 (24)	NS	8 (17)	NS
Dementia	83 (84)	6 (67)	12 (100)	23 (92)	NS	41 (89)	NS
Lung disease	9 (9)	1 (11)	2 (17)	4 (16)	NS	4 (9)	NS
Atrial fibrillation	4 (4)	0 (0)	2 (17)	0 (0)	NS	2 (4)	NS
Bedridden state	66 (67)	6 (67)	9 (75)	16 (64)	NS	31 (67)	NS
Brain computerized tomography findings							
Leukoaraiosis, grade (0 – 2)	0.9 ± 0.7	0.3 ± 0.5[d,e]	1.3 ± 0.7	1.3 ± 0.5	$P = 0.001$	1.1 ± 0.7	NS
Lacunae	85 (86)	3 (33)[c,d]	12 (100)	21 (84)	$P < 0.001$	36 (78)	NS
Cortical deficit	40 (40)	4 (44)	5 (42)	7 (28)	NS	16 (35)	NS
Ventricular enlargement	60 (61)	3 (33)	8 (67)	14 (56)	NS	25 (54)	NS
Aortic arch calcification, grade (0 – 3)	1.0 ± 1.2	2.4 ± 0.7[c]	2.6 ± 0.7[c]	1.5 ± 1.2	$P < 0.001$	2.0 ± 1.1	$P < 0.001$

Characteristic	Control: no SAS (n = 99)	Obstructive SAS (n = 9)	Central SAS (n = 12)	Mixed SAS (n = 25)	Statistical significance[b]	Total SAS (n = 46)	Statistical significance[a]
TABLE 1 (continued): Demographic and clinical characteristics of 145 elderly Japanese inpatients according to the absence or presence of different subtypes of sleep apnoea syndrome (SAS)							
Severity of SAS							
Apnoea–hypopnoea index (events/h)	1.3 ± 1.4	19.3 ± 10.7[c]	24.5 ± 14.4[c]	23.3 ± 14.7[c]	$P < 0.001$	22.8 ± 13.7	$P < 0.001$
Grade (0 – 3)	0	2.1 ± 1.7[c]	2.5 ± 1.0[c]	1.7 ± 1.0[c]	$P < 0.001$	2.0 ± 1.1	$P < 0.001$

Data presented as mean ± SD, n, or n (%) of patients.
[a]Statistical significance between total SAS and control group calculated by Mann–Whitney U-test, with significance set at $P < 0.05$.
[b]Statistical significance between the four groups was analysed by Kruskal–Wallis test and Mann–Whitney U-test with post hoc Bonferroni corrections, with significance set at $P = 0.008$ (two-group comparisons from four groups gives a statistical significance of $P = 0.008$ [$P = 0.05$ divided by 6]). For analyses between groups: [c]versus control group; [d]versus C-SAS; and [e]versus M-SAS.
NS, not statistically significant ($P \geq 0.05$).

TABLE 2:
Cause of death among 55 elderly Japanese inpatients who died during the 36-month follow-up period, according to the absence or presence of different subtypes of sleep apnoea syndrome (SAS)

Cause of death	Control: no SAS (n = 99)	Obstructive SAS (n = 9)	Central SAS (n = 12)	Mixed SAS (n = 25)	Statistical significance[b]	Total SAS (n = 46)	Statistical significance[a]	Summary (n = 145)
Pneumonia	16 (16)	2 (22)	1 (8)	9 (36)	NS	12 (26)	P = 0.049	28 (19)
Cardiovascular disease (total)	5 (5)	2 (22)	7 (58)[c]	3 (12)	P < 0.001	12 (26)	P < 0.001	17 (12)
Myocardial infarction	2 (2)	1 (11)	3 (25)[c]	2 (8)	P = 0.002	6 (13)	P = 0.007	8 (6)
Sudden death	1 (1)	0 (0)	0 (0)	1 (4)	NS	1 (2)	NS	2 (1)
Congestive heart failure	2 (1)	1 (11)	4 (33)[c]	0 (0)	P < 0.001	5 (11)	P = 0.006	7 (5)
Stroke	3 (3)	1 (11)	0 (0)	0 (0)	NS	1 (2)	NS	4 (3)
Other causes	6 (6)	0 (0)	0 (0)	0 (0)	NS	0 (0)	NS	6 (4)
Total	30 (30)	5 (56)	8 (67)	12 (48)	NS	25 (54)	P = 0.006	55 (38)

Data presented as n (%) of patients.
[a]Statistical significance between total SAS and control group calculated by Mann–Whitney U-test, with significance set at P < 0.05.
[b]Statistical significance between the four groups was analysed by Kruskal–Wallis test and Mann–Whitney U-test with *post hoc* Bonferroni corrections, with significance set at P = 0.008 (two-group comparisons from four groups gives a statistical significance of P = 0.008 [P = 0.05 divided by 6]). For analyses between groups, [c]versus control group.
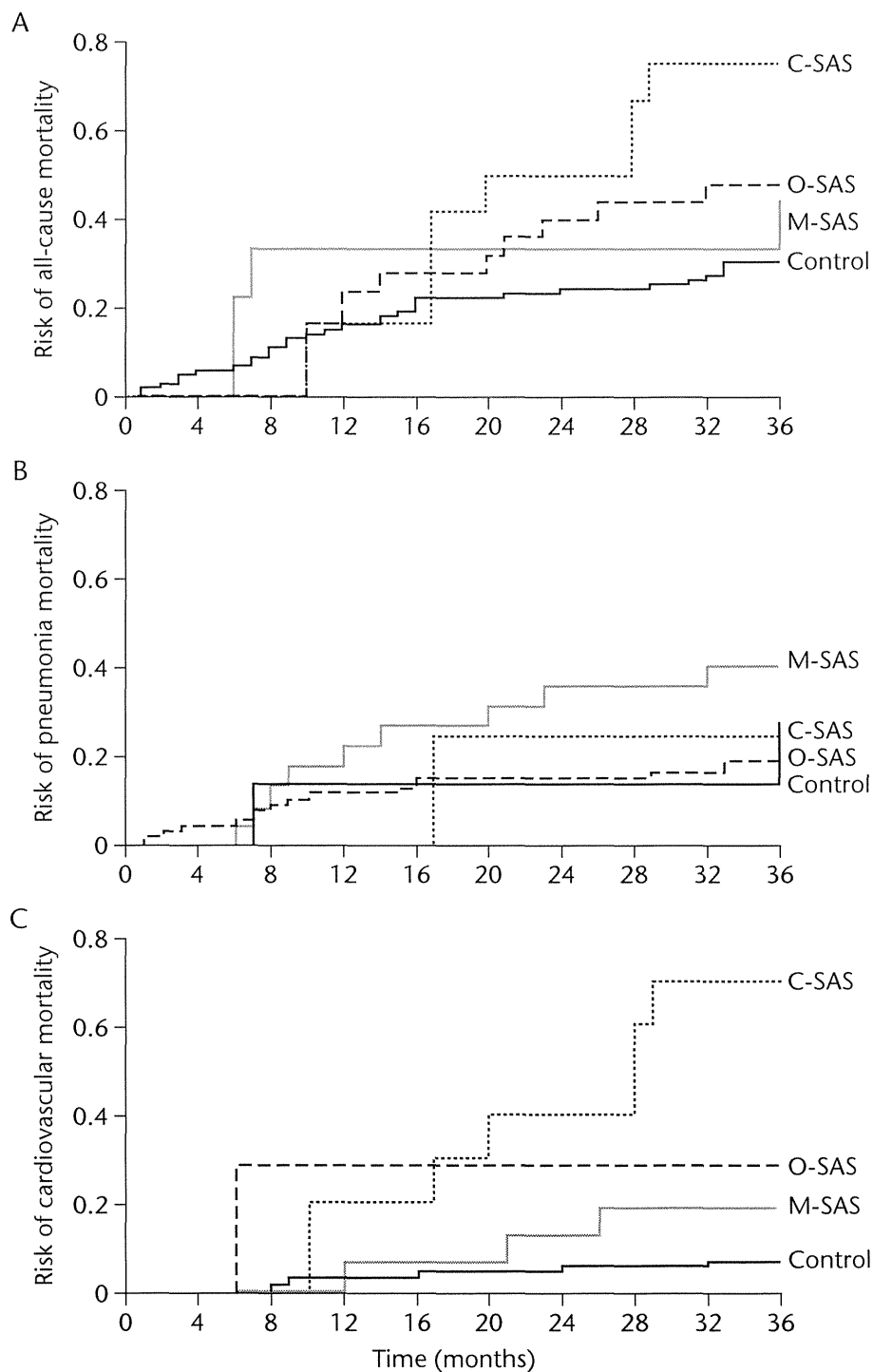NS, not statistically significant (P ≥ 0.05).

FIGURE 1: Kaplan–Meier plots of cumulative mortality amongst 55 elderly Japanese inpatients during the 36-month follow-up period, according to the absence or presence of different of sleep apnoea syndrome (SAS) subtypes: control, free from SAS (*n* = 30); C-SAS, central SAS (*n* = 8); O-SAS, obstructive SAS (*n* = 5); M-SAS, mixed SAS (*n* = 12). (A) Risk of all-cause mortality. (B) Risk of pneumonia mortality. (C) Risk of cardiovascular mortality

respectively). There was no association between any cause of death and SAS severity or AHI.

Discussion

The prevalence of SAS in the elderly inpatients in the present study was 32%,

which is much higher than that reported in Japanese industrial workers,[2] but consistent with other reports.[8,9] The present study revealed a predominance of mixed and central SAS among elderly SAS inpatients, in contrast to previous reports in young and middle-aged subjects[3] and in the elderly[9] in which obstructive SAS was the predominant subtype. This difference may be due to the fact that almost all the subjects in the present study were disabled elderly inpatients.

Multiple logistic regression analysis revealed that factors known to be related to SAS in younger subjects[3,23] were not associated with SAS in the elderly, although higher BMI[14] was found to be associated with SAS. The present study revealed that AAC, a known risk for coronary heart disease and ischaemic stroke,[24] was an independent risk factor for obstructive and central SAS in elderly inpatients. The patients with obstructive SAS in the present study were relatively free from ischaemic impairment of the brain, such as lacunae and leukoaraiosis, compared with controls and other SAS subtypes. A higher grade of leukoaraiosis was independently related to the risk of mixed SAS in this population. These observations are in contrast to the findings of Davies *et al.*,[25] who reported no significant difference in the prevalence of either lacunae or leukoaraiosis between obstructive SAS patients and controls aged 30 – 80 years. Mixed SAS is thought to develop in patients with obstructive SAS who also experience episodes of apparent central SAS.[7] Mild hypoxaemia and/or mild hypocapnia due to hypoxaemia induced hyperventilation have been reported to contribute to the shift from obstructive to mixed SAS.[26] In addition, central SAS can be secondary to damage to the respiratory centre of the brain, as seen in cases of ischaemic brain stem infarction.[7] These observations suggest that age-related ischaemic brain damage represented by lacunae and/or leukoaraiosis may result in a decrease in the prevalence of obstructive SAS and instead a predominance of mixed and/or central SAS.

The main cause of death in the present study was pneumonia followed by cardiovascular disease, a finding that is partly in accordance with reports from a disabled elderly population,[11] and elderly patients with SAS.[27] The present study showed SAS to be an independent predictor of reduced survival due to all-cause mortality and also mortality due to pneumonia and cardiovascular disease. In addition, an independent association between mixed SAS and increased mortality due to pneumonia was found. The precise mechanism of this association is not clear but severe leukoaraiosis predicted pneumonia death (with a hazard ratio of 8.3) in a study of patients with neurological deficit.[28] Since leukoaraiosis was associated with increased risk of mixed SAS in the present study, the relationship between mixed SAS and pneumonia mortality may be mediated by leukoaraiosis.

Obstructive, central and mixed SAS were all independent risk factors for both all-cause mortality and mortality from cardiovascular disease. Obstructive SAS increases mortality from cardiovascular disease in the general population[5,6] and in the elderly.[29] Central SAS has also been associated with increased mortality from cardiovascular disease in the general population[30] and in an elderly population.[31] The present study also revealed an independent contribution of mixed SAS to mortality from cardiovascular disease, in addition to death from pneumonia.

Neither AHI nor SAS severity were associated with any cause of death in the

present study. Previous studies have found a significant association between severity of obstructive SAS and coronary artery disease,[32] and severity of central SAS and congestive heart failure mortality.[31] Lavie *et al.*[33] found that the association between SAS severity and increased mortality disappeared in older SAS patients. The high mean age of the patients in the present study may be one of the causes of the lack of association between SAS severity and mortality of any cause.

In conclusion, the present study found an increased risk of cardiovascular and all-cause mortality in elderly inpatients with obstructive, central and mixed SAS. Mixed SAS was associated with an increase in mortality from pneumonia. There was no relationship between mortality and severity of SAS. Future trials should be conducted to determine a definite relationship between SAS and mortality using a larger number of patients.

Conflicts of interest

The authors had no conflicts of interest to declare in relation to this article.

References

1 Yaggi HK, Concato J, Kernan WN, *et al*: Obstructive sleep apnea as a risk factor for stroke and death. *N Engl J Med* 2005; **353**: 2034 – 2041.

2 Chin K, Oga T, Takahashi K, *et al*: Associations between obstructive sleep apnea, metabolic syndrome, and sleep duration, as measured with an actigraph, in an urban male working population in Japan. *Sleep* 2010; **33**: 89 – 95.

3 Durán J, Esnaola S, Rubio R, *et al*: Obstructive sleep apnea–hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr. *Am J Respir Crit Care Med* 2001; **163**: 685 – 689.

4 Djonlagic I, Malhotra A: Risk of stroke from sleep apnea in men and women. *Expert Rev Neurother* 2010; **10**: 1267 – 1271.

5 Lurie A: Cardiovascular disorders associated with obstructive sleep apnea. *Adv Cardiol* 2011; **46**: 197 – 266.

6 Lavie L, Lavie P: Molecular mechanisms of cardiovascular disease in OSAHS: the oxidative stress link. *Eur Respir J* 2009; **33**: 1467 – 1484.

7 Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. *Sleep* 1999; **22**: 667 – 689.

8 Hoch CC, Reynolds CF 3rd, Kupfer DJ, *et al*: Sleep-disordered breathing in normal and pathologic aging. *J Clin Psychiatry* 1986; **47**: 499 – 503.

9 Janssens JP, Pautex S, Hilleret H, *et al*: Sleep disordered breathing in the elderly. *Aging (Milano)* 2000; **12**: 417 – 429.

10 Bliwise DL, Bliwise NG, Partinen M, *et al*: Sleep apnea and mortality in an aged cohort. *Am J Public Health* 1988; **78**: 544 – 547.

11 Kammoun S, Gold G, Bouras C, *et al*: Immediate causes of death of demented and non-demented elderly. *Acta Neurol Scand Suppl* 2000; **176**: 96 – 99.

12 Kuroda K, Tatara K, Takatorige T, *et al*: Factors related to long-term stay in hospital by elderly people in a Japanese city. *Age Ageing* 1992; **21**: 321 – 327.

13 Gillum RF, Fortmann SP, Prineas RJ, *et al*: International diagnostic criteria for acute myocardial infarction and acute stroke. *Am Heart J* 1984; **108**: 150 – 158.

14 Young T, Peppard PE, Taheri S: Excess weight and sleep-disordered breathing. *J Appl Physiol* 2005; **99**: 1592 – 1599.

15 Cadilhac DA, Thorpe RD, Pearce DC, *et al*: Sleep disordered breathing in chronic stroke survivors. A study of the long term follow-up of the SCOPES cohort using home based polysomnography. *J Clin Neurosci* 2005; **12**: 632 – 637.

16 Ideno Y, Takayama M, Hayashi K, *et al*: Evaluation of a Japanese version of the Mini-Mental State Examination in elderly persons. *Geriatr Gerontol Int* doi: 10.1111/j.1447-

0594.2011.00772.x (epub ahead of print).

17 Papanas N, Symeonidis G, Maltezos E, *et al*: Evaluation of aortic arch calcification in type 2 diabetic patients. *Vasa* 2005; **34**: 113 – 117.

18 Raymond B, Cayton RM, Chappell MJ: Combined index of heart rate variability and oximetry in screening for the sleep apnoea/hypopnoea syndrome. *J Sleep Res* 2003; **12**: 53 – 61.

19 Franklin KA, Eriksson P, Sahlin C, *et al*: Reversal of central sleep apnea with oxygen. *Chest* 1997; **111**: 163 – 169.

20 van Swieten JC, Hijdra A, Koudstaal PJ, *et al*: Grading white matter lesions on CT and MRI: a simple scale. *J Neurol Neurosurg Psychiatry* 1990; **53**: 1080 – 1083.

21 Hijdra A, Verbeeten B Jr, Verhulst JA: Relation of leukoaraiosis to lesion type in stroke patients. *Stroke* 1990; **21**: 890 – 894.

22 Maldonado G, Greenland S: Simulation study of confounder-selection strategies. *Am J Epidemiol* 1993; **138**: 923 – 936.

23 Hayashi M, Fujimoto K, Urushibata K, *et al*: Nocturnal oxygen desaturation correlates with the severity of coronary atherosclerosis in coronary artery disease. *Chest* 2003; **124**: 936 – 941.

24 Iribarren C, Sidney S, Sternfeld B, *et al*: Calcification of the aortic arch: risk factors and association with coronary heart disease, stroke, and peripheral vascular disease. *JAMA* 2000; **283**: 2810 – 2815.

25 Davies CW, Crosby JH, Mullins RL, *et al*: Case control study of cerebrovascular damage defined by magnetic resonance imaging in patients with OSA and normal matched control subjects. *Sleep* 2001; **24**: 715 – 720.

26 Mahamed S, Mitchell GS: Is there a link between intermittent hypoxia-induced respiratory plasticity and obstructive sleep apnoea? *Exp Physiol* 2007; **92**: 27 – 37.

27 Ancoli-Israel S, Kripke DF, Klauber MR, *et al*: Morbidity, mortality and sleep disordered breathing in community dwelling elderly. *Sleep* 1996; **19**: 277 – 282.

28 Briley DP, Haroon S, Sergent SM, *et al*: Does leukoaraiosis predict morbidity and mortality? *Neurology* 2000; **54**: 90 – 94.

29 Sanner B, Sturm A, Konermann M: Coronary heart disease in patients with obstructive sleep apnea. *Dtsch Med Wochenschr* 1996; **121**: 931 – 935 [in German, English abstract].

30 Hanly PJ, Zuberi-Khokhar NS: Increased mortality associated with Cheyne–Stokes respiration in patients with congestive heart failure. *Am J Respir Crit Care Med* 1996; **153**: 272 – 276.

31 Ancoli-Israel S, DuHamel ER, Stepnowsky C, *et al*: The relationship between congestive heart failure, sleep apnea, and mortality in older men. *Chest* 2003; **124**: 1400 – 1405.

32 Peker Y, Hedner J, Kraiczi H, *et al*: Respiratory disturbance index: an independent predictor of mortality in coronary artery disease. *Am J Respir Crit Care Med* 2000; **162**: 81 – 86.

33 Lavie P, Lavie L, Herer P: All-cause mortality in males with sleep apnoea syndrome: declining mortality rates with age. *Eur Respir J* 2005; **25**: 514 – 520.

Author's address for correspondence
Dr Shigeto Morimoto
Department of Geriatric Medicine, Kanazawa Medical University, 1-1 Daigaku, Uchinada-machi, Kahoku-gun, Ishikawa 920-0293, Japan.
E-mail: shigeto@kanazawa-med.ac.jp

Journal of
Experimental
and
Clinical
Medicine

LETTER TO THE EDITOR

Guidelines for Nonmedical Care Providers to Manage the First Step of Emergency Triage of Elderly Evacuees: Downloaded via Smart Phones in Japan *

Japan experienced strong earthquakes in 1995,[1] 2004,[2] and 2007.[3] These disasters hit the elderly population of the communities particularly hard. Surviving older adults were largely left to their own devices and were marginalized in shelters. Elderly evacuees tended not to complain about their problems, so their excessive mental and/or physical stress under the altered environment tended to be underestimated. Therefore, it is important for nonmedical care providers (NMCPs) to detect medical conditions quickly in elderly evacuees. The NMCP include volunteers, helpers, and family members who are taking care of the elderly.

The Study Group on "Guidelines for the First Steps and Emergency Triage to Manage Elderly Evacuees" was established with funding from the Ministry of Health, Labor, and Welfare of Japan in April 2010. The study group aimed to complete and revise the guidelines. After the Great East Japan Earthquake of 2011, we quickly published the Japanese guidelines for NMCP, public health

nurses (PHN), or certified social workers (CSW) to manage elderly evacuees.[4,5] The guidelines for the elderly have three chapters: (1) features and prevention of critical diseases in evacuation areas, (2) signs of acute diseases, and (3) symptoms of anxiety in shelters. We would like NMCP, PHN, and CSW for their permission to use the guidelines to rapidly detect illnesses in the elderly in shelters or homes. NMCP, PHN, or CSW should immediately inform attending medical staff when those with the signs or symptoms are detected.

We uploaded and started to provide the guidelines for NMCP, PHN, or CSW on the personal digital assistant (PDA) system on May 11, 2011. Figure 1 shows the guidelines downloaded via PDA (i.e., Android and iPhone versions were made by Google and Apple companies, respectively). The guidelines' numbers distributed to the smart phones are increasing, even up to the time of writing this letter (June 2, 2012), suggesting that general interest regarding measures against the natural disasters is continued among Japanese people. International provision of the guidelines written in English is now being promoted on the PDA system. Feedback concerning the guidelines downloaded will need to be collected from the NMCP, PHN, or CSW to evaluate the guidelines' usability. Previous guidelines failed to cover because of the unexpected phenomena following the 2011 Japan quake. We further should investigate the morbidity and mortality from disaster-related illnesses among the elderly to clarify efficacy and limitation of the guidelines.
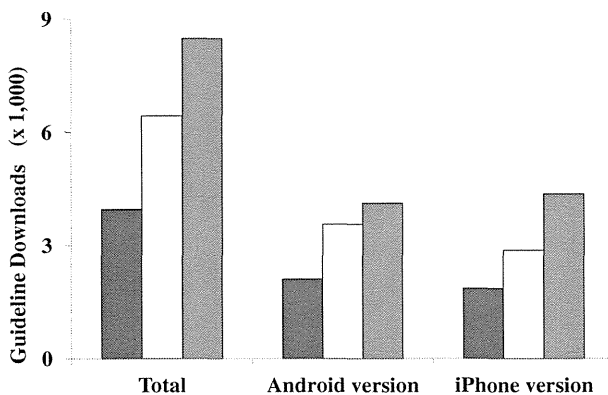

Figure 1 Numbers of the guidelines downloaded via personal digital assistant (Android and iPhone versions were made by Google and Apple companies, respectively) from May 11, 2011 through June 2, 2012 in Japan. The numbers distributed to the smart phones are increasing, even up to the time of writing this letter (June 2, 2012). Black column, September 11, 2011; open column, January 14, 2012; light gray column, June 2, 2012. The Android and iPhone versions can be downloaded from the corresponding sites (https://play.google.com/store/apps/details?id=jp.co.kgc.android. oneswingviewer.WJGSM001G#?t=W251bGwsMSwyLDIxMiwianAuY28ua2djLmFuZH JvaWQub25lc3dpbmd2aWV3ZXIuV0pHU01VMDFHIzA and http://itunes.apple.com/jp/app/id434573392?mt=8).

References

1. Kario K, Matsuo T, Kobayashi H, Yamamoto K, Shimada K. Earthquake-induced potentiation of acute risk factors in hypertensive elderly patients: possible triggering of cardiovascular events after a major earthquake. *J Am Coll Cardiol* 1997;**29**:926–33.
2. Sato M, Fujita S, Saito A, Ikeda Y, Kitazawa H, Takahashi M, Ishiguro J, et al. Increased incidence of transient left ventricular apical ballooning (so-called 'Takotsubo' cardiomyopathy) after the mid-Niigata Prefecture earthquake. *Circ J* 2006;**70**:947–53.
3. Nomura K, Murai H, Nakahashi T, Mashiba S, Watoh Y, Takahashi T, Morimoto S. Outbreak of norovirus gastroenteritis in elderly evacuees after the 2007 Noto Peninsula earthquake in Japan. *J Am Geriatr Soc* 2008;**56**:361–3.
4. Takahashi T, Iijima K, Kuzuya M, Hattori H, Yokono K, Morimoto S. Guidelines for non-medical care providers to manage the first steps of emergency triage of elderly evacuees. *Geriatr Gerontol Int* 2011;**11**:383–94.
5. Morimoto S, Iijima K, Kuzuya M, Hattori H, Yokono K, Takahashi T. Guidelines for non-medical care providers to detect illnesses in elderly evacuees after the 2011 earthquake off the Pacific coast of Tohoku. *J Am Geriatr Soc* 2011;**59**:2189–91.

Takashi Takahashi*
Laboratory of Infectious Diseases, Graduate School of Infection Control Sciences, Kitasato University, Tokyo, Japan

Shuichi Matsumoto
Division of Marketing Mobile Phone Business, Fujitsu Personal System Ltd., Tokyo, Japan

Katsuya Iijima
Institue of Gerontology, The University of Tokyo, Chiba, Japan

Department of Geriatric Medicine, The University of Tokyo, Tokyo, Japan

Shigeto Morimoto
Department of Geriatric Medicine, Kanazawa Medical University, Ishikawa, Japan

* Corresponding author. Takashi Takahashi, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641, Japan.
E-mail: T. Takahashi <taka2si@lisci.kitasato-u.ac.jp>

Jul 5, 2012

LETTERS TO THE EDITOR

RESEARCH

DEPOPULATION WITH RAPID AGING IN MINAMISOMA CITY AFTER THE FUKUSHIMA DAIICHI NUCLEAR POWER PLANT ACCIDENT

To the Editor: On March 11, 2011, a strong earthquake (magnitude 9.0) occurred off the Pacific coast and hit the northeast of Japan, followed by devastating tsunamis, which destroyed many coastal cities.[1,2] The three operating reactors at Fukushima Daiichi nuclear power plant shut down automatically just after this earthquake,[3] but 41 minutes later, a massive wall of rolling water burst through the plant's defenses and inundated the reactor buildings. The tsunami flooded emergency generators, leaving the plant without power for cooling systems while radioactive decay kept heating the cores. In the control room, plant workers desperately tried to run crucial instruments, using torches and car batteries scavenged from nearby vehicles, but the last line of emergency systems failed, and the three reactors melted down several days later. This process induced release of hydrogen gas, which caused explosions in the reactor buildings.

People in Fukushima mistrust the actions of the government and the Tokyo Electric Power Company because of poor provision of accurate information concerning the plant accident, even 1 year and 4 months after the disaster. Volatile radioactive chemicals including iodine-131 and cesium-137 started to spread into the air and sea. Investigation of radionuclide was conducted on bamboo sampled from six sites within a 25- to 980-km radius of the Fukushima plant in July to August 2011.[4] Strikingly high concentrations of radiocesium-134 and -137 activity were detected in mature leaves from Fukushima city (65 km from the Fukushima plant), in excess of 71 and 79 kBq/kg of dry weight (DW). In Kashiwa city (195 km from the plant), sample concentrations were in excess of 3.4 and 4.3 kBq/kg DW. In Toyohashi city (440 km from the plant), concentrations were below the measurable limits of up to 4.5 Bq/kg DW.

Last summer, a comprehensive public health study was established with a large budget at Fukushima Medical University.[3] This investigation was designed to follow up on the health of some 2 million people in the region for 30 years. According to the latest data (February 20, 2012), 99.3% of 9,747 people living in towns or villages close to the plant received an accumulated effective dose of less than 10 mSv during the first 4 months after the accident. The highest dose was 23 mSv, well below the acute exposure level (100 mSv) related to a slight increase in risk of malignant diseases. In Minamisoma, there were 305 disaster-associated deaths, 298 (97.7%) of which were in elderly adults.

Minamisoma Municipal General Hospital, which is located in the evacuation area 20 km from the plant, has served as a regional core institute for evacuees. Medical care providers have been performing health monitoring and medical care, including vaccination programs, for more than 4,000 victims.

In April 2012, the government released newly revised guidelines regarding the evacuation zones from the plant, but wide-area evacuation still continues in Fukushima. The population of 72,000 in Minamisoma before the accident decreased to approximately 10,000 just after the accident. On March 29, 2012, it had recovered to approximately 45,000. The proportion of those aged 65 and older increased from 25.9% to 32.1% (Figure 1A). In addition, the retention rate of population according to age group has dramatically changed (Figure 1B). Many younger than 40, especially infants, children, and young parents, moved out of the communities because of fear regarding radiation exposure, causing a rapid increase in the proportion of elderly people. In addition, loss of ordinary lifestyle may inhibit activities of daily living of older adults. Elderly adults dislike moving, and many continued to live there, suggesting the breakup of communities and families. The average age of the population in Minamisoma has increased by 14 years because of the nuclear disaster, with younger people leaving, whereas older people have stayed behind, reaching the level that it had been estimated it would reach by 2025. Similar events have been observed in Futaba county and Iitate village near Minamisoma.

Public attention for the nuclear plant workers[5] and people living in Fukushima is fading rapidly. We should continue to pay attention to depopulation with rapid aging, which may make rebuilding populations in stricken areas difficult.

Kazunobu Ishikawa, MD
Center for Medical Education and Career Development
Fukushima Medical University, Fukushima, Japan
and Department of Cardiology, Fukushima Medical
University Hospital, Fukushima, Japan

Yukio Kanazawa, MD
Department of Gastrointestinal Medicine, Minamisoma
Municipal General Hospital, Minamisoma, Japan

Shigeto Morimoto, MD
Department of Geriatric Medicine, Kanazawa Medical
University, Kahoku-gun, Japan

Takashi Takahashi, MD
Laboratory of Infectious Diseases, Graduate School of
Infection Control Sciences, Kitasato University
Minato-ku, Japan

A

Male   105-109 3
                        1   100-104 13   **Female**
                      36   95-99   ▌108
                     138   90-94   417 ▄
                    ▌508   85-89   944 ▄▄▄
                ▄ 1,001   80-84   1,616 ▄▄▄
  80.2 %   ▄ 1,324   75-79   1,820 ▄▄▄   75.8 %
            ▄ 1,559   70-74   1,693 ▄▄
            ▄ 1,587   65-69   1,626 ▄▄
  ▄ 2,635   60-64   2,418 ▄▄▄
     ▄ 2,015   55-59   1,974 ▄▄▄
  69.2 %   ▄ 1,634   50-54   1,651 ▄▄▄   65.8 %
             ▄ 1,339   45-49   1,167 ▄▄
             ▄ 1,333   40-44   1,114 ▄▄
           ▄ 1,437   35-39   1,075 ▄▄▄
            ▄ 1,119   30-34   850 ▄▄▄
  55.2 %   ▄ 951   25-29   720 ▄▄▄   45.4 %
            ▄ 899   20-24   697 ▄▄
  55.1 %   ▄ 1,002   15-19   926 ▄▄▄   56.9 %
            ▄ 827   10-14   805 ▄▄▄
  36.8 %   ▄ 620   5-9   548 ▄▄▄   35.7 %
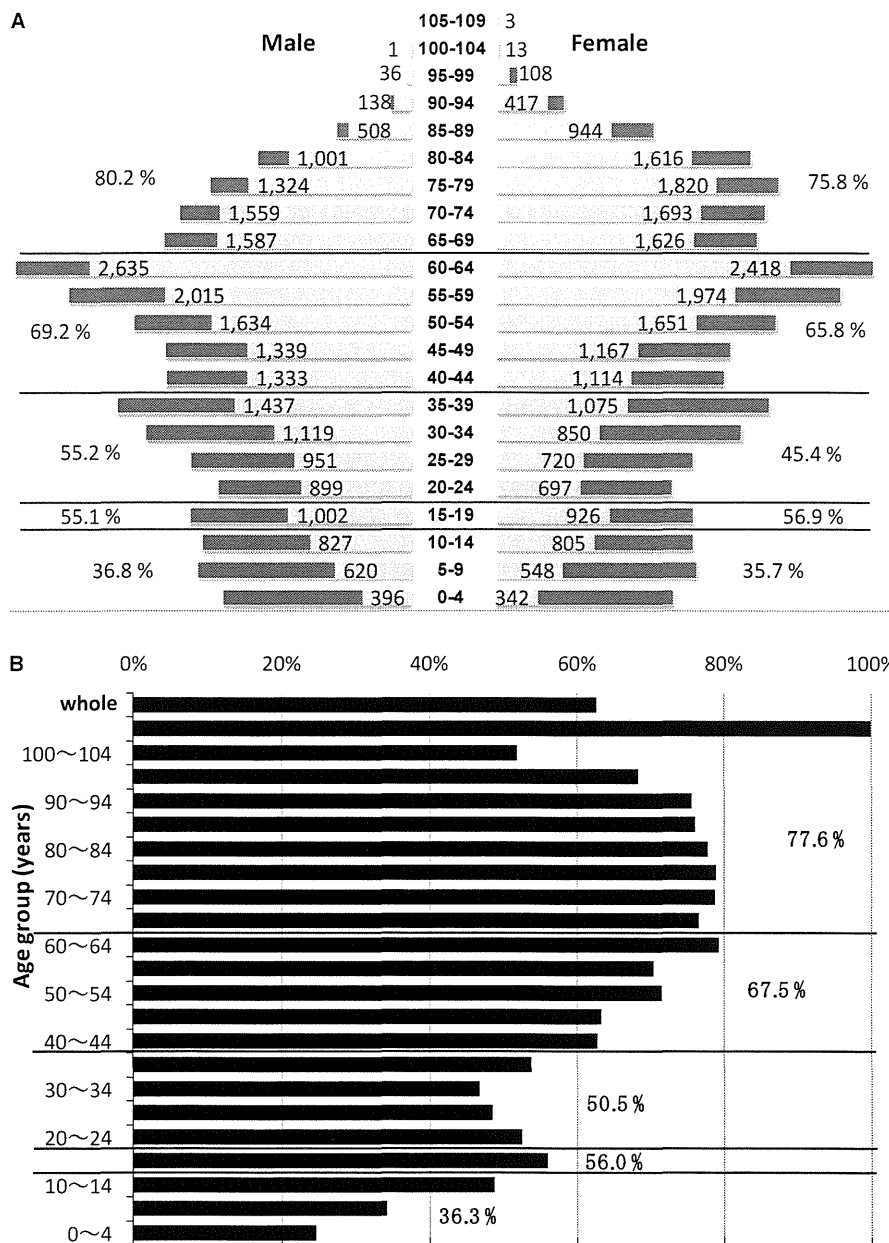   ▄ 396   0-4   342 ▄▄▄

B

Figure 1. (A) Age-dependent decrease in population in Minamisoma city after the Great East Japan Earthquake and Fukushima Daiichi nuclear power plant accident. (B) Retention rate of population according to age group. Population data in Minamisoma on March 29, 2012 were compared with those on March 1, 2011.

Author Contributions: Ishikawa K. and Morimoto S.: Study concept and design. Kanazawa Y.: Acquisition of data. Ishikawa K.: Analysis and interpretation of data. Ishikawa K. and Takahashi T.: Preparation and writing of the letter.

Sponsor's Role: None.

REFERENCES

1. Shibahara S. The 2011 Tohoku earthquake and devastating tsunami. Tohoku J Exp Med 2011;223:305–307.
2. Morimoto S, Iijima K, Kuzuya M et al. Guidelines for non-medical care providers to detect illnesses in elderly evacuees after the 2011 earthquake off the Pacific coast of Tohoku. J Am Geriatr Soc 2011;59:2189–2191.
3. Brumfiel G, Fuyuno I. Japan's nuclear crisis: Fukushima's legacy of fear. Nature 2012;483:138–140.
4. Higaki T, Higaki S, Hirota M et al. Radionuclide analysis on bamboos following the Fukushima nuclear accident. PLoS ONE 2012;7:e34766.
5. Tanimoto T, Yuji K, Kodama Y et al. The long and winding road for the Fukushima nuclear workers. Lancet 2012;379:e34.

ASSOCIATION BETWEEN TEA CONSUMPTION AND DEPRESSIVE SYMPTOMS IN OLDER CHINESE ADULTS

To the Editor: Depression is a common mental illness in elderly adults that is associated with substantial disability,

第 55 回日本老年医学会学術集会記録
〈シンポジウム 1：高齢者 common disease の現状と展望〉

5. 高齢者肺炎の現状と新たな予防策

大類　孝

要　約　抗菌薬の開発が目覚ましい現在でも肺炎による入院および死亡者数は増加傾向にあり，厚生労働省の 2011 年度の疾患別死亡者数の報告によれば，肺炎はついに脳血管障害を抜いて第 3 位になり正に現代病の様相を呈している．また，近年のデータから肺炎で亡くなる方の約 95％ が 65 歳以上の高齢者で占められ，肺炎は高齢者の生命予後を規定する重要な疾患である．高齢者の肺炎の大部分が誤嚥性肺炎であると報告されている．誤嚥とは，雑菌を含む唾液，食物，まれに胃内容物を気道内に吸引することで，結果として生じる肺炎を誤嚥性肺炎という．その危険因子として最も重要なものは，脳血管障害および変性疾患に併発しやすい不顕性誤嚥である．不顕性誤嚥は，大脳基底核病変を有している人に多く認められる．降圧剤の ACE 阻害薬，ドーパミン作動薬のアマンタジン，抗血小板薬のシロスタゾール，漢方薬の半夏厚朴湯，胃運動改善薬のモサプリドなどの不顕性誤嚥の予防薬はハイリスク高齢患者において肺炎の予防効果を有する．また，高齢者肺炎の約 6 割を占める医療・介護関連肺炎（NHCAP）の起炎菌として肺炎球菌が重要であり，肺炎球菌ワクチンは NHCAP の抑制効果を有する．
Key words：誤嚥性肺炎，不顕性誤嚥，大脳基底核病変，嚥下反射，咳反射

はじめに

　高齢者の感染症として呼吸器感染症，尿路感染症，皮膚感染症（褥瘡など）の 3 つが重要であり，これらの中で日常診療上最も遭遇する頻度が高い疾患（common disease）は呼吸器感染症である．さらに，高齢者の呼吸器感染症のうち最も重要な疾患は肺炎である．高齢者の肺炎の大部分が誤嚥性肺炎であると報告されている．誤嚥性肺炎（広義）は，臨床上 Aspiration pneumonia（通常型）と Aspiration pneumonitis（メンデルソン症候群など）に分けられるが，両者はオーバーラップする事もある．本講演では，初めに高齢者肺炎として特に多い通常型誤嚥性肺炎についてその発症機序を解説し，次に発症の危険因子及び診断上の留意点を示し，最後に誤嚥性肺炎の予防策をこれまでの私どものエビデンスを基に解説したい．

誤嚥性肺炎の概念

　諸家の報告により異なるが，高齢者の肺炎のおよそ

Current status of elderly pneumonia and its novel preventive strategies
Takashi Ohrui：東北大学加齢医学研究所高齢者薬物治療開発寄付研究部門

70％ 以上が誤嚥性肺炎であるといわれている[1]．誤嚥（Aspiration）とは，雑菌を含む唾液などの口腔・咽頭内容物，食物，まれに胃内容物を気道内に吸引することで，結果として生じる肺炎を広義の誤嚥性肺炎という．誤嚥性肺炎（広義）は，臨床上おおまかに Aspiration pneumonia（通常の誤嚥性肺炎）と Aspiration pneumonitis（誤嚥性肺障害：メンデルソン症候群も含む）に分けられるが，両者はオーバーラップする事もある[2][3]．Aspiration pneumonia は，不顕性誤嚥（Silent aspiration：無意識のうちに細菌を含む口腔・咽頭分泌物を微量に誤嚥する現象）を基にした細菌性肺炎であり，一方，Aspiration pneumonitis は，意識障害時の嘔吐物（胃液を含む食物）の顕性誤嚥（周囲の者が明らかにそれと認識できる誤嚥）を基にした急性肺障害であり重症度が高い．他に，誤嚥性肺炎（広義）の中にびまん性嚥下性細気管支炎および人工呼吸器関連肺炎が含まれる[4]．

誤嚥性肺炎（通常型）の危険因子

　高齢者の肺炎の多くは Aspiration pneumonia（通常の誤嚥性肺炎）であり，その危険因子として重要なものは不顕性誤嚥を併発し易い大脳基底核の脳血管障害，脳変性疾患および認知症などの脳疾患である．その他の危険因子として，寝たきり状態（bed-ridden condition），

表1　誤嚥をきたしやすい病態

誤嚥をきたしやすい病態（文献5　日本呼吸器学会「医療・介護関連肺炎診療ガイドライン」より一部改変）

1）神経疾患 　脳血管性障害（急性期，慢性期） 　中枢性変性疾患 　パーキンソン病 　認知症（脳血管性，アルツハイマー型） 2）寝たきり状態 　（原因疾患を問わず） 3）口腔の異常 　歯の噛み合わせ障害（義歯不適合を含む） 　口内乾燥 　口腔内悪性腫瘍	4）胃食道疾患 　食道憩室 　食道運動異常（アカラシア，強皮症） 　悪性腫瘍 　胃―食道逆流（食道裂孔ヘルニアを含む） 　胃切除（全摘，亜全摘） 　イレウス，慢性便秘症※ 5）医原性 　抗精神病薬，鎮静薬，睡眠薬 　抗コリン薬など口内乾燥をきたす薬剤 　経管栄養

※ガイドラインに追加

口腔内不衛生，胃食道逆流，抗精神病薬の多剤使用などが重要である（表1）[5]．

誤嚥性肺炎（通常型）の発症機序

　肺炎を繰り返す高齢者の多くは，不顕性誤嚥によって口腔内雑菌を気管や肺に吸引し，肺炎を発症するのではないかと考えられる．実際に当教室の研究によって，高齢の市中肺炎患者でも不顕性誤嚥が高率に認められる事が明らかにされている[3]．さらに，通常，口腔・咽頭内容物が気道内に侵入すると，健常人では激しい咳によってこれを排除しようとする咳反射が働くが，肺炎を繰り返す高齢者ではこの咳反射の低下もしばしば認められる．不顕性誤嚥は，脳血管障害の中でも特に日本人に多い大脳基底核病変を有している人に多く認められる．大脳基底核は穿通枝領域にあり，もともと脳梗塞を起こしやすい部位であるが，その障害はこの部位にある黒質線条体から産生されるドーパミンを減少させる．ドーパミン産生の減少は，迷走神経知覚枝から咽頭や喉頭・気管の粘膜に放出されるサブスタンスP（以下，SP）の量を減少させる[3]．SPは嚥下反射および咳反射の重要なトリガー（引き金）であるため，SPの減少は嚥下反射と咳反射を低下させる．実際に，繰り返し肺炎を起こす高齢者から得られた喀痰中のSPの量は，健常人に比べて減少していた[3]．高齢者肺炎患者では嚥下反射と咳反射の低下が認められ，不顕性誤嚥をベースに肺炎を発症するものと考えられる．

誤嚥性肺炎を疑う愁訴・症状

　高齢者の肺炎の症状としては，青壮年者の肺炎と同様に咳，痰，発熱，呼吸困難が見られるが，高齢患者ではその20〜30%に典型的な症状を欠くケースがあり注意が必要である．すなわち，いつもより元気がない，食欲

低下，意識障害，不穏，せん妄，失禁などの非典型的症状を呈する事もある．食事中のむせ込み，食後の嗄声および繰り返す微熱などは誤嚥を疑う根拠となる．これらの症状に，周囲にウイルスをはじめ原因となる病原体の流行感染もなく，誤嚥の直接確認あるいは誤嚥を起こしやすい基礎疾患の存在が確認されれば本疾患と診断される[4]〜[6]．

誤嚥性肺炎の予防策[3][4][6]

（1）薬物

　誤嚥性肺炎の最良の予防法は，脳血管障害ならびに脳変性疾患の適切な予防ならびに治療であるが，他に，降圧剤のACE阻害薬，ドーパミン作動薬のアマンタジン，抗血小板薬のシロスタゾール，漢方薬の半夏厚朴湯，クエン酸モサプリドなどの不顕性誤嚥の予防薬は肺炎のハイリスク高齢患者において肺炎の予防効果を有する（表2）[3][4][6]．

（2）肺炎球菌ワクチン

　高齢者肺炎の約6割を占めるといわれる医療・介護関連肺炎（NHCAP）の発症にも誤嚥が関与する割合が高く，その重要な起炎菌が肺炎球菌であり検出頻度は5.5%〜41.2%とそれぞれの国で差があるが，わが国では24.7%と報告されている[5]．肺炎球菌は咽頭および口腔の常在菌としてみられ，健常成人の5〜10%，小児の20〜40%から分離される．肺炎球菌ワクチンの効果として欧米での大規模臨床試験では，肺炎球菌性髄膜炎および菌血症などの侵襲性肺炎球菌感染症による入院抑制効果が確認されている．わが国のデータは極めて少なかったが，当教室で高齢者介護施設の寝たきり高齢者に対する肺炎球菌ワクチンの有用性について検討がなされた．その結果，ワクチン投与群では非投与群に比べて総発熱日数の有意な減少と，肺炎による入院回数の有意な

表2　不顕性誤嚥の予防法

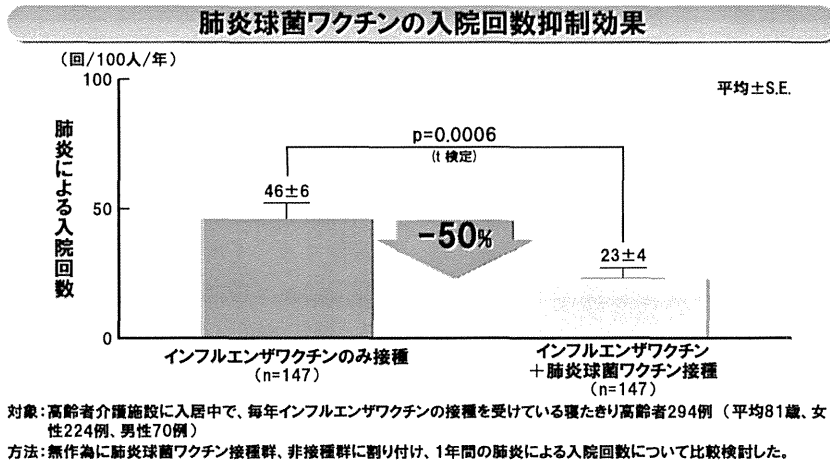| 1）薬物療法 　　a）ACE 阻害薬 　　b）ドーパミンおよびアマンタジン 　　c）シロスタゾール 　　d）半夏厚朴湯 　　e）クエン酸モサプリド	2）口腔ケア 3）食後2時間の座位保持 4）抗精神病薬の使用頻度の抑制

図1　寝たきり高齢者における肺炎球菌ワクチンとインフルエンザワクチンとの併用効果
　　　文献7より作図

減少を認めた（図1）[7]．寝たきり高齢者における肺炎球菌ワクチンの投与は有効で，今後，これらの方々にインフルエンザワクチンに加え肺炎球菌ワクチン投与を積極的に推奨すべきと考える．

（3）その他の予防法

誤嚥性肺炎のその他の予防として，食後2時間の座位保持および抗精神病薬の使用頻度の抑制が有用である．以上の薬剤，ワクチンおよび口腔ケアやリハビリテーションを積極的に組み合わせて用い，不顕性誤嚥からの肺炎を予防する（表2）[3)6)]．

おわりに

近年，MRIによる脳ドック検診の普及に伴い，65歳以上の健常人の約2割に大脳基底核のロイコアライオーシスなどの脳虚血所見が認められると報告されており，このような人では大脳基底核のドーパミンの減少があり，不顕性誤嚥から肺炎発症の可能性が高いと考えられる．肺炎は日本のような超高齢社会ではより身近な疾患であり，再発性かつ難治性である一方かなりの程度予防が可能である事が明らかにされ，今後は，ハイリスク群を早期に同定し積極的に予防策を講じることが重要と考えられる．

日本老年医学会 COI 開示

本原稿に関連し，開示すべき COI 関係にある企業などはありません．

参考文献

1) Teramoto S, Fukuchi Y, Sasaki H, Sato K, Sekizawa K, Matsuse T: High incidence of aspiration pneumonia in community- and hospital-acquired pneumonia in hospitalized patients: a multicenter, prospective study in Japan. J Am Geriatr Soc 2008; 56: 577-579.
2) Marik PE: Aspiration pneumonitis and aspiration pneumonia. N Engl J Med 2001; 344: 665-671.
3) Ohrui T: Preventive strategies for aspiration pneumonia in elderly disabled persons. Tohoku J Exp Med 2005; 207: 3-12.
4) 嚥下性肺疾患研究会：嚥下性肺疾患の診断と治療，ファイザー，東京，2013.
5) 日本呼吸器学会 NHCAP 診療ガイドライン作成委員会編：医療・介護関連肺炎診療ガイドライン 2011，メディカルレビュー社.
6) 大類　孝，海老原孝枝，荒井啓行：高齢者肺炎・誤嚥性肺炎. 日本内科学会雑誌　2010; 99: 2746-2751.
7) Chiba H, Ohrui T, Matsui T, Fukushima T, Sasaki H: Benefits of pneumococcal vaccination for bedridden patients. J Am Geriatr Soc 2004; 52: 1410.

Royal Jelly Prevents the Progression of Sarcopenia in Aged Mice In Vivo and In Vitro

Kaijun Niu,[1,2] Hui Guo,[3] Yinting Guo,[4] Satoru Ebihara,[5] Masanori Asada,[6] Takashi Ohrui,[7]
Katsutoshi Furukawa,[6] Masakazu Ichinose,[8] Kazuhiko Yanai,[9] Yukitsuka Kudo,[10] Hiroyuki Arai,[6]
Tatsuma Okazaki,[8] and Ryoichi Nagatomi[2]

[1]Lab of Nutritional Epidemiology, Department of Nutrition and Food Science, School of Public Health,
Tianjin Medical University, Tianjin, People's Republic of China.
[2]Division of Biomedical Engineering for Health & Welfare, Tohoku University Graduate School of Biomedical
Engineering, Sendai, Japan.
[3]Tianjin University of Sport, Tianjin, China.
[4]Department of Behavioral Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan.
[5]Department of Internal Medicine and Rehabilitation Science, Tohoku University Graduate School of Medicine, Sendai, Japan.
[6]Department of Geriatrics and Gerontology, Division of Brain Sciences, Institute of Development, Aging and Cancer, Tohoku
University, Sendai, Japan.
[7]Division of Geriatric Pharmacotherapy, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan.
[8]Department of Respiratory Medicine, Tohoku University Hospital, Sendai, Japan.
[9]Department of Pharmacology, Graduate School of Medicine, Tohoku University, Sendai, Japan.
[10]Clinical Research, Innovation and Education Center, Tohoku University Hospital, Sendai, Japan.

Address correspondence to Kaijun Niu, MD, Lab of Nutritional Epidemiology, Department of Nutrition and Food Science, School of Public Health,
Tianjin Medical University, 22 Qixiangtai Road, Heping District, 300070 Tianjin, People's Republic of China. Email: nkj0809@gmail.com

Sarcopenia is characterized by the age-related loss of muscle mass and strength. One of the mechanisms of sarcopenia is
the loss in the function and number of muscle satellite cells. Royal jelly (RJ) is a health food used worldwide. To obtain
better digestion and absorption than RJ, protease-treated RJ (pRJ) has been developed. RJ and pRJ have been suggested
to have potential pharmacological benefits such as prolonging the life span and reducing fatigue. Because these effects
may improve sarcopenia and the functions of satellite cells, we examined the effects of RJ or pRJ treatment on the skel-
etal muscles in an animal model using aged mice. In vivo, RJ/pRJ treatment attenuated the decrease in the muscle weight
and grip strength and increased the regenerating capacity of injured muscles and the serum insulin-like growth factor-1
levels compared with controls. In vitro, using isolated satellite cells from aged mice, pRJ treatment increased the cell pro-
liferation rate, promoted cell differentiation, and activated Akt intracellular signaling pathway compared with controls.
These findings suggest that RJ/pRJ treatment had a beneficial effect on age-related sarcopenia.

Key Words: Aged mice—Sarcopenia—Satellite cells—Royal jelly—Insulin-like growth factor-1—Akt signaling.

THE population of people aged 60 and older is currently growing at the rate of 2.6% per year, which is more than twice the rate of growth of the total population in the world (1). In general, aging is accompanied by frailty, functional limitations, and disabilities that interfere with the activities of daily life. These factors reduce the quality of life of the elderly patients and eventually cause their loss of autonomy in daily life. Sarcopenia is the age-related loss of the muscle mass and strength, which causes frailty, functional limitations in daily living, disabilities, and, finally, a higher mortality rate in the elderly patients (2).

Satellite cells are resident myogenic progenitors in the skeletal muscles. They play a central role in the growth and regeneration of the skeletal muscles (3). In response to stimulation, satellite cells form myoblasts, fuse together, and generate new fibers (4). The age-related functional disability and decrease in the number of satellite cells contribute to the development of sarcopenia (5). Thus, maintaining the functions of satellite cells and their numbers may reduce sarcopenia and, furthermore, may improve the regenerating capacity of the skeletal muscles in the elderly patients. However, to isolate satellite cells, specific cell surface markers were not available until recently (6).

Among the factors that stimulate satellite cells, insulin-like growth factor-1 (IGF-1) plays a central role. IGF-1 stimulates satellite cell proliferation, their differentiation into myoblasts, and, finally, their differentiation into myotubes (4). IGF-1 is the most important mediator of muscle growth and repair (7). Furthermore, a recent study suggested the potential of IGF-1 to improve sarcopenia in the elderly patients (7).

1482