Table 3 Correlation between platelet activation and clinical indices

	PNC	*PNC (ADP)*	*Δ-PNC*	*P-selectin*	*P-selectin (ADP)*	*Δ-P-selectin*
Age	0.51**	0.61**	0.52**	0.36*	0.38*	0.32
Systolic blood pressure	0.41*	0.53**	0.48**	0.41*	0.43*	0.35*
Diastolic blood pressure	0.43*	0.49**	0.40*	0.25	0.40*	0.36*
Pulse rate	0.28	0.25	0.16	0.04	0.15	0.15
Blood sugar	0.09	−0.18	−0.31	−0.17	0.13	0.16
Total cholesterol	−0.14	−0.07	0.001	−0.10	−0.13	−0.11
Blood urea nitrogen	−0.01	0.12	0.18	−0.05	0.05	0.06
Creatinine	0.05	−0.13	−0.22	0.04	−0.17	−0.18
Gender						
Male	10.3±5.9	19.7±8.7	9.4±6.9	13.1±1.8	35.5±9.3	22.4±9.0
Female	8.8±3.8	20.7±11.4	11.9±6.8	13.0±1.7	37.7±9.2	24.7±9.3

PNC = platelet neutrophil complexes; ADP = adenosine diphosphate; Δ-PNC = PNC (ADP)−PNC; Δ-P-selectin = P-selectin (ADP)−P-selectin; hb-PWV = heart–brachial pulse wave velocity; ba-PWV = brachial–ankle pulse wave velocity.
For parameters from age to creatinine, values are correlation coefficients.
*$P<0.05$.
**$P<0.01$.
For gender, values are mean±s.d., with differences evaluated with ANOVA.

Table 4 Relation between platelet activations and PWV

	PNC	*PNC (ADP)*	*Δ-PNC*	*P-selectin*	*P-selectin (ADP)*	*Δ-P-selectin*
Not adjusted						
hb-PWV	0.62**	0.74**	0.63**	0.45**	0.57**	0.50**
ba-PWV	0.59**	0.71**	0.61**	0.47**	0.51**	0.43*
Adjusted for age						
hb-PWV	2.86**	6.95**	4.09*	0.75	6.55**	5.80*
ba-PWV	0.79	2.01**	1.22*	0.28	1.75*	1.47
Adjusted for systolic blood pressure						
hb-PWV	3.20**	7.23**	4.04**	0.59	5.09*	4.50*
ba-PWV	1.21**	2.64**	1.44*	0.23	1.48	1.25
Adjusted for diastolic blood pressure						
hb-PWV	3.08**	7.67**	4.59**	0.87*	5.32**	4.46*
ba-PWV	0.97**	2.50**	1.54**	0.34*	1.45*	1.10
Adjusted for age and systolic blood pressure						
hb-PWV	2.80*	6.43**	3.63*	0.58	5.93*	5.35*
ba-PWV	1.08	2.32*	1.24	0.24	1.72	1.48
Adjusted for age and diastolic blood pressure						
hb-PWV	2.63*	6.59**	3.97**	0.78	6.06*	5.28*
ba-PWV	0.76	2.17*	1.40	0.40	1.66	1.26

PNC = platelet neutrophil complexes; ADP = adenosine diphosphate; Δ-PNC = PNC (ADP)−PNC; Δ-P-selectin = P-selectin (ADP)−P-selectin; hb-PWV = heart–brachial pulse wave velocity; ba-PWV = brachial–ankle pulse wave velocity.
'Not adjusted' — values are correlation coefficients between PWVs and indices of platelet activation before adjustment.
*$P<0.05$.
**$P<0.01$.
Other values are regression coefficients between PWVs and indices of platelet activation adjusted for age and/or blood pressures as indicated.
*$P<0.05$.
**$P<0.01$.

carotid arterial stiffness and the degree of coronary artery disease. Popele *et al*[26] recently reported that aortic stiffness as measured by PWV is strongly associated with common carotid intima-media thickness, carotid arterial plaques, and the presence of peripheral arterial disease. Moreover, some population-based studies have demonstrated higher blood pressure, increased age, and male gender to be associated with increased PWV.[16,20,21] Pulse pressure may also relate to arterial stiffness and cardiovascular events, with higher pulse pressure reflecting elevated systolic pressure and reduced diastolic pressure due to increased arterial stiffness. In the present study, significant relationships were observed between PWVs and age, blood pressure, and pulse rate, in accordance with previous studies.

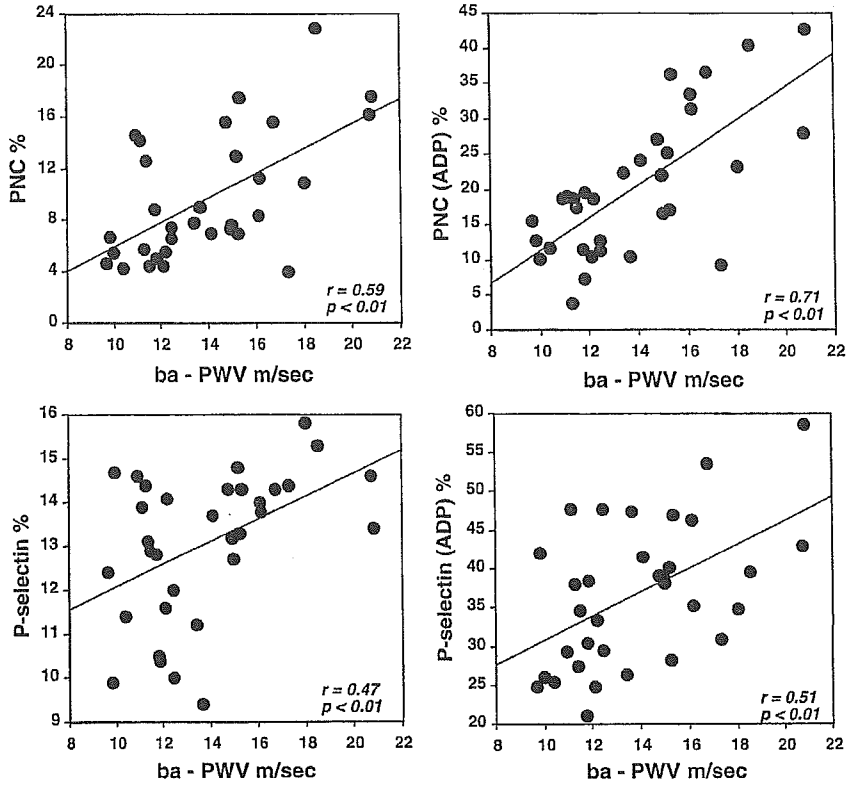

Figure 1 Correlation between ba-PWV and PNC (upper two panels). PNC = platelet neutrophil complexes; ADP = adenosine diphosphate; Δ-PNC = PNC (ADP)−PNC; Δ-P-selectin = P-selectin (ADP)−P-selectin; hb-PWV = heart–brachial pulse wave velocity; ba-PWV = brachial–ankle pulse wave velocity.

P-selectin is a component of α-granules that is expressed on the platelet surface membrane and released into the plasma upon platelet activation. Although the bulk of circulating soluble P-selectin appears to be platelet derived,[27] the substance is also found in the Weibel–Palade bodies of endothelial cells.[28] Direct measurement of platelet membrane P-selectin is therefore a more sensitive method of assessing platelet activation. In the present study, we evaluated platelet activation by measuring membrane activation markers using flow cytometry with activation-dependent monoclonal antibodies. PNC levels were also measured using the same method. P-selectin levels in our normal subjects aged 49±15 years were 13.1±1.7%; this was higher than that in quoted by other studies, possibly due to the differences in monoclonal antibodies or in sample manipulation.

P-selectin expressed on activated platelets causes formation of PNC. Moreover, platelets and platelet-derived P-selectin play an important role in thrombus growth at the site of atherosclerosis.[2] *In vivo* and *in vitro* studies have shown that shear stress and exposure to atherogenic stimuli, such as oxidization by low-density lipoprotein or cigarette smoking, induce rapid P-selectin-dependent aggregation and accumulation of leukocytes and platelets.[4,5,11] Activated platelets accumulating in thrombi at the site of ruptured atherosclerotic plaques will express CD62P. In clinical studies, P-selectin has been shown to be a marker of platelet activation related to adverse cardiovascular events such as hypertension, coronary artery disease, cerebrovascular disease, and peripheral arterial disease,[6,7,10–12] and also to be a predictor of cardiovascular events.[8,12] PNC, forming as a result of the interaction of platelet P-selectin and neutrophils also promotes platelet activation.[24] This is the first study to demonstrate that P-selectin and PNC were significantly correlated with arterial stiffness evaluated by PWV in normal subjects. In an analysis of four randomized trials, Hebert *et al*[29] showed that aspirin therapy was beneficial in the primary prevention of vascular disease. Higher levels of other membrane markers such as von Willebrand factor receptor are observed in activated platelets, which are affected by aspirin or ticlopidine.[30] Therefore, our results indicate that, in the normal population, antiplatelet agents may play a role in preventing cardiovascular events through factors other than P-selectin.

Although the exact mechanism accounting for the relationship between platelet activation and arterial stiffness is unknown, it is possible to make

the following speculations. When arterial stiffness is raised, shear stress might play an important role in platelet activation. Using cone-plate viscometry,[3] Goto *et al* showed that platelet activation (measured by P-selectin surface expression, von Willebrand factor-mediated platelet aggregation and translocation of GP Ibα) was induced by high shear rate of $10\,800\,s^{-1}$. Higher arterial stiffness increases blood flow velocity and produces a steep systolic pressure waveform,[31] and it is possible that the resulting increased shear stress could promote platelet activation. Another possible mechanism is that endothelial dysfunction may interact with arterial stiffness and platelet hyperactivity. Kobayashi *et al*[32] showed significant correlation between endothelial dysfunction measured by flow-mediated dilatation and ba-PWV. Platelets are also activated by endothelial dysfunction. On the other hand, activated platelets themselves may cause arterial stiffness via vascular smooth muscle cell growth factors and extracellular matrix modulator released from platelets, that is, PDGF.[33] However, this response also occurs at the site of endothelial injury. Further study is therefore required to clarify whether arterial stiffness causes platelet activation or alternatively whether platelet activation might result in arterial stiffness.

Limitations

Despite the small sample size, it is possible that the broad age range (23–77 years) of our subjects caused outliers in PWV and platelet activation. However, significant correlations were found when age and blood pressure were adjusted for, suggesting that the influence of age did not entirely explain the correlation between PWV and platelet activation. In the present study, ba-PWV was 14.1 ± 3.0 m/s in men and 13.6 ± 3.1 m/s in women; values higher than those reported by Yamashina *et al*.[20] Furthermore, it is not known whether such a relationship between arterial stiffness and platelet activation is found in patients with conditions such as hypertension, diabetes mellitus, coronary heart disease, and stroke. Further studies should be therefore performed in such patients, using larger sample sizes.

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ORIGINAL ARTICLE

Trunk deformity is associated with a reduction in outdoor activities of daily living and life satisfaction in community-dwelling older people

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Abstract We have evaluated the association between trunk deformities of the sagittal plane and functional impairment of daily living in community-dwelling elderly subjects. The analysis involved a detailed assessment of indoor and outdoor activities of daily living, satisfaction with life, and mental status. The participants in this study were 236 community-dwelling older adults, aged 65 years and older, living in Kahoku district of Kochi in Japan. The participants were classified based on their posture, which was assessed using photographs of the subjects, and interviewed to assess their basic activities of daily living (BADL), instrumental ADL (IADL), and cognitive well-being in the cross-sectional study. The statistical analysis was performed using the Mann-Whitney *U*-test. The lumbar kyphosis group received significantly lower BADL and IADL scores than the normal group. The trunk deformity group which were defined as kyphosis, flat back, and lumbar lordosis groups exhibited decreases in activities that included going out, shopping, depositing and withdrawing money, and visiting friends in the hospital. These activities require going outdoors; thus, this study showed that the trunk deformity group had limitations in outdoor activities. There was no significant difference between the geriatric depression score (GDS) and the pattern of posture. The abnormal trunk deformity groups tended to score lower than the normal group with regard to subjective healthiness and life satisfaction measures, including subjective health condition, everyday feeling, satisfaction with human relationships, satisfaction with economic condition, and satisfaction with present life.

Keywords Activities of daily living · Kyphosis · Life satisfaction · Trunk deformity

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Introduction

Several studies have reported on the relationship between trunk deformity and lumbago [1,2]. It is predictable that patients with abnormal posture would be at increased risk for falling, as their balance is perturbed by the posture abnormality [3,4]. Loss of distal lumbar lordosis is the main cause of sagittal imbalance in individuals who do not maintain sagittal alignment [5]. This abnormal posture could lead to the limitation of daily activities.

There have been several evaluations of posture and functional activities to date [6]; however, very few involve elderly subjects. Ettinger et al. [7] reported that kyphotic women did not have greater back pain, disability caused by back problems, or poorer health than non-kyphotic women. Another study showed a poor correlation between quality of life and abnormal findings on radiography or densitometry [8].

Vertebral body compression fractures have been shown to be associated with the severity of kyphosis [9]. Ryan et al. [10] reported that there was a significant association between scores of osteoporosis severity and limitations in functional activity. Vertebral compression fractures associated with osteoporosis can be self-limiting, causing considerable pain and disability [8].

Vertebral compression fractures are associated with significant impairments in physical, functional, and psychosocial performance in the elderly [11,12,13]. It is crucial to improve the mental status of the elderly. However, there have been few reports regarding the

association between trunk deformity and psychogenic activity in elderly patients.

In this study, we have evaluated the daily activities and mental condition of community-dwelling elderly subjects with regard to the severity of trunk deformity in the sagittal plane.

Materials and methods

Subjects

Participants who applied in 1999 included 236 community-dwelling older adults, aged 65 years and older, living in Kahoku district in Kochi prefecture, who had been enrolled in one of several studies involving annual medical check-ups (beginning in 1994). The population of Kahoku rural area is 5800 people, 50% of whom are engaged in agricultural work.

Study participants were observed from July to August 1999, and then classified based on their posture, which was assessed using photographs taken by researchers. In total, there were 145 females (mean; 79.0 years) and 91 males (mean; 80.3 years) with a mean age of 80 years (range, 65–94 years), and a mean height of 149.1 cm. Functional status of the lumbar spine [14] and knee [15] were measured using the assessment of the Japanese Orthopaedic Association (JOA). In this study, JOA scores for assessing treatment of low back pain was calculated without incorporating urinary bladder function. Comorbidities were hypertension (31.6%), cardiac arrhythmia (6.1%), diabetes mellitus (5.7%), cerebrovascular disorder (4.2%), coronary artery disease (3.2%), senile dementia (2.1%), and Parkinson's disease (0.4%).

Methods

Interviews and examinations, conducted at the community plaza of Kahoku, consisted of a questionnaire covering physical health, functional status, and mental status. The analysis of trunk deformity was examined by photography. The presence or absence of disease was based on the subjects' self-report of a doctor's diagnosis. Informed consent was obtained from all participants.

Postural analysis

In order to protect the participants' privacy when undergoing the community health check-ups, we constructed a device with which to assess trunk posture without requiring that the subjects disrobe. Participants wore clothes typical of the summer season, and the device was equipped with a band that, when twisted, would reveal the alignment of the body. Each participant had reflective surface markers attached at various locations, including C7, T6 (xyphoid process level), L4 (Jacob line level), the left greater trochanter, the left lateral chondyle of the femur, and the left lateral malleous, as shown in Fig. 1. For the photograph, participants were positioned carefully and asked to remain relaxed while standing up straight. Posture in the sagittal plane was classified into one of the following five types: I normal, II thoracic

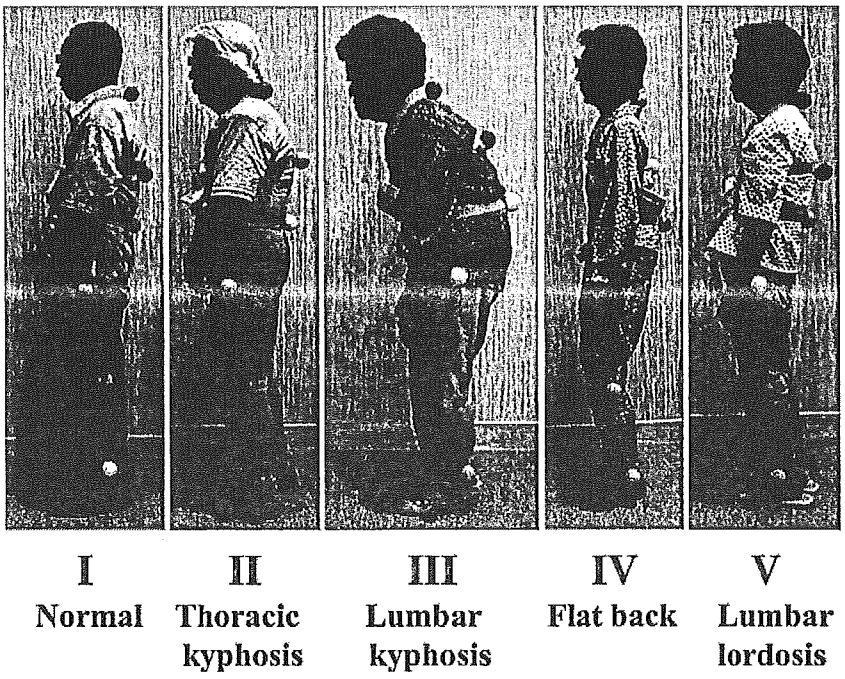

Fig. 1 Classification of trunk deformity from photographs

kyphosis, III lumbar kyphosis, IV flat back, and V lumbar lordosis, as described by Ando et al. [16,17,18]. Three orthopaedic doctors independently determined the classification, and we adopted the classification given by at least two doctors. In cases in which none of the doctors' classifications agreed, we discussed the case and jointly decided on the classification. The classification system is shown in Fig. 1, which includes photographs of patients representing each of the posture groups.

ADL analysis

The subjects were asked questions regarding basic activities of daily living (BADL) (walking, ascending and descending stairs, feeding, dressing, using the toilet, bathing, grooming, and taking medicine) and instrumental ADL (IADL) (using public transportation, shopping for groceries, preparing meals, paying bills, depositing and withdrawing money, writing, reading newspapers, reading magazines or books, taking an interest in news of health, visiting friends, giving advice to family or friends, visiting friends in the hospital, and talking to young people) [19]. We assessed the ADL score using a 4-point scale, based on the help required for each activity: 3 completely independent; 2 some help needed; 1 much help needed; and 0 completely dependent.

Mental state analysis

Geriatric Depression Scale

The Geriatric Depression Scale (GDS) [20,21], a measure of depressive symptomatology assessed on scale of 0–30, was administrated. We assessed the short form of 15 items, it is interpreted that a score >5 points is suggestive of depression, a score >10 points is almost always depression.

Visual analog scale (VAS)

Each year, we conducted an assessment of subjective quality of life (QOL), especially subjective healthiness and life satisfaction, using a validated self-reported visual analogue scale (VAS) [22]. The components of questions were subjective health condition, everyday feeling, satisfaction with human relationship to others, satisfaction with human relationship to family, satisfaction with economic condition, satisfaction with present life, and subjective happiness. The VAS questionnaire ended with a summing-up graph in the form of a 100 mm bar, graded with the subjectively worst condition on the left and the best one on the right. The subject was asked to place a mark on the 100 mm bar based on his or her condition. We defined the distance (mm) from the left to the marked position as the VAS score (0–100), with high scores indicating a high QOL [23].

Statistical analysis

For the classification of posture, Cohen's kappa coefficients were used to test statistical reliability. To determine inter-observer reliability, each reviewer's responses were compared with those of the other reviewers.

Data concerning ADL, GDS and life satisfaction were expressed by mean, SD, and SEM. The differences among the pattern of trunk deformities were evaluated using Kruskal-Wallis test, between with (II–V) and without trunk deformities (I) were evaluated using Mann-Whitney test. Differences were considered significant at $P<0.05$.

Results

The classification of trunk deformity resulted in five groups: I normal group (109 subjects; 46.2%), II thoracic kyphosis group (47 subjects; 19.9%), III lumbar kyphosis group (41 subjects; 17.4%), IV flat back group (28 subjects; 11.9%), and V lumbar lordosis group (11 subjects; 4.7%). There was a mean inter-observer kappa coefficient of 0.47 for both observation times, with a mean inter-observer agreement of 60.2%. We calculated a mean intra-observer kappa coefficient of 0.55 for the two observation times, with a mean inter-observer agreement of 68.3%. Table 1 shows the baseline characteristics in each group. There was no significant difference in age, sex, and overall health status such as comorbidities among the groups.

The mean BADL score of abnormal trunk posture (II–V) was 23.1; that of the normal (I) group was 23.6. The lumbar kyphosis group had significantly lower BADL scores than the normal group ($P=0.017$) (Table 2). With regard to BADL, walking was more likely to be limited in the abnormal trunk posture group (II–V) than in normal participants (I) ($P=0.02$).

The mean IADL score of abnormal trunk posture (II–V) was 10.3, that of the normal (I) group was 11.2. There was no significant difference in IADL among these groups ($P=0.1$) (Table 3). However, the abnormal posture groups (II–V) had lower IADL scores that differed significantly from the normal group (I) ($P=0.047$) (Table 3).

The achieved ratio of transportation of IADLs was associated with trunk deformity ($P=0.04$) (Table 4). The group with trunk deformity group had significant disturbances in certain IADLs, including transportation, shopping for groceries, depositing and withdrawing money, and visiting friends in the hospital (Table 4). Subjects with lumbar lordosis did not exhibit significant differences from the normal group, because of the small size of this group.

There was no significant difference between GDS and the pattern of trunk deformity ($P=0.70$) (Table 5). Measures of subjective healthiness and life satisfaction (Table 6), assessed using a validated, self-reported, visual analogue scale (VAS), were not significantly dif-

Table 1 Baseline characteristics of participants. All data are expressed as mean (95% confidence interval). *I* normal, *II* thoracic kyphosis, *III* lumbar kyphosis, *IV* flat back, and *V* lumbar lordosis

	I	II	III	IV	V	Total
Number	109	47	41	28	11	236
Age	78.4 (68.9, 87.8)	81.3 (71.3, 91.4)	80.8 (70.0, 91.8)	80.2 (70.9, 89.5)	80.6 (71.8, 89.5)	80
Gender (Female, Male)	55, 54	30, 17	34, 7	18, 10	7, 4	144, 92
Height	152.0 (133.5, 170.6)	145.7 (128.8, 162.7)	142.8 (126.3, 159.2)	150.8 (134.8, 166.9)	151.6 (133.4, 169.8)	149.1
Weight	54.3 (33.7, 74.9)	47.3 (33.1, 61.5)	47.4 (29.3, 65.5)	48.1 (31.0, 65.3)	53.0 (28.5, 77.5)	50.9
JOA score (lumbar)	25.6 (18.2, 33)	25.2 (18, 32.4)	24.1 (14.7, 33.5)	24.4 (15.4, 33.4)	27.5 (23.5, 31.5)	25.2
JOA score (knee)	92.0 (67.03, 116.9)	88.9 (59.18, 118.65)	88.0 (58.53, 117.45)	89.6 (66.81, 112.45)	93.3 (63.11, 123.49)	90.5
Coexisting illness						
Hypertension	34	15	17	6	2	74
Cardiac arrhythmia	5	4	4	1	0	14
Diabetes mellitus	5	2	2	3	1	13
Cerebrovascular disorder	3	2	2	1	0	10
Coronary artery disease	4	1	2	0	0	7
Senile dementia	1	2	0	2	0	5
Parkinson disease	0	0	1	0	0	1

Table 2 Total BADL score (points) by the classification of trunk deformity in comparison with the normal trunk group (I). *I* normal, *II* thoracic kyphosis, *III* lumbar kyphosis, *IV* flat back, and *V* lumbar lordosis

	Mean	SD	95% confidence intervals
I	23.6	0.9	21.8; 25.4
II	23.3	1.56	20.18; 26.42
III	22.7	3.81	15.08; 30.32
IV	23.3	1.76	19.78; 26.82
V	23.7	0.65	22.4; 25.0
II–V	23.1	2.51	18.1; 28.12

Table 3 Total IADL score (points) by the classification of trunk deformity in comparison with the normal trunk group (I). *I* normal, *II* thoracic kyphosis, *III* lumbar kyphosis, *IV* flat back, and *V* lumbar lordosis

	Mean	SD	95% confidence intervals
I	11.2	3.13	4.94; 17.46
II	10.6	3.09	4.42; 16.78
III	9.8	4.09	1.62; 17.98
IV	10	4.42	1.16; 18.84
V	12	1.41	9.18; 14.82
II–V	10.3	3.68	2.94; 17.66

ferent from normal in participants with trunk deformity ($P=0.08$). However, the abnormal trunk deformity group tended to have lower scores with regard to subjective health condition ($P=0.03$), everyday feeling ($P=0.007$), satisfaction with human relationships to family ($P=0.035$), satisfaction with economic condition ($P=0.03$), and satisfaction with present life ($P=0.051$) than those of the normal group.

Discussion

Trunk posture in the elderly, especially kyphosis, is known to be associated with vertebral compression fractures. Measurement of kyphosis may be useful in assessing the severity of spinal osteoporosis [9]. The high prevalence of back pain demonstrates the importance of pain management in the treatment of osteoporosis [24]. The number of recent vertebral fractures was also a significant predictor of poor performance in functional reach and walking speed tests [25]. Women with multiple vertebral deformities had significantly greater impairment of ADL function than women without such deformities [26].

Lyles et al. [12] showed that patients with vertebral compression fractures had reduced levels of functional performance, pain with activity, and difficulty in activities in comparison with patients that did not have fractures. Kyphosis is associated with qualitatively and quantitatively diminished function, especially with regard to the performance of mobility tasks [27]. Our results also showed that the walking activity of the

Table 4 The accomplished ratio (%) of IADL items compared between subjects with and without trunk deformity. Kruskal-Wallis test: among five groups, Mann-Whitney test: between with (II–V) and without trunk deformities (I). *I* normal, *II* thoracic kyphosis, *III* lumbar kyphosis, *IV* flat back, and *V* lumbar lordosis

Classification	I	II	III	IV	V	*P*-value	II–V	*P*-value
Going out using public transportation	93.1(%)	82.2(%)	75(%)	76.9(%)	77.8(%)	0.04	78.4(%)	0.003
Shopping for groceries	100	95.6	94.6	96	100	0.24	95.8	0.037
Preparing meals	98.1	93.5	91.9	92.3	100	0.37	93.3	0.09
Paying bills	99	93.3	94.6	92.3	100	0.27	94.1	0.052
Depositing and withdrawing money	98	91.3	91.9	88.5	100	0.17	91.7	0.035
Writing paper	93.2	83	86.5	80	100	0.13	85	0.053
Reading newspaper	82.4	75.6	67.6	76.9	90.9	0.32	74.8	0.17
Reading magazine or book	81	72.1	72.2	72	81.8	0.66	73	0.17
Taking an interest in news of health	97	90.7	86.5	91.7	100	0.17	90.4	0.052
Visiting friends	79	78.6	73	80	81.8	0.94	77.4	0.78
Giving advice to family or friend	85.1	75	73	80	100	0.19	77.6	0.16
Visiting friend in the hospital	98	89.1	91.9	88.5	100	0.12	90.8	0.023
Talking to young people	92.2	87	86.5	80.8	90.9	0.52	85.8	0.14

Table 5 Geriatric depression scale (GDS) by the classification of trunk deformity. *I* normal, *II* thoracic kyphosis, *III* lumbar kyphosis, *IV* flat back, and *V* lumbar lordosis

	Mean	SD	95% confidence intervals
I	5.8	3.65	−1.5; 13.1
II	5.9	3.79	−1.68; 13.48
III	6.6	3.76	−0.92; 14.12
IV	6.4	3.14	0.12; 12.68
V	5.4	3.78	−2.16; 12.96
II–V	6.2	3.62	−1.04; 13.44

abnormal trunk deformity group was more limited than that of normal participants. In contrast, kyphosis is associated with decreased bone mineral density (BMD) and loss of height, but does not cause substantial chronic back pain, disability, or poor health in older women [7]. However, previous studies have not assessed patterns of trunk deformity in the context of detailed assessments of functional impairment of daily living in the elderly.

In this study, we classified trunk deformity into five groups: I normal; II thoracic kyphosis; III lumbar kyphosis; IV flat back; and V lumbar lordosis. Previously, we reported that standing trunk posture was closely associated not only with distance and time parameters of gait, but also with functional performance measures such as functional reach and timed up and go tests in elderly subjects dwelling in a rural community [17]. In the present study, we evaluated if trunk deformity is associated with the results of a detailed assessment of indoor and outdoor activities of daily living, satisfaction with life, and mental status.

This study demonstrated that the lumbar kyphosis group had decreased activities of daily living, manifested primarily in the basic ADL of walking. Of the IADL, the trunk deformity group exhibited decreased activities of daily life such as going out, shopping, depositing and withdrawing money, and visiting friends in the hospital. These activities require going out of doors. This means the abnormal trunk deformity group experienced limited outdoor activities. The lumbar kyphosis group had greater interest in their own health, possibly because they have plenty of time to think about their own health at home, as their outdoor activities are limited.

So far, few reports have discussed the association between trunk deformity and mental status. However, vertebral deformity was shown to be associated with psychological morbidity in elderly Chinese women [28].

With regard to subjective healthiness and life satisfaction, there was no significant difference among the trunk deformity groups; however, the abnormal posture group tended to score lower than the normal group on measures of their own subjective health condition, everyday feeling, satisfaction with human relationships,

Table 6 Satisfaction-with-life score by the trunk deformity. Mann-Whitney test: between with (II–V) and without trunk deformities (I). *I* normal, *II* thoracic kyphosis, *III* lumbar kyphosis, *IV* flat back, and *V* lumbar lordosis

	Mean; SD		
	Normal (I)	Abnormal (II–V)	*P*-value
Subjective health condition	64.9; 17.85	59.3; 18.75	0.033
Everyday feeling	68.5; 18.56	61.7; 19.52	0.007
Satisfaction with human relationship to others	80.8; 16.31	77.6; 19.17	0.29
Satisfaction with human relationship to family	82.1; 14.55	77.5; 16.61	0.035
Satisfaction with economic condition	62.1; 20.91	55.6; 22.72	0.03
Satisfaction with present life	68.3; 20.55	62.5; 23.2	0.051
Subjective happiness	67.1; 20.09	64.0; 21.37	0.32
Total	457.8; 181.07	428.7; 155.95	0.08

satisfaction with economic condition, and satisfaction with present life. Therefore, the trunk deformity group experienced less subjective healthiness and satisfaction with life. This result may be explained by the limitation of outdoor activities that can lead to a limited social life and difficulty in enjoying a healthy and active life in the community.

Schreiner et al. reported that Geriatric Depression Scale was accurate and reliable in dementia among Japanese subjects [29]. Although the subjective impression of mental status in the trunk deformity group was not as favorable as that of normal group, the GDS in the trunk deformity group did not reveal significant difference in that of normal group. In another study, a significant association was found between BMD of the hip and depressive symptoms after adjustment for osteoporosis risk factors [30]. They suggested the relationship between low BMD and depression was associated with endogenous steroid. We should evaluate the GDS of the larger number of participants by the classification of trunk posture and detailed background of participants to clarify the relation of depression and spinal deformity.

In this study, we did not take X-rays of thoracic and lumbar lesions in the participants, and therefore cannot speculate on the association between spinal posture and vertebral fracture. Further examinations of the radiography of spine and bone densities, such as dual energy X-ray absorptiometry (DXA) or quantitative ultrasound, are necessary to assess the association between spinal posture and vertebral osteoporosis in the community-dwelling elderly. Further studies are also needed to evaluate the cause of the limitation in outdoor activities experienced by study participants with lumbar kyphosis, and to clarify and assess the relationship between mental status and trunk deformity through long-term follow-up.

In conclusion, patients in this study with trunk deformities exhibited decreases in activities that require going outdoors.The abnormal trunk deformity groups also tended to score lower than the normal group with regard to subjective healthiness and life satisfaction measures.

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第46回日本老年医学会学術集会記録
〈シンポジウム1：高齢者総合的機能評価ガイドライン，健康増進と介護予防〉
2. 老年症候群の評価と介護予防：生活改善に機能評価を生かす

2) 栄養と生活機能

西永　正典[1]　高田　淳[1]　奥宮　清人[2]
松林　公蔵[3]　小澤　利男[4]　土居　義典[1]

Key words：後期高齢者，生活機能，アルブミン，魚摂取，イコサペンタエン酸（EPA）
（日老医誌　2005；42：174—176）

はじめに

近年，生活習慣病と糖尿病，高脂血症との関連から，栄養過多や肥満を問題として取り上げられることが多いが，高齢者では反対に低栄養が問題となることが少なくなく，生活機能障害や予後を左右することが多い．栄養と生活機能障害との関連について，特に地域在住の後期高齢者を対象とした本邦の報告は少なく，栄養管理の指針は十分とはいえない．そこで，今回，地域在住高齢者の生活機能評価の経年的変化から，生活機能維持に関連する栄養学的マーカーについて検討した．

地域在住高齢者のこれまでの知見

1) 香北町健康長寿計画

高知大学老年病科と高知県香北町では，官学共同事業として，「健やかに老いるために」をテーマにこれまでさまざまな取り組みを展開してきた．地域高齢者に対する老年医学的総合機能評価（Comprehensive Geriatric Assessment：CGA）を地域在住高齢者に適用し，その結果に基づいた介入を試みた．内容は大きく3つに分かれる．すなわち，ADL等の調査を目的とした65歳以上の住民アンケート，後期高齢者を中心とした機能検診，これらの結果に基づく運動教室や文化教室などの介入事業である．

2) 1991年参加集団の動向

松林ら[1]は，1991年アンケート参加集団1,488例の解析を行い，10年後の生死やADL低下に関連する因子について解析し，歩行や階段昇降，摂食，入浴，更衣，整容などの基本的日常活動度低下が生存に，また，ADL低下すなわち要介護の出現に関連する危険因子として，年齢，性（女性），視聴覚などの情報関連機能低下，脳卒中などが関連することを明らかにした．同じように，今回私たちは，1991年に機能検診を受診した後期高齢者330例を追跡したが，機能検診連続参加者は4年後には半減以下，7年後には72例に，10年後には39例にまで減少した．その原因は死亡が年々増加したこともあるが，機能検診には参加できず，アンケート調査のみに参加する高齢者も増加した．図1に示すように検診連続参加者の基本的ADLは，全体の加齢に伴うと考えられるADL低下と比べて，明らかに良好に保たれており，逆にアンケートのみの参加者は全体の動向と同様に低下していた．

ADLばかりでなく，認知機能検査のMMSや歩行機能を総合的に判定するアップアンドゴーテストも機能検診連続参加者には低下がほとんどみられず，機能が維持

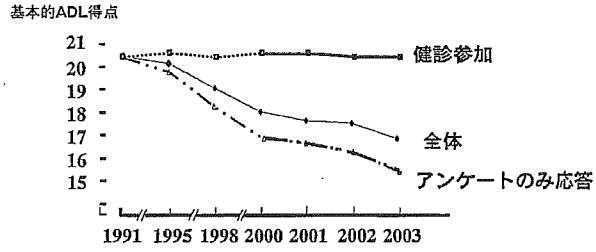

図1　1991年時長寿健診後期高齢者の基本的ADLの変化
歩行，階段昇降，摂食，入浴，排泄，更衣，整容の7項目（3段階：21点満点）
330例（男154，女176）平均年齢　80±4歳

Nutritional factors and functional assessment
1) Masanori Nishinaga, Jun Takata, Yoshinori Doi：高知大学老年病科
2) Kiyohito Okumiya：総合地球環境学研究所研究所
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4) Toshio Ozawa：東京都老人医療センター

表1　1991年時長寿健診後期高齢者：10年後（2001年）自立に関連する要因

	調整オッズ比	p	95%信頼区間
年齢	0.87	0.026	0.764～0.983
MMS	1.16	0.040	1.007～1.342
Up&Go	0.83	0.003	0.737～0.940
アルブミン	4.32	0.055	0.969～19.22
総コレステロール	0.99	0.286	0.982～1.005

（性，血圧，高血圧歴で補正）

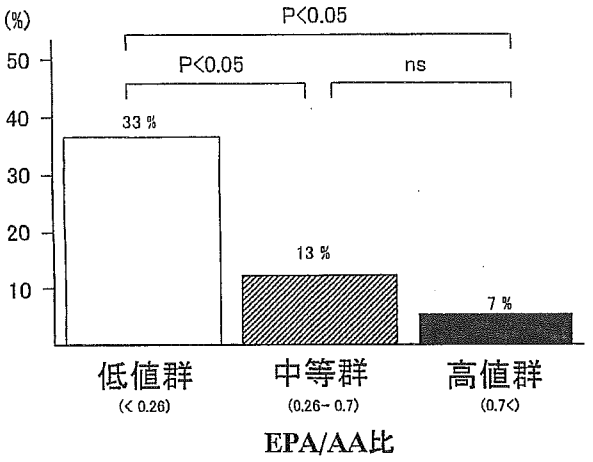

図2　追跡2年後の基本的ADL低下の頻度

されている高齢者のみが連続して機能健診に参加している実態が明らかになった．

(1) アルブミン

高齢者の栄養状態を最もよく反映すると言われるアルブミン[2)3)]は，連続健診参加者では，男女ともに高齢になるほどむしろ増加し，一般に言われるように加齢とともには減少しなかった．これは，他の研究でもみられるように，アルブミン低下がみられる対象は順次死亡したり，ADLの低下が見られたりして，機能検診受診をしなくなるため（選択的脱落）に生じると考えられる．

(2) 血清総コレステロール

女性は男性より高いが，2002年までは低下せず，逆に男性では2002年以降増加する．男女ともに加齢とは関係なく，血清総コレステロール値はほぼ一定に保たれていた．この結果にも選択的脱落が生じたためと考えられる．

(3) 自立に関連する要因

1991年時の検診参加者を対象として，4年後，7年後，10年後(表1)の自立に関連する要因について検討した．後期高齢者では，血清学的なアルブミンやコレステロール値は自立に関連する有意な要因とはならず，むしろ，MMSやアップアンドゴーテスト等の機能検査の方がより強く，将来の高齢者の自立を予測しうることが明らかとなった．

これまで多くの研究で，血清アルブミン値や総コレステロール値が生命・機能予後の推定に有用であることが示されている[2)3)]．しかし，先に述べたように，私たちの後期高齢者を対象とした集会型の健診では，生活機能が維持されている高齢者のみが参加する傾向が強く，機能的予後推定に血清アルブミン，コレステロールの測定が大きな役割を果していなかった．

栄養に関するアンケート型問診と生活機能との関連

長寿健診は，基本健診をベースとして，さらに機能健診を合わせて実施されている．基本健診の健康診査受診票の中での問診項目には，食事に関する問診項目があり，その中で近年報告されている魚の摂取頻度に焦点を当て，生活機能との関連について検討した．近年，魚の摂取頻度が高いほど，動脈硬化性疾患の発生が減少すると報告されている[4)~6)]．しかし，動脈硬化の進展した高齢者において，魚の摂取の習慣と動脈硬化性疾患発症や，生活機能障害との関連を検討した報告は少ない．

そこで，後期高齢者の魚摂取の実態を知るために，その魚摂取頻度と，血清イコサペンタエン酸（EPA）とアラキドン酸（AA）を測定し，その比（EPA/AA）によって，魚摂取と肉類摂取のバランスの指標とした(EPA/AAが高値ほど魚摂取が多い)．対象は65歳以上の地域在住高齢者（平均年齢78±5歳），生活機能障害として，開始時および2年後に歩行，階段，食事，着替え，排泄，入浴，洗面・整髪の7項目を21点満点とする基本的・日常生活活動度（BADL）得点および認知機能検査としてMini-Mental State Examination（MMS：30点満点）を追跡開始時と2年後に施行した．

(1) 血清EPA/AA比の分布によって，3つのグルー

プに，すなわち，低値群(～0.25)，中等度群(0.26～0.70)，高値群（0.71～）に分類した．欧米人の平均は0.04，日本人の平均は0.4～0.6と報告されている．実際の魚摂取頻度と血清EPA/AAの相関は，魚摂取の頻度が高いほどEPA/AAが高く，食事摂取の質をよく反映していた．

(2) 血清EPA/AA比の再現性について，追跡開始時と1年後の血清EPA/AAの相関について検討したが，比較的良好な相関が認められ（n＝217，r＝0.582，P＜0.001），食生活の内容が年単位ではそれほど大きく変わらないことが推測された．

(3) EPA/AA比の低値，中等度，高値群の間で，年齢，性，血圧，総コレステロール（TC），HDLコレステロール（HDL），LDLコレステロール（LDL），リポプロテイン(a)(Lp(a))，高感度CRP（hsCRP）に有意な差はなかった．

(4) 動脈硬化の一つの指標である平均脈波速度（PWV）は，低値群，中等度群の順で高値群で有意に高く(低値群：1,896，中等度群：1,787，高値群：1,724cm/s，p＜0.05)，魚摂取の低い群での動脈硬化の進展が推測された．

(5) 認知機能（MMS）との関連では，高値群，中等度群とは同様であったが，低値群で有意に他の2群と比べて，認知機能が低下していた（低値群：19.2±4.9，中等度群：20.6±1.2，高値群：20.7±1.1，p＜0.05)．

(6) 基本的ADLとの関連では，低値群で，他の2群に比べて，高値で基本的ADLが保たれていた(低値群：26.2±4.3，中等度群：27.5±2.5，高値群：27.4±2.2，p＜0.05)．

(7) 自立喪失（要介護）高齢者の割合：2年後の基本的ADLが20点未満になった高齢者を自立喪失（要介護）と定義した．その割合は，魚摂取頻度低値群で高く約3割にのぼり，逆に高値群では5%と有意に低かった(図2)．

おわりに

高齢者にとって栄養の問題は重要である．血清アルブミン値や血清蛋白の値が低いことが高齢者の虚弱性と関連があることが報告されている[3]．今回，我々が示したように，すべての高齢者健診の現場で，これらの指標が有用な栄養学的マーカーとは限らない．後期高齢者の集会型の健診には「選択的脱落」が生じ，十分なスクリーニング機能が発揮されない可能性もある．

今回の我々の検討では，魚食の多い日本人においても，EPAを多く含む魚油を摂取する食習慣のあるグループでは動脈硬化の進展が遅く，認知機能低下や要介護状態を回避できる可能性が示され，今後，栄養指導等の地域介入を勧める一つの根拠となりえる．

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Lifelong Left Ventricular Remodeling of Hypertrophic Cardiomyopathy Caused by a Founder Frameshift Deletion Mutation in the Cardiac Myosin-Binding Protein C Gene Among Japanese

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OBJECTIVES We studied the longitudinal evolution of hypertrophic cardiomyopathy (HCM) caused by a founder frameshift mutation in the cardiac myosin-binding protein C (MyBPC) gene.

BACKGROUND Mutations in the MyBPC gene have been associated with delayed expression of HCM and a good prognosis. Few studies, however, demonstrated the phenotype-genotype correlations in the longitudinal study.

METHODS We studied long-term evolution of clinical features of 15 unrelated families who were found to have an identical frameshift mutation in the MyBPC gene: a one-base deletion of a thymidine at nucleotide 11645 (V592fs/8).

RESULTS Thirty-nine individuals in 15 families were genotype-positive. Thirty of the 39 individuals with the mutation were phenotype-positive. The disease penetrance was 100% in subjects ≥50 years and 65% in those <50 years. "End-stage" HCM (ejection fraction <50%) was observed in 7 (18%) of the 39 genotype-positive individuals (7 [23%] of the 30 phenotype-positive patients); 6 of them were 60 years or older. Seven patients were hospitalized for treatment of repeated congestive heart failure, and four patients died or had implantable cardioverter-defibrillator discharge (13%; incidence, 1.4%/year) during a mean follow-up period of 9.2 ± 5.5 years.

CONCLUSIONS Elderly patients with a V592fs/8 mutation in the MyBPC gene may evolve into the "end-stage" HCM, characterized by left ventricular systolic dysfunction, cavity dilation, and irreversible heart failure. The clinical course in patients with this mutation is not benign in the long run, with progressive left ventricular remodeling with advancing age. (J Am Coll Cardiol 2005;46:1737–43) © 2005 by the American College of Cardiology Foundation

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disorder with heterogeneous morphologic, functional, and clinical features (1–4). Recent molecular genetic studies have revealed that HCM is caused by mutations in 10 genes that encode sarcomeric contractile proteins (5–9).

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Cardiac myosin-binding protein C (MyBPC) is one of these sarcomeric proteins, and mutations in the MyBPC gene have been reported to be associated with delayed expression of hypertrophy and a relatively good prognosis (10–14). On the other hand, a recent report showed that patients with mutations in the MyBPC gene did not differ significantly from patients with thick-filament HCM or thin-filament HCM with respect to age at diagnosis or severity of phenotype (15).

Few studies, however, have demonstrated longitudinal evolution of phenotype in relation to genotype, although the HCM phenotype itself is recognized to be a slowly progressive disorder that manifests remarkable evolution of clinical features throughout life (16).

We analyzed the MyBPC gene in probands from families with HCM and had the opportunity to study 15 unrelated families living in Kochi prefecture, Japan, who were found to have an identical frameshift mutation in the MyBPC gene: a one-base deletion of a thymidine at nucleotide 11645 (V592fs/8) (17). The results of clinical and genetic investigations in these 15 families during a long period of time are presented herein.

METHODS

Subjects. The subjects were 94 probands with familial or sporadic HCM. Twenty-two subjects were familial HCM,

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Abbreviations and Acronyms

AF	= atrial fibrillation
ECG	= electrocardiogram/electrocardiographic
EF	= ejection fraction
HCM	= hypertrophic cardiomyopathy
ICD	= implantable cardioverter-defibrillator
LVEDD	= left ventricular end-diastolic diameter
LVH	= left ventricular hypertrophy
MLVWT	= maximum left ventricular wall thickness
MyBPC	= cardiac myosin-binding protein C

whereas the other 72 subjects were not confirmed to have relatives with HCM. All probands were evaluated at the Kochi Medical School Hospital for confirmation of diagnosis, risk assessment, and symptom management between 1982 and 2004. The diagnosis of HCM was based on echocardiographic demonstration of an unexplained left ventricular hypertrophy (LVH) (i.e., maximum left ventricular wall thickness [MLVWT] ≥15 mm). Relatives of probands were contacted by probands themselves and visited our clinic of their own free will. After the identification of a V592fs/8 mutation, pedigree analysis, including both clinical evaluation and genotyping, was performed. Informed consent was obtained from all subjects or their parents in accordance with the guidelines of the Ethics Committee on Medical Research of Kochi Medical School.

Clinical evaluation. The evaluation of probands and relatives included medical history, clinical examination, 12-lead electrocardiography, M-mode, two-dimensional and Doppler echocardiography, and ambulatory 24-h Holter electrocardiographic (ECG) analysis. The severity and distribution of LVH were assessed in the parasternal short-axis plane at mitral valve and papillary muscle levels (18,19). Maximum left ventricular wall thickness was defined as the greatest thickness in any single segment. Left ventricular end-diastolic diameter (LVEDD) and end-systolic diameter were measured from M-mode and two-dimensional images obtained from parasternal long-axis views. Ejection fraction (EF) was determined from apical two- and four-chamber views because the left ventricle is of heterogeneous shape and the septum itself is usually hypokinetic in HCM. Left ventricular outflow tract gradient was calculated from continuous-wave Doppler using the simplified Bernoulli equation.

Disease penetrance was determined by the following criteria for relatives: 1) MLVWT ≥13 mm; 2) presence of major abnormalities on the ECG (i.e., Q-wave ≥0.04 s in duration or one-fourth of the ensuing R-wave in depth in at least two leads, significant ST-T changes, and Romhilt-Estes score >4); or 3) a combination of criteria 1 and 2.

Data regarding survival and clinical status of patients were collected during serial clinic visits. Evaluation of the phenotype was completed before determination of the genotype. Three modes of HCM-related death were defined: 1) sudden and unexpected death (including resuscitated cardiac arrest), in which the collapse occurred in the absence or <1 h from the onset of symptoms in patients who previously experienced a relatively stable or uneventful course; 2) heart failure-related death, which was in the context of progressive cardiac decompensation ≥1 year before death, particularly if complicated by pulmonary edema or evolution to the end-stage phase (including patients with heart transplantation); and 3) stroke-related death, which occurred in patients who died as a result of embolic stroke.

Genetic analysis. Peripheral blood samples were taken at the time of clinical evaluation, and they were frozen and stored at −20°C. We extracted DNA using a DNA purification kit from QIAGEN Inc. (no.51104; Hilden, Germany). In vitro amplification of genomic DNA was performed using polymerase chain reaction. Oligonucleotide primers were used to amplify exon 18 of the MyBPC gene. Information on primer sequences and polymerase chain reaction conditions is available upon request. Sequencing was performed using a BigDye Terminator Cycle Sequencing Kit from Applied Biosystems Inc. (no.4336774; Foster City, California). The sequences were analyzed on an ABI PRISM 3100-Avant Genetic Analyzer in accordance with the manual of the manufacturer.

In patients in whom the mutation was identified, confirmation was obtained by reanalysis with direct sequencing from a second blood sample. The presence of a V592fs/8 mutation, which abolishes a *Bsm*FI restriction site, was confirmed by digestion of genomic DNA with this enzyme.

To investigate if families carrying the identical mutation were related, haplotype analysis was performed using microsatellite markers defining the MyBPC gene locus. Markers MyBPC3-CA, D11S4109, D11S1784, and D11S1326, flanking the MyBPC gene, were used. To describe haplotype results, the length (base pair) of allele was put in parentheses after each marker.

RESULTS

Genetic results. A V592fs/8 mutation, a frameshift mutation that causes truncation of cardiac MyBPC protein, was identified in 15 of 94 probands. Relatives of 15 probands were studied further, totaling 64 members, including 15 probands, of the various families (Figs. 1A to 1G). Of the 64 individuals, 39 had a V592fs/8 mutation in the MyBPC gene. This mutation was thought to be disease-causing based on presence of the mutation in all affected individuals and absence of the sequence variation in at least 200 chromosomes from healthy individuals.

Haplotype analysis with highly polymorphic markers was performed in these families to investigate whether a V592fs/8 mutation was likely to have arisen from a common ancestor (founder effect). We found that a unique haplotype, MyBPC3-CA(282)-D11S4109(151)-D11S1784(138)-D11S1326(249), was linked to the V592fs/8 mutation in all 15 families, indicating that a common founder of the mutation was likely in these families.

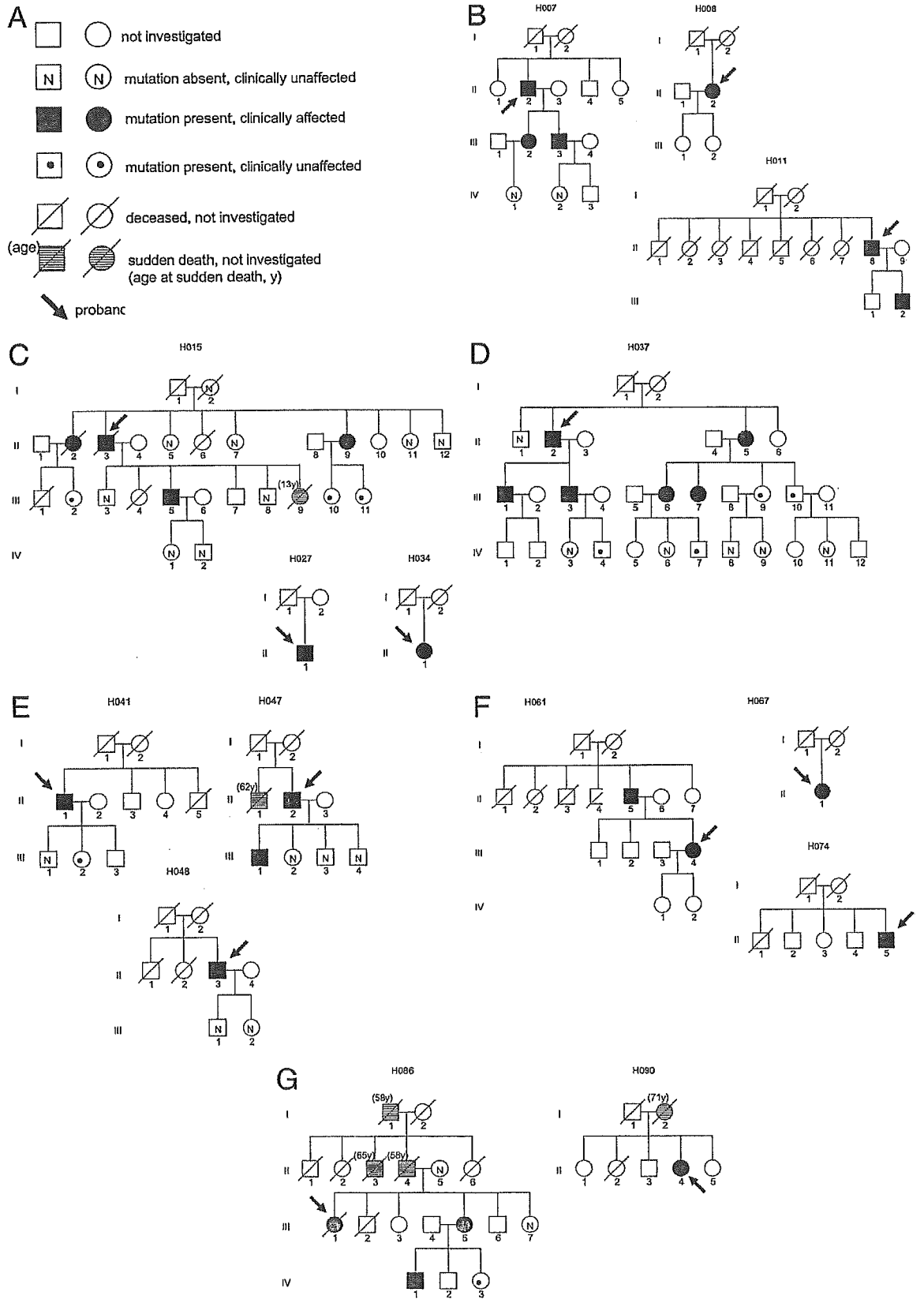

Figure 1. (A to G) Pedigree of families H007, H008, H011, H015, H027, H034, H037, H041, H047, H048, H061, H067, H074, H086, and H090. The genotypic status and phenotypic status of subjects are indicated.

Table 1. Clinical Characteristics of 30 Phenotype-Positive Patients at Presentation

Age at presentation, yrs (range)	48 ± 14 (16–83)
Gender: male, n (%)	17 (57)
Age at diagnosis, yrs (range)	47 ± 15 (14–76)
Reason for diagnosis, n (%)	
Symptoms	16 (53)
Incidental findings	4 (13)
Family or gene screening	10 (33)
Presence of symptoms, n (%)	19 (63)
Dyspnea, n (%)	14 (47)
Palpitation, n (%)	11 (37)
Syncope, n (%)	3 (10)
Chest pain, n (%)	7 (23)
NYHA functional class	
I	16 (53)
II	10 (33)
III and IV	4 (13)
History of AF (chronic or paroxysmal)	4 (13)

Data shown as mean value ± SD or number (%).
AF = atrial fibrillation; NYHA = New York Heart Association.

Clinical manifestation. Clinical evaluation was performed in the 64 individuals from the 15 proband families studied. The mean follow-up period in the all 39 genotype-positive individuals was 8.0 ± 5.4 years (range, 0.2 to 19.3 years). Thirty patients were phenotype-positive, all with echocardiographic evidence of LVH. Two adults developed hypertrophy (MLVWT ≥13 mm) after the age of 40. Nine of the 39 individuals were not affected phenotypically (average age at last evaluation: 33 ± 11 years; range, 12 to 43 years). The disease penetrance was 100% in subjects ≥50 years and 65% in those <50 years of age.

The clinical characteristics of the 30 phenotype-positive patients at presentation were summarized in Table 1. The age at diagnosis was 47 ± 15 years. Most patients (86%) were evaluated because of symptoms or family screening of HCM. A total of 19 patients (63%) reported cardiac symptoms. Table 2 shows the echocardiographic characteristics of the 30 phenotype-positive patients at presentation and at last follow-up. At presentation, MLVWT was 21 ± 5.3 mm. Six (20%) of those 30 patients had systolic anterior movement of the mitral valve, and three (10%) showed a significant LV outflow tract gradient (pressure gradient at rest ≥30 mm Hg).

Sudden death occurred in six individuals from four families (Fig. 1; families H015, H047, H086, and H090). Three individuals were from one family. Five of them were older than 50 years of age.

Clinical course. During a mean follow-up period of 9.2 ± 5.5 years after the first clinical evaluation, paroxysmal or chronic atrial fibrillation (AF) was detected in 10 (33%; incidence, 3.6%/year) of the 30 phenotype-positive patients, eight of whom were 60 years of age or older. Two of those patients experienced severe embolic stroke, which was the cause of their death at the ages of 61 and 68 years, respectively. One patient (H015-II-2) was on oral anticoagulation with warfarin. In the other patient (H086-III-1), AF was detected at the time of the stroke for the first time.

Figure 2 shows longitudinal changes in LVEDD, ejection fraction (EF), and MLVWT in each of the 39 genotype-positive individuals. Figure 2A shows that LVEDD gradually became larger with advancing age. On the other hand, LV systolic function was preserved until middle age. After middle age, reduction of EF occurred in some patients (Fig. 2B). "End-stage" HCM (EF <50%) was observed in seven (18%) of the 39 individuals; six of them were 60 years or older. Five of them showed LVEDD ≥55 mm. Figure 2C shows that MLVWT was thinner in elderly patients than in young patients with HCM and that it was within normal limits in the phenotype-negative individuals.

Table 3 shows the clinical characteristics of seven patients with "end-stage" HCM. More specifically, the average age when they were first identified as in the end-stage phase was 60 years (range, 46 to 70 years). Three patients (H011-II-8, H015-II-3, and H086-III-1) were already in the end-stage phase at presentation. The other four patients progressed to "end-stage" HCM during follow-up. Regarding the cause of LV systolic dysfunction, none of them was considered to have atherosclerotic coronary artery disease because three of them (H007-II-2, H011-II-8 and H086-III-1) had normal coronary angiography, and the remaining four patients had normal thallium-201 myocardial scintigraphy. No one suffered from myocardial infarction. All patients with "end-stage" HCM showed deterioration of New York Heart Association functional class together with a development of paroxysmal or chronic AF at last follow-up. All of them were treated for heart failure and/or arrhythmias: diuretics (n = 6), angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (n = 5), beta-blockers (n = 3), and amiodarone (n = 2). One patient (H007-II-2), who was on amiodarone (maintenance dose 100 to 200 mg/day) for sustained ventricular tachycardia for 10 months, received an implantable cardioverter-

Table 2. Echocardiographic Characteristics of 30 Phenotype-Positive Patients

	At Presentation	At Last Follow-Up
Age, yrs	48 ± 14 (16–83)	56 ± 15 (28–83)
MLVWT, mm	21 ± 5.3 (13–38)	21 ± 6.0 (13–39)
IVST, mm	19 ± 4.7 (11–28)	18 ± 4.9 (10–32)
PWT, mm	11 ± 1.7 (7–14)	11 ± 2.3 (7–19)
Left atrial diameter, mm	40 ± 8.3 (27–60)	46 ± 9.0 (30–69)
LV end-diastolic diameter, mm	44 ± 7.4 (29–64)	47 ± 8.1 (37–67)
LV end-systolic diameter, mm	27 ± 7.8 (12–48)	31 ± 9.2 (21–55)
Ejection fraction, %	66 ± 9.9 (36–85)	61 ± 13.9 (22–81)
Gradient >30 mm Hg, n (%)	3 (10)	2 (7)
SAM, n (%)	6 (20)	6 (20)
Pattern of LVH, n		
Asymmetric	27	27
Diffuse	2	1
Apical	0	0
Others	1	2

Data shown as mean value ± SD (range) or number (%).
IVST = interventricular septal wall; LV = left ventricular; LVH = left ventricular hypertrophy; MLVWT = maximum left ventricular wall thickness; PWT = left ventricular posterior wall thickness; SAM = systolic anterior movement.

Figure 2. Longitudinal echocardiographic changes in 39 genotype-positive individuals during the follow-up period. (**A**) Changes in left ventricular end-diastolic diameter (LVEDD). (**B**) Changes in ejection fraction (EF). (**C**) Changes in maximum left ventricular wall thickness (MLVWT).

Table 3. Clinical Characteristics of Seven Patients With "End-Stage" HCM

Patient	Gender	Age (yrs) at Diagnosis	Age (yrs) at End-Stage	Echocardiography at Initial Evaluation/ at Last Evaluation				NYHA Functional Class, Initial to Last	Rhythm, Initial to Last	Hospitalization for CHF (Age, yrs)	Status (Event Age, yrs)
				Age (yrs)	LVEDD (mm)	EF (%)	MLVWT (mm)				
H007-II-2	M	65	70	65/78	49/58	62/22	17/14	I to III	SR to AF	+ (69)	ICD discharge (76)
H007-III-2	F	14	46	35/47	49/58	74/30	28/17	I to III	SR and PAF	+ (46)	Alive
H011-II-8	M	40	58	58/68	64/62	48/25	15/17	II to III	SR to AF	+ (63)	Alive, CRT, MVR
H015-II-3	M	54	54	54/73	56/67	36/37	20/18	II to IV	AF to AF	+ (54)	CHF death (73)
H015-II-2	F	45	60	45/60	42/42	66/46	10/20	II to III	SR to AF	+ (60)	Stroke death (61)
H034-II-1	F	46	68	52/68	41/46	65/49	18/17	I to III	SR to AF	—	Alive
H086-III-1	F	64	64	64/67	47/55	43/40	20/18	II to III	SR to AF	+ (64)	Stroke death (68)

AF = atrial fibrillation; CHF = congestive heart failure; CRT = cardiac resynchronization therapy; EF = ejection fraction; LVEDD = left ventricular end-diastolic diameter; MLVWT = maximum left ventricular wall thickness; MVR = mitral valve replacement; NYHA = New York Heart Association; PAF = paroxysmal AF; SR = sinus rhythm.

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defibrillator (ICD) because of amiodarone-induced pulmonary fibrosis. One patient (H011-II-8) underwent mitral valve replacement and cardiac resynchronization therapy for medically-refractory heart failure.

During follow-up (9.2 ± 5.5 years), seven (23%) of the 30 patients (mean age: 62 ± 10 years; range, 46 years to 76 years) were hospitalized for treatment of heart failure, and four patients died or had ICD discharge (one heart failure-death, two stroke-deaths, one ICD discharge; 13%; incidence, 1.4%/year) (Table 3).

DISCUSSION

Hypertrophic cardiomyopathy is a heterogeneous myocardial disorder and the phenotype is not a static manifestation; LVH can appear at virtually any age and increase or decrease dynamically throughout life (16,20). However, there have been few studies on the phenotype-genotype correlation in terms of longitudinal clinical evaluation. In this study, we examined the clinical courses of patients with a founder mutation (V592fs/8) in the MyBPC gene from 15 unrelated proband families. We observed the longitudinal evolution of phenotype caused by this mutation and concluded that the patients with this mutation were likely to progress to "end-stage" HCM, characterized by LV systolic dysfunction and cavity dilation, with advancing age. To the best of our knowledge this is the first report demonstrating direct longitudinal evolution of phenotype in relation to genotype.

Disease penetrance and clinical manifestation. In the present study, the mean age of patients at diagnosis was 47 ± 15 years. During follow-up, two adults showed development of LVH in mid-life, appearing for the first time after 40 years of age. We found that disease penetrance was 100% in subjects ≥50 years and 65% in those <50 years of age. Our data are in accordance with previously reported data for MyBPC mutations (12,14,21–24). Onset of the disease seems to be late in life, although two patients are diagnosed as having the disease at teenagers (H007-III-2 and H047-III-1). These findings indicate that relatives of the patients, even if they are old, should be screened for this mutation. If genetic diagnosis is not available, middle-aged or older relatives of the patients should be evaluated at least every five years for family-screening strategies (2–4,14,25). From a morphologic point of view, the degree of MLVWT varied significantly (13 to 38 mm). None of the subjects showed apical hypertrophy. Sudden death occurred in six individuals from four families in the present study. It is notable that most of sudden deaths occurred in subjects >50 years of age (83%; five of the six individuals) because sudden death occurs most commonly in children and young adults, although the risk extends across a wide age range through mid-life and beyond (3,26,27).

Clinical course and prognosis. It was previously suggested that LV remodeling involving some degree of LV cavity enlargement and wall thinning could occur slowly over the course of decades (28–32), although direct longitudinal evidence in relation to gene abnormality was insufficient. In the present study, we were able to demonstrate longitudinal LV remodeling in those with a V592fs/8 mutation and also evolution to "end-stage" HCM in the elderly (Fig. 2). HCM generally has been associated with only mild disability and normal life expectancy if sudden death can be avoided (27,33–35). In this study, the clinical manifestation caused by this mutation was late onset and prognosis was not poor in terms of survival (4 [13%] of the 30 patients died or had ICD discharge; incidence, 1.4%/year). However, a significant subset of the patients is likely to suffer from HCM-related cardiovascular events (repeated heart failure, stroke, and sudden death) later in their lives. The clinical course in patients with this mutation is therefore not benign in the long run, and careful management is needed, particularly in middle-aged and older patients.

Genotype/phenotype relations. A V592fs/8 mutation in the MyBPC gene is predicted to result in a truncation of the protein, including loss of C-terminal myosin and titin binding sites (36). Konno et al. (21) recently reported that a missense mutation (Arg820Gln) in the MyBPC gene is responsible for HCM with LV systolic dysfunction and dilation in elderly patients. The function of MyBPC protein has been elucidated by two recent studies using knockout mouse models (37,38). Homozygous-null mice in which full-length MyBPC protein was absent were viable and had significant cardiac hypertrophy with decreased fractional shortening. Furthermore, heterozygous MyBPC-null mice presented a slight-but-significant decrease in MyBPC amount and developed asymmetric septal hypertrophy (38). Thus, we speculate that a collapse of sarcomere stability compensated by residual MyBPC in heterozygous patients may occur with advancing age and may lead to impaired contractile function in the elderly.

Kokado et al. (39) reported that a Lys183 deletion mutation in the troponin I gene in HCM patients was associated with LV systolic impairment and dilation in those older than 40 years of age. Moolman et al. (22) presented that none of the subjects with a single-base insertion in exon 25 of the MyBPC gene showed LV systolic dysfunction and cavity enlargement, although the subjects included several elderly patients. Thus, underlying mutations may relate to the progress to the stage of LV dysfunction and dilation. However, the fact that not all elderly patients with the identical mutation develop "end-stage" disease suggests that other genetic and/or environmental factors are involved and underscores the genetic/phenotypic heterogeneity of HCM. Further investigations are needed to clarify these modifying factors.

Study limitations. Whether this particular mutation is more related to the progression to "end-stage" HCM than the other mutations in MyBPC gene or abnormal MyBPC itself is more prone to this phenotype than the other sarcomeric abnormalities is unknown. Further studies on the phenotype-genotype correlation in terms of longitudinal evolution are needed.