第100回日本精神神経学会総会

シンポジウム

老年症候群，転倒寝たきり予防のために

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高齢者医療においては，ひとりで多くの疾患をもち（多病），臓器を診るのではなく，全人的医療を行う必要があるが，老年症候群の理解と包括的アプローチの戦略である「総合的機能評価」の理解と実施が，全人的医療を実現する具体的手段となる．痴呆は高齢者医療の中でもっとも重要な病態の一つである．痴呆を老人医療の中で捉えると，診断と治療面では，痴呆の合併症の診断と治療の問題，総合的機能評価による診断と治療効果の判定の問題が重要であり，ケアと社会体制では問題行動に対するケア技術の問題，ケア技術の効果判定に資する指標の開発と痴呆を支える介護保険上の変更問題が高齢者医療の重点領域である．失禁も高齢者医療の中で，苦慮する重要な問題領域である．高齢者では蓄尿，排尿機能以外に，認知機能やADL，糖尿病や尿路感染症などの全身疾患に配慮し，「排尿誘導」をまず実施して，効果を判定することが重要である．効果判定のためには，ADL以外に，痴呆患者のQOLを簡易に測定する「意欲の指標」が有用である．寝たきりの危険因子は，痴呆，意欲の低下，低栄養，転倒が特に重要で，参加，運動が予防のキーワードである．

＜索引用語：老年症候群，総合的機能評価，排尿誘導，意欲の指標，参加と運動＞

1．痴呆の合併症としての老年症候群

高齢者に頻度が高くケアが問題となる一連の症状所見を「老年症候群」と呼ぶ．老年症候群は大きく3つに分類される[1,2]．

1）主に急性疾患に付随する症候で，若い人と同じくらいの頻度でおきるが，対処方法は高齢者では若い人と違って工夫が必要な症候群．

2）主に慢性疾患に付随する症候で，65歳の前期老年者から徐々に増加する症候群．

3）75歳以上の後期高齢者に急増する症候で，日常生活活動度（ADL）の低下と密接な関連を持ち，介護が重要な一連の症候群．

意義：この3つの老年症候群の分類と加齢変化（図1）は高齢者の複合的疾患構造を説明し，医療と介護が不可分であることの実証である．

80歳以上の入院高齢者では，平均8以上の老年症候群を同時に保有する．

逆に痴呆患者で，どのような老年症候群を合併しやすいか検討してみた．対象は入院症例で痴呆と診断された38例（平均年齢80.1±1.1歳）で，改訂長谷川式簡易知能スケールは11.3±1.4（0～27）である．平均疾患数は4.6個，老年症候群は4.8個と平均よりやや少ない．痴呆のため十分身体的側面が評価されていない可能性もある．

日常生活活動度はBarthel Index（100点満点）で63.4±4.7と中等度にADLが阻害されている．

合併する老年症候群の頻度を図2に示す．

高頻度の老年症候群は，主としてケアに直結する一連の症候群（譫妄，失禁，転倒）やコミュニケーション障害（難聴，視力障害），栄養に関連する症候（やせ，便秘）などに分類される．

また中等度に見られる症候も，合併病態や関連病態である栄養関連（脱水，食欲低下，低栄養，褥瘡），骨関節系（骨粗鬆症，骨折，関節変形），精神神経系（失調，うつ，不眠），呼吸器系（喀

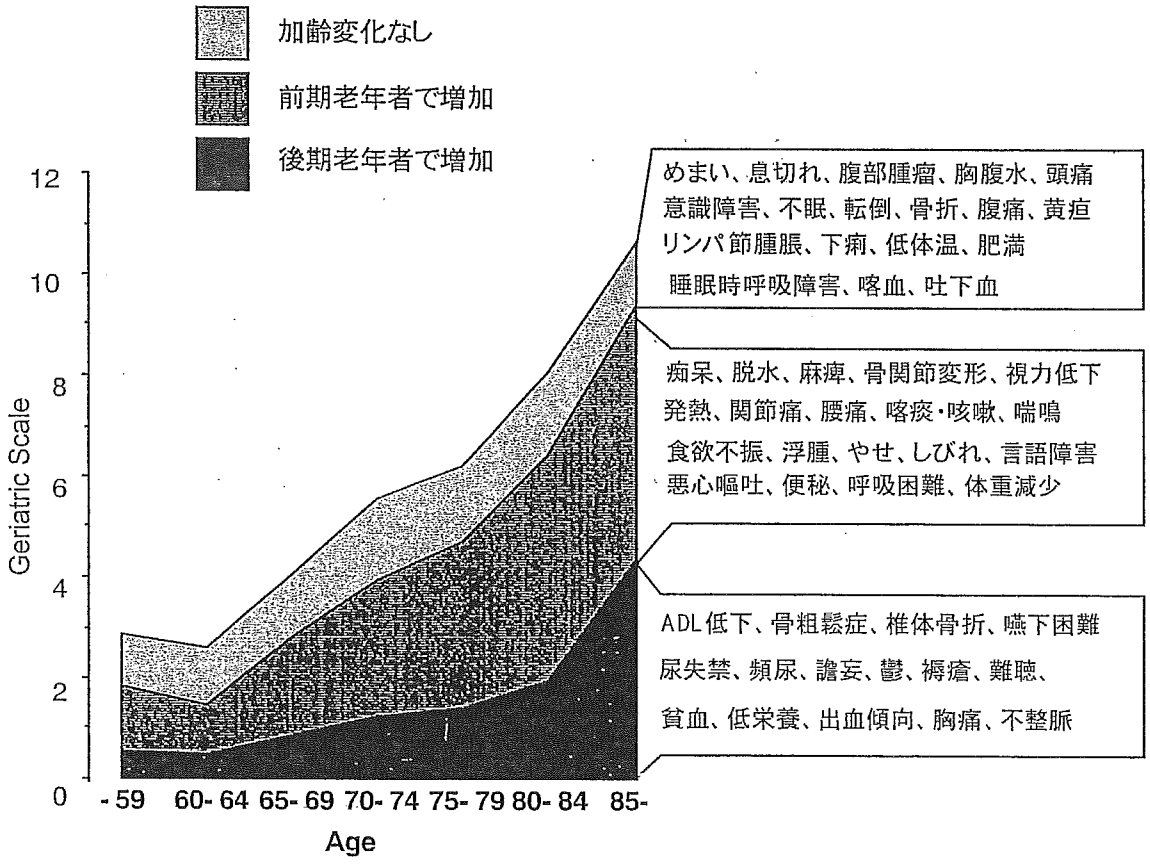

図1　3つの老年症候群

痰，喘鳴）などに大別される．頻度の極端に少ないものは吐き気（5％），肥満（0％）であった．

このように，痴呆は他の代表的な老年症候群である尿失禁，転倒骨折，誤嚥性肺炎，低栄養，廃用性症候群などを高頻度に合併し，さらに譫妄やうつなども問題となる複雑な医療分野といえる．

2．機能評価を行い機能低下の早期発見をする

痴呆の重症度では，自立困難や日常生活動作の困難などが判定で重要視されるが，治療効果では「記憶検査」以外長く省みられることがなかった．進展予防に有効な薬剤が開発され，記憶力の保持には著明な効果が見られないことが分かって，ようやくこれらを加味した評価が取り入れられるようになった．

高齢者の総合的機能評価はもともと，認知能だけでなく，うつ，ADL，生活自立，家庭環境，サービス利用，介護負担などを総合的に評価するものであり，老年医学における痴呆医療の最も重要な領域である．

杏林大学高齢医学では，物忘れ外来開設以来全例に総合的機能評価を施行し，治療判定に役立てている．これまでの成績では，薬物療法（塩酸ドネペジルなど）や行動療法（回想法，オリエンテーション療法，運動療法）などで，最も改善効果が強い機能は，生活自立と関連する手段的ADL[3]であった．手段的ADLは，交通手段を使って外出する，買い物をする，電話をかける，金銭管理をする，服薬管理をする，炊事をする，掃除などの家事をする，洗濯をするの8項目であり，在宅の生活自立に直結している．これに次いで感度のよい機能評価は，短期記憶力（HDSR, MMSE）であり，問題行動28項目の調査（痴呆行動障害尺度）は介護負担と良い相関があるが，

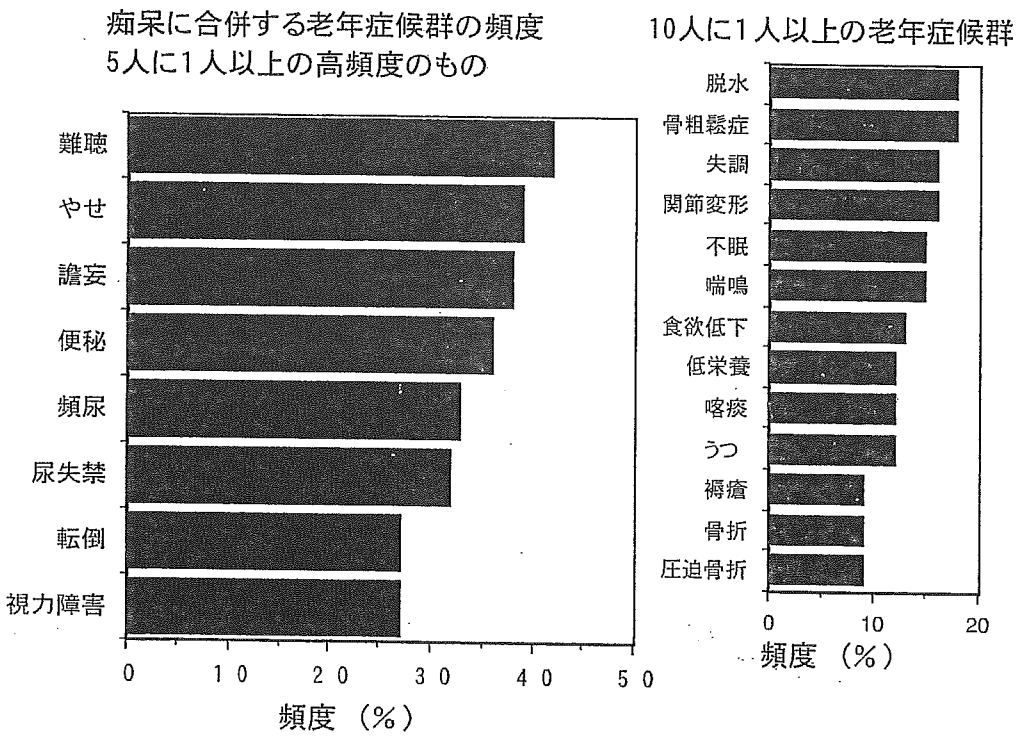

図2　合併する老年症候群の頻度

症例によって改善と不変に分かれ，今後の検討課題である．

3．寝たきりのケアを評価する

今後痴呆のケア技術は急速に発展し，いいケアをして良くなったことを客観的に評価して介護者に報いることである．そのためには，重症痴呆患者のQOLを評価する手技が必要である．意欲の指標（表1）は痴呆の程度や生命予後と強い相関をもち（図3），このような需要に最も的確に応える指標と考えられる[4]．また，今後重症痴呆の言語，非言語能力を定量的に評価する手技の開発と応用も，高齢者医療の重点領域である．

4．ねたきり予防

寝たきり高齢者が100万人を越え大きな国民的課題であるが，最近の東京都の調査では，脳卒中や骨折などの後，そのまま寝たきりになるのは3分の1に過ぎず，残りは寝たきりの直接間接の原因や寝たきりになっていく過程が不明なままである．寝たきりプロセスの解明と，早期発見のための寝たきりリスクチェック表の開発，医療福祉政策に反映しうる実効性のある，寝たきりを減らす介入方法の実証研究が必要である．本講演では寝たきりプロセスの解明と，これに立脚した医療福祉政策として実現可能な有効性のある寝たきり予防研究の最近の展開を紹介したい．

対象と方法の概要は以下の通りである．

1）施設入所高齢者1964名に対し，継続して転倒，ADLなどの縦断的調査．

2）15施設のグループホームのADL，痴呆，問題行動の縦断的変化の測定．

3）全国9市町地域高齢者（12000名）——愛媛県大三島町，熊本県相良町，高知県香北町，京都府園部町，滋賀県余呉町，北海道浦臼町，福岡県自治体，宮城県仙台市，群馬県中之条町の機能変化．

4）体操会員8000名に対し，活力度調査（36項目）

表1　意欲の指標　Vitality Index

1）起床（Wake up）		4）排泄（On and Off Toilet）	
いつも定時に起床している	2	いつも自ら便意尿意を伝える，あるいは，自分で排尿，排便を行う	2
起こさないと起床しないことがある	1	時々尿意，便意を伝える	1
自分から起床することがない	0	排泄に全く関心がない	0
2）意志疎通（Communication）		5）リハビリ，活動（Rehabilitation, Activity）	
自分から挨拶する，話し掛ける	2	自らリハに向かう，活動を求める	2
挨拶，呼び掛けに対し返答や笑顔がみられる	1	促されて向かう	1
反応がない	0	拒否，無関心	0
3）食事（Feeding）			
自分で進んで食べようとする	2		
うながされると食べようとする	1		
食事に関心がない，全く食べようとしない	0		

除外規定；意識障害，高度の臓器障害，急性疾患（肺炎などの発熱）
判定上の注意：1）薬剤の影響（睡眠薬など）を除外．起座できない場合，開眼し覚醒していれば2点．2）失語の合併がある場合，言語以外の表現でよい．3）器質的消化器疾患を除外．麻痺で食事の介助が必要な場合，介助により摂取意欲があれば2点（口まで運んでやった場合も積極的に食べようとすれば2点）．4）失禁の有無は問わない．尿意不明の場合，失禁後にいつも不快を伝えれば2点．5）リハビリでなくとも散歩やリクリエーション，テレビなどでもよい．
寝たきりの場合，受動的理学運動に対する反応で判定する．

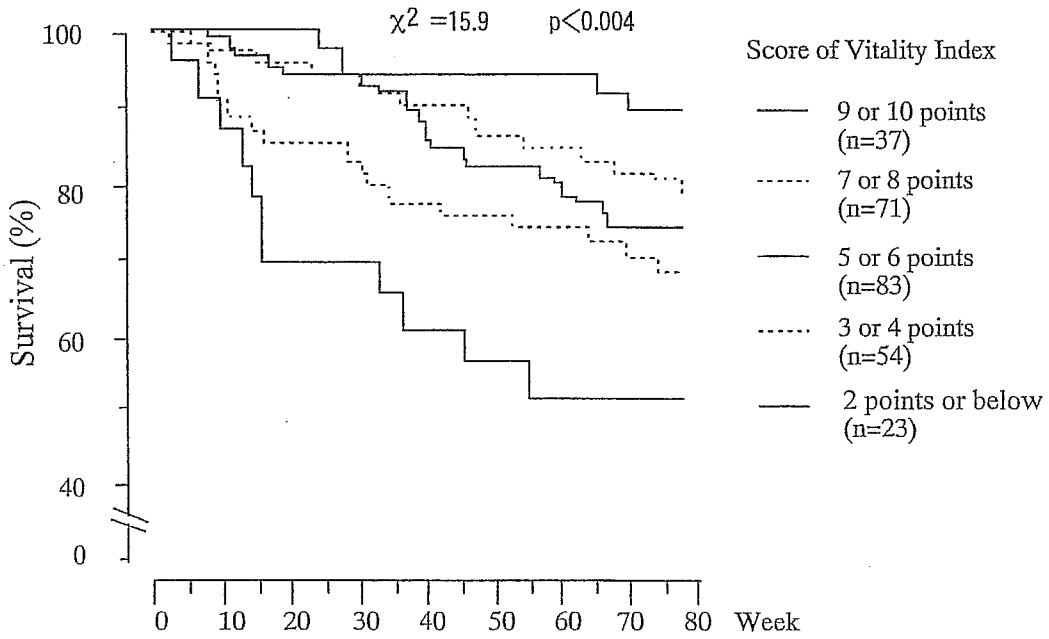

図3　Vitality Index and Survival

寝たきりプロセスの解明と予防因子の抽出：

地域縦断調査2000名から，脳血管障害，痴呆，転倒，うつなどの危険因子と，飲酒，長寿教室への参加などの，ADL低下予防因子が抽出された．脳血管障害に関しては，西永は，家庭血圧148 mmHg以上で要介護率が4倍以上になることが示された．

特養，老健入所者1176名の縦断調査を施行し，開始時のADLに関する意欲（意欲の指標）の低下は寝たきり度（JABCランク）の悪化予測因子

として最も有用であった．

急性期病院における高齢者のADL低下要因として，70歳までの加齢，入院時ADL，緊急入院の有無は関連がなく，90歳以上の高齢，多病，低体重，痴呆，意欲の低下が危険因子として抽出された．

寝たきり過程の促進因子では，介護施設におけるADLや自立度低下に関し，重要な徴候は，転倒，大腿骨頸部骨折，麻痺，息切れが最も重要で，ついで，感染症徴候（発熱），痴呆の進行に注意すべきである．

この中で，大腿骨頸部骨折は意欲が保持されており，早期のリハビリが重要と考えられた．また転倒を繰り返すと意欲が低下することが判明した．

施設縦断調査1194名により，骨折率は年間2.7％（32件）であった．

転倒に関する危険予測因子として，在宅住民調査により，下肢筋力低下，柔軟性減少，バランス不安定，重心動揺の増大，歩行時つま先が上がらないなどが抽出され，下肢筋力強化，歩行によるバランス獲得，靴の工夫などが転倒予防に資することが判明した．

意欲の減退に関しては，転倒，痴呆，食欲不振が有意な要因であった．

危険因子に対する介入：

転倒予防

転倒スコア（仮称）の策定と有用性の検討：相良村，浦臼町，杏林大学，東北大学，高知医大など在宅，外来における大規模調査を実施した．スコアと転倒（既往）とは，正の良好な関係が得られた．重回帰分析及び因子分析では，主として歩行機能，運動機能，コミュニケーション能力が有意な因子で，環境要因の関与は少なかった．

運動の効果

高齢者を取り巻く介護力が向上することで，各ADL項目の自立度が向上するという知見は，早期に適切な介入を行うことが，短期的にも介護予防に効果的であることを示唆している．

閉じこもりを防ぐための，高齢者の閉じこもりと，生活における楽しみの調査において，散歩，動物の世話，老人クラブへの参加が閉じこもりの予防に対して有用な活動である可能性が示された．

全国規模の体操教室調査により（縦断調査の1年目），運動の心身面への好影響，適切な運動量による寝たきり予防効果が示唆された[5]．

文　献

1）鳥羽研二：シンポジウム　介護保険と高齢者医療：施設介護の問題点．日本老年医学会雑誌　34(12)：981-986, 1997

2）鳥羽研二，大内尉義：老年症候群の特徴と検査の重要性．総合臨床，47, 1, 1998

3）Lawton, M.P & Brody, E.M.: Assessment of older people: Self-Maintaing and instrumental activities of daily living. Gerontologist: 9, 179-188, 1969

4）Kenji Toba, Ryuhei Nakai, Masahiro Akishita, et al.: Geriatrics Gerontology International 2: 23-29, 2002

5）厚生労働省効果的医療技術の確立推進研究「寝たきりプロセスの解明と主たる因子に対する介入研究」班（班長：鳥羽研二），平成15年度報告書

Original Article

High Morning Home Blood Pressure Is Associated with a Loss of Functional Independence in the Community-Dwelling Elderly Aged 75 Years or Older

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To elucidate the relationship between home systolic blood pressure (SBP) and functional impairment in the elderly 75 years or older, 461 community-dwelling subjects (192 men, 269 women, mean age: 80 years) were studied. Home blood pressure was measured twice in the morning and twice in the evening for 5 consecutive days with an automatic cuff-oscillometric device. Total/high-density lipoprotein cholesterol and several functional assessments were evaluated. A subject was determined to exhibit a loss of independence according to the activities of daily living (ADL) score in a study conducted in 2001. Based on the mean home SBPs (mSBP) and morning–evening SBP differences (dSBP), the subjects were classified into 4 groups as follows: hypertensive/morning-dominant (HM; mSBP≥135 mmHg, dSBP≥15 mmHg), hypertensive/sustained (HS; mSBP≥135 mmHg, dSBP<15 mmHg), normotensive/morning-dominant (NM; mSBP<135 mmHg, dSBP≥15 mmHg), and normotensive/controlled (NC; mSBP<135 mmHg, dSBP<15 mmHg). There were no differences in sex, cholesterol levels, history of stroke, other cardiovascular diseases (CVDs), and cognitive function, but there were significant differences in age, antihypertensive medications, the neurobehavioral test scores, and ADL scores. There were no significant differences in terms of mortality and CVD events. In the survivors, HM and HS were independent risk factors for a loss of independence, after adjustments were made for onset of stroke, age, antihypertensive therapy, history of CVD, as well as neurobehavioral test scores and ADL scores (odds ratio [OR]: 12.2 and 3.78, respectively). After the same adjustments as those mentioned above were made, HM and HS were found to be negative determinants of survival and maintenance of independence (OR: 0.082, 0.270, respectively). In conclusion, high home SBP (≥135 mmHg) and high dSBP (≥15 mmHg) were found to be important in determining the levels of disability for the very elderly. (*Hypertens Res* 2005; 28: 657–663)

Key Words: home blood pressure, elderly, morning hypertension, independence, successful aging

Introduction

Recently there have been rapid increases in both the population and life span of the elderly in developed countries, which has resulted in a considerable increase in the number of frail elderly people. "The project to reduce the number of dependent elderly persons" has been promoted as an important

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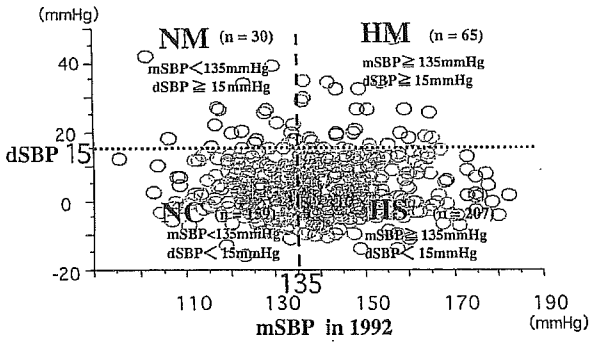

Fig. 1. *Classification of four groups according to the distribution of mean home SBP (mSBP) and morning–evening home SBP differences (dSBP). HM, hypertensive/morning-dominant; HS, hypertensive/sustained; NM, normotensive/morning-dominant; NC, normotensive/controlled.*

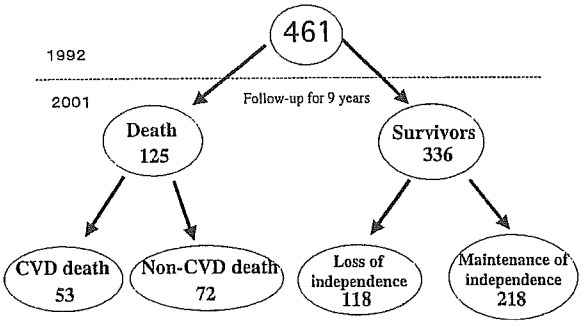

Fig. 2. *Outcome after a 9-year follow-up period. CVD, cardiovascular disease, including stroke.*

issue not only from the medical, but also from the socioeconomic point of view. This project should be considered a top priority, and appropriate measures should be taken to improve the current situation (*1*). Although stroke is a major cause of mortality and disability in the elderly (*2–4*), the management of hypertension in the community has contributed to an outstanding reduction in the incidence of stroke (*5*, *6*).

In many previous epidemiological studies on blood pressure (BP) in the elderly, the mortality and morbidity associated with stroke and other cardiovascular diseases (CVDs) have been selected as the endpoint (*7–9*). There have been also several epidemiological studies of the relationship between hypertension and dementia (*10*, *11*). However, assessments of functional abilities, the most important factor for elderly persons and their caregivers, have been rarely conducted.

Improving the management of BP for the prevention of stroke and other CVDs has led to the popularization of home BP monitoring devices among the general public (*12*, *13*). However, there have been few reports concerning home BP values in the elderly. Increased BP in the morning is considered as a strong risk factor for stroke and other CVDs (*14–17*). It remains to be clarified whether such an elevation in BP in the morning is also a risk factor for a loss of functional independence in the elderly.

In the present study, we recruited community-dwelling elderly people 75 years of age or older, and conducted medical and functional assessments. We followed the subjects for 9 years. The purpose of our study was to clarify the relationship between home BP values and functional disabilities, as well as that between home BP and the mortality/incidence of stroke. Furthermore, we studied morning–evening home BP differences in this very elderly sample.

Methods

Subjects

The study subjects were elderly people, aged 75 years or older, who resided in Kahoku Town, Kochi Prefecture, Japan in 1992. All subjects applied to participate in the home BP monitoring program. Subjects with atrial fibrillation were excluded because of the potential inaccuracy of their home BP measurements. A total of 461 people were recruited as the subjects of our study (192 men, 269 women, mean age: 81 years).

Home BP Measurement

Home BP was measured in 1992 with an automatic device (HEM-755C; OMRON Life Science Co., Ltd., Kyoto, Japan) based on the cuff-oscillometric method. The validity of BP measurement according to this method has been reported in several studies (*18–20*). The subjects and their caregivers were taught by community nurses how to measure the BP at home using this device. According to a previously reported method (*21*), BP was measured in the non-dominant arm after taking at least a 5-min rest in a sitting position, twice in the morning (6–7 AM) and twice in the evening (8–9 PM), for 5 consecutive weekdays.

We obtained the data regarding the total mean systolic BP (mSBP), morning and evening systolic BP (SBP), morning and evening diastolic BP (DBP) and pulse rates (PR). The mean morning–evening SBP differences (dSBP) were calculated. We defined subjects with mSBP≧135 mmHg as hypertensive or poorly controlled subjects, according to the Japanese Society of Hypertension (JSH) Guidelines for the Self-Monitoring of Blood Pressure at Home (*12*). We also divided our subjects into two groups by using mean+1SD of the dSBP. There were no subjects whose mean DBP values alone exceeded 85 mmHg.

Table 1. Basic Characteristics (1992)

	NC (n=159)	NM (n=30)	HS (n=207)	HM (n=65)
Age (years)*	80.3±4.5	81.5±5.1	80.5±5.1	81.4±5.3
Men (n [%])	74 (46.5)	13 (43.3)	79 (38.1)	26 (40.0)
SBP (mmHg)**	125±8	124±8	148±11	150±10
DBP (mmHg)**	72±7	73±9	80±11	81±9
PR(/min)*	68±8	67±7	69±8	68±12
Morning SBP (mmHg)**	126±9	135±9	149±12	162±11
Evening SBP (mmHg)**	123±9	113±9	148±12	138±11
Total cholesterol (mg/dl)	190±35	210±39	186±38	195±42
HDL cholesterol (mg/dl)	48±14	56±10	45±13	44±12
ADL (full score: 21)	20.4±1.9	20.8±0.8	20.2±2.6	20.2±1.9
MMSE (full score: 30)	27.2±4.4	28.4±2.2	27.3±3.2	27.5±3.2
Up and Go test (s)	13.0±3.2	13.0±2.8	14.1±4.6	14.9±5.4
Antihypertensive drugs** (Yes, n [%])	38 (23.9)	10 (33.3)	89 (43.0)	40 (61.5)
History of CVD (Yes, n [%])	16 (10.0)	1 (3.3)	13 (6.3)	4 (8.1)

NC, normotensive/controlled; NM, normotensive/morning-dominant; HS, hypertensive/sustained; HM, hypertensive/morning-dominant; SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate; HDL, high-density lipoprotein; ADL, activities of daily living; MMSE, mini-mental state examination; CVD, cardiovascular disease, including stroke. *ANOVA, $p<0.05$, **ANOVA, $p<0.01$.

Annual Self-Administered Questionnaire

In the baseline survey (1992), the self-administered questionnaire was addressed to the study subjects to obtain information about characteristics potentially related to their BP, mortality, and disability; the data collected included a history of stroke, heart disease, and bone disease or arthropathy, antihypertensive medications, current and past cigarette smoking, current intake of alcohol, and activities of daily living (ADL). All of the response sheets submitted by the subjects were reviewed by community nurses to ascertain their information.

Assessment of ADL, Cognitive Function, Neurobehavioral Function, Mood and Serum Lipid Analysis

The questionnaire regarding the ADL was conducted in 1992 and 2001 in the same manner as was used in our previous study (*22*). Briefly, ADL were assessed with respect to the following seven items: walking, ascending and descending stairs, feeding, dressing, using the toilet, bathing, and grooming. Each ADL item was scored on a 0–3 scale: 0 = completely dependent, 1 = needs a lot of help, 2 = needs some help, and 3 = completely independent. The scores for these seven items were summarized to obtain a total ADL score ranging from 0 to 21. When a subject did not maintain a score of 21 or 20 points in 2001, he or she was defined as a person that was losing independence.

The mini-mental state examination (MMSE) was used to evaluate each subject's level of cognitive functioning (*23*). The Up and Go test was used to evaluate neurobehavioral function (*24*). This latter test measures, in s, the time it takes the subject to stand up from an armchair, walk a distance of 3 m, walk back to the chair, and sit down again. This simple test is a comprehensive evaluation of the subject's balance, gait speed, and functional ability. Since Okumiya and co-workers (*25*) reported its usefulness in predicting a decline in ADL in the Japanese community-dwelling elderly, the test has been widely accepted for this purpose in many fields. The Geriatric Depression Scale 15 (GDS 15) was also used to evaluate the mood of the subjects (depressive state) (*26*). Total serum cholesterol and serum high-density lipoprotein (HDL) cholesterol were analyzed in 1992.

During the period between 1992 and 2001, a total of 125 subjects (66 men, 59 women) died. In addition, the information regarding the events of stroke, myocardial infarction, congestive heart failure, and bone/joint diseases as causes of disability were collected by checking the responses provided on the annual questionnaire and the subjects' medical records.

Written informed consent was obtained from each subject at the time of the annual questionnaire. Our study was approved by the Research Ethics Committee of Kochi Medical School, Kochi University, Japan.

Statistical Analysis

All of the values were expressed as mean±SD. Mean values among the groups were compared using ANOVA. A χ^2 test was used to compare the 4 groups with respect to total mortality and incidence of stroke, as well as other CVDs. A logistic multivariate analysis was used to identify the factors that predicted a loss of functional independence or the survival and maintenance of functional independence 9 years after the initial assessment, using Stat View 5.0 for Windows (SAS Institute Inc., Cary, USA).

Table 2. Total/CVD Death and Non-Fatal Stroke

	NC (n=159)	NM (n=30)	HS (n=207)	HM (n=65)
Total death (%)*	36 (22.6)	3 (10.0)	62 (30.0)	24 (36.9)
Non-fatal stroke(%)	16 (10.1)	1 (3.3)	12 (5.8)	4 (6.2)
CVD death (%)	17 (10.7)	1 (3.3)	24 (11.6)	11 (16.9)
CVD events (%)	33 (20.8)	2 (6.7)	36 (17.4)	15 (23.1)

NC, normotensive/controlled; NM, normotensive/morning-dominant; HS, hypertensive/sustained; HM, hypertensive/morning-dominant; CVD, cardiovascular disease, including stroke. *ANOVA $p<0.1$.

Results

The distribution of mSBP and dSBP are shown in Fig. 1. The subjects were classified into the following 4 groups:

Hypertensive/morning-dominant (HM: mSBP≥135 mmHg, dSBP≥15 mmHg; n=65), hypertensive/sustained (HS: mSBP≥135 mmHg, dSBP<15 mmHg; n=207), normotensive/morning-dominant (NM: mSBP<135 mmHg, dSBP≥15 mmHg; n=30), and normotensive controlled (NC: mSBP<135 mmHg, dSBP<15 mmHg; n=159). The NC group, which was expected to be the lowest risk group because both the mSBP and the dSBP were lower than others, was used for reference.

A total of 461 elderly subjects, who were 75 years of age or older in 1992, were followed for 9 years until 2001 (Fig. 2). During that interval, 125 (27%) subjects died; 53 of these subjects had died of stroke and other CVDs. A total of 336 of the subjects were alive 9 years later (2001). One hundred-eighteen subjects had undergone a loss of their functional independence (HM, 17 [41%]; HS, 65 [45%]; NM, 7 [26%]; NC, 29 [24%]).

The basic characteristics of the 4 groups in 1992 are shown in Table 1. The subjects in the NC group were younger than those in the other 3 groups. The percentage of subjects who were taking antihypertensive agents was also the lowest in the NC group. There were no significant differences in terms of sex, PR, total serum cholesterol, HDL cholesterol, the scores of ADL, MMSE, the Up and Go test, or history of CVD among the 4 groups. There were also no differences in the scores on the GDS 15, history of bone/joint diseases, current and past cigarette smoking, and current intake of alcohol (data not shown).

Table 2 shows the total number of deaths, the number and percentage of deaths caused by stroke and other CVDs, and the incidence of non-fatal stroke during the 9-year follow-up period in the 4 groups. Although there was a difference in the total number of deaths among the 4 groups before adjustment for age, the significance of this difference disappeared after adjustment for age. There were no significant differences in the percentage of deaths from stroke or other CVDs. Although 33 subjects suffered from symptomatic strokes, no significant differences were seen in the incidence of strokes among the 4 groups.

The risk factors for loss of functional independence are shown in Table 3. Although a non-fatal event of stroke was one of the most important risk factors for loss of functional independence, HM and HS were also important risk factors, even after adjustment for age, sex, antihypertensive therapy, scores on the Up and Go test in 1992, and the ADL scores in 1992. The adjusted odds ratio (OR) of the HM group (12.2) was significantly higher than that of the HS group (3.78). Therefore, values of mSBP≥135 mmHg and dSBP≥15 mmHg were independent risk factors for a loss of functional independence (Fig. 3).

The factors associated with successful aging that contributed to the survival and maintenance of functional independence, even among the most elderly (age of 84 or older), are shown in Table 4. Although the non-fatal event of stroke was a significantly negative determinant, the HM and HS also remained as significant independent negative determinants of successful aging, after adjustment for age, sex, antihypertensive therapy, scores on the Up and Go test in 1992, and ADL scores in 1992.

As regards the elderly people aged 75 years or older living in the community, values of mSBP≥135 mmHg and dSBP≥15 mmHg were independent determinants of a loss of functional independence or successful aging, even when non-fatal stroke and these home SBP variables were simultaneously incorporated into a logistic multivariate analysis model.

In addition, since many of our subjects with morning hypertension had high home SBP, we added dSBP (≥15 mmHg) to the same model of multivariate logistic analysis, in order to elucidate whether dSBP was an independent determinant of a loss of functional independence or alive and independence. dSBP remained a significant determinant of a loss of independence (adjusted OR: 3.84, 95% confidence interval [CI]: 1.003–14.73), or alive and independence (adjusted OR: 0.46, 95% CI: 0.183–0.973), in our hypertensive subjects.

Discussion

Our prospective longitudinal study evaluating the maintenance of independence in the elderly aged 75 years or older demonstrated that a mean home SBP of ≥135 mmHg was a significantly important risk factor for a loss of functional independence. In addition, morning hypertension was an

Table 3. Independent Risk Factors for Loss of Independence in 336 Survivors

Factors	Adjusted odds ratio	95% CI	*p*
Stroke	17.4	3.67–82.8	0.0003
HM	12.2	3.00–50.0	0.0005
HS	3.78	1.45–9.83	0.0064
Age	1.17	1.05–1.30	0.0036

Data were adjusted for sex, antihypertensive therapy, Up and Go score, and activities of daily living (ADL) score in 1992. CI, confidence interval; HM, hypertensive/morning-dominant; HS, hypertensive/sustained.

Table 4. Independent Negative Factors for Survival and Maintenance of Independence (n=461)

Factors	Adjusted odds ratio	95% CI	*p*
Stroke	0.058	0.012–0.273	0.0003
HM	0.082	0.020–0.334	0.0005
HS	0.271	0.104–0.704	0.0073
Age	0.855	0.768–0.951	0.0038

Data were adjusted for sex, antihypertensive therapy, Up and Go score, and activities of daily living (ADL) score in 1992. CI, confidence interval; HM, hypertensive/morning-dominant; HS, hypertensive/sustained.

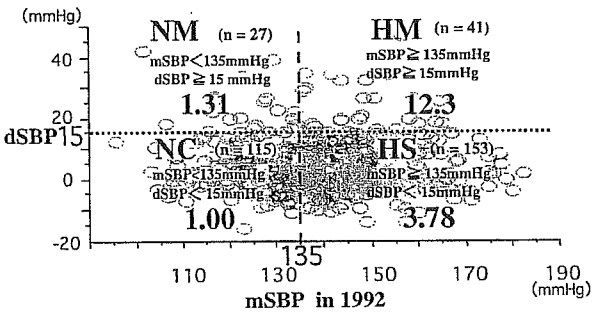

Fig. 3. *Adjusted odds ratios for loss of independence among the 4 groups. The abbreviations are the same as those introduced in Fig. 1.*

important independent predictor for the functional prognosis of our elderly subjects. The significance of dSBP should be further evaluated.

There were no differences in mortality and incidence of non-fatal stroke among the 4 groups. However, when a loss of functional independence was selected as the endpoint, significant differences were found among these groups. Home BP monitoring in the morning and in the evening was useful in predicting functional prognosis in elderly subjects aged 75 years or older.

Recent large clinical trials have clarified the importance of BP control, even among the elderly (*7–9*). However, the optimum home BP value for the elderly has not been established, and further prospective studies on the elderly will be necessary to define an adequate home BP value (*27*).

In the present study, there was no significant difference in the incidence of CVD death, stroke, and other CVD events among the 4 groups. Although the reason for this result is uncertain, further studies with a larger number of subjects may resolve this ambiguity.

Since a relationship between elevation of BP in the morning and stroke and other CVD events (*14–17*) has been reported, the importance of morning BP has been emphasized in studies of home BP monitoring (*28, 29*). However, in most of these studies the mortality and morbidity of stroke and other CVDs, as well as organ damage, were selected as the endpoints. Functional independence, which is important for the elderly as well as for the social economy, is not mentioned in these previous studies. Thus, in our present study, we added a loss of functional independence and successful aging as two new endpoints for geriatric study. Furthermore, we evaluated morning–evening home BP differences in terms of the usefulness of this information for the prognosis of the elderly aged 75 years or older.

Skoog *et al.* (*30*) reported the relationship between the presence of hypertension at the age of 70 and the development of dementia 10 to 15 years later. In subsequent large studies including SCOPE (*10*), the association between impaired cognitive function and BP values has been evaluated, although sufficient data on the relationship between BP control and cognitive function have yet to be accumulated. In our previous study (*31*), a J-curve phenomenon was demonstrated with respect to the profile of the association between BP values and cognitive function 3 years later in an elderly sample. Those findings indicate that BP exerted an effect on cognitive function, not only in the group with high BP, but also in the group with low BP. In our previous study, casual BP was measured twice with the subject in the supine position at the time of physical examination. Here, to avoid the inclusion of various other factors affecting BP measurements, we used 20 home BP measurements in order to calculate the mean value. This method of measurement appeared to have eliminated some of the potential problems with BP monitoring.

Because the follow-up period was so long (9 years), it was difficult to reexamine cognitive function in all of the subjects examined in 2001; some subjects were too old for us to obtain reliable data from them (*i.e.*, among those at least aged 84 years of age and older). Due to our small sample size in the MMSE evaluation (n=64, 19%), we did not observe any significant differences between the group with high home BP values (≥135 mmHg) and the group with normal home BP values (<135 mmHg). There were also no significant differences in dSBP (≥15 mmHg). Evaluation of the cognitive functions (MMSE) of the most elderly subjects included in the sample was difficult; thus, an appropriate, reliable method

will still need to be developed for the evaluation of this group in future studies.

A variety of factors, including stroke events and other CVDs, as well as the progression of bone/joint diseases and dementia, contributes to disability among the elderly (*32*). The present study demonstrated for the first time that those elderly persons with a mean home SBP≥135 mmHg were susceptible to a loss of functional independence, even if they did not experience an event of symptomatic stroke. However, the present study did not reveal any direct mechanism to generate this relationship between hypertension reflected by the home BP monitoring value and a loss of independence. The relationships between hypertension or morning BP elevation and pathological conditions such as asymptomatic small infarctions and white matter lesions have previously been reported (*33–36*). It is thus possible that these lesions are related to BP elevation and may be involved in the impairment of functional abilities required for daily life. To clarify the association between home BP values, asymptomatic brain lesions, and disability among the very elderly, further study is warranted.

References

1. Sasaki H, Sekizawa K, Yanai M, Arai H, Yamaya M, Ohrui T: Elongation of life expectancy may accompany shift of medical cost to older adults. *J Am Geriatr Soc* 1997; **45**: 254–255 (Letter).
2. Carolei A, Sacco S, De Santis F, Marini C: Epidemiology of stroke. *Clin Exp Hypertens* 2002; **24**: 479–483.
3. Kobayashi S: Data bank project for acute stroke patients. *Rinsho Shinkeigaku* 2002; **42**: 1176–1178.
4. Ikebe T, Ozawa H, Lida M, Shimamoto T, Handa K, Komachi Y: Long-term prognosis after stroke: a community-based study in Japan. *J Epidemiol* 2001; **11**: 8–15.
5. Neal B, MacMahon S, Chapman N: Effects of ACE inhibitors, calcium antagonists, and other blood-pressure lowering drugs: results of prospectively designed overviews of randomized trials. *Lancet* 2000; **356**: 1955–1964.
6. Sutton-Tyrrell K, Wildman R, Newman A, Kuller LH: Extent of cardiovascular risk reduction associated with treatment of isolated systolic hypertension. *Arch Intern Med* 2003; **163**: 2728–2731.
7. Fagard RH, Staessen JA: Treatment of isolated systolic hypertension in the elderly: the Syst-Eur trial. Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. *Clin Exp Hypertens* 1999; **21**: 491–497.
8. SHEP Cooperative Research Group: Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program. *JAMA* 1991; **265**: 3255–3264.
9. MRC Working Party: Medical Research Council trial of treatment of hypertension in older adults: principal results. *BMJ* 1992; **304**: 405–412.
10. Lithell H, Hansson L, Skoog I, *et al*: The study on cognition and prognosis in the elderly (SCOPE): principal results of a randomized double-blind intervention trial. *J Hypertens* 2003; **21**: 875–886.
11. Birkenhager WH, Forette F, Seux ML, Wang JG, Staessen JA: Blood pressure, cognitive functions, and prevention of dementias in older persons with hypertension. *Arch Intern Med* 2001; **161**: 152–156.
12. Imai Y, Otsuka K, Kawano Y, *et al*: Japanese Society of Hypertension (JSH) Guidelines for Self-Monitoring of Blood Pressure at Home. *Hypertens Res* 2003; **26**: 771–782.
13. Pickering TG: How should we take blood pressure in clinical practice? *Br Med J* 2003; **327**: E150–E151.
14. Kario K, Pickering TG, Umeda Y, *et al*: Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives: a prospective study. *Circulation* 2003; **107**: 1401–1406.
15. Imai Y, Hozawa A, Ohkubo T, *et al*: Predictive values of automated blood pressure measurement: what can we lean from the Japanese population—the Ohasama study. *Blood Press Monit* 2001; **6**: 335–339.
16. Gosse P, Cipriano C, Bemurat L, *et al*: Prognositic significance of blood pressure measured on rising. *J Hum Hypertens* 2001; **15**: 413–417.
17. Kuwajima I, Mitani K, Miyao M, Suzuki Y, Kuramoto K, Ozawa T: Cardiac implications of the morning surge in blood pressure in elderly hypertensive patients: relation to arising time. *Am J Hypertens* 1995; **8**: 29–33.
18. Stergiou GS, Voutsa AV, Achimastos AD, Mountokalakis TD: Home self-monitoring of blood pressure: is fully automated oscillometric technique as good as conventional stethoscopic tequnique? *Am J Hypertens* 1997; **10**: 428–433.
19. Yarows SA, Amerena JV: Determination of accuracies of 10 models of home blood pressure monitors using an oscillometric simulator. *Blood Press Monit* 1999; **4**: 45–52.
20. Yarows SA, Brooks R: Measurement variation among 12 electronic home blood pressure monitors. *Am J Hyperttens* 1999; **13**: 45–52.
21. Okumiya K, Matsubayashi K, Wada T, *et al*: A U-shaped association between home systolic blood pressure and four-year mortality in community-dwelling older men. *J Am Geriatr Soc* 1999; **47**: 1415–1421.
22. Matsubayashi K, Okumiya K, Osaki Y, Fujisawa M, Doi Y: Frailty in elderly Japanese. *Lancet* 1999; **353**: 1445.
23. Folstein MF, Folstein SE, McHugh PR: A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; **12**: 189–198.
24. 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.
25. Okumiya K, Matsubayashi K, Nakamura T, *et al*: The timed "Up & Go" test and manual button score are useful predictors of functional decline in basic and instrumental ADL in community-dwelling older people. *J Am Geriatr Soc* 1999; **47**: 497–498.
26. Brink TL, Yesavage JA, Lum O, *et al*: Screening tests of geriatric depression. *Clin Gerontol* 1982; **1**: 37–43.
27. Aoki Y, Asayama K, Ohkubo T, *et al*: Progress report on the HOMED-BP study: hypertension objective treatment based on measurement by electrical devices of blood pressure study. *Clin Exp Hypertens* 2004; **26**: 119–127.

28. Ikeda T, Gomi T, Shibuya Y, *et al*: Morning rise in blood pressure is a predictor of left ventricular hypertrophy in treated hypertensive patients. *Hypertens Res* 2004; **27**: 939–946.
29. Kamoi K, Kaneko S, Miyakoshi M, Nakagawa O, Soda S: Usefulness of home blood pressure measurement in the morning in type 2 diabetic patients. *Diabetes Care* 2002; **25**: 2218–2223.
30. Skoog I, Lernfelt B, Landahl S, *et al*: 15-year longitudinal study of blood pressure and dementia. *Lancet* 1996; **347**: 1141–1145.
31. Okumiya K, Matsubayashi K, Wada T, Osaki Y, Doi Y, Ozawa T: J-curve relation between blood pressure and decline in cognitive function in older people living in community, Japan. *J Am Geriatr Soc* 1997; **45**: 1032–1033.
32. Kattainen A, Koskinen S, Reunanen A, Martelin T, Knekt P, Aromaa A: Impact of cardiovascular diseases on activity limitations and need for help among older persons. *J Clin Epidemiol* 2004; **57**: 82–88.
33. Yoshitake T, Kiyohara Y, Kato I, *et al*: Incidence and risk factors of vascular dementia and Alzheimer's disease in a defined elderly Japanese population: the Hisayama Study. *Neurology* 1995; **45**: 1161–1168.
34. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM: Silent brain infarcts and the risk of dementia and cognitive decline. *N Engl J Med* 2003; **348**: 1215–1222.
35. Vermeer SE, Hollander M, van Dijk EJ, Hofman A, Koudstaal PJ, Breteler MM: Silent brain infarcts and white matter lesions increase stroke risk in the general population: the Rotterdam Scan Study. *Stroke* 2003; **34**: 1126–1129.
36. Artero S, Tiemeier H, Prins ND, Sabatier R, Breteler MM, Ritchie K: Neuroanatomical localisation and clinical correlates of white matter lesions in the elderly. *J Neurol Neurosurg Psychiatry* 2004; **75**: 1304–1308.

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Arterial stiffness independently predicts cardiovascular events in an elderly community – Longitudinal Investigation for the Longevity and Aging in Hokkaido County (LILAC) study

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Abstract

We investigated the predictive value of arterial stiffness to assess cardiovascular risk in elderly community-dwelling people by means of a multivariate Cox model. In 298 people older than 75 years (120 men and 178 women, average age: 79.6 years), brachial-ankle pulse wave velocity (baPWV) was measured between the right arm and ankle in a supine position. The LILAC study started on July 25, 2000, consultation was repeated yearly, and the last follow-up ended on November 30, 2004. During this follow-up span of 1227 days, there were nine cardiovascular deaths, the cause of death being myocardial infarction for two men and three women or stroke for two men and two women. In Cox proportional hazard models, baPWV as well as age, Mini-Mental State Examination (MMSE), Hasegawa Dementia Scale Revised (HDSR) and the low-frequency/high-frequency (LF/HF) ratio showed a statistically significant association with the occurrence of cardiovascular death. A two-point increase in MMSE and HDSR score significantly protected against cardiovascular death, the relative risk (RR) being 0.776 (P = 0.0369) and 0.753 (P = 0.0029), respectively. The LF/HF ratio also was significant (P = 0.025), but the other indices of HRV were not. After adjustment for age and HDSR, a 200 cm/s increase in baPWV was associated with a 30.2% increase in risk (RR = 1.302, 95% CI: 1.110–1.525), and a 500 cm/s increase in baPWV with a 93.3% increase in risk (RR = 1.933, 95% CI: 1.300–2.874, P = 0.0011), whereas the LF/HF ratio was no longer associated with a statistically significant increase in cardiovascular mortality. In elderly community-dwelling people, arterial stiffness measured by means of baPWV predicted the occurrence of cardiovascular death beyond the prediction provided by age, gender, blood pressure and cognitive functions. baPWV should be added to the cardiovascular assessment in various clinical settings, including field medical surveys and preventive screening. The early detection of risk

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by chronomics allows the timely institution of prophylactic measures, thereby shifting the focus from rehabilitation to prehabilitation medicine, as a public service to several Japanese towns.

Keywords: Pulse wave velocity; Cardiovascular risk; Cognitive function; Elderly community-dwelling people

1. Introduction

As the incidence of myocardial infarction has increased in Japan and since cardiovascular disease, including stroke is the leading cause of mortality and morbidity, the prevention of these conditions is a major goal. Atherosclerosis is an important cause of morbidity and mortality in the elderly, and arterial stiffness may predict cardiovascular events [1]. Several cardiovascular indices, such as blood pressure (BP), heart rate (HR) and heart rate variability (HRV) are predictors of vascular disease risk [2]. This study aimed at assessing their role in association with arterial stiffness in predicting cardiovascular mortality. Arterial stiffness can be assessed non-invasively by measuring pulse wave velocity (PWV), which is a simple and reproducible endpoint.

Recent cohort studies suggested that PWV might be a strong predictor of atherosclerotic cardiovascular events, cardiovascular mortality, and all-cause mortality, independently of age and conventional atherosclerotic risk factors [3–5]. Most studies, however, focused on patients of occidental ancestry, often affected by specific diseases, rather than on Japanese populations. In 2000, we began a community-based study to longitudinally investigate the longevity and aging of a rural population in Hokkaido County (LILAC), and to evaluate this population's neurocardiological function. Our goal was the prevention of cardiovascular events, including strokes and myocardial ischemic events, and to prevent the associated decline in cognitive function of the elderly in this community dwelling.

As the first step of the LILAC study, we focused on the relationship between aortic stiffness measured by PWV and cardiovascular mortality. We assessed the predictive value of arterial stiffness in predicting cardiovascular risk in an elderly population using a multivariate Cox model.

2. Methods

2.1. Subjects and LILAC study design

We examined 298 people older than 75 years (average age, 79.6 years). BP was measured in a sitting position at the beginning of the study, and 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. ECG electrodes were placed on both wrists, a microphone for detecting heart sounds was placed on the left edge of the sternum, and cuffs were wrapped on both arms and ankles. The cuffs were connected to a plethysmographic sensor that determines the volume pulse form and oscillometric pressure waveforms were recorded using a semiconductor pressure sensor (the sample acquisition frequency for PWV was set at 1200 Hz). baPWV was measured in duplicate after at least a 5-min rest in each case. Only baPWV measures from participants showing an ankle/brachial pressure index (ABI) value above 0.90 were used for analysis.

We used the first hour of ambulatory ECG recording obtained during routine medical examinations conducted each year in July. The data were processed for HRV using a Fukuda-Denshi Holter analysis system (SCM-280-3). Time-domain measures (SDNN, pNN50, SDANN and Lorenz plot indices: Length (L), Width (W), and L/W ratio) and frequency-domain measures (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) were determined. Except for SDNN and HR, calculated over the whole 1-h record, all indices were computed as averages 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 versions of the Mini-Mental State Examination (MMSE) and the Hasegawa Dementia Scale Revised (HDSR) tests were used to measure the overall cognitive function, including verbal orientation, memory, and constructional ability (Kohs' block test). The Up and 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. 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 calculated 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.

2.2. Cardiovascular mortality

The LILAC study was started on July 25, 2000 and consultations were repeated every year (end of July, or beginning of August). In addition, one or two doctors of our team visited every 3 months and offered several kinds of health consultation, rehabilitation of disordered function, healthy lifestyle modification by promoting complete cessation of smoking, weight reduction, reduction of salt intake, moderation in the consumption of fruits and vegetables and alcohol intake, as well as providing prescription advice to the local general medical practitioner.

In this investigation, the follow-up ended on November 30, 2004. During this follow-up span, there were nine cardiovascular deaths, the cause of death being myocardial infarction or stroke. Follow-up time was defined as the time elapsed between the first (reference) examination and the time of first cardiovascular event or death.

2.3. Statistical analysis

All data were analyzed with the Statistical Software for Windows (StatFlex Ver.5.0, Artec, Osaka, http://www.statflex.net). The effects of classic risk factors on baPWV were assessed by a multivariate regression analysis. We used Cox's regression analysis to calculate the unadjusted and adjusted relative risks (RRs) and 95% confidence intervals (CIs) for cardiovascular death. To identify independent predictors of cardiovascular death in relation to baPWV, we used a multivariate Cox regression analysis with stepwise selection. Variables included in the multivariate models were age, gender, BP, HR, HRV, MMSE, HDSR and Kohs' block test.

An abnormal value of baPWV (>2500 cm/sec) was independently assessed by logistic regression analysis. Kaplan–Meier event probability curves were computed with two groups, stratified by the abnormal value of baPWV, and the cumulative probability of events of two groups was compared by means of the log-rank test. Statistical significance was considered at a value of $P < 0.05$.

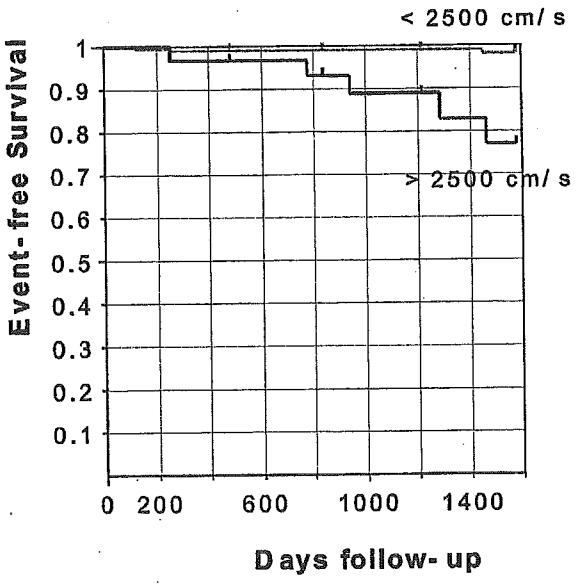

Fig. 1. Kaplan–Meier event probability curves for cardiovascular death.

3. Results

The characteristics of the 298 subjects at the start of study (reference) are given in Table 1. The sample comprises 120 men and 178 women. The mean age of participants at entry was 79.6 years. The mean follow-up time was 1227.2 days, during which 9 subjects died (myocardial infarction: 2 men and 3 women; stroke: two men and two women).

Out of the 298 participants, baPWV was measured in 245 subjects, and a baPWV above 2500 cm/s was observed in 33 subjects, five of whom died (three from a myocardial infarction and two from a stroke). Their reference characteristics are given in Table 2, which shows that an increased baPWV is associated with older age, higher systolic and diastolic BP, increased pulse pressure and shorter FR. Subjects with an increased value of baPWV included fewer event-free survivors. Kaplan–Meier curves for event-free survival revealed a significant difference between the two groups stratified by a baPWV of 2500 cm/s ($P < 0.00005$, log-rank test) (Fig. 1).

Among the variables used in Cox proportional hazard models, PWV as well as age, MMSE, HDSR and the LF/HF

Table 1
Reference characteristics of subjects

Endpoint	Mean	SD
Gender	0.403	
Age	79.0	4.75
BMI	23.4	3.74
SBP	141.2	19.56
DBP	75.5	10.57
PP	65.8	16.41
HR	70.8	11.46
PWV	2097	504.6
ABI	1.02	0.14
Up&Go	16.5	6.54
FR	25.6	7.77
Button	15.7	7.16
MMSE	24.2	4.43
HDSR	23.6	5.30
Kohs	19.1	11.17
GDS	4.8	2.96
VLF	912.3	743.3
LF	207.2	299.0
HF	102.7	250.3
LF/HF	2.84	1.70
pNN50	4.36	8.87
CVRR	5.04	1.95
RMSSD	22.6	12.5
SDNN	37.4	16.0

Gender: Man = 1, Woman = 0 (120 men and 178 women)

Table 2
Reference Characteristics of Subjects with Acceptable or Increased baPWV

Endpoint	$n = 212$ baPWV <2500		$n = 33$ baPWV >2500		t-value	p-value
	Mean	S.D.	Mean	S.D.		
Gender	0.396		0.424		0.304	N.S.
Age	78.7	4.39	80.4	4.54	2.045	0,0420
BMI	23.5	3.88	23.0	3.41	-0.722	N.S.
SBP	139.2	18.14	154.2	25.81	4.087	0,0001
DBP	74.3	9.82	79.6	14.33	2.635	0,0090
PP	64.9	15.80	74.7	18.66	3.158	0,0018
HR	70.1	11.24	72.5	12.77	1.090	N.S.
PWV	1949	292.0	3045	555.0	17.298	0,0000
ABI	1.03	0.12	0.99	0.17	-1.704	N.S.
Up&Go	16.1	6.36	17.5	6.77	1.128	N.S.
FR	26.2	7.66	22.5	7.64	-2.533	0,0120
Button	15.2	7.05	16.1	4.53	0.682	N.S.
MMSE	24.3	5.18	23.7	5.33	-0.827	N.S.
HDSR	24.0	5.18	22.6	5.13	-1.444	N.S.
Kohs	19.6	11.08	17.1	10.42	-1.177	N.S.
GDS	4.8	2.85	4.8	3.16	0.125	N.S.
VLF	938.7	788.5	738.6	440.9	-1.187	N.S.
LF	211.1	303.7	133.2	113.7	1.216	N.S.
HF	98.8	235.1	63.8	52.1	-0.711	N.S.
LF/HF	2.88	1.70	2.70	1.51	-0.482	N.S.
pNN50	4.28	8.24	2.70	3.68	-0.908	N.S.
CVRR	4.98	1.55	4.79	1.34	-0.571	N.S.
rMSSD	22.1	9.7	20.8	7.3	-0.624	N.S.
SDNN	37.7	16.2	33.3	9.8	-1.242	N.S.

Gender: Man = 1, Woman = 0.
Statistical significance of difference in PWV between the 2 groups validates classification.

Table 3
RR of CV Death in relation to PWV, HRV, Cognitive function and classic CV Risk factors

Endpoint	RR	95% CI	p-value
Gender			N.S.
Age (5)	1.859	1.008–3.427	0.0469
BMI			N.S.
SBP			N.S.
DBP			N.S.
PP			N.S.
HR			N.S.
PWV (200)	1.335	1.147–1.553	0.0002
PWV (500)	2.058	1.410–3.005	0.0002
PWV (200)*	1.302	1.110–1.525	0.0011
PWV (500)*	1.933	1.300–2.874	0.0011
ABI			N.S.
Up&Go			N.S.
FR			0.0696
Button			N.S.
MMSE (2)	0.776	0.612–0.985	0.0369
HDSR (2)	0.753	0.624–0.907	0.0029
Kohs			0.0991
GDS			N.S.
VLF			N.S.
LF			N.S.
HF			N.S.
LF/HF (0.20)	0.821	0.690–0.976	0.0255
pNN50			N.S.
CVRR			N.S.
RMSSD			N.S.
SDNN			N.S.

* After adjustment for age and HDSR

ratio were statistically significantly associated with the occurrence of cardiovascular death (Table 3). In univariate analyses, a 200 or 500 cm/s increase in baPWV was associated with a RR of cardiovascular death of 1.335 or 2.058, respectively ($P < 0.0002$). A two-point increase in MMSE and HDSR score significantly protected against cardiovascular death, being associated with RRs of 0.776 ($P = 0.0369$) and 0.753 ($P = 0.0029$), respectively. The LF/HF ratio also showed significant predictive value ($P = 0.025$), but other HRV indices did not.

In multivariate analyses, when both baPWV and age were used as continuous variables in the same model, baPWV remained statistically significantly associated with the occurrence of cardiovascular death. After adjustment for age and HDSR, a 200 cm/s increase in baPWV was associated with a 30.2% increase in risk (RR = 1.302, 95% CI: 1.110 to 1.525), and a 500 cm/s increase in baPWV with a 93.3% increase in risk (RR = 1.933, 95% CI: 1.300 to 2.874), $P = 0.0011$. In multivariate analyses, when both the LF/HF ratio and age were used as continuous variables in the same model, the LF/HF ratio was no longer statistically significantly associated with cardiovascular mortality.

4. Discussion

The main result of the present study is that in elderly community-dwelling people, arterial stiffness measured by means of baPWV predicted the occurrence of cardiovascular death beyond the prediction provided by age, gender, blood pressure and cognitive functions, assessed by a multivariate Cox model. The baPWV measure is a novel noninvasive technique, which has been developed to assess pulse wave transmission between the brachial and tibial arteries [6]. PWV is known to be an indicator of arterial stiffness and a marker of vascular damage [7]. Traditionally, carotid-femoral PWV is an established method for measuring PWV. Contrary to this traditional PWV, baPWV includes peripheral components of the arterial tree. We need to consider the role of this arterial tree because the influence of age changes in different parts of the arterial tree. Although baPWV values are larger compared to those obtained by the traditional method, their validity has been demonstrated by Yamashina et al. [6]. Findings herein suggest the usefulness of baPWV for clinical use. It has also been argued that baPWV is strongly affected by blood pressure [8] and that this effect should be considered in clinical

practice. This investigation showed that baPWV but not BP was predictive of cardiovascular mortality. Hence, baPWV should be added to the cardiovascular assessment in various clinical settings, including field medical surveys and preventive screenings. Other advantages of this method are that it is not time consuming, that it has good reproducibility, and that it does not require highly skilled technicians.

We have started a novelty medicine focusing on a comprehensive cardiovascular assessment, namely a new field of chrono-ecology in medicine, which is important for a better diagnosis and a more effective treatment. We need to get information about the disease not only from the patient, but also from the natural environment. Often the most important key originates not from the patients themselves, but from their whole environment. Most organisms on Earth, including humans, have developed "clock" genes underlying the circadian, and probably many other components in the spectral element of chronomes, beyond about-yearly (circannual) and about-weekly (circaseptan) features, as a product of adaptation to, or rather integration with, cycles in the cosmos. While life originally integrated itself into the cycles of an anthropogenically unpolluted environment, the environmental cycles are now being changed in keeping with the schedules of societal life, as in the case of global temperature, and perhaps the geomagnetic index.

Hence, a variety of cognitive, neurobehavioral and neuropsychological as well as cardiovascular functions will need to be investigated to more precisely map their chronomes in space and time, in order to understand chronoastrobiology, based on both the system times and time horizons yielded by chronomes assessed in communities worldwide. Fortunately, this mapping in the field has been sought not only in several rural Japanese towns, but also in old towns in the Karakoram and the Andes, by Matsubayashi et al. We have also started a novelty project for stroke prevention based on a comprehensive assessment, especially of elderly community-dwelling people, as shown herein. This kind of new project stands on the viewpoint of chronomics, aiming at prehabilitation medicine in preference to sole rehabilitation. It is offered as a public service in several Japanese towns, according to plans originally made in the city of Roseville, a suburb of St. Paul, Minnesota.

Acknowledgements

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References

[1] Meaume S, Benetos A, Henry OF, Rudnichi A, Safar ME. Aortic pulse wave velocity predicts cardiovascular mortality in subjects >70 years of age. Arterioscler Thromb Vasc Biol 2001;21:2046–50.

[2] Fujiwara Y, Chaves P, Takahashi R, Amano H, Kumagai S, Fujita K, et al. relationships between brachial-ankle pulse wave velocity and conventional atherosclerotic risk factors in community-dwelling people. Preventive Medicine 2004;39:1135–42.

[3] Boutouyrie P, Tropeano AI, Asmar R, Gautier I, Benetos A, Lacolley P, et al. Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: a longitudinal study. Hypertension 2002;39:10–15.

[4] Laurent S, Katsahian S, Fassort C, Tropeano AI, Gautier I, Laloux B, Boutouyrie P. Aortic stiffness is an independent predictor of fatal stroke in essential hypertension. Stroke 2003;34:1203–1206.

[5] Dijk JM, van der Graaf Y, Grobbee DE, Banga JD, Bots ML on behalf of the SMART Study Group. Increased arterial stiffness is independently related to cerebrovascular disease and aneurysms of the abdominal aorta. The second manifestations of arterial disease (SMART) study. Stroke 2004;35:1642–46.

[6] 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;25:359–364.

[7] Asmar R. Arterial stiffness and pulse wave velocity. Amsterdam: Elsevier; 1999. p 9–15.

[8] Yamashina A, Tomiyama H, Arai T, Koji Y, Yambe M, Motobe H, et al. Nomogram of the relation of brachial-ankle pulse wave velocity with blood pressure. Hypertens Res 2003;26:801–806.

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Fractal analysis of heart rate variability and mortality in elderly community-dwelling people – Longitudinal Investigation for the Longevity and Aging in Hokkaido County (LILAC) study

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Abstract

Aim. – Fractal analysis of heart rate (HR) variability (HRV) has been used as a new approach to evaluate the risk of mortality in various patient groups. Aim of this study is to examine the prognostic power of detrended fluctuation analysis (DFA) and traditional time- and frequency-domain analyses of HR dynamics as predictors of mortality among elderly people in a community.

Methods. – We examined 298 people older than 75 years (average age: 79.6 years) and 1-h ambulatory ECG was monitored. During the last 10 min, deep respiration (6-s expiration and 4-s inspiration) was repeated six times in a supine position. Time-domain and frequency-domain measures were determined by the maximum entropy method. Scaling exponents of short-term (<11 beats, alpha 1) and longer-term (>11 beats, alpha 2) were determined by the DFA method. Six estimates, obtained from 10-min segments, were averaged to derive mean values for the entire recording span. These average values were denoted Alpha 1 and Alpha 2, estimates obtained during the first 10-min segment Alpha 1 S and Alpha 2 S, and those during the last 10-min segment Alpha 1E and Alpha 2E, respectively. The LILAC study started on July 25, 2000 and ended on November 30, 2004. We used Cox regression analysis to calculate relative risk (RR) and 95% confidence interval (CI) for all-cause mortality. Significance was considered at a value of $P < 0.05$.

Results. – Gender, age and Alpha 2E showed a statistically significant association with all-cause mortality. In univariate analyses, gender was significantly associated with all-cause mortality, being associated with a RR of 3.59 ($P = 0.00136$). Age also significantly predicted all-cause mortality and a 5-year increase in age was associated with a RR of 1.49 ($P = 0.01809$). The RR of developing all-cause mortality predicted by a 0.2-unit increase in Alpha 2E was 0.58 ($P = 0.00390$). Other indices of fractal analysis of HRV did not have predictive value. In multivariate analyses, when both Alpha 2E and gender were used as continuous variables in the same model, Alpha 2E remained significantly associated with the occurrence of all-cause mortality ($P = 0.02999$). After adjustment for both gender and age, a 0.2-unit increase in Alpha 2E was associated with a RR of 0.61 (95% CI: 0.42–0.90, $P = 0.01151$).

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Conclusion. – An intermediate-term fractal-like scaling exponent of RR intervals was a better predictor of death than the traditional measures of HR variability in elderly community-dwelling people. It is noteworthy that the longer-term (alpha 2) rather than the short-term fractal component (alpha 1) showed predictive value for all-cause mortality, which suggests that an increase in the randomness of intermediate-term HR behavior may be a specific marker of neurohumoral and sympathetic activation and therefore may also be associated with an increased risk of mortality.

Keywords: Fractal; Heart rate variability; Detrended fluctuation analysis; All-cause mortality; Elderly community-dwelling people

1. Introduction

Fractal analysis of heart rate (HR) variability (HRV) has been used as a new approach to evaluate the risk of mortality in various patient groups [1–3]. Several new methods have been developed to quantify complex HR dynamics and to complement the conventional measures of HR variability. These methods have provided powerful prognostic information in different populations, but their prognostic power has not been studied in elderly community-dwelling people. In this study, we examine the prognostic power of fractal detrended fluctuation analysis and traditional time- and frequency-domain analyses of HR dynamics as predictors of mortality among elderly people in a community.

2. Methods

2.1. Subjects and LILAC study design

We examined 298 people older than 75 years (average age: 79.6 years). One hour of ambulatory ECG recording was obtained during routine medical examination conducted each year in July. During the last 10 min, deep respiration (6-s expiration and 4-s inspiration) was repeated six times in a supine position. The data were processed for HRV using a Fukuda-Denshi Holter analysis system (SCM-280-3). Time-domain measures (CVRR, SDANN, rMSSD and pNN50) and frequency-domain measures (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 LF/HF ratio) were determined. All indices were computed as averages 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 detrended fluctuation analysis technique was used to quantify the fractal scaling properties of short- and intermediate-term RR intervals. The root-mean-squares fluctuation of integrated and detrended time series is measured at different observation windows and plotted against the size of the observation window on a log–log scale. The details of this method were shown elsewhere by Peng et al. [4]. The HR correlations were defined separately for short-term (<11 beats, alpha 1) and longer-term (>11 beats, alpha 2) RR interval data (scaling exponent). Six estimates of both alpha 1 and alpha 2, obtained from 10-min segments based on 4000 RR intervals, were averaged to derive mean values for the entire recording span. These average values were denoted Alpha 1 and Alpha 2, respectively. Estimates obtained during the first 10-min segment were denoted Alpha 1 S and Alpha 2 S, respectively, and those obtained during the last 10-min segment Alpha 1E and Alpha 2E, respectively.

2.2. Follow-up

The LILAC study started on July 25, 2000. Consultations were repeated every year (end of July, or beginning of August). In addition, one or two doctors of our team visited every 3 months and offered several kinds of health consultation regarding the rehabilitation of disordered functions, healthy lifestyle modifications, such as the promotion of complete smoking cessation, weight reduction, reduction of salt intake, moderation in the consumption of fruits and vegetables and alcohol intake, and advice in terms of medical prescriptions for the local general practitioner.

In this investigation, the follow-up ended on November 30, 2004. The follow-up time was defined as the time elapsed between the date of first (reference) examination and the date of all-cause mortality.

2.3. 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 and adjusted relative risk (RR) and 95% confidence interval (CI) for all-cause mortality. To identify independent predictors of all-cause mortality, we used multivariate Cox regression analyses with stepwise selection. Variables included in the multivariate models were age, gender, body mass index (BMI) and HR variability indices. Significance was considered at a value of $P < 0.05$.

3. Results

The reference characteristics of the 298 subjects are given in Table 1. The sample comprised 120 men and 178 women. The mean age of the participants at entry was 79 years. The mean follow-up time was 1152 days, during which 30 subjects died (21 men and nine women). Out of the 298 participants, HR variability was analyzed in 260 subjects, excluding subjects with cardiac arrhythmias, such as atrial fibrillation and frequent atrial and ventricular ectopies. Out of the 260 subjects, fractal analysis of HR variability was done in 184 subjects.

Table 1
Reference characteristics of the 298 subjects

Variables	Number	Mean	S.D.	Minimum	Maximum
Days Follow-up	298	1152.0	462.2	114.0	1578.0
Gender	298	0.403	0.491	0	1
Age	298	79.0	4.7	70.0	96.0
BMI	284	23.5	3.5	13.9	33.3
Average HR	273	74.4	12.4	44.0	117.0
CVRR	260	5.21	2.13	1.80	22.47
SDANN	258	37.9	13.8	12.9	109.3
rMSSD	261	23.6	17.3	5.2	169.6
pNN50	261	4.6	9.1	0	76.3
VLF	261	926.9	720.8	62.7	6124.0
LF	260	212.1	274.7	6.8	1898.7
HF	259	108.0	261.4	5.1	2717.1
L/H	260	3.02	1.97	0.32	10.99
Alpha 1	184	1.045	0.234	0.45	1.49
Alpha 2	184	1.054	0.121	0.58	1.33
Alpha 1 S	184	1.028	0.271	0.35	1.52
Alpha 2 S	184	1.060	0.185	0.56	1.51
Alpha 1 E	184	1.061	0.250	0.35	1.53
Alpha 2 E	184	1.099	0.202	0.36	1.73

Gender: $M = 1$, $F = 0$ (120 men and 178 women).

Among the variables used in Cox proportional hazard models, gender, age and Alpha 2E showed a statistically significant association with all-cause mortality (Table 2). In univariate analyses, gender was significantly associated with all-cause mortality, being associated with a relative risk of 3.59 ($P = 0.00136$). Age also significantly predicted all-cause mortality and a 5-year increase in age was associated with a relative risk of 1.49 ($P = 0.01809$). The relative risk of developing all-cause mortality predicted by a 0.2-unit increase in Alpha 2E was 0.58 ($P = 0.00390$). Other indices of fractal analysis of HRV did not have predictive value. In multivariate analyses, when both Alpha 2E and gender were used as continuous variables in the same model, Alpha 2E remained significantly associated with the occurrence of all-cause mortality ($P = 0.02999$). After adjustment for both gender and age, a 0.2-unit increase in Alpha 2E was associated with a relative risk of 0.61 (95% CI: 0.42 to 0.90, $P = 0.01151$).

Table 2
Relative risk (RR) of the all-cause mortality in elderly community-dwelling people

Variables	Number	β	S.E. (β)	z-value	P-value	RR	95% CI	
Gender	298	1.277	0.398	3.204	0.00136	3.59	1.64	7.83
Age (5)	298	0.080	0.034	2.364	0.01809	1.49	1.07	2.08
BMI	284	-0.049	0.054	0.905	N.S.			
Average HR	273	0.016	0.015	1.059	N.S.			
CVRR	260	0.055	0.088	0.622	N.S.			
SDANN	258	0.003	0.015	0.181	N.S.			
rMSSD	261	0.008	0.009	0.952	N.S.			
pNN50	261	0.012	0.017	0.721	N.S.			
VLF	261	0.000	0.000	0.775	N.S.			
LF	260	0.000	0.000	0.428	N.S.			
HF	259	0.000	0.000	0.030	N.S.			
L/H	260	-0.168	0.116	1.456	N.S.			
Alpha 1	184	-1.364	0.873	1.563	N.S.			
Alpha 2	184	-2.899	1.547	1.874	0.06090			
Alpha 1 S	184	-0.890	0.765	1.163	N.S.			
Alpha 2 S	184	-1.112	1.192	0.934	N.S.			
Alpha 1 E	184	-1.198	0.816	1.468	N.S.			
Alpha 2E (0.20)	184	-2.760	0.956	2.886	0.00390	0.58	0.40	0.84
Alpha 2E (0.2) Gender adjusted	184	-2.079	0.958	2.170	0.02999	0.66	0.45	0.96
Alpha 2E (0.2) Gender-, age-adjusted	184	-2.452	0.970	2.527	0.01151	0.61	0.42	0.90

Gender: $M = 1$, $F = 0$ (120 men and 178 women).

4. Discussion

The main finding of this study is that an intermediate-term fractal-like scaling exponent of RR intervals is a better predictor of death than the traditional measures of HR variability in elderly community-dwelling people. It is noteworthy that the longer-term (alpha 2) rather than the short-term fractal component (alpha 1) showed predictive value for all-cause mortality. This result contrasts with most previous studies reporting that a short-term fractal component was a better predictor in different patient populations [1–3]. It should also be kept in mind that in this study, a predictive value was found for alpha 2E, corresponding to the last 10 min of ambulatory ECG monitoring, when deep breathing was repeated in a supine position.

The advantages of fractal exponent analysis over traditional indices of HR variability have been well known. The higher sensitivity of this approach stems from its ability to detect abnormalities in HR behavior in cases where abrupt temporal changes in RR intervals occur in a window of time of seconds or minutes. This observation suggests that an increase in the randomness of intermediate-term HR behavior may be a specific marker of neurohumoral and sympathetic activation and therefore may also be associated with an increased risk of mortality.