ORIGINAL ARTICLE

Incidence of adverse drug reactions in geriatric units of university hospitals

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Background: Adverse drug reactions (ADR) in elderly people are often attributed to functional decline and polypharmacy.

Methods: In this study, a multi-institutional retrospective survey was undertaken to investigate the current status of ADR in geriatric units of university hospitals. The inpatient databases from 2000 to 2002 for five university hospitals were studied, and a total of 1289 patients were analyzed.

Results: The incidence of ADR, as determined by attending physicians, was 9.2% on average, but varied from 6.3 to 15.8% among the institutions. Factors significantly related to ADR were the number of diagnoses, the number of geriatric syndromes, the number of prescribed drugs, an increase of two or more drugs during hospitalization, longer hospital stay, emergency admission, depression and apathy.

Conclusion: These results are mostly consistent with previous reports and provide important information on drug treatment in elderly people.

Keywords: adverse drug reaction, elderly, medication error.

Introduction

Adverse drug reactions (ADR) in elderly people are common causes of admission to hospitals and are important causes of morbidity and mortality.[1,2] The risk of ADR has been shown to be related to the number of prescribed drugs and elderly people tend to receive more medications than younger people,[3] which are sometimes inappropriately prescribed.[4] Indeed, the risk of ADR is exponentially rather than linearly related to

the number of medications taken.[5] Factors that predispose to pharmacological ADR include the dose, drug formulation, pharmacokinetic or pharmacodynamic abnormalities and drug interactions. Frail elderly patients may be more vulnerable because of impaired homeostatic reserve, multiple medication use, cognitive decline and impaired functional status. Drug therapy taking account of safety as well as effectiveness is still needed in the elderly, although there is accumulating evidence on drug therapy in the elderly with hypertension and hyperlipemia.[6,7]

Although the incidence of ADR for specific drugs can be obtained by large-scale examination and postmarketing surveillance studies by pharmaceutical companies, little data are available on ADR in the elderly as a whole. Previously, we reported the incidence of ADR in inpatients of the geriatric unit of the University of

Tokyo Hospital, and showed that drug overdose and polypharmacy are important factors in ADR.[8,9] However, it is necessary to confirm whether similar results are obtained in geriatric units of other hospitals. Therefore, in this study, we analyzed the inpatient databases of five university hospitals with geriatric units, and examined the incidence of ADR and factors related to ADR.

Methods

Subjects

We performed a retrospective investigation of the hospital records of five university hospitals with geriatric units: Kyorin University Hospital, University of Tokyo Hospital, Kyoto University Hospital, Kanazawa Medical University Hospital and Tohoku University Hospital. We surveyed the records of inpatients from January 2000 to December 2002 in these hospitals, and a total of 1289 cases were used for analysis.

Investigation and analysis

We studied the incidence of ADR as judged by attending physicians during hospitalization, along with the number of medications taken on admission and on discharge. We also examined the number of final diagnoses on discharge, the length of hospital stay, age, sex and body weight of each patient, and whether or not the admission was emergent. We investigated the number of geriatric syndromes in the cases at Kyorin University Hospital and the University of Tokyo Hospital and performed comprehensive geriatric assessments (CGA). The 30 most significant of 51 geriatric syndromes are listed in Table 1. The CGA included Barthel Index on admission and discharge to evaluate activities of daily living (ADL), Hasegawa's Dementia Scale-Revised (HDS-R) to assess cognitive function, Geriatric Depression Scale 30-items (GDS-30) to assess depressive mood, and Vitality Index to assess energy.[10]

The data were expressed as means ± SD. The unpaired *t*-test was used to compare the data between two groups, and comparison among multiple groups was performed by ANOVA followed by Newman-Keuls' test. The incidences were compared using the χ^2 test. Correlation was analyzed according to Pearson's correlation coefficient. A value of $P < 0.05$ was considered statistically significant.

Results

Frequency of adverse drug reaction

In the analysis of a total of 1289 cases, the incidence of ADR was 9.2%. We analyzed the incidence at each hospital and found that the lowest incidence was 6.6%, while the highest was 15.8% among the five hospitals studied (Fig. 1).
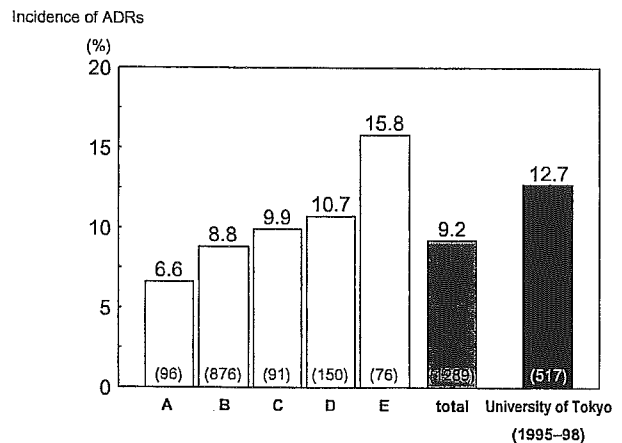

Figure 1 Incidence of ADR in inpatients of geriatric units of five university hospitals. The incidence of ADR in the geriatric unit of University of Tokyo Hospital in 1995–98 is shown as a reference.[9] The numbers of patients surveyed are shown in parentheses.

Table 1 List of major geriatric syndromes

Consciousness disturbance	Chest pain/chest oppression	Edema
Delirium	Palpitation/shortness of breath	Dehydration
Dementia	Arrhythmia	Hearing impairment
Insomnia	Abdominal pain	Motor disturbance
Depression	Constipation	Visual impairment
Dizziness/vertigo	Diarrhea	Back pain
Headache	Body weight loss	Fever
Anemia	Appetite loss	Arthralgia
Pressure ulcers	Nausea/vomiting	Osteoporosis
Falls	Malnutrition	Bleeding tendency
Hemoptysis	Dyspnea	Dysphasia
Urinary incontinence	Pollakisuria	Cough/sputum

Factors related to adverse drug reactions

Background factors related to ADR in cases with or without ADR are summarized in Table 2. There was no significant difference in sex, age or body weight between the two groups. However, patients with ADR had more diagnoses, were taking more drugs on discharge, and stayed longer in hospital than those without ADR ($P <$ 0.05). They also showed a tendency to be taking more drugs on admission ($P = 0.08$). When we analyzed the relationship between ADR and the increase in medication during hospitalization, the incidence of ADR in patients with an increase of two or more drugs was 14.4%, which was significantly higher than in those with an increase of one drug (7.9%) and those without an increase (7.8%). Moreover, the incidence of ADR was higher in patients who received emergency admission than in those with scheduled admissions (12.5% vs 7.8%, $P < 0.05$).

The relationship between the factors related to ADR and the variation in ADR among the hospitals was analyzed. In hospital A, where the incidence of ADR was lowest, the number of diagnoses at discharge (2.8 ± 1.1

diseases), number of medications (4.3 ± 1.9 drugs), and the length of hospital stay (28.5 ± 6.8 days) were lowest among the five hospitals. Intriguingly, the mean age of the patients in hospital A was 82 years, while it was 67 years in hospital E, where the incidence of ADR was highest. The mean age of the patients was 71–72 years at other hospitals.

Age was positively correlated with the number of diagnoses ($r = 0.219$, $P < 0.001$) and the number of drugs at discharge ($r = 0.213$, $P < 0.001$), as previously reported.[8,9]

Geriatric syndrome and CGA were analyzed in relation to ADR in the cases at University of Tokyo Hospital and Kyorin University Hospital. The number of geriatric syndromes was significantly higher in patients with ADR than in those without ADR (Table 3). Patients with ADR showed depressed moods and apathy, as assessed by GDS and the Vitality Index, compared to those without ADR, while cognitive function and basic ADL, as assessed by HDS-R and Barthel index, did not differ between the two groups (Table 3).

Discussion

In this study, we surveyed ADR in the geriatric units of five university hospitals and found that the number of diagnoses, number of geriatric syndromes, number of prescribed drugs, an increase of two or more drugs during hospitalization, longer hospital stay, emergency admission, depression, and apathy were related to the incidence of ADR in elderly inpatients. Our study indicates that the number of diagnoses and drugs would be a better predictor for ADR in the elderly than age.

According to reports on ADR from the USA and Europe, the incidence of ADR in elderly inpatients is 6–15%.[11] The incidence was 1.5–2 fold higher in patients older than 70 years than in patients younger than 60 years. In nursing home residents, the incidence of ADR per year has been reported to be 15–20%.[11] In the outpatient setting, ADR were found in more than 10%

Table 2 Characteristics of patients with or without adverse drug reactions (ADR)

	ADR (–)	ADR (+)
Number of patients	1170	119
Sex (female, %)	46%	50%
Age (years)	72 ± 14	73 ± 14
Body weight (kg)	56 ± 14	54 ± 14
Number of diagnoses	4.1 ± 2.0	$4.9 \pm 2.3^{*}$
Number of drugs on admission	5.0 ± 3.6	$5.7 \pm 4.1^{**}$
Number of drugs on discharge	5.3 ± 3.3	$6.2 \pm 3.7^{*}$
Length of hospital stay (days)	28 ± 27	$38 \pm 27^{*}$

$^{*}P < 0.01$; $^{**}P = 0.08$ by unpaired t-test.
Data are means $\pm$ SD.

Table 3 Geriatric syndrome and comprehensive geriatric assessment in patients with or without adverse drug reactions (ADR)

	ADR (–)	ADR (+)
Number of geriatric syndromes	4.6 ± 3.8 (866)	$6.4 \pm 4.7^{**}$ (85)
Barthel Index on admission	84 ± 28 (854)	80 ± 31 (82)
Barthel Index on discharge	86 ± 27 (840)	85 ± 28 (79)
HDS-R	23.0 ± 8.2 (358)	24.4 ± 6.3 (35)
GDS-30	10.2 ± 6.0 (325)	$12.5 \pm 6.8^{*}$ (33)
Vitality index	9.0 ± 2.1 (535)	$8.4 \pm 2.6^{*}$ (52)

$^{*}P < 0.05$; $^{**}P < 0.01$ by unpaired t-test. Data are mean $\pm$ SD. Numbers in parentheses indicate number of patients studied.
HDS-R, Hasegawa dementia scale-revised; GDS-30, Geriatric depression scale-30 items.

of elderly patients, although the study relied on self-reporting and review of medical records.[11] Only a few studies have been reported in Japan; the incidence was 12.7% in elderly inpatients of the geriatric unit of University of Tokyo Hospital.[9] In the present survey, the average incidence was 9.2%, ranging from 6.6 to 15.8% among facilities, but was similar to that reported previously.[9] Although the incidence varied among hospitals, it is important to note that the incidence of ADR was more than 5% in all hospitals.

Adverse drug reactions were judged by attending physicians in this study, whereas they were determined by objective review of the medical records in addition to judgment by attending physicians in the previous report from the geriatric unit of University of Tokyo Hospital. In the present study, the incidence of ADR in this facility was 8.8%, which was 30% lower than that in our last survey. This difference may be attributable to underestimation by the attending physicians rather than a decrease in ADR over this short period of 3 years. Therefore, if another authorized person judged the ADR strictly, the overall incidence rate might have been slightly higher.

Our results on the incidence of ADR in elderly patients may add important information. However, all the facilities in this survey were geriatric units of university hospitals, where most of the inpatients were older than 65 years and the doctors in those units are careful in prescribing medication to elderly patients. Therefore, our data might not be directly applicable to elderly patients in other hospitals or units. In fact, ADR were found in nearly half of elderly inpatients of the neuropsychiatry unit of University of Tsukuba Hospital (unpubl. obs, Mizukami *et al.*). In addition, our data in university hospitals, which are acute care hospitals, might not be applicable to chronic care facilities such as long-term care facilities. Since the introduction of the fixed payment system, Diagnosis Procedure Combination system, to university hospitals in Japan in 2003, drug treatment in university hospitals might be changing in the future. Therefore, the incidence of ADR in various types of hospitals in Japan needs to be studied.

In this study, depression and apathy were found to be associated with ADR in addition to the accumulation of diseases and geriatric syndromes, polypharmacy, an increase of prescribed drugs during hospitalization, longer hospital stay and emergency admission. This result is consistent with other reports.[9] However, the causal relationship remains unknown. A higher number of diseases or geriatric syndromes can lead to an increase in ADR through polypharmacy[8,9] while ADR themselves may increase diseases or geriatric syndromes. Similarly, longer hospital stays can increase the risk of ADR, while ADR prolong the duration of hospitalization. The latter point is critical to medical economics as well. Age was not associated with ADR in this study, inconsistent with other studies. This might be due to effects of education

on pharmacotherapy in elderly patients for several years at university hospitals. Although we did not analyze the types or classes of ADR in this survey, it has been reported that severe ADR such as neuropsychiatric disorders or cardiovascular injury occur in elderly patients.[9]

Recently, evidence has been accumulating on drug therapy in the elderly. However, there are very few data available in people aged 75 years and older or in frail elderly people. Therefore, it is necessary to establish the safety and effectiveness of drug therapy in these patients in the future. Evidence-based medicine in the elderly aims to discontinue unnecessary drugs and to avoid polypharmacy. On the other hand, a fixed payment system such as the long-term care insurance system in Japan forces doctors to reduce prescribed drugs from a business viewpoint. Indeed, it has been reported that 0.6 drugs were on average discontinued within a month after admission to long-term care facilities, although adverse drug withdrawal events were very few.[12] Because minimally prescribed drugs have not increased ADR in patients with dementia and a low capacity for medication management,[13] it is necessary to cut down unnecessary drugs in frail elderly patients based on evidence-based medicine. In the USA, Beers' criteria are available to identify potentially inappropriate medication use, in order to reduce drug-related problems.[14] In Japan, however, we do not have such guidelines for drug treatment in the elderly. Because the drugs and medical situation in Japan are different from those in the USA, we need to establish our own guidelines, which will be published this year. In addition, we need to accumulate clinical evidence to support the guidelines. We also need to utilize pharmacists more efficiently, because they are an underused resource in avoiding medication errors and can provide important safeguards for elderly patients in hospitals and nursing homes.

Elderly patients are exposed to more medications and have an increased risk of ADR, many of which are avoidable. Knowledge of pharmacological principles and age-related effects on pharmacokinetics/pharmacodynamics is essential to promote safe prescribing. Other factors related to ADR such as polypharmacy, long admission and depression should also be evaluated during hospitalization.

Acknowledgments

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Original Article

Impact of Blood Pressure Variability on Cardiovascular Events in Elderly Patients with Hypertension

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Blood pressure variability is one of the characteristic features of hypertension in the elderly. However, its clinical significance remains to be determined. We therefore examined the impact of blood pressure variability on the development of cardiovascular events in elderly hypertensive patients. A total of 106 consecutive hypertensive patients aged more than 60 years old (mean age, 73.9±8.1 years old; male, 54%), all of whom underwent 24-h ambulatory blood pressure monitoring, were followed up (median, 34 months; range, 3–60 months). During the follow-up period, 39 cardiovascular events were observed, including 14 cases of cerebral infarction and 7 cases of acute myocardial infarction. The coefficient of variation (CV) of 24-h systolic blood pressure (SBP) values was used as an index of blood pressure variability. The patients showed a mean CV value of 10.6%, and were divided into two groups according to this mean value as a cut-off point: a high CV group (*n*=46) and a low CV group (*n*=60). Although baseline clinical characteristics were similar in the two groups, Kaplan-Meier plots for event-free survival revealed that the rate of cardiovascular events was significantly higher in high CV group than in low CV group (*p*<0.05). Cox's proportional hazards analysis showed that increased blood pressure variability (a high CV value of 24-h SBP) was an independent predictive variable for cardiovascular events. The CV value of daytime SBP and the SD value of both 24-h SBP and daytime SBP also had positive correlations with the onset of cardiovascular events. These results suggest that increased blood pressure variability may be an independent risk factor for cardiovascular events in elderly hypertensive patients. (*Hypertens Res* 2005; 28: 1–7)

Key Words: elderly hypertension, blood pressure variability, cardiovascular events, ambulatory blood pressure monitoring

Introduction

Hypertension has been well established as a major predisposing factor for cardiovascular disease (*1*). The goal of treatment for hypertensive patients is not only to reduce blood pressure, but also to prevent cardiovascular events. The prevalence of hypertension increases with age (*2*), and elderly hypertensive patients are known to have some specific clinical features, such as isolated systolic hypertension (*3*), blood pressure variability (*4, 5*), orthostatic hypotension (*6, 7*) and postprandial hypotension (*8*).

Blood pressure variability is a characteristic feature of hypertension in the elderly (*4, 5*). The arterial baroreflex

Table 1. Baseline Clinical Characteristics

	Total (n=106)	Low CV group (n=60)	High CV group (n=46)	p value
Age (years old; mean±SD)	73.9±8.1	74.4±7.9	73.2±8.3	NS
(range)	(60–91)	(60–91)	(60–87)	
Sex (men) (n (%))	58 (54%)	36 (60%)	22 (48%)	NS
WHO class (n (%))				
I	31 (29%)	22 (37%)	9 (20%)	NS
II	22 (21%)	12 (20%)	10 (22%)	
III	53 (50%)	26 (43%)	27 (58%)	
Smoking (n (%))	53 (50%)	32 (53%)	21 (46%)	NS
Antihypertensive drug (n (%))				
ACE inhibitor	19 (18%)	10 (17%)	9 (20%)	NS
β-Blocker	7 (7%)	4 (7%)	3 (7%)	
Ca channel blocker	82 (77%)	48 (80%)	34 (74%)	
Diuretics	13 (12%)	8 (13%)	5 (11%)	
Complicaton (n (%))				
Hypercholesterolemia	33 (31%)	21 (35%)	12 (26%)	NS
Diabetes	36 (34%)	22 (37%)	14 (30%)	NS
Cerebrovascular disease	32 (30%)	19 (32%)	13 (28%)	NS
Coronary artery disease	19 (18%)	9 (15%)	10 (22%)	NS
Total cholesterol (mg/dl; mean±SEM)	189.5±12.2	180.5±13.3	209.1±11.4	NS
Creatinine (mg/dl; mean±SEM)	1.0±0.1	0.9±0.1	1.0±0.1	NS

CV, coefficient of variation; ACE, angiotensin converting enzyme.

plays a pivotal role in the neural regulation of blood pressure, and blood pressure variability is regulated by this compensatory reflex mechanism. Arterial baroreflex function is decreased in elderly individuals (*9, 10*), and as a result, their blood pressure fluctuates (*11*). Although the mechanism of blood pressure variability in the elderly has been well elucidated, its clinical significance remains to be determined. In particular, there is little available information on the relationship between blood pressure variability and cardiovascular events in elderly hypertensive patients.

We hypothesized that blood pressure variability would be an independent risk factor for cardiovascular events in elderly patients with hypertension. To test this hypothesis, we investigated the outcome of elderly patients who underwent ambulatory blood pressure monitoring (ABPM). The results demonstrated that increased blood pressure variability is an independent predictive variable for cardiovascular events.

Methods

Patients

We recruited a total of 106 consecutive hypertensive patients, aged 60 years or older, who underwent 24-h ABPM at the University of Tokyo Hospital. The age, sex, smoking status, World Health Organization/International Society of Hypertension (WHO/ISH) classification, presence or absence of hypercholesterolemia and diabetes, history of cerebrovascu-

lar disease and history of coronary artery disease of each patient were investigated as baseline clinical characteristics according to their medical records. Hypertension was defined as an office systolic blood pressure (SBP) level above 140 mmHg and/or an office diastolic blood pressure (DBP) level above 90 mmHg on more than two occasions or the use of antihypertensive drugs. Smokers were defined as current smokers. Hypercholesterolemia was defined as a serum total cholesterol concentration above 220 mg/dl or the use of lipid-lowering drugs. Diabetes mellitus was defined as a fasting plasma glucose concentration above 140 mg/dl or use of antidiabetic medication. None showed severe renal failure (serum creatinine>2.0 mg/dl). Informed consent for this study was obtained from all patients.

Twenty-Four-Hour ABPM

Ambulatory blood pressure was recorded with a noninvasive automatic ABPM device (ABPM-630; Nippon Colin, Komaki, Japan) every 30 min for 24 h. The data used in this study were obtained by the oscillometric method. The accuracy of this device was previously described (*12*). Patients were not included in the study if their blood pressure could not be evaluated because of artifacts in more than 10% of the total measurements.

The mean values of 24-h, daytime (from 6:00 to 21:00) and nighttime (from 21:30 to 5:30) SBP and DBP were calculated for each patient. We calculated the coefficient of variation

Table 2. Profiles of 24 h, Daytime, Nighttime and Casual Blood Pressure

	Total ($n=106$)	Low CV group ($n=60$)	High CV group ($n=46$)
24 h blood pressure			
Systolic blood pressure (mmHg)	142.4±17.2	143.3±17.2	141.2±16.6
Diastolic blood pressure (mmHg)	78.1±10.3	79.2±10.6	76.8±9.9
CV of systolic blood pressure (%)	10.6±2.9	8.8±1.4	13.1±2.5*
Daytime blood pressure			
Systolic blood pressure	143.7±17.0	143.9±17.2	141.9±16.5
Diastolic blood pressure (mmHg)	79.2±10.4	79.7±10.9	78.6±9.9
Nighttime blood pressure (mmHg)			
Systolic blood pressure (mmHg)	140.1±20.3	142.0±18.5	137.7±20.7
Diastolic blood pressure (mmHg)	75.2±11.3	77.0±11.1	73.0±11.4
Casual blood pressure			
Systolic blood pressure (mmHg)	148.7±19.1	150.5±15.5	146.0±22.8
Diastolic blood pressure (mmHg)	81.4±11.6	82.0±10.0	81.0±13.0
Pulse pressure (mmHg)	67.3±16.6	69.1±16.0	64.8±17.3

Data are expressed as mean±SD. CV, coefficient of variation. *$p<0.01$.

(CV; CV=SD/mean value×100%) of 24-h SBP as an index of blood pressure variability. The CV values of daytime SBP and nighttime blood pressure as well as the SD values of 24-h SBP, daytime SBP and nighttime blood pressure were also calculated. Casual blood pressure was measured by the standard cuff method in the morning (9:00 to 12:00) when the ambulatory blood pressure was monitored.

To confirm the reproducibility, we compared the two subsequent measurements in 23 patients who underwent 24-h ABPM twice within 1 month. There were significant positive correlations between the two measurements of 3 parameters of 24-h blood pressure (24-h SBP, $r=0.808$, $p<0.01$; 24-h DBP, $r=0.693$, $p<0.01$; CV of 24-h SBP, $r=0.564$, $p<0.01$, $n=23$).

Follow-Up

Patients were followed up in the outpatient clinic of the hospital. Cardiovascular endpoints consisted of new onset of angina pectoris, acute myocardial infarction, coronary artery bypass graft surgery, percutaneous coronary intervention, sudden cardiac death, heart failure, cerebral infarction, cerebral hemorrhage, transient cerebral ischemic attack, acute aortic dissection and aortic graft replacement surgery for aortic aneurysm. Angina pectoris was diagnosed based on a history of chest pain and reversible ischemic change on electrocardiography during a spontaneous attack or exercise stress test. Acute myocardial infarction was diagnosed based on a history of chest pain, transient ST elevation on electrocardiography and increased serum myocardial enzyme concentrations. Sudden cardiac death was defined as a death that occurred within 1 h after the onset of symptoms. Heart failure was diagnosed based on clinical symptoms and signs and

chest roentgenographic findings. Cerebral infarction and cerebral hemorrhage were diagnosed based on focal neurological deficits and brain computed tomographic findings. Transient cerebral ischemic attack was diagnosed based on focal neurological deficits that disappeared completely less than 24 h after the onset. Acute aortic dissection was diagnosed based on a history of chest, back and/or abdominal pain and thoracic and abdominal computed tomographic findings.

Data Analysis

To explore the clinical significance of blood pressure variability on cardiovascular events, we divided the patients into two groups: a high CV group and a low CV group, using the mean CV value of 24-h SBP (10.6%) as a cut-off point and compared the two groups in terms of baseline clinical characteristics, blood pressure profiles and the incidence of cardiovascular events. In addition, we divided the patients into two groups according to the mean values of CV of daytime and nighttime SBP and SD of 24-h, daytime and nighttime SBP and analyzed the data for each group. Data are expressed as the mean±SD. Categorical variables were compared by χ^2 test. Continuous variables were compared by Student's t-test. Kaplan-Meier curves were plotted for event free survival and compared by log rank test. Finally, Cox's proportional hazards analysis was performed to examine the relative risk for cardiovascular events using age, sex, WHO/ISH class, smoking, hypercholesterolemia, diabetes, history of cerebrovascular disease, history of coronary artery disease, mean 24-h blood pressure, mean daytime blood pressure, mean nighttime blood pressure, casual blood pressure, pulse pressure and CV (or SD) of SBP as variables. A value of $p<0.05$ was considered to be significant.
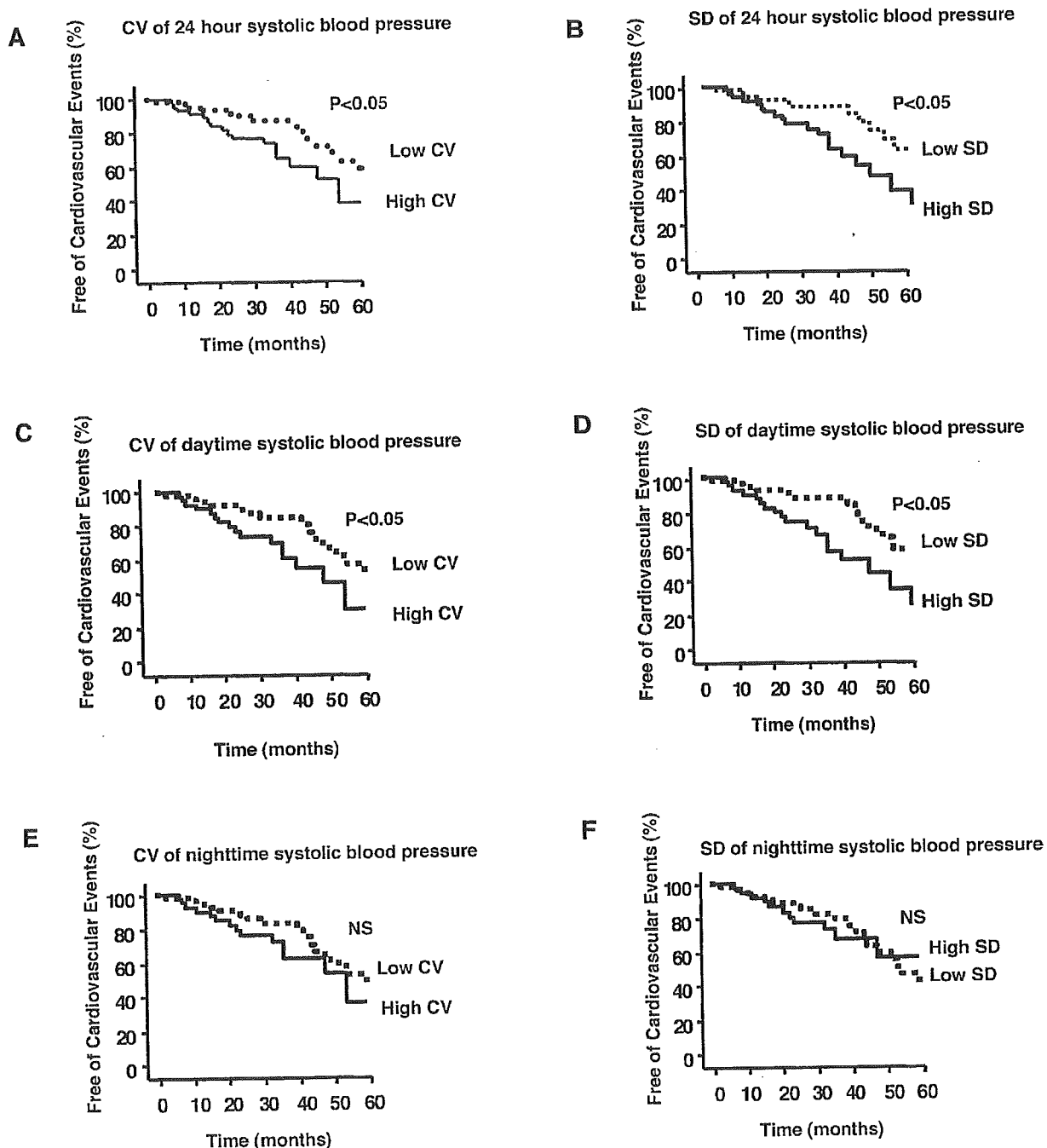
Fig. 1. *Cumulative event-free rates of cardiovascular events. Patients were divided into two groups according to the mean values of the CV of 24-h blood pressure (A), daytime blood pressure (C) or nighttime blood pressure (E), or those of the SD of 24-h blood pressure (B), daytime blood pressure (D) or nighttime blood pressure (F). CV, coefficient of variation.*

Results

The baseline clinical characteristics are shown in Table 1. All

patients were treated with one or two antihypertensive drugs. Calcium channel blockers were used in 77% of the patients. ACE inhibitors, β-blockers and diuretics were used in 18%, 7% and 12% of the patients, respectively (Table 1). The

Table 3. Relative Risk of Cardiovascular Events

	Relative risk	95% CI
A		
Sex (male)	3.28	1.22–8.81*
24-h SBP ($\geq$150 mmHg)	5.17	2.03–13.1**
CV of 24-h SBP ($\geq$10.6%)	3.58	1.63–7.85*
B		
History of coronary artery disease	4.88	1.41–16.9*
24-h SBP ($\geq$150 mmHg)	6.57	2.24–24.9*
SD of 24-h SBP ($\geq$15.0 mmHg)	3.26	1.25–8.52*
C		
Sex (male)	3.22	1.14–9.09*
History of coronary artery disease	5.00	1.38–18.1*
24-h SBP ($\geq$150 mmHg)	7.46	2.37–30.5*
CV of daytime SBP ($\geq$11.4%)	3.72	1.08–15.1*
D		
History of coronary artery disease	4.94	1.41–18.1*
24-h SBP ($\geq$150 mmHg)	6.63	2.23–25.8*
SD of daytime SBP ($\geq$16.4 mmHg)	3.72	1.06–8.00*

Clinical characteristics, mean values of 24-h, daytime, nighttime and casual blood pressure, pulse pressure and SD of daytime, nighttime SBP are used as variables. *$p<0.05$, **$p<0.01$. CI, confidence interval; SBP, systolic blood pressure; CV, coefficient of variation.

results of ABPM and casual blood pressure measurement are summarized in Table 2. Table 1 shows that there were no significant differences between the two groups in baseline clinical characteristics, including the history of cerebrovascular disease and that of coronary artery disease. Table 2 shows that mean 24-h blood pressure, mean daytime blood pressure, mean nighttime blood pressure, casual blood pressure and pulse pressure were also similar between the two groups.

The median follow-up period was 34 months (range, 3–60 months). A total of 39 cardiovascular events occurred during the follow-up period. The events consisted of 3 cases of angina pectoris, 7 of acute myocardial infarction, 1 of coronary artery bypass graft surgery, 3 of sudden cardiac death, 3 of heart failure, 14 of cerebral infarction, 1 of cerebral hemorrhage, 5 of transient cerebral ischemic attack and 2 of aortic graft replacement surgery. Neither percutaneous coronary intervention nor acute aortic dissection was observed.

To investigate the impact of blood pressure variability on the onset of cardiovascular events, we plotted Kaplan-Meier curves for event-free survival and compared them between the two groups. Figure 1A shows that the rate of cardiovascular events was significantly higher in the high CV group than in the low CV group. When the patients were divided into two groups according to the mean value of SD of 24-h SBP, a significantly higher rate of cardiovascular events was observed in the high SD group (Fig. 1B). With respect to daytime SBP, patients with high CV values of daytime SBP as well as those

with high SD values also had significantly more cardiovascular events (Fig. 1C, D). On the other hand, no difference in the rate of cardiovascular events was observed between the two groups when the mean value of CV or SD of nighttime SBP was used as a cut-off point (Fig. 1E, F).

To determine the independent predictive factors for cardiovascular events, the Cox's proportional hazards analysis was performed. This analysis identified male sex, high mean 24-h SBP and increased blood pressure variability (high CV value of 24-h SBP) as independent predictors for cardiovascular events (Table 3, A). In addition, the SD value of 24-h SBP was used as a variable rather than CV and the analysis was performed. History of coronary artery disease, high mean 24-h SBP and high SD value of 24-h SBP were significantly correlated with the onset of cardiovascular events (Table 3, B). Next, CV values of both daytime and nighttime blood pressure were used as variables. Male sex, history of coronary artery disease, high mean 24-h SBP and high CV value of daytime SBP were independent predictors (Table 3, C). Finally, the SD values of both daytime and nighttime blood pressure were used instead of the CV values and the analysis was performed. History of coronary artery disease, high mean 24-h SBP and high SD value of daytime SBP had significant correlations with the onset of cardiovascular events (Table 3, D).

Discussion

Hypertension is one of the leading causes of cardiovascular events (*1*) and the prevalence of hypertension increases with age (*2*). Therefore, it is important to clarify how to manage elderly hypertensive patients in clinical practice on the basis of their clinical features. Indeed, recent clinical trials have demonstrated that some antihypertensive drugs have a beneficial effect in elderly patients with isolated systolic hypertension (*13, 14*). However, the clinical significance of blood pressure variability remains to be determined in elderly hypertensive patients. Therefore, in this study, we analyzed the relationship between blood pressure variability and cardiovascular events in those patients.

Many studies concerning the clinical values of blood pressure variability have focused on circadian rhythm (*15–23*). Very recently, several clinical studies have been published to clarify the significance of blood pressure variability (*24–31*). The degree of blood pressure variability is related to hypertensive target organ damage (*24, 25*). The SD value of daytime blood pressure has a significant positive correlation with the progression of intima-media thickness of carotid arteries (*26*) and with the occurrence of lacunar infarction (*27*) in the hypertensive population. It has also been reported that the SD value of daytime blood pressure is correlated with left ventricular mass index both in hypertensive patients (*28*) and in the general population (*29*). In addition, an increase in the SD value of blood pressure variability is associated with cognitive impairment (*30*). Furthermore, it has been shown that a

high SD value of daytime blood pressure is an independent predictor for cardiovascular mortality in the general population (*31*). In addition to these studies, the present study on elderly patients with hypertension showed that high values of blood pressure variability of both 24-h blood pressure and daytime blood pressure were independent predictors of cardiovascular events in those specific patients.

The mechanisms underlying the positive correlation between blood pressure variability and the incidence of cardiovascular events could not be addressed in this study. The blood pressure variability is influenced by baroreflex regulation. The afferent fibers of this reflex arise from the aortic arch and carotid artery bifurcations and, therefore, in patients with arteriosclerosis, the afferent signal of the baroreflex may be decreased owing to low compliance of the arteriosclerotic vascular wall (*32*). In the present study, there was no significant difference in baseline clinical background or mean blood pressure values between the high CV group and low CV group. However, there is a possibility that subclinical arteriosclerosis may have been more advanced in the high CV group, and that blood pressure variability was increased as a consequence. This might explain the finding that more cardiovascular events occurred in the high CV group. On the other hand, another possibility is that blood pressure variability could have a direct effect on clinical outcome. The acute hemodynamic change observed in the high CV group might be a trigger for acute catastrophic events. In addition, blood pressure variability itself could induce vascular and organ damage, which might subsequently lead to cardiovascular events. Indeed, it has been reported that structural alteration of arteries (*33*) and cardiac hypertrophy (*34*) are observed in an animal model of high blood pressure variability.

Our study has some limitations. We used the discontinuous method of measuring blood pressure. This method is indeed less invasive to the patients but did not permit their full range of activity, and thus did not allow the recording of their full potential range of variability compared with the invasive continuous method. Indeed, we measured blood pressure only every 30 min. Because this measurement represents a low frequency sampling, the accuracy of blood pressure variability estimates assessed by ABPM may be reduced (*35*). In addition, our pilot study showed statistically significant correlations in terms of the short-term reproducibility of parameters obtained with 24-h ABPM, but absolute values of the correlation coefficient were not high enough. Furthermore, the possibility cannot be excluded that patients with excess nocturnal fall of blood pressure (extreme dippers), a condition that has already been shown to be associated with cerebrovascular disease (*17*), may have been defined as high CV patients in the present study. Moreover, it has been reported that some antihypertensive drugs reduce blood pressure variability (*36*). Because all patients were treated with one or two antihypertensive drugs in this study, there is a possibility that patients with lower blood pressure variability may have received more effective treatment, leading to better cardiovascular out-

comes, despite the fact that the average blood pressure levels were identical between the two groups. Patients with and without organ damage at baseline were mixed together for analysis. It is possible that the significance of blood pressure variability in patients with organ damage could be different from that in patients without organ damage, because the autoregulatory function in response to acute change in blood pressure might be impaired in patients with organ damage, and thus these patients might be more susceptible to cardiovascular events. To clarify this point, subgroup analysis with a larger number of patients is required.

The present study was performed retrospectively in a longitudinal fashion. We made only a single measurement of 24-h blood pressure for the prediction of further events. Therefore, a prospective study with larger sample size and with repeated measurement should be conducted in the future to confirm the findings obtained in this study.

In conclusion, our data indicate that blood pressure variability is an independent risk factor for cardiovascular events in elderly hypertensive patients. This finding suggests that not only the average blood pressure level but also blood pressure variability should be taken into consideration for the management of elderly hypertensive patients.

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2. 老化の理解と活き活き長寿

鳥羽 研二

始 め に

老化に関しては様々な誤解や錯覚がある．加齢の事実をめぐるPalmoreのクイズ[1]を解くことで誤解が認識される（一部改変）．

以下の文章が正しいか，誤っているかを判定せよ（解答は文末）

1) 大多数の高齢者には記憶喪失，見当識障害，痴呆症などの老化現象が見られる（ ）

2) 高齢になると，5感（視覚，聴覚，味覚，触覚，嗅覚）のすべてが衰えがちになる（ ）

3) 殆どの高齢者は，性欲がなく性的不能である（ ）

4) 肺活量は高齢者になると落ちる傾向にある（ ）

5) 殆どの高齢者は，いつも惨めさを感じている

6) 体力は高齢になると衰える（ ）

7) 1割の高齢者は介護施設に入所または入院している（ ）

8) 車を運転する高齢者の事故をおこす割合は，65歳以下より低い（ ）

9) 高齢労働者の仕事効率は若い人より低い（ ）

10) 4分の3以上の高齢者は，日常生活に差し支えないほど健康である（ ）

11) 大多数の高齢者は，時勢の変化に順応できない（ ）

12) 高齢者は通常，新しいことを学ぶのに時間がかかる（ ）

13) 平均的高齢者にとって，新しいことを学のは大変である（ ）

14) 高齢者は，若い人より反応が遅い（ ）

15) おしなべて，高齢者は似通っている（ ）

16) 大多数の高齢者は，めったに退屈しない（ ）

17) 大多数の高齢者は，社会的に孤立している（ ）

18) 高齢労働者は，若い労働者より職場で事故にあうことが少ない（ ）

19) 65歳以上の高齢者は日本の総人口の15％未満である（ ）

20) 殆どの医療専門家は高齢者を軽視する傾向がある（ ）

21) 大多数の高齢者の収入は，100万円以下である（ ）

22) 大多数の高齢者は働いているか，何らかの仕事をしたいと思っている（ ）

23) 高齢者は年をとるにつれて信心深くなる（ ）

24) 大多数の高齢者はめったにいらいらしたり，怒ったりすることがない（ ）

25) 2010年の高齢者の健康状態と経済的地位は若い人に比べ悪化する（ ）

老化の基本的理解

1. 「老化」はどう定義されるか？

広義の老化；生殖，発生，成熟，衰退，死亡にいたる全過程をさす．

狭義の老化；成熟期後加齢とともに非可逆的に進行する多くの分子的，生理的及び形態学的な衰退現象である．通常老化は狭義の意味をさす．

2. 生理的老化と病的老化の違いは何か？

生理的老化；精神的肉体的疾患や事故などがない，天寿を全うする人にも起こる表現形である．天寿は110歳〜120歳と考えられている．

病的老化；種々の遺伝要因，疾患やストレス（環境，外傷など）によって，老化の過程が短縮し，寿命が短縮することをいう．

3. 老化度

1) 現在までのところ，暦年齢以上に個人の総合的老化度を表現する簡便な方法は確立されていない．

An appreciation of the successful aging
Kenji Toba：杏林大学医学部 高齢医学

表1　年齢区分　Neugarten, J Sociol 1965

青年	18−22
女性の結婚適齢期	19−24
卒業して働くべき年齢	20−22
男性の結婚適齢期	20−25
美しい女性	20−35
男盛り	35−50
中年男性	40−50
働き盛り	45−50
退職年齢	60−65
老人	65−75

n=472, R=0.5, P<0.0001

図1　加齢による老年症候群の増加

2）暦年齢による区分：何歳以上を老人と呼ぶか

　年齢区分を Age Norm というが，現在，世界保健機構（WHO）や健康保険，年金などで，65歳以上を老人としている．この根拠は必ずしも定かではないが，アメリカの老年社会学者ノイガルテン女史の研究[2]が出典とされる．1965年，ノイガルテンはシカゴ近郊の中流以上の住民にアンケートを行い，80％以上が同意した年齢区分を発表した（表1）．40年以上前の調査のため，結婚適齢期など，現状にそぐわない年齢区分も少なくない．老人の定義も，総務庁の調査では70歳以上とする考え方が70％以上であり，年齢区分を見直すべき時期にきている．

　老化現象

　老化によって身体に認められる変化を老化現象とよぶ．生理的老化現象は必ずしも有害性を有しないことも多い．

　生理的加齢変化は外見上の変化に代表されるが，様々な観点から取り上げられている．

　1）外観上変化；白髪，禿，皮膚のしみ，しわ，角膜周辺部の輪状白濁（老人環）

　2）予備能・恒常性保持能低下；運動時心拍出量増加量減少，運動時呼吸機能低下，蛋白過剰摂取時の糸球体濾過量増加量減少，脱水時の電解質保持能低下，糖負荷時の血糖維持能低下

　3）感染防御能低下；リンパ球数及び機能の低下，遅延性アレルギー反応低下

　4）減少性変化：骨量減少，細胞内液量減少，筋肉量減少，筋力低下

　5）血管硬化性変化：大動脈脈波速度の増加

　6）乾燥性変化：毛髪水分量減少，皮膚弾性低下

　7）感覚器系変化：感音性の聴力低下，照度の需要増大，暗順応低下，味覚低下

　8）運動機能低下：最大歩行速度低下，瞬発力低下，柔軟性減少
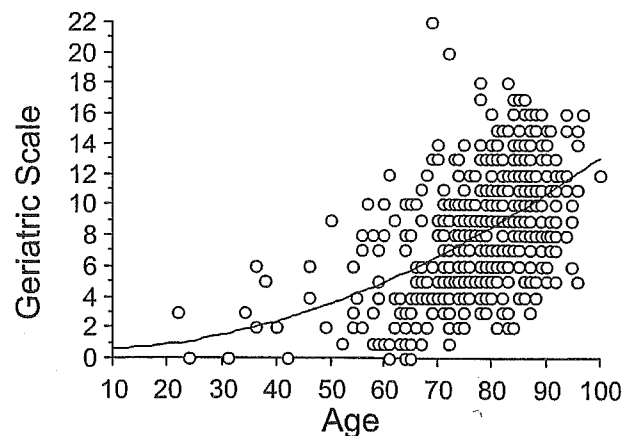
　臓器機能の老化[3]

　高齢者において疾患をもたない群での縦断的研究によって，通説と異なり，腎機能の代表的指標である糸球体濾過率は健常老年者では殆ど低下しないと報告された．しかしながら，多くの老年者はなんらかの疾病や異常を同時に持っている方が普通で，顕在性でない病的老化が生理的老化に加わった総体像としての加齢変化の概念としての Shock & Davis の成績の価値は全く失われていない．

生理的老化と病的老化の合計による老化度の測定

　高齢者は何らかの訴えを持つことが多く，厚生省の有訴率調査では，85歳以上では半数が何らかの症状を有している．我々は入院入所症例や在宅看護症例で患者の症状所見を調査し，症状所見の合計数に加齢変化を認めている（図1）．生理的老化と病的老化を合わせた老化度の表現形と考え Geriatric Scale と呼んでいる[4]．

機能老化しやすい（寝たきりになりやすい）集団とはなにか

　前期高齢者の寝たきり原因の第一位である脳血管障害においては，高血圧，糖尿病などの疾患や，加齢，男性など避けえぬ要因と，日本酒に換算して2合以上の飲酒，喫煙などといったライフスタイルの要因が縦断研究によって明らかにされている．一方痴呆では，代表的なアルツハイマー痴呆において，ApoE ε4 の遺伝的危険と高血圧が危険因子であることが明らかにされ，栄養学的にも，野菜不足，肉食過多などのライフスタイルの影響も注目を浴びている．しかしながら，健診レベルで調査

指導を行う体制はまだ確立していない.

　虚弱に対する最近の包括的アプローチ研究では，複数の生体システムに同時発生して虚弱を引き起こす障害に注目している.

　多数の生理的組織が症候的，臨床的機能不全の限界に近づき，複数の系統において予備能力の限界を越えた結果生じる症状または症候群という考え方で，極めて老年症候群に近い考え方である. 実際の測定方法としては，運動系機能として，握力，up&go テスト，トレッドミル，6分間歩行などを行い，認知機能として MMSE,バランス機能として片足立ち試験，栄養状態として BMI，周囲径などが挙げられている. これらは，「高齢者総合的機能評価ガイドライン」[5] に推奨した方法と図らずも一致している. 同様の考え方に，虚弱は自立と終末期の中間点と見なす考え方で，ハイリスクの因子として，75歳以上の高齢，ADL および IADL 障害・依存状態，転倒・骨折，多剤投与，慢性病，認知機能低下，抑うつ，栄養障害を指摘している[6]. これも，老年症候群に対する総合的機能評価が有用な指摘である.

老化予防と運動

　体操教室に参加した4,541人と参加していない一般市民395人（いずれも女性）との間で，活力度の加齢変化に対する運動効果を検討した結果では，両群とも65歳以降から活力度と健康意識が低下傾向にあり，老年症候群（頻尿，視力低下，不眠，関節痛），物忘れ，うつが増加傾向であったが，一般市民群に比べて体操教室参加群では老化にともなう変化が予防されていた. 活力度の維持に役立つ運動要因については，運動継続年数と運動頻度が有意に関与した. 運動をしないは70歳代以降では活力度が低下したが，運動教室参加群では維持されており，いきいき長寿増進効果が認めらた.

おわりに

　老化度を見かけ上や各臓器で測定し，一喜一憂することはない. 残された機能をいかに上手につかって，日常生活活動や知的活動に工夫を凝らすほうが建設的である.

　運動や栄養による老化予防研究は今後の有望な研究分野である.

　（Palmore のクイズ　正解は偶数番，間違いは奇数番. 2/3 以上出来れば老化通）

文　献

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頻尿・尿失禁
—中高年の明るい過ごし方—

司会 **東間 紘**　　出席者 **山口 脩**
井上裕美
鳥羽研二

I　蓄尿障害の現状

東間　高齢化の進む現代社会において，健康で充実した日々を送りたいという患者の要求に応えることが，臨床に携わる者の新たな使命となっています．頻尿や尿失禁など，蓄尿障害の問題は，患者の行動を制限し，快適で明るい自立した生活の障壁ともなる重大事です．本日はこの問題について，先生方にそれぞれの立場からご意見をおうかがいしたいと思います．山口先生，まず蓄尿障害をとりまく現状についてお話しいただけますか．

山口　高齢者のQOLを著しく損なう蓄尿障害ですが，日本排尿機能学会による過活動膀胱（over active bladder：OAB）の疫学調査によると，40歳以上の方の12.4％が過活動膀胱であるとされ，わが国には推定で810万人もの患者がいることが示唆されました．40〜50歳代の有病率は6〜7％ですが，60歳代では12％，80歳代では36％以上と，加齢に伴って増加することも明らかになっています．

過活動膀胱は尿意切迫感，切迫性尿失禁，頻尿，夜間頻尿などの症状をきたす疾患ですが，例えば夜間頻尿は高齢者の転倒骨折の主要な原因であることがデータとして示されており，また睡眠障害の要因にもなっています．男性においては，生存率にも影響するという報告もあります．

経産婦に多くみられる腹圧性尿失禁も，更年期のころから増え始めますが，やはりQOLを大きく損

なっています．男性の前立腺肥大症のような，過活動膀胱の症状と排尿障害が共存する厄介な疾患も含め，蓄尿障害に悩む中高年の患者はきわめて多く，重大な問題になっています．

II　蓄尿障害とQOL

東間　悩んでいる患者は多くても，医師に相談しづらいという理由から，実際に受診する方はどうしても少なくなってしまうようですね．井上先生，婦人科の立場からいかがでしょうか．

井上　高齢者が多いという湘南の地域特性もあるのでしょうが，日常診療のなかで蓄尿障害の患者を診る機会は非常に多いと感じています．高齢者のQOLを損なう婦人科系の代表的な疾患として，性器脱があります．膀胱瘤や子宮脱等の加齢，分娩，結合織異常，子宮摘出等が原因と考えられている疾患ですが，近年ようやく性器脱に合併する尿失禁が注目され始めました．湘南鎌倉総合病院に性器脱を主訴として受診した患者の46〜50％の方は，尿失禁を合併しています．反対に尿閉を合併する例もありますが，そのうちの10〜20％は潜在性の尿失禁を伴っている可能性があり，性器脱の手術後に尿失禁を再発させない工夫が必要と感じます．

性器脱の患者約450名の平均年齢を調べたところ，71歳でした．89歳で手術を行ったケースもあります．患者本人と向き合って話をすると，残された人生の質を高めたいとおっしゃるケースがほとんどです．

尿失禁のせいで外出が制限される，重度の性器脱で温泉に行くこともできない，そういった訴えをする患者は非常に多く，高齢者のQOLの問題について，われわれはこれまで以上に取り組まなければならないと実感しています．

東間 もう少し我慢できるのではないか，という医師や患者家族の思惑は，患者本人の意思と相当ずれているのですね．鳥羽先生，高齢医学からみたQOLの問題にはどのようなものがあるのでしょうか．

鳥羽 東京大学病院の外来で統計をとったのですが，一晩に2回以上トイレに立つ夜間頻尿は60歳以上では60％にもなり，尿失禁も5％にみられました（臨床看護 23：1944〜1946, 1997）．その後発表された厚生労働省の調査でも，85歳以上では3分の1がおむつを使用している，つまり蓄尿障害があるということです．

転倒骨折との関連についても，長期療養施設に入所している1,200名について調査したところ，夜間頻尿が独立した危険因子であることがわかりました．在宅の1,400名ではそれほど強い関係は認められませんでしたから，患者の状態が悪いほど，夜間頻尿は転倒骨折の危険因子になると考えています．

在宅での不眠や苦痛の度合に関する調査では，2回までなら許容範囲にあるようでした．しかし，1人でトイレに行くのが困難な場合には，介護者もそのたびに起きなければなりません．頻尿とQOLの問題は，日常生活活動度（activities of daily living：ADL）のレベルによっては，家族の問題でもあるのです．高齢化がますます進むなかで，今後さらに大きな問題になってくるのではないかと思っています．

III 患者に対する 啓発活動の重要性

東間 外来で診療をされていて，問題を感じる点はありますか．

山口 まず診療以前の問題として，受診率の低さが挙げられます．市民公開講座などでアンケートをとると，頻尿や尿失禁で生活に深刻な影響が出ているにもかかわらず，「年齢のせいなので仕方がない」「恥ずかしい」といった理由で，半数は医師に相談

したことがないようです．頻尿や尿失禁は適切な治療によって治すことができるのだと，広く一般に啓発していくことが重要だと思います．

**東間** 初診時に問診票を使う施設は多いと思いますが，そこに蓄尿障害についての項目を加えておけば，かなり効果があると思うのですが……．

鳥羽 そうですね．かつては，骨が脆くなるのも，食べ物が飲み込みにくくなるのも，加齢のせいだとされてきました．しかし現在では，骨粗鬆症や嚥下障害は広く一般に知られている疾患であり，医師への相談を「恥ずかしい」と感じる患者はいないでしょう．蓄尿障害もこれと同列に扱うべき疾患であることを，一般市民や医師に対してもアピールしていく必要があります．一般の内科でも，外来患者に「夜，何回トイレに起きますか」と，必ず聞かなければなりません．内科の治療と夜間頻尿には密接な関係があるにもかかわらず，それを軽視する医師が多い現在の状況は，憂慮すべき問題だと思っています．

山口 鳥羽先生のおっしゃる通りだと思います．やっと決意してかかりつけ医を受診しても，その医師が蓄尿障害に関心をもっていなければ，加齢のせいにして治療を施さないなど，正しい対処がなされません．これは患者にとって大変不幸なことですから，われわれ専門医がさらに啓発活動を活発に行い，改善していかなければなりません．

IV プライマリ・ケア医に対する 啓発活動の重要性

東間 鳥羽先生，今お話しいただいた内科の治療と蓄尿障害の関係について，もう少し詳しくご説明いただけますか．

鳥羽 例えば降圧利尿薬は，高血圧症の第一選択薬として頻繁に使われている薬です．しかし過活動膀胱を合併している高齢者に投与すると，実に75％もの患者で尿失禁を引き起こすというデータが示されています．ですから少なくとも頻尿のある患者には降圧利尿薬を使うべきではないと思いますが，高血圧症の治療ガイドラインでは蓄尿障害について全く触れられていません．つまり循環器を専門にしている医師は，夜間頻尿についての問診をせず，誤った
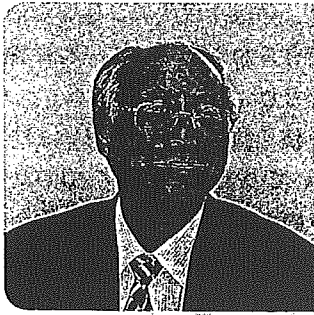
東間　紘先生

東京女子医科大学病院
院長

治療をしている可能性があるわけです.

東間　その意味で, 内科系の医師にもっと関心をもってもらいたいということですね. 婦人科でも蓄尿障害に対して興味があまりないと感じられることはありますか.

井上　若い医師の関心の低さは感じています. 尿失禁や性器脱の治療より, 癌の外科手術や腹腔鏡を使った手技を習得するほうが魅力的なものに見えるようです. 癌患者と性器脱の患者の間に優劣などない, どちらも同じように治療に取り組み, 患者のQOLを少しでも向上させる努力をしなければならないということを, しっかり教育する必要があると思います.

東間　最先端の研究についての講義ばかり重視される傾向にあり, 頻度の高い疾患や症状に対して, もっと関心をもてるような教育があまりなされていないことは, 大きな問題といえますね.

V　蓄尿障害の先端的研究

鳥羽　確かにそうですね. しかし, 例えば認知症や骨粗鬆症の領域では, 薬物療法などの先端的な研究が進むにつれて若い医師が関心をもって参加するようになってきました. 血管の分野で進んでいる平滑筋研究が, なぜ膀胱では遅れているのか, 明確に答えられる泌尿器科医はおそらくいないのではないでしょうか. 基礎研究の分野でダイナミックな進展がみられれば, 若い医師も多く入ってくると思います.

山口　鳥羽先生のおっしゃることに関連しますが, 膀胱は尿路上皮, 膀胱粘膜, 粘膜下層, 平滑筋という, 血管とほぼ同じ構造をもっています. 研究についていえば, 例えば尿路上皮では, 血管内皮と同様

にプロスタグランジン, NO, ATPなどが合成されていることがわかってきています. 尿がたまって膀胱が伸展すると, その刺激によりNOやATP, プロスタグランジンが放出され, それが求心性ニューロンを刺激することで尿意切迫感などの臨床症状がみられるわけです. このようなトピックスは, 若い医師にとっても魅力的なはずです.

東間　脳や神経と蓄尿障害の関連についても, 新しい研究成果が出ているようですね.

鳥羽　蓄尿障害は, 下部尿路の病態であるとともに, 中枢神経系の疾患でもあります. 杏林大学では, 側脳室周囲病変 (periventricular hyperintensity：PVH), 深部皮質下白質病変 (deep and subcortical white matter hyperintensity：DSWMH) など脳室周囲の白質におけるMRIでの強度が, 頻尿と関係していることを明らかにしました. このような所見は30歳くらいから徐々に増えてきますので, 加齢に伴う頻尿の一部は, 中枢性の循環障害を介したメカニズムによって引き起こされている可能性があります. 遺伝子や液性因子の関与についても研究中ですが, 非常に興味ある分野であることは間違いないと思っています.

東間　泌尿器科でも, 脳障害と排尿についての研究をしている若い医師は増えているようですね.

山口　はい. もともと泌尿器科領域における蓄尿障害の研究は, 脳血管障害や脊髄障害にみられる神経因性膀胱から始まっています. 中枢の循環障害と蓄尿障害は, 確かに深い関係にありますが, 最近では神経障害によって蓄尿障害を起こしている患者はかなり少ないとされています. 頻尿, 尿失禁, 尿意切迫感などの原因疾患として今注目されているのは前立腺肥大症で, 閉塞膀胱による局所変化としてとらえられるようになってきました.

　また, 尿意切迫感が突然襲ってくる過活動膀胱ですが, そのうちの90％以上を特発性過活動膀胱が占めています. 尿意切迫感という病的な膀胱知覚と, 膀胱に尿がたまって感じる通常の尿意が混在しているのが特徴ですが, 病因はわかっていません.

鳥羽　頭部のMRIを検討されたことはありますか.

山口　まだ端緒についたばかりの研究ですが, PETによる検討は行われています. 最近のデータでは,

尿意切迫感と通常の尿意を感じる大脳皮質の部位には，解離がみられることがわかってきました．また，過活動膀胱は女性にきわめて多い疾患ですが，更年期以降のエストロゲン分泌の変化が中枢神経に及ぼす影響も，原因の一つとして考えられています．さらに，膀胱を弛緩させるβ_3受容体は遺伝子変異を起こしやすく，不完全なβ_3受容体しかつくれなくなってくると，膀胱が十分に弛緩できなくなってしまうという，遺伝子レベルでの機序解明も試みられています．今，さまざまな角度からの研究が世界的に始められているところです．

東間 過活動膀胱とエストロゲンとの関係はよく話題になりますが，エビデンスはあるのでしょうか．

井上 今，山口先生のご指摘以外で，エストロゲンと直接組織への関係をみてみると，両者の関与は考えられます．組織を支えるコラーゲンが加齢により減ってくる要因に，エストロゲンの分泌量低下が関与するといわれていますし，過活動膀胱の非神経性の病因として加齢や，骨盤底の脆弱化が指摘されていますので，両者（過活動膀胱とエストロゲン）に何らかの関係はあると思います．ただ，エビデンスがあるとまではいえません．一般に，高齢者では性器脱や尿失禁の発生率が上昇します．エストロゲンは性器脱や尿失禁によい効果や症状の改善をもたらしますが，エストロゲン単独でこれらを完全には治療することはできていません．

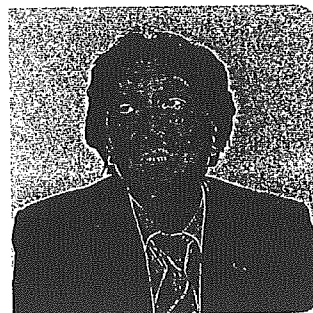**東間** これらの先進的な研究で，膀胱がただの蓄尿袋ではないことを，他科の医師にも広く知っていただきたいですね．

VI 過活動膀胱の診療とガイドライン

東間 続いて，蓄尿障害の診断と治療についてお話をうかがいたいと思います．

山口 過活動膀胱の薬物療法には，今のところ抗コリン薬しか選択肢がありません．今後高齢化がさらに進み，専門医ではない医師が蓄尿障害を診る機会が増えていくと思われますが，このとき懸念されるのが，投与すべきではない患者への抗コリン薬の使用です．過活動膀胱様の症状を訴えてくる中高年の

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男性では，まず前立腺肥大症を疑わなければなりませんし，もしそうならα_1遮断薬が第一選択になります．また高齢者では排尿筋の収縮障害があり，安易に抗コリン薬を投与すると，尿閉をきたすことになります．

このような事態を防ぐため，過活動膀胱の診療ガイドラインが作成されました．専門医ではない医師を対象とした診療アルゴリズムがつくられており，問診，検尿，残尿量測定を必ず行うよう記載されています．脳血管障害や脊髄障害の既往がなく検尿が正常で，超音波による残尿測定が50mL以下であれば抗コリン薬を処方してもかまわないとしています．

検尿で膀胱炎などの所見があれば尿路感染症として治療し，神経因性膀胱の疑われる既往がある，血尿がある，残尿量が多いなどの所見があれば，複雑な病態をもつ疾患である可能性がありますから，専門医に紹介していただきたいと思います．

東間 日本泌尿器科学会のガイドラインですね．ぜひ活用していただきたいですし，専門医の側も啓発活動をさらに推し進めなければなりませんね．

山口 プライマリ・ケア医に対し，蓄尿障害がQOLを大きく損なう重大な疾患であることを広く認識してもらい，対応するための手順を明示することが今後ますます重要になってくると思います．

VII 高齢者の頻尿の診断と治療

東間 高齢者の頻尿の診療にあたるうえで，特に注意すべき点はありますか．

山口 高齢者では，糖尿病，高血圧症，心疾患，腎機能障害など，さまざまな合併症がみられます．そ

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のようなケースでは，多尿が頻尿や尿失禁の原因になっていることが非常に多くなっています．頻尿の直接的な原因疾患がないのに，降圧利尿薬の治療によって利尿亢進状態になり，排尿記録（frequency-volume chart）で1日の尿量が3Lを超えるような多尿となっているのです．さらに，「水を飲めば血液が薄くなり脳梗塞や心筋梗塞を回避できる」と医師に勧められ，大量の水分を摂取して多尿になっているケースもあります．夜間頻尿の80％は夜間多尿が原因ですから，頻尿や尿失禁の診断にはfrequency-volume chartが不可欠といってよいでしょう．

東間 Frequency-volume chartは，泌尿器科領域では普及している排尿回数と1回ごとの尿量を24時間記録してもらうシートですね．外来に，frequency-volume chartや尿量を計るためのカップなどは用意してあるのでしょうか．

山口 はい．3日間続けて記録すればより正確なデータが得られますが，1日でもいいからと伝えて記録方法を指導し，目盛り付きの紙コップとともに患者に渡します．特に起床時間，就寝時間，そして夜間に起きた時間をきちんと記録するようにお願いしておきます．

鳥羽 夜間の血管内脱水は心血管障害の危険因子ですから，私も水を飲むようにと勧めます．ただ，血管内脱水を防ぐためには就寝前にコップ1杯飲めばよいわけで，多量に飲むのは無意味だと思います．

睡眠時や安静時にはバソプレシンが上昇し，皮膚や筋肉への血流が低下し，内臓の血流が増加します．特に高齢者では，腎臓での濃縮力が低下していますので，夜間のほうがより多尿になりやすいわけです．濃縮力を強化することができれば，血管内脱水と多尿の両方を解決することができますが，適当な薬剤

がないのが現状です．降圧利尿薬を朝に服用させて昼間の尿量を増やすと，夜間頻尿が抑えられるという研究もあります．少なくとも降圧利尿薬は，夜には処方しない工夫が必要ではないでしょうか．

東間 高齢者ではバソプレシン分泌の日内リズムが変動しているのでしょうか．

鳥羽 確かに，若年層のようなしっかりしたリズムではないですね．ですからデスモプレシンを夜に使い，翌朝にバソプレシンV_2アンタゴニストでたまった水分を排出できるのではないかと試みたことがあるのですが，うまくいきませんでした．

山口 デスモプレシンはスプレーで簡単に吸収させられるようになっていますね．

鳥羽 はい．投与後に排尿させる働きをもつ薬剤があれば，治療法として可能性があると思います．

VIII 中枢系の合併症と蓄尿障害の治療

東間 脳血管障害と蓄尿障害との関連はどうなっているのでしょうか．

鳥羽 長期介護施設では，麻痺のある患者の80〜90％に尿失禁がみられるのに対して，麻痺がない患者では40％程度と大きな差がありますから，やはり関連があると考えられます．

東間 ほかにも関連する疾患はありますか．

鳥羽 認知症と蓄尿障害とは，疾患としての関連は強くないと思いますが，治療に使う薬剤についての問題があります．認知症の治療薬であるコリンエステラーゼ阻害薬の治験がいくつか行われていますが，副作用として頻尿や尿失禁が出ているようです．逆に，頻尿に対して処方される抗コリン薬が認知症を引き起こす可能性も指摘されています．軽度の認知症患者に頻尿がみられたとき，私は漢方などを使っているのですが，泌尿器科の先生方は，どのように対処されているのでしょうか．

山口 オキシブチニンは古くからある抗コリン薬ですが，これが認知障害を誘発したという報告があり，高齢であるほど危険率が増すといわれています．オキシブチニンはムスカリン受容体の拮抗薬ですが，M_1，M_2，M_3とあるサブタイプに選択性がないため，