nifedipine increased heart rate by only 1 beat/min but reduced blood pressure significantly. Such treatment over the long term also reduced the rate of new overt heart failure as well as the need for coronary angiography or bypass surgery in patients with stable angina, suggesting that long-acting nifedipine might be effective in the treatment of heart failure (Poole-Wilson et al., 2004). The mechanism underlying such efficacy has remained unclear, however. We have now investigated the effects of long-term administration of nifedipine by continuous subcutaneous infusion with an osmotic minipump on left ventricular remodeling, oxidative stress, and gene expression during the progression from left ventricular hypertrophy to diastolic heart failure in Dahl salt-sensitive (DS) rats fed a high-salt diet, an animal model of hypertensive heart disease.

2. Methods

2.1. Animals and experimental protocol

Male inbred DS rats were obtained from Eisai (Tokyo, Japan) and handled in accordance with the guidelines of Nagoya University Graduate School of Medicine as well as with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health). Weaned rats were fed laboratory chow containing 0.3% NaCl until 7 weeks of age. DS rats fed an 8% NaCl diet after 7 weeks manifest compensated concentric left ventricular hypertrophy secondary to hypertension at 12 weeks and a distinct stage of diastolic heart failure with lung congestion at 19 weeks. DS rats were therefore fed an 8% NaCl diet from 7 weeks of age and were randomized to treatment with vehicle (Vehicle, $n=8$) or with nifedipine (Bayer) at either a non-antihypertensive dose of 1 mg/kg of body mass per day (Nif-L, $n=8$) or mild-antihypertensive dose of 3 mg/kg per day (Nif-H, $n=8$) from 12 to 19 weeks of age. The doses of nifedipine were determined from the results of a preliminary study. Nifedipine or vehicle was administered subcutaneously with an osmotic minipump (Alzet model 2ML2; Alza, Palo Alto, CA). DS rats maintained on the 0.3% NaCl diet after 7 weeks of age served as age-matched controls (Control, $n=8$). Each diet and tap water was provided ad libitum throughout the experimental period. Systolic blood pressure was measured weekly by the indirect tail-cuff method. At 19 weeks of age, rats were anesthetized by intraperitoneal injection of sodium pentobarbital (50 mg/kg) and the heart and lungs were removed for analysis.

2.2. Echocardiography and hemodynamics

At 19 weeks of age, rats were subjected to transthoracic echocardiography as described (Nagata et al., 2002). Left ventricular end-diastolic dimension and left ventricular end-systolic dimension as well as the thickness of the left ventricular posterior wall were measured. Fractional shortening was calculated as: [(left ventricular end-diastolic dimension − left ventricular end-systolic dimension)/left ventricular end-diastolic dimension] × 100%. After echocardiography, a 2-F high-fidelity manometer-tipped catheter (SPR-407; Millar Instruments) that had been calibrated relative to atmospheric pressure was introduced through the right carotid artery into the left ventricle. Tracings of left ventricular pressure and the electrocardiogram were digitized to determine left ventricular end-diastolic pressure.

2.3. Histology

Transverse sections (thickness, 3 μm) from the left ventricle were prepared from paraffin-embedded tissue and stained either with hematoxylin–eosin for routine histological examination or with Azan Mallory solution for evaluation of fibrosis, as described (Nagata et al., 2006). The cross-sectional area of myocytes was determined from cells that were cut transversely and exhibited both a nucleus and an intact cell membrane; at least 100 cells were assessed per specimen, and the average value was used for analysis. The extent of fibrosis was determined at the papillary muscle level as a percentage of the total area of the myocardium with the use of Image Processor for Analytical Pathology (IPAP) software (Sumika Technoservice).

2.4. Quantitative RT-PCR analysis

Total RNA was extracted from left ventricular tissue, and the abundance of specific mRNAs was determined by reverse transcription (RT) and real-time polymerase chain reaction (PCR) analysis with a Prism 7700 Sequence Detector (Perkin-Elmer, Foster City, CA), as described (Nagata et al., 2002). The sequences of primers and TaqMan probes specific for atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), β-myosin heavy chain (β-MHC), collagen types I or III, matrix metalloproteinase (MMP)-2 or -9, tissue inhibitor of MMP (TIMP)-2, connective tissue growth factor (CTGF), and the $p22^{phox}$ or $gp91^{phox}$ subunits of NADPH oxidase were described previously (Nagata et al., 2002; Ichihara et al., 2006). TaqMan rodent glyceraldehyde-3-phosphate dehydrogenase (GAPDH) control reagents (Perkin-Elmer) were used for detection of GAPDH mRNA as an internal standard.

2.5. Immunoblot analysis

Tissue samples (80 μg of protein) were isolated from left ventricular tissues as previously described (Cheng et al., 2008) and subjected to immunoblot analysis with antibodies to $p22^{phox}$ (1:1000 dilutions; both from Santa Cruz Biotechnology, Santa Cruz, CA) or $gp91^{phox}$ (1:1000 dilutions; BD Transduction Laboratories, Lexington, NY). Antibodies to GAPDH (Santa Cruz Biotechnology) were used to confirm equal loading samples.

2.6. Zymography

In vitro gelatin zymography was performed as previously described (Saka et al., 2006). Given that this method may overestimate net functional activity of MMPs as a result of dissociation of MMP-TIMP complexes induced by SDS, we also performed film in situ gelatin zymography with the use of a kit (MMP in situ Zymo-Film, Wako) (Sakata et al., 2004) and in the absence or presence of TIMP-2 (1 μg/ml; Sigma-Aldrich), the broad-spectrum MMP inhibitor GM6001 (10 μmol/l; Calbiochem), or the serine protease inhibitor phenylmethylsulfonyl fluoride (PMSF, 2 mmol/l; Sigma-Aldrich).

2.7. Superoxide production

NADPH-dependent superoxide production by homogenates from freshly frozen left ventricular tissue was measured with an assay based on lucigenin-enhanced chemiluminescence as described previously (Ichihara et al., 2006). Chemiluminescence was measured with a luminometer (20/20n; Turner, Sunnyvale, CA). Superoxide production in tissue sections was examined by dihydroethidium staining as described (Tojo et al., 2005). Dihydroethidium is rapidly oxidized by superoxide to yield fluorescent ethidium. They were then examined with a laser-scanning confocal microscope. For negative controls, we performed DHE staining after superoxide dismutase SOD (300 U/ml) incubation and confirmed that this procedure abolished the fluorescence (data not shown).

2.8. Glutathione redox ratio and oxidized glutathione

Left ventricular homogenates were prepared in 20 mmol/l phosphate buffer (pH 7.4) and assayed for total glutathione [reduced (GSH) plus oxidized (GSSG)] with the use of the glutathione reductase-based 5,5′-dithiobis (2-nitrobenzoic acid) recycling assay as previously

described (Ichihara et al., 2006). The amount of GSSG was determined by Griffith's method (Griffith, 1980).

2.9. Statistical analysis

Data are presented as means ± S.E.M. Differences among groups were assessed by one-way factorial ANOVA followed by Fisher's multiple-comparison test. A P value of <0.05 was considered statistically significant.

3. Results

3.1. Cardiac function, remodeling and gene expression

Heart rate did not differ significantly among the four groups of rats at 19 weeks of age (Table 1). Systolic blood pressure was higher in the Vehicle than in Control at 8 weeks of age and thereafter. Systolic blood pressure was reduced in Nif-H at 14 weeks and thereafter compared with that in Vehicle, but there was no difference in systolic blood pressure between Vehicle and Nif-L (Fig. 1). The ratio of left ventricular weight to body weight (an index of left ventricular hypertrophy) and the ratio of lung weight to body weight (an index of pulmonary congestion) were increased in Vehicle at 19 weeks compared with those in Control (Table 1). The left ventricular weight ratio was decreased in Nif-H, but not in Nif-L, whereas the lung weight ratio was decreased in both Nif-H and Nif-L compared with those in Vehicle.

Echocardiography revealed that the thickness of the left ventricular posterior wall was increased in Vehicle compared with that in Control, whereas it was reduced in Nif-H relative to that in Vehicle (Table 1). Left ventricular end-diastolic dimension and left ventricular fractional shortening did not differ significantly among the four groups.

Hemodynamic analysis revealed that the maximal first derivative of left ventricular pressure with respect to time (dP/dt_{max}) did not differ significantly among the four groups (Table 1). The pressure half-time ($T_{1/2}$), an index of left ventricular early-diastolic function, was increased in Vehicle, and this increase was attenuated in Nif-H and Nif-L. Left ventricular end-diastolic pressure was increased in Vehicle compared with that in Control, and this increase was again attenuated in both Nif-H and Nif-L.

Histological analysis revealed that the cross-sectional area of cardiomyocytes was increased in Vehicle relative to that in Control, and that the extent of load-induced cardiomyocyte hypertrophy was reduced in Nif-H, but not in Nif-L (Fig. 2A and B). Hemodynamic overload resulted in marked up-regulation of the expression of fetal-type cardiac genes, including those for ANP, BNP, and β-MHC, in Vehicle (Fig. 2C–E). The up-regulation of these genes was significantly inhibited in Nif-H. The extents of perivascular and interstitial fibrosis in the left ventricle were also increased in Vehicle, and these increases were reduced in both Nif-H and Nif-L (Fig. 3A–C). The amount of collagen type I mRNA in the left ventricle was increased in Vehicle relative to that in Control (Fig. 4A). This increase in collagen type I mRNA abundance was inhibited in both Nif-H and Nif-L. The ratio of collagen type I to type III mRNA levels was also increased in Vehicle compared with that in Control, and this increase was attenuated in both Nif-H and Nif-L (Fig. 4B). The abundance of CTGF mRNA was increased in Vehicle and this increase was also inhibited in both Nif-H and Nif-L (Fig. 4C).

The amount of MMP-2 mRNA (Fig. 4D) and the ratio of MMP-2 to TIMP-2 mRNA levels (Fig. 4E) were increased in Vehicle compared with those in Control, and these increases were attenuated in both Nif-H and Nif-L.

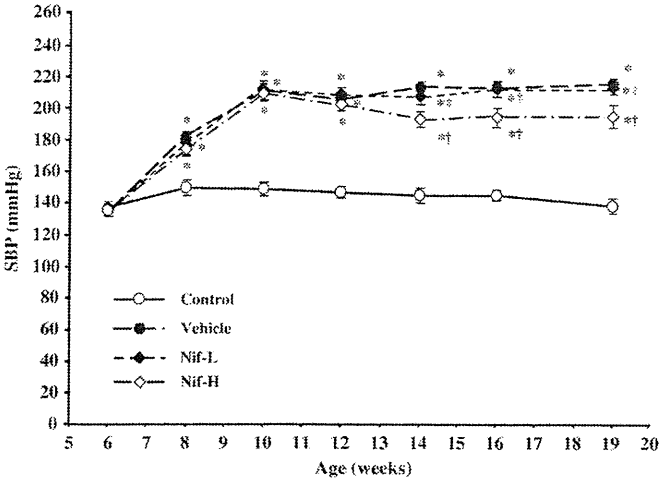

Fig. 1. Time course of systolic blood pressure in rats of the four experimental groups. Data are means ± S.E.M ($n = 8$ rats per group). *$P<0.05$ versus Control; †$P<0.05$ versus Vehicle; ‡$P<0.05$ versus Nif-H.

3.2. Gelatinolytic activity revealed by in vitro and in situ zymography

In vitro zymography revealed that the activity of MMP-2 was increased in Vehicle relative to that in Control and that this increase was significantly attenuated in both Nif-H and Nif-L (Fig. 4F). The activity of MMP-9 was not detected in rats of any of the four groups (data not shown). Net functional gelatinolytic activity, as assessed by in situ zymography, was also increased in Vehicle, and this increase was inhibited in both Nif-H and Nif-L (Fig. 5A). The activity apparent in Vehicle was sensitive to exposure of the slides to TIMP-2 or GM6001, but it was resistant to PMSF (Fig. 5B), suggesting that the observed gelatinolysis reflected MMP activity rather than activity of a serine protease such as plasmin or plasminogen activator.

3.3. Myocardial oxidative stress

Staining with dihydroethidium revealed that superoxide production in myocardial tissue sections was increased in Vehicle relative to that in Control, and that this increase was attenuated in both Nif-H and Nif-L (Fig. 6A). The amount of oxidized glutathione (GSSG) was increased (Fig. 6B) and the glutathione redox ratio (GSH/GSSG) was decreased (Fig. 6C) in Vehicle compared with those in Control. These differences were attenuated in both Nif-H and Nif-L. The activity of NADPH oxidase (Fig. 6D) as well as the amounts of mRNAs and proteins for the $p22^{phox}$ and $gp91^{phox}$ subunits of this enzyme (Fig. 6E–G) in the left ventricle

Table 1
Echocardiographic, hemodynamic, and other parameters in rats of the four experimental groups at 19 weeks of age.

Parameter	Control	Vehicle	Nif-L	Nif-H
Heart rate (beats/min)	461 ± 9	475 ± 19	473 ± 19	480 ± 6
SBP (mm Hg)	155 ± 2	233 ± 5[a]	230 ± 5[a,c]	212 ± 5[a,b]
LVW (mg)/BW (g)	2.2 ± 0.1	3.7 ± 0.5[a]	3.2 ± 0.2[a]	2.9 ± 0.1[a,b]
LungW (mg)/BW (g)	3.5 ± 0.1	5.9 ± 1.0[a]	3.6 ± 0.1[b]	3.6 ± 0.1[b]
LVPWT (mm)	1.9 ± 0.1	2.4 ± 0.1[a]	2.2 ± 0.0	2.1 ± 0.0[b]
LVDd (mm)	7.2 ± 0.2	7.8 ± 0.4	7.7 ± 0.1	7.4 ± 0.2
LVFS (%)	44 ± 2	41 ± 1	46 ± 1	45 ± 3
dP/dt_{max} (mm Hg/s)	9774 ± 735	9320 ± 435	9609 ± 692	9753 ± 1058
$T_{1/2}$ (ms)	3.3 ± 0.1	5.9 ± 0.5[a]	4.7 ± 0.4[a,b]	4.2 ± 0.1[a,b]
LVEDP (mm Hg)	4 ± 1	12 ± 1[a]	8 ± 1[a,b]	6 ± 1[b]

Abbreviations not defined in text: SBP, systolic blood pressure; LVW, left ventricular weight; BW, body weight; Lung W, lung weight; LVPWT, left ventricular posterior wall thickness; LVDd, left ventricular end-diastolic dimension; LVFS, left ventricular fractional shortening; LVEDP, left ventricular end-diastolic pressure. Data are means ± S.E.M ($n = 8$ animals per group).

[a] $P<0.05$ versus Control.

[b] $P<0.05$ versus Vehicle.

[c] $P<0.05$ versus Nif-H.

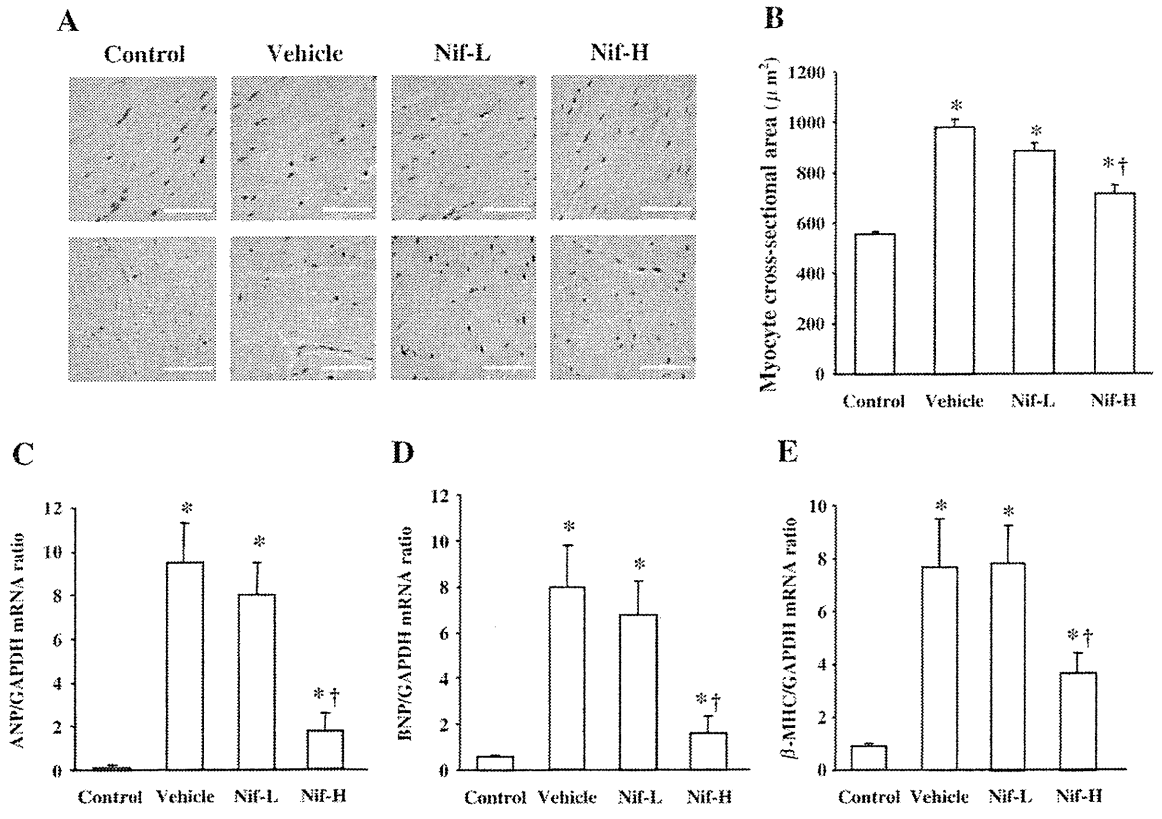

Fig. 2. Cardiomyocyte size and expression of fetal-type cardiac genes in the left ventricle of rats of the four experimental groups at 19 weeks of age. (A) Hematoxylin-eosin staining of transverse sections of the left ventricular myocardium. Scale bars, 50 μm. (B) Cross-sectional area of cardiac myocytes determined from sections similar to those shown in (A). (C–E) Quantitative RT-PCR analysis of ANP, BNP, and β-MHC mRNAs, respectively. The abundance of each mRNA was normalized by that of GAPDH mRNA. Data in (B) through (E) are means ± S.E.M ($n = 8$). *$P<0.05$ versus Control; †$P<0.05$ versus Vehicle.

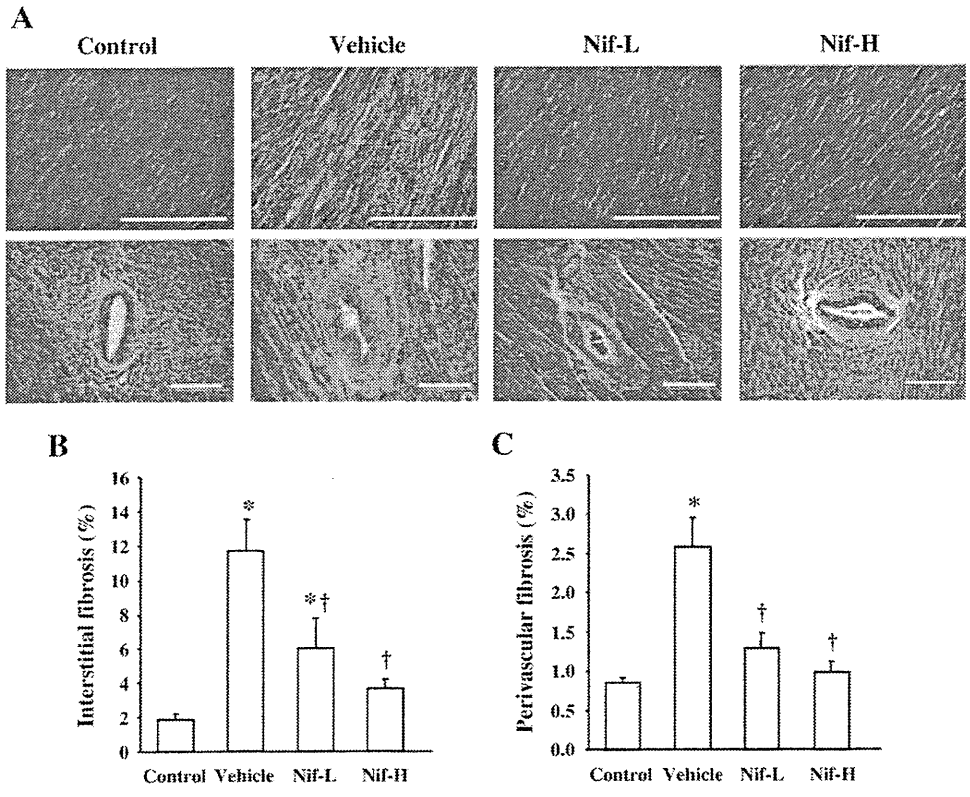

Fig. 3. Fibrosis in the left ventricle of rats of the four experimental groups. (A) Azan Mallory staining of transverse sections of the left ventricular myocardium for interstitial (upper panels) and perivascular (lower panels) fibrosis. Scale bars, 200 μm. (B, C) Areas of interstitial and perivascular fibrosis, respectively, determined from sections similar to those shown in (A). Data in (B) and (C) are means ± S.E.M ($n = 8$). *$P<0.05$ versus Control; †$P<0.05$ versus Vehicle.

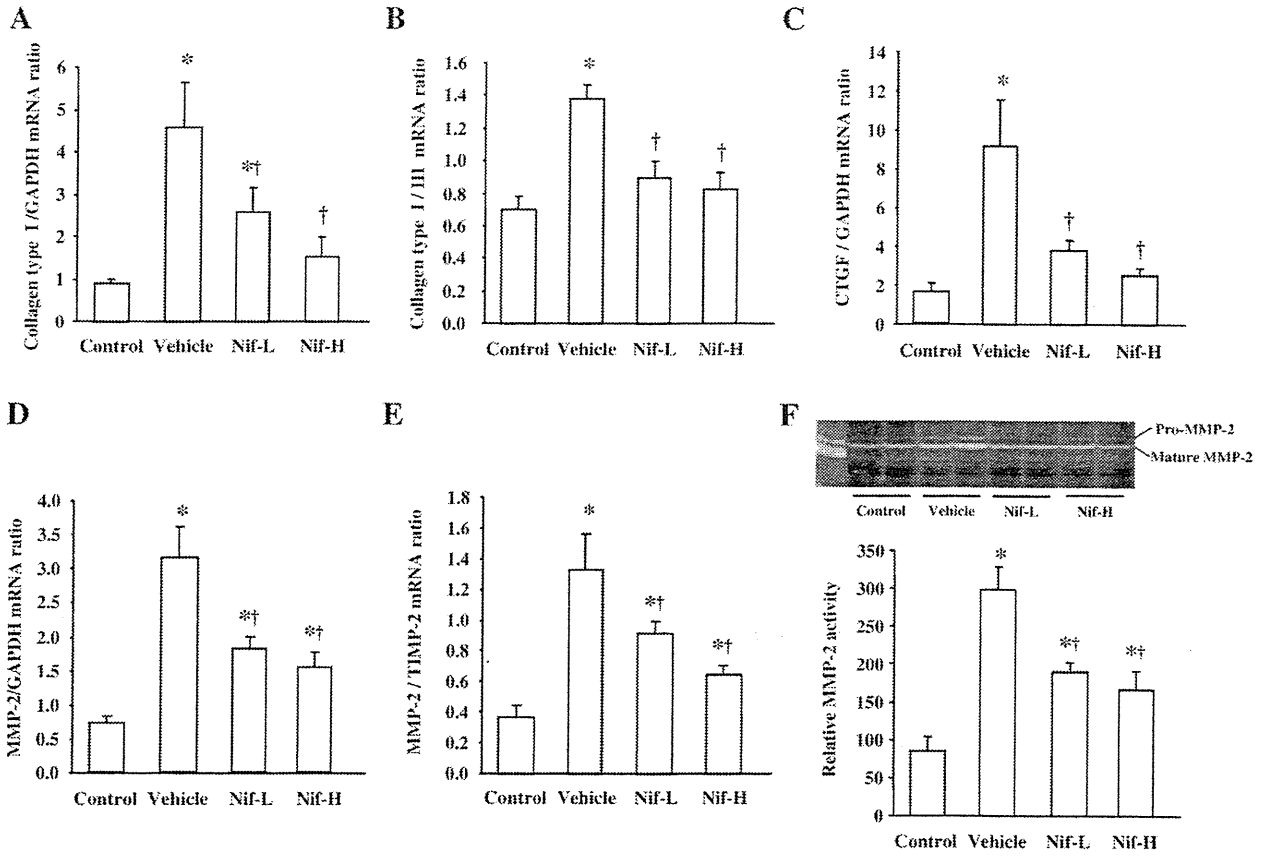

Fig. 4. The amounts of collagen, CTGF, and MMP-2 gene expression as well as MMP-2 activity in the left ventricle of rats of the four experimental groups. (A, B) Quantitative RT-PCR analysis of collagen type I mRNA (A) and the collagen type I/III mRNA ratio (B), respectively. (C, D, E) Quantitative RT-PCR analysis of CTGF mRNA (C), MMP-2 mRNA (D) and the MMP-2/TIMP-2 mRNA ratio (E), respectively. (F) Gelatin zymography of MMP-2 activity. A representative gel is shown in the upper panel, with the gelatinolytic bands corresponding to the pro and mature forms of MMP-2 indicated. The total amount of MMP-2 activity was determined by densitometric analysis (lower panel). Quantitative data in all panels are means ± S.E.M ($n = 8$). *$P<0.05$ versus Control; †$P<0.05$ versus Vehicle.

were increased in Vehicle, and these increases were reduced in both Nif-H and Nif-L. The NADPH-dependent production of superoxide in left ventricular homogenates of all groups of rats was largely abolished by the flavoprotein inhibitor diphenyleneiodonium (data not shown), suggesting that NADPH oxidase was the likely source of the superoxide.

4. Discussion

In this study, we have shown that long-term administration of nifedipine reduced myocardial oxidative stress as well as attenuated the progression of myocardial collagen remodeling and the development of

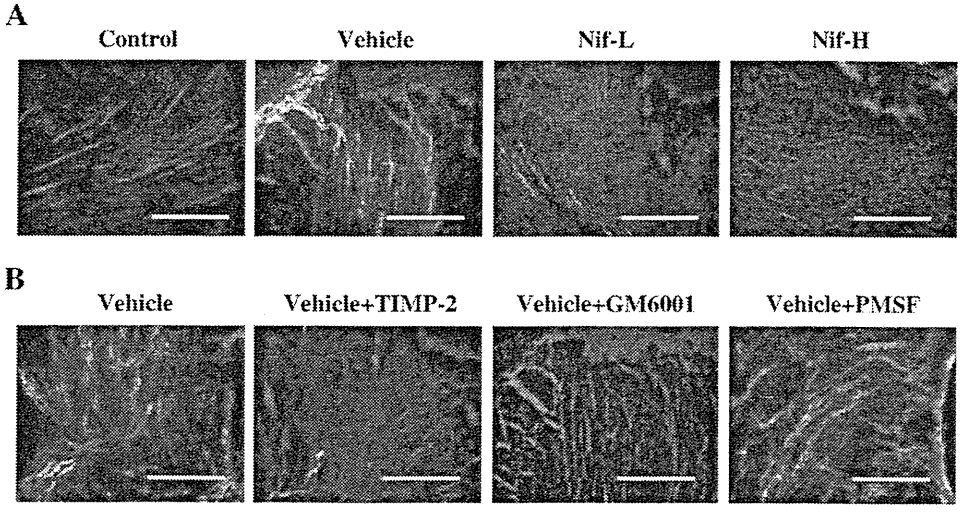

Fig. 5. Net gelatinolytic activity as revealed by film in situ zymography in the left ventricle of rats of the four experimental groups. (A) Representative sections for rats of each experimental group. Bright areas under the light microscope represent gelatinolytic activity. (B) Sensitivity of gelatinolytic activity to TIMP-2, GM6001, or PMSF in sections from Vehicle. Scale bars, 600 μm.

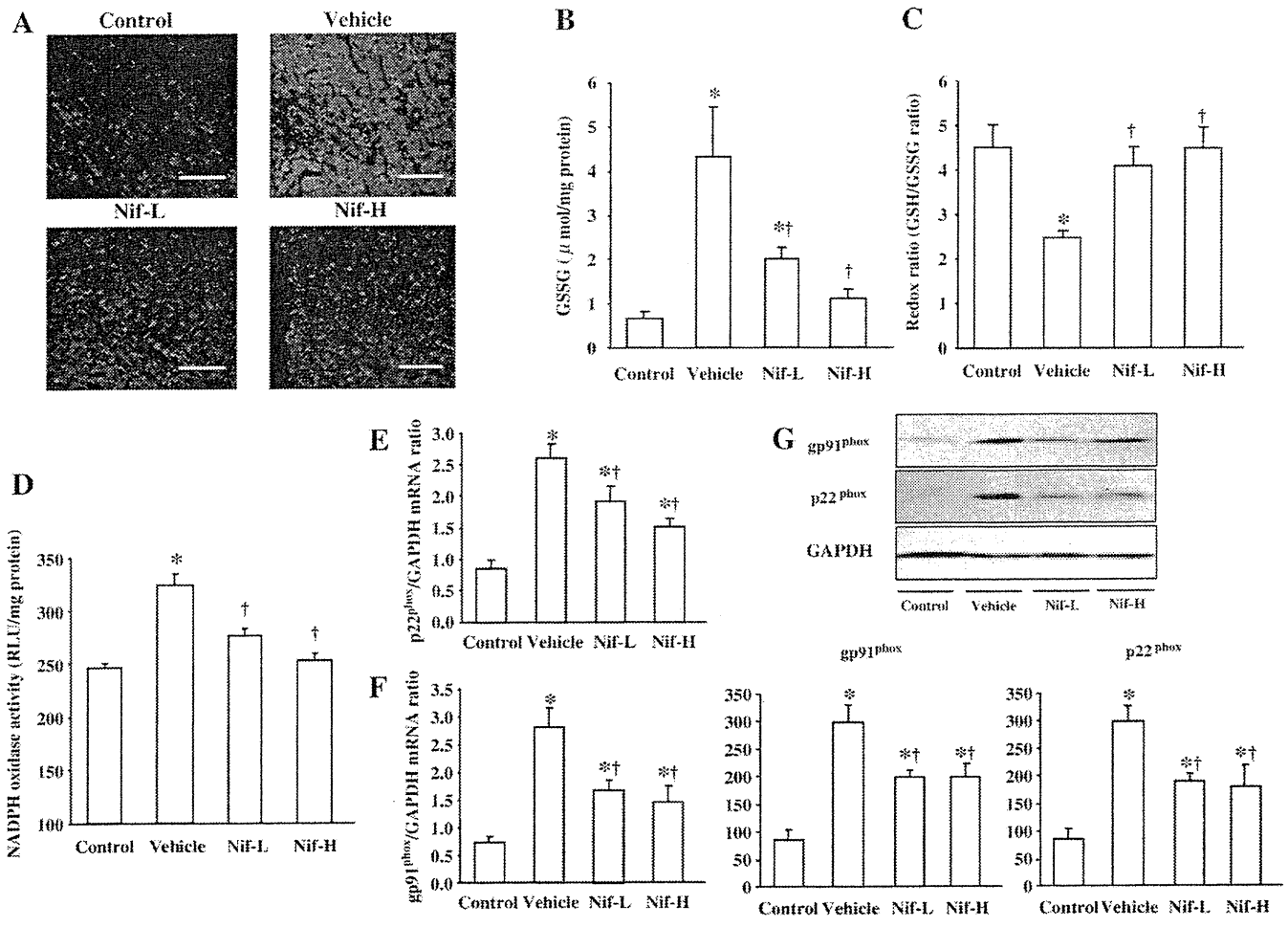

Fig. 6. Superoxide production, glutathione redox status, as well as NADPH oxidase activity and gene expression in the left ventricle of rats of the four experimental groups. (A) Dihydroethidium staining of sections of the left ventricle for the superoxide anion in the left ventricle of rats of the four experimental groups. Scale bars, 100 μm. (B, C) The abundance of GSSG (B) and the GSH/GSSG ratio (C), respectively, in left ventricular tissue. (D) NADPH oxidase activity in left ventricular homogenates. Data are expressed as relative light units (RLU) per milligram of protein. (E, F) Quantitative RT-PCR analysis of $p22^{phox}$ (E) and $gp91^{phox}$ (F) mRNAs, respectively. (G) Immunoblot analysis of NADPH oxidase subunits of the left ventricle. Representative blots are shown in the upper panel, and quantitative data are shown in lower panel; band intensity was normalized by that for GAPDH. Quantitative data in all panels are means ± S.E.M ($n = 8$). *$P < 0.05$ versus Control; †$P < 0.05$ versus Vehicle.

diastolic heart failure, in a manner independent of its antihypertensive effect, in DS rats fed a high-salt diet.

Nif-H, mild-antihypertensive dose of nifedipine, significantly inhibited the progression of both cardiac hypertrophy and fibrosis, though this antihypertensive effect was not enough to normalize the blood pressure to the level of Control level. Whereas, Nif-L, a non-antihypertensive dose of nifedipine, significantly inhibited the progression of cardiac fibrosis but not hypertrophy, though it did not reduce blood pressure. The overall protective action of nifedipine is likely attributable to its antioxidant effect as well as to the observed reduction in systolic blood pressure. Evidence indicates that cardiomyocyte hypertrophy is primarily load dependent, whereas fibroblast growth is mostly load independent (Manabe et al., 2002). Our present results are consistent with the notion that a reduction in load inhibits the development of cardiac hypertrophy, and they suggest that the antioxidant properties of nifedipine are largely responsible for its inhibitory effect on the development of myocardial fibrosis.

Cardiac remodeling results from an imbalance between the synthesis and degradation of extracellular matrix proteins and is thought to be central to the pathophysiology of heart failure (Spinale et al., 2000). Collagen constitutes up to 85% of extracellular matrix in the heart (Heeneman et al., 2003), with the myocardial collagen network consisting predominantly of collagen types I and III (Marijianowski et al., 1995). Whereas collagen type I confers rigidity, collagen type III contributes to tissue elasticity. Collagen type I is thus thought to be a major determinant of myocardial stiffness (Heeneman et al., 2003), and an increase in the ratio of collagen type I to type III mRNA levels has been associated with increased myocardial stiffness (Nishikawa et al., 2001). In the present study, the ratio of collagen type I to type III mRNA levels in the left ventricle was increased in Vehicle, and this increase was attenuated in both Nif-H and Nif-L. These data are consistent with previous results showing that the long-acting Ca^{2+} channel blocker amlodipine attenuated myocardial stiffening and inhibited the phenotypic shift from collagen type III to type I in the left ventricular myocardium of the same rat model (Nishikawa et al., 2001). The synthesis of collagen type I in cardiac fibroblasts is inhibited by antioxidants (Chen et al., 2004), suggesting that the ratio of collagen type I to type III mRNA levels might be regulated by oxidative stress.

MMPs and TIMPs are important players in extracellular matrix degradation (Nagase and Woessner, 1999). The relative levels of MMP-2 and MMP-9 are increased in the left ventricular myocardium of humans with end-stage heart failure (Spinale et al., 2000). Reactive oxygen species also stimulate MMP production by macrophage-derived foam cells in atherosclerotic plaques (Grote et al., 2003). The activation of MMP-2 was found to accompany progressive myocardial fibrosis and was independent of left ventricular dilation, whereas MMP-9 was activated in the dilation phase of heart failure in rats (Nishikawa et al., 2003; Sakata et al., 2004). Consistent with these observations, in the present study, the activity of MMP-2, but not that of MMP-9, was increased in Vehicle, which did not manifest left

ventricular dilation. The increases in MMP-2 mRNA and activity levels apparent in Vehicle were attenuated in both Nif-H and Nif-L.

An imbalance between MMPs and their specific inhibitors (TIMPs) is thought to contribute to pathological remodeling of the heart. Expression of TIMP-2 was shown to be increased in the left ventricular myocardium of rats with diastolic heart failure (Sakata et al., 2004), possibly reflecting a compensatory mechanism to counteract the associated increase in MMP expression. We found that the ratio of MMP-2 to TIMP-2 mRNAs was increased in Vehicle and that this increase was inhibited in both Nif-H and Nif-L. Deposition of new extracellular matrix in response to up-regulation of MMP activity is an important aspect of the overall process of tissue remodeling, and stimulation of extracellular matrix synthesis by products of extracellular matrix degradation has been demonstrated in the heart (Kim et al., 2000). Our present results thus suggest that inhibition of the increase in MMP-2 activity by treatment with nifedipine might prevent extracellular matrix degradation and consequent synthesis of new extracellular matrix.

Evidence from experimental models of heart failure shows that oxidative stress is increased in the failing heart and contributes to the pathophysiological changes associated with heart failure (Dhalla et al., 2000). A major source of reactive oxygen species in cardiovascular cells, including vascular smooth muscle cells, endothelial cells, and adventitial fibroblasts, is a phagocyte-type NADPH oxidase (Griendling et al., 2000). The $p22^{phox}$ and $gp91^{phox}$ subunits of NADPH oxidase have also been shown to be expressed in cardiomyocytes, and reactive oxygen species generation by this enzyme was shown to contribute to the progression of cardiac hypertrophy to heart failure (Heymes et al., 2003; Li et al., 2002). In addition, reactive oxygen species levels, NADPH oxidase activity, and the expression of $p22^{phox}$ and $gp91^{phox}$ were recently shown to be increased in the myocardium of DS rats fed a high-salt diet (Guo et al., 2006). Consistent with these observations, we found that both NADPH-dependent superoxide generation and the abundance of $p22^{phox}$ and $gp91^{phox}$ mRNAs and proteins were increased and that the GSH/GSSG ratio was decreased in Vehicle. Furthermore, all of these changes in Vehicle were attenuated in Nif-L as well as in Nif-H. Expression of $p22^{phox}$ is regulated in a redox-sensitive manner in endothelial cells (Djordjevic et al., 2005), suggesting that nifedipine might inhibit the expression of this NADPH oxidase component through its antioxidant effect. Regardless, these data suggest that nifedipine inhibited the development of myocardial oxidative stress in a manner independent of its antihypertensive effect.

Whereas the activity of NADPH oxidase in rats treated with nifedipine was similar to that in control rats, the amounts of $p22^{phox}$ and $gp91^{phox}$ mRNAs and proteins in the nifedipine-treated rats remained substantially greater than those in control rats. This apparent discrepancy might be attributable to the fact that the active NADPH oxidase complex is composed of both membrane-associated ($p22^{phox}$, $gp91^{phox}$) and cytosolic (Rac, $p67^{phox}$, $p47^{phox}$, $p40^{phox}$) components (Bokoch and Diebold, 2002), with a deficiency in a cytosolic component possibly limiting enzyme activity in the nifedipine-treated rats. On the other hand, it has been reported that a number of dihydropyridine Ca^{2+} channel blockers have mineralocorticoid receptor antagonist activity (Jessica et al., 2008), suggesting that nifedipine may exert its antioxidant effect through inhibition of mineralocorticoid receptor. However, the mechanism underlying antioxidant effect of nifedipine still is unclear in this study. Further study is required for elucidation of its antioxidant effect.

In this study, we have shown that the development of cardiac hypertrophy was inhibited by a high dose, but not by a low dose of nifedipine in DS rats, whereas the progression of cardiac fibrosis was blocked by either dose of the drug. Furthermore, Nif-L inhibited the production of superoxide in the left ventricular myocardium and ameliorated myocardial stiffening significantly in a manner independent of its antihypertensive effect. This latter effect was likely attributable, at least in part, to inhibition both of the deposition of extracellular matrix and of the shift in collagen phenotype from type III to type I associated with oxidative stress. In addition, our results obtained with the same drug as that used in the ACTION trial suggest that the observed clinical effects of nifedipine in this trial might have been attributable in part to a reduction in myocardial oxidative stress. Nifedipine may thus be beneficial for the treatment of hypertensive heart disease not only as a result of its antihypertensive action but also because of its antioxidant effect.

Acknowledgements

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INCREASED CAREGIVER BURDEN ASSOCIATED WITH HEARING IMPAIRMENT BUT NOT VISION IMPAIRMENT IN DISABLED COMMUNITY-DWELLING OLDER PEOPLE IN JAPAN

To the Editor: It has been demonstrated that older people feel that hearing and vision impairments are substantially disabling, that these impairments are associated with lower-than-average quality of life, and that they predict future loss of functional abilities and independence.[1–5] However, whether these sensory impairments add to the burden of caregivers of disabled older people living in the community has not been evaluated.

The present study examined the association between vision or hearing impairment in community-dwelling older people with disabilities and the subjective burden of their caregivers. The study used baseline data on care recipient and family caregiver pairs in the Nagoya Longitudinal Study for Frail Elderly.[6,7] The study population consisted of 1,208 community-dwelling older people (448 men and 760 women; mean age ± standard deviation 80.9 ± 7.8, range 65–104) and paired caregivers (286 men and 922 women; mean age 64.7 ± 12.4, range 31–90). The baseline data included the recipients' demographic characteristics and basic activities of daily living (ADLs), physician-diagnosed chronic conditions including dementia, the presence of behavioral problems, living arrangement, and history of falls in the previous 6 months. Data were also obtained from caregivers concerning their own personal demographic characteristics, including caregiver relationship to care recipient, and the caregiver's subjective burden as assessed according to the Japanese version of the Zarit Burden Interview (ZBI),[8] which has an 88-point scale, with higher values indicating greater burden. The primary caregivers were also asked to rate their own current overall health in three categories of subjective health status. Recipients with vision or hearing impairment were identified according to a yes answer to the following question: "Do you have trouble seeing or hearing for daily life, even when wearing glasses or using a hearing aid?" When the recipients were unable to answer or had cognitive impairment, surrogates or caregivers were asked. The Student *t*-test and analysis of covariance (ANCOVA) were used to compare caregiver ZBI scores for recipients with and without sensory impairment. Covariates of ANCOVA included recipient sex, age, ADL score, presence or absence of dementia and behavior problems and caregiver sex, age, and subjective health status. To determine which variables were associated with ZBI score, a stepwise multiple linear regression analysis with a forward selection strategy was performed, using an F value with $P<.05$ as the selection criterion. All analyses were performed using SPSS version 16.0 (SPSS, Inc., Chicago, IL).

Table 1. Stepwise Multiple Linear Regression of Care Recipients' and Caregivers' Variables on Zarit Burden Interview Score

Variable	B	Standard Error	β	*P*-Value
Care recipient sex male	−2.610	1.063	−0.074	.01
Care recipient age	−0.181	0.072	−0.081	.01
ADL score (range 0–20)	−0.521	0.090	−0.176	<.001
Fall in previous 6 months	2.852	1.065	0.079	.008
Presence of behavioral problems	8.402	1.464	0.197	<.001
Presence of dementia	3.622	1.242	0.103	.004
Hearing impairment	3.645	1.160	0.100	.002
Health status of caregiver	3.344	0.773	0.130	<.001

Coefficient of determination (R^2) = 0.176; adjusted R^2 = 0.170.
The following variables were added to the analysis: care recipient age and sex, fall history in the previous 6 months, living arrangement, activity of daily living (ADL) scores, presence of dementia and behavioral problems, number of community-based services used, age and sex of caregiver, type of caregiver–care recipient relationship (spouse, child, daughter-in-law), and subjective health status of caregiver.

Of the care recipient participants, 334 (28.5%) had vision impairment and 387 (32.1%) had hearing impairment. Participants with impairment in vision or hearing were older on average. Although no difference in average caregiver ZBI score was observed between recipients with and without vision impairment (with vision impairment mean ± standard error, 29.8 ± 0.9; without 28.4 ± 0.6, $P=.22$ on Student *t*-test), a significantly higher average caregiver ZBI score was detected for recipients with hearing impairment than for those without (with hearing impairment, 31.3 ± 0.9; without 27.8 ± 0.6, $P<.001$). This statistical significance persisted even after adjusting for confounders (ANCOVA, with hearing impairment, 31.6 ± 0.9; without 27.4 ± 0.6, $P<.001$).

The stepwise multiple regression analyses revealed that the best set of predictors of caregiver burden was recipient sex, age, ADL score, fall history in the previous 6 months, presence or absence of dementia and behavioral problems associated with dementia, and hearing status and health status of caregiver (Table 1).

The present study demonstrated for the first time that hearing impairment of elderly care recipients is associated with greater caregiver burden. This association persists even after controlling for various possible confounding factors such as ADL status and the presence of chronic diseases, including dementia. However, vision impairment of recipients was not associated with caregiver burden. It has been reported that caregivers who desired more communication with patients had significantly higher caregiver burden scores than did caregivers who did not.[9] It is possible that hearing impairment of care recipients may affect recipient–caregiver communication more strongly than vision impairment.

There are potential limitations in this study. Hearing ability and visual activity were not evaluated using audiometry or direct measurement of visual acuity. Therefore, the evaluation of impairments may not be accurate. The present findings may not be generalizable to other populations given

that health practices, a variety of social and economic factors, ethnic attitudes about caring for very old people, and the cost of health care may have influenced these results.

In conclusion, these results suggest that hearing impairment of care recipient is associated with caregiver burden in Japan, even after adjusting for potential confounders. It is possible that improvement in hearing or correcting hearing impairment may lead to reduced caregiver burden.

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STROKE IN ELDERLY PEOPLE: A GREAT CHALLENGE FOR THE 21ST CENTURY

To the Editor: The recent population-based epidemiological studies covering the end of the 20th and the beginning of the 21st centuries have largely contributed to emphasizing the burden of stroke in elderly people in developed countries.[1–3] Their findings have provided clear evidence of a dramatic increase in the absolute number of cerebrovascular events in people aged 80 and older over the last past 20 years due to the aging of the population of these countries. Hence, the profile of patients admitted to stroke units and emergency departments has changed considerably, because the mean age at stroke onset is now significantly older than in the past.[1–3] Nevertheless, randomized clinical trials conducted so far have systematically excluded elderly people from enrollment. As a result, these patients have been denied the opportunity to benefit from therapeutic strategies, including thrombolysis, whose efficacy in reducing mortality and handicap after ischemic stroke has been demonstrated in younger patients.[4] Consequently, for physicians, there is currently a lack information concerning evidence-based acute therapeutic strategies to use in patients aged 80 and older in day-to-day practice of vascular neurology. The problem is similar for secondary prevention, which is consequently limited in this age group, particularly concerning the use of anticoagulants in elderly patients with stroke with atrial fibrillation.

The absence of such strategies is alarming, given that demographic projections clearly indicate that the number of elderly people is expected to increase. Hence, in Europe, the proportion of the population aged 65 and older, in which most stroke events occur, will increase from 20% in 2000 to 35% in 2050, leading to continued growth in the number of older stroke patients in the community.[5] Therefore, the improvement in stroke outcome observed between the end of the 20th century and the beginning of the 21st,[3] which is related, at least in part, to better acute management of patients, will probably be rapidly annihilated if elderly people continue to be excluded from large randomized trials. Furthermore, such a scenario would inevitably be associated with a considerable socioeconomic effect, because older stroke patients have a longer hospital stay and are less likely to be discharged to their original place of residence.[6]

Epidemiological studies have played their role by pointing out the threat of the increasing burden on healthcare systems of stroke in elderly people. It is now essential and urgent for scientists to design new clinical trials recruiting patients aged 80 and older to provide the means to respond to this demographic evolution.

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地域在住高齢者のQuality of Life（QOL）と慢性疾患およびその発症との関連性
—4年間の縦断調査の結果から—

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要　約　目的：地域在住高齢者の4年間の縦断調査の結果から，慢性疾患の有無とその発症が生活の質（Quality of Life：QOL）とその変化に及ぼす影響について検討する．**方法**：65歳以上の地域在住高齢者2,762人（男性：47.0%，平均年齢±SD：76.7±5.8歳）に対し，脳卒中，高血圧，心臓病，癌，糖尿病，骨折，胃腸病，肺や気管支の病気，関節や筋肉の病気の9つの慢性疾患の有無とQOLに関する調査を行い，4年後に同様の調査をした．QOLの評価は「生活活動力」，「健康満足感」，「人的サポート満足感」，「経済的ゆとり満足感」，「精神的健康」，「精神的活力」の6つの下位尺度から成る「地域高齢者のためのQOL質問表」を用いた．初回に疾患がなく，4年間で発症がないものを，「疾患なし・発症なし」群，初回に疾患がなく，4年間で9つの疾患のいずれか1つ以上が発症したものを「疾患なし・発症あり」群，初回に疾患があり，4年後にもありと答えたものを，「疾患あり」群の3群に分けた．初回のQOL得点をベースライン値とし，3群間で比較した．さらに各下位項目について，4年間の変化量と割合を算出し，この変化の大きさを3群間で比較した．**結果**：ベースライン値では，「人的サポート満足感」以外で，疾患の有無による差が見られ，「健康満足感」と「精神的健康」において3群間に有意差があった．4年間の変化についても「疾患なし・発症あり」群で「健康満足感」と「精神的活力」の低下が大きく，「疾患あり」群では「生活活動力」の低下がみられた．**結論**：慢性疾患の有無とその発症がQOLとその変化に及ぼす影響について，1）慢性疾患のある人はない人に比べ，QOLが低かった．2）新たに疾患が発症するとQOLは低下した．3）1）および2）において，QOL下位項目が一様に影響を受けるわけではなく，慢性疾患の有無や経時的変化においては，影響を受ける項目とそうでない項目がみられた．

Key words：Quality of Life（QOL），慢性疾患，地域在住高齢者，縦断調査

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はじめに

地域在住の高齢者はしばしば慢性疾患を有しており，複数の疾患を持つことも多いが，それにも関らず比較的自立した生活を送っている．長寿社会となり，日本人の平均寿命は延びているが，高齢者の生活の質（Quality of Life：QOL）を考えるとき，第一に考慮すべきはやはり健康であろう．

健康関連QOLを測定する評価法は，効用値などを測定する選好に基づく尺度と，健康を多次元的に測定するプロファイル型尺度がある．プロファイル型はQOLに含まれるさまざまなドメインを1つにまとめず，多次元（multi-dimension）のままに表現するものである．プロファイル型尺度はさらに，症状インデックス尺度，包括的尺度，疾患特異性尺度に分類される．包括的尺度は，さまざまな疾患をもつ人や一般に健康といわれる人に共通する要素によって構成される．すなわち，身体機能（Physical Functioning），メンタル・ヘルス（Mental Health），日常役割機能（Role Functioning），社会生活機能（Social Functioning）などである．したがって，包括的尺度は病気にかかっている人の健康関連QOLから，一般的に健康といわれる人の健康関連QOLまでを連続的に測定できるし，疾患が異なっていても健康状態の比較が可能である[1)]．

SF-36はこれら4項目をすべて含んでいる[2)~5)]が疾患特異性はない．疾患特異性がない評価法は経過を追うには不利であるが，広い範囲をカバーしているので全体を概観するには適している．一方，疾患特異的な評価法は

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経過を追うには便利だが，患者のQOL全体を評価するには適していない．

我々はすでに，地域在住高齢者のQOLと認知機能の関連性を報告してきた[6]が，高齢者は治療を必要とする何らかの，場合によっては複数の疾患をかかえていることもあり，身体的・心理的影響だけでなく，服薬や医療費などの負担がQOLに影響を与えると考えられる．

本研究は，地域において生活する比較的自立度の高い住民を対象としているが，身体的自立と疾患の有無は必ずしも相関しない場合がある．疾患とQOLの関連性については，それぞれの疾患の患者に特有の評価を行う疾患特異性尺度が用いられ，さまざまな疾患のQOL評価が報告されている[7)~11)]．しかし，地域在住高齢者のように，治療中の疾患があっても自立度が高い場合は，個々の疾患についてのQOL評価ではなく，「生活者としての高齢者」のQOLを包括的に評価する必要がある．これまで，自立した在宅高齢者において，治療中の疾患の有無やその発症と，それらがQOLに及ぼす影響についての報告はあまり見られない．

今回我々は4年間の縦断調査の結果から，慢性疾患の有無とその発症が高齢者のQOLとその変化に及ぼす影響について，1）慢性疾患を持っている人とそうでない人ではQOLに違いがあるか，2）新たに疾患が発症するとQOLに変化が出るか，3）1）および2）において，QOLの下位項目間の違いはあるかについて検討したので報告する．

対象と方法

2002年に，愛知県O市の65歳以上の全住民を対象に郵送による自記式の生活実態調査を実施し，その際，継続して調査への協力を依頼した．2006年に同市の65歳以上の全住民を対象に同様の調査を実施し，そのうち2002年に継続調査への同意が得られている対象者2,762人（男性：47.0%，平均年齢±SD：76.7±5.8歳）について，2回の調査結果を結合した．調査内容は調査時点での疾病の有無，自立度，栄養や身体活動，QOL等に関するものであり，生活実態調査全体の有効回答率は2002年は65.1%，2006年は62.1%であった．

疾病の有無に関して，初回の調査時に，治療中の疾患として，脳卒中，高血圧，心臓病，癌，糖尿病，骨折，胃腸病，肺や気管支の病気，関節や筋肉の病気の9つの慢性疾患を選択肢として，複数回答で答えてもらった．これらの疾患は高齢者におけるcommon diseasesであり，先行研究においても同様の疾患が選ばれている[12)13)]．神経疾患やうつ病などの精神疾患は，QOLの評価が身体疾患とは異なる面があり，また，今回のような自記式調査の場合，これらの疾患の記載がなされない可能性もあり除外した．治療中の定義は，上記疾患により服薬，その他の理由で定期的に医療機関に通院しているものとした．これらの疾患のいずれかを1つ以上選択した人を「疾患あり」群とした．治療中の病気はないと答えた人を「疾患なし」群とした．4年後の調査で同様の質問をし，初回に疾患がなく，4年間で発症がないものを，「疾患なし・発症なし」群，初回に疾患がなく，4年間で9つの疾患のいずれか1つ以上が発症したものを「疾患なし・発症あり」群，初回に疾患があり，4年後にもありと答えたものを「疾患あり」群の3群に分けた．

QOLの評価はすでに報告した，「地域高齢者のためのQOL質問表」[14)]を用いた．これは，「生活活動力」(5点満点)，「健康満足感」(3点満点)，「人的サポート満足感」(3点満点)，「経済的ゆとり満足感」(2点満点)，「精神的健康」(3点満点)，「精神的活力」(3点満点）の6つの下位尺度より成り，各尺度に2~5つの質問が含まれる．各尺度の回答は「はい」と「いいえ」の二者択一であり，点数は好ましい回答を1点，好ましくない回答を0点とした場合の合計点とした．

今回の解析では，2002年のQOL得点をベースライン値とし，「疾患なし・発症なし」群，「疾患なし・発症あり」群，「疾患あり」群の3群間で比較した．さらに各下位項目について，2002年を基準とした2006年の変化量と満点に対する割合を算出し，この変化の大きさを3群間で比較した．対象者の年齢の検定にはOne-way ANOVA，2002年のQOL各項目の基礎値および4年間の変化量の群間検定はSteel-Dwass testを用いた．統計処理はすべてSPSS ver. 17.0 for Windowsを用いて行った．

調査に関しては，国立長寿医療センター，認知症介護研究・研修大府センターの各倫理委員会の承認を得た．解析時には，データはすべてID番号で管理し，個人情報は別途，管理した．

結　果

対象者は「疾患なし・発症なし」群566人（男性：54.9%，平均年齢±SD：75.7±6.0歳)，「疾患なし・発症あり」群419人（45.3%，76.0±5.5歳)，「疾患あり」群1,782人（44.7%，77.2±5.8歳）であった．平均年齢は「疾患あり」群で他の2群より有意に高かった（$p<0.001$）．

QOLの質問に無回答が含まれた対象者は除いたので，QOL下位項目について解析した人数は表1の如くであった．また，QOL下位項目の2002年におけるベース

表1　QOL下位項目得点（mean±SE）のベースライン値

群	（人数）	QOL基礎値（2002年）*	p-value†
生活活動力（5点満点）			
疾患なし・発症なし	(n = 516)	4.727±0.035	
疾患なし・発症あり	(n = 377)	4.695±0.044	< 0.001
疾患あり	(n = 1,510)	4.540±0.026	0.005
健康満足感（3点満点）			
疾患なし・発症なし	(n = 467)	2.685±0.035	
疾患なし・発症あり	(n = 328)	2.479±0.053	< 0.001
疾患あり	(n = 1,264)	1.951±0.033	< 0.001
人的サポート満足感（3点満点）			
疾患なし・発症なし	(n = 517)	2.814±0.023	
疾患なし・発症あり	(n = 372)	2.780±0.029	
疾患あり	(n = 1,533)	2.762±0.015	
経済的ゆとり満足感（2点満点）			
疾患なし・発症なし	(n = 475)	1.491±0.036	
疾患なし・発症あり	(n = 338)	1.479±0.043	0.017
疾患あり	(n = 1,376)	1.369±0.023	
精神的健康（3点満点）			
疾患なし・発症なし	(n = 468)	2.199±0.046	
疾患なし・発症あり	(n = 337)	2.033±0.056	< 0.001
疾患あり	(n = 1,296)	1.762±0.031	0.039
精神的活力（3点満点）			
疾患なし・発症なし	(n = 467)	2.289±0.044	
疾患なし・発症あり	(n = 331)	2.245±0.054	< 0.001
疾患あり	(n = 1,341)	1.971±0.029	< 0.001

*Values are means±SE
†Steel-Dwass test

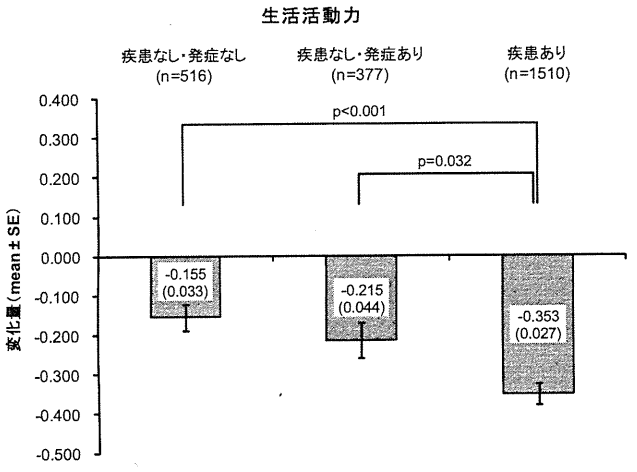
ライン値および各群間の有意差検定の結果を表1に示した．すなわち，「生活活動力」については，ベースラインで疾患がなかった2群に比べ，「疾患あり」群は有意に得点が低かった．「健康満足感」では，3群のそれぞれの2群間で有意差がみられた．「人的サポート満足感」では3群間に有意差はなかった．「経済的ゆとり満足感」では，「疾患なし・発症なし」群は「疾患あり」群より有意に高い得点を示した．「精神的健康」では3群のそれぞれの2群間で有意差がみられた．「精神的活力」の得点は，「疾患あり」群で「疾患なし」の2群より低下していた．

次に，QOL下位項目の2002年から2006年までの変化量をみると，「生活活動力」に関しては，3群すべてにおいて低下がみられ，「疾患あり」群では他の2群に比べて変化量および変化の割合が有意に大きかった（$p<0.001$，$p=0.032$）．「健康満足感」では3群でQOL得点が低下し，「疾患なし・発症あり」群では，他の2群に比べて変化量が有意に大きく，変化の割合も11.4%と大きかった（いずれも$p<0.001$）．「人的サポート満足感」では，「疾患なし・発症なし」群では得点がわずかに上昇したが，他の2群では4年間で得点の軽度低下がみられ，3群間には有意差はなかった．「経済的ゆとり満足感」は3群で低下し，3群間には有意差はなく，変化量の割合も5%以下であった．「精神的健康」については，「疾患なし・発症なし」群でわずかに得点が上昇したが，他の2群では低下し，3群間での有意差はなく，変化量の割合も5%以下であった．「精神的活力」に関しては3群で低下がみられ，「疾患なし・発症なし」群は他の2群に比べて変化量，割合とも有意に少なかった（$p<0.001$，$p=0.019$）（図1A～F）．

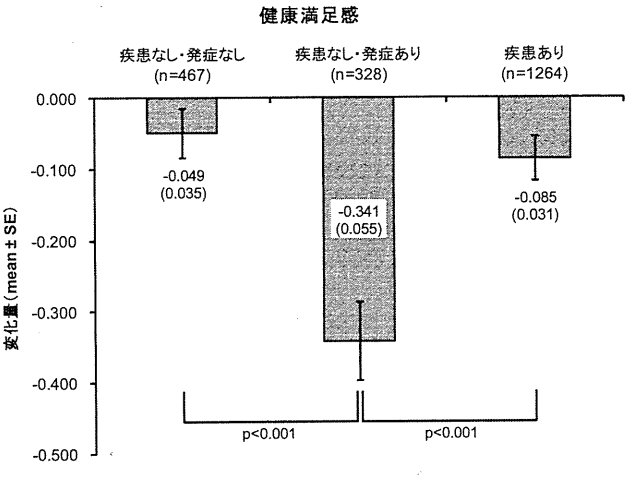
考　察

今回用いたQOL質問表は，LawtonのBehavior Competence，Perceived QOL，Psychological Well-beingの3つの要素の下位項目を含み[15]，QOLの広い範囲を包括すると考えられ，妥当性が確認されており[14]，コホート研究もおこなわれている[6)16)～18)]．健康関連QOLの尺度として汎用されているSF-36に比べても，高齢者の特性を考慮し，「生活者としての高齢者」を対象とした包括的な評価法であるといえる．

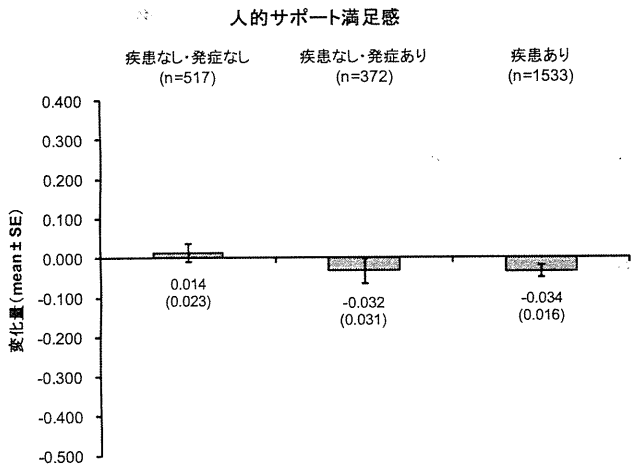
一方，在宅の高齢者では，何らかの慢性疾患を持って



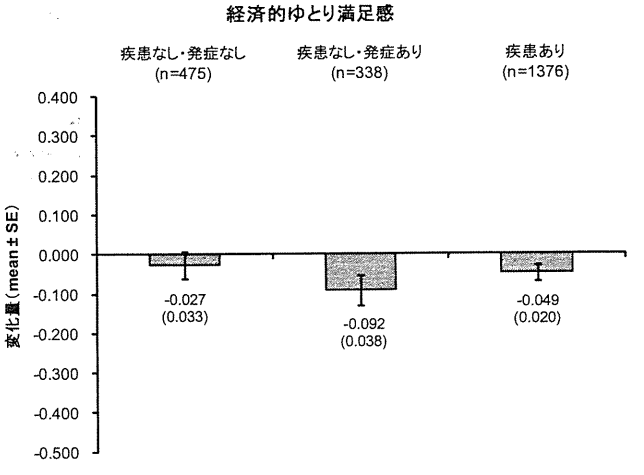
A「生活活動力」



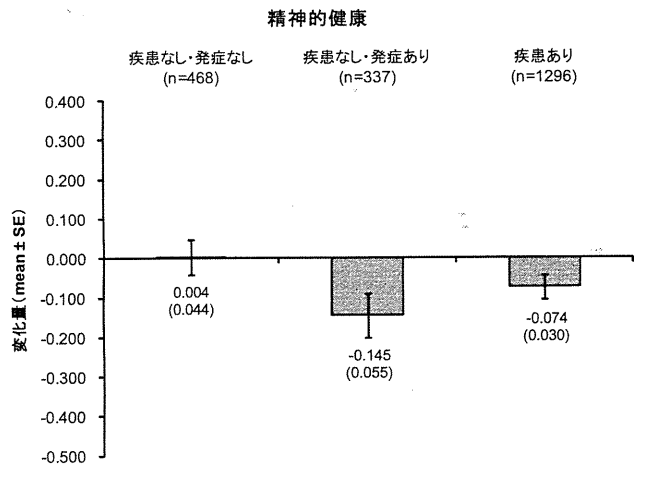
B「健康満足感」



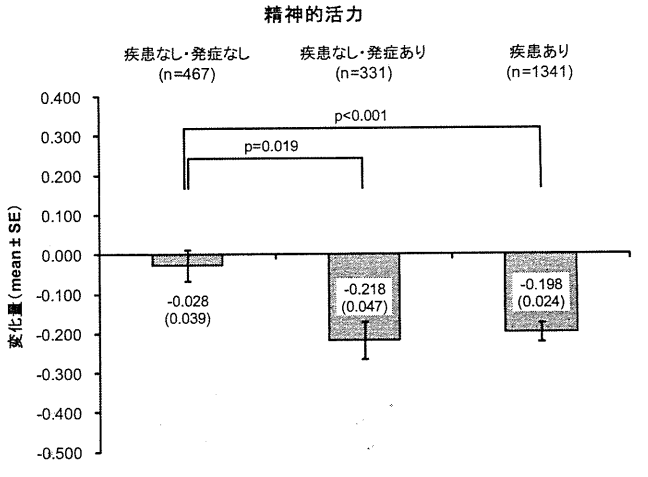
C「人的サポート満足感」



D「経済的ゆとり満足感」



E「精神的健康」



F「精神的活力」

図1　QOL下位項目得点の4年間の変化量
変化量＝2006年－2002年
図中の値はmean（SE），Steel-Dwass testによるp-value

いる人が多く，通院や服薬をしていると考えられる．しかし，重篤な疾患でなければ，比較的自立した生活を送っており，今回の対象者でもベースラインで，1,782人（全体の64.5%）が治療を必要とする疾患ありと答えた．また，4年後には，これに「疾患なし・発症あり」の419人が加わり，2,201人（79.7%）と約8割の人が何らかの疾患を有していた．慢性疾患の有病率に関しては，1つの慢性疾患を持つ人の割合が31.3%～55.1%，2つ以上の慢性疾患がある人の割合が34.5%～30.2%，合計すると65.8%～85.3%とする報告[13)19)]があり，高齢者では慢性疾患を持つ人が多いことでは今回の結果と一致する．

慢性疾患のある人はない人よりQOLが低く[19)20)]，1つの慢性疾患を持っている人に比べ，2つ以上の慢性疾患を持っている人はQOLがより低下するとされる[21)22)]．また，慢性疾患はQOLのドメインに対し，さまざまに影響する[20)22)～25)]．

本研究のベースラインのQOLの下位項目については，ADLを表す「生活活動力」は「疾患あり」群で他の2群より有意に低い得点であり，慢性疾患は身体的機能に負の影響がある[12)21)]とする報告とも一致する結果である．しかし，それでも得点率は95%以上であり，今回の対象者では慢性疾患のADLへの影響はそれほど大きくはないと考えられた．

また，慢性疾患があり，医療費がかかると考えられる人でも，「経済的ゆとり満足感」はさほど低くなく，「人的サポート満足感」も「疾患なし」の2群と差はなく，今回の対象者が慢性疾患の有無に関わらず，比較的自立しており，家族や友人との付き合いにも満足していることが分かった．

「疾患あり」群で「健康満足感」，「精神的健康」，「精神的活力」の得点が「疾患なし」群より低下しており，治療を要する疾患がある人は，主観的健康感が低くなり，うつ状態に陥りやすく，精神的に不安定になると考えられる．

慢性疾患を持つ人とそうでない人との間で，精神的な機能に違いがあるとする研究がある[21)]一方で，慢性疾患の有無では精神的な機能に違いはないとする報告もある[26)27)]．しかし，今回の検討では慢性疾患のある人では「健康満足感」や「精神的健康」の得点が低下しており，主観的幸福感は慢性疾患による影響が少ないが，主観的健康感はもっとも影響されるという報告[12)]とも一致する．

次に4年間における，QOLの変化をみると，疾患の有無にもっとも関連すると考えられる主観的健康感を表す，「健康満足感」において各群間の差が著明であった．日常生活のADLを表す，「生活活動力」はベースラインの値が3群とも高く，身体的に自立している対象者が多かったが，4年間でいずれの群でも得点は低下し，加齢による影響が考えられた．しかし「疾患あり」群では低下量が大きく，やはり何らかの慢性疾患を持つ人は時間的経過においてもQOLの身体面が低下するという既報告[13)28)]と一致する．「人的サポート満足感」もベースライン得点が高く，4年間の変化は下位項目の中で最も少なく，在宅高齢者は疾患があっても家族や友人のサポートがあり満足していると考えられた．「経済的ゆとり満足感」もベースラインでは「疾患あり」群でやや低い値であったが，4年間の変化量は少なく，服薬や医療費の負担にも関わらず，経済的ゆとりが低下することは少なかった．うつ状態を表す「精神的健康」は，「発症あり」群で最も低下し，新たな疾患の発症が精神的な面に影響を及ぼしていることがうかがえる．しかし3群間では有意差はなく，変化量の割合も少なかった．これは，QOLに関して，たとえ環境の変化があっても，ひとは良い状態を維持しようとするので，疾患の発症後しばらくすると主観的幸福感は安定するという説[12)25)]を裏付けている．また，生きがい等を反映する「精神的活力」は，「疾患なし・発症なし」群以外で同程度の低下が見られ，何らかの慢性疾患があったり，新たな疾患が加わった人は，生きがいを感じにくくなると考えられた．

慢性疾患の有無とQOLの関連をみた縦断研究は少ないが，時間的経過によるQOLの変化はドメインによって異なるとされる．すなわち，1年間でADLは低下するが，健康感，社会的役割は変化がなく，メンタルヘルスはむしろ良くなった[13)]．別の2年間の前向き研究では，高血圧症，I型糖尿病以外では健康関連QOLはほとんど維持されていた[29)]．慢性疾患があってもメンタルヘルス面は4年間維持されたが，身体面は低下したという報告もある[28)]．従って，在宅高齢者の日常生活におけるQOLを評価する場合，慢性疾患の影響は多次元的に評価する必要がある．

本研究の限界としては，ベースラインの疾患の有無と4年間の発症だけで，疾患の数，医療費，疾患の重症度について区別していない点，病名選択が回答者にゆだねられており，医師による確認がなされていないことである．しかし，在宅高齢者を対象として，慢性疾患の有無および発症とQOLの関連を調べた報告はない．さらに，対象者数が多く4年間という縦断的研究であり，有意義であると考える．

今回の研究の結果から，1）慢性疾患を持っている人

はそうでない人に比べ，QOLが低下している．2）新たに疾患が発症するとQOLは低下する．3）1）および2）において，すべてのQOL下位項目が一様に影響を受けるわけではなく，慢性疾患の有無や経時的変化においては，影響を受ける項目とそうでない項目がみられた．

高齢者のQOLを評価することは，医療分野に限らず，特定高齢者などに対する介護予防や介入などにおいても，身体能力や認知機能の評価だけでなく，高齢者自身の主観的なQOLをアウトカムとして評価できるという意義がある．そして，在宅の高齢者は慢性疾患を持っている人が多いことから，そのような評価時に疾患の有無，発症などを考慮してQOLを評価する必要がある．

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Relationship between quality of life and chronic illnesses in community-dwelling elderly people

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Abstract

Aim: Chronic illnesses are common among elderly people, and may considerably affect to their quality of life (QOL). We investigated the impact of chronic conditions on QOL among community-dwelling elderly people, and the stability of QOL over time.

Methods: A total of 2,762 community-dwelling elderly persons (men: 47.0%, age 76.7 ± 5.8 [mean ± SD]) completed postal QOL questionnaires twice over 4 years. Chronic illnesses were selected from the following 9 conditions: cerebrovascular disease, hypertension, heart disease, cancer, diabetes mellitus, bone fracture, chronic digestive disease, chronic respiratory disease, and the diseases of joints or muscles. The QOL questionnaire was developed based on the QOL components proposed by Lawton, and consisted of 6 subscales: daily activity, health satisfaction, human support satisfaction, economic state satisfaction, symptoms of depression, and positive mental attitude. The subjects were divided into 3 groups regardless of the presence of chronic illnesses. QOL subscale scores were compared among the 3 groups, and fluctuations over 4 years were also evaluated.

Results: The baseline QOL scores showed significant differences among the 3 groups, especially regarding health satisfaction, but not in satisfaction with human support. There were significant differences among the 3 groups in fluctuations over 4 years in health satisfaction, daily activity, and positive mental attitude.

Conclusions: Chronic illnesses have a negative impact on the QOL of elderly people, and also influence fluctuations in QOL over time. Degrees of impacts differed according to each QOL subscale. Therefore, evaluation of QOL in community-dwelling elderly needs multi-dimensional assessment.

Key words: *Quality of Life (QOL), Community-dwelling elderly, Chronic illness, Longitudinal study*
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高齢者の栄養、現状と対処法

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栄養は健康を維持し、疾病の予防や治療にも不可欠なものですが、高齢者の栄養状態として低栄養や脱水が危惧されています。こうした高齢者の心配される栄養状態の背景や対処法、そして予防法などについて解説していただきましょう。

はじめに

2009年3月には介護予防における「栄養改善マニュアル」の改訂版が、また5月には「日本人の食事摂取基準（2010年版）」が出されました。これまで食事摂取基準では、各栄養素に関する記述のなかで高齢者についての記載がありましたが、2010年版では、栄養素別の章のほかに高齢者に関する章が設けられました。これは、食事摂取基準が健康な人を対象としていますが、高齢者の現状では、通院者率が70歳以上で67%、入院受療率が44%、また要介護認定を受けている者が65歳以上の16%を占め、何らかの疾病や介護サービスを受けている人を除外すると、限られた一部の非常に健康な高齢者のみを対象とした基準になってしまうと考えられたからです。そこで、ほぼ自立した日常生活をおくることができる高齢者、すなわち、加齢に伴う身体機能の変化に

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専門は栄養生理学、運動生理学。現在は、身体活動量の評価、生活習慣病や自立度低下を予防するための身体活動と栄養の関係に関する研究に従事。

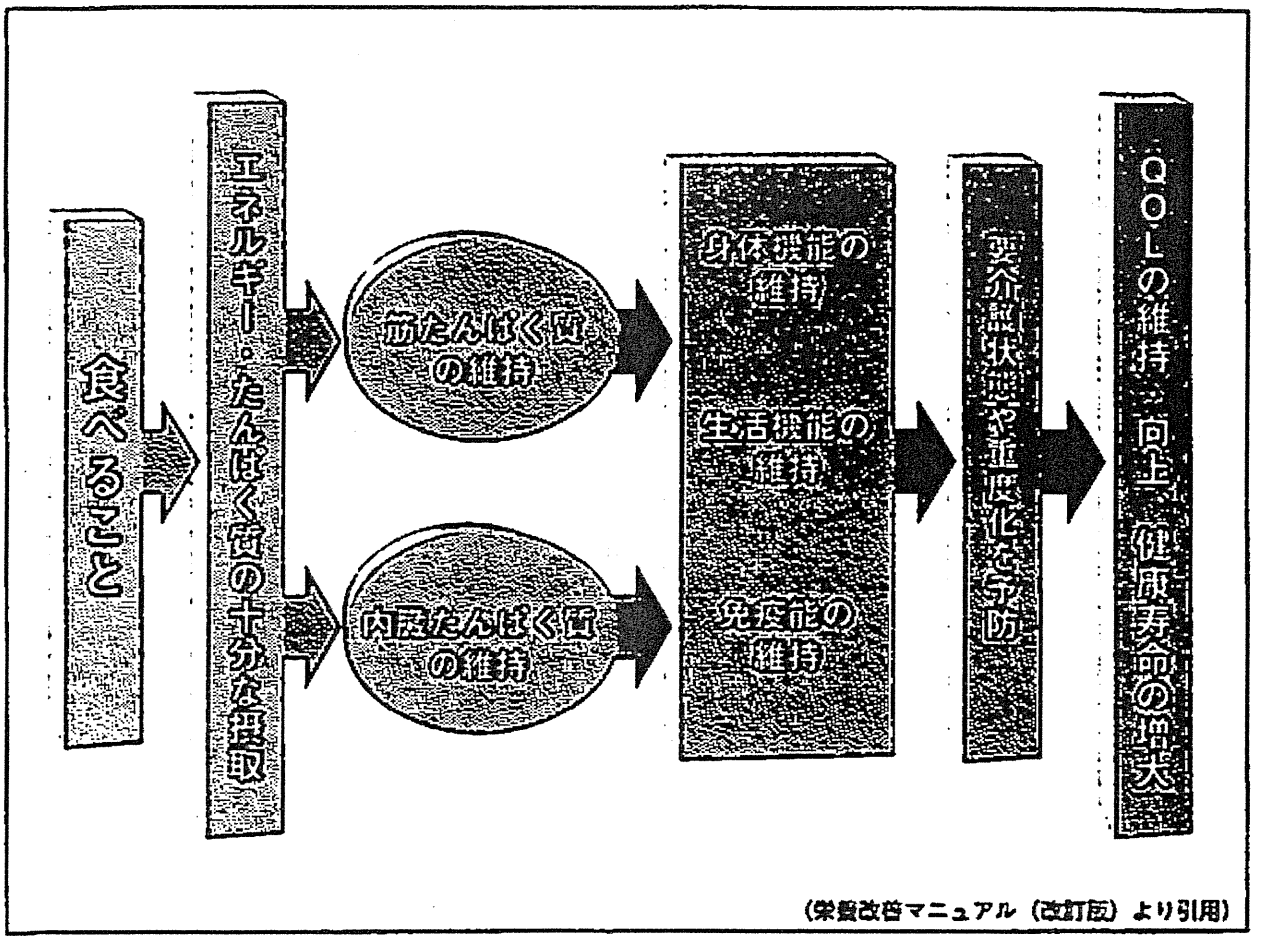

図1　高齢者の「食べること」の意義

よって発症すると考えられる疾患や障害を有する場合も、食事摂取基準の対象とするという観点にたって、高齢者の栄養に関する記述が加えられています。

一方、介護予防の観点からは、高齢者の「食べること」は楽しみや生き甲斐のうえから重要であり、「食べること」への支援を通して、社会参加、生活機能の向上、コミュニケーションの回復、食欲の回復や規則的な便通といった生体リズムの保持を目指しています。また、高齢者が十分に食べることで、身体機能や生活機能を維持し、要介護状態への移行や重度化の予防が期待できます(図1)。

中高年期から高齢期への移行に際しては、健康状態や身体の変化に伴い、食事や栄養に対する注意を変えるべきです。しかし実際には、中年期に受けた指導にもとづいて、生活習慣病予防や肥満予防を目的とした

食事への配慮のみが続いていたり、口腔機能の低下に伴う食事量の減少に気づかない、あるいは高齢者だからそれほど食べなくてよいといった配慮の不足が目立っています。本稿では、とくに低栄養と脱水予防の観点から、高齢期の栄養について記述します。

低栄養予防

1.低栄養の問題点

低栄養状態とは、たんぱく質やエネルギーが不足した状態です。それらの不足による高齢者の低BMIや体重の減少は、身体機能の低下や免疫能の低下による疾病の発症を引き起こし、要介護状態や介護状態の重度化を招きます（図1）。図2はPitchfordらが、アメリカのアラバマ州において在宅で生活している65歳以上の高齢者の状態を4年間調査した結果です。ADL（日常生活動作）は、食事、排泄、着替え、移動、入浴、歩行の6項目について、半年ごとに実施できるかを調査し、実施できる場合を3点、まったくできない場合を0点として合計点を示しました。その結果、BMIが18・5未満ではそれ以上の者に比べて、明らかにADLの低下が大きく（図2A）、また、1年間に10ポンド（約4.5kg）を超える意図しない体重減少のある者においてADLの低下が大きかったのです（図2B）。そのため、介護予防においては、低BMI、体重減少などを含む低栄養のリスクのある者（血清アルブミン値や食事摂取量などから判断）を対象に、栄養改善のプログラムを実施することとしています。

2.低栄養の現状

厚生労働省老人保健事業推進等補助金「介護予防事業等の効果に関する総合的評価・分析に関する研究」（主任研究者　辻一郎、2009）では、介護認定を受けておらず、健診等で把握された介護予防のハイリスク者である特定高齢者において低栄養に該当する者の割合を検討しています。特定高齢者2067名中、6ヵ月間に2～3kgの体重減少のあった者は15・0%、BMI18・5未満は8.3%、両方に該当した者は4.0%でした。一方、介護認定を受けた要支援者7013名中では、6ヵ月間に2～3kgの体重減少は15・7%、BMI18・5未満は10・8%、両方に該当した者は5.1%、そのいずれかに該当した者は31・6%となっています。

3.低栄養予防の対応

多くの研究の結果をまとめたCochrane Reviewでは、高齢者へのたんぱく質とエネルギー補給の効果について検討しています。このレビューによれば、たんぱく質とエネルギーを補給することで22%の体重

増加が認められました。また、研究対象の高齢者全体では、死亡率の低下の効果は認められませんでしたが、栄養状態の悪い高齢者に栄養補給した場合には、死亡率が21%低下しました。栄養補給には、補助食品を使用した研究と、一般の食品を使用した研究がありますが、補給量はエネルギーで1日に175～1350kcal、たんぱく質で10～50gと大きく差がありました。

低栄養予防を意図した栄養改善では、対象者の体重が食事摂取基準で示されている基準体位に満たないことが多く、そのため、目標とする栄

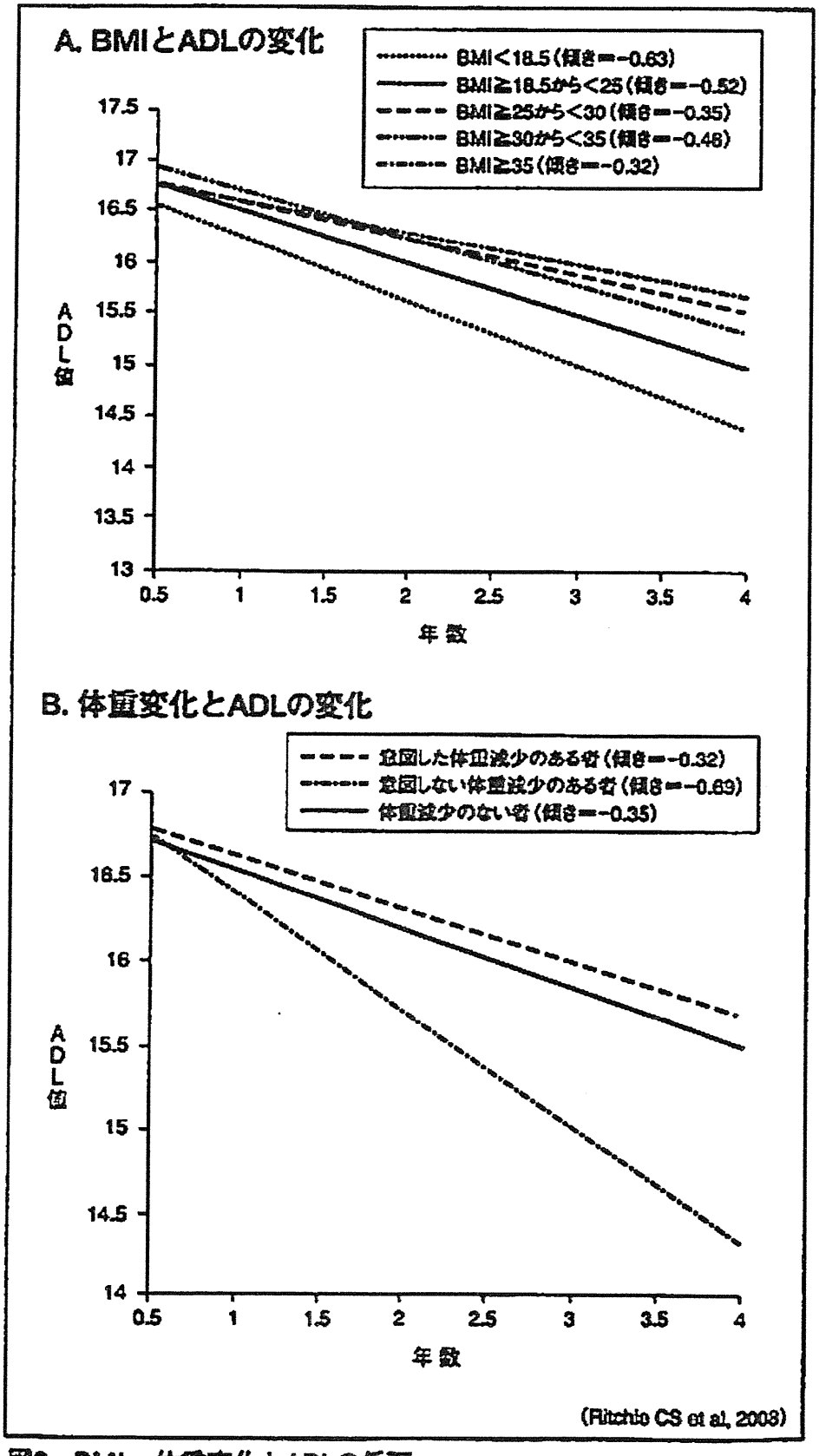

図2　BMI、体重変化とADLの低下