十分な時間をとって診療すべきであるが，患者数が極端に多く，一人の患者にかける時間が少ないという現状では，会話の中にスクリーニングを含め，効率的に診療することが迫られている．もちろん，CGA7（表1，2）などのスクリーニングで問題があれば，別室で標準的なツールを用いて総合的機能評価を行う（表3）[9, 10]．

残薬の評価

高齢者の高血圧の管理は24時間を通じた厳格な降圧が重要である．このためには，家庭血圧計や24時間血圧計を用いて，血圧値と降圧の程度を把握することは言うまでもないが，降圧薬の服用が確実に実施されていることを確認することも重要である．

表1　アセスメント簡易版：CGA 7

1.	外来または診察時や訪問時に，被験者の挨拶を待つ
2.	「これから言う言葉を繰り返してください（桜，猫，電車）」 「あとでまた聞きますから覚えておいてくださいね」
3.	外来の場合：「ここへどうやって来ましたか？」 それ以外の場合：「普段，ひと駅離れた町へどうやって行きますか？」
4.	「先ほど覚えていただいた言葉を言ってください」
5.	「お風呂は自分ひとりで入って，洗うのも手助けは要りませんか？」
6.	「漏らすことはありませんか？」 「トイレに行けないときは，尿瓶を自分で使えますか？」
7.	「自分が無力だと思いますか？」

（文献10より引用）

表2　CGA 7の正否とおおまかな解釈

項目番号	調査内容	出　典	正　否	おおまかな解釈
1	意　欲	Vitality Index	自分からすすんで挨拶をする＝○ 返事はするまたは反応なし＝×	挨拶意欲が× →趣味，レクリエーションもしていない可能性が大きい
2	認知機能	改訂長谷川式簡易知能評価スケール	可能＝○ 不能＝×（できなければ4の認知機能は省略）	復唱ができない →失語，難聴などなければ，中等度以上の認知症が疑われる
3	手段的ADL	IADL尺度（Lawton & Brody）	自分でバス，電車，タクシー，自家用車を使って移動できる＝○ 付き添いが必要＝×	付き添いが必要 →タクシーも自分で使えなければ，虚弱か中等度の認知症が疑われる
4	認知機能	改訂長谷川式簡易知能評価スケール	ヒントなしで全部可能＝○ 上記以外＝×	遅延再生ができない →軽度の認知症が疑われる，遅延再生が可能なら認知症の可能性は低い
5	基本的ADL	Barthal Index	自立＝○ 部分介助または全介助＝×	入浴，排泄の両者が× →要介護状態の可能性が高い，入浴と排泄が自立していれば他の基本的ADLは自立していることが多い
6	基本的ADL	Barthal Index	失禁なし，集尿器自立＝○ 上記以外＝×	
7	情緒・気分	GDS	いいえ＝○ はい＝×	無力であると思う →うつの傾向がある

＊あくまでスクリーニングなので，異常（×）が検出された場合は，【標準版】で評価することが必要．

（文献10より引用）

表3　高齢者高血圧外来におけるCGAツール例

1.	医学的評価
2.	身体的評価 ・基本的日常生活動作能力検査（Basic ADL）：Barthal Index ・手段的日常生活動作能力検査（Instrumental ADL）：老研式活動能力指標 ・Up & Goテスト（歩行能力と姿勢反射の評価）
3.	精神心理的評価 ・ミニメンタルテスト（MMS(E)）、改訂長谷川式簡易知能評価スケール（HDS-R） ・Geriatric Depression Scale（GDS）15 ・Vitality Index（意欲の評価）
4.	社会的評価 ・介護者の有無・介護状況 ・住宅状況

後期高齢者や超高齢者の中には，短い診察時間内では，一見正常で服薬コンプライアンスにも問題がなさそうであるが，認知機能が低下し，日常生活に破綻をきたしている高齢者は少なくない．特に高齢者高血圧で血圧の変動が大きい例や難治性高血圧例では，二次性高血圧を検索するとともに，服薬コンプライアンス，すなわち，残薬チェックを心がけるべきである．ただし，面と向かって画一的に残薬があることをとがめても解決にはならない．「余った薬を調整しましょう．薬代もばかにならないでしょう」などといって自尊心を傷つけないように誘導するのがコツである．

また，情報は本人ばかりでなく，介護者やケアマネジャー，介護士，院外薬局，薬剤師，看護師，受付事務など医療介護関係者をはじめ，さまざまなところから情報が得られるように，日ごろからネットワークを構築しておくことが重要である．

日時を聞く

「きょうは何月何日でしょう」と唐突に切り出したのでは，患者自身がびっくりしてしまい，警戒心をあおるばかりである．「前回来院されたのはいつだったでしょうか」や「昨日は何時に寝ましたか」，「きょうは朝ごはんを何時に食べましたか」など，日常会話と変わらないレベルでスクリーニングすることにより，認知機能低下を疑い，問題がある場合に正式なツール（MMSE，HDSなど）を用いて確認することが効率的である．

生活習慣の変化を聞く

毎日ちゃんと食事がとれているか，規則正しい習慣が崩れていないか．例えば，散歩の習慣やデイケアにいかなくなったなどは，認知機能低下やうつ状態の可能性があり，精査が必要である．

手指の巧緻性

指で薬のシートから薬を容易に取り出せて，服用できるかどうかの巧緻性の評価は高齢者診療では，特に重要である．診察時に着衣を脱ぐのに時間がかかる場合やボタンの着脱がうまくできるかどうか観察することで，手指の巧緻性をある程度評

図3　ボタンテスト（手指の巧緻性評価）

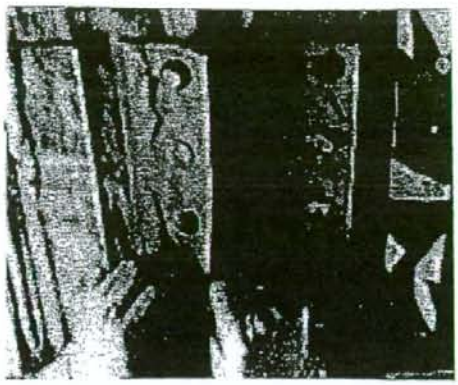

図4　高齢者高血圧外来におけるCGAの流れの例

価できる．外来で一人の医師が経過を追えないような場合には，客観的データを得るために，ボタンの着脱に要する時間を測定する「ボタンテスト」が有用である（図3）．

以上のような診察ごとの評価とは別に，定期的に（半年に1回くらい）は，CGA7などの簡潔な機能評価を行い，問題がある高齢者に対しては，さらに標準的な機能評価を行う（図4）．このように，客観的なデータを残しながら，経過を追うことが，その後の介入の方法を決定するのに重要である．

評価に対する介入

高血圧診療においては，薬をしっかり服用していることが，薬効評価に不可欠である．したがって，残薬評価で異常が見出された場合には，認知機能やうつなどの評価を行うとともに，服薬コンプライアンスをあげるための工夫が必要である．薬剤の種類や用法の整理・単純化，一包化をはじめ，薬箱の使用は服薬コンプライア

ンスをあげるための手法として知られているが，自己管理が無理な場合には服薬管理を家族にお願いするなどの介入が必要である．ミニメンタルテスト（MMS）30点満点中23点未満では，薬の自己管理が難しくなるとの報告もあるが，利尿薬などを含む場合や，複雑な用法であると，この点数より高くても自己管理が難しくなることが少なくない．服薬コンプライアンスにおけるMMSの評価はあくまでも参考値として，個別に対応すべきである．

また，高齢者高血圧の場合には，家庭血圧値の記載にも留意し，24時間血圧計やメモリー付家庭血圧計を用いて客観的データを得る努力も必要である．

〈文献〉

1）厚生労働省平成15年国民健康・栄養調査．第3部身体状況調査の結果．p155-161.

2）SHEP Cooperative Research Group: Prevention of stroke by antihypertensive drug treatment in olderpersons with isolated systolic hypertension: Final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA 1991; 265: 3255—3264.

3）Liu L, Wang JG, Grong L, Liu G, Staessen JA, for the Systolic Hypertension in China (Syst-China) Collaborative Group: Comparison of active treatment and placebo in older Chinese patients with isolated systolic hypertension. J Hypertens 1998; 16: 1823—1829.

4）Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, et al.: Treatment of Hypertension in Patients 80 Years of Age or Older. NEJM. www.nejm.org. March 31, 2008 (10.1056/NEJMoa 0801369).

5）Di Bari M, Pahor M, Franse LV, Shorr RI, Wan JY, Ferrucci L, et al: Dementia and disability outcomes in large hypertension trials: lessons learned from the systolic hypertension in the elderly program (SHEP) trial. Am J Epidemiol 2001; 153(1): 72—78.

6）Tzourio C, Anderson C, Chapman N, Woodward M, Neal B, MacMahon S, et al; PROGRESS Collaborative Group: Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. Arch Intern Med 2003; 163: 1069—1075.

7）Lithell H, Hansson L, Skoog I, Elmfeldt D, Hofman A, Olofsson B, et al; SCOPE Study Group: 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.

8）Rabkin JG, Charles E, Kass F: Hypertension and DSM-III depression in psychiatric outpatients. Am J Psychiatry 1983; 140: 1072—1074.

9）長寿科学総合研究CGAガイドライン研究班：高齢者総合的機能評価ガイドライン．鳥羽研二監修，厚生科学研究所，東京，2003，p14—15.

10）西永正典：高齢者高血圧の特徴と管理のコツ．高血圧を識る・個別診療に生かす，新・心臓病診療プラクティス11（苅尾七臣・島田和幸編），文光堂，東京，2008，p376—380.

ORIGINAL ARTICLE

B-type natriuretic peptide is predictive of hospitalization in community-dwelling elderly without heart diseases

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Aim: To examine prospectively the relationship between plasma B-type natriuretic peptide (BNP) levels in community-dwelling elderly and their hospitalization.

Methods: A total number of 644 subjects aged 65 years or older were recruited from the annual community health examinations. Those with a history of stroke or neurological findings were not included. After excluding those with old myocardial infarction, left ventricular dysfunction, moderate or severe valvular disorders, atrial fibrillation, renal insufficiency, and history of hospitalization within 1 year, 602 participants (226 men, 376 women; mean age, 80.3 ± 6.2 years) remained eligible for this study. Antihypertensive medications, activities of daily living (ADL) score and history of hospitalization were assessed by annual interview. Measurement of casual blood pressure, Mini-Mental State Examination, electrocardiography and echocardiography were performed. Plasma BNP, serum creatinine, total cholesterol, albumin and hemoglobin A1c levels were also examined. A follow-up survey was performed for the occurrence and reasons for hospitalization.

Results: During a median follow up of 37 months, 112 subjects were hospitalized. After adjustment for conventional risk factors of hospitalization using the Cox proportional hazard model, each increment of 1 standard deviation in log BNP levels was associated with a 36% increase in the risk of hospitalization ($P = 0.02$). Plasma BNP levels were significantly higher in the hospitalized subjects due to stroke, heart diseases, dementia, pneumonia and also difficulty to live alone than those of the subjects without hospitalization.

Conclusion: Plasma BNP level is a very useful biochemical marker predictive of future hospitalization in community-dwelling independent elderly people without apparent heart diseases.

Keywords: B-type natriuretic peptide, community-dwelling elderly, hospitalization.

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Author contribution: Y. S. conceived this study and protocol, echo study, analysis and interpretation of data, drafting and preparation of the manuscript; M. N. performed echo study, analysis and interpretation of data, and preparation of the manuscript; J. T. and I. M. provided technical assistance in echo study and analysis; K. O. and K. M. performed study design and analysis; N. Y. performed study design and preparation of the analysis; and Y. D. performed study design and protocol, and preparation of the manuscript.

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Introduction

In our rapidly aging societies, it is very important to take preventive intervention for elderly people requiring care and medical treatment to reduce the numbers of frail elderly.[1] There have been many approaches to predict the risk of care-requiring, frail conditions based on the actual status of activities of daily living (ADL) of the elderly. However, there are few biochemical markers that represent frailty of the elderly, except for markers of poor nutrition, such as serum total cholesterol and albumin,[2,3] or electrolyte.[4]

B-type natriuretic peptide (BNP) is a member of the natriuretic peptide family;[5] biosynthesis of BNP is known to increase in the presence of cardiac failure.[6] Recent reports have suggested that elevated plasma BNP level is related to the development of stroke and transient cerebral ischemic attack.[7,8] A relationship between plasma BNP level and mortality was also reported in the elderly.[9] However, many of these reports are either limited to the very elderly accommodated in nursing homes[10,11] or the functionally-impaired elderly,[12] or have focused on the elderly with heart diseases.[13,14]

Thus, in the elderly living independently in the community, the clinico-epidemiological relevance of elevated plasma BNP level is unclear. We have therefore examined plasma BNP level in community-dwelling elderly people without apparent heart diseases, and discuss its usefulness as a marker of future hospitalization which can be thought as one of the events representing frailty of the elderly.

Methods

Subjects

A total of 644 independent subjects aged 65 years or older had been recruited from the annual community health examination between 2000 and 2003. The end of follow-up survey was 2004. By definition, those with a history of stroke and those with neurological findings were not included in this study. The patients had consented that the results of their health examinations be used. The study was performed in "K town", in a rural area of Japan, in which subjects older than 65 years account for 37% of the total population. We excluded 32 subjects who had been diagnosed with old myocardial infarction, moderate to severe mitral or aortic valvular disorders, or moderate to severe left ventricular dysfunction with fractional shortening of less than 20%, on first health examinations. Three subjects whose serum creatinine levels exceeded 2.0 mg/dL, and seven subjects who were diagnosed with atrial fibrillation were also excluded. Thus, 602 subjects (226 men, 376 women; mean age, 80.3 ± 6.2 years) remained eligible for this study.

Parameters

All subjects completed questionnaires regarding current ADL and antihypertensive medications. When the subjects had a history of brain magnetic resonance imaging (MRI) examination, a questionnaire regarding asymptomatic findings of MRI including lacunae and white matter lesions was also obtained. Seven items of ADL were assessed; namely, walking, ascending and descending stairs, feeding, dressing, toileting, and bathing, noting the help required on a 4-point scale as our previous study:[15] 3, completely independent; 2, need some help; 1, need much help; 0, completely dependent. The Barthel index[16] adjusted for Japanese lifestyle was also assessed. Cognitive function was evaluated by Mini-Mental State Examination (MMSE). Casual blood pressure with the average value of two readings at rest in sitting position was measured. All subjects had blood drawn when they participated in their first health examination. These blood samples were placed in cold storage immediately after collection and were measured within 48 h. As blood biochemical examination, plasma BNP, serum creatinine, total cholesterol, albumin and hemoglobin A1c (HbA1c) levels were determined. Plasma BNP was measured using a radioimmunoassay method with Sionoria (Shionogi, Tokyo, Japan). Electrocardiography was also performed. To examine the left ventricular systolic function and valvular disorder, echocardiography was performed by cardiologists.

Follow-up survey

We had followed up all of the subjects concerning hospitalization and evaluated the reasons for hospitalization following the first health examination till 2004. The district nurses confirmed the reasons for hospitalization. The median follow-up period was 37 months (range, 2–48 months). Concerning 112 subjects who were hospitalized, duration to hospitalization was also analyzed; the median duration to hospitalization was 22 months (range, 2–48 months). Six of the 602 subjects moved out of the community over the course of the investigation and were treated as censored data.

Statistical analysis

Hospitalized subjects were compared with those without hospitalization, according to demographic characteristics, age, sex, serum creatinine, total cholesterol, albumin, plasma BNP and HbA1c levels, systolic blood pressure, MMSE score, ADL score and antihypertensive medications.

Then, to confirm the usefulness of plasma BNP level as a predictive marker for hospitalization, we used age, sex, serum creatinine, total cholesterol, albumin and

plasma BNP levels and asymptomatic brain MRI findings as covariates with the Cox proportional hazard model. In this analysis, log-transformed plasma BNP level was used for analysis because log plasma BNP exhibited a normal distribution.

Results

Characteristics of the study population

A total of 112 subjects were hospitalized during the follow up: 47 subjects died during hospitalization and 65 subjects survived. There were 490 healthy subjects who survived without hospitalization (Fig. 1). As shown in Table 1, compared with subjects without hospitalization, hospitalized subjects were older ($P < 0.001$) and included more men ($P = 0.02$). They had significantly higher plasma log BNP levels ($P < 0.001$). They also had higher serum creatinine levels ($P < 0.001$), lower serum total cholesterol levels ($P = 0.008$), lower serum albumin levels ($P = 0.003$), lower MMSE scores ($P < 0.001$) and lower ADL scores ($P < 0.001$). They had higher prevalence of asymptomatic brain MRI findings ($P < 0.001$) (Table 1).

Factors related to hospitalization

Plasma BNP level, ADL score, and asymptomatic brain MRI findings remained as factors significantly related to hospitalization, after analysis with the Cox proportional hazard model using age, sex, serum creatinine, serum total cholesterol, serum albumin and plasma BNP levels, MMSE score, ADL score and asymptomatic brain MRI findings as covariates. The adjusted hazard ratio of 1 standard deviation (SD) increment of log plasma BNP level was 1.36 (95% confidence interval [CI], 1.05–1.75; $P = 0.02$). That of one point decrement in ADL score was 1.23 (95% CI, 1.08–1.40; $P = 0.001$), and that for asymptomatic brain MRI findings was 3.24 (95% CI, 1.96–5.36; $P < 0.001$). Age, sex, serum creatinine, total cholesterol and albumin levels were not independently related to hospitalization (Table 2). The area under the receiver–operator curve (ROC) for plasma BNP and hospitalization was 0.620 (95% CI, 0.557–0.682).

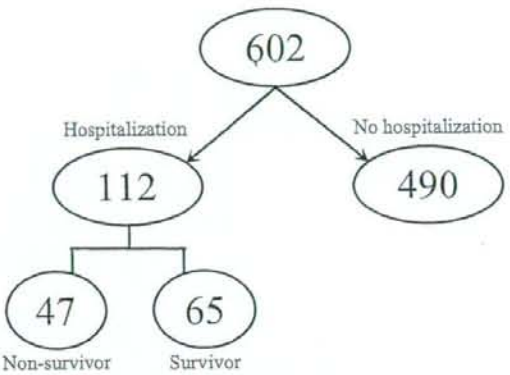

Figure 1 Study subjects and clinical course. Six hundred and two subjects were eligible for this study. A total of 112 subjects were hospitalized. A total of 47 subjects died during follow up. There were 65 subjects who were hospitalized but survived. There were 490 healthy subjects who survived without hospitalization.

Table 1 Baseline characteristics

Characteristics	Hospitalized subjects ($n = 112$)	Subjects without hospitalization ($n = 490$)	P-value*
Age (years)	83.2 ± 6.3	79.6 ± 5.9	<0.001
Men (%)	52/112 (46.4%)	174/490 (35.6%)	0.02
Creatinine (mg/dL)	0.86 ± 0.25	0.78 ± 0.18	0.001
Total cholesterol (mg/dL)	189 ± 39	199 ± 32	0.008
Albumin (mg/dL)	4.18 ± 0.36	4.26 ± 0.25	0.003
Log BNP (pg/mL)	1.75 ± 0.42	1.58 ± 0.34	<0.001
Hemoglobin A1c (%)	5.38 ± 0.64	5.46 ± 0.86	0.33
Casual systolic blood pressure (mmHg)	143 ± 21	143 ± 24	0.85
MMSE	25.9 ± 3.8	27.0 ± 2.8	0.005
ADL score (range 0–21)	20.2 ± 1.9	20.7 ± 1.1	<0.001
Asymptomatic brain MRI findings (%)	25/109 (22.9%)	39/486 (8.0%)	<0.001
Antihypertensive medications (%)	44/105 (41.9%)	176/445 (39.6%)	0.69

*P-value was computed using two-sample Student's t-test (when continuous) or Fisher's exact test (when dichotomous). ADL, activities of daily living; BNP, B-type natriuretic peptide; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging.

Table 2 Hazard ratios for hospitalization

Characteristics	Hazard ratios (95% CI)	P-value§
Age	1.03 (0.99–1.07)*	0.20
Men	1.48 (0.87–2.49)	0.14
Creatinine	1.11 (0.88–1.41)†	0.38
Total cholesterol	0.82 (0.64–1.04)†	0.10
Albumin	0.97 (0.77–1.23)†	0.81
Log BNP	1.36 (1.05–1.75)†	0.02
MMSE	1.05 (0.98–1.12)‡	0.15
ADL score	1.23 (1.08–1.40)‡	0.001
Asymptomatic brain MRI findings	3.24 (1.96–5.36)	<0.001

*1 year older. †1 standard deviation increment. ‡1 point decrement. §P-value was computed using the Cox proportional hazard model. ADL, activities of daily living; BNP, B-type natriuretic peptide; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging.

With an alternative analysis using tertiles of the BNP level, the accumulated rate of hospitalization was significantly higher in subjects with highest plasma BNP levels (27.5%) than those with middle (14.4%) and lowest plasma BNP levels (13.4%) ($P < 0.001$). The difference of those with middle and lowest plasma BNP level was not significant. The odds ratio of highest tertile compared with lowest tertile as a risk for hospitalization was 2.07 (95% CI, 1.32–3.25; $P = 0.002$). Thus, there was no linear relationship between plasma BNP and hospitalization. The risk of hospitalization seemed to be drastically elevated in those with highest plasma BNP levels.

Reasons for hospitalization

Among the 112 subjects with hospitalization, malignancy was the most common reason for hospitalization ($n = 18$, 16.1%), followed by difficulty to live alone due to decline in ADL or cognitive function ($n = 13$, 11.6%), stroke ($n = 12$, 10.7%), heart diseases ($n = 11$, 9.8%), orthopedic problems ($n = 10$, 8.9%), dementia ($n = 9$, 8.0%), pneumonia ($n = 6$, 5.4%), renal failure ($n = 4$, 3.6%) and other causes ($n = 16$, 14.3%). The reason for hospitalization of 13 subjects (11.6%) could not be specified (Table 3).

The common reasons for hospitalization among 47 non-survivors were malignancy, heart diseases, stroke and pneumonia. On the other side, the common reasons for hospitalization among 65 survivors were difficulty to live alone, stroke, orthopedic problems and dementia. These conditions accorded well with the diseases ranked highly among the reasons for hospitalization in Japan according to past statistics.[1]

Table 3 Reasons for hospitalization

Reasons	n
Malignancy	18 (16.1%)
Difficulty to live alone	13 (11.6%)
Stroke	12 (10.7%)
Heart diseases	11 (9.8%)
Orthopedic problems	10 (8.9%)
Dementia	9 (8.0%)
Pneumonia	6 (5.4%)
Chronic kidney disease	4 (3.6%)
Sepsis	2 (1.8%)
Liver failure	2 (1.8%)
Gallstone	2 (1.8%)
Asthma	2 (1.8%)
Others*	8 (7.1%)
Unknown causes	13 (11.6%)
Total	112 (100%)

*Bowel obstruction, diabetes mellitus, old tuberculosis, cataract, anorexia, pacemaker generator exchange, senile decay and accident.

Plasma BNP levels of subjects according to reasons for hospitalization

We compared plasma BNP levels of hospitalized subjects to those of subjects without hospitalization according to the reasons for hospitalizations (Table 4). Plasma BNP levels of hospitalized subjects due to difficulty to live alone, heart diseases, stroke, dementia and pneumonia were significantly higher than those of the subjects without hospitalization. When heart disease and stroke were considered as cardiovascular disease, the adjusted hazard ratio of 1 SD increment of log plasma BNP level was 2.59 (95% CI, 1.53–4.40; $P < 0.001$). Plasma BNP levels of hospitalized subjects probably due to non-cardiovascular diseases including malignancy and orthopedic problems were not significantly different when compared with subjects without hospitalization (Table 4).

Discussion

Heart diseases and plasma BNP level

High plasma BNP level was an independent risk factor for future hospitalization in community-dwelling elderly without apparent heart diseases, even after adjustment for several confounding factors, including age, sex, serum creatinine, total cholesterol and albumin levels, MMSE score, ADL score and asymptomatic brain MRI findings. Thus, plasma BNP level can be considered as an independent predictive biomarker for hospitalization. As far as we know, no previous studies have shown a relationship between plasma BNP level and hospitalization of the community-dwelling

Table 4 Plasma BNP levels according to reasons for hospitalization

Reasons (*n*)	Log BNP (pg/mL)	*P*-value†
Malignancy (18)	1.66 ± 0.35	0.3
Difficulty to live alone (13)	1.82 ± 0.43	0.01
Stroke (12)	1.85 ± 0.45	0.006
Heart diseases (11)	1.84 ± 0.40	0.01
Orthopedic problems (10)	1.59 ± 0.37	0.86
Dementia (9)	1.94 ± 0.41	0.001
Pneumonia (6)	1.96 ± 0.40	0.006
Chronic kidney disease (4)	1.80 ± 0.39	0.17
Others (29)*	1.65 ± 0.40	0.26

*Including unknown cause. †*P*-value was computed using two-sample Student's *t*-test vs subjects without hospitalization. BNP, B-type natriuretic peptide.

independent elderly. Measurement of plasma BNP level at health examination could be a simple and useful means of prediction for future hospitalization in the community-dwelling healthy elderly.

Plasma BNP level is elevated due to biosynthesis under conditions of heart failure. Many cardiac conditions, including systolic dysfunction,[17] diastolic dysfunction,[18,19] mitral regurgitation,[20] aortic stenosis,[21,22] pulmonary hypertension,[23] cardiomyopathy[24] and senile cardiac enlargement,[25] are associated with increase in BNP. In the present study, despite the fact that subjects with moderate to severe valvular disorders, old myocardial infarction and moderate to severe left ventricular systolic dysfunction were excluded, there were 11 subjects who were hospitalized because of newly developed conditions such as heart failure. Because plasma BNP is known to be useful to detect preclinical ventricular systolic and diastolic dysfunction,[26] it may also be useful for community-dwelling elderly who are at high risk of future hospitalization due to preclinical cardiac dysfunction.

Stroke and plasma BNP level

Among hospitalized subjects, there were 12 subjects who developed stroke and nine subjects with dementia. There have been several reports indicating a correlation between the occurrence of stroke and high plasma BNP level.[7,27-29] Relation of plasma BNP level and cognitive function was also reported.[30] Although the mechanism of these relationships remains unresolved, the elderly at high risk of stroke and dementia may show the elevation of plasma BNP level as seen in our study subjects.

There were 13 subjects who were hospitalized because of difficulty to live alone that was suggestive of decline in ADL by dementia and stroke. In fact, seven of these 13 subjects had asymptomatic brain MRI findings. The plasma BNP levels of these hospitalized subjects because of difficulty to live alone were significantly higher than that of subjects without hospitalization.

There were 10 hospitalized subjects with orthopedic problems with fracture and lower back pain. Although this can potentially be explained by the fact that decline in ADL due to stroke results in falls and fractures, plasma BNP levels in these subjects were not significantly increased. There are no clinical reports concerning the relationships among BNP level, bone fracture and osteoporosis. Further investigation of these relationships is required.

Chronic kidney disease and plasma BNP level

There were four subjects who were hospitalized due to chronic kidney disease. Plasma BNP level was elevated in these four subjects although it was not statistically significant. A correlation between chronic kidney disease and BNP elevation has been reported previously.[31,32] Many elderly subjects with normal creatinine may have impaired kidney function.[33] In addition, mild chronic kidney disease has been recently reported to be associated with the likelihood of decline in ADL and walking speed.[34] Further investigation regarding chronic kidney disease, BNP elevation and hospitalization may be warranted.

Study limitations

In this study, although district nurses conducted a follow-up survey of the diseases that caused hospitalization, the precision of the data can be challenged. For example, although subjects who were diagnosed with atrial fibrillation at the health examinations were excluded, those with paroxysmal atrial fibrillation might have been included. Also, it is possible that asymptomatic mild systolic and diastolic dysfunction might have been included.

Conclusion

High plasma BNP level was found in the community-dwelling elderly subjects who were later hospitalized

because of heart diseases, stroke and chronic kidney disease, which were known to be closely related to the frail elderly. Thus, plasma BNP level is a very useful serological biomarker for future hospitalization in apparently healthy elderly people living in the community.

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References

1 Health, Labor and Welfare Ministry. *The Heisei 13 (2001) Fiscal Year Version*. Tokyo, Japan, 2001.
2 Reuben DB, Ix JH, Greendale GA, Seeman TE. The predictive value of combined hypoalbuminemia and hypocholesterolemia in high functioning community-dwelling older persons: MacArthur studies of successful aging. *J Am Geriatr Soc* 1999; **47**: 402–406.
3 Okamura T, Hayakawa T, Hozawa A *et al.* Lower levels of serum albumin and total cholesterol associated with decline in activities of daily living and excess mortality in a 12-year cohort study of elderly Japanese. *J Am Geriatr Soc* 2008; **56**: 529–535.
4 Auyeung TW, Lee JS. Prognostic significance of admission electrolyte disturbances in older people: a retrospective cohort study. *Geriatr Gerontol Int* 2007; **7**: 110–113.
5 Sudoh T, Kangawa K, Minamino N, Matsuo H. A new natriuretic peptide in porcine brain. *Nature* 1988; **332**: 78–81.
6 Mukoyama M, Nakao K, Hosoda K *et al.* Brain natriuretic peptide as a novel cardiac hormone in humans. Evidence for an exquisite dual natriuretic peptide system, atrial natriuretic peptide and brain natriuretic peptide. *J Clin Invest* 1991; **87**: 1402–1412.
7 Wang TJ, Larson MG, Levy D *et al.* Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *N Engl J Med* 2004; **350**: 655–663.
8 Kistorp C, Raymond I, Pedersen F, Gustafsson F, Faber J, Hildebrandt P. N-terminal pro-brain natriuretic peptide, C-reactive protein, and urinary albumin levels as predictors of mortality and cardiovascular events in older adults. *JAMA* 2005; **293**: 1609–1616.
9 Wallén T, Landahl S, Hedner T, Nakao K, Saito Y. Brain natriuretic peptide predicts mortality in the elderly. *Heart* 1997; **77**: 264–267.
10 Ueda R, Yokouchi M, Suzuki T, Otomo E, Katagiri T. Prognostic value of high plasma brain natriuretic peptide concentrations in very elderly persons. *Am J Med* 2003; **114**: 266–270.
11 Knight EL, Kiely DK, Fish LC, Marcantonio ER, Minaker KL. Atrial natriuretic peptide level contributes to a model of future mortality in the oldest old. *J Am Geriatr Soc* 1998; **46**: 453–457.
12 Witham MD, Gillespie ND, Hutcheon SD, Struthers AD, McMurdo ME. B-type natriuretic peptide is associated with mortality in older functionally impaired patients. *J Am Geriatr Soc* 2005; **53**: 1991–1995.
13 Heidenreich PA, Gubens MA, Fonarow GC, Konstam MA, Stevenson LW, Shekelle PG. Cost-effectiveness of screening with B-type natriuretic peptide to identify patients with reduced left ventricular ejection fraction. *J Am Coll Cardiol* 2004; **43**: 1019–1026.
14 Nakamura M, Endo H, Nasu M, Arakawa N, Segawa T, Hiramori K. Value of plasma B type natriuretic peptide measurement for heart disease screening in a Japanese population. *Heart* 2002; **87**: 131–135.
15 Matsubayashi K, Okumiya K, Osaki Y, Fujisawa M, Doi Y. Frailty in elderly Japanese. *Lancet* 1999; **353**: 1445.
16 Mahoney FI, Barthel DW. Functional evaluation: the Barthel index. *Md State Med J* 1965; **14**: 61–65.
17 McDonagh TA, Robb SD, Murdoch DR *et al.* Biochemical detection of left ventricular systolic dysfunction. *Lancet* 1998; **351**: 9–13.
18 Lubien E, DeMaria A, Krishnaswamy P *et al.* Utility of B-natriuretic peptide in detecting diastolic dysfunction: comparison with Doppler velocity recordings. *Circulation* 2002; **105**: 595–601.
19 Dahlström U. Can natriuretic peptides be used for the diagnosis of diastolic heart failure? *Eur J Heart Fail* 2004; **6**: 281–287.
20 Detaint D, Messika-Zeitoun D, Avierinos JF *et al.* B-type natriuretic peptide in organic mitral regurgitation: determinants and impact on outcome. *Circulation* 2005; **111**: 2391–2397.
21 Bergler-Klein J, Klaar U, Heger M *et al.* Natriuretic peptides predict symptom-free survival and postoperative outcome in severe aortic stenosis. *Circulation* 2004; **109**: 2302–2308.
22 Kupari M, Turto H, Lommi J. Diagnosing heart failure in aortic valve stenosis. *J Intern Med* 2004; **256**: 381–387.
23 Nagaya N, Nishikimi T, Uematsu M *et al.* Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. *Circulation* 2000; **102**: 865–870.
24 Maron BJ, Tholakanahalli VN, Zenovich AG *et al.* Usefulness of B-type natriuretic peptide assay in the assessment of symptomatic state in hypertrophic cardiomyopathy. *Circulation* 2004; **109**: 984–989.
25 Sayama H, Nakamura Y, Saito N, Kinoshita M, Suda M. Relationship between left ventricular geometry and brain natriuretic peptide levels in elderly subjects. *Gerontology* 2000; **46**: 71–77.
26 Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC Jr. Plasma brain natriuretic peptide to detect preclinical ventricular systolic or diastolic dysfunction: a community-based study. *Circulation* 2004; **109**: 3176–3181.
27 Ariyarajah V, Apiyasawat S, Najjar H, Mercado K, Puri P, Spodick DH. Frequency of interatrial block in patients with sinus rhythm hospitalized for stroke and comparison to those without interatrial block. *Am J Cardiol* 2007; **99**: 49–52.
28 Igarashi Y, Kashimura K, Makiyama Y, Sato T, Ojima K, Aizawa Y. Left atrial appendage dysfunction in chronic nonvalvular atrial fibrillation is significantly associated with an elevated level of brain natriuretic peptide and a prothrombotic state. *Jpn Circ J* 2001; **65**: 788–792.
29 Mabuchi N, Tsutamoto T, Maeda K, Kinoshita M. Plasma cardiac natriuretic peptides as biochemical markers of recurrence of atrial fibrillation in patients with mild congestive heart failure. *Jpn Circ J* 2000; **64**: 765–771.
30 Gunstad J, Poppas A, Smeal S *et al.* Relation of brain natriuretic peptide levels to cognitive dysfunction in adults >55 years of age with cardiovascular disease. *Am J Cardiol* 2006; **98**: 538–540.
31 Buckley MG, Sethi D, Markandu ND, Sagnella GA, Singer DR, MacGregor GA. Plasma concentrations and comparisons of brain natriuretic peptide and atrial natriuretic

peptide in normal subjects, cardiac transplant recipients and patients with dialysis-independent or dialysis-dependent chronic renal failure. *Clinical Science* 1992; **83**: 437–444.
32 Akiba T, Tachibana K, Togashi K, Hiroe M, Marumo F. Plasma human brain natriuretic peptide in chronic renal failure. *Clin Nephrol* 1995; **44** (Suppl 1): S61–64.
33 Giannelli SV, Patel KV, Windham BG, Pizzarelli F, Ferrucci L, Guralnik JM. Magnitude of underascertainment of impaired kidney function in older adults with normal serum creatinine. *J Am Geriatr Soc* 2007; **55**: 816–823.
34 Shlipak MG, Stehman-Breen C, Fried LF *et al.* The presence of frailty in elderly persons with chronic renal insufficiency. *Am J Kidney Dis* 2004; **43**: 861–867.

COMMUNITY-DWELLING ELDERLY FALLERS IN JAPAN ARE OLDER, MORE DISABLED, AND MORE DEPRESSED THAN NONFALLERS

To the Editor: We read with interest the article published by Somadder et al.[1] The authors document a correlation between depressive symptoms and self-reported numbers of falls in older subjects attending a day hospital in the United Kingdom. They reported that there were no significant differences in age, comorbidities, or performance on activities of daily living (ADLs) between fallers and infrequent fallers in their small population. We reexamined this important issue in community-dwelling elderly people in Japan and found findings different from those of Somadder et al.

The study population consisted of 1,261 people aged 65 and older (men 529, women 732, mean age 75.4 ± 7.2) living in T town, Kochi Prefecture, Japan. Fallers were screened using self-reported questionnaires, along with additional tests of ADLs and subjective quality of life (QOL) for community-dwelling older people in 2006. The question "Do you have any history of a fall within the past year?" was used for detecting fallers. Subjects who answered yes to the question were considered to be fallers. For the assessment of basic ADLs, the scores for seven items (walking, ascending and descending stairs, feeding, dressing, using the toilet, bathing, and grooming) were summed using a rating scale from 0 (completely dependent) to 3 (completely independent) to obtain a basic ADL score (0–21). For advanced ADLs, the Tokyo Metropolitan Institute of Gerontology index of competence rating scale of 0 to 13 was used.[2] This scale includes instrumental self-maintenance (0–5), intellectual activity (0–4), and social role (0–4). Five indicators of QOL (sense of subjective health, relationship with family, relationship with friends, financial satisfaction, and subjective happiness) were rated on a 100-mm visual analogue scale (worst QOL on the left end of the scale, best to the right).[3,4] The 15-item Geriatric Depression Scale (GDS-15)[5] was used for the assessment of depression; a score of 10 or more was considered to indicate depression. A fall risk index[6,7] with a score ranging from 0 (low risk of fall) to 21 (high risk of fall) was added to those and used for the assessment of risk of falls. Statview version 5.0 (SAS Institute, Inc., Cary, NC) was used for calculating chi-square tests for categorical variables, unpaired *t*-test for continuous variables, and Spearman correlation (r_s) between number of falls and GDS-15 and between fall risk index and GDS-15.

The proportion of fallers was 31.6% in this population. Fallers were significantly older (76.9 vs 74.7) and had significantly lower scores for each item of the ADLs and QOLs than nonfallers, even after the adjustment for age (Table 1). The proportion of subjects with depression was significantly

Table 1. Comparison of Activities of Daily Living (ADLs), 15-Item Geriatric Depression Scale (GDS-15) and Quality of Life (QOL) Scores of Fallers and Nonfallers

Characteristic	Fallers n = 399 (31.6%)	Nonfallers n = 862 (68.4%)	*P*-Value
Age, mean ± SD	76.9 ± 7.5	74.7 ± 6.9	<.001
Male, %	40.2	42.6	.40
Basic ADLs score, mean ± SD	19.1 ± 3.5	20.2 ± 2.5	<.001
Tokyo Metropolitan Institute of Gerontology index of competence (range 0–13), mean ± SD	9.3 ± 3.8	10.7 ± 3.2	<.001
Self-maintenance (range 0–5), mean ± SD	4.0 ± 1.6	4.4 ± 1.3	<.001
Intellectual activity (range 0–4), mean ± SD	2.7 ± 1.3	3.2 ± 1.1	<.001
Social role (range 0–4), mean ± SD	2.6 ± 1.4	3.2 ± 1.2	<.001
GDS-15 score			
Mean ± SD	6.6 ± 4.1	4.8 ± 3.7	<.001
>10, %	26.8	11.6	<.001
Fall risk index (range 0–21), mean ± SD	11.8 ± 3.8	7.0 ± 3.9	<.001
QOL score, mean ± SD			
Sense of subjective health	47.7 ± 21.8	56.7 ± 20.9	<.001
Relationship with family	72.3 ± 21.7	76.9 ± 20.3	<.001
Relationship with friends	69.5 ± 23.1	74.3 ± 20.7	<.001
Financial satisfaction	43.8 ± 24.9	51.2 ± 23.8	<.001
Subjective happiness	54.8 ± 22.0	62.0 ± 21.5	<.001

Unpaired *t*-test for continuous variables, chi square test for categorical variables.
Variables were adjusted for age when they were significantly correlated with age.
SD = standard deviation.

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higher in fallers (26.8% vs 11.6%, $P < .001$). Although only 59.6% of the fallers answered the numbers of falls, there was weak but significant correlation between number of falls and GDS-15 scores in those who had fallen ($r_s = 0.17$, $P = .002$). The mean fall risk index score was significantly higher in fallers than nonfallers, and there was significant correlation between fall risk index and GDS-15 ($r_s = 0.53$, $P < .001$) in fallers.

We confirmed the higher prevalence of depression in fallers than nonfallers, and there was a significant correlation between the number of falls and GDS-15, as Somadder et al. reported. However, unlike with the findings of Somadder et al., community-dwelling elderly fallers in Japan were significantly older and had lower quantitative ADL and QOL scores, as well as higher GDS-15 scores than nonfallers, even after adjustment for age.

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REFERENCES

1. Somadder M, Mondal S, Kersh R et al. Are recurrent fallers depressed? J Am Geriatr Soc 2007;55:2097–2099.
2. Koyano W, Shibata H, Nakazato K et al. Measurement of competence: Reliability and validity of the TMIG index of competence. Arch Gerontol Geriatr 1991;13:103–116.
3. Matsubayashi K, Okumiya K, Osaki Y et al. Quality of life of old people living in the community. Lancet 1997;350:1521–1522.
4. Morrison DP. The Crichton Visual Analogue Scale for the assessment of behaviour in the elderly. Acta Psychiatr Scand 1983;68:408–413.
5. Sheikh JI, Yesavage JA. Geriatric Depression Scale(GDS) Recent evidence and development of a shorter version. In: Brink TL, ed. Clinical Gerontology: A Guide to Assessment and Intervention. New York: Haworth Press, 1986;pp 165–173.
6. Toba K, Okochi J, Takahashi T et al. Development of a portable fall risk index for elderly people living in the community. Nippon Ronen Igakkai Zasshi 2005;42:346–352.
7. Okochi J, Toba K, Takahashi T et al. Simple screening test for risk of falls in the elderly. Geriatr Gerontol Int 2006;6:223–227.

SUBJECTIVE SLEEP DISTURBANCES WERE CLOSELY ASSOCIATED WITH COMPREHENSIVE GERIATRIC FUNCTIONS IN DOSE-RESPONSIVE MANNER IN THE COMMUNITY-DWELLING ELDERLY PEOPLE IN JAPAN

To the Editor: Sleep disturbance and insomnia increase greatly with age. Because of its multifactorial origins, sleep disturbance should be regarded as a geriatric syndrome and a comprehensive geriatric assessment should be performed for its improvement.[1,2] The association between sleep satisfaction and activities of daily living (ADLs), depression, and qualities of life (QOL) was assessed in community-dwelling elderly people in Japan. Elderly people with poor and moderate sleep satisfaction had lower comprehensive geriatric function (CGF) scores than those with good sleep satisfaction.

The study population consisted of 1,432 subjects aged 65 and older (male:female 594:838, mean age 75.6 ± 7.2) living in a rural Japanese town, Tosa, in Kochi prefecture. Sleep satisfaction was assessed using a self-reported questionnaire, and subjects were classified into three classes using a sleep satisfaction scale; each subject was asked, "Do you sleep well?" Possible answers were good, moderate, and poor. Seven basic ADL items (walking, ascending and descending stairs, feeding, dressing, using the toilet, bathing, grooming) were assessed, each on a 4-level scale, with 3 = completely independent, 2 = needs some help, 1 = needs much help, and 0 = completely dependent. Scores for each item were summed to generate a total basic ADL score ranging from 0 to 21.[3] Higher-level daily activities were assessed using the Tokyo Metropolitan Institute of

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ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Stress-induced blood pressure elevation in subjects with mild cognitive impairment: Effects of the dual-type calcium channel blocker, cilnidipine

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Aim: We investigated whether mental stress-induced blood pressure elevation was related to cognitive function in the elderly, and further examined the effects of the dual-type calcium channel blocker, cilnidipine, on stress induced hypertension in subjects with mild cognitive impairment.

Methods: In study I, 39 consecutive outpatients (mean age ± standard deviation, 77 ± 8 years), who were referred to our memory clinic and were not taking any medications, were studied. They were divided into three groups according to cognitive function on the Hasegawa Dementia Scale-Revised (HDSR): group 1 ($n = 8$), 28 points or more; group 2 ($n = 18$), 21–27 points; and group 3 ($n = 13$), 20 points or less. In study II, 14 outpatients with hypertension and mild cognitive impairment (aged 79 ± 8 years; HDSR score, 24 ± 4) were assigned to receive cilnidipine (10–20 mg/day). The control group ($n = 10$) matched for age, HDSR and blood pressure was followed without cilnidipine.

Results: In study I, although age and basal blood pressure were similar among the three groups, the blood pressure response to a mental arithmetic test was twice as large in group 2 (26 ± 12 mmHg in systolic pressure and 11 ± 8 mmHg in diastolic pressure) as those in groups 1 and 3. In study II, after 4 weeks, cilnidipine treatment significantly decreased the blood pressure responses to the mental arithmetic test compared to the baseline as well as to those of the control group.

Conclusions: Stress-induced blood pressure elevations are exaggerated in subjects with mild cognitive impairment. Cilnidipine may have inhibitory effects on stress-induced hypertension.

Keywords: calcium antagonists, dementia, hypertension, mental stress.

Introduction

Mental stress-induced increases in blood pressure (BP) and heart rate are often experienced during daily living. Psychophysiological cardiovascular reactivity is caused by autonomic nervous system activation via the hypothalamus–pituitary–adrenal axis,[1–3] and is

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modulated by individual characteristics, environmental exposures, interpersonal and social contexts and genetic factors.[4–7] It has been reported that the subjects with exaggerated cardiovascular reactivity to mental stress are predisposed to hypertension,[8,9] atherosclerosis[10–12] and cerebrovascular disease such as stroke and silent cerebral infarction.[13,14]

Although the central nervous system plays an important role in mental stress-induced cardiovascular reactivity,[1–3] little is known about the relationship between the reactivity and cognitive function or dementia. Association of increased short-time BP variability with cognitive impairment[15] suggests but does not directly demonstrate the link between BP responses to mental stress and cognitive function. Because the patients with cognitive impairment cannot easily perform cognitive tasks, we hypothesized that exaggerated mental stress responses would result in BP elevation in such patients.

To test this hypothesis, we conducted a cross-sectional study examining the relationship between cognitive function and BP responses to a mental arithmetic test using the subjects who were referred to our memory clinic and not taking any medications. Furthermore, we examined the effects of cilnidipine, an N- and L-type calcium channel blocker, on BP responses to a mental arithmetic test in hypertensive patients with mild cognitive impairment.

Methods

Subjects

The subjects who were referred to our memory clinic and were suspected to have hypertension on the first visit were enrolled. Depressive patients (15-item Geriatric Depression Scale score of ≥10 points) and post-stroke patients were excluded from the study. Each subject gave written informed consent before enrollment in this study. The study protocol was approved by the ethics committee of Kyorin University School of Medicine.

In study I, 39 consecutive patients (20 men and 19 women, aged 77 ± 8 years), who showed high-normal or higher BP (>130 mmHg in systolic or >85 mmHg in diastolic) and were not taking any medications, were enrolled. They underwent mental stress tests and were divided into three groups according to cognitive function on the Hasegawa Dementia Scale-Revised (HDSR): group 1 ($n = 8$), 28 points or more; group 2 ($n = 18$), 21–27 points; and group 3 ($n = 13$), 20 points or less. All the patients in group 3 and five patients in group 2 were clinically diagnosed to have Alzheimer's disease, but none were so in group 1.

In study II, 14 patients with hypertension (>140 mmHg in systolic or 90 mmHg in diastolic BP, or taking antihypertensive agents) and mild cognitive impairment (aged 79 ± 8 years; HDSR score, 24 ± 4 points; HDSR range, 21–27) were assigned to receive cilnidipine. Nine patients of group 2 in study I, who showed more than 140 mmHg in systolic or 90 mmHg in diastolic BP, were included in study II. Fifteen treated ($n = 11$) or untreated ($n = 4$) hypertensive patients were additionally included in study II. The dose of cilnidipine was initiated at 10 mg/day, and was increased to 20 mg/day if systolic BP was more than 150 mmHg or diastolic BP was more than 90 mmHg 2 weeks later. The patients were followed for an additional 2 weeks. Separately, the control group ($n = 10$) matched for age, HDSR and baseline BP were followed for 4 weeks. Mental stress tests were performed before and after the 4-week study period. Any medications except for cilnidipine were not changed throughout the study period.

Mental arithmetic test

After resting for 5 min in a quiet room, baseline BP and pulse rate (PR) were measured using an automated, digital electro sphygmomanometer (HEM-727IC; Omron Healthcare, Kyoto, Japan) on the non-dominant arm in the sitting position. Then, each subject was instructed to continuously subtract 7 from 213 as accurately as possible. BP and PR were measured again after 1 min of subtraction to evaluate the response to mental arithmetic. Measurements of BP and PR were repeated twice at each step, and the average values were used in the analyses. This test was modified for patients with cognitive impairment from the original version.[16] The correlation coefficients between the two repeated measurements of a 4-week interval were 0.971 for systolic BP and 0.850 for diastolic BP ($n = 15$, $P < 0.01$) after mental arithmetic.

Data analysis

The values are expressed as mean ± standard deviation in the text, tables and figures unless otherwise specified. Differences between the groups were analyzed using one-factor ANOVA, followed by a Newman–Keuls test. Changes in BP and PR during the study period were analyzed using a paired Student's t-test. $P < 0.05$ was considered statistically significant.

Results

Study I: Stress-induced BP elevation in the subjects as categorized by cognitive function

The characteristics of the subjects in the three groups are shown in Table 1. There were no significant differences

Table 1 Characteristics of subjects in study I

	Group 1 (HDSR, ≥28 points)	Group 2 (HDSR, 21–27 points)	Group 3 (HDSR, ≤20 points)
No. of subjects (men/women)	8 (4/4)	18 (10/8)	13 (6/7)
HDSR, points	29.0 ± 1.0	24.6 ± 1.9[§]	14.7 ± 3.8[†]
Age, years	75 ± 8	78 ± 7	78 ± 7
SBP, mmHg	150 ± 14	148 ± 20	145 ± 20
DBP, mmHg	84 ± 12	77 ± 10	74 ± 11
Pulse rate (b.p.m.)	71 ± 11	73 ± 11	73 ± 11

Values are expressed as mean ± standard deviation. [§]$P < 0.01$ vs group 1; [†]$P < 0.01$ vs group 2. All other variables are not significantly different among the groups. DBP, diastolic blood pressure; HDSR, Hasegawa Dementia Scale-Revised; SBP, systolic blood pressure.

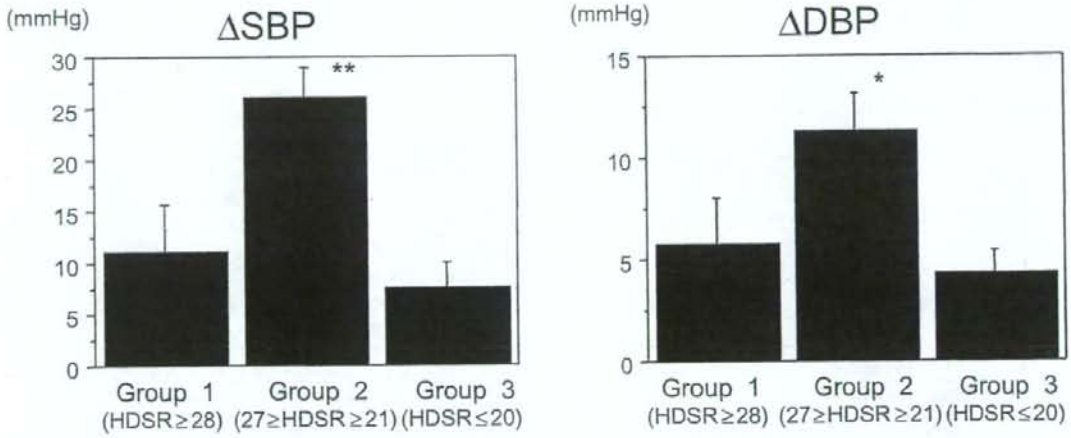

Figure 1 Influence of cognitive function on stress-induced blood pressure elevation. The changes of systolic (SBP) and diastolic blood pressure (DBP) during the mental arithmetic test in study I are shown. Values are expressed as mean ± standard error of the mean. Group 1, Hasegawa Dementia Scale-Revised (HDSR) score of ≥28 points; group 2, 21–27 points; and group 3, ≤20 points. *$P < 0.05$, **$P < 0.01$ vs groups 1 and 3.

in sex, age and baseline BP between the groups. As shown in Figure 1, the responses of both systolic and diastolic BP to the mental arithmetic test were twice as large in group 2 as those in groups 1 and 3.

Study II: Effects of cilnidipine on stress-induced BP elevation

All the subjects completed the protocol of study II. The characteristics of the subjects are shown in Table 2. The average dose of cilnidipine used in the cilnidipine group was 13 ± 5 mg/day. There were no significant differences in cognitive function, age and resting BP between the control group and the cilnidipine group, although resting systolic and diastolic BP fell significantly by the treatment with cilnidipine for 4 weeks. Figure 2 shows the BP responses to the mental arithmetic test. In the control group, BP responses did not change during the study period. In the cilnidipine group, however, BP responses to the mental arithmetic test were significantly decreased after 4 weeks. As a result, there were significant differences in the responses of systolic and diastolic BP to the mental arithmetic test between the control group and the cilnidipine group at the end of the study. We attempted to calibrate the reactivity by baseline BP. The percent changes of systolic BP during the mental arithmetic test were significantly smaller in the cilnidipine group than in the control group after treatment (12 ± 5% cilnidipine vs 18 ± 6% control, $P < 0.05$), although they were comparable in both groups before treatment (18 ± 6% cilnidipine vs 20 ± 9% control).

Table 2 Characteristics of subjects in study II

	Control	Cilnidipine
No. of subjects (men/women)	10 (5/5)	14 (6/8)
HDSR, points	26.0 ± 3.0	25.0 ± 4.0
Age, years	81 ± 8	79 ± 8
Pretreatment drugs		
ACEI/ARB, *n* (%)	3 (30%)	3 (21%)
CCB, *n* (%)	3 (30%)	3 (21%)
Before treatment		
SBP, mmHg	153 ± 17	161 ± 20
DBP, mmHg	80 ± 7	85 ± 11
Pulse rate, b.p.m.	75 ± 9	74 ± 13
4 weeks after treatment		
SBP, mmHg	151 ± 18	144 ± 16†
DBP, mmHg	79 ± 7	76 ± 9†
Pulse rate, bpm	75 ± 8	77 ± 13

Values are expressed as mean ± standard deviation. †$P < 0.01$ vs baseline. No significant differences were found between the control and cilnidipine groups. ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; CCB, L-type calcium channel blocker; DBP, diastolic blood pressure; HDSR, Hasegawa Dementia Scale-Revised; SBP, systolic blood pressure.

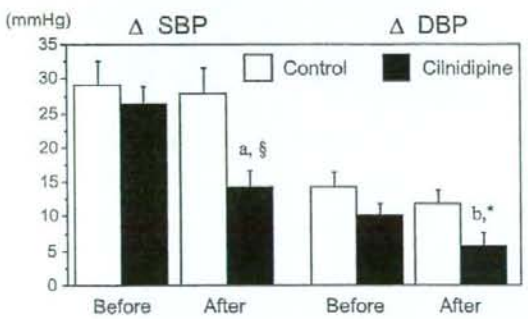

Figure 2 Effects of cilnidipine on stress-induced blood pressure elevation in elderly hypertensives with mild cognitive impairment. The changes of systolic (SBP) and diastolic blood pressure (DBP) during the mental arithmetic test before and after the treatment in study II are shown. Values are expressed as mean ± standard error of the mean. [a]$P < 0.01$, [b]$P < 0.05$ vs before treatment. §$P < 0.01$, *$P < 0.05$ vs control.

Discussion

In study I, we investigated whether mental stress-induced BP elevation was related to cognitive function in the elderly who were referred to our memory clinic. A few studies have shown the relationship between mental stress-induced BP responses and cognitive function. Pierce *et al.*[17] have reported that BP responses during neuropsychological testing were unrelated to cognitive performance in college-aged subjects. Alternatively, Waldstein *et al.*[18] have reported that higher stress-induced BP reactivity is associated with poorer performance on tests of cognitive function in stroke- and dementia-free middle-aged and older adults (ages 54–79 years). In the present study, using older subjects with or without cognitive impairment, we found that the relation between mental stress-induced BP elevation and cognitive function was inverted U-shaped, and that stress-induced BP elevations were exaggerated in subjects with mild cognitive impairment.

Subjects with mild cognitive impairment can recognize their cognitive decline,[19] thus anxiety and irritation during the mental arithmetic test may arouse the accelerated BP response. By contrast, the mental arithmetic test is not likely to impose a heavy burden on demented subjects, because they display deficits in executive function,[20] often associated with depression and apathy.[21] Recently, greater variability in BP on 24-h ambulatory monitoring has been associated with poorer cognitive performance or cognitive impairment in samples of older adults.[15,22] Murakami *et al.*[23] investigated the relation between pressor responses to mental arithmetic tests and 24-h BP variability in normotensive subjects and hypertensive patients. They reported that the pressor response during the mental arithmetic test was significantly correlated with the value of 24-h BP variability in both subjects. Taken together, it is possible that mental stress-induced BP elevation in daily life is a strong determinant of BP variability in subjects with mild cognitive impairment.

In study II, we found that cilnidipine had inhibitory effects on stress-induced BP elevation in subjects with hypertension and mild cognitive impairment. Cilnidipine is a 1,4-dihydropyridine derivative calcium antagonist with potent inhibitory actions against not only L-type but also N-type voltage-dependent calcium channels.[24] Fujita *et al.*[25] have recently reported that cilnidipine is superior to amlodipine in preventing the progression of proteinuria in hypertensive patients with chronic kidney disease. The N-type voltage-dependent calcium channel plays an important role in sympathetic neurotransmission and regulates the release of norepinephrine from sympathetic nerve endings.[26] Accordingly, several studies have reported the inhibitory effects of cilnidipine on ambulatory BP and "white coat effect" in patients with essential hypertension.[27–30] The present results found in elderly hypertensives with mild cognitive impairment are consistent with these studies, and may provide a therapeutic implication in elderly hypertension.

Controversy exists as to prognostic significance of stress-induced BP elevation, typically known as the white coat effect, clinic-ambulatory BP difference.[31]

Verdecchia *et al.*[32] reported that white coat effect does not predict cardiovascular morbidity and mortality in subjects with essential hypertension. Also, Khattar *et al.*[33] reported that white coat hypertensives had a significantly lower incidence of cardiovascular events than sustained hypertensives. In contrast, Mulè *et al.*[34] reported that left ventricular mass was greater in the group with higher systolic and diastolic white coat effect, suggesting an end-organ damage in white coat hypertension. Amado *et al.*[35] reported that elderly hypertensives with white coat effect have more previous history of ischemic cardiovascular or cerebrovascular disease than those with no white coat effect. Other numerous studies also found a considerable association between the white coat effect[36,37] or the exaggerated cardiovascular reactivity to mental stress[8–14] and cardiovascular mortality or target organ damage. Recent studies suggest that hypertension is associated with the onset and exacerbation of Alzheimer's disease.[38–42] Thus, the control of stress-induced hypertension may be a therapeutic target in the management of elderly hypertensives.

This study has some limitations. First, the number of subjects examined was small, and, therefore, the results of the present study should be carefully interpreted and be confirmed in large-scale studies. Second, we studied only the response to a mental stress. BP is influenced by all kinds of stress associated with daily activities, such as mental stress, static exercise, dynamic exercise and temperature variation.[23] We also assessed the responses to hand grip exercise and found similar results to the mental arithmetic test, but did not show the data because of low reproducibility of the responses to the modified and weakened hand grip load. Third, significant increases in PR in response to the mental arithmetic test were not observed in this study. It has been known, however, that the heart rate reactivity to mental stress was attenuated in older adults compared to younger adults and children.[43–45] This phenomenon is attributable, at least in part, to the age-related decline of β-adrenergic sensitivity.[46] Consequently, it is not surprising that PR reactivity was dissociated from BP reactivity in elderly subjects in the present study. Fourth, we only measured BP and PR as physiological responses to stress. There are many indicators of the quantity of stress received, such as BP, heart rate, sympathetic activity, and catecholamine and cortisol levels.[47–49] Particularly, many investigators evaluated plasma norepinephrine and epinephrine concentrations together with BP and heart rate.[50,51] The lack of PR responses to the mental arithmetic test in the present study may have been recompensed if we had measured plasma catecholamine.

In summary, stress-induced BP elevations were exaggerated in elderly subjects with mild cognitive impairment. Cilnidipine decreased the BP responses to the mental arithmetic test in elderly hypertensives with mild cognitive impairment. These findings may provide insight into the mechanistic link between hypertension and cognitive impairment, and therapeutic implication on the management of elderly patients.

References

1 Pickering TG. The effects of environmental and lifestyle factors on blood pressure and the intermediary role of the sympathetic nervous system. *J Hum Hypertens* 1997; **11** (Suppl. 1): S9–S18.
2 McEwen BS. Protective and damaging effects of stress mediators. *N Engl J Med* 1998; **338**: 171–179.
3 Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. *Circulation* 1999; **99**: 2192–2217.
4 Everson SA, McKey BS, Lovallo WR. The effect of trait hostility on cardiovascular responses to harassment in young men. *Int J Behav Med* 1995; **2**: 172–191.
5 Kamarck TW, Peterman AH, Raynor DA. The effects of the social environment on stress-related cardiovascular activation: current findings, prospects, and implications. *Ann Behav Med* 1998; **20**: 247–256.
6 Smith TW, Christensen AJ. Cardiovascular reactivity and interpersonal relations: psychosomatic processes in social context. *J Soc Clin Psychol* 1992; **11**: 279–301.
7 Steptoe A, Cropley M, Joekes K. Job strain, blood pressure and response to uncontrollable stress. *J Hypertens* 1999; **17**: 193–200.
8 Markovitz JH, Raczynski JM, Wallace D, Chettur V, Chesney MA. Cardiovascular reactivity to video game predicts subsequent blood pressure increases in young men: the CARDIA study. *Psychosom Med* 1998; **60**: 186–191.
9 Carroll D, Smith GD, Sheffield D, Shipley MJ, Marmot MG. Pressor reactions to psychological stress and prediction of future blood pressure: data from the Whitehall II Study. *BMJ* 1995; **310**: 771–776.
10 Kamarck TW, Everson SA, Kaplan GA *et al.* Exaggerated blood pressure responses during mental stress are associated with enhanced carotid atherosclerosis in middle-aged Finnish men: findings from the Kuopio Ischemic Heart Disease Study. *Circulation* 1997; **96**: 3842–3848.
11 Barnett PA, Spence JD, Manuck SB, Jennings JR. Psychological stress and the progression of carotid artery disease. *Hypertension* 1997; **15**: 49–55.
12 Nakashima T, Yamano S, Sasaki R *et al.* White-coat hypertension contributes to the presence of carotid arteriosclerosis. *Hypertens Res* 2004; **27**: 739–745.
13 Everson SA, Lynch JW, Kaplan GA, Lakka TA, Sivenius J, Salonen J. Stress-induced blood pressure reactivity and incident stroke in middle-aged men. *Stroke* 2001; **32**: 1263–1270.
14 Waldstein SR, Siegel EL, Lefkowitz D *et al.* Stress-induced blood pressure reactivity and silent cerebrovascular disease. *Stroke* 2004; **35**: 1294–1298.
15 Kanemaru A, Kanemaru K, Kuwajima I. The effects of short-time blood pressure variability and nighttime blood pressure levels on cognitive function. *Hypertens Res* 2001; **24**: 19–24.
16 Muneta S, Dazai Y, Iwata T *et al.* Baroreceptor reflex impairment in climacteric and ovariectomized hypertensive women. *Hypertens Res* 1992; **15**: 27–32.
17 Pierce TW, Elias MF. Cognitive function and cardiovascular responsivity in subjects with a parental history of hypertension. *J Behav Med* 1993; **16**: 277–294.

18 Waldstein SR, Katzel LI. Stress-induced blood pressure reactivity and cognitive function. *Neurology* 2005; **64**: 1746–1749.

19 Crowe M, Andel R, Wadley V *et al.* Subjective cognitive function and decline among older adults with psychometrically defined amnestic MCI. *Int J Geriatr Psychiatry* 2006; **21**: 1187–1192.

20 Levinoff EJ, Phillips NA, Verret L *et al.* Cognitive estimation impairment in Alzheimer disease and mild cognitive impairment. *Neuropsychology* 2006; **20**: 123–132.

21 Lyketsos CG, Lopez O, Jones B, Fitzpatrick AL, Breitner J, Dekosky S. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. *JAMA* 2002; **288**: 1475–1483.

22 Bellelli G, Pezzini A, Bianchetti A, Trabucchi M. Increased blood pressure variability may be associated with cognitive decline in hypertensive elderly subjects with no dementia. *Arch Intern Med* 2002; **162**: 483–484.

23 Murakami E, Matsuzaki K, Sumimoto T, Mukai M, Kazatani Y, Kodama K. Clinical significance of pressor responses to laboratory stressor testing in hypertension. *Hypertens Res* 1996; 133–137.

24 Fujii S, Kameyama K, Hosono M, Hayashi Y, Kitamura K. Effect of cilnidipine, a novel dihydropyridine Ca++-channel antagonist, on N-type Ca++ channel in rat dorsal root ganglion neurons. *J Pharmacol Exp Ther* 1997; **280**: 1184–1191.

25 Fujita T, Ando K, Nishimura H *et al.* Cilnidipine versus Amlodipine Randomised Trial for Evaluation in Renal Disease (CARTER) Study Investigators. Antiproteinuric effect of the calcium channel blocker cilnidipine added to renin-angiotensin inhibition in hypertensive patients with chronic renal disease. *Kidney Int* 2007; **72**: 1543–1549.

26 Hirning LD, Fox AP, McCleskey EW *et al.* Dominant role of N-type Ca2+ channels in evoked release of norepinephrine from sympathetic neurons. *Science* 1988; **239**: 57–61.

27 Yamagishi T. Beneficial effect of cilnidipine on morning hypertension and white-coat effect in patients with essential hypertension. *Hypertens Res* 2006; **29**: 339–344.

28 Hoshide S, Kario K, Ishikawa J, Eguchi K, Shimada K. Comparison of the effects of cilnidipine and amlodipine on ambulatory blood pressure. *Hypertens Res* 2005; **28**: 1003–1008.

29 Morimoto S, Takeda K, Oguni A *et al.* Reduction of white coat effect by cilnidipine in essential hypertension. *Am J Hypertens* 2001; **10**: 1053–1057.

30 Mansour G, Mansour J. Cilnidipine in management of patients with uncontrolled hypertension and white-coat effect. *Curr Hypertens Rep* 2007; **9**: 489–490.

31 Lantelme P, Milon H, Gharib C, Gayet C, Fortrat JO. White coat effect and reactivity to stress: cardiovascular and autonomic nervous system responses. *Hypertension* 1998; **31**: 1021–1029.

32 Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Porcellati C. Prognostic significance of the white coat effect. *Hypertension* 1997; **29**: 1218–1224.

33 Khattar RS, Senior R, Lahiri A. Cardiovascular outcome in white-coat versus sustained mild hypertension: a 10-year follow-up study. *Circulation* 1998; **98**: 1892–1897.

34 Mulè G, Nardi E, Cottone S *et al.* Relationships between ambulatory white coat effect and left ventricular mass in arterial hypertension. *Am J Hypertens* 2003; **16**: 498–501.

35 Amado P, Vasconcelos N, Santos I, Almeida L, Nazaré J, Carmona J. Arterial hypertension difficult to control in the elderly patient. The significance of the "white coat effect". *Rev Port Cardiol* 1999; **18**: 897–906.

36 Munakata M, Saito Y, Nunokawa T, Ito N, Fukudo S, Yoshinaga K. Clinical significance of blood pressure response triggered by a doctor's visit in patients with essential hypertension. *Hypertens Res* 2002; **25**: 343–349.

37 Strandberg TE, Salomaa V. White coat effect, blood pressure and mortality in men: prospective cohort study. *Eur Heart J* 2000; **21**: 1714–1718.

38 Skoog I, Lernfelt B, Landahl S *et al.* 15-year longitudinal study of blood pressure and dementia. *Lancet* 1996; **347**: 1141–1145.

39 Wu C, Zhou D, Wen C, Zhang L, Como P, Qiao Y. Relationship between blood pressure and Alzheimer's disease in Linxian County, China. *Life Sci* 2003; **72**: 1125–1133.

40 Kivipelto M, Helkala EL, Laakso MP *et al.* Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. *BMJ* 2001; **322**: 1447–1451.

41 Sakurai T, Yokono K. Comprehensive studies of cognitive impairment of the elderly with type 2 diabetes. *Geriatr Gerontol Int* 2006; **6**: 159–164.

42 Kim KI, Cho YS, Choi DJ, Kim CH. Optimal treatment of hypertension in the elderly: a Korean perspective. *Geriatr Gerontol Int* 2008; **8**: 5–11.

43 Kudielka BM, Buske-Kirschbaum A, Hellhammer DH, Kirschbaum C. Differential heart rate reactivity and recovery after psychosocial stress (TSST) in healthy children, younger adults, and elderly adults: the impact of age and gender. *Int J Behav Med* 2004; **11**: 116–121.

44 Barnes RF, Raskind M, Gumbrecht G, Halter JB. The effects of age on the plasma catecholamine response to mental stress in man. *J Clin Endocrinol Metab* 1982; **54**: 64–69.

45 Steptoe A, Fieldman G, Evans O, Perry L. Cardiovascular risk and responsivity to mental stress: the influence of age, gender and risk factors. *J Cardiovasc Risk* 1996; **3**: 83–93.

46 Boutcher SH, Stocker D. Cardiovascular response of young and older males to mental challenge. *J Gerontol B Psychol Sci Soc Sci* 1996; **51**: 261–267.

47 Yoshiuchi K, Nomura S, Ando K *et al.* Hemodynamic and endocrine responsiveness to mental arithmetic task and mirror drawing test in patients with essential hypertension. *Am J Hypertens* 1997; **10**: 243–249.

48 Sawai A, Ohshige K, Yamasue K, Hayashi T, Tochikubo O. Influence of mental stress on cardiovascular function as evaluated by changes in energy expenditure. *Hypertens Res* 2007; **30**: 1019–1027.

49 Hiramatsu R. Direct assay of cortisol in human saliva by solid phase radioimmunoassay and its clinical applications. *Clin Chim Acta* 1981; **117**: 239–249.

50 Paran E, Neumann L, Cristal N. Effects of mental and physical stress on plasma catecholamine levels before and after beta-adrenoceptor blocker treatment. *Eur J Clin Pharmacol* 1992; **43**: 11–15.

51 Grossman E, Oren S, Garavaglia GE, Schmieder R, Messerli FH. Disparate hemodynamic and sympathoadrenergic responses to isometric and mental stress in essential hypertension. *Am J Cardiol* 1989; **64**: 42–44.

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ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Switch to oral hypoglycemic agent therapy from insulin injection in patients with type 2 diabetes

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Aim: We aimed to determine the feasibility of substituting thiazolidinedione-based therapy for insulin injection therapy in patients with type 2 diabetes.

Methods: Thirty-six subjects (17 men and 19 women) aged 67.8 ± 11.3 years with an average insulin dose of 0.46 ± 0.17 U/kg bodyweight, a duration of insulin therapy of 6.1 ± 8.2 years and an average hemoglobin A1c (HbA1c) of 6.8 ± 1.3% were switched from insulin injection therapy to pioglitazone, glimepiride and voglibose combination therapy.

Results: The number of subjects achieving HbA1c levels of less than 7% at 4 months was 30. The success rate of switch therapy was 83% (30/36). HbA1c was significantly reduced from 6.7 ± 1.3% to 5.9 ± 0.7% at 4 months after the switch ($P < 0.01$) in 32 patients who completed the planned 4-month study. No adverse effects including heart failure, liver dysfunction or severe hypoglycemia were observed. The insulin dose and the maximum blood glucose on the switch day were significantly lower and the age was significantly higher in the subjects who achieved HbA1c less than 7% at 4 months compared to those who did not ($P < 0.05$).

Conclusion: Thiazolidinedione-based oral combination therapy may efficiently and safely substitute relatively high-dose insulin injection therapy in patients with type 2 diabetes.

Keywords: insulin injection, oral hypoglycemic agent, switch therapy.

Introduction

As the population with diabetes increases, those receiving insulin injections increase in number proportionally. Insulin injection treatment is associated with pain and puts a heavy physical, mental and financial burden on patients. The occurrence of hypoglycemia is relatively high in those having multiple insulin injections,[1] which causes deterioration of cognitive function and thus induces dementia.[2]

In this study, we aimed to develop a method to change the route of administration of hypoglycemic agents from needle-mediated to oral, thereby enabling patients, especially elderly patients, with diabetes to have a more comfortable life by being liberated from painful procedures and recurrent insulin-induced hypoglycemic incidents. Although reports on this area are scarce, one study showed a success rate of switching from insulin injection to oral agents of approximately 50% in those who had maintained insulin therapy for a relatively long period of time with an insulin dose of less than 0.3 U/kg

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