likelihood of a Type II statistical error in the published interpretation, by which an actual effect would be undetected by the analysis as conducted.[5]

Although openly critical of studies associated with the pharmaceutical industry, Dr. Finucane fails to note the substantial risk for sponsor bias in AD 2000, which the principal payor for medications in the United Kingdom funded. Dr. Finucane also omits mention of the incomplete status of the proposed revision from the recently renamed National Institute for Health and Clinical Excellence regarding medications for Alzheimer's disease. The text accompanying the revision explicitly states: "Note that this document does not constitute the Institute's formal guidance on this technology. The recommendations made in Section 1 are preliminary and may change after consultation."[6]

Dr. Finucane's assertion of a data/rhetoric mismatch therefore appears to apply quite well to his own criticism of treatments for Alzheimer's disease.

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RESPONSE LETTER TO DR. THOMAS FINUCANE

To the Editor: We appreciate Dr. Finucane's letter regarding our paper published in the Journal of the American Geriatrics Society in January 2005.[1] The methodology of our observational study was reported, at length, in a previous publication.[2] The study was conducted in 135 patients with probable Alzheimer's disease (AD) who used cholinesterase inhibitors (CEIs) for at least 1 year and who were matched using Mini-Mental State Examination scores, age, duration of the dementia symptoms, and education level with a nontreated group, which allowed us to increase the statistical power. Furthermore, the nontreated subjects were enrolled contemporaneously to the treated group. This is particularly important because referral sources vary over time, and patients in the late 1980s and early 1990s did not receive the same medical treatment as those in the late 1990s (e.g., 3-hydroxy-3 methylglutaryl coenzyme A reductase inhibitors, angiotensin-converting enzyme inhibitors). This cohort reflected the experience of a memory clinic during the 1990s, where some subjects with AD were reluctant to initiate any type of treatment.

Although our results were similar to the study conducted by Geldmacher et al.,[3] the methodology was different. Those authors classified the subjects as "minimal-use," "early moderate-use," "delayed-start," or "maximal-use" based on the medication they received during the placebo-controlled and open-label phases and found a delay in nursing home (NH) admission in those classified as "maximal-use" compared with the "minimal-use" group. In our study, all subjects used CEIs from study entry through last contact or death.

We welcome the opportunity to comment on the AD 2000 trial,[4] which had serious methodological problems that make its results difficult to interpret. This study recruited only individuals whose treating physicians were uncertain about the benefits of the treatment, 16% had vascular dementia, and there was a high attrition rate; 48% dropped out during the first 48 weeks, and only 0.7% completed the 3 years of follow-up. The majority of the critical events occurred within the first 48 weeks of the study (49 of 85 (58%) of the NH admissions and 36 of 48 (75%) of the deaths), suggesting that these individuals were severely impaired. By contrast, none of the patients in our study went to a NH during the first year of follow-up, and 25.5% died during a mean follow-up of 3.5 years. Thus, the AD 2000 study had a highly biased sample, and the follow-

up rate was quite low, especially compared to our[1] or Geldmacher et al's study.[3]

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DELAYED REFLECTION PRESSURE WAVE: NEW ASPECTS FOR POSTPRANDIAL HYPOTENSION

To the Editor: Postprandial hypotension (PPH), a potent risk factor for dizziness, syncope, and falls,[1] is common in elderly persons.[2] Recently, a higher incidence of coronary events, stroke, and total mortality was reported in PPH subjects.[3] A significant association has also been reported between PPH and asymptomatic cerebrovascular damage.[4] A prevalence of PPH, defined as a more than 20-mmHg decline in systolic blood pressure (BP), has been estimated at 24% to 36% in elderly persons living in nursing homes.[5,6] In elderly patients with cardiovascular disease and hypertension, the prevalence is thought to be greater.[2,7] Decreased distensibility of the aorta is one of the major mechanisms of elderly hypertension. An augmentation of arterial pressure by early return of the reflection pressure wave is thought to be another underlying mechanism.[8] Recently, a significant association has been reported between the decreased augmented pressure and orthostatic hypotension.[9] In the present study, the relationship between reduced augmented pressure, caused by a delayed return of reflection pressure wave, and PPH was evaluated in healthy, community-dwelling elderly subjects.

The study subjects consisted of nine elderly women and nine young women recruited from the Shimanami Health Promoting Program cohort.[10] All subjects were free from any antihypertensive treatment and had no known history or symptoms of cardiovascular diseases. Brachial BP was measured in the supine position using a cuff-oscillometric device (form PWV/ABI, Colin Co. Ltd., Aichi, Japan). The carotid arterial pressure waveform was measured using a tonometric tracing simultaneously. Carotid BP and the augmentation index (AIx) were then calculated from the pressure waveform.[9] The AIx is the ratio of augmented pressure to pulse pressure. Larger AIx values indicate increased wave reflection from the periphery or an earlier return of the reflected wave as a result of increased arterial stiffness. Pulse wave velocity (PWV) was also determined as the phase contrast between the brachial waveform and the ankle waveform. All measurements were conducted at 5 minutes before and 30 minutes after lunch, and the difference between the two measurements was considered to be the postprandial change.

Table 1 summarizes the postprandial changes in the brachial and carotid hemodynamics. In the elderly subjects, brachial and carotid systolic BP, as well as mean BP and diastolic BP, were significantly lower after lunch. Carotid AIx and arterial PWV, one of the regulatory factors for carotid AIx, were also lower after lunch. The lower AIx indicates the attenuation of augmented pressure by the reflection pressure wave. Although splanchnic blood pooling appears to be an important initial event in the development of postprandial hypotension, the postprandial decline in the augmented pressure may cause further decline in carotid systolic BP.

The postprandial changes in AIx were significantly associated with the reduction of carotid systolic BP in elderly subjects (correlation coefficient $(r) = 0.67$, $P = .049$). No associations were observed in young subjects ($r = 0.07$, $P = .86$), although carotid AIx was significantly lower after lunch (Table 1). In the young subjects, basal and postprandial carotid AIx were negative, which indicates the lack of augmented pressure. The lack of augmented pressure was partially associated with the absence of postprandial changes in systolic BP in spite of the mild to moderate reduction of mean BP and diastolic BP. In the elderly subjects, the higher basal AIx, representing greater arterial stiffness, could be one of the underlying mechanisms of the development of postprandial hypotension.

This is the first study representing the significant association between enhanced arterial stiffness, as well as delayed reflection pressure wave, and postprandial BP decline. These findings contain several important aspects

Table 1. Postprandial Changes in Brachial and Carotid Hemodynamics

Characteristic	Young Subjects (n = 9)			Elderly Subjects (n = 9)		
	Preprandial	Postprandial		Preprandial	Postprandial	
	Mean ± SD		*P*-value	Mean ± SD		*P*-value
Age (range)	21 ± 1 (20–21)			67 ± 3 (64–73)		
Body mass index, kg/m^2	21 ± 2			23 ± 3		
Brachial systolic BP, mmHg	108 ± 2	109 ± 4	.68	122 ± 17	114 ± 18	.01
Carotid systolic BP, mmHg	109 ± 7	111 ± 5	.41	119 ± 21	111 ± 22	.03
Mean BP, mmHg	80 ± 4	77 ± 3	.09	95 ± 14	87 ± 14	.009
Diastolic BP, mmHg	65 ± 2	61 ± 4	.03	76 ± 11	68 ± 11	<.001
Carotid augmentation index, %	−3 ± 13	−19 ± 11	<.001	41 ± 6	32 ± 7	.004
Brachial-ankle pulse wave velocity, cm/sec	1,004 ± 93	890 ± 69	.001	1,421 ± 338	1,343 ± 245	.12
Heat rate, beat/min	57 ± 10	64 ± 9	.01	58 ± 6	62 ± 4	.04

Note: Statistical significance was analyzed using paired *t* test.
SD = standard deviation; BP = blood pressure.

that help further understanding of BP dysregulation in the elderly subjects.

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IS ESTABLISHING AN APPROPRIATE BLEEDING RISK PROFILE IN ELDERLY PATIENTS TREATED WITH LOW-MOLECULAR-WEIGHT HEPARINS NEEDED?

To the Editor: We have read with interest the report by Conde et al.[1] and would like to comment on some interesting points. Briefly, the authors reported a retrospective series of geriatric patients who developed retroperitoneal hematomas after receiving treatment with low-molecular-weight heparin (LMWH). All patients were aged 70 and older. Twelve of 15 cases (75%) received an anticoagulant dose of LMWH (a high dose). Ten patients (66%) received, antiplatelet drugs simultaneously, and seven (50%) had an increased serum creatinine value.

Aging, high dose, renal-function impairment, and concomitant use of drugs affecting hemostasis are the most-classic and best-known risk factors for bleeding in patients receiving LMWH.[2] The authors state that "most of the patients described had a potential risk factor for bleeding"; but it may be more appropriate to say that this series had a high, or perhaps, very high risk profile for hemorrhagic events, although a cumulative risk profile for each patient was not

provided. Thus, the designation as "spontaneous" to retroperitoneal hematomas in their series may be questioned.

Almost half of the cases (7 patients) had elevated serum creatinine level. The presence of cardiovascular risk factors such as hypertension (8 patients) and diabetes mellitus (4 patients) may explain this unexpected high frequency of renal insufficiency, but the authors make no reference to what the creatinine clearance (CrCl) in the other eight patients was. This information is significant because the authors discuss the fact that a "normal serum creatinine value" does not exclude a reduced CrCl. Another study[3] revealed that measured CrCl was low in a series of 26 elderly patients despite a normal serum creatinine level. Other authors have confirmed this.[4,5] Decreased CrCl has been associated with increased hemorrhagic risk.[5] Renal function plays an important role in the clearance of LMWH, and a dose adjustment (up to 65% of the recommended dose) may be necessary in patients with reduced CrCl ($\leq$30 mL/min) receiving enoxaparin to reduce bleeding risk.[6,7] Conde et al.[1] did not indicate whether such dose adjustment was given to their patients.

Finally, the authors state that "anti-Factor-Xa activity should be monitored in high-risk patients receiving LMWH," but this has been questioned previously because bleeding events could appear in patients with anti-Xa level within the therapeutic range.[8] In conclusion, patients with high risk of bleeding receiving LMWH should be identified, and appropriate measures such as close monitoring and dose adjustment should be applied.

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RESPONSE LETTER TO DR. ENRIQUE ANTON

To the Editor: In reply to the letter from Anton et al., we would like to point out the following. We agree that our series had a high risk profile for hemorrhagic events, but these are the standard patients admitted to our department because of cardiovascular disease. Most of our patients receive a combination of low-molecular-weight heparin (LMWH) and antiplatelet drugs if admitted because of acute coronary syndrome. Thus, this profile is frequently found and probably not only in our department. Lately, we are becoming more aggressive in treating elderly patients. As a consequence, we see more complications due to this aggressiveness. In addition, the cases presented are those that had a complication. Thus, it is not a surprise that these are the ones with a higher risk profile.

Alternatively, the designation "spontaneous" is appropriately used to differentiate it from other hematomas that develop after a trauma or an invasive procedure, as mentioned in the Methods part of our article. The reference Anton et al. cite stating that bleeding can occur with a normal anti-Factor-Xa level is only a case report of a 74-year-old man who underwent an invasive procedure.[1] This is not an adequate comparison with our spontaneous hematomas. Creatinine clearance (ClCr) is indeed the most accurate way of measuring renal function, particularly in elderly subjects in whom a "normal" serum creatinine value might represent a significantly reduced ClCr. Unfortunately, as has happened to other authors before, it could not be included in the analysis because of the lack of data for the whole series. The creatinine value reported is the first renal parameter usually available when hospitalizing a patient. Because most patients had a creatinine value of approximately 1 mg/dL, dose adjustment was not performed. It has not been until recently that the Food and Drug Administration has approved revisions to the labeling of enoxaparin sodium injections,[2] specifying that "a dosage adjustment is now recommend for patients with severe renal impairment (ClCr $<$30 mL/min), and no specific dosage adjustment is required in patients with mild or moderate renal impairment." Finally, one of the most important conclusions of our series is to point out again the importance of considering renal function when prescribing LMWH, particularly in the elderly population with a normal creatinine value.

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LOW COMORBIDITY AND MALE SEX IN NONAGENARIAN COMMUNITY-DWELLING PEOPLE ARE ASSOCIATED WITH BETTER FUNCTIONAL AND COGNITIVE ABILITIES: THE NONASANTFELIU STUDY

To the Editor: The nonagenarian population represents an unusual age group at the extreme limits of human life. Nonagenarians are predominantly female (and mostly widows), and an important proportion of them are functionally independent.[1–4] Elderly women are more likely to be disabled than elderly men,[3,4] and functional and cognitive status are worse in nonagenarians with higher comorbidity. The aim of this study was to evaluate the functional and cognitive capacity of a cohort of community-living nonagenarians and to assess the influence of sex and comorbidity on their incapacities.

The NonaSantfeliu study is a population-based study of nonagenarian inhabitants in Sant Feliu de Llobregat (Barcelona, Spain). All 305 inhabitants aged 90 and older were contacted. Sixty-one percent replied (n = 186). Participants did not differ significantly from nonparticipants according to age or sex. Institutionalization (n = 49) was the only exclusion criterion.

A geriatric assessment was conducted, and comorbidity (Charlson Comorbidity Index) and sociodemographic data were evaluated. The Barthel Index (BI) of basic activities of daily living (ADLs) and the Lawton and Brody scale for instrumental ADLs were measured. The Spanish version of the Mini-Mental State Examination (MEC),[5] with a score up to 35 ($\leq$23 indicates cognitive impairment), the short version of the Mini Nutritional Assessment questionnaire (short-MNA),[6] and the Barber test (assesses social risk)[7] were also used. Near visual acuity (Snellen chart) and hearing competence (Whisper test) were evaluated.[8] Information on hypertension, diabetes mellitus, dyslipidemia, heart failure, stroke, ischemic cardiopathy, chronic obstructive pulmonary disease, and chronic drug prescription was collected. Nonincapacitated nonagenarians (successful aging) were considered to be those aged 90 and older scoring 91 or more on the BI and 24 or more on the MEC. They were compared with the rest. Normally distributed continuous variables are reported as means ± standard deviations. Categorical variables are reported as proportions. The Student *t* test, the chi-square or Fisher exact, and multiple logistic regression analysis were performed. $P<.05$ indicated statistical significance

The sample consisted of 99 women (72%) and 38 men; mean age was 93.1 ± 0.7. There were 115 (84%) widowed, 15 (11%) married, and seven (5%) unmarried. Eighteen percent had dementia—25 of the 114 in the unsuccessful aging group. Fifty-six (41%) had a hearing impairment; 51 (37%) had a vision impairment, and 24 had (17.5%) combined sensorial impairment. The mean values of geriatric assessment were Lawton and Brody scale 2.5 ± 2.3, BI 65.3 ± 23.0, MEC 22 ± 11, short-MNA 11.2 ± 2.4, and Barber test 3.0 ± 1.5. The mean Charlson Comorbidity In-

Table 1. Characteristics of the Subjects

Characteristic	Successful Aging (n = 23)	Unsuccessful Aging (n = 114)	*P*-value
Age, mean ± SD	93.1 ± 4.4	93.1 ± 4.5	.86
Female, n (%)	11 (47)	88 (77)	.009
Previous smoker, n (%)	6 (26)	16 (14)	.26
Barthel Index, mean ± SD	96.3 ± 2.2	59.1 ± 27	<.001
Spanish Mini-Mental State Examination score, mean ± SD	31.4 ± 5	20.7 ± 11	<.001
Lawton-Brody index, mean ± SD	5 ± 2.2	2 ± 2	<.001
Mini Nutritional Assessment questionnaire (short form) score, mean ± SD	12. ± 1.1	10.9 ± 2.5	.005
Barber questionnaire, mean ± SD	1.4 ± 0.7	3.3 ± 1.4	<.001
Hearing impairment, n (%)	9 (39)	47 (41)	.96
Decreased visual acuity, n (%)	4 (17)	47 (41)	.03
Combined sensorial impairment n (%)	0	24 (21)	.01
Charlson Comorbidity Index, mean ± SD	0.4 ± 0.9	1.5 ± 1.9	.007
Hypertension, n (%)	12 (52)	69 (60.5)	.57
Diabetes mellitus, n (%)	2 (8.5)	17 (15)	.52
Dyslipidemia, n (%)	2 (8.5)	21 (18.5)	.36
Previous stroke, n (%)	1 (4)	26 (23)	.04
Ischemic heart disease, n (%)	3 (13)	12(12.5)	.71
Chronic obstructive lung disease, n (%)	4 (17)	17 (15)	.74
Heart failure, n (%)	3 (13)	29 (25.5)	.28
Number of drugs taken, mean ± SD	3.4 ± 3	4.2 ± 2.5	.17
More than three drugs, n (%)	10 (43)	66 (58)	.29

SD = standard deviation.

dex was 1.43 ± 1.7. Fifty-nine percent had hypertension, 14% diabetes mellitus, 17% dyslipidemia, 11% ischemic cardiopathy, 25% heart failure, and 15% chronic obstructive lung disease and 20% had suffered a stroke. Patients were taking an average of 4.1 ± 2.4 drugs, and 76 patients (55%) took more than three drugs. The differences between the two groups are displayed in Table 1. Using multiple logistic regression analysis, successfully aging nonagenarians were significantly associated with male sex (odds ratio (OR) = 4.23, 95% confidence interval (CI) = 1.58–11.38; $P = .004$) and with lower comorbidity (OR = 1.94; 95% CI = 1.13–3.35; $P = .01$).

Physical and cognitive dysfunction represent two of the most dreaded states in older people because they can lead to dependency and social isolation. In our study, in the more-successful aging group, a significant predominance of men was found. These results confirm previous data showing greater female incapacity within this age range.[3,4] More than differences in incidence, the higher prevalence of disability in women may explain the greater survival rate of women with severe disability.[3] Global comorbidity, evaluated using the Charlson Comorbidity Index, was higher in the group with worse functional and cognitive capacity. This unsuccessful aging group had a higher prevalence of patients who had previously had a stroke, but this did not attain significance in multivariate analyses. Loss of auditory acuity and sensory deprivation can affect some ADLs.[9] The better-aging group had a lower percentage of visual and combined sensory deficits, not significant in the multivariate analysis.

In the oldest old, several known predictors of mortality, such as sociodemographic factors, smoking, and obesity, have lost importance, but high disability level and poor physical and cognitive performance are useful for predicting mortality.[10]

This study has several limitations. We examined the association between current diseases and disability but did not evaluate previous disability. The small sample size, especially because of the few men included, may suggest some careful ratification to the sex differences found.

In conclusion, male nonagenarians with low comorbidity probably undergo more successful aging than do women or those with high comorbidity.

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MARKED ELEVATION OF THE ST SEGMENT IN CEREBELLAR HEMORRHAGE

To the Editor: Electrocardiographic changes occur most frequently in patients with acute cerebrovascular disease,[1] and the sympathetic nervous system appears to be important in the pathogenesis of these electrocardiographic changes. Excessive sympathetic nervous activity can result from increased intracranial pressure.[2] Hydrocephalus often complicates cerebellar hemorrhage, which increases intracranial pressure, because of mass effects on the fourth ventricle. Electrocardiographic changes with subarachnoid hemorrhage have often been found, but those with cerebral hemorrhage are rare.[3,4] There has not been any previous report of electrocardiogram (ECG) showing marked elevation of the ST segment in a patient with cerebellar hemorrhage.

CASE REPORT

The patient, a 90-year-old female, was brought to our hospital by ambulance November 14, 2003, because of chest

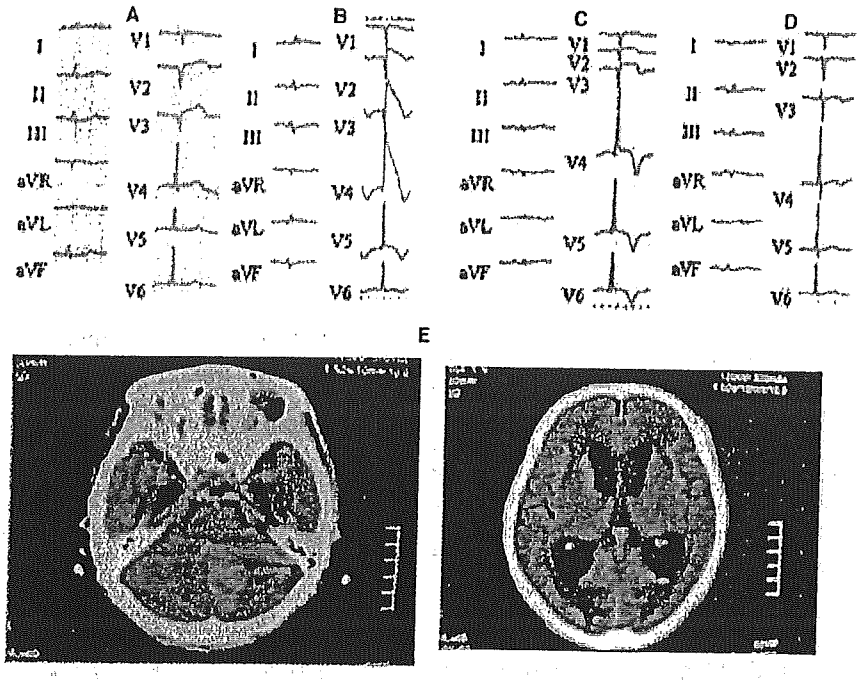

Figure 1. A. Electrocardiography on admission. B. Electrocardiography 1 day after admission. C. Electrocardiography 2 days after admission. D. Electrocardiography 1 month after admission. E. Cranial computed tomography scan 1 day after admission demonstrated cerebellar hemorrhage and hydrocephalus.

pain with nausea and vomiting. She did not have a history of chest pain or other contributory medical history. On admission, she remained completely awake, blood pressure was 173/103 mmHg, and pulse rate was 75 beats/min. Her creatine phosphokinase (CPK) level was 111 IU/mL (normal rang: 43–165IU/L). ECG on admission showed Q waves in V1 and V2 leads (Figure 1A). Transthoracic cardiac ultrasonography showed reduced left ventricular wall motion in the anteroseptal area.

One day after admission, she showed a decreased level of consciousness. Her blood pressure was 155/92 mmHg and pulse rate was 98 beats/min. ECG demonstrated marked elevation of the ST segment in V2, V3, and V4 leads (Figure 1B). Cranial computed tomography (CT) scan demonstrated cerebellar hemorrhage and hydrocephalus (Figure 1E). Two days after admission, cranial CT scan showed improved hydrocephalus, and ECG showed negative T waves in the V4, V5, and V6 leads (Figure 1C). The patient was alert. The maximal CPK level was 237 IU/mL 24 hours after the elevation of the ST segment.

One month after admission, cranial CT scan did not show hydrocephalus. ECG findings normalized except for the negative T waves in the V3 and V4 leads (Figure 1D). Her stay was not complicated by arrhythmia or congestive heart failure. Left ventricular wall motion in the anteroseptal area was reduced.

DISCUSSION

In this case, the patient developed cerebellar hemorrhage on admission, and ECG had not shown elevation of the ST segment. One day after admission, CT demonstrated a mass effect in the fourth ventricle, and ECG showed marked elevation of the ST segment. There has not previously been any reported association between marked elevation of the ST segment and hydrocephalus due to cerebellar hemorrhage.

In this case, ECG showed marked ST segment elevation. ECG changes have been described after various types of cerebrovascular accidents. Most ST segment abnormalities have involved depression of the ST segment or inverted T waves, whereas elevation of the ST segment has been rare.[3,4] ECG abnormalities after cerebrovascular events have been associated with increased intracranial pressure and have not always involved ST segment elevation.[5]

Electrocardiographic changes in this case were similar to those of myocardial ischemia.[6] Transient left ventricular wall motion abnormalities, such as stunned myocardium, have been reported in myocardial injury, triggering conditions such as emotional exposure, physical stress, and cerebrovascular disease.[7] The mechanism of this myocardial injury has been postulated to be multiple vasospastic angina pectoris due to enhanced sympathetic activities. Coronary angiography was not performed in this case because the patient was elderly. In this patient, excessive sympathetic activity, inferred from the pulse rate increase, might have contributed to the triggering of marked elevation of the ST segment. Variant angina pectoris might cause myocardial ischemia, resulting in a transient increase in coronary vasospasm, which might be due to excessive sympathetic nervous activity induced by increased intracranial pressure.

The increased intracranial pressure due to hydrocephalus associated with intracranial hemorrhage might induce electrocardiographic abnormalities and cardiac damage and be associated with severe cardiac arrhythmia and con-

gestive heart failure. Therefore, careful electrocardiographic monitoring might be required after intracranial hemorrhage. In elderly patients, when marked ST elevation is present on ECG, we must differentiate acute cerebrovascular disease.

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NOROVIRUS OUTBREAKS IN NURSING HOMES

To the Editor: Some clinicians may not be familiar with recent recommendations developed by public health officials after experiences controlling norovirus (formerly known as "Norwalk-like viruses") outbreaks on cruise ships. Noroviruses are also a common cause of gastrointestinal outbreaks in nursing homes.[1–3] This illness is known as "stomach flu" or "winter vomiting disease," although it tends to be associated more with diarrhea in older patients.[1] The incubation period ranges from 11 to 48 hours, with disease duration from 12 to 60 hours.[1,4] Infection does not generally appear to confer long-term immunity.[1,5] Norovirus illness typically has an abrupt onset and is characterized by nausea, vomiting, nonbloody diarrhea, and variable systemic symptoms including fatigue, myalgia, headache, chills, and fever. (Residents are often not febrile.)[1,2,4,6] Bismuth subsalicylate has been demonstrated to provide symptomatic treatment and reduce the duration of abdominal cramps and gastrointestinal symptoms in adults in an experimental study.[7] Affected individuals should be considered infectious and isolated/separated for 2 to 3 days after their last symptoms.[8] The disease is usually self-limited but in the frail elderly may be associated with life-threatening dehydration and mortality.[9] If transmission of this illness within a nursing home is suspected, public health officials should be contacted to facilitate diagnostic testing and consult regarding control measures.

Transmission may be person-to-person after contact between stool or vomit and mouth, or may be food-borne.[1,4] Sharing bathrooms is a risk factor for transmission.[6] Affected residents should have a private bathroom or commode. Practitioners may not be aware of transmission via aerosolization, especially during vomiting in a confined space.[4,6,8,10] In one well-documented report, airborne transmission occurred in a restaurant after a single episode of vomiting. Attack rates showed a clear inverse relationship with distance from the vomiter.[4] In other studies, exposure to nearby vomiting (6 feet) or sharing a cabin with someone who vomited in the cabin was a significant risk factor for acquiring gastroenteritis.[6,10] Aerosolization may also occur when caregivers clean toilets, clean up body fluid spills, vacuum carpets, strip linen from beds, or manipulate soiled laundry.[1,9] Therefore, appropriate secretion precautions include contact precautions, including the use of gowns, gloves, and masks, especially if the resident is vomiting or when cleaning areas contaminated with feces or vomit.[1,8,9] Because of the high attack rates that may be seen during norovirus outbreaks, strong consideration should be given to restricting and controlling visitors, interactions between outbreak units and nonoutbreak units, and separating staff.[8]

Clinicians may not be familiar with the fact that the usual quaternary ammonia disinfectants do not provide adequate disinfection.[3,8] Noroviruses are small, nonenveloped ribonucleic acid viruses that are not reliably inactivated by quaternary ammonia compounds.[3] Rather, a fresh 10% bleach solution should be used. Two other products, potassium peroxomonosulfate and parachlorometaxylenol, have demonstrated experimental efficacy against feline caliciviruses.[8,9] Practitioners are advised to consult local public health officials regarding the use of these alternate products. Outbreaks in hotels and on cruise ships have occurred that involve successive cohorts of guests, implying that contamination of the environment may be a factor in transmission.[5,6] Because small numbers of viral particles may be infectious, significantly enhanced environmental cleaning should be emphasized. Some authorities recommend increasing the frequency of cleaning to two times per day, especially for frequently touched objects such as door handles, light switches, faucet handles, and physical therapy equipment.[8] Finally, thorough steam cleaning or disinfection with bleach is recommended for contaminated carpets and upholstery.[5,8,9] In vitro studies with a related feline virus indicate that ethanol fails to completely inactivate the virus; an antiseptic "soap" with friction and running water should provide better disinfection.[3]

Medical directors will need a "case definition" to facilitate staff's ability to track the outbreak. A sensitive and specific case definition is optimal. One definition

to consider: "Acute onset of vomiting or nonbloody diarrhea lasting at least 24 hours that could not be explained by another cause (i.e., medications, pre-existing pattern or disease)."[2]

It is important for physicians to recognize outbreaks of gastrointestinal illness caused by noroviruses and to know that the usual quaternary ammonia disinfectants and alcohol hand gels do not provide optimal antimicrobial activity and that the pathogen may be transmitted by aerosolization, especially during vomiting, requiring the use of masks. Caregivers should avoid mechanical events that may produce aerosolization of body fluids. Practitioners are advised to contact local public health authorities when outbreaks are suspected.

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SONOGRAPHY AND VISUALIZING ROTATOR CUFF INJURIES IN OLDER PEOPLE

To the Editor: A 63-year-old man was seen in June 2004 for complaints of pain in the right shoulder, neck, and low back regions. He denied any trauma or a specific incident to be contributory. Physical examination of the spine was consistent with impaired motion of the cervical and lumbar segments in all directions. Shoulder motions were normal, and resisted tests were negative, but the biceps muscles were suspected to have ruptured bilaterally because of their abnormal configuration. Radiographs of the patient uncovered cervical/lumbar spondylosis with C3-C4 and L5-S1 anterolisthesis and degenerative changes in the shoulder joints. Ultrasonography (US) of the shoulders revealed fluid in the left acromioclavicular joint, absent right supraspinatus tendon and thin subscapularis tendon, and absent bicipital tendons (long head) bilaterally. Because his shoulder functions did not seem to be significantly affected, he was treated with nonsteroidal antiinflammatory drugs and isometric exercises for strengthening the shoulders, neck, and low back.

He was seen again in January 2005 for acute exacerbation of right shoulder pain. He described the pain to have ensued nearly 1 week before when he was doing garden work (cutting roses). He added that he had otherwise been well with the aforementioned treatment. On physical examination, a gross discoloration (yellow-blue) was observed on the anteromedial side of the right arm; shoulder mobility was again normal with negative resisted tests. Considering the place of discoloration and his previous history of bicipital tendon rupture, a likely diagnosis of a new rupture pertaining to the short head of biceps muscle was suspected. Repeat US of the patient depicted right subscapularis tendon rupture in addition to previous US findings. He was treated conservatively.

More than one third of people aged 60 and older suffer significant rotator cuff (RC) disease.[1] The underlying etiology is multifactorial but is often related to the tensile strength of the RC tendon and the amount of force applied. History of an acute traumatic event is common in patients younger than 60, but as the senescent changes of the RC progress, less force is needed to precipitate failure of the tendon. Older patients may present with a gradual onset of shoulder pain, often affecting them at rest and disturbing their sleep, with clinical evidence of a full-thickness RC tear but without a clear history of antecedent trauma.[1] In addition, depending on the size of the tear, some patients may also develop symptoms (e.g., decreased daily activity) after a few years of silent disease course.[2]

Radiographic findings consistent with degeneration (sclerosis, osteophytic spurs, subchondral pseudocysts on the greater tuberosity or the acromion process) correlate with the presence of a tear,[3] but US, magnetic resonance imaging, and arthrography have proven to provide better estimates of the rotator cuff pathology.[4] Nonetheless, imaging findings must be considered in a clinical context and should never be used as the sole basis for a surgical decision, although the critical amount of intact tendon or muscle that is necessary to maintain normal range of motion and strength has not been clarified.

This case implies some interesting points. The patient had bilateral chronic rupture of the biceps tendon and a recent unilateral subscapularis tendon rupture with pain but no functional loss. Isolated rupture of the subscapularis tendon without supraspinatus tendon pathology is rare; moreover, a hematoma would normally be expected to

ensue nearby its insertion. At first glance, the injury seemed to be a biceps rupture, but further sonographical evaluation discovered the pathology. Keeping in mind that age of 65 and older[5] and the concomitance of biceps tendon ruptures, especially in women,[1] have been associated with an inferior postoperative outcome, treating these patients conservatively would not be unfounded. Finally, US seems to be convenient and promising for better diagnosing this group of patients with regard to their commonly seen shoulder problems.

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SUBCORTICAL VASCULAR DISEASE DETECTED WITH COMPUTED TOMOGRAPHY AND 1-YEAR PHYSICAL DECLINE IN HIGH-FUNCTIONING OLDER ADULTS

To the Editor: In their article recently published in the *Journal of the American Geriatrics Society,*[1] Rosano et al. found that subclinical structural brain abnormalities (i.e., ventricular enlargement, white matter hyperintensities, subcortical and basal ganglia small brain infarcts) in high-functioning older adults can increase the risk of developing physical disabilities and declining in motor performances.

Because of the clinical relevance and the prognostic implications of this topic, we decided to investigate the risk of declining motor performance in a similar population using a low-cost neuroimaging tool (computed tomography (CT) of the brain) to detect subcortical vascular disease (SVD, white matter hyperintensities, subcortical and basal ganglia small brain infarcts)

Between January 2003 and January 2004, 349 patients were consecutively admitted to our Rehabilitation and Aged Care Unit after orthopedic surgery (n = 82) or as a

Table 1. Characteristics of 203 Elderly Patients Stratified by Functional Change from Discharge to 12-Month Follow-Up

Variable	Functional Status at 12 Months		
	Improved/Unchanged (n = 104)	Worse (n = 99)	*P*-value*
Age	76.1 ± 5.7	80.3 ± 5.5	<.005
Female, n (%)	84 (80.8)	75 (75.8)	.77
Living alone at home before hospital admission, n (%)	57 (54.8)	57 (57.6)	.77
Body mass index, kg/cm^2, mean ± SD	25.2 ± 4.9	24.4 ± 4.2	.20
Charlson Comorbidity Index, mean ± SD	2.1 ± 1.4	2.8 ± 1.6	.002
Diabetes mellitus, n (%)	15 (14.4)	18 (18.2)	.56
History of coronary heart disease, n (%)	7 (6.7)	11 (11.1)	.32
Mini-Mental State Examination score, mean ± SD (range 0–30)	24.6 ± 3.2	22.7 ± 5.0	.002
Geriatric Depression Scale score, mean ± SD (range 0–15)	5.4 ± 3.5	7.0 ± 3.6	.002
Barthel Index 1 month before hospital admission, mean ± SD (range 0–100)	93.0 ± 8.4	90.1 ± 8.8	.01
Barthel Index at hospital admission, mean ± SD (range 0–100)	77.2 ± 18.9	75.3 ± 20.5	.48
Barthel Index at hospital discharge, mean ± SD (range 0–100)	93.8 ± 6.1	91.8 ± 6.0	.02
Drugs at hospital discharge, n, mean ± SD	5.2 ± 1.5	5.0 ± 1.9	.47
Subcortical vascular disease, mean ± SD	20.3 ± 16.7	26.4 ± 15.9	.009

*Significance using *t* test or chi-square.
SD = standard deviation.

consequence of stroke (n = 25), Parkinson's disease (n = 31), and gait and balance disorders (n = 211). All underwent a multidimensional assessment including sociodemographics (age, sex, living conditions), nutritional and somatic status (body mass index, Charlson Index, number of drugs on admission and at discharge, and presence of diabetes mellitus and ischemic heart disease), cognitive status (Mini-Mental State Examination (MMSE)), affective disorders (Geriatric Depression Scale (GDS)), and functional status (Barthel Index). The Barthel Index from 1 month before admission was compared with the Barthel Indexes at admission and discharge. The presence and severity of cortical, white-matter, and deep subcortical lesions and of leukoariosis were assessed on CT film with a standardized visual rating scale, which has been previously validated and used in elderly patients.[2,3]

Of the 349 patients, 217 (62.2%) had a Barthel Index at discharge greater than 80/100, indicating a high-functioning level. At 12 months, 14 (6.5%) of these subjects had died. For subjects who were still alive, information about two specific items of Barthel Index—12-month transfer and walking abilities—was gathered using phone interviews. A sumscore for these items was created to measure mobility and walking performance at discharge and at 12 months, and the difference between the discharge and 12-month sumscores was computed; patients were therefore stratified in two groups according to change in functional status (difference in sumscore <1 denoted improvement or stability, whereas difference in sumscore ≥ 1 denoted decline). Table 1 shows that SVD ($P = .009$); age ($P < .005$); comorbidity (Charlson Index, $P = .002$); and cognitive (MMSE, $P = .002$), affective (GDS, $P = .002$), and functional status (Barthel Index before admission, $P = .01$, and Barthel Index at discharge, $P = .02$) were significantly different in the two groups.

Our findings support those of Rosano et al. that SVD, in addition to other typical variables of geriatric assessment, is associated with functional decline in high-functioning older patients. Alternatively, they suggest that brain CT may be useful in predicting long-term outcomes and accurate. In rehabilitation, barriers to widespread neuroimaging use include costs and availability of diagnostic tools.[4] From this perspective, CT may be viewed as a valid option.

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SUBJECTIVE ESTIMATES OF COGNITIVE IMPAIRMENT IN OLDER SURGICAL PATIENTS: IMPLICATIONS FOR GIVING INFORMED CONSENT

To the Editor: Assessing cognitive function in older patients is of prime importance if consent for invasive procedures is being sought. Although cognitive impairment is prevalent in the older inpatient population, health professionals tend to underrecognize it.[1] One important ethical and legal consequence of cognitive impairment may be a reduction in the capacity to give consent.

Objective rating scales such as the Abbreviated Mental Test (AMT) are often used to screen for cognitive impairment. Although cognitive impairment does not preclude the capacity to give consent in a particular situation, recognizing impairment should raise the possibility that capacity needs to be specifically assessed.[2] The UK Department of Health guidelines state that this evaluation of capacity is

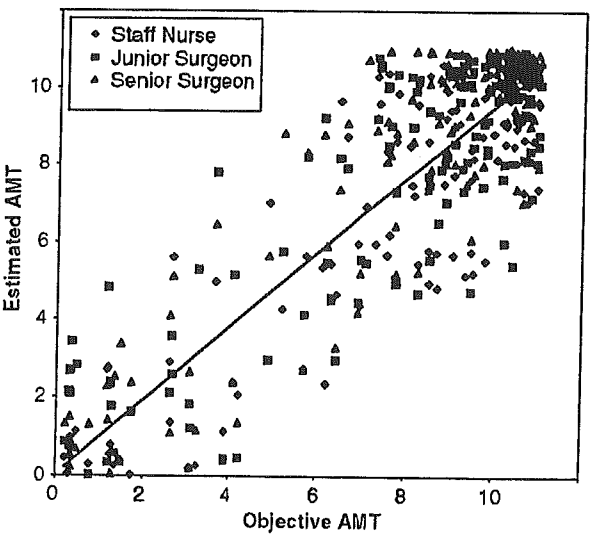

Figure 1. Scatterplot of actual Abbreviated Mental Test (AMT) score versus predicted AMT score. (Diagonal line indicates perfect agreement; random noise was added to the data before plotting to avoid points being plotted on top of each other.)

essential before an invasive procedure. In England, there is a standardized "Consent Form 1" used as evidence of a patient's consent. A separate "Consent Form 4" exists when an adult patient is determined not to have the capacity to give or withhold consent.[3]

This report examines how accurately staff on surgical wards can detect cognitive impairment if the formal assessment of capacity is not undertaken and how these subjective judgments may influence the process of obtaining consent.

METHODS

One hundred fifty-one subjects aged 65 and older consecutively admitted to general and orthopedic surgical wards were approached to participate (age range 65–98, mean 78, median 80). Twelve patients whose cognitive function had already been objectively assessed using an AMT (or other test) were excluded, leaving 139.

Three groups of health professionals involved in the care of each patient (staff nurse, junior surgeon, senior surgeon) were asked to subjectively estimate the cognitive function of their patient based on routine clinical contact. Professionals were given copies of the AMT questions on which to base their estimations. Subjective estimates were blinded. A single rater (DD) then objectively evaluated the cognitive function of each participant using performance on the AMT. A score of 0 to 7 was taken to indicate cognitive impairment. All estimates and evaluations took place on the same working day. The chairperson of the local research ethics committee approved the protocol. Statistical analyses were conducted using Stata (StataCorp., College Station, TX).

RESULTS

Subjective estimates were plotted against objective AMT scores to demonstrate the level of agreement between each evaluation (Figure 1). Weighted kappa values quantify this as: staff nurses 0.62, junior surgeons 0.61, and senior surgeons 0.66. Overall, no staff group was significantly better at estimating the cognitive function of patients.

Forty-eight of 139 (35%) participants had an AMT score between 0 and 7. Of these, staff nurses incorrectly labeled eight (17%) patients as cognitively intact. Of the 59 patients judged by nurses to have cognitive impairment, 19 (32%) had AMT scores of 8 or more. Similarly, junior surgeons incorrectly labeled 11 of 48 (23%) as cognitively intact and 15 of 52 (29%) cognitively impaired. Senior surgeons judged 13 of 48 (27%) and 10 of 45 (22%) incorrectly as cognitively intact and impaired, respectively. For those participating, 68 procedures were performed, with consent being documented using Consent Form 1 in 64 cases. Of these, 52 (81%) had AMT scores between 8 and 10. Based on AMT score, 12 (19%) procedures were performed in patients whose cognitive impairment had not been determined and so may have lacked capacity. In these cases, Consent Form 4 may have been more appropriate.

DISCUSSION

This study demonstrates that guessing at a patient's cognitive function commonly leads to error, and this can result in procedures being undertaken without proper legally valid consent.

Across the full range of cognitive function, comparison of actual and estimated AMT scores indicates good levels of agreement, but the estimates are less accurate when only patients with actual AMT scores of 0 to 7 are compared (staff nurses 0.56, junior surgeons 0.50, senior surgeons 0.52). Furthermore, for patients with AMT scores of 3 to 7, staff predictions were poor (staff nurses 0.30, junior surgeons 0.25, senior surgeons 0.28). Although staff found it easier to recognize extremes of cognitive functioning, when a patient's degree of cognitive impairment was intermediate, estimates were only slightly better than that expected by chance. This is in keeping with previous findings in medical patients.[4]

Any surgeon obtaining consent is at risk of misjudging a patient's capacity if cognitive function is not specifically evaluated. This possibility is highest when moderate impairment is present and may result in patients undergoing procedures without their capacity to consent being properly assessed.

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ANTICOAGULANT USE FOR ATRIAL FIBRILLATION IN OLDER PEOPLE

To the Editor: We read with interest the Brophy et al.[1] article, published in the July issue, on anticoagulant use for atrial fibrillation (AF) in older people.

The attitude of physicians toward anticoagulation use in older people over the past decade is an interesting study.[2] In a 1989 survey based in New Hampshire (with a response rate of 49%), Chang et al.[3] demonstrated that 34.6% of internists would elect to use warfarin in a 73-year-old man with new-onset AF. In a study based in New York, Kutner et al.,[4] in 1991, found that warfarin was used in only 18.3% of subjects aged 65 and older with AF of any cause. By

1995, McCrory,[2] in a vignette-based questionnaire survey that used a national sample with a response rate of 38%, showed that 63% of the respondents would choose to use anticoagulation in subjects aged 75 and older with AF and left atrial enlargement, but there is a difference between physicians' attitude and practice (based on chart reviews) on the use of anticoagulants (51% vs 24%).[5] Dr. Brophy's article confirms that advancing age is a deterrent to the use of anticoagulation in Department of Veterans Affairs (VA) subjects.

There are a few critiques of the article. Both the cohorts had variable follow-up that was dependent on the time of encounter with the MUSE database and the number of encounters in the VA clinical database. In addition, the risk factor identification appeared to select incidence as well as prevalence of disease. The exclusion of 747 subjects because of the presence of AF on electrocardiogram but not in the *International Classification of Diseases, Ninth Revision*, codes is of concern. It points to the problems with database analysis, and the sensitivity analysis with the addition of this group to the anticoagulant-free group would dramatically alter the rate of anticoagulation. The use of any prescription of warfarin as a marker of anticoagulation leaves the question of intensity and adequacy of the anticoagulation unanswered. The database fails to capture the fact that age may be a marker of multiple comorbidities and physicians' perception of risks and benefits. The proportional increase in rates of anticoagulation in this study as the numbers of risk factors increases in both cohorts despite advancing age is a hopeful sign.

In conclusion, we believe that this study has several limitations and results could change with a different study. Further in-depth studies examining risks and benefits of anticoagulation and barriers to anticoagulant use will help in reducing reluctance to use them in older people with AF.

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RESPONSE LETTER TO DR. PATEL

To the Editor: Patel raises a number of concerns about the design of our study. Using administrative and patient-care databases, we identified subjects with atrial fibrillation (AF), identified risk factors (comorbidities) for stroke, and found that advancing age was a deterrent to warfarin administration for stroke prevention. The case definition of AF required both a healthcare encounter with a diagnostic code (International Classification of Diseases, Ninth Revision (ICD-9)) for AF as well as a recorded electrocardiogram (EKG) tracing for this arrhythmia. A medical record–based validation substudy demonstrated 97% accuracy of the diagnosis in the cohort. Patel noted that 747 potential subjects were excluded because ICD-9 diagnostic data did not confirm the EKG finding and suggest that inclusion of these individuals might have "dramatically" changed the results. Because a validation substudy of these excluded subjects confirmed AF in only 26% of the sample (unpublished data), we felt it prudent to exclude them from further analyses.

Patel makes note of potential weaknesses in our method of ascertaining comorbidities and further point out that the "use of any prescription of warfarin as a marker of anticoagulation leaves the question of intensity and adequacy of the anticoagulation unanswered." We agree with these concerns and note only that the available data limit the methods used and the questions that can be addressed in a nonexperimental (database) study. Such studies are rarely comprehensive or definitive but rather inform in an exploratory or confirmatory capacity. Despite this, we feel that our study clearly demonstrates that, in clinical practice, age is a deterrent to anticoagulant use for stroke prevention in AF.

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Nocturnal Hypoxia Is Associated With Silent Cerebrovascular Disease in a High-Risk Japanese Community-Dwelling Population

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Background: Sleep-disordered breathing (SDB) is recognized as a risk factor for cerebrovascular disease. The objective of this study was to investigate the relationship between nocturnal hypoxia and silent cerebral infarct (SCI) in the general population.

Methods: In the 2001 annual health check in Nishiarita, Japan, 170 individuals at high risk were screened who met more than three of the following criteria: high blood pressure, hypercholesterolemia, left ventricular hypertrophy by electrocardiography, hemoglobinA_1c >6.5%, proteinuria, central obesity, heavy smoking habit, heavy drinking, and family history of stroke. Overnight pulse oximetry, brain magnetic resonance imaging, and carotid/cardiac ultrasonography were performed in 146 (mean age 67.4 ± 9.0 years) of the 170 individuals in whom pulse oximetry was successfully performed.

Results: Subjects were classified into a nocturnal hypoxia group (n = 36) and a nonhypoxia group (n = 110) based on a 3% oxygen desaturation index (ODI) 5.6 times per hour during sleep (highest quartile) by pulse oximetry. The presence of silent cerebral infarct (SCI) (57% v 35%, P = .03) was significantly higher in the hypoxia group than in the nonhypoxia group. The number of SCI was positively correlated with age (r = 0.23, P < .01), systolic blood pressure (r = 0.196, P < .05), and 3% ODI (r = 0.318, P < .001). Even after adjustment for confounding factors using logistic regression analysis, nocturnal hypoxia (odds ratio = 2.2, 95% confidence interval = 1.10 to 5.30, P = .026) as well as systolic blood pressure and age (10-year increase: odds ratio = 1.22, 95% confidence interval 1.00 to 1.48, P = .048) were independently associated with SCI in the study subjects.

Conclusions: Based on the study results, SDB assessed by overnight pulse oximetry was associated with silent cerebral disease in a high-risk, community-dwelling Japanese population. Am J Hypertens 2005;18: 1489–1495 © 2005 American Journal of Hypertension, Ltd.

Key Words: Nocturnal hypoxia, silent cerebral infarct, overnight pulse oximetry, community screening.

Sleep-disordered breathing (SDB) is an important health problem affecting 2% to 4% of the middle-aged population in a random sample of state employees in Wisconsin.[1] This disorder has been reported to be associated with hypertension, cardiovascular diseases, future stroke,[2,3] and greater morbidity.[1] The disorder is composed of habitual snoring, increased upper airway resistance syndrome, periodic breathing, and sleep apnea disorder. The type, severity, and therapeutic indication of SDB can be diagnosed by polysomnography as a "gold standard" diagnostic tool; but it requires an overnight stay at a sleep laboratory, which is somewhat complicated, troublesome, and not always useful for community screening of SDB. An overnight pulse oximetry is helpful for screening of SDB.[4–6] Early detection of silent cerebral infarct (SCI) is important because SCI is associated with higher rates of mortality and subsequent clinical cerebral infarction.[7–9] It has been reported that SCI is associated with many traditionally recognized cerebrovascular risk factors in-

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cluding age, hypertension, atrial fibrillation, and diabetes,[10] and it can be used as a surrogate endpoint for subclinical cerebrovascular damage.

It remains controversial whether SDB is a cause or a consequence of cardiovascular disease (CVD). Previous articles have reported a prognostic value of SDB in terms of functional recovery or survival or both, either for nocturnal desaturation (ND) or directly demonstrating respiratory events during the night in patients with stroke.[11–13] Data from the Sleep Heart Health Study[14] showed a relationship between the presence of apnea and stroke in a cross-sectional population-based study. However, longitudinal data are still lacking. Both SDB and SCI share several common cardiovascular risk factors such as aging, hypertension, and obesity. In addition, relationships between SDB and silent cerebrovascular damage have not been clarified yet in a community screening. Therefore we performed this study to investigate whether SDB is related to silent cerebrovascular damage in a high-risk but apparently healthy Japanese general population.

Methods

Because this study was originally designed to reduce the prevalence of stroke, we enrolled a study population with a high risk of stroke.

Study Population

We studied 146 asymptomatic subjects (108 women and 38 men, mean age 67.4 ± 9.0 years, range 42 to 89 years). We enrolled the subjects into our study from the annual health screening in Nishiarita town, Saga prefecture, Japan. The number of town residents >40 years of age was 5323. Those who underwent their companies' health check or who were unwilling to have this health check were excluded in advance as potential subjects. Of the 2784 residents invited, 1511 subjects participated in the conventional health check in 2001. A total of 283 high-risk subjects (187 female and 96 male) were identified. In addition, 170 subjects who visited the hospital to undergo further examination (65.2% for women and 50.0% for men) were recruited; of those, 146 subjects who successfully underwent overnight pulse oximetry were finally recruited for this study (Fig. 1). High-risk subjects were defined as meeting more than three of the following nine criteria; 1) blood pressure (BP) >140/90 mm Hg; 2) total cholesterol >250 mg/dL; 3) left ventricular (LV) hypertrophy by electrocardiography and meeting either the Cornell voltage criteria (RaVL + SV_3 >28 mm in men and 20 mm in women) or Sokolow-Lyon criteria (SV_1 + RV_5 or RV_6 >35 mm, R aVL >11 mm, RaVF >20 mm); 4) hemoglobin A_1c >6.5%; 5) proteinuria, 6) high waist-to-hip ratio (men >0.95, women >0.80); 7) current heavy smoker (>30 cigarettes/day); 8) heavy drinker (ethanol >84 g/day); or 9) family history of stroke. We excluded patients with respiratory illness (such as chronic obstructive pulmonary disease), renal failure, hepatic damage, secondary or malignant hypertension, ischemic or other cardiac disease, congestive heart failure, arrhythmia (including atrial fibrillation or other arrhythmia), stroke (including transient ischemic attacks), or other severe concomitant disease. Data on duration of hypertension, smoking status, alcohol intake, and family history of stroke were based mainly on self-reported information.

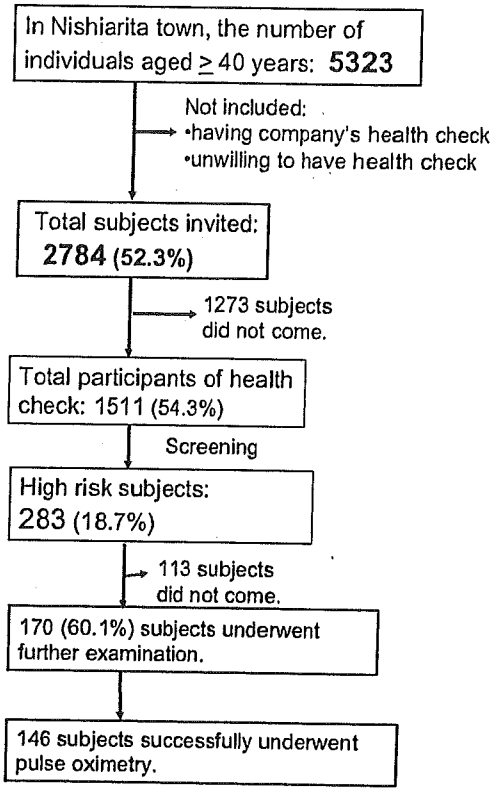

FIG. 1. Selection of subjects for the study.

This study was approved by the Research Ethics Committee, Jichi Medical School, Tochigi, Japan. All subjects studied were ambulatory and all gave informed consent for the study.

Pulse Oximetry

A pulse oximetry PULSOX-3Si (Minolta Co., Osaka, Japan) was used to evaluate nocturnal oxygen saturation change. We performed nocturnal pulse oximetry only for outpatients. The device was attached to the left arm when the subjects went to bed and was removed after they awakened. The sensor probe was fitted to the second or third finger and secured with tape or a finger glove to prevent detaching. The internal memory of this device stores the values of blood oxygen saturation by performing a moving average for the last 5 sec, updated every 1 sec; this sampling time was short enough to avoid underestimation of oxygen desaturation.[15] Data were downloaded to a personal computer via an interface (PULSOX IF-3; Minolta) and analyzed using proprietary software supplied with the equipment (DS-3 version 2.0a; Minolta) as previously described.[16] We used the value of oxygen desaturation per hour (oxygen desaturation index [ODI]) as an indicator of

Table 1. Baseline characteristics of the patients studied

Characteristic	Hypoxia (n = 36)	Nonhypoxia (n = 110)	P value
Age (y)	70.8 ± 7.0	66.3 ± 9.3	.008
Male sex (%)	11 (31%)	27 (25%)	.514
Body mass index (kg/m^2)	24.1 ± 3.5	23.3 ± 2.9	.174
Hypertension (%)	15 (42%)	48 (44%)	1.000
Diabetes (%)	4 (11%)	10 (9%)	.747
Smoking (%)	5 (14%)	13 (12%)	.773
Systolic BP (mm Hg)	154 ± 14	159 ± 19	.23
Diastolic BP (mm Hg)	89 ± 8.9	86 ± 11	.24
LV mass index (g/m^2)	133 ± 32	124 ± 40	.23
Total cholesterol (mg/dL)	219 ± 33	228 ± 41	.24
Triglyceride (mg/dL)	126 ± 53	122 ± 86	.82
Hematocrit (%)	40.3 ± 3.8	40.7 ± 3.5	.65
Serum creatinine (mg/dL)	1.00 ± 0.2	0.96 ± 0.2	.049
HemoglobinA_1c (%)	5.5 ± 0.9	5.3 ± 0.6	.25
Urinary microalbumin (mg/g · Cr)	51 ± 126	43 ± 141	.76
3% ODI (dips/h)	10.1 ± 4.0	2.2 ± 1.4	<.001
4% ODI (dips/h)	6.2 ± 3.4	1.2 ± 1.2	<.001
Time spent SpO_2<90% (min)	11.8 ± 35	2.9 ± 9	.017
Time spent SpO_2<90% (%)	2.2 ± 6.6	0.6 ± 1.8	.022
Sleep time (h)	7.9 ± 1.0	7.5 ± 1.4	.064

BP = blood pressure; HbA_1c = hemoglobinA_1c; LV = left ventricular; ODI = oxygen desaturation index; SpO_2 = pulse oximetry oxygen saturation.

Data are shown as number (%) or as mean ± SD.

SDB. A 3% ODI was selected as an index of oxygen desaturation, representing the number of events per hour of recording time in which blood oxygen fell by >3%. The 3% ODI, 4% ODI, and time spent pulse oximetry oxygen saturation (SpO_2) <90% (%) during the estimated sleep time >4 h computed for each subject was used for the analysis. We defined the hypoxia group by the highest quartile of 3% ODI level as >5.5 times per hour in this study, and others were defined as nonhypoxia group.

Brain MRI

Brain MRI was carried out in all 146 subjects using a superconducting magnet with a main strength of 0.5 T (Toshiba MRT50GP, Tokyo, Japan). The brain was imaged in the axial plane at a 7-mm slice thickness. T_1-weighted images were obtained using a short spin-echo pulse sequence with a repetition time of 470 msec and an echo time of 15 msec. T_2-weighted images were obtained using a long spin-echo pulse sequence with a repetition time of 4000 msec and echo times of 120 msec. The matrix size was 256 × 256 pixels. An SCI was defined exclusively as a low signal intensity area (>3 mm, but all were <15 mm), depicted on T_1-weighted images, that was also visible as a hyperintense lesion on T_2-weighted images, as previously described.[17] The MRI images of the subjects were randomly stored and interpreted by reviewers who were blind to the subjects' names and characteristics.

Other Measurements

The LV mass index detected by echocardiography (SSD 2200, Aloka, Tokyo, Japan) was calculated by a method previously described.[18] Carotid plaque was assessed by carotid ultrasonography (LOGIQ500, GE Yokogawa Medical Systems, Tokyo, Japan), and carotid plaque score was calculated by a method previously reported.[19] Mean and maximal intima-media thicknesses (IMT) were measured as described.[20] Urinary microalbumin was measured by a latex agglutination photometric immunoassay with an automated immunochemistry analyzer (LX-6000; Eiken Chemical Co., Tokyo, Japan).

Sleep time was estimated from self-reports.

Statistical Analysis

All statistical analyses were carried out with SPSS/Windows, version 11.0J (SPSS Inc., Chicago, Illinois). Data are expressed as the mean (± standard deviation) or as percentages. The χ^2 test was used to calculate proportions. Unpaired t tests were used for comparison of variables between the hypoxia and nonhypoxia groups (Tables 1 and 2). Factors correlated with the number of SCI, carotid plaque score, LV mass index, and urinary microalbumin were calculated with simple regression analysis (Table 3). Multiple logistic regression analysis was performed to analyze factors associated with the prevalence of SCI (Table 4). Because we considered that nocturnal desaturation involves various confounding factors, we examined nine essential variables to confirm the independence of nocturnal hypoxia as the determinant of SCI. Spearman's correlation was used for bivariate analysis. A two-sided P value < .05 was considered to be statistically significant.

Table 2. Comparison of hypertensive target organ damages

Characteristic	Hypoxia (n = 36)	Nonhypoxia (n = 110)	P value
Number of SCI (/person)	1.0 ± 1.5	0.7 ± 1.2	.21
Prevalence of SCI (%)	57	35	.029
Carotid plaque score	2.9 ± 3.9	1.6 ± 2.5	.019
Mean IMT (mm)	0.81 ± 0.12	0.71 ± 0.11	.352
Maximum IMT (mm)	0.90 ± 0.14	0.88 ± 0.13	.364
Prevalence of carotid plaque (%)	69	49	.036
LV mass index (g/m^2)	133 ± 32	124 ± 40	.23
Prevalence of LVH (%)	69	52	.082
Urinary microalbumin (mg/g · Cr)	51 ± 126	43 ± 141	.764
Presence of albuminuria (%)	26	22	.643

IMT = intima-media thickness; LV = left ventricular; LVH = left ventricular hypertrophy; SCI = silent cerebral infarct.
Data are shown as the number (%) or as mean ± SD.

Results

Baseline Characteristics of the Study Population

Table 1 shows the characteristics of the 146 study subjects separated into two groups: the hypoxia group (n = 36) and the nonhypoxia group (n = 110). Sex, body mass index (BMI), smoking, diabetes, total cholesterol, triglyceridea, hematocrit, and urinary microalbumin, systolic BP, and diastolic BP were similar between the two groups, but age and serum creatinine were higher in the hypoxia than in the nonhypoxia group.

Nocturnal Hypoxia

The mean 3% ODI value was 4.2 ± 4.1/h in the subjects overall. The histogram of 3% ODI (times/h) is shown in Fig. 2. The 3% ODI values of hypoxia group were widely distributed, ranging from mild to severe. Age was significantly correlated with 3% ODI (r = 0.293, P < .001). There were no hypoxic subjects <54 years of age, but the percentage of hypoxia > 55 years was not increased as the age increased. When the subjects were divided into groups according to each 1 (kg/m^2) BMI, the hypoxic subjects were not increased by higher BMI values. Both obese and nonobese subjects had similar ratios of nocturnal hypoxia, but the percentage of hypoxia was lowest in the groups with BMI of 21 and 22.

Subjectively assessed quality of sleep were similar between the hypoxia and nonhypoxia groups (75% v 78%, P = .456).

Silent Cerebral Infarcts

As shown in Table 2, the prevalence of SCI was significantly higher in the hypoxia than in the nonhypoxia group

Table 3. Factors correlated with hypertensive target organ damages

Characteristic	Number of SCI (number/person)	Carotid plaque score (number/person)	LV mass index (g/m^2)	Urinary microalbumin (mg/g · Cr)
Age (y)	0.230*	0.354†	0.289†	−0.001
Male sex	0.099	0.243*	0.322†	−0.206
Body mass index (kg/m^2)	0.033	−0.152	−0.031	0.107
Diabetes	0.084	−0.053	0.016	0.278*
Smoking	0.126	0.135	0.089	−0.138
Waist circumference (cm)	0.054	0.031	0.161	0.030
Serum creatinine (mg/dL)	0.100	0.184‡	0.043	−0.082
HbA_1c (%)	0.037	0.023	0.036	0.149
Systolic blood pressure (mm Hg)	0.196*	0.155	0.286†	0.109
Total cholesterol (mg/dL)	−0.081	−0.062	−0.456†	0.004
Hematocrit (%)	−0.064	0.062	−0.119	0.006
3% ODI (dips/h)	0.318†	0.172‡	0.126	0.099
4% ODI (dips/h)	0.327†	0.127	0.130	0.110
Time spent SpO_2<90% (%)	0.171‡	0.100	0.164‡	0.026

ODI = oxygen desaturation index; other abbreviations as in Tables 1 and 2.
Data are shown as correlation coefficient (r) calcurated with simple regression analysis (Speaman). Dummy code was defined as sex: male = 1, female = 0; diabetes: present = 1, absent = 0; smoking: present = 1, absent = 0.
* P < .01, † P < .001, ‡ P < .05.

Table 4. Determinants of silent cerebral infarct (SCI)

Variable	SCI	*P* value
Systolic blood pressure (10 mm Hg)	1.22 (1.00–1.48)	.048
Nocturnal hypoxia	2.42 (1.10–5.30)	.026

Adjusted odds ratios for silent cerebral infarcts were calculated by stepwise method (forward selection method). The following conventional risk factors were selected as independent variables: age, male gender, body mass index, total cholesterol, systolic blood pressure, hematocrit, hemoglobinA_1c, serum creatinine and presence of nocturnal hypoxia.

(57% *v* 35%, $P = .029$). Table 3 shows the factors correlated with hypertensive target organ damage, determined by simple regression analysis. Age ($r = 0.23$, $P < .01$), systolic BP ($r = 0.196$, $P < .05$), 3% ODI ($r = 0.318$, $P < .001$), 4% ODI ($r = 0.327$, $P < .001$), and time spent SpO_2 <90% ($r = 0.171$, $P < .05$) were significantly correlated with the number of SCI. As shown in Table 4, we calculated the adjusted odds ratios for the relational factors of silent cerebral infarcts by the stepwise method (ie, forward selection method). We selected the following conventional risk factors as independent variables: age, sex, BMI, total cholesterol, systolic BP, hematocrit, hemoglobinA_1c, serum creatinine, and presence of nocturnal hypoxia. Even after the adjustment for these confounding factors, nocturnal hypoxia found to be an independent relational factor of SCI in our population.

In the present study, the locations of SCI were predominantly deep white matter or basal ganglia. We compared the dominance of these locations between the hypoxia and nonhypoxia groups, and found that there were no significant differences in the SCI location between these two groups.

Nocturnal Hypoxia and Target Organ Damages

The prevalence of carotid plaque and the carotid plaque score were significantly higher in the hypoxia than in the nonhypoxia group, but there were no significant differences in mean IMT and maximal IMT (Table 2). As shown in Table 3, age ($r = 0.354$, $P < .001$), male sex ($r = 0.243$, $P < .01$), serum creatinine ($r = 0.184$, $P < .05$), and 3% ODI ($r = 0.172$, $P < .05$) were significantly and positively correlated with carotid plaque score. However, the relationships between carotid plaque score and age, sex, creatinine, and 3% ODI were diminished after the multivariate analysis.

As shown in Tables 2 and 3, LV mass index and urinary microalbumin were not significantly different between the hypoxia and nonhypoxia groups and were not significantly correlated with 3% ODI value.

Discussion

In the present study, nocturnal hypoxia assessed with overnight pulse oximetry was found to be independently associated with the prevalence of SCI among a high-risk community-dwelling Japanese population. To our knowledge, this is the first report to demonstrate the relationships between SDB and SCI. In a previous Japanese epidemiologic study (the Hisayama study), the determinants of SCI were high BP, diabetes, atrial fibrillation, and history of coronary heart disease.[21] Although these risk factors overlapped that of SDB, no data have been published that direct showing the relationship of SDB with SCI.

Cause–Effect Relationships Between SDB and SCI

In previous studies, no relationsips were found between SDB and white matter disease or silent cerebral infarcts.[22–24] However in the present study we found a relationship between SDB and prevalence of SCI. The location of SCI in the present study was mainly in basal ganglia or deep white matter lesions but not in the respiratory center. Therefore it does not seem that breathing patterns were directly influenced by SCI.

In previous reports, a higher percentage of SDB was observed in stroke patients, and SDB was associated with poor functional outcomes in survivors and higher mortality.[11] A higher prevalence of SDB was observed in stroke patients having similar frequencies of risk factors compared with age-matched control subjects.[25] The mechanism of abnormal breathing patterns (periodic breathing) in stroke patients regardless of lesion site are explained by prolonged blood circulation from the heart to brain. Because SCI can be recognized as a subclinical stroke,[7–9] the same pathogenic mechanisms as those in stroke patients can be suggested in SCI patients.

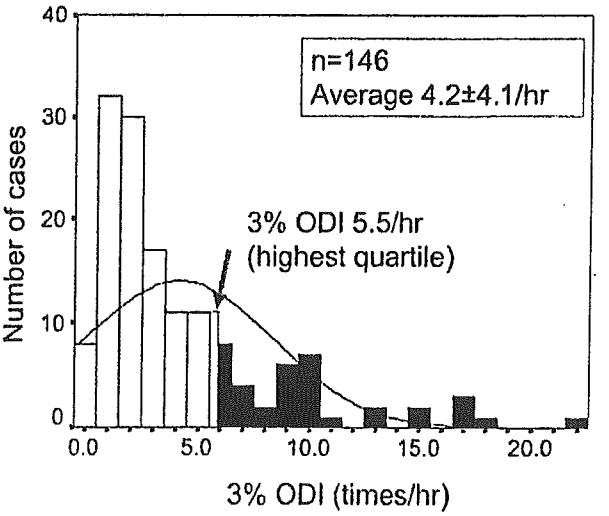

FIG. 2. Histogram of 3% O_2 desaturation index (3% oxygen desaturation index, times per hour).

On the other hand, there are several pathophysiologic mechanisms of stroke in SDB patients. Alteration of cerebral hemodynamics, hypoxemia, and dysfunction of cerebral autoregulation are suggested as the main mechanisms of cerebral ischemia in patients with SDB.[2] The decrease in arterial blood pressure and gradual rise in intracranial pressure during apnea result in decreased cerebral perfusion pressure.[26] Pronounced cerebral blood flow velocity changes during apneic episodes and the concomitant alterations of vessel wall tension might lead to chronic strain on the brain vessels and formation of atherosclerosis.[2,27] Augmented mechanical stress on the cardiovascular system and increased variability of blood flow by augumented BP variability increases sheer stress induced platelet activation at atherosclerotic stenotic sites.[28] In SDB subjects SCI may be formed by the same mechanism.

In the present study, although the BP level was not different between the hypoxia and nonhypoxia groups, age and serum creatinine were higher in the hypoxia than in the nonhypoxia group. Although more advanced age was significantly correlated with the extent of SDB,[29] when the ages were divided into 5-year groups, the percentages in the hypoxia group >55 years of age was not different in the present study. However, more advanced age itself could be a predictor of SDB, as older patients have a significant number of respiratory events without clear clinical indications. Systolic BP level was another significant determinant of SCI. Although we could not perform ambulatory BP monitoring for all subjects, not only BP levels but also both short and long term BP variation would have been enhanced in the hypoxia group.[28] Further studies are needed to clarify whether the BP variability would be augmented in SDB subjects.

Characteristics of Japanese Population

As is widely known, obesity is one of the strongest risk factors for SDB. However, in our population, the rate of hypoxia was similar among the different BMI groups. It has been reported that in Asian subjects with SDB the relative risk of obstructive sleep apnea attributable to obesity was less than in subjects of white ethnicity.[30]

We previously reported the associations between SCI and nondipper hypertension,[31] extreme dipping,[32] diabetic hypertension,[33] and insulin resistance.[34] There is a possibility that greater numbers of subjects with SDB were included in these high-risk population groups. The common pathologic pathway in the population may be higher sympathetic activity and resulting higher peripheral resistance. In previous reports, higher sympathetic tone was reported in nondipper,[35] insulin resistant,[36] and diabetic[36] populations. The strength of our study is that even in a nonobese population, SDB reflects not only target organ damages but also increased sympathetic tone resulting from hypoxic stress during sleep. We hypothesize that even among nonobese older women, those with greater risk factors for sleep apnea could have a greater presence of SCI.

Accuracy of Pulse Oximetry

The accuracy of overnight pulse oximetry was recently reported.[5,6,37] Magalang et al reported that oxygen desaturation indexes and the Δ index provided similar levels of diagnostic accuracy.[5] The combination of indexes improved the precision of the predicted apnea–hypopnea index (AHI) and may offer a potentially simpler alternative to polysomnography (sensitivity 90%, specificity 70%). Using case designation criteria of 15/h for AHI and respiratory disturbance index, the sensitivity and specificity were 98% and 88%, respectively.[5] In clinical practice, other SDB such as upper airway resistance syndrome, central sleep apnea syndrome, and mixed type exist. Nakamata et al reported that the validity of the pulse oximetry was fairly good for detecting an AHI of >5 by polysomnography using a cutoff threshold of 3% ODI = 5.[6] However specificity, sensitivity, and predictive value depend on the previous likelihood of developing the disease, and accuracy data obtained when evaluating patients with suspected sleep apnea would not be the same in a different group of patients with a previously low likelihood of having sleep apnea.

Our study has several limitations. The first is that we did not use a respiratory recording device. The diagnosis of SDB cannot be confirmed only by pulse oximetry. Second, the relatively small sample size presumably limited the ability to detect differences in IMT, LV mass, and other markers of risk. Third, we did not conduct a precise sleep respiratory survey (extent of snoring, apnea, or sleep quality), because this study originally did not target SDB patients.

In conclusion, SDB assessed by overnight pulse oximetry was associated with SCI in a high-risk, nonobese, Japanese, community-dwelling population at cardiovascular risk.

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