ations with physical impairment among Japanese women: the Hizen-Oshima Study. Osteoporos Int 13:723–730
27. Ryan SD, Fried LP (1997) The impact of kyphosis on daily functioning. J Am Geriatr Soc 45:1479–1486
28. Lau EMC, Woo J, Chan H, Chan MKF, Griffith J, Chan YH, Leung PC (1998) The health consequences of vertebral deformity in elderly Chinese men and women. Calcif Tissue Int 63:1–4
29. Schreiner AS, Hayakawa H, Morimoto T, Kakuma T (2003) Screening for late life depression: cut-off scores for the Geriatric Depression Scale and the Cornell Scale for depression in dementia among Japanese subjects. Int J Geriatr Psychiatr 18:498–505
30. Robbins J, Hirsch C, Whitmer R, Cauley J, Harris T (2001) The association of bone mineral density and depression in an older population. J Am Geriatr Soc 49:732–736

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

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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．

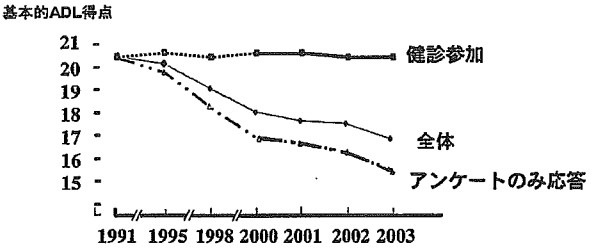

図1　1991年時長寿健診後期高齢者の基本的ADLの変化
歩行，階段昇降，摂食，入浴，排泄，更衣，整容の7項目（3段階：21点満点）
330例（男154，女176）平均年齢　80±4歳

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

Nutritional factors and functional assessment
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3）Kozo Matsubayashi：京都大学東南アジアセンター
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）

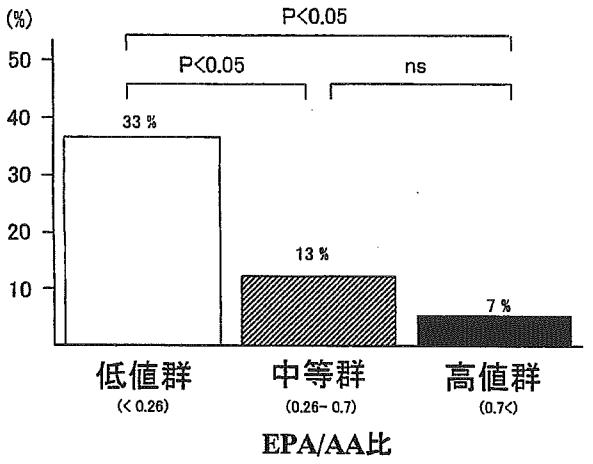

図2　追跡2年後の基本的ADL低下の頻度

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．

文　献

1) 松林公蔵：要介護状態発現の危険因子―香北町縦断研究から―．日老医誌　2001；38：614―616.
2) Reuben DB, Moore AA, Damesyn M, Keeler E, Harrison GG, Greendale G：Correlates of hypoalbuminemia in community-dwelling older persons. Am J Clin Nutr 1997；66：38―45.
3) Corti M-C, Guralnik JM, Salive ME, Sorkin MJ：Serum albumin level and physical disability as predictors of mortality in older persons. JAMA 1994；272：1036―1042.
4) Nakamura T, Azuma A, Kuribayashi T, Sugihara H, Okuda S, Nakagawa M：Serum fatty acid levels, dietary style and coronary heart disease in three neighbouring areas in Japan：the Kumihama study. Br J Nutr 2003；89：267―272.
5) Bang HO, Dyerberg J, Sinclair HM：The composition of the Eskimo food in north western Greenland. Am J Clin Nutr 1980；33：2657―2661.
6) Guallar E, Hennekens CH, Sacks FM, Willett WC, Stampfer MJ：A prospective study of plasma fish oil levels and incidence of myocardial infarction in U.S. male physicians J Am Coll Cardiol 1995；25：387―394.

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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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Kochi and Tokyo, Japan

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).

See page 1744

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.

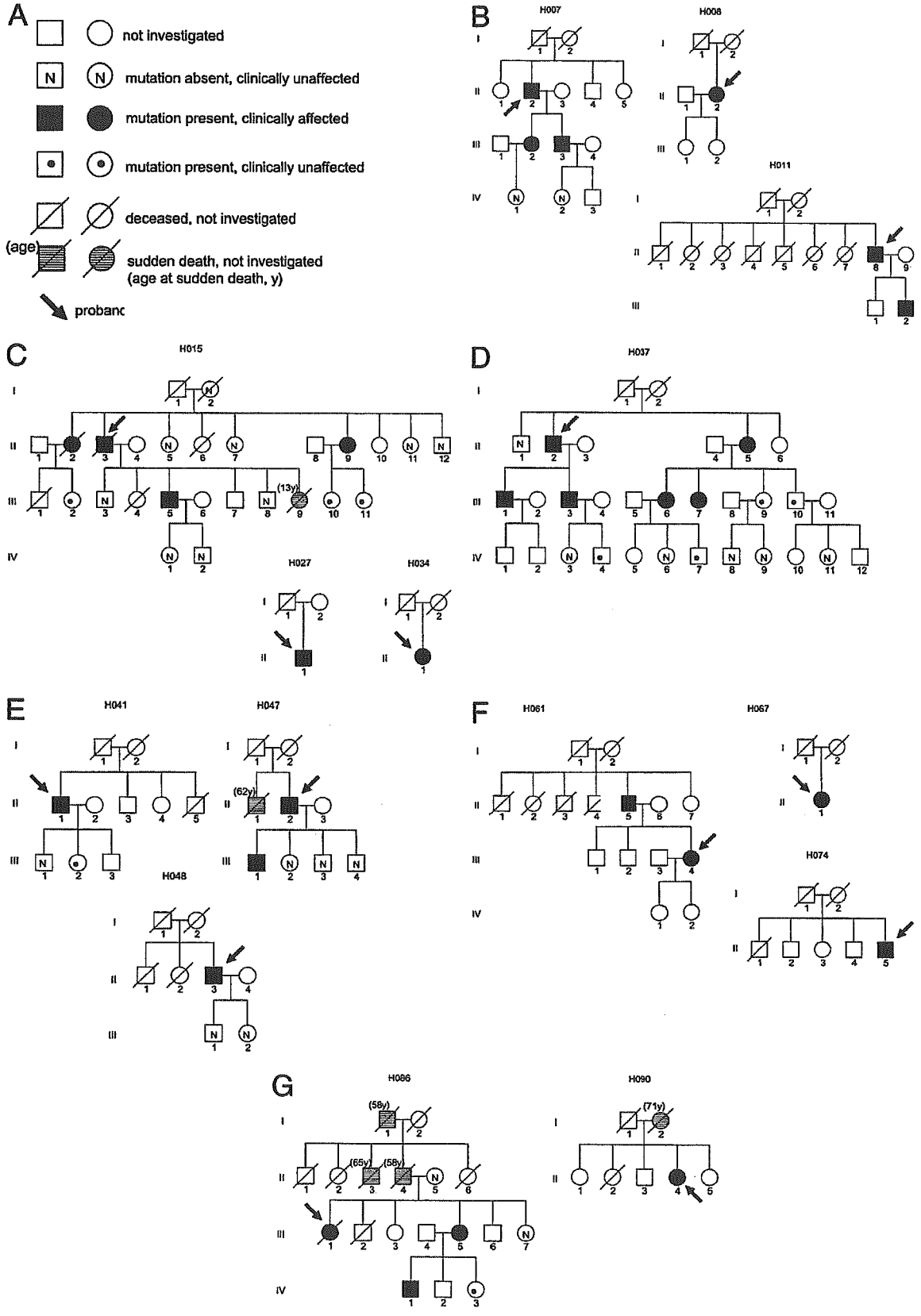

Figure 1. (A to G) Pedigree of families H007, H008, H011, H015, H027, H034, H037, H041, H047, H048, H061, H067, H074, H086, and H090. The genotypic status and phenotypic status of subjects are indicated.

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.

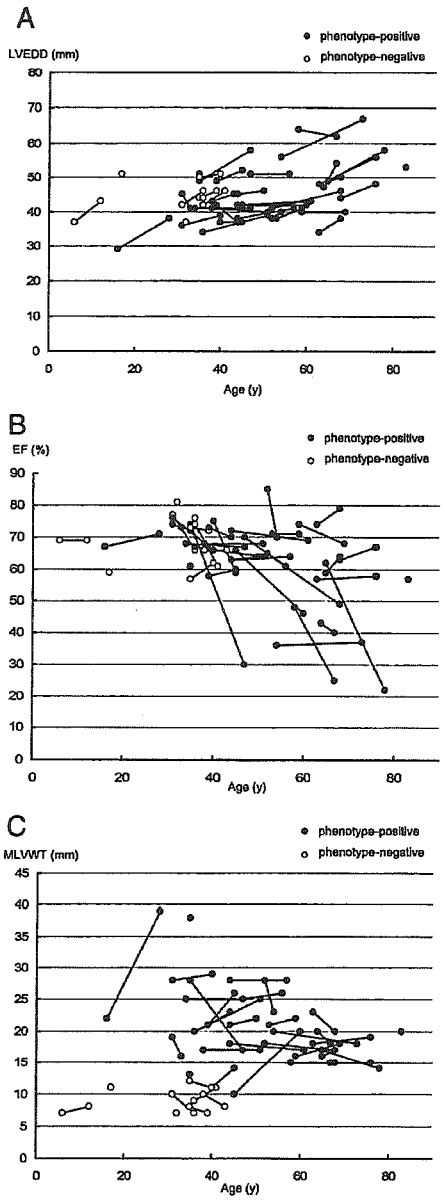

Figure 2. Longitudinal echocardiographic changes in 39 genotype-positive individuals during the follow-up period. **(A)** Changes in left ventricular end-diastolic diameter (LVEDD). **(B)** Changes in ejection fraction (EF). **(C)** Changes in maximum left ventricular wall thickness (MLVWT).

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.

Conclusions. A founder V592fs/8 mutation in the MyBPC gene was identified in 15 of 94 Japanese families with HCM. Elderly patients in particular may evolve to the "end-stage" HCM, characterized by LV systolic dysfunction, cavity dilation, and irreversible heart failure. Although the manifestation is late in onset, the clinical course in patients with this mutation is not benign in the long run with progressive LV remodeling with advancing age.

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REFERENCES

1. Spirito P, Seidman CE, McKenna WJ, Maron BJ. The management of hypertrophic cardiomyopathy. N Engl J Med 1997;336:775–85.
2. Maron BJ, McKenna WJ, Danielson GK, et al. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. J Am Coll Cardiol 2003;42:1687–713.
3. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. JAMA 2002;287:1308–20.
4. Elliott P, McKenna WJ. Hypertrophic cardiomyopathy. Lancet 2004; 363:1881–91.
5. Jarcho JA, McKenna WJ, Pare JA, et al. Mapping a gene for familial hypertrophic cardiomyopathy to chromosome 14q1. N Engl J Med 1989;321:1372–8.
6. Geisterfer-Lowrance AA, Kass S, Tanigawa G, et al. A molecular basis for familial hypertrophic cardiomyopathy: a beta cardiac myosin heavy chain gene missense mutation. Cell 1990;62:999–1006.
7. Kimura A, Harada H, Park JE, et al. Mutations in the cardiac troponin I gene associated with hypertrophic cardiomyopathy. Nat Genet 1997;16:379–82.
8. Towbin JA. Molecular genetics of hypertrophic cardiomyopathy. Curr Cardiol Rep 2000;2:134–40.
9. Bonne G, Carrier L, Richard P, Hainque B, Schwartz K. Familial hypertrophic cardiomyopathy: from mutations to functional defects. Circ Res 1998;83:580–93.
10. Watkins H, Conner D, Thierfelder L, et al. Mutations in the cardiac myosin binding protein-C gene on chromosome 11 cause familial hypertrophic cardiomyopathy. Nat Genet 1995;11:434–7.
11. Bonne G, Carrier L, Bercovici J, et al. Cardiac myosin binding protein-C gene splice acceptor site mutation is associated with familial hypertrophic cardiomyopathy. Nat Genet 1995;11:438–40.
12. Niimura H, Bachinski LL, Sangwatanaroj S, et al. Mutation in the gene for cardiac myosin-binding protein C and late-onset familial hypertrophic cardiomyopathy. N Engl J Med 1998;338:1248–57.
13. Arad M, Seidman JG, Seidman CE. Phenotypic diversity in hypertrophic cardiomyopathy. Hum Mol Genet 2002;11:2499–506.
14. Maron BJ, Niimura H, Casey SA, et al. Development of left ventricular hypertrophy in adults with hypertrophic cardiomyopathy caused by cardiac myosin-binding protein C gene mutations. J Am Coll Cardiol 2001;38:315–21.
15. Van Driest SL, Vasile VC, Ommen SR, et al. Myosin binding protein C mutations and compound heterozygosity in hypertrophic cardiomyopathy. J Am Coll Cardiol 2004;44:1903–10.
16. Maron BJ, Spirito P. Implications of left ventricular remodeling in hypertrophic cardiomyopathy. Am J Cardiol 1998;81:1339–44.
17. Doi YL, Kitaoka H, Hitomi N, Satoh M, Kimura A. Clinical expression in patients with hypertrophic cardiomyopathy caused by cardiac myosin-binding protein C gene mutation. Circulation 1999; 100:448–9.
18. Shapiro LM, McKenna WJ. Distribution of left ventricular hypertrophy in hypertrophic cardiomyopathy: a two-dimensional echocardiographic study. J Am Coll Cardiol 1983;2:437–44.
19. Maron BJ, Gottdiener JS, Epstein SE. Patterns and significance of distribution of left ventricular hypertrophy in hypertrophic cardiomyopathy. A wide angle, two dimensional echocardiographic study of 125 patients. Am J Cardiol 1981;48:418–28.
20. Ogimoto A, Hamada M, Nakura J, et al. 17-year follow-up study of a patient with obstructive hypertrophic cardiomyopathy with a deletion mutation in the cardiac myosin binding protein C gene. Circ J 2004;68:174–7.
21. Konno T, Shimizu M, Ino H, et al. A novel missense mutation in the myosin binding protein-C gene is responsible for hypertrophic cardiomyopathy with left ventricular dysfunction and dilation in elderly patients. J Am Coll Cardiol 2003;41:781–6.
22. Moolman JA, Reith S, Uhl K, et al. A newly created splice donor site in exon 25 of the MyBP-C gene is responsible for inherited hypertrophic cardiomyopathy with incomplete disease penetrance. Circulation 2000;101:1396–402.
23. Erdmann J, Raible J, Maki-Abadi J, et al. Spectrum of clinical phenotypes and gene variants in cardiac myosin-binding protein C mutation carriers with hypertrophic cardiomyopathy. J Am Coll Cardiol 2001;38:322–30.
24. Charron P, Dubourg O, Desnos M, et al. Clinical features and prognostic implications of familial hypertrophic cardiomyopathy related to the cardiac myosin-binding protein C gene. Circulation 1998;97:2230–6.
25. Maron BJ, Seidman JG, Seidman CE. Proposal for contemporary screening strategies in families with hypertrophic cardiomyopathy. J Am Coll Cardiol 2004;44:2125–32.
26. Elliott PM, Poloniecki J, Dickie S, et al. Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. J Am Coll Cardiol 2000;36:2212–8.
27. Maron BJ, Olivotto I, Spirito P, et al. Epidemiology of hypertrophic cardiomyopathy-related death: revisited in a large non-referral-based patient population. Circulation 2000;102:858–64.
28. Spirito P, Maron BJ. Relation between extent of left ventricular hypertrophy and age in hypertrophic cardiomyopathy. J Am Coll Cardiol 1989;13:820–3.
29. Lewis JF, Maron BJ. Elderly patients with hypertrophic cardiomyopathy: a subset with distinctive left ventricular morphology and progressive clinical course late in life. J Am Coll Cardiol 1989;13:36–45.
30. Lever HM, Karam RF, Currie PJ, Healy BP. Hypertrophic cardiomyopathy in the elderly. Distinctions from the young based on cardiac shape. Circulation 1989;79:580–9.
31. Fay WP, Taliercio CP, Ilstrup DM, Tajik AJ, Gersh BJ. Natural history of hypertrophic cardiomyopathy in the elderly. J Am Coll Cardiol 1990;16:821–6.
32. Thaman R, Gimeno JR, Reith S, et al. Progressive left ventricular remodeling in patients with hypertrophic cardiomyopathy and severe left ventricular hypertrophy. J Am Coll Cardiol 2004;44:398–405.
33. Spirito P, Chiarella F, Carratino L, Berisso MZ, Bellotti P, Vecchio C. Clinical course and prognosis of hypertrophic cardiomyopathy in an outpatient population. N Engl J Med 1989;320:749–55.
34. Maron BJ, Casey SA, Poliac LC, Gohman TE, Almquist AK, Aeppli DM. Clinical course of hypertrophic cardiomyopathy in a regional United States cohort. JAMA 1999;281:650–5.
35. Cecchi F, Olivotto I, Montereggi A, Santoro G, Dolara A, Maron BJ. Hypertrophic cardiomyopathy in Tuscany: clinical course and outcome in an unselected regional population. J Am Coll Cardiol 1995;26:1529–36.
36. Flashman E, Redwood C, Moolman-Smook J, Watkins H. Cardiac myosin binding protein C: its role in physiology and disease. Circ Res 2004;94:1279–89.
37. Harris SP, Bartley CR, Hacker TA, et al. Hypertrophic cardiomyopathy in cardiac myosin binding protein-C knockout mice. Circ Res 2002;90:594–601.
38. Carrier L, Knoll R, Vignier N, et al. Asymmetric septal hypertrophy in heterozygous cMyBP-C null mice. Cardiovasc Res 2004;63:293–304.
39. Kokado H, Shimizu M, Yoshio H, et al. Clinical features of hypertrophic cardiomyopathy caused by a Lys183 deletion mutation in the cardiac troponin I gene. Circulation 2000;102:663–9.

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Common carotid intima–media thickness is predictive of all-cause and cardiovascular mortality in elderly community-dwelling people: Longitudinal Investigation for the Longevity and Aging in Hokkaido County (LILAC) study

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Abstract

Several cohort studies have examined the association of carotid intima–media thickness (IMT) with the risk of stroke or myocardial infarction in apparently healthy persons. We investigated the predictive value of IMT of cardiovascular mortality in elderly community-dwelling people, beyond the prediction provided by age and MMSE, assessed by means of a multivariate Cox model. Carotid IMT and plaque were evaluated bilaterally with ultrasonography in 298 people older than 75 years (120 men and 178 women, average age: 79.6 years). The LILAC study started on July 25, 2000. Consultations were repeated every year. The follow-up ended on November 30, 2004. During the mean follow-up span of 1152 days, 30 subjects (21 men and nine women) died. Nine deaths were attributable to cardiovascular causes (myocardial infarction: two men and three women; stroke: two men and two women). The age- and MMSE-adjusted relative risk (RR) and 95% confidence interval (95% CI) of developing all-cause mortality was assessed. A 0.3 mm increase in left IMT was associated with a RR of predicted 1.647 (1.075–2.524), and a similar increase in right IMT with a RR of 3.327 (1.429–7.746). For cardiovascular mortality, the corresponding RR values were 2.351 (1.029–5.372) and 2.890 (1.059–7.891), respectively. Carotid IMT assessed by ultrasonography is positively associated with an increased risk of all-cause and cardiovascular death in elderly community-dwelling people.

Keywords: Carotid intima–media thickness; All-cause mortality; Cardiovascular mortality; Cognitive function; Elderly community-dwelling people

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1. Introduction

Several prospective population-based studies documented that carotid intima–media thickness (IMT) was positively associated with stroke and myocardial infarction in highly selected patients. Carotid IMT has also been shown to predict fatal coronary death and fatal stroke in elderly people [1–5]. It is now considered to constitute a surrogate marker of cardiovascular morbidity and mortality risk not only in patients, but also quite generally in young, middle-aged and elderly populations.

In 2000, we began a community-based study to Longitudinally Investigate the Longevity and Aging in Hokkaido County (LILAC), and to evaluate the population's neurocardiological function. Our goal is the prevention of cardiovascular events, including stroke and myocardial ischemic events, to prevent the decline in cognitive function of the elderly in a community dwelling. In this investigation, we estimated the ability of carotid IMT to predict all-cause and cardiovascular mortality in an elderly population. We already found that the cognitive function, estimated by MMSE and HDS-R, and age statistically significantly predicted cardiovascular death in this population. Herein, we examine the predictive value of all-cause and cardiovascular mortality offered by the carotid IMT, beyond the prediction provided by age and MMSE, as assessed by means of a multivariate Cox model.

2. Methods

2.1. Subjects and LILAC study design

We examined 298 subjects (120 men and 178 women) older than 75 years (average age: 79.6 years). BP was measured at the beginning of the study in a sitting position, and the brachial-ankle PWV (baPWV) was measured between the right arm and ankle in a supine position, using an ABI/Form instrument (Nippon Colin Co., Ltd., Komaki, Japan). The baPWV was measured using a volume-plethysmographic method. baPWV was measured in duplicate after at least a 5-min rest. Only baPWV measurements from participants with normal ankle/brachial pressure index (ABI) values (>0.90) were considered. The maximal value among the four readings was used for analysis. An echocardiogram and a conventional ECG record were also obtained as usual.

2.2. Carotid artery assessment

To measure the carotid intima–media thickness, ultrasonography of the common carotid artery, carotid bifurcation, and internal carotid artery of the left and right carotid arteries was performed with a 7.5-MHz linear-array transducer (SonoSite 180PLUS, Olympus, Tokyo). On a longitudinal, two-dimensional ultrasound image of the carotid artery, the anterior (near) and posterior (far) walls of the carotid artery are displayed as two bright white lines separated by a hypoechogenic space. The distance between the leading edge of the first bright line of the far-wall (lumen–intima interface) and the leading edge of the second bright line (media–adventitia interface) indicates the intima–media thickness. For the near-wall, the distance between the trailing edge of the first bright line and the trailing edge of the second bright line at the near-wall provides the best estimate of the near-wall intima–media thickness. When an optimal longitudinal image was obtained, it was frozen and the frozen images were digitized. The beginning of the dilatation of the distal common carotid artery served as a reference point for the start of measurement. The average of the intima–media thickness of each of the three frozen images was calculated. For each individual, the common carotid intima–media thickness was determined as the average of near- and far-wall measurements of both the left and right arteries. Usual lumen parameters including the common carotid artery (CCA), systolic peak velocity (VPS) and end-diastolic velocity (VED), measured by Doppler ultrasonogram, and the resistive index (RI) were also measured.

2.3. Heart rate variability

The first 1-h record of an ambulatory ECG obtained during routine medical examination conducted each year in July was processed for HRV, using a Fukuda-Denshi Holter analysis system (SCM-280-3). Time-domain (SDNN) and frequency-domain (spectral power in the "very low frequency" – VLF: 0.003–0.04 Hz, "low frequency" – LF: 0.04–0.15 Hz, and "high frequency" – HF: 0.15–0.40 Hz regions, and the LF/HF ratio) measures were determined. SDNN was calculated over the whole 1-h record, whereas the frequency-domain endpoints were computed as averages from estimates obtained over consecutive 5-min intervals. Spectral indices were obtained by the maximum entropy method (MEM) with the MemCalc/CHIRAM program (Suwa Trust Co., Ltd., Tokyo, Japan).

The Japanese version of the Mini-Mental State Examination (MMSE) and the Hasegawa Dementia Scale Revised (HDSR) were used to assess the overall cognitive function, including verbal orientation, memory, and constructional ability (Kohs block test). The Up & Go test measured, in seconds, the time it took the subject to stand up from a chair, walk a distance of 3 m, turn, walk back to the chair, and sit down again. This test is a simple measure of physical mobility and demonstrates the subject's balance, gait speed, and functional ability (Up & Go). A lower time score indicates better physical mobility. Functional Reach (FR), used to evaluate balance, represents the maximal distance a subject can reach forward beyond arm's length while maintaining a fixed base of support in the standing position. A higher score indicates better balance. Manual dexterity was assessed using a panel with combinations of 10 hooks, 10 big buttons, and five small buttons. There were three discrete measurements of time recorded for each participant (10 "hook-on"s, 10 big "button-on-and-off"s, and five small "button-on-and-off"s). The total manual dexterity time in seconds, defined as the button score (Button-S), was calcu-

lated by adding the average times for one hook-on and one big or small button-on-and-off. A lower button score indicates better manual dexterity.

2.4. All-cause and cardiovascular mortality

The follow-up span herein ended on November 30, 2004. The follow-up time was defined as the time elapsed between the date of the first (reference) examination and the date of death.

2.5. Statistical analysis

All data were analyzed with the Statistical Software for Windows (StatFlex Ver.5.0, Artec, Osaka, http://www.statflex.net). We used Cox regression analysis to calculate the unadjusted or adjusted relative risk (RR) and corresponding 95% confidence interval (CI) for all-cause and cardiovascular mortality. To identify independent predictors of mortality, we used multivariate Cox regression analyses with stepwise selection. Variables included in the multivariate models were age, gender, BMI and HR variability indices. Significance was considered at a value of $P < 0.05$.

3. Results

During the mean follow-up time of 1152 days, 30 subjects (21 men and nine women) died. Nine deaths were attributable to cardiovascular causes (myocardial infarction: two men and three women; stroke: two men and two women).

3.1. All-cause mortality

Among the variables considered herein, Cox proportional hazard models adjusted for age and MMSE found a statistically significant association with all-cause mortality only for gender, baPWV and carotid IMT, Table 1 (left). Being a man had a relative risk of 3.570 (95% CI: 1.619–7.874). A 200 or 500 cm/s increase in baPWV was associated with a relative risk of 1.122 (95% CI: 1.001–1.258) or 1.333 (95% CI: 1.002–1.774), respectively. A 0.2 or 0.3 mm increase in left carotid IMT was associated with a relative risk of 1.395 (95% CI: 1.049–1.854) or 1.647 (95% CI: 1.075–2.524), respectively. For the right carotid IMT, the relative risk was 2.228 (95% CI: 1.268–3.915) or 3.327 (95% CI: 1.429–7.746), respectively.

3.2. Cardiovascular mortality

Age- and MMSE-adjusted predictors of cardiovascular mortality were found to be baPWV and the carotid IMT, Table 1 (right). A 200 or 500 cm/s increase in baPWV was associated with a relative risk of 1.321 (95% CI: 1.120–1.558) or 2.005 (95% CI: 1.327–3.031), respectively. A 0.2 or 0.3 mm increase in left carotid IMT was associated with a relative risk of 1.768 (95% CI: 1.019–3.067) or 2.351 (95% CI: 1.029–5.372), respectively. For the right carotid IMT, the relative risk was 2.029 (95% CI: 1.039–3.963) or 2.890 (95% CI: 1.059–7.891), respectively.

4. Discussion

The findings herein indicate that in elderly community-dwelling people, independently of cognitive function, an increased common carotid IMT is associated with an elevated risk of both all-cause and cardiovascular mortality. Among the many variables considered in this study, including lumen parameters of the carotid artery, various kinds of parameters of echocardiography, heart rate variability, QT interval, behavioral activities (Up and Go, functional reach and button test), time perception and depressive mood, it is noteworthy that only carotid IMT and baPWV predicted the occurrence of all-cause mortality and cardiovascular death. It is important to realize that arterial blood flow in the common carotid artery, estimated by systolic peak velocity, end-diastolic velocity and the resistive index is virtually normal in these subjects. Kuller et al. [6] showed a considerably increased risk of cardiovascular morbidity and mortality for subjects with subclinical disease compared with subjects with no signs of subclinical disease. These results are in accordance with our finding that among subjects free from symptomatic cerebrovascular and cardiovascular disease, an increased IMT is associated with an increased risk of cardiovascular mortality.

To our knowledge, this is the first prospective study for a community-dwelling population to demonstrate statistically significant associations with cardiovascular mortality of carotid atherosclerosis, in a multivariate Cox model adjusted for cognitive function. It is also noteworthy that carotid IMT predicted not only cardiovascular mortality but also all-cause mortality. Since an impaired cognitive function was associated with all-cause mortality in several populations, our observation after adjustment for age and MMSE may have applications in clinical practice.

Several cross-sectional studies [7] have shown that increased common carotid IMT may be useful as a marker of atherosclerosis elsewhere in the arterial system, in keeping with our finding that not only carotid IMT but also baPWV conferred an increased risk of cerebro- and cardiovascular mortality. It should be noted that the relative risk of an increased IMT was higher than that of an increased baPWV, suggesting that IMT may be a better predictor than baPWV. baPWV is a novel noninvasive technique assessing pulse wave transmission between the brachial and tibial arteries [8]. It is considered to be an indicator of arterial stiffness and a marker of vascular damage [9].

Our data suggest that measurement of IMT in subclinical subjects may be useful to obtain an estimate of mortality risk that is more precise than that based on the measurement of conventional risk factors alone, and may thus have additional predictive value. In addition, using IMT as a primary outcome measure in intervention trials on the efficacy of blood pressure or lipid lowering regimens, especially from the viewpoint of chronodiagnosis and chronotherapy, may lead to major applications in clinical practice to reduce the progression of atherosclerosis.

Table 1
Age- and MMSE-adjusted relative risk of all-cause and cardiovascular mortality in elderly population

Variables	All-cause mortality				Cardiovascular mortality			
	n	RR	95% CI	*P*-value	n	RR	95% CI	*P*-value
Gender	291	3.570	1.619–7.874	0.0016	271			N.S.
BMI	279			N.S.	260			N.S.
SBP	279			N.S.	259			N.S.
DBP	278			0.0733	259			N.S.
PP	278			N.S.	259			N.S.
Postural BP change	276			0.0818	256			0.0818
Pulse rate	279			N.S.	259			N.S.
Up and Go	288			N.S.	269			N.S.
FR	287			N.S.	268			N.S.
Button	289			N.S.	269			N.S.
HDSR	291			N.S.	271			0.0762
Kohs	272			N.S.	253			N.S.
GDS	273			N.S.	254			N.S.
Time estimation (60A)	258			N.S.	244			N.S.
Time estimation (60B)	252			N.S.	240			N.S.
HR	243			N.S.	229			N.S.
VLF	191			N.S.	182			N.S.
LF	189			N.S.	180			N.S.
HF	192			N.S.	183			N.S.
LF/HF	192			0.0936	183			0.0936
SDNN	191			N.S.	182			N.S.
Lown	273			N.S.	253			N.S.
PWV (200)	242	1.122	1.001–1.258	0.0487	223	1.321	1.120–1.558	0.0010
PWV (500)	242	1.333	1.002–1.774	0.0487	223	2.005	1.327–3.031	0.0010
ABI	260			N.S.	241			N.S.
IMT Lt (0.1)	130	1.181	1.024–1.362	0.0220	128	1.330	1.010–1.751	0.0426
IMT Lt (0.2)	130	1.395	1.049–1.854	0.0220	128	1.768	1.019–3.067	0.0426
IMT Lt (0.3)	130	1.647	1.075–2.524	0.0220	128	2.351	1.029–5.372	0.0426
IMT Rt (0.1)	129	1.493	1.126–1.979	0.0053	126	1.424	1.019–1.991	0.0383
IMT Rt (0.2)	129	2.228	1.268–3.915	0.0053	126	2.029	1.039–3.963	0.0383
IMT Rt (0.3)	129	3.327	1.429–7.746	0.0053	126	2.890	1.059–7.891	0.0383
Lt CCA	131			0.0682	128			N.S.
Rt CCA	127			0.0699	124			N.S.
Lt VPS	130			N.S.	127			N.S.
Rt VPS	129			N.S.	126			N.S.
Lt VED	130			N.S.	127			N.S.
Rt VED	128			N.S.	125			N.S.
Lt RI	123			N.S.	120			N.S.
Rt RI	114			0.1069	111			N.S.
LVMI	135			N.S.	126			N.S.
Calcification of M-valve	151			N.S.	141			N.S.
Calcification of A-valve	150			N.S.	140			N.S.
LVDd	135			N.S.	126			N.S.
%FS	135			N.S.	126			N.S.
EF	135			N.S.	126			N.S.
E	146			N.S.	137			N.S.
A	146			N.S.	137			N.S.
E/A	146			0.0624	137			N.S.
DT	143			N.S.	134			N.S.
QTd	134			N.S.	125			N.S.
QT	177			N.S.	167			0.0505
QTc	175			N.S.	165			N.S.

Gender: male versus female; Lt = left; Rt = right.

We conclude that carotid IMT assessed by ultrasonography is positively associated with an increased risk of all-cause mortality and cardiovascular death in particular. This study provides supportive evidence for the use of IMT measurements as an intermediate endpoint in intervention trials.

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References

[1] Chambless LE, Heiss G, Folsom AR. Association of coronary heart disease incidence with carotid artery wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) study, 1987–1993. Am J Epidemiol 1997;146:483–94.

[2] Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid intima–media thickness and risk of stroke and myocardial infarction. The Rotterdam study. Circulation 1997;96:1432–7.

[3] Hodis HN, Mack WJ, LaBree L, Seizer RH, Liu C-r, Liu C-h, et al. The role of carotid arterial intima–media thickness in predicting clinical coronary events. Ann Intern Med 1998;128:262–9.

[4] Chambless LE, Folsom AR, Clegg LX, Sharrett AR, Shahar E, Nieto FJ, et al. Carotid wall thickness is predictive of incident clinical stroke: the Atherosclerosis Risk in Communities (ARIC) study. Am J Epidemiol 2000;15:478–87.

[5] Kitamura A, Iso H, Imano H, Ohira T, Okada T, Sato S, et al. Carotid intima–media thickness and plaque characteristics as a risk factor for stroke in Japanese elderly men. Stroke 2004;35:2788–94.

[6] Kuller LH, Shemanski L, Psaty BM, Borhani NO, Gardin J, Haan MN, et al. Subclinical disease as an independent risk factor for cardiovascular disease. Circulation 1995;92:720–6.

[7] Bots ML, Witteman JCM, Grobbee DE. Carotid intima–media wall thickness in elderly women with and without atherosclerosis of the abdominal aorta. Atherosclerosis 1993;102:99–105.

[8] Yamashina A, Tomiyama H, Takeda K, Tsuda H, Arai T, Hirose K, et al. Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. Hypertens Res 2002;25:359–64.

[9] Asmar R. Arterial stiffness and pulse wave velocity. Amsterdam: Elsevier, 1999, pp. 9–15.

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VERTICAL GROUND REACTION FORCE SHAPE IS ASSOCIATED WITH GAIT PARAMETERS, TIMED UP AND GO, AND FUNCTIONAL REACH IN ELDERLY FEMALES

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Objective: **The aim of this study was to evaluate the relationship between knee pain and various indicators of the combined performance of the lower extremity (including gait parameters, functional performance such as timed up and go, and functional reach test) and to determine whether the classification of vertical ground reaction forces correlates with gait parameters and functional performance.**

Subjects and Methods: **Simultaneous analysis of gait, time-distance parameters and vertical ground reaction force. Timed up and go, and functional reach test were examined in 130 elderly women. The vertical component of the ground reaction force was grouped into 2 categories: M-shaped and non-M-shaped.**

Results: **No significant association was found between knee pain and timed up and go, functional reach test, or gait parameters in elderly female participants. There were significant differences between subjects with M- and non-M-shaped vertical ground reaction forces with regard to timed up and go, functional reach test and Japan Orthopaedic Association score. There were also significant differences between the 2 groups (M shaped and non-M-shaped) in gait parameters.**

Conclusion: **Evaluation of the vertical ground reaction force to determine its shape may be a useful and simple tool in the analysis of gait and functional performance.**

Key words: knee pain, gait analysis, elderly females, ground reaction force, osteoarthritis.

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INTRODUCTION

Osteoarthritis of the knee is one of the most common diseases in elderly females. There are several ways of testing locomotor function of the lower extremity, including measures of muscle strength, gait analysis and some types of knee evaluation scales (1–3). However, there is limited evidence that these parameters are highly correlated with the functional state of the knee. Gait analysis is becoming recognized as an important clinical tool in orthopaedics, in pre-surgery planning, post-surgery monitoring and in a posterior evaluation of various corrective interventions (4, 5). However, it is sometimes difficult for clinicians to analyse the large amounts of data gathered in the assessment of gait time and distance parameters (5).

Objective quantitative assessment of mobility and balance is important for older people because problems with gait and balance can result in a restriction of activity. The Timed Up and Go (TUG) test correlates with gait speed, balance and movement of the lower extremities (6). The Functional Reach (FR) test is a simple measurement of standing balance that can predict falls in elderly people (7, 8).

There have been several reports concerning gait analysis in osteoarthritis of the knee (1, 9). The vertical ground reaction force (VGRF) has been shown to be a reliable and repeatable feature of gait (10–11). There have been numerous studies regarding ground reaction forces during walking (12–14). Gait speed significantly affects VGRF (12, 13, 16). The VGRF varies continually from the instant of initial contact until the foot leaves the supporting surface (17). Body mass, proportions, walking style and balance all affect VGRF (17).

There have been only a few reports regarding the relationship between VGRF and various gait parameters in elderly females with osteoarthritic knees. Analyses that include a classification of VGRF have also been limited. Thus, in this study, we focused on the vertical ground force component, classified into 2 groups: M-shaped, also known as a "dual-hump" shape (18) and non-M-shaped. The purpose of this study was to evaluate the relationship between knee pain and various indicators of the combined performance of the leg, including gait parameters, functional performance, TUG and FR and to determine whether the classification of VGRF is correlated with gait parameters and functional performance.

MATERIAL AND METHODS

Subjects

We defined the subjects with osteoarthritic knee as having knee pain and less than 100 points of Japan Orthopaedic Association (JOA) score. We have been performing annual medical checks of adults aged 65 years and

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Table I. *Japan Orthopaedic Association scores based on the osteoarthritic knee evaluation form*

Pain on walking (maximum 30 points)	*Score*
No pain, walking unlimited	30
Pain, walking unlimited	25
Pain, walking distance of 0.5–1 km	20
Pain, walking less than 0.5 km	15
Pain, walking only indoors	10
Cannot walk	5
Cannot stand	0
Pain on ascending or descending stairs (maximum 25 points)	
No pain	25
Pain, relieved by using handrails	20
Pain, with handrails, but no pain with each step	15
Pain, with each step, pain relieved by using handrails	10
Pain, with each step even with handrail use	5
Cannot ascend or descend	0
Range of motion (maximum 35 points)	
Kneeling	35
Sideways or cross-legged sitting	30
More than 110°	25
75°–109°	20
35°–74°	10
Less than 35°	0
Joint effusion (maximum 10 points)	
No effusion	10
Occasional puncture required	5
Frequent puncture required	0
Maximum total points	100

over who live in the community in Kahoku of Kochi prefecture since 1994. We then examined the locomotor ability of the subjects.

The mean age of the 130 participants was 80 years (range 65–94 years), with a mean height of 143.0 cm. Knee pain while walking was classified into 3 groups: no pain (45%), unilateral pain (28%) or bilateral pain (26%).

Average maximum flexion for all subjects was 140.9 ± 13.4 degrees. Average maximum extension was 5.2 ± 6.1 degrees. JOA scores determined from the osteoarthritic knee evaluation form (Table I) were used for the evaluation of knee function (19). JOA (0–100 points) scores averaged 90.1 ± 12.9 points. The distance between the medial chondyles was evaluated, and averaged 2.5 ± 1.4 fingers breadth.

Co-morbidities of the subjects included hypertension (31.6%), cardiac arrhythmia (6.1%), coronary artery disease (3.2%) and diabetes mellitus (5.7%). Eighteen subjects with the following conditions were excluded from this study: knee disorders after total knee arthroplasty (5 patients), high tibial osteotomy (2 patients), miscellaneous knee operations (2 patients), osteosynthesis (1 patient), multiple cerebral infarctions (7 patients) and Parkinson's disease (1 patient).

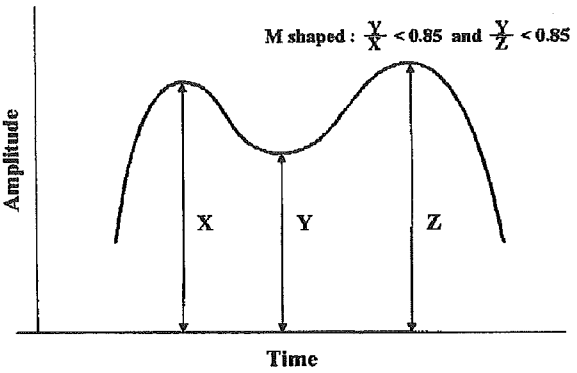

Fig. 1. Calculation of M-wave shape of vertical ground reaction force. M-shaped was defined as Y/X and Y/Z less than 0.85. All others were defined as non-M-shaped.

Gait analysis

The interviewer asked to record the gait parameters of subjects who were able to walk a distance of 10 metres. Subjects were allowed to wear their usual clothes and use their preferred (normal) speed while walking a 7-metre-long course. The first and last 2–3 metres on the walkway were not considered for measurement.

A Gait Scan® 8000 (Nitta Co. Ltd, Osaka, Japan) of gait-pattern measurement system consisting of a thin-film sensor walkway, a computer for automatic recording of the data was used in this study. This gait analysis device consists of a sensor seat (264 × 52 cm), a connector unit which fixes the sensor seat, and an interface board with a personal computer and software for data analysis.

Gait parameters, temporal distance and time factors, and ground reaction forces were measured simultaneously. Ground reaction force data for both legs was collected at a self-selected walking speed. The peak force was measured as the highest VGRF that occurred anytime during the stance phase, while the lowest VGRF occurred during the mid-stance phase.

Patients were classified into 2 groups based on the VGRF: M-shaped and non-M-shaped (Fig. 1). We defined M-shaped as lowest/highest × 100 (%) of less than 85. We assessed the shape of the VGRF for every step and classified individuals based on the result that was obtained for the greater number of steps. The mean gait variables measured in this study were walking speed (metres/sec), stride length, step width (cm), time of stride, time of single stance and time of double stance (sec). The distance parameters of stride length and step width were normalized for the height of the subject (15).

Functional performance

Timed up and go

To measure TUG, subjects were given oral instructions to stand up from

Table II. *Data (mean (SD)) for patients without pain, with unilateral and bilateral pain in elderly females*

	No pain ($n = 59$)	Unilateral pain ($n = 37$)	Bilateral pain ($n = 34$)
Body weight (kg)	45.2 (7.53)	47.2 (7.49)	52.2 (8.94)
Timed up and go (sec)	13.0 (3.0)	13.8 (4.51)	15.1 (7.28)
Functional reach (cm)	20.6 (7.2)	21.0 (7.07)	23.1 (6.89)
Stride length (cm)	63.2 (9.21)	61.1 (11.7)	61.7 (10.9)
Stride width (cm)	5.4 (2.20)	5.7 (2.14)	5.6 (1.92)
Time of stride (sec)	1.1 (0.117)	1.1 (0.179)	1.2 (0.167)
Time of single stance (sec)	0.58 (0.059)	0.59 (0.073)	0.60 (0.082)
Time of double stance (sec)	0.16 (0.037)	0.17 (0.052)	0.18 (0.069)
Gait speed (m/s)	0.6 (0.115)	0.56 (0.147)	0.54 (0.135)

Table III. *Participant characteristics given as mean (SD)*

	Height (cm)	Weight (kg)	JOA (point)	TUG (sec)	FR (cm)
Right side					
M-shaped ($n=32$)	143.8 (7.2)	46.1 (8.6)	95.2 (10.3)	11.6 (2.3)	22.5 (6.9)
Non-M-shaped ($n=47$)	142.4 (5.2)	45.9 (7.4)	86.6 (13.5)	14.6 (4.5)	18.4 (8.2)
	$p=0.187$	$p=0.96$	$p=0.0013$	$p<0.0001$	$p=0.026$
Left side					
M-shaped ($n=29$)	143.1 (8.1)	45.8 (8.1)	96.9 (6.25)	11.35 (2.25)	22.9 (7.56)
Non-M-shaped ($n=50$)	142.9 (4.7)	46.2 (7.8)	86.1 (14.1)	14.5 (4.44)	18.45 (7.74)
	$p=0.41$	$p=0.92$	$p=0.0002$	$p<0.0001$	$p=0.026$

JOA: Japan Orthopaedic Association; TUG: timed up and go; FR: functional reach

a chair, walk 3 metres as quickly and as safely as possible, cross a line marked on the floor, turn around, walk back and sit down (6).

Functional reach. FR represents the maximal distance a subject can reach forward beyond arm's length while maintaining a fixed base of support in the standing position (7, 20).

Statistics

Data were expressed as a mean and standard deviation (SD). Differences between groups were evaluated using a Kruskal Wallis test for the analysis of knee pain (Table II) and a Mann-Whitney U test for the analysis of VGRF (Tables III and IV). Statistical significance was set at $p<0.05$.

RESULTS

Occurrence of knee pain showed a significant association with body weight; however, there was no significant difference between patients with or without pain and TUG, FR, or any gait parameters (Table II).

The shape of the VGRF was associated with certain measures of functional performance, as well as the JOA score (Table III). Patients exhibiting an M-shaped VGRF on the right and left sides had shorter TUGs and longer FRs than patients with a non-M-shaped VGRF. The total JOA score was greater for the M-shaped group than for the non-M-shaped group. Within both groups, the ground reaction forces were similar on left and right sides.

Several gait parameters varied according to the shape of the VGRF (Table IV). Stride length was longer for the M-shaped VGFR group than for the non-M-shaped VGRF group. The times of stride and single and double stance were shorter in the M-shaped VGRF group than in the non-M-shaped group. The walking speed of the M-shaped group was faster than that of the non-M-shaped group. There was no significant difference between the 2 groups in the step width on both sides.

DISCUSSION

Osteoarthritis of the knee is common in elderly females and it is well-known that it is associated with gait disturbances. There have been numerous reports regarding the relationship between osteoarthritis and gait parameters. An evaluation of the relationship between gait parameters and knee pain in elderly females found no significant association between knee pain and gait parameters or functional performance. Findings such as these have suggested that numerous factors, such as the posture of the trunk, lumbar lesions, the condition of other joints (such as the hip and ankle) and mental status, all contribute to gait parameters in elderly females. Therefore, it is important to consider these factors in the analysis of people with knee pain.

An advantage of gait analysis as a diagnostic or research tool is that many factors can be assessed at one time; however, proper evaluation of the resulting data can be complex. Quantitative data of time and distance parameters of gait analysis is difficult to understand and interpret whether it is within normal or not.

One study showed no overall abnormality in the shape or amplitude of the ground reaction force measured for the natural gait of knee-pain subjects (21). The present study, which involved the evaluation of one simple aspect of the VGRF (classified as M-shaped and non-M-shaped), showed that the shape of the ground reaction force was correlated with the pain

Table IV. *Gait parameters (mean (SD)) for subjects with M-shape and non-M-shape of vertical ground reaction force*

	Stride length (cm)	Step width (cm)	Time of stride (sec)	Time of single stance (sec)	Time of double stance (sec)	Gait speed (m/s)
Right side						
M-shaped ($n=32$)	70.1 (8.7)	5.5 (2.1)	1.03 (0.09)	0.5 (0.04)	0.1 (0.02)	0.7 (0.11)
Non-M-shaped ($n=47$)	55.8 (89.9)	5.8 (2.3)	1.2 (0.15)	0.6 (0.07)	0.2 (0.047)	0.5 (0.1)
	$p<0.0001$	$p=0.712$	$p<0.0001$	$p<0.0001$	$p<0.0001$	$p<0.0001$
Left side						
M-shaped ($n=29$)	70.6 (9.2)	5.5 (2.08)	1.0 (0.087)	0.54 (0.042)	0.1 (0.02)	0.69 (0.12)
Non-M-shaped ($n=50$)	56.5 (9.9)	6.0 (2.47)	1.8 (0.15)	0.61 (0.075)	0.2 (0.046)	0.5 (0.11)
	$p<0.0001$	$p=0.146$	$p<0.0001$	$p<0.0001$	$p<0.0001$	$p<0.0001$

component of the JOA score. In another study, increased gait speed was associated with shorter force periods and larger peak forces (16).

In the present study we found that there were no differences between the right and left legs with respect to gait parameters, functional performance or the shape of the ground reaction force. Consistent with our findings, another study showed no significant differences between the right and left foot with respect to ground reaction force during walking (22).

In our study we found that both gait parameters and functional performance were significantly correlated with the shape of the VGRF. Several previous studies have examined VGRFs in normal subjects and patients with osteoarthritis; however, prior to the present study, there was little known concerning the relationship between the VGRF and gait parameters or functional performance in elderly females with knee osteoarthritis. In one study it was found that the 2 peaks in the vertical component measured for the affected side in knee-osteoarthritis patients became less apparent, with significantly lower magnitudes than in normal subjects (18). In addition, patterns of VGRFs were nearly identical during overground and treadmill walking (23) and the general waveform and its characteristic features did not seem to be affected by the sex of normal subjects (18). In the present study, we could not find a correlation between pain and the mechanism of the shape of VGRF. Further study is needed to clarify the changing mechanism of VGRF in osteoarthritic knee.

In the present study, we did not examine inter-rater reliability: future study is needed to investigate this and the validity with respect to M-shape and gait analysis.

In conclusion, our classification of VGRF is a simple and useful tool for assessment of gait function. It was correlated with many parameters of gait and functional performance, such as TUG and functional reach. Our study indicated that a change in the VGRF, from non-M-shaped to M-shaped, is crucial to the improvement of gait parameters and gait performance. Further studies are needed to seek methods for altering the shape of the ground reaction force.

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REFERENCES

1. Murray MP, Gore DR, Sepic SB, Mollinger LA. Antalgic maneuvers during walking in men with unilateral knee disability. Clin Orthop 1985; 199: 192–200.
2. Prince F, Corriveau H, Hebert R, Winter DA. Gait in the elderly. Gait Posture 1997; 5: 128–135.
3. Stauffer RN, Chao EYS, Gyory AN. Biomechanical gait analysis of the diseased knee joint. Clin Orthop 1977; 126: 246–255.
4. Kaufman KR, Sutherland DH. Future trends in human motion analysis. In: Harris GF, Smith PA, eds. Human motion analysis. Current applications and future directions. New York: IEEE Press; 1996, p. 187–215.
5. Bertani A, Cappello A, Benedetti MG, Simoncini L, Catani F. Flat foot functional evaluation using pattern recognition of ground reaction data. Clin Biomech 1999; 14: 484–493.
6. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc 1991; 39: 142–148.
7. Duncan PW, Weiner DK, Chandler J, Studenski S. Functional reach: a new clinical measure of balance. J Gerontol 1990; 45: 192–197.
8. Weiner DK, Duncan PW, Chandler J, Studenski SA. Functional reach: a marker of physical frailty. J Am Geriatr Soc 1992; 40: 203–207.
9. Goh JC, Bose K, Khoo BC. Gait analysis study on patients with varus osteoarthritis of the knee. Clin Orthop 1993; 294: 223–231.
10. Kadaba MP, Ramakrishnan HK, Wootten ME, Gainey J, Gorton G, Cochran GVB. Repeatability of kinematic, kinetic, and electromyographic data in normal adult gait. J Orthop Res 1989; 7: 849–860.
11. Olsson E, Oberg K, Ribbe T. A computerized method for clinical gait analysis of floor reaction forces and joint angular motion. Scand J Rehabil Med 1986; 18: 93–99.
12. Andriacchi TP, Ogle JA, Galante JO. Walking speed as a basis for abnormal gait measurements. J Biomech 1977; 10: 261–268.
13. Alexander RM, Jayes AS. Fourier analysis of forces exerted in walking and running. J Biomech 1980; 13: 383–390.
14. Balmaseda MT, Koozekanani SH, Fatehi MT, Gordon C, Dreyfuss PH, Tanbonlinog EC. Ground reaction forces, center of pressure, and duration of stance with and without an ankle-foot orthosis. Arch Phys Med Rehabil 1988; 69: 1009–1112.
15. Chao EY, Laughman RK, Schneider E, Stauffer RN. Normative data of knee joint motion and ground reaction forces in adult level walking. J Biomech 1983; 16: 219–233.
16. Nilsson J, Thorstensson A. Ground reaction forces at different speeds of human walking and running. Acta Physiol Scand 1989; 136: 217–227.
17. Cook TM, Farrell KP, Carey IA, Gibbs JM, Wiger GE. Effects of restricted knee flexion and walking speed on the vertical ground reaction force during gait. J Orthop Sports Phy Ther 1997; 25: 236–244.
18. Schneider E, Chao EY. Fourier analysis of ground reaction forces in normals and patients with knee joint disease. J Biomech 1983; 16: 591–601.
19. Takahashi T, Wada Y, Tanaka M, Iwagawa M, Ikeuchi M, Hirose D, Yamamoto H. Dome-shaped proximal tibial osteotomy using percutaneous drilling for osteoarthritis of the knee. Arch Orthop Trauma Surg 2000; 120: 32–37.
20. Okumiya K, Matsubayashi K, Wada T, Kimura S, Doi Y, Ozawa T. Effects of exercise on neurobehavioral function in community-dwelling older people more than 75 years of age. J Am Geriatr Soc 1996; 44: 569–572.
21. Radin EL, Yang KH, Riegger C, Kish VL, O'Connor JJ. Relationship between lower limb dynamics and knee joint pain. J Orthop Res 1991; 9: 398–405.
22. Herzog W, Nigg BM, Read LJ, Olsson E. Asymmetries in ground reaction force patterns in normal human gait. Med Sci Sports Exerc 1989; 21: 110–114.
23. White SC, Yack HJ, Tucker CA, Lin HY. Comparison of vertical ground reaction forces during overground and treadmill walking. Med Sci Sports Exerc 1998; 30: 1537–1542.