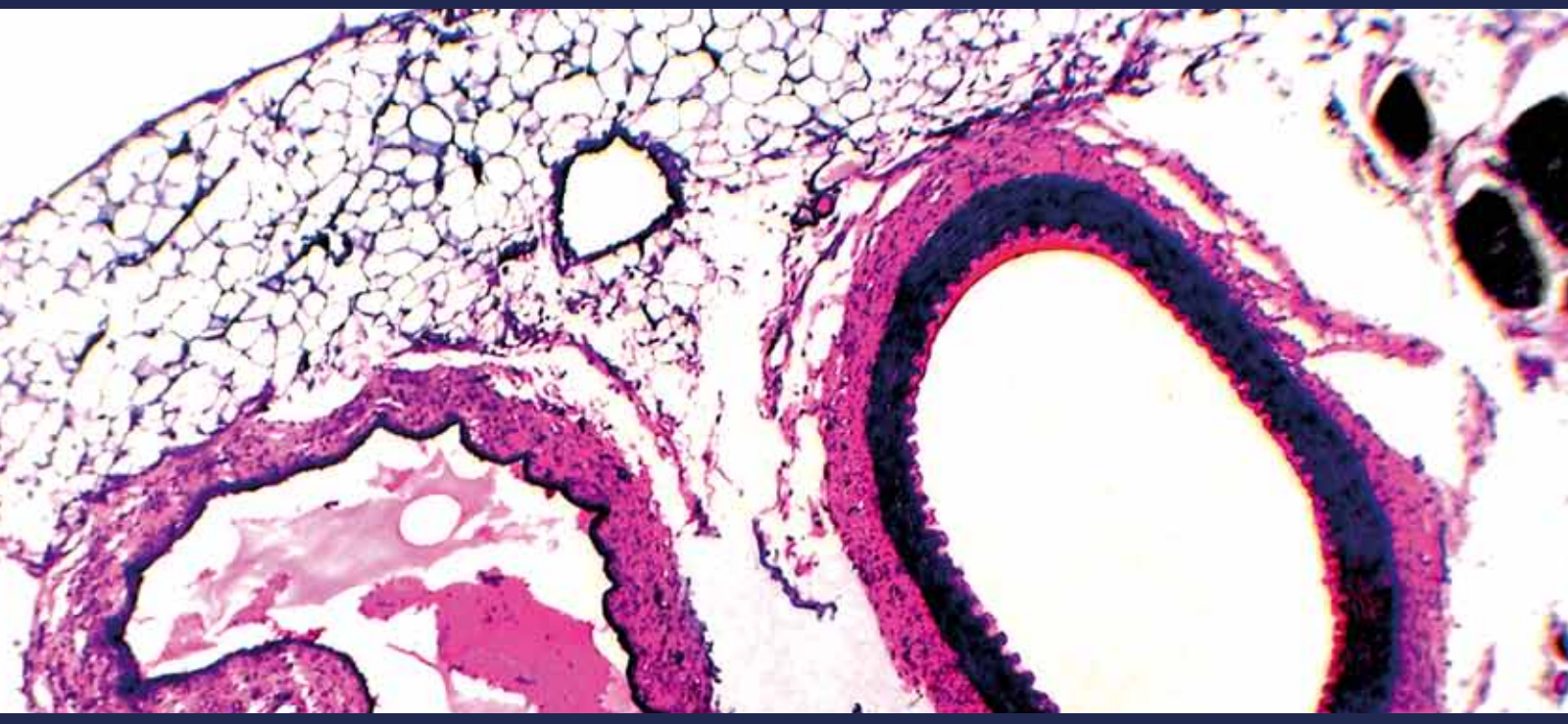
International Journal of Hypertension

Hypertension in the Elderly

Guest Editors: Blas Gil-Extremera, Jaako Tuomilehto, and Pedro Cía-Gómez



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Editorial Board

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Editorial

Blood Pressure in Old Population

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This monograph issue of the journal is dedicated to the most frequent cardiovascular disorders in the Western countries: hypertension, mostly in the elderly. In this situation, two patterns can be found: (a) increased systolic and diastolic blood pressure and (b) isolated systolic hypertension.

A total of fourteen selected papers are included; nine of them are about clinical aspects of the disease and the remaining about pathophysiological profile of hypertension in old population.

The papers by A. Paganini-Hill and M. Igase et al. of this issue address the relationship between hypertension and dementia. The authors showed the deleterious role of cardiovascular risk factors—mostly increased blood pressure—on the incidence of dementia; 13978 old people (mean age 74 years old) after followup from 1981 to 2010 were studied. In summary, high blood pressure and its treatment have different effects in men and women in the elderly. The second one also establishes the relationship between hypertension and dementia; recent clinical trials suggest that blockades of RAS system could have reduced cognitive decline seen in Alzheimer's disease and vascular dementia. The paper of B. Gil-Extremera1 and P. Cía-Gómez is a background, by the clinical point of view, of hypertension in older population with special attention to the combination therapy of hypertension with more benefits than monotherapy. The study done by A. Siennicki-Lantz and S. Elmståhl concluding: "hypertension and vascular risk factors in a cohort of 68-years-old men do not result in higher ambulatory blood pressure monitoring (ABPM) at age 82, possibly due to inflection point in their pressure development" [sic]. The next one study analyses ABPM in the elderly, because the prevalence of hypertension by AMBP is not well known in this particular population. The paper by N. K. Patel et al. highlights the relevance of effectiveness, culturally responsive hypertension management among the high-risk Hispanic patients for achieving positive health results. The paper by B. Gil-Extremera reports some ideas concerning the clinical experience of the author on lipid disorders and some frequent errors observed in his clinical practice; for example, some physicians take as normal lipid values clearly high, and many patients do not receive any treatment; statin/fibrate combination therapy is not recommended, but unfortunately this procedure is maintained in many cases; another common error is the discontinuation of lipid lowering therapy when normal values are reached.

Other two papers raise the benefit of antihypertensive treatment on very old hypertensive patients according to the HYVET Study, and one of them reports that control of elderly hypertension in sub-Saharan Africans was effective and required at least two antihypertensive drugs.

Additional five papers belong to the experimental or basic aspects of hypertension; the role of C-reactive protein in atherosclerosis, the mechanisms related to hypertension in the elderly, the biochemical and molecular aspects of vascular adrenergic regulation of blood pressure, the putative role of protein Klotho in cardiovascular and renal disease, and,

finally, the role of cortisol secretions in hypertensive elderly patients.

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Clinical Study

Associations between High-Sensitivity C-Reactive Protein and Membrane Fluidity of Red Blood Cells in Hypertensive Elderly Men: An Electron Spin Resonance Study

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Recent evidence indicates that high-sensitivity C-reactive protein (hs-CRP), an acute phase of an inflammatory marker, might be associated with atherosclerosis, hypertension, and other cardiovascular diseases. The present study was performed to assess the possible link between plasma hs-CRP and membrane fluidity (a reciprocal value of membrane microviscosity) in hypertensive elderly men. We measured the membrane fluidity of red blood cells (RBCs) in hypertensive and normotensive elderly men using an electron spin resonance and spin-labeling method. Membrane fluidity of RBCs was decreased in hypertensive elderly men compared with normotensive elderly men. Plasma hs-CRP levels were significantly higher in hypertensive elderly men than in normotensive elderly men. In contrast, plasma nitric-oxide- (NO-) metabolite levels were lower in hypertensive elderly men than in normotensive elderly men. The reduced membrane fluidity of RBCs was associated with increased plasma hs-CRP and decreased plasma NO-metabolite levels. In a multivariate regression analysis, plasma hs-CRP was an independent determinant of membrane fluidity of RBCs after adjustment for general risk factors. The results suggest that CRP might have a close correlation with the rheologic behavior of RBCs and the microcirculation and would contribute, at least in part, to the circulatory dysfunction and vascular complications in hypertensive elderly men.

1. Introduction

Evidence indicates that inflammation may actively participate in the development and progression of atherosclerosis and cardiovascular disease processes [1]. It is well recognized that high-sensitivity C-reactive protein (hs-CRP), an acute-phase of inflammatory marker, might be associated with increased risk of cardiovascular events [2, 3]. Recently, it has been shown that CRP could reduce the nitric oxide (NO) bioavailability by itself, which would induce endothelial and cardiovascular dysfunctions. Venugopal et al. demonstrated that CRP directly decreased endothelium type of NO synthase (eNOS) expression in human aortic endothelial cells in vitro [4]. Qamirani et al. showed that CRP inhibited endothelium-dependent NO-mediated dilatation of porcine coronary arterioles [5]. In a clinical study, it was also demonstrated that increased levels of hs-CRP were associated with reduced endothelium-mediated dilatory responses of the arteries [6]. However, the precise role of inflammation in the circulatory dysfunction in hypertension remains unclear.

It has been proposed that abnormalities in physical properties of the cell membranes may underlie the defects that are strongly linked to hypertension, stroke, and other cardiovascular disease conditions [7–9]. An electron spin resonance (ESR) and spin-labeling method has been developed to evaluate the membrane fluidity (a reciprocal value of membrane microviscosity) and perturbations of the membrane function by external agents [8, 9]. The membrane fluidity is a physicochemical feature of biomembranes and is an important factor in modulating the cell rheologic behavior [8, 9]. Using

Table 1: Clinical characteristics and laboratory findings of hypertensive (HT) and normotensive (NT) men.

	NT	HT
Number of subjects	18	29
Age (y.o.)	64 ± 2	63 ± 2
Body mass index (kg/m^2)	24.2 ± 0.7	24.1 ± 0.5
Systolic blood pressure (mmHg)	124 ± 2	147 ± 1*
Diastolic blood pressure (mmHg)	69 ± 2	87 ± 1*
Heart rate (beats/min)	75 ± 2	72 ± 2
Erythrocyte counts (10^4 cells/μL)	458 ± 11	474 ± 8
Hemoglobin (g/dL)	14.2 ± 0.4	14.1 ± 0.2
Hematocrit (%)	43.2 ± 1.0	42.9 ± 0.6
Leucocyte counts (10^3 cells/μL)	5.5 ± 0.3	5.4 ± 0.2
Platelets (10^4 cells/μL)	21 ± 1	23 ± 1
Total cholesterol (mg/dL)	211 ± 6	209 ± 7
High-density lipoprotein cholesterol (mg/dL)	51 ± 2	52 ± 3
Low-density lipoprotein cholesterol (mg/dL)	134 ± 6	127 ± 7
Triglycerides (mg/dL)	120 ± 11	131 ± 12
Serum sodium (mmol/L)	140.8 ± 0.1	140.1 ± 0.2
Serum potassium (mmol/L)	4.0 ± 0.1	4.0 ± 0.1
Serum creatinine (mg/dL)	0.8 ± 0.1	0.9 ± 0.1
Fasting plasma glucose (mg/dL)	109 ± 3	116 ± 8

Values are mean ± SEM. *$P < 0.05$ between HT and NT.

the ESR method, we have been performing a series of experiments regarding the membrane fluidity of red blood cells (RBCs) in hypertension and have shown that membrane fluidity was significantly lower in hypertensive subjects than in normotensive subjects, particularly in the elderly [10–15]. Because the deformability of RBCs might be highly dependent on the membrane fluidity [8, 9], the reduction in membrane fluidity could cause a disturbance in the blood rheologic behavior and the microcirculation, which might contribute to the pathophysiology of hypertension and other circulatory disorders. In the present study, in order to assess the role of inflammation in the regulation of membrane function in hypertension in the elderly, we investigated the relationships between plasma hs-CRP and membrane fluidity of RBCs in hypertensive and normotensive elderly men using the ESR and the spin-labeling method.

2. Subjects and Methods

2.1. Subjects. A total of 29 men with untreated essential hypertension (age 63 ± 2 years old) were studied and compared with 18 age-matched normotensive men (age 64 ± 2 years old) (Table 1). The characteristics and laboratory findings in both groups were shown in Table 1. All subjects had no history of haematologic or hepatic disorders. All men were nonsmokers. They had similar life styles and dietary habits and were instructed to avoid any changes in dietary habits at least 12 weeks before the study. The study was approved by a local research committee of Kansai University of Health Sciences. Written informed consent was obtained from all participants when they were informed about the nature and objective of the study.

2.2. Electron Spin Resonance (ESR) Measurements of RBCs. Blood sampling was performed by venipuncture after 30 minutes of bed rest while fasting. The procedures of RBC preparation and ESR measurements were shown previously [9–15]. We evaluated the values of outer and inner hyperfine splitting ($2T'_{\parallel}$ and $2T'_{\perp}$ in tesla (T), resp.) in the ESR spectrum for the spin label agents (5-nitroxide stearate, Aldrich Co., Ltd., Milwaukee, WI, USA) (Figure 1), and calculated the order parameter (S) [10–16]. The greater the value of the order parameter (S) was, the lower the membrane fluidity of RBCs was.

2.3. Nitric Oxide (NO) Metabolites (Nitrite and Nitrate) Analysis. The plasma levels of NO metabolites (nitrite and nitrate) were measured according to the method described previously [17].

2.4. Statistical Analysis. Values are expressed as mean ± SEM. The differences between hypertensive and normotensive men were analyzed using an unpaired Student's t-test. Linear regression analysis was performed to assess the relationships between membrane fluidity (order parameter: S) of RBCs and plasma hs-CRP or NO metabolite levels. Multivariate regression analysis with membrane fluidity (order parameter: S) of RBCs as a dependent variable and plasma hs-CRP, age, body mass index (BMI), hypercholesterolemia (more than

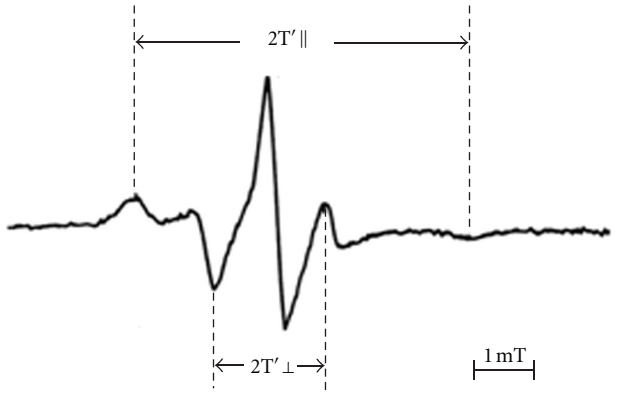

Figure 1: Representative electron spin resonance (ESR) spectrum of red blood cells (RBCs) for the fatty acid spin-label agents (5-nitroxide stearate). We calculated the order parameter (S) from outer and inner hyperfine splitting (2T′ || and 2T′ ⊥ [10–16]). The greater the value of the order parameter (S) was, the lower the membrane fluidity of RBCs was [10–16]. (S: order parameter, 2T′ ||: outer hyperfine splitting, 2T′ ⊥: inner hyperfine splitting, T: tesla.)

220 mg/dL), hyperglycemia (more than 110 mg/dL), and systolic blood pressure as independent variables was also performed. A P value less than 0.05 was accepted as the level of significance.

3. Results

3.1. Membrane Fluidity of RBCs in Hypertensive and Normotensive Elderly Men. The order parameter (S) for 5-nitroxide stearate in the ESR spectra of RBCs was significantly higher in hypertensive elderly men (HT) than in normotensive elderly men (NT) (HT 0.729 ± 0.002, mean ± SEM, $n = 29$, NT 0.718 ± 0.002, $n = 18$, $P < 0.01$). The finding indicated that membrane fluidity of RBCs was significantly lower in hypertensive elderly men than in normotensive elderly men.

3.2. Plasma High-Sensitivity C-Reactive Protein and Plasma Nitric-Oxide-Metabolite Levels in Hypertensive and Normotensive Elderly Men. The plasma hs-CRP levels were significantly higher in hypertensive elderly men than in normotensive elderly men (HT: 0.157 ± 0.022 mg/dL, $n = 29$, NT: 0.072 ± 0.009 mg/dL, $n = 18$, $P < 0.01$). In contrast, the plasma NO metabolites were lower in hypertensive elderly men than in normotensive elderly men (HT: 36.0 ± 2.4 μmol/L, $n = 29$, NT: 52.5 ± 5.2 μmol/L, $n = 18$, $P < 0.01$). In addition, in the overall analysis of hypertensive and normotensive elderly men, plasma hs-CRP levels were inversely correlated with plasma NO metabolites ($r = -0.291$, $n = 47$, $P < 0.05$) (Figure 2).

3.3. Relationship between Membrane Fluidity of Red Blood Cells and Plasma High-Sensitivity C-Reactive Protein, or Plasma Nitric-Oxide-Metabolite Levels in Hypertensive and Normotensive Elderly Men. The order parameter (S) of RBCs was significantly correlated with plasma hs-CRP levels

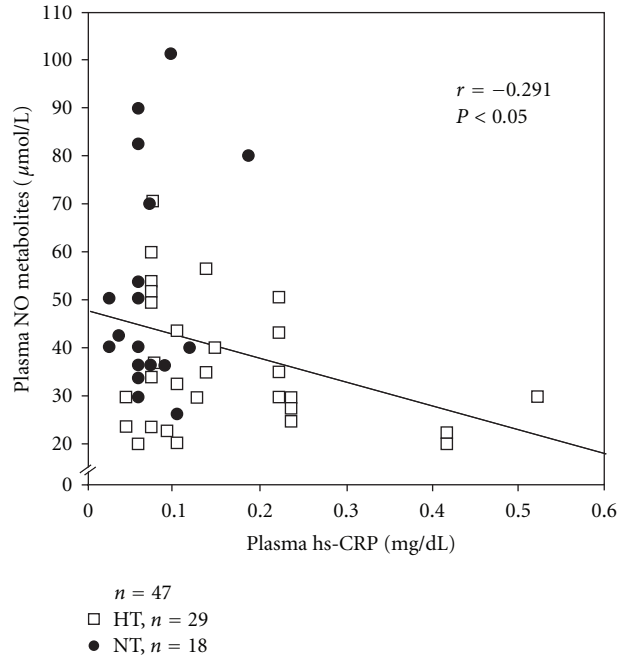

Figure 2: Inverse correlation between plasma high-sensitivity C-reactive protein (hs-CRP) and plasma nitric-oxide- (NO-) metabolite levels in hypertensive and normotensive elderly men.

($r = 0.416$, $n = 47$, $P < 0.01$) (Figure 3) and was inversely correlated with plasma NO metabolite levels ($r = -0.362$, $n = 47$, $P < 0.05$).

In a multivariate regression analysis after adjustment for general risk factors, plasma hs-CRP was an independent determinant of membrane fluidity (order parameter: S) of RBCs (Table 2).

4. Discussion

Evidence indicates that hs-CRP, an acute-phase of inflammatory marker, might be associated with increased risk of cardiovascular events [2, 3]. In the present study, we assessed the relationships between plasma hs-CRP levels and the membrane fluidity (a reciprocal value of membrane microviscosity) of RBCs in hypertensive and normotensive elderly men using the ESR and the spin-labeling method. The present study showed that the membrane fluidity of RBCs was decreased in hypertensive elderly men compared with normotensive elderly men. The result might be consistent with our previous findings showing that the cell membranes were stiffer and less fluid in hypertensive subjects [10–15]. Plasma hs-CRP levels were significantly higher in hypertensive elderly men than in normotensive elderly men and correlated with the order parameter (S) of RBCs, indicating that the reduced membrane fluidity of RBCs might be associated with elevated inflammatory status. To our knowledge, this is the first report demonstrating that CRP might have a close correlation with membrane fluidity of RBCs in humans.

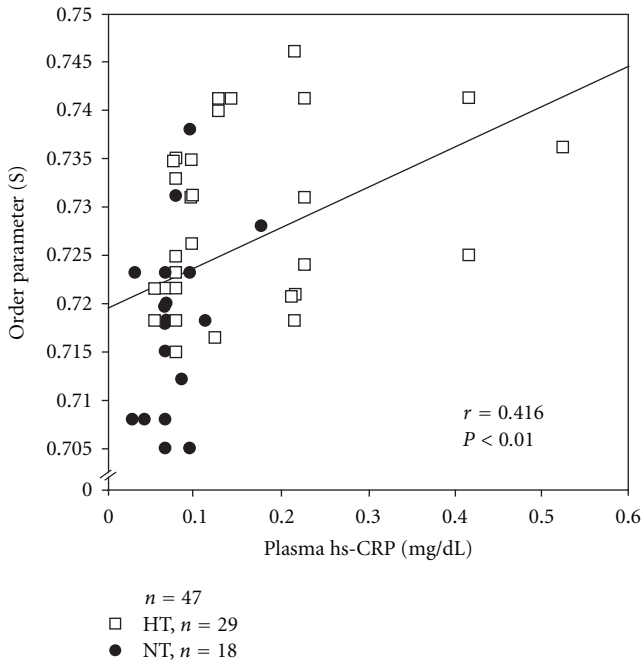

Figure 3: Correlation between plasma high-sensitivity C-reactive protein (hs-CRP) and membrane fluidity (order parameter: S) of red blood cells (RBCs) in hypertensive and normotensive elderly men.

Table 2: Multivariate regression analysis for predicting order parameter (S) of RBCs.

	SRC	t-value	P value
Age (y.o)	−0.215	−1.288	0.2053
Body mass index (kg/m^2)	−0.197	−1.190	0.2409
Hypercholesterolemia (≧220 mg/dL)	−0.269	−1.986	0.0539
Hyperglycemia (≧110 mg/dL)	0.178	1.318	0.1951
Systolic blood pressure (mmHg)	0.339	2.552	0.0146
Plasma hs-CRP (mg/dL)	0.353	2.603	0.0129

$R^2 = 0.373$, $n = 47$, $F = 3.972$, $P = 0.0033$.
SRC: standard regression coefficient.

Multivariate regression analysis also showed that plasma hs-CRP was an independent determinant of membrane fluidity of RBCs after adjustment for general risk factors. Because the deformability of RBCs might be highly dependent on the membrane fluidity [8, 9], the reduction in membrane fluidity associated with increased hs-CRP levels could cause a disturbance in the blood rheologic behavior and the microcirculation.

It was shown that shear rate, shear stress, and blood viscosity were correlated with membrane fluidity of RBCs [18]. The finding proposed that in vivo shear forces might participate in the control of RBC membrane fluidity and that RBCs might adapt their membrane properties to blood flow conditions. It was also demonstrated that RBC membranes might become more rigid after myocardial infarction, which could contribute to the decreased RBC deformability and the increased blood viscosity in this group of patients [19]. On the other hand, Cazzola et al. [20] reported that the membrane fluidity of RBCs was decreased in the obese subjects and proposed that a decrease in RBC membrane fluidity could contribute to a reduction of the rate of blood flow and the oxygen diffusion through the RBC membranes and its exchange with tissues. It might be, therefore, possible that alterations in RBC membrane fluidity with elevated hs-CRP levels would be strongly linked to the progression of circulatory disorders.

Recently, it was demonstrated that CRP might directly impair the NOS expression in human aortic endothelial cells in vitro [4]. It was also shown that endothelium-dependent vasodilatory responses or microvascular endothelial functions were reduced in humans with elevated plasma hs-CRP levels [6, 21]. The results of the present study demonstrated that plasma hs-CRP levels were inversely correlated with plasma NO metabolites in the overall analysis of hypertensive and normotensive elderly men. One hypothesis is that higher hs-CRP levels could be accompanied by the reduced NO production and endothelial dysfunction. In a study presented earlier, it was shown that an NO donor significantly improved membrane fluidity of RBCs in hypertensive subjects, indicating that NO could have a beneficial effect on the rheologic behavior of RBCs and the microcirculation in hypertension [13–15]. We also demonstrated that the reduced membrane fluidity of RBCs was associated with the decreased plasma NO metabolites in overall analysis of hypertensive and normotensive elderly men, which might be consistent with our previous findings [13, 17]. It is, therefore, strongly suggested that the effects of CRP on membrane fluidity of RBCs might be mediated, at least in part, by the impaired NO bioavailability, although direct actions of CRP on membrane structural and functional properties cannot be excluded. Further studies should be performed to assess more precisely the relationships between CRP and NO and their role in the regulation of membrane functions and circulatory mechanisms in hypertension.

5. Conclusion

The results of the present study demonstrated that plasma hs-CRP levels were elevated in hypertensive elderly men compared with normotensive elderly men. In addition, it was shown that the reduced membrane fluidity of RBCs was correlated with higher plasma hs-CRP and lower plasma NO metabolite levels, indicating that abnormalities in RBC membranes might be associated with increased inflammatory status and endothelial dysfunction in hypertension. Although this is a cross-sectional and correlative study in Japanese men, the results of the present study suggest that CRP might have a close correlation with the rheologic behavior of RBCs and the microcirculation and would contribute, at least in part, to the circulatory dysfunctions and vascular complications in hypertensive elderly men. Moreover, a better knowledge of the inflammatory biomarker and cellular mechanisms underlying membrane abnormalities could provide useful information concerning the pathogenesis, treatment, and prognosis of hypertension in the elderly.

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Clinical Study

Study on the Dynamics of Cortisol Secretions in Hypertensive Elderly Patients

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Ageing is defined as a slow, irreversible process of cellular changes, that are due to a lack of balance between degradation and repair, a continuous interaction between physiological and pathological processes. Physiological aspects in elderly people are often confused with disease. Given these general considerations, we would make observations about the dynamics of cortisol secretion in healthy elderly subjects and patients with a diagnosed cardiovascular disease, more precisely hypertension. The study was conducted during 2003–2010, on a number of 135 patients older than 65 years of age, who were divided into two groups: one group counting 66 patients and consisting of healthy elderly controls (without systemic disease, renal, endocrine, or cardiovascular known issues) and group 2 who consists of 69 elderly patients who associate known hypertensive and other cardiovascular issues.

1. Introduction

Ageing is a worldwide recognized fact, implying social and economic aspects, wich lay in the way ageing is controled, because it could have an enormous impact regarding healthcare, hospitalization, and/or reconstructive surgery costs. Ageing is a degrading, progressive, inward-oriented, universal process, and the threshold between physiological and pathological is very thin [1]. Although the general approach towards elderly patients is to increase the quality of life (free prescriptions, occupational therapy, medical healthcare at home), there are a lot of real and recognized situations when the ageing phenomenon may lead to discrimination that can range from providing poor medical healthcare to restricted accessibility to some healthcare programs (e.g., screening for breast cancer in women over 65). However, we must be aware that the ageing process is in steady growth in all developed countries for two main reasons: on the one hand due to reduced mortality and on the other due to decreasing tendency of birth rate and fertility.

Aging is defined as being a slow, irreversible changing process that occurs within single cells—the seat of some remarkable biochemical activity, whose development is genetically programmed in advance [2]. The notion of time in biology equals a measurement of motion in the form of rhythms and cycles, of which the circadian biorhythms of the endocrine functions are the most important. Variations in normal hormonal secretions differ from one hormone to another in the course of 24 hours, so ACTH and cortisol levels reach their peaks during early morning [3]. One of the most well-spread theories regarding aging is based on neuroendocrinology [4], and it well suits the global concept stating the lack of balance between degradation and repair, balance influenced by many internal and external factors [5].

Circadian rhythm of cortisol secretion is stable, with little influence from light and sleep, and it is also highly reproductibile. It "matures" around the age of 4, remaining unchanged into elder years, with no difference in the two sexes. The rhythm of cortisol secretion is dependent on the circadian secretion of ACTH, its acrophase being around 4 AM.

Feedback on the hypothalamic-pituitary axis, is exerted by cortisol on the autonomous circadian rhythm [6]. Hormones are secreted periodically, in a pulsatory manner. Hormonal secretion fluctuations may vary compared to time of day, month, or year. The rhythm is defined by a peak between the hours of 6–8 AM, the lowest value being recorded in the evening [7]. If more determinations of hormone levels are analysed, an ultradian rhythm is revealed, with a daily pulsatile secretion which reflects the episodic secretion of the zona fasciculata, in four phases over night : before bed, low cortisol secretion; during sleep, between 3–5 AM, higher secretion levels; from the last hours of sleep and the first hour after awakening, maximum discharge; during activity periods, intermittent discharge [8]. Clinical and paraclinical evaluation of the degree of impaired hormonal secretions in diseases—general and endocrine disorders—open new perspectives that will optimize chronomodulated therapeutic methods and means in relation to biological rhythms [9].

Starting from these general considerations, we wanted to make some observations on the dynamics of cortisol secretion in healthy elderly people and those with known cardiovascular disease, especially those with hypertension.

2. Methods

The study was conducted in two locations: the Municipal Clinical Hospital "Philanthropy" and the Emergency Clinical County Hospital in Craiova during 2003–2010, with both a prospective and a retrospective component. Case studies presented are based on a number of 135 patients, over 65 years of age, who were divided into two groups: group one (SUBSET 1) consisting of 66 healthy elderly people (control group), without systemic, renal, endocrine, or cardiovascular known issues at the time of enrollment in the group and group 2 (SUBSET 2) consisting of 69 elderly patients who associate diagnosed hypertensive disease and other cardiovascular issues (ischemic heart disease, degenerative valvular heart disease, or arrhythmias, all of the patients being in compensated stages of heart failure—grade I or II NYHA, without any endocrine disorders). Of these, only 41 patients can be considered as "true" hypertensive patients, because the hypertension was the dominant issue compared to the others associated problems.

The cases were investigated by means of clinical examination and cardiovascular evaluation carried out on standard protocol, supplemented by laboratory tests and further investigation (hematological, biochemical, enzymatic, hormonal, immunological, and imaging tests). Blood pressure measurement was made under the same circumstances in all subjects in the morning and evening, in supine and standing positions. Blood pressure was also measured in both arms due to the presence of atherosclerotic lesions, which in the elderly patients can lead to variations in the levels of the blood pressure values. Measurements were recorded for three consecutive days, and each individual patient's values was averaged to determine systolic and diastolic blood pressure. The WHO criteria for defining hypertension were commonly used. We considered as significant for the inclusion in the category of hypertensive patients, values higher than 140 mm Hg (regarding systolic pressure), and also values higher than 80 mm Hg (regarding the diastolic values). In order to be able to correctly classify hypertension, in addition to blood pressure measurement values, we aimed to assess whether or not target organ damage could be recorded, optic blood vessels were analysed, ECG and echocardiography (for left ventricular hypertrophy) were performed, as well as urinary protein dosage.

Patients in both groups were put through further hematological and biochemical sorting investigations, along with serum cortisol determination. The dosage system "Elecys 1010" found in the laboratory of the Emergency Clinical County Hospital of Craiova was used to measure cortisol levels. The sorting and assessment of trial groups were completed by specific-cardiovascular oriented investigations (echocardiography and electrocardiogram) and the complex imaging explorations (radiology, ultrasound, and MRI).

The results were processed by statistical methods (Student's *t*-test, Bartlett's test, Kruskal-Wallis' test, Chi-squared test, the arithmetic mean, standard deviation, ANOVA test, and simple linear regression), using the "Data Analysis" subpackage module Microsoft Excel program and also the "EP12000" program, specialized in the execution of graphs, tables, and statistical tests.

In this study, we will use data from the measurements of cortisol levels, with normal values admitted to this study for cortisol serum levels in the morning (measured between 7–10 AM) ranging between 171 and 536 nmol/L (cortisol 1), while cortisol values in the evening (measured between the hours of 6–8 PM) range between 64 and 327 nmol/L (cortisol 2).

3. Results

In this study, we analyzed two groups of patients in order to observe the dynamics of hormonal secretion in elderly patients: a control group (subset 1) consisting of 66 healthy elderly people and a study group (subset 2) consisting of 69 elderly patients diagnosed with hypertensive disease associated with various cardiovascular diseases. The percentage analysis of cases grouped by age showed that the largest share of older people in both groups belonged to age group of 75–84 years. The average values of biochemical and hematological parameters were within normal limits of age in both groups, except for some values of glucose or lipid fractions.

Subset 1 or the control group was represented by healthy elderly, who had been submitted for routine clinical and laboratory tests. Following the recollection of past medical history, anamnesis, clinical examination, and laboratory tests, 66 healthy elderly people have been selected for the study. The subset was composed of people over 65 years of age (limits between 65 and 92 years), mean age being 78.31 in men and 78.53 in women. Three age groups have been made: first age group ranging between 65 and 74, second one ranging from 75 to 84, and the last group for patients older than 84. The group's structure included more men (40 male cases) than women (26 cases), sex ratio equaling 1.53 in the studied group.

Cortisol 1 values were measured in the morning, between 7 and 8 AM. Mean cortisol measured at this time among the cases in SUBSET 1 was 336.92 nmol/L (limits at 172–537 nmol/L, CI95% 306.47–367.38 nmol/L). A statistically significant difference between mean values of cortisol 1 was not recorded in subjects from subset 1 regarding age differences ($P = 0.168$), but mean cortisol 1 was higher in women (mean 396.38 nmol/L; limits 266–536 nmol/L, CI95% 360.16–432.61 nmol/L) than in men (mean 298.27 nmol/L, limits 172–537 nmol/L, CI95% 257.14–339.4 nmol/L) with about 100 nmol/L. *t*-test to compare mean values identified a high statistical significance for the difference between the two areas ($P = 0.0012$).

Cortisol 2 values were measured in the evening, between 6 and 8 PM. An average value of 205.58 nmol/L (limits 67–327 nmol/L; CI95% 186.27–224.88 nmol/L) was identified in all the subjects in group 1. Measurements in the evening recorded no significant variation regarding age groups in the healthy eldery ($P = 0.09$), but mean cortisol 2 was higher in women (mean 238.81 nmol/L, limits 144–317 nmol/L, CI95% 217.27–260.34 nmol/L) than in men (mean 183.97 nmol/L, limits 67–327 nmol/L, CI95% 156.76–211.19 nmol/L), with high statistical significance for the difference between the two areas ($P = 0.0047$).

Subset 2 consisted of elderly patients with hypertension and cardiovascular disease, but not endocrine issues. These patients were admitted for previously diagnosed cardiovascular issues or newly diagnosed disease. Following the anamnesis, physical examination, and laboratory findings, a total of 69 patients were selected for the study. Similar to subset 1, subset 2 was composed of elderly over 65 years of age (ages ranging from 65 to 90 years); the patients were also divided into three age groups the same as group 1. Men were at a slight advantage (40 cases—58%) over women (29 cases—42%), sex ratio equaling 1.38 in the studied group. Women taken into study from this group had ages between 65 and 89 years of age (mean age 77.69); the men had ages ranging from 65 to 90 years old (mean age 78.22).

Mean cortisol 1 measured at 8 am, in subjects included in group 2, was 392.93 nmol/L (limits 172–536 nmol/L, CI95% 363.66–422.19 nmol/L), while average cortisol 2 measured at 8 PM, among the cases in group 2, was 228.55 nmol/L (limits 73–326 nmol/L, CI95% 210.58–246.52 nmol/L). There was no statistically significant link between the age of the subjects of subset 2 and cortisol values 1 or 2.

Knowing that, in the elderly multiple pathology is very frequent; it was quite difficult to select patients with one cardiovascular disease. Thus, we have selected for the study the most frequently encountered heart diseases in clinical practice: high blood pressure (59%), ischemic heart disease (58%), heart failure (29%), and fibrillation (28%). The associations between the above-mentioned issues are as follows: first pairing was represented by hypertension—ischemic heart disease (17 cases, 24.6%), followed by the association of hypertension-heart failure (11 cases, 15.9%), hypertension and atrial fibrillation (5 cases, 7.2%), and finally hypertension, ischemic heart disease, heart failure, and atrial fibrillation (3 cases, 4.3%).

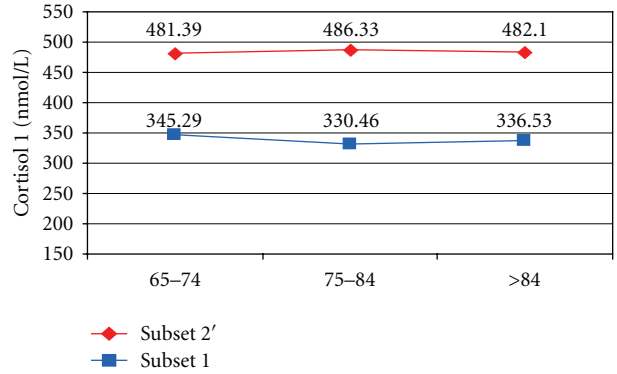

Figure 1: Mean cortisol 1 in subset 1 and 2′ by age groups.

For these reasons we have formed a group of patients called *subset 2′*, with cardiovascular issues, but with clinical dominating hypertension symptoms, consisting of 41 subjects.

3.1. A Comparative Analysis of Cortisol 1 in the Two Groups. Mean cortisol 1, measured within the hypertension dominant group (subset 2′), was 483.73 nmol/L (limits 321–536 nmol/L, CI95% 471.46–496.01 nmol/L).

Comparing the mean morning cortisol in the control group (336.92 nmol/L) to that obtained in patients from subset 2′, we noticed that the average value is higher for the latter (483.73 nmol/L); the difference between the two values being highly significant in statistical terms ($P < 0.001$) (Table 1).

By groups of age, mean cortisol 1 values were over 130 nmol/L higher in hypertensive subjects compared with the subjects in group 1, regardless of age pairings. A mean cortisol 1 was averaging at about 480 nmol/L in group 2′, while the subjects in group 1 did not record a value higher than 346 nmol/L (Figure 1).

Regardless of the grading of the hypertensive disease, patients with hypertension in group 2′ had an average value of cortisol 1 higher than the one recorded in the control group.

Also, as the severity of the hypertensive disease was greater, mean cortisol 1 was higher, the difference being highly significant ($P < 0.001$). Thus, the subjects in subset 1 had a mean cortisol 1 of 336.92 nmol/L, while patients' cortisol 1 value (from subset 2′) increased proportional to the grading of the hypertensive disease (grade 1—450 nmol/L, grade 2—482.31 nmol/L, and grade—522.17 nmol/L) (Figure 2).

3.2. A Comparative Analysis of Cortisol 2 in the Two Groups. Cortisol 2 measured at 8 PM averaged at 205.58 nmol/L in subset 1 (limits 67–327 nmol/L; CI95% 186.27–224.88 nmol/L). In subset 2, the average value of cortisol measured at 8 PM was higher—228.55 nmol/L (limits 73–326 nmol/L; CI95% 210.58–246.52 nmol/L). The difference between the 2 obtained values was not significant in statistical terms.

Comparing the average value of cortisol 2 in subset 1 (205.58 nmol/L) with the one obtained from the subjects of subset 2′, we can clearly observe that the average value in hypertensive patients (281.42 nmol/L) is higher than

Table 1: Mean cortisol 1 in patients from subset 1 and 2′.

Cortisol 1	*N*	Average	CI95%	SD	Minimum	Maximum	*P*
Subset 1	66	336.92	306.47–367.38	123.89	172	537	<0.001
Subset 2′	41	483.73	471.46–496.01	38.89	321	536	

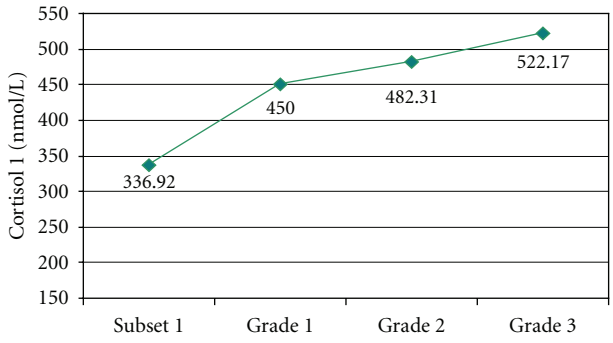

Figure 2: Mean cortisol 1 value in subset 1 and in hypertensive subjects.

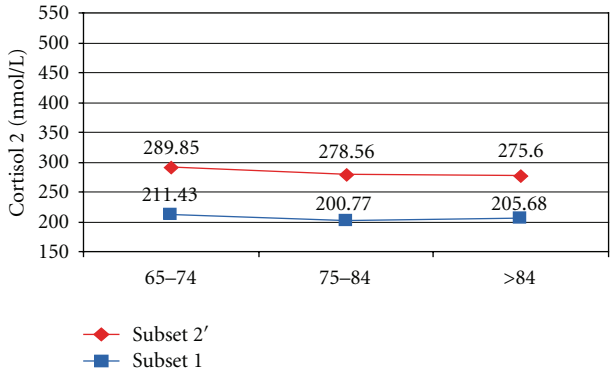

Figure 3: Mean cortisol 2 in patients from subsets 1 and 2′ by age groups.

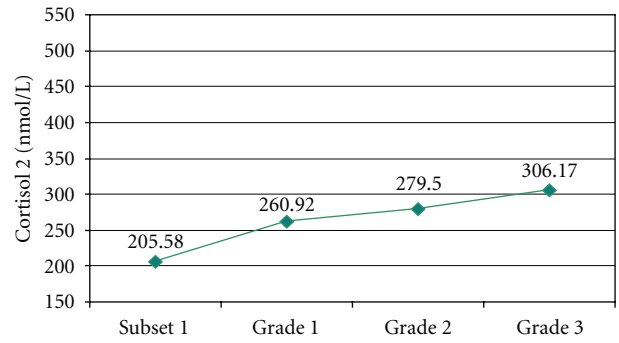

Figure 4: Mean cortisol 2 in subset 1 and 2′ by grade of hypertension.

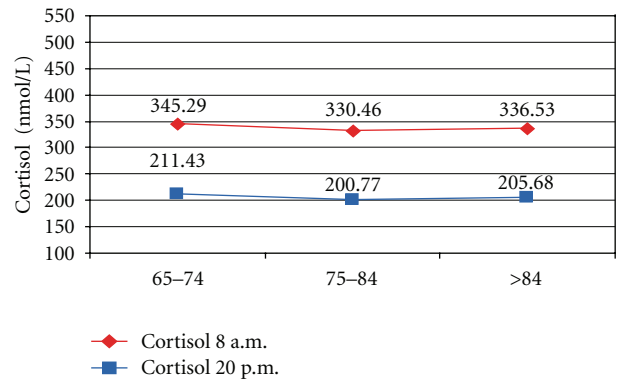

Figure 5: Dynamics of cortisol values in group 1.

the average value of cortisol 2 in the control group, this being highly significant ($P < 0.001$) (Table 2).

If we analyse by age group, mean values of cortisol 2 (measured in the evening) were about 70 nmol/L higher in group 2′ compared to the subjects of the control group in all age groups (Figure 3).

Regardless of the grade of the hypertensive disease, mean cortisol 2 values were higher than in group 1, and the more severe the hypertension was, the higher the mean value of cortisol 2 was. The difference recorded to the control group is highly significant in statistical terms ($P < 0.001$) (Figure 4).

3.3. A Comparative Analysis of Cortisol 1 and 2 Values in the 2 Study Groups. For group 1 the mean cortisol 1 value was 336.92 nmol/L, and for cortisol 2 a mean value of 205.58 nmol/L was identified. We can clearly say that in control group subjects, for all age groups, mean cortisol 2 values were about 130 nmol/L lower than those recorded during the mornings (Figure 5).

Mean morning cortisol measured in subjects enrolled in group 2 was 392.93 nmol/L, and mean cortisol value measured at 8 PM in the same group was 228.55 nmol/L. Just like in the case of the control group, we can clearly state that the patients with cardiovascular issues, in all age groups, have mean values of cortisol 2 lower than the morning value with over 150 nmol/L (Figure 6).

Patients in group 2 had a more pronounced decrease in cortisol 2 values than in cortisol 1 (over 150 nmol/L), compared with the decrease recorded in the control group (about 130 nmol/L).

The patients in group 2 recorded a mean cortisol 1 value higher (392.93 nmol/L) than the one of the control group (336.92 nmol/L), the difference between the two values being statistically significant ($P = 0.009$).

Although average values of cortisol 2 were higher in patients with cardiovascular disease (228.55 nmol/L) compared with the values obtained in the control group (205.58 nmol/L), the difference was not significant in statistical terms.

Table 2: Mean cortisol 2 in patients from subset 1 and 2′.

Cortisol 2	*N*	Average	CI95%	SD	Minimum	Maximum	*P*
Subset 1	66	205.58	186.27–224.88	78.54	67	327	<0.001
Subset 2′	41	281.42	270.76–292.07	33.74	194	326	

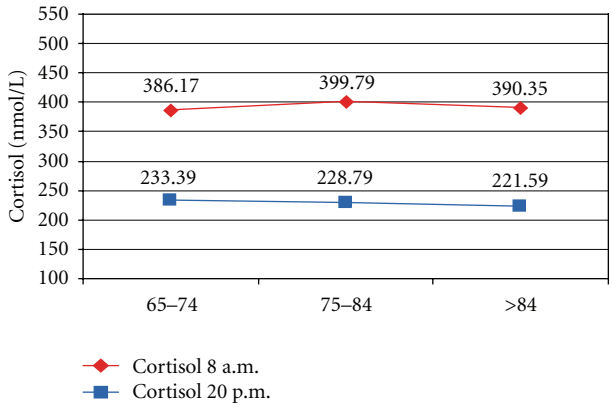

Figure 6: Dynamics of cortisol values in group 2.

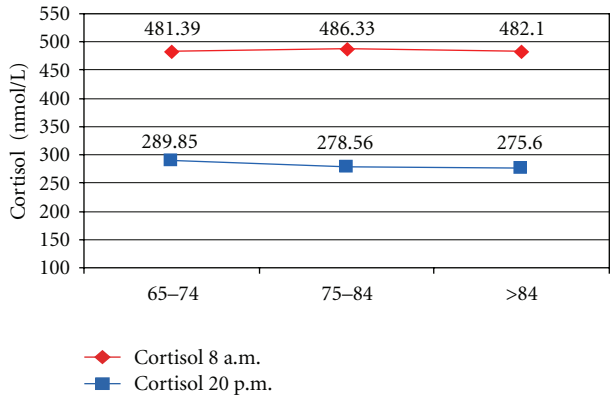

Figure 7: Dynamics of cortisol values in hypertensive patients.

For group 2′ (cardiovascular afflicted patients, with dominating hypertension symptoms), mean morning cortisol was 483.73 nmol/L and the evening cortisol in the same patients was 281.42 nmol/L. In hypertensive patients, mean cortisol 1 values, by age groups, were similar, ranging between 481 and 486 nmol/L, to cortisol 2 values which ranged between 275 and 289 nmol/L (Figure 7).

Decrease in cortisol 2 values in patients with hypertension was around 200 nmol/L to morning cortisol in all age groups. Comparing, the biggest difference between values of cortisol 1 and 2, in patients in group 2′, was recorded in the age groups of 75 to 84 and over 84 years (42.7% and 42.8%) (Figure 8).

4. Discussion

The present study confirms some existing data in the literature, namely that, in the elderly, normal levels of cortisol are recorded. Because of purely economic reasons, multiple

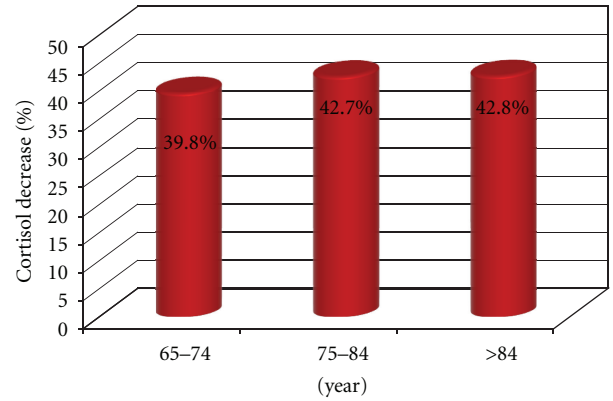

Figure 8: Percentage decrease in cortisol levels, by age groups, in group 2′.

measurements of cortisol levels could not be performed in the same patient.

In some studies, normal values of cortisol in elder patients have been recorded, but with a decrease in the amplitude of its diurnal variations [10]; slightly elevated values have also been recorded [11], especially in men with cardiovascular diseases [12], resistance to cortisol suppression also being noticed in other studies [13].

In this study, the dynamics of cortisol was within normal reference limits, both in healthy elderly and in elderly hypertensive patients, with occasional narrowing or widening of the range of obtained results.

We noted that healthy women over 65 years in group 1 had higher mean cortisol levels than average elderly men from the same set.

Elderly hypertensive patients had mean cortisol values greater than those obtained in healthy people aged over 65 years. It is highly important that the mean values of cortisol, regardless of when they were determined (morning or evening), varied along with the severity of blood hypertension: the higher the degree of hypertension was, the higher the mean cortisol value was.

Patients with cardiovascular disease, especially hypertensive patients, showed a more pronounced decrease of evening determined cortisol values, compared with healthy elderly.

5. Conclusion

(1) Mean morning and evening cortisol measured in both groups were within normal limits, approaching the upper limit of reference.

(2) Mean morning and evening cortisol determined were higher in healthy women compared with men from the same group.

(3) The mean values of morning and evening cortisol recorded in hypertensive patients were higher than the values obtained from healthy patients.

(4) The severity of blood hypertension correlated with cortisol values: the higher the grading of hypertension was, the higher mean cortisol determined during morning or evening was.

(5) We take into account the need to introduce the screening of hormonal levels (specifically cortisol values) in elderly patients, because the modified values of certain hormones may become predictive factors for the evolution and prognosis of cardiovascular diseases.

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Review Article

Lipid Disorders in Elderly Hypertensive Patients

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Lipid disorders are a common clinical challenge in the western countries. In patients with dyslipemia (total cholesterol > 200 mg/dl, HDL cholesterol < 35 mg/dl, LDL cholesterol > 130 mg/dl and triglycerides > 150 mg/dl) it is mandatory to normalize blood pressure (<130/80 mmHg) as well to reduce LDL-C values to normal levels by using drugs to inhibit of endogenous and exogenous cholesterol, to decrease triglycerides, and increases HDL-C up to normal range. It is also essential to maintain for this purpose suitable dietetic measures (reduction of unsatured fats and salt intakes—<2.5 g/daily) and without interruption, to support pharmacologic treatment in most of the patients.

1. Introduction

During many years I have been observing very often some misunderstanding therapeutic ideas from several physicians about the management of patients with lipid disorders mostly in older hypertensive patients. This situation is directly related to an insufficient therapeutic control due to inadequate drug dosages. However, we must not neglected this point because good control is crucial for clinical point of view and for the prognosis of the patients.

It is well established the relevance to provide some measures for the prevention and delay of atherosclerosis that is closely related to the well-known cardiovascular risk factors, such as, hypertension, smoking habit, dyslipemia, obesity, diabetes, and many others disorders. On the other hand, severe or fatal cardiovascular events related to the risk factors are also important in order to offer the patients a better management to reduce stroke, artery coronary disease, peripheral arteriopathy, and other vascular diseases in western countries.

Hypertension, together with smoking habit and high blood lipid levels, represents the most important pathogenic cause for atherosclerosis and subsequent clinical severe diseases.

The following ideas are based on my clinical experience during many years on this particular clinical disorder.

Table 1: Levels of total cholesterol, triglycerides, HDL cholesterol, and LDL cholesterol according to NECP Guidelines. Adult Panel III (2002).

Cholesterol	Goal
Ideal	<200 mg/dL
High limit	200–239 mg/dL
High	>239 mg/dL
HDL cholesterol	40–55 mg/dL
LDL cholesterol	50–130 mg/dL
Triglycerides	50–150 mg/dL

2. Lowering Lipid Levels

As part of an overall strategy to stop atherosclerosis, control of hypertension is very important (BP ≤ 140/80 mmHg) in all cases using general measures (diet, salt restriction, relief of stress, regular aerobic exercise, and dietary management: caloric restriction, reduction of cholesterol and saturated fats intake) as well as drug therapy when necessary [1]. Smoking habit, for example, must be stopped as soon as possible, and Current National Guidelines recommend having cholesterol level screening in adults [2]. They also propose to obtain a fasting lipid profile (including total cholesterol, triglycerides,

Table 2: Drugs recommended to normalise lipid disorders.

Drugs to reduce LDL cholesterol	New statins
	ACAT inhibitors
	MTP inhibitors
	Bile acids transport inhibitors
	Specific cholesterol absorption inhibitors (Ezetimibe)
Drugs that increase HDL cholesterol	Nicotinic acid
	PPAR α/β dual agonists
	Lipoprotein lipase activators
	CETP inhibitors
Drugs to treat Hypertriglyceridemia	Fibric acid derivatives
	Icosapent ethyl ester
	Doconexent ethyl ester

ACAT: Acyl-CoA cholesterol acyl transferase; MTP: microsomal triglyceride transfer protein; PPAR: proliferator-activated receptor; CETP: cholesteryl ester transfer protein.

Table 3: National Cholesterol Education Program. Therapeutic target according with the lipids blood levels.

Category of risk	Target LDL-Ch	LDL-Ch levels for no drugs	LDL-Ch level for drug use
IC (risk to 10 years >20%)	<100	≥100	>130; 100–129 optional therapy
2+ risk factors, risk to 10 years (≤20%)	<130	≥130	Risk to 10 years 10–20% ≥130 risk 10 years <10% ≥160
0-1 risk factors	<160	≥160	≥190; 160–189 LDL-Ch optional lipid drugs

IC: ischemic coronary disease.

LDL cholesterol, and HDL cholesterol) in patients with known vascular diseases and those with several risk factors or elevated total cholesterol levels.

3. Some Frequent Errors Observed in the Clinical Practice

Unfortunately, three types of mistakes are very common present in clinical practice by many physicians: (1) some colleagues take as normal lipid values clearly high and neglecting the reference values expressed on Table 1. At this point, many patients with moderately high cholesterol, triglycerides, LDL-cholesterol and decreased HDL cholesterol with values below ranging between 35 and 40 mg/dL do not receive any treatment; (2) it is well-known that statin/fibrate combination therapy is not recommended in same patient to treat mixed dyslipemia; but unfortunaly, this procedure is maintain by physicians in many cases. These associations are not adequate because of their increasing side effects rhabdomyolysis, severe and even fatal in some patients; (3) in my clinical experience, the most common error that I have observed is the discontinuation of lipid lowering therapy when normal values are reached; obviously expected, lipid values become again pathologically high after suspension of therapy (statins, fibrates, or ezetimibe) (Table 2).

Nevertheles, thanks to the therapeutic arsenal available today, observed normalization of lipid values in a large percentage of patients. The 4S study [3] demonstrated for the first time that intensive treatment to decrease lipid levels achieved reduced mortality rate in patients with coronary heart disease and cholesterol values between 212 and 309 mg/dL (mean: 260 mg/dL). The CARE study [4] showed beneficial effects in patients with history of coronary heart disease and total cholesterol of 175 to 240 mg/dL (mean: 211 mg/dL); the LIPID trial [5] showed an improvement in total cardiovascular mortality rate with cholesterolemia levels below those reported in the 4S study (mean: 220 mg/dL).

The AFCAPS/TexCAPS study [6] showed the benefit of lipid-lowering treatment of cardiovascular morbidity and mortality rate in primary prevention in individuals with levels between 180 and 264 mg/dL (mean, 221 mg/dL) aged 45–75 years, as well as a slight decrease of HDL-C levels in individuals with cholesterol values considered within the normal limits (180–264 mg/dL; mean: 221 mg/dL). The PROVE-IT [7] demonstrated that intensive lipid-lowering therapy versus standard treatment reduced significantly cardiovascular morbidity and mortality rate after acute coronary syndromes.

These studies have cleared the way to recommend statins therapy in patients treated for secondary prevention (high risk) and primary prevention with other related risk factors (Table 3).

Our experience demonstrated in hypertensive patients older than 60 as the coadministration of ezetimibe/simvastatin + fenofibrate improved atherogenic lipid profile with mixed hyperlipidemia [8]. Another recent study, with participation of my group [9] showed that the association of "extended-released niacin and laropiprant (ERN/LRDT) + statin" significantly improved the lipid profile compared to

the run-in dose doubled, and it was generally well tolerated in patients with primary hypercholesterolemia and mixed dyslipemia. The protocol was the following: after a 2- to 6-week run-in statin (simvastatin 10 or 20 mg or atorvastatin 10 mg) period, 1216 patients were randomised equally to one of two treatment groups in a double-blind fashion: group 1 received ERN/LRPT (1 g) plus the run-in statin dose and advanced to ERN/LRPT (2 g) after 4 weeks for an additional 8 weeks, with no adjustments to the run-in statin dose; group 2 received simvastatin or atorvastatin at twice their run-in statin dose and remained on this stable dose for 12 weeks.

Some of the molecules under study (clinical trials phase II or III) in which our unit is participating actively are expressed in Merck Pipeline: cardiovascular: MK-0736, MK 6621 (vernakalant), atherosclerosis MK-0524-A (tredaptive), MK-0524B, and MK-0859 (anacetrapib).

In summary, treatment and control of arteriosclerotic vascular disease in hypertensive patients needs the overall treatment of the risk factors; in particular, in patients with dyslipemia, it is necessary to normalize blood pressure, to reduce LDL-C values to normal levels by the inhibition of endogenous and exogenous cholesterol, as well as to decrease triglycerides, and increase HDL-C levels, so that it is essential to maintain dietetic measures (reduction of salt and unsaturated fat intakes) and continuous pharmacologic treatment in most of the patients.

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Review Article

Ambulatory Blood Pressure Monitoring in the Elderly

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The incidence of hypertension is high in the elderly and is present in 2/3 of the patients older than 65 years. Prevalence can reach 90% in patients older than 80 years. The presence of isolated systolic hypertension (ISH) is characteristic of this population. However, the prevalence of hypertension by ambulatory blood pressure monitoring (ABPM) is not well known. In this study, we analyzed the special characteristics of hypertension in this population, giving special emphasis on ABPM readings.

1. Introduction

The incidence of hypertension is high in the elderly, and it is present in 2/3 of the patients older than 65 years [1]. Prevalence can reach 90% in patients older than 80 years [2]. Systolic blood pressure (SBP) increases with age [3], and the presence of isolated systolic hypertension (ISH) is characteristic of this population. However, the prevalence of hypertension diagnosed by ambulatory blood pressure monitoring (ABPM) is not well known. The PROOF study [4] carried out in French patients aged older than 65 years showed that clinical blood pressure (CBP) was elevated in 58% of the patients, and 31% had diurnal SBP >135 mmHg by ambulatory monitoring. In this study, we analyzed the special characteristics of hypertension in this population, giving special emphasis on ABPM readings.

2. Characteristics of Hypertension in the Elderly

Ageing results in a decline in the cardiac output and cardiac frequency (beta-receptors-mediated response), as well as a trend towards ventricular hypertrophy, reduction of the left ventricular filling, renal plasma flux and renin plasma, and an increase in renal and peripheral resistances.

Ageing also produces an increase in arterial stiffness, a reduction of the *compliance,* and an increase in the pulse pressure; this, together with an increase in peripheral resistances, leads to ISH. Several systems are involved in the increase of peripheral resistances, such as reduction of beta-2 receptors involved in vasodilation, or reduction in sodium ions, potassium and calcium ions, renin-angiotensin system, sympathetic nervous system, hormones, natriuretic factors, and endothelial factors. All this can explain the frequency of ISH, blood pressure (BP) variability, and the episodes of associated orthostatic hypotension. Old subjects present more frequently essential hypertension (except for renovascular secondary hypertension) and more severe target organ damage than the younger population. Hypertension affects subjects with a higher prevalence of ischemic heart disease, myocardial infarction, diastolic dysfunction, a tendency to arrhythmia and in general cerebral arteriosclerosis and peripheral arterial disease. There are also present other factors such as diabetes, and other concomitant diseases like pulmonary disease, depression, neoplasia, and so forht that should be considered when making diagnosis and treatment decisions.

3. Normality Values

Normality values of ABPM are based on several studies [5] (Table 1) on adult populations older than 65 years, despite that it is less represented by subjects aged 70–75

Table 1: Blood pressure values in adults according to ABPM.

	Optimal values	Normal values	High values
Wake cycle	<130/80	<135/85	>140/90
Sleep cycle	<115/65	<130/70	>135/75

years or older. Published reports of patients older than 65 years showed mean daytime BP values ranging from 128/77 mm Hg [6] to 140/78 mm Hg in a UK study (including ambulatory and hospitalized patients), 134/81 mm Hg in a healthy population [7, 8] in Germany, and values of 138/82 mm Hg were found in patients aged 60–79 years and 147/83 mm Hg in patients older than 80 years [9]. These values could be higher in diabetics or high vascular risk patients.

Therefore, normality values must be carefully studied in patients older than 80 years. It is not known yet the benefit of reducing clinical BP in this population group. Previous studies like HYVET, demonstrated a reduction in the mortality rate in 3.845 patients with SBP >160 mm Hg, with the aim of reaching values of SBP <150 mm Hg, but this study included patients with good physical and mental conditions, without previous cardiovascular disease, and only 7% of them were diabetics.

Bejan-Angoulvant et al. [10] carried out a meta-analysis in patients older than 80 years and demonstrated that intensive treatment reduced 35% of the risk of stroke, 50% of the risk of heart failure, and 27% of cardiovascular events, without differences in total mortality.

Evidences of reducing BP under 140/90 mm Hg in old subjects has been recently discussed; however, any active treatment trial versus placebo therapy has been able to reduce SBP under 140 mm Hg [11]. Therefore, there is no clinical evidence showing which are the normal BP values in old patients and even less by ABPM measurement.

4. Isolated Systolic Hypertension

ABPM data of patients with ISH are mainly reported in the SYST-EUR study [12], in patients older than 60 years with baseline clinical systolic blood pressure (CBP) values of 160–219 mm Hg and diastolic BP values lower than 95 mm Hg. Patients were randomized and treated with nitrendipine (10–40 mg/d) and the possible addition of enalapril (5–20 mg/d) according to BP values and/or hydrochlorothiazide (12,5–25 mg/d) and were compared to placebo. SBP was associated with a poorer prognosis.

Clinical SBP of 160 mm Hg was correlated with a 24-h SBP monitoring of 142 mm Hg, 145 mm Hg for daytime BP, and 132 mm Hg for nighttime BP. Differences of the SBP between clinical and ambulatory BP measurement were higher in old subjects (Figure 1).

A study [13] carried out in 578 patients aged older than 70 years demonstrated not only the predictive capacity of ABPM with respect to cardiovascular morbidity but also the capacity to diagnose hypertensive patients with normal BP values at the doctor's office.

Today, the US and European consensus for ABPM agrees that ABPM measures are important in children and old people, since CBP does not reflect accurately real BP values in these population groups [14]. This is very important to control antihypertensive therapy and establish the most adequate treatment.

5. Pulse Pressure and Arterial Distensibility

Both conditions are more frequently found altered in older ages. It is well known that pulse pressure (PP) is an independent cardiovascular risk factor especially present in old subjects [15, 16] as a result of a decline in left ventricular ejection, arterial distensibility, and reflected wave velocity. ABPM is a better estimate of PP than CBP. SYST-EUR analyzed PP by ABPM in 808 patients.

In the placebo group, 24-h and nighttime PP was predictive of total and cardiovascular mortality, stroke, and cardiac events. Daytime PP was a predictor of cardiovascular mortality, all cardiovascular events, and stroke. The hazard rates for 10 mm Hg rise was from 1.25 to 1.68; however, conventional measurement of pulse pressure was 1.35. No significant differences were found in the active treatment group.

Staessen et al. [17] reported that PP estimated by ABPM was a better predictor of events than that measured using CBP in old people with ISH.

In the PIUMA study [18], ABPM values were observed in 2010 untreated hypertensive patients. In this study 24-h PP distribution into terciles was associated with an increase in cardiovascular mortality of 1.19, 1.81, and 4.92 after adjustment for other risk factors. It is suggested that 24-h PP is a good predictor especially when values are higher than 53 mm Hg. Later, in a 3.8-year follow-up study [19] carried out in patients older than 60 years, the highest SBP and PP and lower DBP were correlated with mortality. A median nighttime PP of 78 mm Hg of the 4th quartile showed a 4.4 times greater risk when compared with the first quartile of PP.

However, Masahiro et al., in a study carried out in 1542 Ohasama residents, found that the ambulatory arterial stiffness index (AASI) and PP were reliable to measure arterial stiffness and to predict vascular mortality, although PP when adjusted for age and gender was less efficient in the prognostic value of vascular events of the ABMP or AASI [20].

Arterial distensibility can be measured indirectly by pulse wave velocity, which is altered with age. Asmar et al. [21] found a good correlation between ABPM and arterial distensibility; therefore, ABPM could provide indirectly a reliable assessment of arterial distensibility.

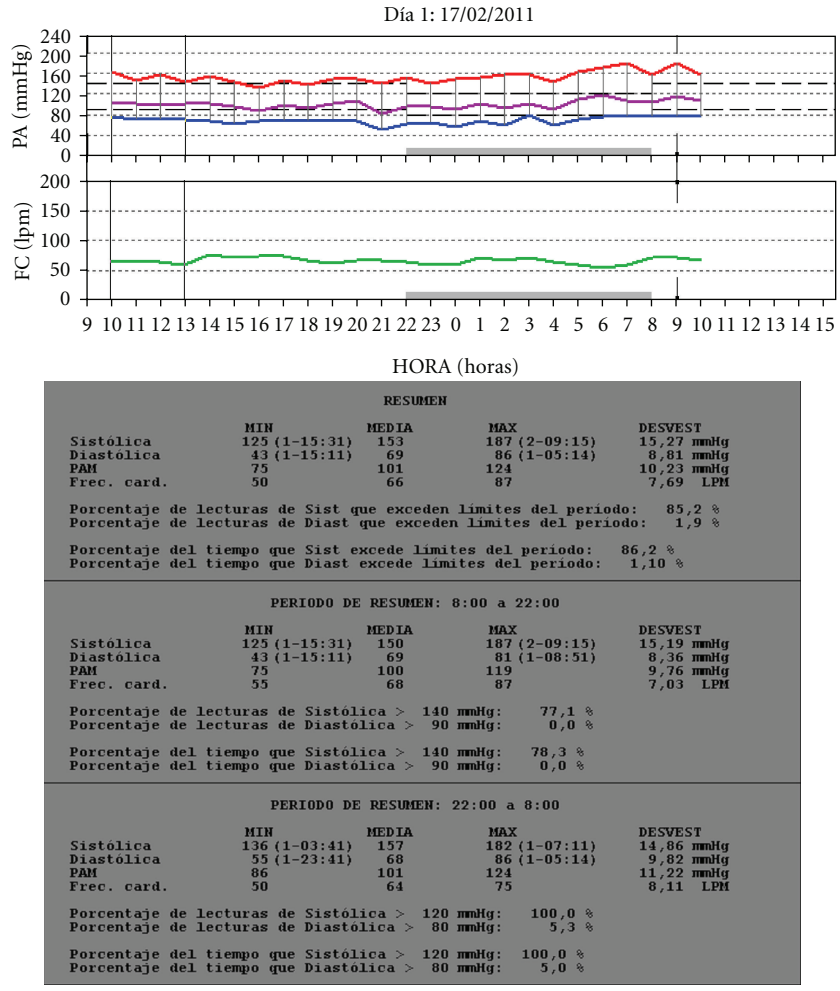

Figure 1: Patient aged 78 years with isolated systolic hypertension and riser pattern.

6. Nighttime Systolic Blood Pressure

Nighttime SBP is becoming more and more important, as reported in the SYST-EUR study [12] or HOPE substudy [22] in which the effect of nighttime administration of ramipril produced a significant fall (17/8 mm Hg) in nighttime BP values, not appreciated in CBP measurement. In an Anglo-Scandinavian cardiac outcomes trial substudy (ASCOT) [23] carried out in patients with a mean age of 63 years, nighttime SBP was a predictor of vascular events. The decrease in nighttime SBP was higher in the amlodipine-perindopril group than in the atenolol-thiazide group without differences in the daytime BP values. The differences found in the nighttime BP could explain the higher benefit obtained in the amlodipine-perindopril group. DUBLIN study [24] analzed the relationship between CBP, ABPM, and mortality in 1144 patients aged older than 65 years, and found that nighttime SBP was the best correlated, with a risk ratio estimation of 1.18 (1.11–1.25, $P < 0.001$).

7. Hypotension

Orthostatic hypotension can occur at any age; however, it is more frequent in the elderly. It is defined as a decrease in the SBP of at least 20 mm Hg or a decrease in the DBP of 10 mm Hg in the orthostatic position 3 minutes after BP measurement in the supine position [25]. It is generally associated with dizziness, slight sweating, and sometimes it is asymptomatic. ABPM is a better predictor of these events than CBP [26]. Many of these events are related to medication (diuretics and beta blockers), diabetes, or disautonomy (baroreceptors) and are more frequently found in the elderly.

Postprandial hypotension is more frequently found in old subjects [27] and is defined as a decrease in SBP of more than 20 mm Hg up to 1 hour after eating, without alteration of heart rate. Postprandial hypotension has been reported as predictor of mortality in some studies [28, 29]. Figure 2 shows the ABPM readings of an old subject with hypotension episodes.

8. White-Coat Hypertension

The white-coat effect occurs when CBP is temporary elevated in the clinical setting but not at home. This phenomenon was described by Scipione Riva-Rocci in 1897, but it was really studied in the clinical setting after the introduction of

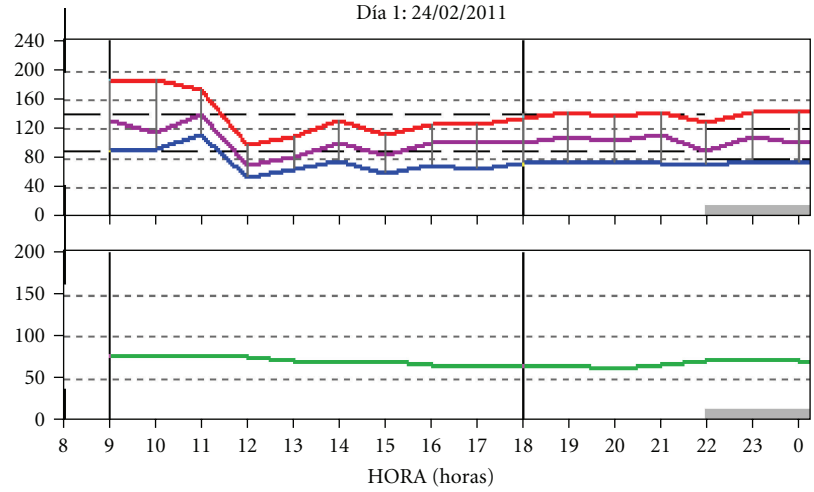

Figure 2: Patient of 79 years old with hypertension and diabetes. Combined therapy with 4 antihypertensive agents. Hypotensive episodes.

ABPM. Its prognostic significance is not yet clear. In some studies [30–32] mortality rate was 2 or 3 times higher, and it was considered an independent factor for left ventricular mass hypertrophy, increase of arteriosclerosis, or increase in carotid intima-media. Other authors [33, 34] think that white-coat hypertension (WCH) does not correlate with organ damage or cardiovascular events. Age was found to be an independent and common factor influencing WCH in the multivariate analysis of different studies [35–37]. WCH clearly increases with age. In old patients with ISBP [38] the effect of SBP reached 21 mm Hg. These authors reported that the elevation of CSBP in untreated old patients is the main factor to suspect white-coat effect.

9. Masked Hypertension

Masked hypertension is defined as a normal blood pressure (BP) in the clinic or office (<140/90 mm Hg), but an elevated BP out of the clinic (ambulatory daytime BP or home BP >135/85 mm Hg) [39]. Its prevalence is not well known, but it has been suggested to be about 10–20% of the general population [40, 41]. It is well known that it is associated with a more severe lesion of the target organ [42–44] and cardiovascular events [13, 45]. It seems that MH is not more frequent in old patients. Bobrie et al. [46] in a study carried out in 4939 patients older than 65 years, reported a prevalence of MH of 9.4%, with CBP <140/90 mm Hg for office BP and 135/85 mm Hg for home BP. In fact, it has been suggested that masked hypertension must be suspected in smoker young men, with unhealthy lifestyle, high vascular risk, diabetics, presence of renal disease with proteinuria, daytime hyperactivity, and patients with transient hypertension [47].

10. Circadian Blood Pressure Patterns

ABPM allows knowing BP absolute values and gives information about circadian BP rhythm. According to these patterns, patients are classified as *dipper* (a decrease of BP at night >10%), *nondipper* (BP decrease <10%), *extreme dipper* (BP decrease >20%), and *riser pattern* (an elevation of BP at night). There are increasing evidences that nondipper pattern is associated with a poorer cardiovascular prognosis [48, 49], which has been reported by Staessen et al. [12] in old patients with ISH. Other authors reported that the non-decrease of BP at night is related to the degree of concurrent lesion of the target organ, severity of cardiovascular disease, and alterations in sleep quality [50].

Patients with a lower decrease of BP at night due to insomnia do not seem to present a poorer vascular prognosis, or, if so, it is not related to the nondipping pattern but probably due to a higher value of nocturnal BP [51]. Sleep quality alterations are more frequent in the elderly; therefore, the circadian pattern in these patients must be carried out more carefully. The 24-hour diary to record daily ABPM is indispensable in these patients to adjust the sleep-wake cycle.

A prevalence of 25–35% of the nondipping pattern was observed in the general population. A Spanish study [52] carried out in 42,947 patients showed a nondipping pattern of 41%, which reached 53% in treated hypertensive patients. This pattern can reach up to 60% in high-risk patients [53]. It must be remembered that old patients present higher levels of SBP and a higher vascular risk, target organ damage, diabetes, renal disease, or associated disease, all of them being related to the nondipping pattern [52]. Generally, the loss of the circadian pattern with a lower decrease of nocturnal BP is associated with age, both in men [54] and very old women [7], and in centenarian patients [8, 55].

The morning elevation of BP is also important [42, 56]. Kario et al. [57] in a study carried out in old patients found a clear correlation between lesions in the white substance and the morning elevation of BP, independently of the absolute values of BP.

Further studies are needed in order to determine whether morning elevation of BP is especially relevant in the old population.

Table 2: Studies published on ABPM in subjects older than 65 years.

Study (year)	No. of patients	Age range	Time of followup	Results
Lee et al. (1995) [8]	102	65–93	NA	Normality values
Fotherby and Potter (1995) [7]	108	65–>80	NA	Normotensive values of ABPM Nondipping pattern
Sega et al. (1997) [6]	800	65–74	NA	Population base. Normality values
Hoshide (2002) [67]	811		41 months	ABPM was more useful than CB P in extreme dipper and riser patterns
Wing (2002) [68]	713	65–83	N/A	ABPM prevents overtreatment
O'Sullivan et al. (2003) [9]	156	78	NA	SBP was associated with age Nondipping pattern and age
Björklund et al. (2004) [13]	872 (men)	70	9.5 yrs	Prognosis of cardiovascular risk
Burr et al. (2008) [24]	1144	72	6.7 yrs	ABPM as mortality predictor. Nighttime SBP as best predictor
Ungar et al. (2009) [19]	805	72	3.8 yrs	SBP, PP with low DBP, and mortality
Gosse et al. (2010) [4]	955	>65	N/A	Population base. Prevalence of hypertension
Andrade et al. (2010) [62]	106	83	30 months	ABPM predicts cardiovascular events. SBP loads

NA: not applicable.

Diurnal and nocturnal BP variability (defined by quantification of SD of mean BP) is associated with an increased cardiovascular risk, left ventricular mass, and progression of carotid intima-media thickness [58, 59]. Mediavilla García et al. [60] reported a significant relationship between BP variability, age, and glomerular filtration. In the PIUMA study [61] cardiovascular morbidity was associated with BP variability and age. In a SYST-EUR substudy of 744 old patients, which analzed BP variability in 24 h, daytime, and nighttime, nocturnal BP variability of 5 mm Hg was associated with an increased risk of cardiovascular event of 80% with respect to the placebo group.

11. Blood Pressure in Very Old Subjects

Although several studies have reported the relationship between ABPM and cardiovascular risk in the elderly (Table 2), few studies have been published on subjects older than 80 years. Generally these studies [7, 9, 55] are carried out in patient samples with a different population base too small to obtain valid conclusions; however, in this population subset older than 80 years, SBP by ambulatory measurement was higher than that of the subgroup of younger patients. Andrade et al. [62] recently studied 126 patients with a mean age of 83.8 years. The variables associated with the number of cardiovascular events during followup were patients with a clinical history of cerebrovascular event and higher diurnal SBP values.

12. High Blood Pressure and Dementia

Dementia from all causes has a prevalence of about 8% of the population over 65 years. Between 15 and 30% of these cases are vascular. In the elderly, subcortical small vessel disease is known to be associated with vascular dementia. Mild cognitive impairment (MCI) is described as a transition phase between healthy cognitive aging and dementia.

This concept facilitated case identification in early stage, and its progression may be preventable through modification of vascular risk factors as hypertension.

The SYST-EUR study [12] showed that a decrease of 7 mm Hg in SBP and 3,2 mm Hg in DBP over 3,9 years will reduce significantly the incidence of dementia. In the Women's Health Initiative Memory Study (WHIMS, [63]), the cognitive function of 7.149 women aged >65 years was assessed using the modified minimental state examination. During a follow-up period of 4,5 years, women with hypertension appeared to be at greater risk of dementia or MCI. Based on these studies, hypertension is associated with the development of MCI and dementia.

ABPM has been shown to provide a better predictive value for cardiovascular events than clinic BP. Recent studies have shown that ambulatory BP variation is associated with cognitive function. High nocturnal SBP level [64], Nondipper status [65], and exaggerated BP variability are suggested to be significant determinants of cognitive impairment. In addition, 24-hour SBP has been shown to be a independent factor for brain atrophy in the elderly [66]. So an strict BP control, including nighttime, may have a neuroprotective effect and prevent the incidence of dementia. The recent literature support that ABPM would help us in an earlier diagnosis of MCI.

13. Conclusions

In conclusion, there are many reasons to recommend ABPM in hypertensive old patients, such as ISBP, differences

between clinical and ambulatory BP, PP, magnitude of the white-coat effect, assessment of orthostatic hypotension values and its relationship with the patient medication, nighttime hypertension, mild cognitive impairment and BP variability. These important variables demonstrate that just the fact of being an aged patient is a sufficient reason to perform ABPM. We support that the diagnosis of hypertension by ABPM may have substantial clinical and epidemiological implications.

Even so, further studies are needed to demonstrate the importance of ABPM values in the study of the morbidity and mortality in these patients.

Abbreviations

HORA:	Hours
PA:	BP
FC:	HR
LPM:	BPM
Dia 1:	Day 1
Horas:	Time (hours)
Sistólica:	SBP
Diastólica:	DBP
PAM:	M BP
Frec. Card:	HR
MIN:	Minimum
MEDIA:	Mean
MAX:	Maximum
DESVEST SD:	Standard deviation
Lpm:	bpm (beats per minute)
Porcentaje de lecturas de sist que exceden limites del periodo:	Percentage of SBP readings of the period
Porcentaje de lecturas de diastolica que exceden limites del periodo:	Percentage of DBP readings of the period
Porcentage del tiempo que diastólica excede limites del period:	Time percentage of SBP readings.

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Research Article

Hypertension and Dementia in the Elderly: The Leisure World Cohort Study

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Recent studies have highlighted the deleterious role of cardiovascular risk factors, including hypertension, on the incidence of dementia. Although midlife hypertension is associated with later development of dementia, the role of late-life hypertension remains unclear. We explored the association of hypertension and its treatment with incident dementia in 13978 older (median = 74 years) adults followed from 1981 to 2010 (median = 13 years) and calculated risk estimates using Cox regression analysis in two age groups (<75 and 75+ years) in men and women separately. Dementia status was determined from in-person evaluations, followup questionnaires, hospital data, and death certificates. In the older women, current users of blood pressure medication at baseline had a 26% increased risk of dementia (95% CI 1.06–1.51). In the younger men, those with untreated hypertension and those with past use of blood pressure medication use had about a 30% nonsignificant increased risk of dementia. High blood pressure and its treatment appear to have different effects in men and women and in the old and older.

1. Introduction

As a result of an aging population, the prevalence of dementia, which in 2005 affected 24.3 million people worldwide, is expected to afflict more than 81 million by 2040 [1]. Recent studies have highlighted the deleterious role of cardiovascular risk factors, including hypertension, on the incidence of dementia and suggested that their therapeutic control may reduce risk of development of dementia in later life [2, 3]. Several longitudinal studies have found midlife hypertension to be related to dementia (reviewed in [3, 4]), but the role of late-life hypertension remains unclear.

The focus of the present study was to examine the possible role of hypertension and its treatment as predictors of dementia in elderly men and women. We report here the results in a large cohort (nearly 14000) of elderly (median age 74 years) men and women followed for up to 29 years (median 13 years).

2. Methods

The Leisure World Cohort Study was established in the early 1980s when 13978 residents of a California retirement community (Leisure World Laguna Hills) completed a postal health survey. Residents were recruited in four waves: those who owned homes in Leisure World on June 1, 1981; new residents who had moved into the community and were living there on June 1, 1982; on June 1, 1983; on October 1, 1985. The baseline survey asked demographic information, brief medical history, medication use, and personal habits including cigarette smoking, exercise, alcohol consumption, and beverage intake. The subjects were asked if a doctor ever told them they had high blood pressure and if they had ever taken or were currently taking specific medications including "Reserpine (please include Raudixin, Ser-Ap-Es, Hydropres, Rauwolfias, Metatensin)" and "other blood pressure medication, water pills." The population and

the cohort are mostly Caucasian, well educated, upper-middle class, and elderly.

Followup of the cohort is maintained by periodic resurvey (1983, 1985, 1992, 1998), review of local hospital discharge data (1981–2001), and determination of vital status by search of governmental and commercial death indexes and ascertainment of death certificates. The 1983 followup questionnaire asked new diagnoses of high blood pressure since the baseline survey. The 1998 questionnaire again asked if the subject had ever been told by a doctor that they had high blood pressure and the frequency of use of high blood pressure medication.

Dementia cases were identified from in-person evaluations as part of a dementia study [5], hospital records, death certificates, and/or followup questionnaires with the date of diagnosis being the date at which dementia was first mentioned. Participants were followed to dementia diagnosis, death or December 31, 2010, whichever came first. To date 37 cohort members have been lost to followup; search of death indices did not reveal that these individuals were deceased.

Chi-square tests were used for comparison of categorical variables and t-tests for testing differences in means of continuous variables. Age-adjusted hazard ratios (HRs) of dementia associated with hypertension were estimated using Cox proportional hazard regression analysis with age at study entry being the age when the baseline survey was completed and the event of interest being age at dementia. Separate analyses were done for two age groups: <75 years and 75+ years of age at baseline, with additional adjustment for age (continuous). Because women differ from men on many variables, women live longer on average than men, and for comparison with other studies limited to one sex, we performed separate analyses for men and women. Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC). No adjustment in the P values was made for multiple comparisons.

Previous reports present details of the methods and the reliability of recall of the self-reported information [6–9]. The Institutional Review Boards of the University of Southern California and the University of California, Irvine approved the study.

3. Results

At study entry, the participants' mean and median age was 74 years (standard deviation = 7). By December 31, 2010, 2429 participants had been diagnosed with dementia and 13134 had died. Age at dementia ranged from 66 to 106 years (median, 90 years). Dementia cases were identified by The 90+ Study (n = 690), hospitalization record (n = 199), followup questionnaire (n = 264), and death certification (n = 1768); these categories are not mutually exclusive.

Characteristics of the study participants are shown in Table 1. Women differed significantly from men on all these variables ($P < 0.001$ for all variables except cancer where $P < 0.02$).

Tables 2 and 3 show the age-adjusted HRs of incident dementia for hypertension and its treatment for women and men, respectively. Forty-three percent of subjects reported not having high blood pressure and not taking hypertensive medication. Of the remaining with high blood pressure, about 21% took no medication, 18% took medication in the past but not currently, and 18% were currently taking blood pressure medication. The only significant risk factor for dementia was current blood pressure medication (HR = 1.26, 95% CI 1.06–1.51) in women aged 75+ years. No effect of current treatment was seen in men. The greatest (though nonsignificant) risks in men were found among men less than 75 years old with untreated hypertension (HR = 1.27, 95% CI 0.95–1.70) and with past use of blood pressure medication (HR = 1.33, 95% CI 1.00–1.79).

Table 1: Characteristics of participants by sex, The Leisure World Cohort.

Number	Men 5101		Women 8877	
	Mean	SD	Mean	SD
Age at baseline (years)	74	7.2	73	7.4
Age at last followup (years)	86	7.0	88	7.0
Followup years	11	7.3	15	7.7
Active activities (hrs/day)	1.1	1.3	0.9	1.1
Other less strenuous activities (hrs/day)	3.6	2.7	4.4	2.6
Alcohol (drinks/day)	1.6	1.5	1.2	1.2
Caffeine (mg/day)	176	172	168	166
Body mass index (kg/m^2)	24	2.9	23	3.5
	No.	%	No.	%
Medical history				
High blood pressure	1843	36	3620	41
Angina	738	14	839	9
Heart attack	847	17	588	7
Stroke	370	7	333	4
Cancer	826	16	1574	18
Diabetes	425	8	442	5
Rheumatoid arthritis	226	4	608	7
Smoke				
Never	1708	33	4883	55
Past	2953	58	2880	32
Current	437	9	1106	12
Deceased by December 31, 2010	4930	97	8204	92

Followup questionnaires identified few additional individuals with hypertension. Of the 9731 who returned the 1983 followup survey, 188 (2%) reported a new diagnosis of high blood pressure. In 1998, 219 (11%) of 1963 who returned the questionnaire reported having high blood pressure in 1998 but not at baseline.

4. Discussion

In recent years the strict division between Alzheimer's disease and vascular dementia has faded with advancing research in neuropathology, neuroradiology, and epidemiology. Most dementia patients, irrespective of their clinical diagnosis,

Table 2: Hazard ratios for dementia by hypertension and its treatment in men, Leisure World Cohort Study, 1981–2010.

	Aged <75 years				75+ years			
	No.	No. with dementia	HR	95% CI	No.	No. with dementia	HR	95% CI
Hypertension and treatment								
No hypertension and no treatment	1160	153	1.00		1171	163	1.00	
Hypertension but no treatment	495	66	1.27	0.95–1.70	480	51	1.02	0.75–1.41
Past treatment	449	64	1.33	1.00–1.79	384	42	0.92	0.66–1.30
Current treatment	430	42	1.00	0.71–1.41	532	56	1.01	0.74–1.37
Current hypertensive medication								
No	2104	283	1.00		2035	256	1.00	
Yes	430	42	0.89	0.64–1.24	532	56	1.02	0.76–1.36

Table 3: Hazard ratios for dementia by hypertension and its treatment in women, Leisure World Cohort Study, 1981–2010.

	Aged <75 years				75+ years			
	No.	No. with dementia	HR	95% CI	No.	No. with dementia	HR	95% CI
Hypertension and treatment								
No hypertension and no treatment	2131	479	1.00		1522	345	1.00	
Hypertension but no treatment	1054	177	0.88	0.74–1.05	937	155	0.91	0.76–1.11
Past treatment	1011	202	0.90	0.77–1.06	685	137	0.92	0.75–1.12
Current treatment	750	148	0.99	0.82–1.19	787	149	1.21	1.00–1.47
Current hypertensive medication								
No	4196	858	1.00		3144	637	1.00	
Yes	750	148	1.04	0.87–1.24	787	149	1.26	1.06–1.51

have mixed pathology (Alzheimer's changes and cerebrovascular lesions) at autopsy [10, 11]. High blood pressure has long been understood to cause stroke, a risk factor for vascular dementia. However, the association between blood pressure and dementia is complex. Midlife hypertension increases risk of cognitive impairment, Alzheimer's disease, and dementia (reviewed in [3, 4]).

Associations in longitudinal studies of late-life hypertension and dementia have been less consistent. Some found blood pressure levels were higher in individuals who developed dementia [12], Alzheimer's disease [13], or vascular dementia [14] than in those who did not. In the Swedish Longitudinal Population Study of 382 participants (aged 70 years) subjects who developed dementia had significantly higher systolic and diastolic blood pressures about 10 to 15 years before cognitive assessment than subjects without dementia [12]. In the Kungsholmen Project, a community-based cohort of 1270 participants (aged ≥75 years) in Sweden followed for 6 years, 339 subjects were diagnosed with dementia [13]. Subjects with high SBP (>180 mmHg) had a risk of 1.6 (95% CI 1.1–2.2) for dementia. High DBP (>90 mmHg) was not associated with increased risk. In Hisayama Study, Japan, in which 828 people (aged 65–98 years) were followed for 7 years, blood pressure was not related to AD but 1 standard deviation increase in SBP increased risk of vascular dementia 60% (95% CI 1.2–2.2) [14]. The Adult Changes in Thought Study included 2356 participants aged ≥65 years followed for 8 years during which time 380 developed dementia [15]. Only in the youngest age group (65–74 years) did those with high SBP (≥160 mmHg) have a significantly increased risk of dementia (HR 1.6, 95% CI 1.01–2.55) and the risk declined with advancing age to 0.64 (95% CI 0.32–1.30) in the oldest age group (>85 years). In the Women's Memory Study blood pressure levels measured 5 and 9 years before dementia assessment did not differ significantly between demented and nondemented [16]. Others have observed that history of hypertension was not related to dementia [17, 18], Alzheimer's disease [19–22] but was related to vascular dementia [22]. Interestingly, in the Canadian Study of Health and Aging, the presence of hypertension did not result in cognitive deterioration across the cohort of subjects (mean age 83 years) [23]. However, subjects with hypertension and cognitive executive dysfunction increasingly progressed to dementia (58% in five years) compared with normotensives (28%) but not in those with hypertension and memory dysfunction (74% versus 67%).

Our study extends the available literature on the role of hypertension and dementia in the very elderly but has several limitations. Information on hypertension and blood pressure medication was self-reported; we performed no blood pressure determinations. However, previous studies in our population and others support the reliability of self-reported health practices, drug usage, and medical history of major chronic disease [8, 9]. Although changes over time in all potential risk factors may affect outcome, new cases of hypertension were reported in only a small minority of subjects. Additionally, the proportion of demented individuals

is undoubtedly an underestimate of the true incidence, and we lacked clinical diagnoses of dementia based on standard criteria for many subjects. Subjects with dementia who had not been seen in person or hospitalized and were not reported as having dementia at the time of the followup surveys or on their death certificates were actually misclassified into the nondemented group. This has, with all likelihood, weakened the associations seen here. For these reasons our results are preliminary and incomplete. Furthermore, our subjects are from a select population—moderately affluent, highly educated, health conscious, and primarily Caucasian. Although this may limit the generalizability of our results, it reduces potential confounding by race, education, SES, and presumed access to health care. Nonetheless, unrecognized and uncontrolled confounders cannot be ruled out in this study or any observational study.

Clinical trials of antihypertensive medication in older subjects have also yielded inconsistent results (reviewed by [2–4]). Randomized controlled trials have demonstrated that blood pressure-reducing agents decrease the incidence of dementia in stroke patients (PROGRESS [24], HOPE [25]) and in older (≥60 years) patients with isolated systolic hypertension (SYST-EUR) [26, 27], but this was not found in SHEP [28], SCOPE [29], and HYVET-COG [30]. These latter three included more elderly patients. The SHEP (Systolic Hypertension in the Elderly Programme) trial of 4736 patients (mean age 72 years) found a nonsignificant 16% reduction in dementia in treatment groups. The SCOPE (Study on Cognition and Prognosis in the Elderly) study of 4964 elderly (mean age 76 years) and HYVET-COG (Hypertension in the Very Elderly Trial-cognitive function assessment) of 3336 patients aged ≥80 years found no effect on cognitive decline, Alzheimer's disease, or vascular dementia. Since different antihypertensive medications were used by our study subjects as well as in the clinical trials which looked for an effect of medication on dementia development, a specific class effect cannot be ruled out.

Others have detailed the possible mechanisms by which hypertension may increase risk of dementia (reviewed in [3, 4]). Hypertension may promote blood vessel wall thickening leading to arteriosclerosis and lipohyalinosis; cause stroke, focal ischemia, chronic hypoperfusion of the white matter, and white matter lesions; cause microcirculation disorders and endothelial dysfunction which may compromise the function of the blood brain barrier leading to increased vascular permeability and extravasation of protein into the cerebral parenchyma.

Although not establishing a cause and effect relationship between incident dementia and high blood pressure and its treatment, this large elderly cohort suggests an increased risk of dementia in the younger (<75 years) men with untreated hypertension and with past use of hypertensive medication. This agrees with the findings of earlier studies showing an increased risk of dementia with higher measured blood pressure levels. In women the risk among current (at baseline) users of blood pressure medication, which was the strongest in the older age group (75+ years), highlights the need for careful monitoring of blood pressure in the elderly. Decline in blood pressure is common at ages above 75 years, and the Kungsholmen Project found low blood pressure to be associated with dementia risk (HR = 1.5, 95% CI 1.0–2.1) [13]. Periods of hypotension, hypoperfusion and hypoxia observed in subjects on antihypertensives might contribute to cognitive decline via reduced cerebral blood flow, causing ischemic lesions in the brain.

5. Conclusion

Although treating hypertension has a clear effect on stroke, cardiovascular disease, and mortality, the effect of hypertension and its treatment on dementia is more complex. While previous studies have found midlife hypertension to be related to dementia, results for late-life hypertension and its treatment are inconsistent. Our study in older adults suggests that the effect varies not only with age (with a difference between those less than 75 years old and those 75+ years old) but also with sex. Future studies examining the role of hypertension in older adults should perform sex-specific analyses.

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Research Article

Differing Pattern of Ambulatory Blood Pressure in Very Elderly Men Expresses Dynamics in Atherosclerotic Load in the Senescence

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To assess an impact of vascular risk factors on ambulatory blood pressure measurement (ABPM) in the elderly, we followed up a population-based cohort of men from 68 until 82 years, when 104 survivors underwent ABPM. *Results*. At age 68, hypertension and high clinic blood pressure (CBP) did not predict ABPM level. Smoking and low ankle-brachial index (ABI) predicted higher ABPM variability and pulse pressure (PP), but not absolute ABPM values. At age 82, hypertension, high or increasing CBP, strongly positively correlated with all variables of ABPM. Carotid stenosis, low or declining ABI during followup, correlated with higher nocturnal ABPM and PP. *Concluding*. Hypertension and vascular risk factors in a cohort of 68-year-old men do not result in higher ABPM at age 82, possibly due to inflection point in their pressure development. Higher ABPM reflects instead an increasing CBP and aggravating atherosclerosis during the preceding decade in that part of the cohort with previously favorable risk factor status.

1. Introduction

Blood pressure levels in the very elderly are more scattered than in younger elderly or middle-aged persons. After initial blood pressure increase, which occurred up to the seventh decade in both sexes, a blood pressure decline has been observed [1, 2]. High initial blood pressure level was typical for elderly subjects with subsequent BP decline [3]. Furthermore, levels of blood pressure in the very elderly have paradoxical inverse relationship to morbidity and mortality. The most described covariates and consequences of blood pressure decline have been shorter survival [4–6], cognitive decline [7, 8], and dementia [9–12]. Heart studies showed that demented patients had lower blood pressure and thinner left ventricle posterior wall [13]. Cognitive impairment was also common in subjects with heart failure combined with hypotension [14, 15].

Studies describing ambulatory blood pressure (ABPM) are mainly focused on younger elderly or middle-aged persons, mainly with essential hypertension, and seldom comprising population-based samples [16–20]. Frequency of sustained, white-coat, and reverse hypertension in the very elderly is also unknown. In most study centers, a profile of ABPM in younger elderly or middle-aged persons was used as a predictor of vascular events later in their life. In the very elderly, level of ABPM should be regarded not only as a predictor of target organ damage, but also as a mirror of general vascular status.

The aim of our study was to assess a profile of ABPM in a cohort of octogenarian men who were longitudinally followed since random inclusion from a population of city of Malmö, Sweden. Contrary to previous studies, we assessed an impact of vascular and life-style risk factors observed at age 68, and a time progress of atherosclerotic disease, on the ABPM profile when subjects reached the age of 82 years.

2. Methods

2.1. Study Sample. A prospective population sample study, "Men born in 1914", has been in progress since 1968. It includes all men born in the even months of 1914 in the city of

Malmö, Sweden. A total of 809 men were invited to participate in the study, and 703 men took part in the first health examination. When they were 68 years old, 465 men in the cohort and additional 95 new residents were invited to attend a new examination. Five hundred of them agreed to participate (Figure 1). The most recent followup of the cohort started when the subjects reached 81-82 years of age, and 281 men were found to be still alive. Of these, 185 agreed to take part (66%) in a new investigation, including both physical and psychological examinations. Blood pressure data and psychological data were available from 171 of them at the ages of 68 and 81. In the following year, 129 subjects underwent ambulatory blood pressure monitoring (ABPM). 25 subjects were excluded according to ABPM quality criteria. 104 subjects were included into the final statistical analysis.

2.2. Health Examination. Study subjects and their spouses answered to a questionnaire focusing on life-style factors, prescribed medicines, and previous diseases. All underwent medical examination including Hachinski ischemic score. To evaluate the role of established vascular risk factors, we measured levels of blood glucose, cholesterol, and triglycerides during fasting conditions and body mass index (BMI) at age 68. The participants were also classified as nonsmokers, former smokers, and smokers. Tobacco consumption of the smokers was measured as g/day. Alcohol consumption was self-reported and calculated in g 100% ethanol per week. At the recent followup at age 81, the medical examination was repeated, and 185 men answered a questionnaire focusing on lifestyle and health markers. Possible dementia was classified according to the DSM-IV criteria, and one subject was diagnosed as being demented.

Two established markers of vascular disease were examined: carotid stenosis, determined using carotid ultrasound at age 81, and low peripheral circulation in the lower extremities, estimated using the ankle-brachial pressure index (ABI) at ages 68 and 81.

2.3. Blood Pressure Measurement. The clinic blood pressure (CBP) was measured sphygmomanometrically in the upper right arm, in the supine position after 15 min of rest at age 68 and at age 81, using a calibrated mercury manometer and rubber cuffs (12×35 cm for normal, and 15 cm for obese subjects). Hypertension was defined as systolic and diastolic brachial BP $\geq$160 mmHg or $\geq$90 mmHg, respectively, or medication for hypertension. These hypertension criteria have been used previously and were valid until the World Health Organization drew up new ones in 1999 [21]. All the subjects had been monitored and treated during their lifetime according to these hypertension criteria, and they were thus used for the statistical analysis in this study.

2.4. Ambulatory Blood Pressure Monitoring at Age 82. Ambulatory blood pressure monitoring was performed using Micro AM Recorder, Model KI5600 (Kontron Instruments). Readings at 20-minute intervals during a day (from 06.20 AM to 09.40 PM) and at 60 min intervals at night (from 10.00 PM to 06.00 AM) were performed. Monitoring was performed in patient's private environment without specific advices regarding physical activity. The ambulatory BP-measurement was performed with auscultatory method, but in case of measurement failure the examination was immediately repeated using an oscillometric method. The accuracy of KI5600 was confirmed by a simultaneous measurement with a standard mercury sphygmomanometer and accepted if they were within 10 mmHg of standard method. The exclusion of patients was made according to the quality criteria: deficit in measurement time intervals at least 6 h accumulated during a daytime or more than 3 h accumulated at nighttime, or more than 3 h consecutively during a daytime or at least 2 h consecutively during a nighttime. For the individual data, the relative nocturnal BP fall was calculated using a formula: (daytime BP-nighttime BP) $\times$ 100/daytime BP, and expressed in %. Preawakening SBP was defined as a mean of measurements at 04.00, 05.00, and 06.00 AM. Postawakening SBP was a mean of measurements: 06.20, 06.40, 07.00, 07.20, 07.40, and 08.00. Morning SBP surge is defined as a difference between Postawakening SBP and Mean SBP nighttime.

2.5. Peripheral Arterial Circulation at Age 68 and 81. Ankle blood pressure was estimated, both at ages 68 and 81 years, by placing a cuff at the ankle level and using Doppler signal on tibial posterior artery or dorsal foot artery to detect peripheral blood flow in the supine position. Reference pressure in the arm was calculated using strain gauge recording system. Arithmetic average of duplicate recordings was used. For each leg, an ankle-brachial pressure index (ABI) was calculated by dividing the ankle systolic pressure with the highest upper arm systolic pressure value.

2.6. Carotid Duplex Ultrasonography. The examination of carotid arteries was made at age 81, using computed sonography system (Acuson XP 10, Acuson, Mountain View, Calif, USA) with a 7 MHz B-mode real-time linear scanner, including a 5 MHz-pulsed and color-coded Doppler. The color-coded Doppler was used to localize areas with high-flow velocities in the internal carotid artery, and the maximum-flow velocity (m/s) was measured with the pulsed Doppler.

2.7. Statistics. Summary values are expressed as mean $\pm$ standard deviation. Correlation analyses were performed using Spearman correlation test. Differences in vascular risk factors/markers were calculated with Mann-Whitney rank sum test. All data analysis has been performed using SPSS (SPSS Inc., Chicago, IU, USA) statistical package. A two-tailed P value of less than 0.05 was considered statistically significant. Local ethical committee at Lund University accepted the study, and informed consent was obtained from all participants.

3. Results

Values of ABPM, that is, daytime and nighttime SBP, DBP, systolic and diastolic variability (mean SD-SBP and SD-DBP), nocturnal SBP fall, morning SBP surge, preawakening

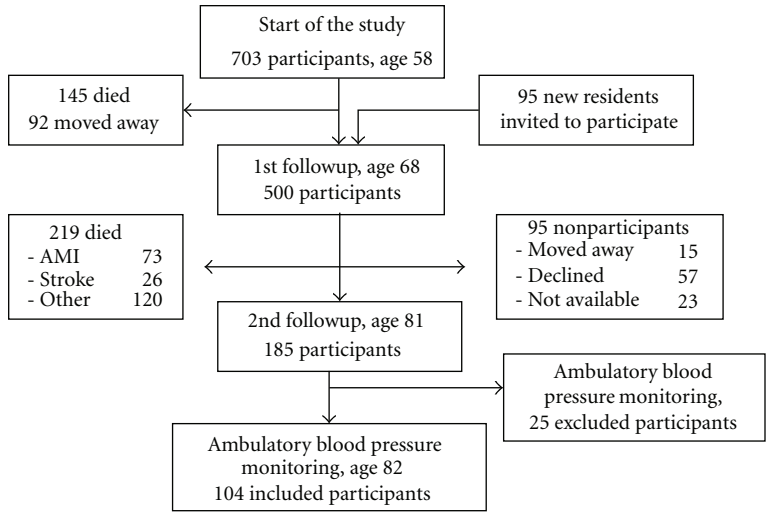

Figure 1: Follow-up of the cohort, "Men born in 1914".

SBP, and postawakening SBP are presented in Table 1. Levels of clinic blood pressure, P-cholesterol, triglycerides, and B-glucose as well as markers of vascular disease, that is, carotid stenosis, ankle-brachial index, and its time-change during follow-up, are also presented.

3.1. ABPM Levels Compared to Previously Published Results on Younger Elderly Persons. Compared to a sample of 70-year-old population of Uppsala, Sweden [22], subjects of this study had lower mean daytime SBP with 9 mmHg, mean DBP, and PP with 5 mmHg but the same variability/standard deviation. At nighttime, data of this cohort and Uppsala cohort were similar concerning SBP, DBP, and PP.

Compared to a sample (age 73 ± 6) from a population of Madrid, Spain [23] at daytime, mean values of SBP, DBP, PP, and SD were very similar with only 1-2 mmHg differences. The same was observed if compared to nighttime values, except for nighttime PP which was lower with 5 mmHg in this study.

Compared to 15-year younger Japanese population-based sample of Ohasama study (mean age 66.7 y) [24], subjects of this study had similar daytime SBP and DBP but higher nighttime SBP with mean 5 mmHg.

Compared to Italian Pamela population study (mean age 69.0 y ± 2.3), subjects of this study had similar daytime values, higher nighttime SBP with 6 mmHg but not DBP [25, 26].

Compared to the oldest sample of population-based study from Dublin, Ireland (age 50–79 y) [27], subjects of this study had lower daytime SBP with 2 mmHg, daytime DBP with 4 mmHg, higher nighttime SBP with 7 mmHg, and equal mean nighttime DBP. Daytime values of the Irish study were similar to this study in the sample at age 40–49 y.

Compared to Uruguayan population sample of men untreated for hypertension at age >70 y [28], subjects of this study had lower mean daytime SBP with 3 mmHg, DBP with 5 mmHg, and mean nighttime SBP with 3 mmHg but similar nighttime DBP. Compared to younger elderly (50–59 and 60–69 y), subjects of this study had similar daytime and nighttime SBP but lower daytime DBP with 7 mmHg and nighttime DBP with 3 mmHg.

In a population study from Denmark [29], several small subgroups in different age intervals were studied. Compared to the subgroup at age 70–79 y, subjects of this study had lower daytime SBP with mean 7 mmHg, daytime DBP with 3 mmHg, higher nighttime SBP with 3 mmHg, and lower DBP with 2 mmHg. Compared to the subgroup at age 60–69 y, subjects of this study had lower daytime SBP with mean 12 mmHg, daytime DBP with 10 mmHg, the same nighttime SBP, and lower DBP with 3 mmHg. Compared to the subgroup at age 50–59 y, subjects of this study had lower daytime SBP with mean 3 mmHg, daytime DBP with 5 mmHg, higher nighttime SBP with 6 mmHg, and lower DBP with 2 mmHg. Small samples of the Danish study were presented by high standard deviation of each BP value.

3.2. Does Hypertension at Age 68 or 81 Predict ABPM Levels? Hypertension, diagnosed or treated during the first followup at age 68, has been tested as possible predictor of ABPM 14 years later (Table 2, right columns). The values of ABPM did not differ between subjects who were hyper- and normotensive at age 68. When hypertension was defined with the same criteria at age 81 (Table 2, left columns), the values of ABPM examined the same year differed between the groups and presented, in hypertensive subjects, higher daytime SBP and PP, and higher nocturnal SBP and PP, and higher pre- and postawakening SBP, but did not differ concerning relative morning surge or diurnal BP variability.

3.3. Does Time Course of Clinic BP between Age 68 and 81 Predict ABPM Levels? We have previously shown that blood pressure dynamics differed in these study subjects during the followup. Those, who presented higher clinic BP levels at age 68, were prone to have declining SBP until age 81 [30]. In this study, time course of SBP correlated positively with mean SBP and daytime, nighttime, and with pre- and postawakening SBP levels (Figure 2). Nighttime SBP was strongest

Table 1: The background data from the 1st and the 2nd followup of the cohort "Men born 1914".

	Age 68 years	Age 81-82 years
Smoking (*n* active/*n* former or never smoked)	28 versus 76	
BMI	24.5 (17.4)	
B-glucose	4.9 (.52)	
P-Cholesterol	6.0 (.94)	
P-triglycerides	1.4 (.66)	
Ankle-brachial index right	1.11 (.11)	.99 (.20)
Ankle-brachial index left	1.07 (.13)	.96 (.21)
Difference ABI-R age 82–68		−.13 (.17)
Difference ABI-L age 82–68		−.11 (.17)
Clinic BP (mmHg)		
Systolic	151.1 (19.9)	144.1 (15.4)
Diastolic	92.2 (10.3)	83.1 (6.2)
Ambulatory BP (mmHg)		
Daytime, average BP		
Systolic		131.1 (12.0)
Diastolic		75.5 (10.4)
Pulse pressure		55.6 (8.2)
Nighttime, average BP		
Systolic		120.9 (12.7)
Diastolic		67.5 (10.9)
Pulse pressure		51.4 (9.7)
Average standard deviation of:		
Daytime systolic		13.1 (3.0)
Daytime diastolic		10.0 (2.9)
Nighttime systolic		11.7 (4.2)
Nighttime diastolic		9.5 (3.4)
Nocturnal SBP fall (%)		7.7 (6.1)
Morning SBP surge (mmHg)		26.3 (16.2)
Preawakening, average SBP		119.2 (14.5)
Postawakening, average SBP		131.3 (15.2)

correlated with increasing clinic SBP. High ambulatory pulse pressure reflected also increasing clinic SBP over time. Highest daytime SBP variability was observed in subjects with increasing office SBP.

3.4. Do Vascular Risk Factors and Markers of Atherosclerosis at Age 68 Predict ABPM Values at Age 82? To estimate the impact of vascular risk factors at age 68 on future ABPM levels, we calculated if there was a correlation between office BP, levels of P-cholesterol, triglycerides, glucose at age 68, and ABPM levels 14 years later (Table 3), without recording any significant values. However, BMI levels at age 68 correlated negatively with daytime DBP and its variability, that is, SD-DBP. In addition, ABI levels at age 68 correlated negatively with future SBP variability and with pulse pressure at daytime, presenting the lowest ABI levels in subjects with highest daytime SBP variability and pulse pressure. ABPM values have been splitted according to their smoking profile at age 68 (Table 4). Those subjects who were still current smokers at age 68 had higher systolic and diastolic pressure variability (SD-SBP, SD-DBP) both daytime and nighttime. The absolute values of SBP or DBP did not differ between these groups, neither daytime nor nighttime.

3.5. Does ABPM Reflect Clinic BP (CBP) and Markers of Atherosclerosis at Age 81? At age 82, the CBP correlated positively with daytime: SBP, SD-SBP, DBP, and PP, and with nighttime: SBP, DBP, and PP as well as with pre- and postawakening SBP (Table 5). Clinic DBP was expressed better by daytime SBP and DBP levels, than clinic SBP. No correlation was observed with nocturnal SBP fall or morning SBP surge. Carotid stenosis correlated positively with nocturnal and preawakening SBP and daytime PP, but not with daytime SBP or DBP values. Ankle-brachial index was lowest in subjects with higher nocturnal: SBP, PP, SBP variability, and preawakening SBP. Daytime BP values did not correlate with ABI. The time course of ABI between age 68 and 82 showed that the largest ABI decline was reflected by higher daytime and nighttime systolic variability, that is, SD-SBP, and by higher PP, as well as by higher pre- and postawakening SBP levels, but not by daytime or nighttime SBP/DBP levels at age 82.

4. Discussion

This study provides a longitudinal observation data on a population-based sample of elderly men between ages of 68 and 82 years. The baseline data of ABPM performed in the study subjects at age 82 should be discussed in the light of other population-based samples. The majority of previously published studies on ABPM included either preselected hypertensive elderly patients or examined younger elderly populations. Compared to latter studies performed in cohorts aged 70–79 y, octogenarians from our study had generally lower daytime levels of SBP/DBP and in some cases even lower nighttime SBP/DBP levels. Our ABPM levels were similar to those registered in men in their 50–60-ties. In the Danish study [29], a similar profile of increasing ABPM values in the younger samples until age of 70 y was observed, but a decreasing ABPM in a subgroup at age 80+. This age-related threshold of ABPM values could be supported by our observation that the higher level of office-BP or suffering from hypertension at age 68 did not predict higher ABPM neither daytime nor nighttime at age 82. Instead, longitudinal change in Clinic BP during 13 years correlated with ABPM values. By analyzing ABPM values in hypertensive and normotensive subjects at age 82, we could conclude that low values of ABPM in the whole cohort were partly due to low ABPM values in those men who were hypertensive at age 68, and at the same time developed decline of Clinic BP until their 80-ties. On the other side, higher values of ABPM were observed not in those subjects who were highly hypertensive at 68 but those who developed hypertension in the last decade and had largest increase in vascular burden during that time.

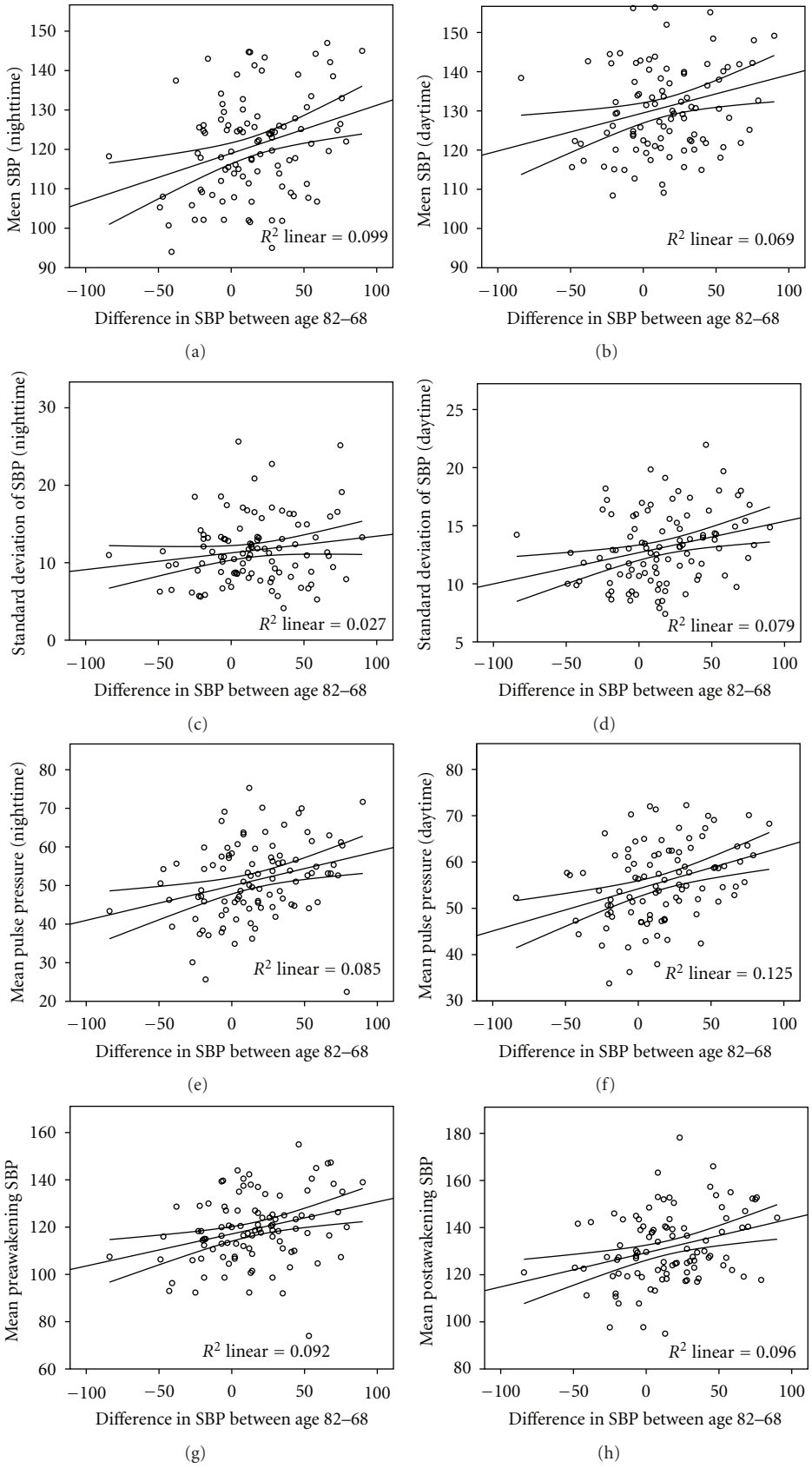

Figure 2: Correlation between an arithmetic difference in SBP, measured at ages 81 and 68 and ambulatory blood pressure measures collected at age 82 (daytime, nighttime, pre- and postawakening SBP, SBP variability, that is, daytime and nighttime standard deviation of SBP measurements and daytime and nighttime pulse pressure). Positive difference in SBP means an increasing SBP during the followup.

Table 2: Ambulatory blood pressure values measured in elderly men at age 82, who were diagnosed hypertensive versus normotensive during examinations at age 81 and 68 years.

	Hypertension at 81			Hypertension at 68		
	Yes ($n = 60$)	No ($N = 44$)		Yes ($n = 59$)	No ($N = 45$)	
ABPM at age 82	Median min–max	Median min–max	*P*	Median min–max	Median min–max	*P*
Daytime (mmHg)						
SBP	132.5 114.9–159.9	126.0 108.4–144.7	.006**	129.1 108.4–159.4	130.0 109.1–159.9	.651
SD-SBP	13.2 7.4–21.9	12.4 7.9–19.7	.180	12.9 7.4–21.9	13.0 7.9–19.7	.580
DBP	72.4 57.8–104.7	75.8 55.3–96.5	.979	71.9 57.8–104.8	76.5 55.3–99.9	.433
SD-DBP	9.5 4.6–18.7	9.5 4.7–15.8	.942	9.3 4.6–18.7	9.3 4.7–16.3	.909
PP	58.7 47.0–72.3	52.4 33.8–72.3	.000**	55.6 33.8–72.0	54.7 36.2–72.3	.759
Nighttime (mmHg)						
SBP	124.4 95.0–145.0	114.4 94.0–147.0	.011*	122.0 94.0–144.7	121.4 101.6–147.0	.552
SD-SBP	11.8 5.2–25.1	10.7 4.1–25.6	.120	11.4 4.1–25.6	10.9 5.3–25.2	.826
DBP	66.3 50.6–102.5	65.4 50.2–93.9	.382	64.7 50.2–102.5	66.3 51.0–93.9	.268
SD-DBP	9.2 2.5–21.3	9.1 3.2–21.7	.679	9.2 3.2–21.7	9.3 2.5–20.2	.224
PP	53.3 22.4–71.7	49.1 25.7–75.3	.023*	48.8 22.4–75.3	53.7 34.9–74.7	.184
Nocturnal SBP fall (%)	7.8 −8.3–17.7	7.4 −7.1–19.8	.430	7.0 −7.1–16.8	8.7 −8.3–16.8	.854
Morning SBP surge (mmHg)	27.7 −.67–56.2	24.1 −2.6–123.0	.139	26.3 −2.6–51	24.5 6–123	.972
Preawakening SBP	120.2 92.0–155.0	113.5 74.0–147.0	.011*	119.3 92.3–155	116.5 74–147	.592
Postawakening SBP	132.5 107.8–78.2	124.9 95.0–155.0	.010*	127.6 97.7–166	130.0 95–178.2	.438

These observations could be confirmed by the data showing that established laboratory risk factors at age 68 did not predict future levels of ambulatory blood pressure. However, lower ankle-brachial index and particularly current smoking at age 68 predicted larger BP variability both daytime and nighttime. Yet, when measured at age 81, Clinic BP and being diagnosed as hypertensive at age 81 could be strongly reflected by higher values of ABPM and especially diurnal pulse pressure (PP). ABPM could also adequately express the grade of atherosclerotic process at age 82 by higher nighttime and preawakening BP-levels, higher nighttime BP variability, and PP values, in those men who had higher grade of carotid stenosis, lower ABI, and extended ABI-decline during the 14-year followup.

Possible explanation of the lower ABPM values in the very elderly, compared to the younger population samples, could be a selective mortality of those subjects from our cohort, who died before age 68, that is, before the first follow-up, due to early hypertension, metabolic syndrome, intensive smoking, and advanced atherosclerosis [31]. Another explanation could be the fact that survivors, who were included in this sample, had been less exposed to vascular risk factors than those who declined to take part in the last followup or died prior to it. However, in the whole examined sample, SBP decreased with mean 7 mmHg and DBP with 9 mmHg, which points to the fact that not only selective mortality is an explanatory factor, but also a part of the cohort expresses a BP decline during the last 14 observation years, which results in lower ABPM levels compared to the younger population.

Cigarette smoking, as the strongest risk factor at age 68, did not predict absolute values of BP in octogenarians, but increasing SBP and DBP variability (SD) by ca 20%, both daytime and nighttime. Similarly, lower ABI level at age 68 predicted higher daytime SBP variability and PP, and not the absolute ABPM values.

At age 81, subjects defined as hypertensive expressed higher nighttime and daytime SBP, post- and preawakening

Table 3: Correlation coefficients calculated for ambulatory blood pressure at age 82 and vascular risk factors (BMI, laboratory levels and clinic blood pressure/BP) as well as for markers of vascular disease at age 68 (ABI: ankle-brachial index).

	BMI	Laboratory levels,			Clinic BP		Ankle-brachial index	
		Glucose	Triglycerides	Cholesterol	SBP	DBP	Right	Left
Daytime								
SBP	−.096	.015	.022	−.066	.047	−.092	.036	−.051
SD-SBP	−.082	−.026	.117	−.022	.087	−.052	−.265**	−.246*
DBP	−.210*	−.186	.005	−.035	.023	−.184	.091	.125
SD-DBP	−.237*	−.092	.008	−.038	.034	−.161	−.035	.003
PP	.052	.151	−.033	−.091	−.019	.086	−.084	−.212*
Nighttime								
SBP	−.019	−.050	.099	−.014	.057	−.035	.071	−.011
SD-SBP	.006	.058	.032	.031	−.092	−.146	−.100	.016
DBP	−.093	−.127	.092	−.026	.013	−.103	.082	.088
SD-DBP	.021	−.027	.104	.078	.081	−.012	−.078	.089
PP	.101	.064	.026	−.114	−.111	−.097	.113	−.049
Nocturnal SBP fall	−.104	.053	−.151	−.114	−.030	−.072	−.81	−.075
Morning SBP surge	−.014	−.005	−.105	−.111	−.139	−.023	−.025	−.139
Preawakening SBP	−.014	−.067	.018	−.088	.066	.010	.042	−.045
Postawakening SBP	−.043	−.110	−.026	−.119	−.062	−.034	.120	−.049

Table 4: Difference in ambulatory blood pressure at age 82 between subjects defined as current and never/former smokers *at age 68.*

	Smoking status at age 68				
	Current smokers ($N = 28$)		Never and former ($N = 76$)		
ABPM at age 82	Median	min–max	Median	min–max	*P*
Daytime (mmHg)					
SBP	131.2	108.4–159.9	128.9	109.1–159.4	.43
SD-SBP	14.5	8.6–21.9	12.6	7.4–19.7	.012*
DBP	77.4	59.7–99.9	72.7	55.3–104.7	.18
SD-DBP	11.6	7.8–17.7	9.2	4.6–18.7	.003**
PP	55.2	33.8–72.0	55.4	36.2–72.3	.75
Nighttime (mmHg)					
SBP	123.5	102.1–147.0	119.2	94.0–145.0	.28
SD-SBP	13.1	4.1–18.5	10.6	5.3–25.6	.023*
DBP	66.6	53.7–93.9	64.9	50.2–102.5	.45
SD-DBP	10.2	6.1–21.7	8.8	2.5–21.3	.019*
PP	53.4	37.1–70.6	52.1	22.4–75.3	.36
Nocturnal SBP fall (%)	6.6	−8.3–17.9	8.6	−7.1–19.8	.52
Morning SBP surge (mmHg)	21.6	−2.6–45.7	26.2	−.25–123.0	.15
Preawakening SBP	119.7	92.3–155.0	118.0	74.0–147.3	.33
Postawakening SBP	125.2	97.7–166.0	129.3	95.0–178.2	.35

SBP, and above all, higher PP. The values of clinic BP at age 81 correlated with values of ABPM, mainly clinic DBP, high values which were reflected by higher daytime and nighttime SBP, DBP, SD-SBP, and pre- and postawakening SBP as well as daytime PP. Clinic SBP at age 81 was reflected only by nighttime SBP and PP. It suggests that in very elderly men clinic DBP seems to express overall 24-h BP profile in a more adequate way that clinic SBP, and that diurnal PP should be used as an important complement to both clinic and diurnal BP measurements.

Nocturnal values of ABPM could be used as a risk factor or marker of vascular burden in the octogenarian men. Nighttime and preawakening SBP and daytime PP correlated best with a grade of carotid stenosis. Similar result were observed concerning ABI, where high nighttime SBP, SD-SBP, PP, and high preawakening SBP were observed in subjects with a diminished peripheral leg circulation. Daytime values did not express that risk. The largest progress in peripheral arterial disease, expressed as a decreasing ABI over 14 years, was observed not in these subjects who had high absolute

Table 5: Correlation coefficients calculated for ambulatory blood pressure at age 82 and clinic blood pressure as well as for markers of vascular disease at age 81 (ABI: ankle-brachial index, ABI progression, and carotid stenosis at ultrasound examination).

	Carotid ultrasound	Clinic BP age 81		Ankle-brachial index		Ankle-brachial index difference age 81–68	
	Mean stenosis	SBP	DBP	Right	Left	Left	Right
Daytime							
SBP	.157	.169	.341**	−.092	−.191	−.124	−.190
SD-SBP	.128	.000	.226*	−.147	−.183	−.264**	−.063
DBP	.003	−.005	.218*	.002	−.068	.051	−.095
SD-DBP	.004	−.038	.176	−.010	−.135	−.077	−.041
PP	.234*	.228**	.215*	−.192	−.174	−.234*	−.210*
Nighttime							
SBP	.194*	.198*	.264**	−.100	−.230*	−.141	−.181
SD-SBP	.070	.132	.036	−.220*	−.319**	−.219**	−.180
DBP	.040	.101	.267**	−.009	−.126	−.016	−.063
SD-DBP	−.083	−.006	−.051	−.018	−.182	−.051	−.032
PP	.174	.287**	.029	−.209*	−.268**	−.194*	−.315**
Nocturnal SBP fall	−.022	.000	.131	.026	.133	.058	.008
Morning SBP surge	−.024	.093	.069	−.125	.000	−.073	−.167
Preawakening SBP	.194*	.148	.259**	−.117	−.255**	−.204*	−.157
Postawakening SBP	.100	.162	.243*	−.141	−.212*	−.144	−.266**

ABPM values, but in those who expressed high PP and high SBP-variability both night- and daytime, and had larger pre- and postawakening SBP.

5. Conclusion

In conclusion, in a population sample cohort of 82-year-old men, high daytime and nighttime ABPM measurements reflected increasing office-BP and aggravating atherosclerosis only in the last decade. Subjects with early developed hypertension, peripheral atherosclerosis and active smokers already in their 60 ties reached an inflection point in their blood pressure development and did not express increasing ABPM values in their eighties any longer.

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Review Article

The Association between Hypertension and Dementia in the Elderly

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Hypertension (HT) and dementia are common disorders in the elderly. HT in the elderly is associated with increased occurrence rates of dementia including Alzheimer's disease (AD) and vascular dementia (VaD). In connection to this, some studies have suggested that HT in old age correlates with the pathogenesis of dementia. Since HT is potentially reversible, a number of randomized trials have examined whether antihypertensive treatment may help in preventing dementia occurrence. We review five studies, all using subjects 60 years or older, which investigated different antihypertensive pharmacological treatments. Data from two trials (Syst-Eur, PROGRESS) open the way toward the prevention of dementia (AD or VaD) by antihypertensive treatments. In the Syst-Eur study, with the dihydropyridine calcium antagonists, a reduction in both types of dementia was demonstrated (risk reduction 55%). The PROGRESS study showed that the use of angiotensin-converting enzyme inhibitors (ACEIs), with or without diuretics, resulted in decrease incidence of stroke-related dementia (risk reduction 19%), but dementia without stroke was not reduced. In contrast, the SHEP trial, treatment with a chlorthalidone-based antihypertensive regimen, did not significantly reduced the incidence of dementia. The SCOPE study (candesartan or hydrochlorothiazide versus placebo) and the HYVET-COG study (indapamide or perindopril versus placebo) found no significant difference between the active treatment and placebo group on the incidence of dementia. We found conflicting results regarding treatment benefits in dementia prevention. Recent clinical trials and studies on animal models suggest that blockades of RAS system could have reduced cognitive decline seen in Alzheimer's disease and vascular dementia. Future trials primarily designed to investigate the effects of antihypertensive agents on impaired cognition are needed.

1. Introduction

In general, the risk of HT, which is defined as a systolic blood pressure (SBP) ≥140 mm Hg and/or a diastolic blood pressure (DBP) ≥90 mm Hg [1], increases with advancing age. In fact, the prevalence of HT in individuals 60 years and older is double that of those aged 49–59 years. In Framingham study, 90% of all 65-year-old men and women with normal BP later developed HT [2]. This condition carries a very high risk for cerebrovascular disease (CVD) as well as coronary heart disease (CHD) [3]. Dementia is one of the most important neurological disorders in the elderly. Many studies have identified HT as marker for the pathogenesis of dementia AD and VaD, while longitudinal studies have suggested that HT is associated with a higher incidence of dementia in old age. It has been observed that long-standing HT may lead to severe atherosclerosis and impaired cerebrovascular autoregulation, which in turn is thought to correlate with dementia [4]. For these reasons, several studies have investigated whether antihypertensive treatment may retard cognitive decline or dementia [5–9]. Although the importance of lowering BP in HT subjects is well known, the relationship between HT and cognitive function is controversial.

2. HT in the Elderly and the Risk of Dementia

To this date, the associations between BP and dementia have been inconclusive. Considering that the incidence of dementia among the elderly population is rising rapidly worldwide [10] and accumulating evidence that HT may contribute to the development of both AD and VaD [11], there is a reason to believe effective management of HT may

translate into major health benefits through the protection of dementia. HT has long been known to cause CV [12]. Midlife HT ranks as an important modifiable risk factor for late-life cognitive decline [13], mild cognitive impairment (MCI) [14, 15], and VaD [16, 17]. In longitudinal cohort studies, elevated BP is associated with cognitive decline although some cross-sectional studies showed mixed relationships between higher BP and cognition, with many studies showing no correlation or even J- or U-shaped associations [18]. Findings from these prospective cohort studies for DBP and cognitive decline are less consistent; however, many have reported a similar inverse relation. The data on the role of BP and HT in later life are not consistent, leaving open the issue of BP treatment in elderly people. The controversy about the association between HT in the elderly and dementia arises because the longitudinal relationship between BP and cognitive change is sensitive to the effects of age, duration of followup and hypertensive treatment status, comorbidity with CVD and CHD, and possibly subclinical dementia [19]. More recently, a total of 668 community-dwelling Japanese individuals without dementia, aged 65 to 79 years, were followed up for 17 years, and examined the associations of late-life and midlife HT with the risk of AD and VaD [20]. During the followup, 123 developed AD, and 76 subjects experienced VaD, and the age- and sex-adjusted incidence of VaD significantly increased with elevated midlife BP levels regardless of late-life BP levels. There were not a significant association between BP levels and AD. Li et al. [21] followed a total of 837 subjects with MCI for 5 years, 298 subjects converted to AD, while 352 remained MCI at the end of the followup. Subjects with HT increased the risk of dementia conversion. Given their results, treatment of HT was associated with a reduced progression in MCI to AD dementia.

3. Can Control of HT Protect against Dementia?

Despite the speculated relationship between HT and dementia, clinical trials examining the preventive effects of antihypertensive therapy on dementia have been inconclusive (Table 1). Among five randomized double-blind placebo-controlled trials surveying antihypertensive treatments and dementia, four (Syst-Eur, PROGRESS, SCOPE, and HYVET-COG) used the Mini-Mental State Examination (MMSE), a widely used screening instrument for cognitive impairment, to assess cognitive function. In the SHEP, cognitive screening was performed by a short-comprehensive assessment and referral evaluation (short CARE) questionnaire. These five studies are described below.

3.1. Syst-Eur. The systolic hypertension in Europe study (Syst-Eur) investigated whether antihypertensive treatment in elderly patients with isolated systolic hypertension (ISH) led to a significant change in stroke morbidity and mortality. Syst-Eur investigated the effects of a calcium channel blocker (CCB; 10–40 mg/day nitrendipine). If necessary, nitrendipine was combined with an ACEI (5–20 mg/d enalapril maleate) and/or a diuretic (12.5–25 mg/day hydrochlorothiazide). Participants had no dementia and were at least 60 years old. Their SBP at the beginning of the trial was between 160 and 219 mm Hg, and their DBP was below 95 mm Hg. Antihypertensive therapy began immediately after randomization in the active treatment group, but only after termination of the double-blind trial in the control patients. The mean difference in BP between treatment groups and the control was 7.0 mm Hg SBP and 3.2 mm Hg DBP; the rates of dementia for patients in the active treatment groups and the control groups were 3.3 and 7.4 cases per 1.000 patient-years (relative risk reduction: 55%; 95% CI: 24–73%), respectively, which is significant.

In Syst-Eur, because active treatment using a CCB resulted in a 42% decrease in the primary end point of fatal and nonfatal stroke, only 2418 of the 4695 randomly assigned patients participated in a substudy on dementia. Compared with the control group, the portion of the treatment group that received only CCB (60%) had a significantly reduced risk of dementia (55%). Interestingly, while the total incidence of dementia was 64 cases, 41 of these showed AD. Therefore, Syst-Eur suggests using a CCB to lower BP may protect against dementia, particularly AD, in elderlywith ISH.

3.2. PROGRESS. The perindopril protection against recurrent stroke study (PROGRESS) was a trial involving 6105 patients, all with prior stroke or transient ischemic attack. Participants were assigned to either active treatment (perindopril for all participants plus indapamide for those with neither an indication nor a contraindication to a diuretic) or a matching placebo. The mean difference in BP between the two groups was 9.0 mm Hg SBP and 4.0 mm Hg DBP; the rates of dementia patients in the active treatment groups and the control groups were 6.3% and 7.1% (relative risk reduction: 12%; 95% CI: −8 to 28%), respectively, which is insignificant. However, the rates of cognitive decline were 9.1 and 11.0% (risk reduction: 19%; 95% CI: 4–32%), respectively, which is significant.

3.3. SHEP. The systolic hypertension in the elderly program (SHEP) study was a trial conducted over an average 5-year follow-up and involved 16 academic clinics. Among the 447.921 candidates aged 60 years and older screened, 4736 (1.06%) were chosen for the study. SBP at baseline ranged from 160 to 219 mm Hg, while DBP was less than 90 mm Hg. Participants were randomized into either an active antihypertensive drug therapy or a matching placebo group. Active treatment consisted of a diuretic (12.5–25 mg/day chlorthalidone) for step 1 and a beta blockade (25–50 mg/day atenolol) for step 2. If atenolol was contraindicated, 0.05 to 0.10 mg reserpine was used instead. The cohort mean difference in BP between the treatment groups and placebo was 12.0 mm Hg SBP and 4.0 mm Hg DBP; the rates of dementia for the active treatment group and the control group were 3.6 and 4.2 cases per 1.000 patient-years (relative risk reduction: 14%; 95% CI: −26 to 54%), respectively, which is insignificant.

3.4. SCOPE. The study on cognition and prognosis in the elderly (SCOPE) was a prospective study conducted from

Table 1: Randomized controlled trials about antihypertensive treatments and dementia/cognitive decline.

Study setting	Participants and follow up	Treatment	Test	Main results
Systolic hypertension in Europe study (Syst- Eur) [5]	2.418 systolic hypertensives; mean age 70 years, followup 3.9 years	CCB (nitrendipine) with possible addition of ACE-I (enalapril), diuretic (hydrochlorothiazide), or both versus placebo	MMSE	Mean difference in BP between treatment groups and the control was 7.0 mm Hg SBP and 3.2 mm Hg DBP. Rates of dementia for patients in the active treatment groups and the control groups were 3.3 and 7.4 cases per 1.000 patient-years (relative risk reduction: 55%), respectively. Significant.
The perindopril protection against recurrent stroke study (PROGRESS) [6]	6.105 subjects with prior stroke or transient ischemic attack; mean age 64 years, followup 3.9 years	ACE-I (perindopril) with possible addition of diuretic (indapamide) versus placebo	MMSE	Mean difference in BP between treatment groups and the control was 9.0 mm Hg SBP and 4.0 mm Hg DBP. Rates of cognitive decline for patients in the active treatment groups and the control groups were 11.0 and 9.1% (relative risk reduction: 19%), respectively. Significant.
Systolic hypertension in the elderly program (SHEP) [7]	4.736 systolic hypertensives; mean age 72 years, followup 4.5 years	Diuretic (chlorthalidone) with possible addition of β blocker (atenolol) or sympathetic nervous blocker (reserpine) versus placebo	Short CARE	Mean difference in BP between treatment groups and the control was 12.0 mm Hg SBP and 4.0 mm Hg DBP. Rates of dementia incidence for patients in the active treatment groups and the control groups were 3.6 and 4.2 cases per 1.000 patient-years (relative risk reduction: 14%), respectively. Not significant.
Study on cognition and prognosis in the elderly (SCOPE) [8]	4.964 hypertensives; SBP160-170/DBP 90–99 mm Hg; aged 70– 89, followup 3.97 years	ARB (candesartan) versus placebo; open-label antihypertensive drugs were added to both groups	MMSE	Mean difference in BP between treatment groups and the control was 3.2 mm Hg SBP and 1.6 mm Hg DBP. Rates of dementia incidence for patients in the active treatment groups and the control groups were 6.3 and 6.8 cases per 1.000 patient-years, respectively. Not Significant.
Hypertension in the very elderly trial cognitive function assessment (HYVET- COG) [9]	3.336 hypertensives; SBP 160–200 and DBP < 110 mm Hg; age ≤80, followup 2.2 years	Diuretic (indapamide) with possible addition of ACE-I (perindopril) versus placebo	MMSE	Mean difference in BP between treatment groups and the control was 15 mm Hg SBP and 5.9 mm Hg DBP. Rates of dementia incidence for patients in the active treatment groups and the control groups were 33 and 38 cases per 1.000 patient-years (hazard ratio 0.86). respectively. Not significant.

BP: blood pressure, SBP: systolic blood pressure, DBP: diastolic blood pressure.

1997 to 2002. The study involved 4964 patients aged 70–89 years with SBP ranging from 160 to 179 mm Hg and/or DBP ranging from 90 to 99 mm Hg. Patients were assigned randomly to receive the angiotensin II receptor blocker (ARB) candesartan or a placebo, with open-label active antihypertensive therapy added as (84% of patients in the control group). The mean difference in blood pressure between the treatment group and control group was 3.2 mm Hg SBP and 1.6 mm Hg DBP; the rates of dementia for the active treatment group and the control group were 6.3 and 6.8 cases per 1.000 patient-years, respectively, which is insignificant. In a subgroup analysis of SCOPE performed later, a significant

positive effect on some cognitive domains (attention and episodic memory) was reported when using testing methods more sensitive than the MMSE.

3.5. HYVET-COG. The Hypertension in the very elderly trial—cognitive function assessment (HYVET-COG) examined antihypertensive medication for patients ≥80 years of age. Eligible patients had no dementia, their SBP at entry was 160 to 200 mm Hg, and their DBP was below 110 mm Hg. Participants were randomly assigned to receive 1.5 mg slow release diuretic (indapamide) with the option of ACEI (2–4 mg/day, perindopril), or a placebo. The target SBP was 150/80 mm Hg. Possible cases of dementia (a fall in the MMSE score to <24 or a drop of three points in one year) were assessed by standard diagnostic criteria and expert review. HYVET-COG was the first randomized control study to report the effects of antihypertensive treatment in participants aged 80 years of age or older, finding a significant decrease in stroke after an average followup of 2.2 years, which led to its early termination. This followup period may be too short to detect any benefit preventing dementia. The mean difference in BP between the treatment and control groups was 15 mm Hg SBP and 5.9 mm Hg DBP; the rates of dementia for active treatment group and the control group were 33 and 38 cases per 1.000 patient-years (hazard ratio 0.86; 95% CI: 0.67–1.09), respectively, which is insignificant.

Of these five studies, only Syst-Eur and PROGRESS showed significant differences in the rate of dementia between the treatment and control groups.

However, when four of these data (Syst-Eur, PROGRESS, SHEP, and HYVET-COG) were combined in a meta-analysis [22], antihypertensive therapy was found to significantly reduce the risk of dementia (HR 0.87, 95% CI: 0.76–1.00, $P = 0.045$). Another study, however, found that combining the antihypertensive therapy results from Syst-Eur, SHEP, and SCOPE reduced the risk of dementia by 11% (odds ratio 0.89; 95% CI: 0.69–1.16), an insignificant effect [23]. Therefore, further long-term randomized trials, designed especially to assess a link between antihypertensive therapy and cognition as the primary outcome, are needed.

4. Renin-Angiotensin-Aldosterone System and Cognitive Function

Blocking the renin-angiotensin-aldosterone system (RAS) is another means that could have benefits on the prevention of dementia [24], but in a manner independent of BP lowering effect [25]. A potential neuroprotective effect on focal cerebral ischemia has been reported by blocking the RAS with an ARB that specifically targets the angiotensin II receptor [26]. Moreover, the Fournier hypothesis proposes that ARB treatment has potential advantages over ACEI treatment in the prevention of stroke and cognitive impairment because of the lower likelihood of harmful effects like vasoconstriction and proatherothrombogenesis while at the same time promoting neutral or even potentially beneficial effects like vasodilatation and endothelial modulation [27, 28].

Consistent with this theory, the ongoing telmisartan alone and in combination with ramipril global endpoint trial (ONTARGET) [29] and the parallel telmisartan randomized assessment study in ACEI intolerant subjects with cardiovascular disease (TRANSCEND) trial [30] have reported the effects of telmisartan, a unique ARB with peroxisome proliferator-activated receptor-gamma (PPAR-gamma-) stimulating activity, and the ACEI ramipril on cognitive function in patients aged 55 years and older with established atherosclerotic cardiovascular disease or diabetes with end-organ damage. In ONTARGET, a 56 month median duration month followup found cognitive impairment occurred in 652 (8%) of the 7865 patients allocated ramipril, 584 (7%) of the 7797 allocated telmisartan, and 618 (8%) of the 7807 allocated a combination of the two (combination versus ramipril, odds ratio [OR] 0.95, 95% CI 0.85–1.07, $P = 0.39$; telmisartan versus ramipril, OR 0.90, 0.80–1.01, $P = 0.06$). Corresponding figures for cognitive decline were 1314 (17%), 1279 (17%), and 1240 (17%), respectively (telmisartan versus ramipril, OR 0.97, 0.89–1.06, $P = 0.53$; combination versus ramipril, OR 0.95, 0.88–1.04, $P = 0.28$). In TRANSCEND, cognitive impairment occurred in 239 (9%) of the 2694 participants allocated telmisartan compared with 245 (9%) of the 2689 allocated a placebo (OR 0.97, 0.81–1.17, $P = 0.76$). The corresponding figures for cognitive decline were 454 (17%) and 412 (16%; OR 1.10, 0.95–1.27, $P = 0.22$), respectively.

Recently, the prevention regimen for effectively avoiding second strokes (PRoFESS) trial [31] investigated the impact of ARBs on cognitive function in a randomized controlled design. There were no significant differences in the rate of cognitive decline or dementia between the treatment and control groups. These results were very similar to those in SCOPE. However, PRoFESS several limitations that obfuscate its conclusions. For example, the duration of the follow-up period was short, and there was a frequent discontinuation of the study drug among subjects, and many patients experienced recurrent stoke requiring termination of the antihypertensive treatments.

Figaro et al. [32] reported that antihypertensive therapy with an ARB and diuretic (telmisartan and hydrochlorothiazide) caused significant improvement in cognitive function compared to therapy using an ACEI and diuretic (lisinopril and hydrochlorothiazide). In addition, the observational study on cognitive function and systolic blood pressure reduction (OSCAR), an open label trial in 28 countries designed to evaluate the impact of the ARB eprosartan on cognitive function, found that a reduction in systolic blood pressure had an independent negative association with cognitive decline (odds ratio 0.77; 95% CI: 0.73–0.82).

More recently, prospective cohort study of old (over 65) subjects demonstrated significantly lower hazard rates for incident dementia with ARBs than with an ACEI (hazard rate 0.81, 95% CI 0.73–0.90) and other cardiovascular drugs (0.76, 0.69–0.84). However, the results may not be generalisable to women because women comprised only 2% of this cohort [33].

Although it is still not exactly clear how the ARBs confer this benefit, Tsukuda et al. [34] demonstrated that a low dose

of telmisartan had a preventive effect on cognitive decline in an AD mouse model (Aβ-injection mouse model). This was in part due to the clearance of Aβ in response to an inhibition of inflammation because of PPAR-gamma activation. Thus, ARBs that can act as a partial agonist for PPAR-gamma may provide a benefit for the treatment of dementia, along with their already blood pressure-lowering effects.

5. Conclusion

It is thought that there is a dependent relationship between the occurrence of HT and the risk of developing dementia in old age. This offers promise in the prevention of dementia because HT is a potentially reversible risk factor.

Recent epidemiological evidence suggests that some antihypertensive medications may reduce the risk for AD. In particular, given that Syst-Eur found treating HT with the dihydropyridine CCB nitrendipine reduced the incidence of AD by 55%, nitrendipine could prove to be a potentially reliable option for protection against dementia. Despite this encouraging evidence, several randomized trials have failed to support the efficacy of antihypertensive agents in AD dementia [7, 8]. Thus, at present there is inconsistent evidence regarding the influence of antihypertensive drugs on dementia incidence and/or pathogenesis.

Because current theories assume AD is triggered by the accumulation of soluble and insoluble forms of β-amyloid, if high BP can increase the risk of AD, they should then also lead to an accumulation of β-amyloid. In vitro study, using primary cortico-hippocampal neuron cultures generated from AD mouse model, at least 7 candidate antihypertensive agents including a calcium blocker, a β-adrenergic blocker, an α-β adrenergic blocker, a diuretic, a vasodilator and ARBs, that significantly reduced AD-type β-amyloid protein (Aβ) accumulation [35]. It is thought that some of these drugs may have clinical benefits in protecting against progressive Aβ-related memory disturbance in AD.

Therefore, further prospective randomized studies comparing different antihypertensive classes are needed to provide more evidence regarding the effects of antihypertensive drugs on dementia risk and to determine whether certain antihypertensive classes provide greater benefits than others. In particular, whether these agents possess specific neuroprotective properties or increase cerebral perfusion remains to be clarified.

Conflict of Interests

The authors declare that there is no conflict of interests.

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Review Article

The Putative Role of the Antiageing Protein Klotho in Cardiovascular and Renal Disease

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Ageing is a multifactorial process often characterized by a progressive decline in physiological function(s). Ageing can and is often associated with an increased incidence of cardiovascular and renal disease. Klotho is a novel antiageing gene that encodes a protein with multiple pleiotropic functions including an emerging role in cardiorenal disease. Mice deficient for this gene display a phenotype of premature human ageing characterized by diffuse vascular calcification, altered calcium/phosphate metabolism, and shortened lifespan. Klotho is mainly expressed in the renal tubules but it also exists as circulating soluble form detectable in the blood, with systemic effects. Reduction in soluble Klotho has been associated with renal disease, hyperphosphataemia, increased oxidative stress, endothelial dysfunction, and diffuse vascular calcification. Conversely, overexpression of Klotho promotes cardiovascular-renal protection. The majority of the research on Klotho has been conducted in vitro and in animal studies but there is emerging data from human studies which suggest that Klotho may be a modifiable factor involved in the pathogenesis of cardiovascular and renal disease in at-risk populations. Further data is required to confirm if this novel protein can emerge as therapeutic tool that may be used to prevent or slow progression of cardiorenal disease.

1. Introduction

Ageing is a complex phenomenon resulting from the interaction between genetic and environmental factors [1]. Advanced age is accompanied by higher prevalence of cardiovascular risk factors such as diabetes, hypertension, and chronic kidney that increase the risk of cardiovascular morbidity and mortality. All these risk factors are associated with endothelial dysfunction, which often precedes the development of overt disease [2]. Endothelial dysfunction is predominantly due to reduced availability of nitric oxide and increased oxidative stress which also promote the development and the progression of atherosclerosis and vascular calcification [3]. Vascular ageing is characterized by arteriosclerosis and calcification [4]. In conditions such as diabetes, there is premature vascular ageing which is associated with increased cardiovascular and renal disease risk. Further markers of vascular calcification appear to predict cardiovascular outcomes independently of conventional risk factors such as hyperlipidaemia, smoking, diabetes, hypertension, and family history of disease. The mechanisms that result in the development of vascular calcification are complex and have been reviewed in detail recently [5].

Klotho is a gene that encodes a novel protein regulating multiple functions, fortuitously discovered in 1997 by Kuro-o and colleagues and named after the goddess who spins the thread of life in Greek mythology [6].

In mice, the deletion of Klotho gene causes a phenotype of premature human aging including vascular calcification, altered calcium/phosphate metabolism with hyperphosphataemia, and shortened lifespan.

Klotho protein exists in two forms: a type I transmembrane protein (1014 amino acids) with a large extracellular domain and a short intracellular portion (10 amino acids), predominantly expressed in the renal tubules, and a circulating soluble factor detectable in blood and in lesser extent in other biological fluids [7].

Soluble Klotho is produced either by proteolytic cleavage of the extracellular domain of the transmembrane form (130 kDa isoform) operated by the membrane-anchored proteases ADAM10 and ADAM17 or by alternative mRNA splicing (isoform 70 kDa) [7, 8]. The systemic effects of this protein appear to be predominantly due to the circulating form. The transmembrane protein forms a complex with fibroblast growth factor (FGF) receptors and works as an obligate coreceptor for FGF23, a bone-derived hor mone that induces phosphate excretion into urine [9–11].

The fact that FGF23 requires Klotho for binding to its receptor explains why Klotho- and FGF23-deficient mice display identical phenotype [12, 13]. The observed hyperphosphataemia in Klotho and FGF23-mutant mice is due to hypervitaminosis D and increased expression/activity of renal sodium-dependent phosphate cotransporters. Interestingly, Klotho-deficient mice display higher levels of FGF23, and a low-phosphate diet reduces the levels of FGF23 and results in a rescue of the features of premature aging [13, 14]. This suggests that FGF23 per se cannot promote a phosphaturic effect in absence of Klotho [9].

Klotho/FGF23 signalling induces phosphaturia by suppressing the sodium-dependent phosphate cotransporters type IIa (NPT2a) expressed on the brush border membrane of renal tubular cells. Soluble Klotho has also been found to regulate directly the phosphate transport, in the proximal tubule of the kidney by deglycosylation of NaPi-2a cotransporters [15]. The resulting reduction in number and activity of NaPi-2a promotes phosphaturia independently of FGF-23. Soluble Klotho also inhibits type III sodium-dependent phosphate cotransporters (Pit1 and Pit2) which are ubiquitously expressed and mediate phosphate uptake [15].

High FGF23 levels in patients with chronic kidney disease are due to the declining renal clearance and also may represent a compensatory response to hyperphosphataemia [16].

Recent observational data suggest that FGF23 is associated with and may represent an independent risk factor for cardiovascular and all-cause mortality in patients with chronic kidney diseases stage of 4 and 5 (eGFR < 30 mL/min) [17, 18].

The reduction in Klotho expression observed in chronic kidney disease may be an important event contributing to the above with accumulation of FGF23 being a compensatory mechanism to the increase of phosphate levels driven by the primary reduction in Klotho. Recent data support this hypothesis as changes in Klotho levels appear to precede changes in phosphate levels, the key driver of FGF23 balance in renal disease [19].

2. Role of Klotho in Cardiovascular and Renal Disease

Klotho expression is affected by physiological and pathological factors. Renal expression of Klotho in rat is minimal in prenatal life but increases after birth [20]. A reduction in renal, serum, and urine levels of Klotho has been observed with normal ageing and in diseases characterised by premature vascular ageing such as renal disease as well as in animal models of disease such as diabetes and hypertension [21–24]. Table 1 summarises the conditions and disease states associated with reduction in Klotho levels.

Table 1: Conditions and disease states associated with reduction in Klotho.

Disease/condition	Species
Ageing	Mouse/human
Diabetes	Mouse
Hypertension	Rat
Chronic kidney disease	Mouse/human
Acute kidney injury	Human
Kidney ischemia	Mouse
Glomerulonephritis	Mouse

Conversely, there is evidence in animals that the overexpression of soluble Klotho can reverse the ageing process and provides cardiovascular-renal protection possibly by inducing resistance to oxidative stress and protecting tissues from oxidative damage [25, 26].

In this paper, we will summarize the key areas of research on the putative role of Klotho in prevention or delay of cardiorenal progression. We performed a Pub Med/Medline search for the terms Klotho, cardiovascular disease, and renal disease from 2000 to 2010 with a focus on recent mechanistic and proof-of-concept studies evaluating the role of Klotho in the prevention and treatment of cardiorenal disease.

3. Nephroprotective Effects of Klotho

Klotho is predominantly expressed in the renal distal tubular cells [6]. Animal studies have showed that the nephroprotective effects of this protein are mostly attributable to the antioxidant properties of its soluble form [27]. As outlined earlier, Klotho is a key mediator of phosphate balance in the nephron.

Klotho expression is reduced in renal distal tubules, urine, and blood of rats subjected to bilateral renal ischemia [28]. Interestingly, the injection of an adenovirus harbouring the Klotho gene (which results in the release of soluble Klotho into the circulation) or the administration of recombinant soluble Klotho protein prior to the induction of the ischemic insult blunts the increase in creatinine and attenuates the tubulointerstitial damage [28–30]. Klotho expression is also downregulated in an animal model of spontaneous hypertension, and the delivery of Klotho has been shown to prevent the progression of hypertension, renal damage, and the proteinuria [31, 32]. Several mechanistic explanations for these observations have been proposed, and these centre on the reduction of renal superoxide and suppression of NADPH oxidase activity that is the main source of reactive oxygen species (ROS) which are all involved in the pathogenesis of renal disease. The observed nephroprotective effects appear to be at least in part independent of an acute (early) effect of Klotho on systemic blood

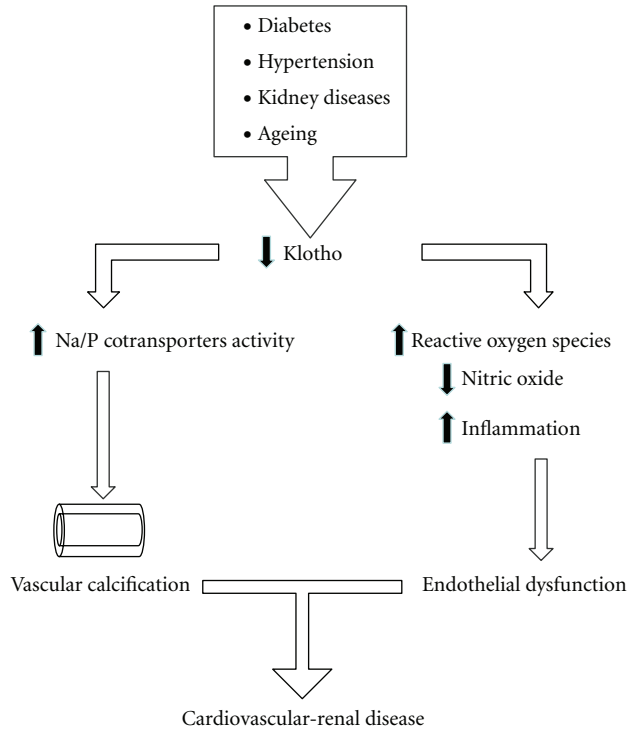

Figure 1: Putative mechanisms by which reduction in Klotho results in cardiorenal disease.

pressure. However, treatment with Klotho does prevent the progression of spontaneous hypertension [32].

The nephroprotective effects of Klotho have also been tested in an animal model of glomerulonephritis [33]. The transgenic overexpression of Klotho in a mouse model of glomerulonephritis resulted in increased survival, attenuated glomerular and tubulointerstitial changes, and reduced proteinuria and blood urea nitrogen [33].

In vivo, the intraperitoneal administration of soluble Klotho recombinant protein, immediately after the induction of unilateral ureteral obstruction, prevents the acute renal fibrosis through the inhibition of TGFβ1 signalling [34]. Specifically Klotho binds to the type II receptor (TGFβR2) suppressing the activation of the type I receptor (TGFβR1) that phosphorylates Smad2/3 proteins (transcription factors regulating the expression of TGFβ1 target genes) [34].

Studies conducted in humans have reported a reduction of Klotho, both tissue (transmembrane) and soluble forms, in acute and chronic kidney disease. Koh et al. examined the kidneys of 10 patients with clinical or histological diagnosis of chronic kidney disease and demonstrated that the expression of Klotho protein was significantly reduced when compared to healthy control [35].

There are limited studies evaluating changes in serum and urine levels of Klotho in humans; Yamazaki and his colleagues were the first to establish a novel assay to detect circulating serum Klotho [24]. In 181 healthy Asian volunteers between 0.1 and 88 years of age, serum concentrations of Klotho ranged from 239 to 1266 pg/mL. Levels were higher in young subjects and lower in older adults and negatively correlated with serum creatinine levels [24].

A reduction of Klotho levels in urine has been reported in patients with acute kidney injury and in subjects with chronic kidney disease [28, 36]. Hu et al. have recently found in 39 patients with different severity of CKD lower levels of Klotho in urine. This decrease in urinary levels of Klotho is early at stage 1 and correlates with the decline of eGFR [36].

Klotho may be an early clinical biomarker of acute and chronic renal injury CKD as its diminution precedes changes of other well-established markers/factors involved in the progression of renal failure. However, further long-term prospective studies are required to establish the utility/value of Klotho as an early marker of acute and chronic renal disease.

4. Vascular Protective Effects of Klotho

Soluble Klotho has an important role in maintaining endothelial wall homeostasis and promoting the health of the vasculature [37–39]. In experimental models, the absence of Klotho gene is associated with endothelial dysfunction and diffuse vascular calcification [36, 38]. Recent experimental studies have confirmed that soluble Klotho may act as a humoral factor that protects the vascular system [39].

Endothelial dysfunction results from the imbalance between the release of vasodilator and vasoconstrictor factors and is an early step in the development and progression of cardiovascular disease. This disrupted equilibrium is

predominantly due to the reduced bioavailability of nitric oxide (NO) because of its inactivation by ROS [3]. NO not only produces vasodilatation but also prevents the atherogenic mechanisms by suppressing smooth muscle cell proliferation and by inhibiting the expression of adhesion molecules and platelet aggregation [2].

Saito et al. demonstrated that in Klotho heterozygous mutant mice endothelium-dependent vasodilatation in the aorta and arterioles in response to acetylcholine is attenuated and the excretion of urinary nitric oxide metabolites is reduced [37]. In Klotho heterozygous mutant mice ischemia-induced angiogenesis is impaired and is accompanied by a decreased number of endothelial progenitor cells, which are important in the repair of damaged vessels, in the peripheral blood [40].

Klotho gene delivery, mediated by adenoviral vector, in a rat model of atherosclerosis, increased endothelium-dependent NO synthesis and prevented adverse vascular remodelling [37].

Klotho is also involved in the modulation of endothelial inflammation as demonstrated in vitro by Maekawa et al. In human umbilical vein endothelial cells (HUVECs), soluble recombinant protein might suppress the expression adhesion molecules involved in the pathogenesis of vascular disease such as intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) [41].

Hu et al. have documented that Klotho is a direct inhibitor of vascular smooth muscle cell (VSMC) calcification. The authors showed in an elegant mouse model that Klotho deficiency is associated with more severe calcification, undetectable levels of soluble Klotho, and higher serum levels of phosphorus, whereas Klotho overexpression was accompanied by less calcification, preserved levels of Klotho and normal renal function [36]. In vitro, the recombinant soluble Klotho prevented the VSMC calcification induced by high phosphate through the inhibition of sodium-phosphate cotransporters Pit1 and Pit2 [36]. However, whether VSMC expresses endogenous Klotho is not known and this remains an important area for further research. In humans, the reduced urinary levels of Klotho in CKD might at least in part explain associated vascular calcification, a predictor of cardiovascular risk. As lack of soluble Klotho is an important factor in the pathogenic mechanisms of vascular calcification, its replacement may be a potential future therapeutic approach in the vascular risk management of patients with CKD [36].

5. Conclusions

Soluble Klotho is a novel humoral factor that confers resistance to oxidative stress associated with ageing and several pathological conditions predisposing to cardiovascular-renal damage. There is emerging evidence highlighting the essential involvement of Klotho in calcium/phosphate metabolism and the maintenance of vascular integrity. Figure 1 summarises the potential mechanisms by which Kotho may afford cardiorenal protection. Since the decline in soluble Klotho levels represents a negative event occurring in the early stages of cardiovascular-renal disease, Klotho might be considered as a useful biomarker that predicts atherosclerosis and vascular calcification. Further long-term clinical studies are required to establish the role of this exciting new potential marker and predictor of cardiorenal disease.

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Review Article

New and Old Mechanisms Associated with Hypertension in the Elderly

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Hypertension is a widely prevalent and important risk factor for cardiovascular diseases that increase with aging. The hallmark of hypertension in the elderly is increased vascular dysfunction. However, the molecular mechanisms by which increased blood pressure leads to vascular injury and impaired endothelial function are not well defined. In the present paper, we will analyze several mechanisms described in the scientific literature involved in hypertension in the elderly as endothelial dysfunction, increased oxygen delivery to tissues, inflammation, cellular apoptosis, and increased concentration of active metabolites. Also, we will focus on new molecular mechanisms involved in hypertension such as telomeres shortening, progenitor cells, circulating microparticles, and epigenetic factors that have appeared as possible causes of hypertension in the elderly. These molecular mechanisms may elucidate different origin for hypertension in the elderly and provide us with new targets for hypertension treatment.

1. Introduction

The elderly, considered as individuals 65 years of age and older, represents the most rapidly growing segment of the population. Age is a powerful risk factor for hypertension, death, and cardiovascular death [1]. In this regard, high blood pressure in the elderly confers a three- to fourfold increase in risk for cardiovascular disease, compared to younger individuals [2]. New guidelines have tried to provide evidence-based treatment algorithms in which control of hypertension is just one aspect of general risk factor control, with the aim of decreasing the total risk. According to the World Health Organization, hypertension is the commonest cause of preventable death in developed countries, and it is increasingly significant in developing countries. Particularly, it has been described that hypertension affects more than one half of those aged 65 and older, and its prevalence continues being increased with age. The incidence of hypertension in the elderly population, over age 60–65 years, is very high with prevalence as high as 60% to 80%. It is estimated that two out of three individuals over 75 years of age suffer hypertension [3].

Large number of studies has revealed that patterns of hypertension change with age. In this regard, systolic blood pressure increases, while diastolic blood pressure decreases after the age of 60. These different patterns indicate us diverse etiologic and hemodynamic mechanisms for hypertension in the elderly population [4]. Several mechanisms involved in hypertension in the elderly have been described in the scientific literature as endothelial dysfunction, increased oxygen delivery to tissues, increased concentration of active metabolites or increased myogenic constriction. Recently, new molecular mechanisms involved in hypertension such as telomeres shortening and endothelial progenitors cells have appeared as possible causes of hypertension in the elderly. These molecular mechanisms may elucidate different origin for hypertension in the elderly and provide us with new targets for hypertension treatment. This paper will be focused in the management and old and new molecular mechanisms associated with hypertension in the elderly.

2. Management of Hypertension in the Elderly

Due to the advances in the treatment of hypertension, the definition of isolated systolic hypertension has been changed from a blood pressure level ≥160/<90 to ≥140/<90 mmHg. Initially, the focus of hypertension studies was only on diastolic blood pressure. Later, multiple hypertension trials demonstrated that systolic blood pressure (SBP) levels were concomitantly lowered with diastolic blood pressure and that SBP was more closely associated with improvements in outcome than diastolic blood pressure, providing more relevance to SBP.

High blood pressure, and in particular, isolated systolic hypertension (ISH), has been in the elderly, as recently as two decades, ignored as a cardiovascular risk factor [5]. In 1985, the European Working Party on High Blood Pressure in the Elderly (EWPHE), provided the first evidences about the benefits of the therapeutic intervention in the elderly hypertensive patients [6]. However, it was not until the 1990′s when it really took into consideration the fact of treating hypertension based solely on systolic pressure. In 1991, the Systolic Hypertension in the Elderly Program (SHEP) demonstrated in 4736 older individuals with SBP levels >160 mmHg and diastolic blood pressure levels <90 mmHg, randomized to treatment with thiazide-type diuretic-based regimen versus placebo, greater reductions in blood pressure in the treated group and reductions in the primary end point by 36%, heart failure by 49%, and coronary events by 27% [7].

In 1997, the Systolic Hypertension in Europe Study (SYS-TEUR) corroborated the results obtained in the SHEP study. In the SYS-TEUR study a group of aging patients were randomized to the dihydropyridine calcium channel blocker nitrendipine or placebo. In this study, blood pressure was not reduced as effective as in SHEP. However, the benefits obtained were higher, showing a significant reduction in stroke by 42% [8].

The Hypertension in the Very Elderly Trial (HYVET) is other remarkable trial of 3854 patients over 80 years of age, who received a combination of indapamide and perindopril. The study was stopped prematurely due to the conclusive results showing that people who received effective antihypertensive treatment were at 74% less risk of developing congestive heart failure and 20% or more at less risk of developing a stroke or dying either from cardiac complications or any other causes of death. These results provided the clinical evidence supporting the most recent guidelines for the treatment of hypertension [9].

3. Main Molecular Mechanisms Associated with Hypertension and Aging

3.1. Vascular Aging: Endothelial Dysfunction. Arterial wall is constituted for three layers: intima, media, and adventitia. Media and especially intima layers are where major alterations occur with age. Intima layer is based in a layer of endothelial cells on a subendothelial space that is separated from media layer due to elastic fibers. Media layer is formed by smooth muscle cells connected by extracellular matrix, muscle cells are also responsible for releasing of extracellular matrix components such as collagen and elastin. In advancing age, lipids are internalized into elastin fibers, and they attract calcium ions that provoke loss of elasticity and degradation of elastin fibers due to elastases.

As Dr. Osler postulated, "A man is so old as his arteries". In this regard, recent studies have concluded that structure and function of arteries change throughout the lifetime of humans [10, 11]. So, it has been demonstrated that in humans central elastic arteries as well as arterial wall dilate with advancing age. In addition, a large number of studies using animal models also found an age-associated restructuring of the central arteries of rats, rabbits, and primates [12, 13].

Endothelial cells play a central role in regulating several arteries properties, such as releasing of nitric oxide (NO), vascular tone, permeability, and, therefore, in the arterial pressure. Nitric oxide is a multifunctional molecule with an important role in the relationship between the cells that compose the microvascular environment. Perhaps, the most important effect of NO is its vasodilating property [14]. NO provokes vasodilation by stimulating soluble guanylate cyclase in the vascular smooth muscle cells [15]. Therefore, alterations in the expression of NO synthase (NOS) isoforms or its functionality has been widely associated with hypertension.

Age alters the amount, arrangement, and structural integrity of the endothelial cells cytoskeleton, which affects the mobility, migration, proliferation, and structural integrity of endothelial cells [16, 17]. At molecular level, numerous studies have associated the age advancing with decreased EC capacity for replication and increasing apoptosis, proinflammatory status and reduced production, and/or bioavailability of NO (Figure 1).

3.2. Alterations in the Production and/or Bioavailability of Nitric Oxide. Several vascular disorders, including a diminished endothelium-dependent relaxation, have been demonstrated in aging humans and even in experimental animals [18, 19]. Different hypothesis have been raised to explain the reduction of the endothelium-dependent vasodilatation described in the aging humans and animals: a decreased number of vasodilator receptors in the endothelium [20], a diminished capability to generate NO by the endothelium [19], and a reduction in guanylate cyclase activity in vascular smooth muscle cells [21]. In this light of evidences, a study performed by Cernadas et al. revealed new evidences about the function of the NO-dependent vasorelaxing mechanisms in aging rats [22]. They found in aging animals a reduced vasorelaxing response to acetylcholine, an endothelium NO-dependent vasodilator. However, paradoxically, blood vessels from aging rats showed a marked capacity to produce NO through the presence of the inducible NOS (iNOS) isoform. This finding highlights the importance of the presence iNOS isoform in aging, because at sites of endothelial damage, the locally released cytokines, such as tumour necrosis alpha (TNFα), could potentially stimulate iNOS expressed in the

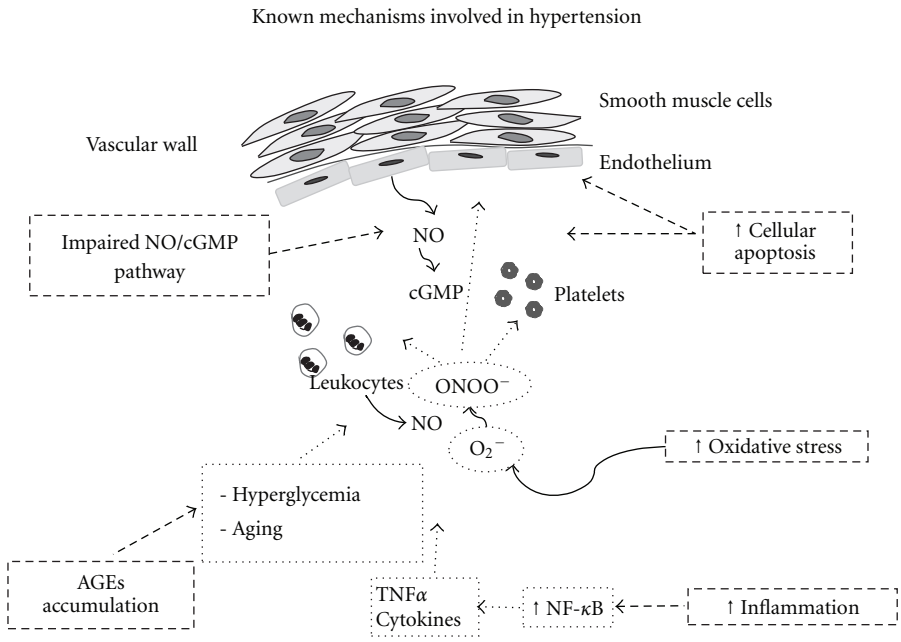

Figure 1: Known mechanisms involved in hypertension in the elderly population. Impairment of the NO/cGMP system, increased cellular apoptosis, and increased concentration of active metabolites such as advanced glycation end products (AGEs) together with an enhanced oxidative an inflammatory state are well-known mechanisms that contributes to the development of hypertension in the elderly population.

vascular wall. In this sense, continuous generation of NO by iNOS has been associated with the impairment of the NO system in endothelial cells which has been speculated to protect the vascular wall from excessive amounts of NO. The NO released by the iNOS activity could decrease the eNOS activity, thus favoring the impaired endothelium-dependent vasorelaxation. Indeed, NO has been also described as a cytotoxic molecule for endothelium, inhibiting their growth [23]. In addition, it is well known that free radicals, which increase in aging, inactivate NO by interacting with high concentrations of superoxide anion and resulting in enhanced peroxynitrite formation. Therefore, iNOS may have an important role in the maintenance of vascular tone with increasing age.

Endothelial dysfunction occurs early in several cardiovascular disorders including atherosclerosis, diabetes, and hypertension. Hypertensive subjects exhibit endothelial dysfunction, indicating that endothelial dysfunction precedes the development of clinical hypertension. Systolic hypertension is the dominant form of hypertension in older individuals [24]. Arterial stiffness, determined by structural properties of the blood vessel wall and by smooth muscle tone, is one of the most important factors underlying the increase in systolic pressure. In this regard, longitudinal studies in humans have shown that arterial stiffness is an independent predictor of the rise in systolic blood pressure and of incident hypertension [25]. All these experimental evidences reveal the stretch linkage between aging and hypertension. Recently, a brilliant article performed by the American Society of Hypertension Writing Group [26] recognized the pivotal role of vascular aging in the continuum of cardiovascular risk leading to hypertension.

3.3. Endothelial Replication and Apoptosis. Human aging is accompanied by a degeneration of various tissues, which lose part of their physiological functions. Apoptotic cell death plays an important role during aging of various tissues in vivo. Tissue damage due to age-dependent apoptosis has been documented in experimental animals for the brain [27], the inner ear [28], among others. It has been also described that the regulation of programmed cell death plays an important role for the ageing process in vivo. In this regard, atherosclerosis, a major age-related disease of humans, is accompanied by a degeneration of vascular endothelial cells and vascular muscle cells due to programmed cell death or apoptosis [29]. However, the mechanisms leading to age-related apoptosis in an endothelial cell remains to be clarified. In this regard, Warner et al. demonstrated that human endothelial cells followed a different senescence program from the program displayed by human fibroblasts [30]. They found that endothelial cells showed an age-related increase in programmed cell death due to DNA rereplication in the absence of mitosis with G1 arrest, leading in the accumulation of "N" DNA content >4 in endothelial cells. In this light of evidences, Asai et al. also postulated a potential mechanism for the endothelial dysfunction based on apoptosis, using a novel monkey model of aging, phylogenetically closer to humans but devoid of complications secondary to associated cardiovascular diseases [31]. They described an increased density of apoptotic cells observed in the endothelium of the aorta and femoral artery in old monkeys compared with young monkeys.

3.4. Oxidative Stress and Inflammation in Aging-Related Diseases. As we have commented during the paper, aging is

the major risk factor for the development of cardiovascular diseases and associated risk factors such as hypertension. In this context, vascular oxidative stress and inflammation significantly increase with age as a consequence of greater production of reactive oxygen species (ROS) and inflammatory markers. One of the main consequences of increased oxidative stress in aging is the functional inactivation of nitric oxide (NO) induced by elevated concentrations of superoxide anion, resulting in enhanced impairment of NO bioavailability and decreased vasodilator capacity [32, 33].

In the same line, inflammation is considered a critical initial step in the development of vascular disease during aging. In this regard, recent studies have demonstrated that arterial aging, in the absence of other known vascular risk factors, is associated with a proinflammatory profile [34, 35]. This proinflammatory state induces, among others, endothelial dysfunction by the upregulation of cellular adhesion molecules (VCAM-1 and ICAM-1), and this enhanced endothelial-leukocyte interactions and alterations in the secretion of different autocrine/paracrine factors which are pivotal in inflammatory response. In this sense, it is well known that the activation of transcriptional factors such as nuclear factor-kappa β (NF-κB) are closely associated with these deleterious effects on vascular function [36]. In addition, NF-κB activation increases during aging and is thought to be responsible of the increased expression of adhesion molecules and inducible nitric oxide synthase found in vascular wall [37]. TNFα signaling, mitochondrial ROS-induced pathways and local renin angiotensin system are known pathways that converge with NF-κB and contribute to the vascular dysfunctionality observed during aging-related diseases.

Molecules strongly related to oxidative stress and aging are advanced glycation end products (AGEs) [38, 39]. Initially, AGEs were considered associated with hyperglycemic states. However, later studies demonstrated that AGEs formation may be stimulated even in normoglycemia although its expression is exaggerated under diabetes. AGEs are markers of carbonyl stress, which accumulates due to an increased level of sugars and reactive dicarbonyl compounds such as glucose, fructose, deoxyglucose glyoxal, and triosephosphates. AGEs, also termed glycotoxins, are well-known triggers of excess reactive oxygen species (ROS) and abnormally high oxidative stress [40, 41] that disrupt the structural integrity of proteins altering their interaction with other proteins and, therefore, affecting its functionality

Large body of evidence has implicated AGEs as pathogenic mediators of the multiple complications associated with aging and cardiovascular diseases, such as arterial stiffness, myocardial relaxation abnormalities, atherosclerotic plaque formation, and endothelial dysfunction. In this sense, AGEs have a wide range of pathological effects, including increased vascular permeability, inhibition of vascular dilation by interfering with the nitric oxide (NO) pathway [42], LDL oxidation [43], and macrophage and endothelial cell activation to induce cytokine release and, thus, increase of oxidative stress [44]. In vitro studies have demonstrated quenching and inactivation of NO by AGEs, modulating NO activity and endothelium-dependent relaxation [45]. In addition, AGEs also induce the production of ROS, which favours the uncoupling of NO synthesis [46]. They also stimulate the synthesis and release of proinflammatory cytokines through the activation of NF-κB [47, 48]. In experimental approaches, circulating levels of AGEs correlate with the level of different oxidative and inflammatory biomarkers, such as C reactive protein [49]. Upon such inflammatory situation, neutrophils, monocytes, and macrophages activate NADPH oxidase, leading to AGEs generation [50]. Also, AGEs have been shown to affect platelet adhesion and aggregation, thrombogenicity, and cell proliferation.

Recent findings have demonstrated that AGEs also are capable to augment hyperglycemia-associated depletion in endothelial nitric oxide production and endothelial nitric oxide synthase, demonstrating its important role in vascular dysfunction, linked to the induction of NO resistance [51]. This study observed an impaired vascular responsiveness to acetylcholine, accompanied by decreased eNOS protein expression and downregulation of cGMP-dependent protein kinase-1 expression.

Another deleterious mechanism on vascular function develop by AGEs is via the interaction with specific receptors called RAGEs. These receptors are members of the immunoglobulin superfamily that modulate the inflammatory response by increasing the expression of NF-κB, proinflammatory cytokines, growth factors, and vascular adhesion molecules [52].

With respect to hypertension, it has been observed that AGEs diminish arterial compliance of large vessels elevating systolic blood pressure and pulse pressure, via inducing alterations in intima-media thickening and modifying collagen and elastic fibrils structure. Recent in vitro and in vivo studies have shown that angiotensin II type 1 receptor blockers can reduce AGEs formation [53, 54] although many doubts still exit about the concrete mechanism by which these molecules exerts this action. In summary, AGEs provide a new target for the development of more potent therapeutic agents in the treatment of vascular diseases.

In summary, the age-associated alterations in arterial structure and functionality, such as endothelial dysfunction and arterial stiffening, are considered as potent risk factors for arterial diseases, even after accounting for traditional cardiovascular risk factors, including arterial pressure.

4. New Molecular Mechanisms Associated with Hypertension and Aging

As we have described above, aging is a major risk factor for hypertension and cardiovascular disease. However, the molecular mechanisms by which increased blood pressure leads to vascular injury, and impaired endothelial function are not well defined. In recent years, new molecular mechanisms have appeared as possible targets to improve the knowledge of this pathology. The new mechanisms proposed include the effect of telomere shortening, dysfunction of progenitor cells, increase of deleterious microparticles, and finally epigenetics and the involvement of life style (Figure 2).

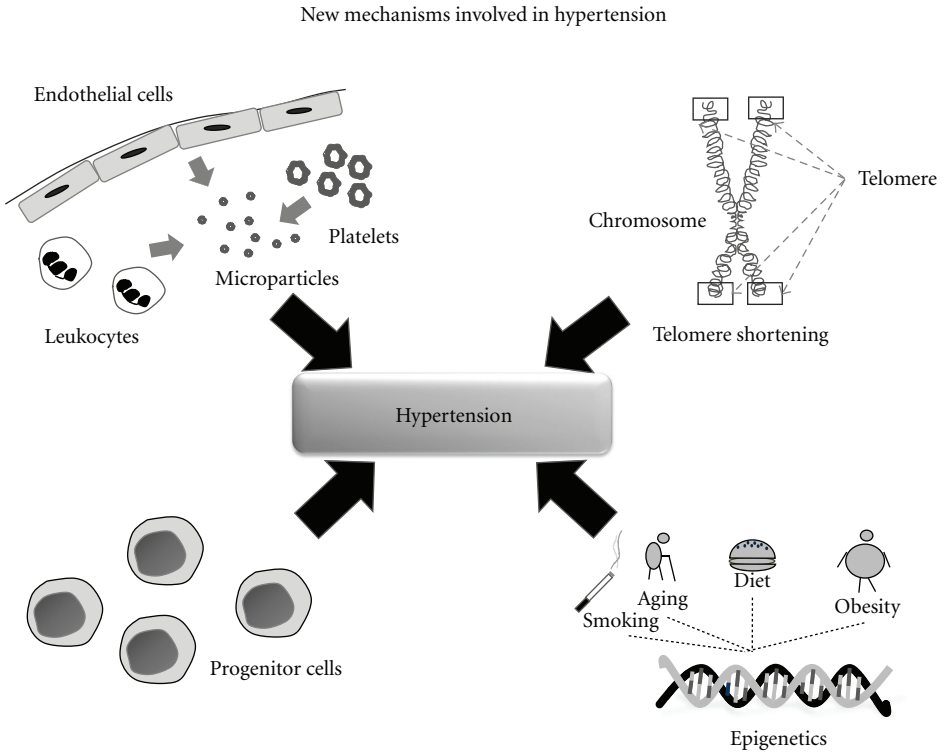

Figure 2: New mechanisms involved in hypertension in the elderly population. Telomere shortening, dysfunction of progenitor cells, increase of platelet, leukocyte, erythrocyte, and endothelial cells-derived microparticles, and epigenetic alterations together with the involvement of life style are proposed as new mechanisms associated with hypertension.

4.1. Telomeres Length. In the last years, the "telomere hypothesis" of aging and its involvement in the development of aging-related diseases such as hypertension has gained importance [55]. Telomeres are distinctive DNA-protein structures at the end of linear chromosomes that preserve genomic integrity and progressively shorten with replication [56]. Telomeres have demonstrated age-dependent shortening in proliferative somatic cells [57], and accumulative evidence suggests that telomere length can be used as a marker of biological aging of the cardiovascular system and as a potential predictor of the risk and variability of developing hypertension and cardiovascular events.

As telomere length becomes critically shortened, the cellular replicative machinery stops functioning and usually leads to replicative senescence. Studies in telomerase-deficient mice have shown a direct link between telomere shortening and hypertension [58]. In human studies, shorter telomere length has been strongly associated with oxidative stress [59], inflammation [60], atherosclerosis, and arterial stiffness [61]. Results of the Framingham Heart Study have also shown a reduced leukocyte telomere length in individuals with a higher renin-to-aldosterone ratio, especially in patients with hypertension [62]. In the same line, a five-year follow-up study has shown shorter leukocyte telomere length in hypertensive patients, who were also more likely to develop in the future atherosclerotic artery disease [63]. Moreover, this study presented telomere length as an independent risk factor for the development of cardiovascular disease both in patients with hypertension and in patients with normal blood pressure.

Interestingly, there are also diverse evidences showing that some of the drugs used in the treatment of hypertension stimulate telomerase activity and the reverse transcriptase that adds telomere repeats onto the ends of chromosomes, allowing the elongation of telomeres. The case of AT1 receptor antagonists of angiotensin II [64], statins [65], and aspirin [66] is becoming, therefore, a new target for future research studies.

During the last years, the number of studies about progenitor cells and its involvement in the development and evolution of vascular diseases has been increasing significatively. In this sense, the ability of endothelial progenitor cells to integrate into the vascular wall favouring endothelial repair has been widely described. Aging-related diseases are closely associated with endothelial injury and a significative reduction in the number and functionality of circulating EPCS. Studies in mouse models have demonstrated a crucial role of telomere shortening in the impairment of the progenitor cells during biological aging. In this regard, a recent study has shown that telomere shortening in EPCs plays an important role in the pathogenesis of cardiovascular disease via increased oxidative-related DNA damage [67].

In summary, telomere shortening could be a useful biomarker of biological aging of the cardiovascular system with a potent predictor value of the risk and variability

of developing hypertension and associated cardiovascular events.

4.2. Progenitor Cells. As we have described previously, endothelial dysfunction is thought to be critical in the development of the vascular dysfunctionality observed in aging-related diseases such as hypertension and cardiovascular disease. Aging is related to the deleterious modifications observed in vascular function. In addition, impairments in endogenous vascular repair mechanisms, such as the conducted by EPCs, are thought to contribute to the manifestation of hypertension and cardiovascular disease. Bone marrow-derived EPCs have been considered as important agents of vascular repair. In addition, aging is associated with reduced number and function of EPCs [68], contributing to the greater cardiovascular risk observed in middle-aged and older adults. However, the real influence of aging on the increased EPCs apoptosis still remains unknown. Recently, Kushner et al. have documented that aging is associated with a proapoptotic EPC phenotype characterized by decreased expression of key antiapoptotic proteins associated with the Phosphoinositol-3-kinase signaling pathway and reduced telomerase activity, contributing to the diminished ability of EPCs to resist the apoptotic stimulus associated with aging [69].

It has been argued that the reduced endothelial repair capacity of EPCs in hypertensive patients is related to EPCs senescence and impaired endothelial function and likely represents an early event in the development of hypertension, contributing to the end-organ damage associated to this pathology [70, 71]. In this sense, infusions of circulating EPCs have been found to be able to augment endothelium-dependent vasodilatation, improving endothelial function [72]. Both, animals and human studies have demonstrated that the impaired EPC function that occurs during hypertension can be corrected with some antihypertensive treatments [73]. Therefore, it makes EPCs a modifiable factor that provides a new interesting line of research in the treatment of hypertension.

4.3. Circulating Microparticles. It was in 1967 when Wolf described the presence of small circulating procoagulant, prothrombotic, and proinflammatory particles in plasma called microparticles [74]. Circulating microparticles are small vesicular structures of about 0.1–1 μm that have been associated with arterial thrombotic processes [75]. Microparticles are shed from the surface of different types of cells in response to activation, injury, and/or apoptosis. Although it is considered that the majority of circulating microparticles are platelet-derived (70%–90% of total), other cells such as red blood cells, leukocytes, and endothelial cells also release microparticles.

Circulating microparticles are increased in patients with cardiovascular risk factors such as hypertension [76]. In this sense, increased number of circulating microparticles has been associated with poor clinical outcome [77] and, recently, microparticles have been defined as potential prognostic markers for vascular disease [78].

The influence of microparticles in vascular function, favouring endothelial dysfunction, has been demonstrated in multiple experimental studies. Microparticles have been shown to induce the expression of endothelial cyclooxygenase type 2, different adhesion molecules, the release of cytokines, and the impairment of nitric oxide release from vascular endothelial cells. Interestingly, these harmful effects on endothelial functionality seem to be mainly mediated by microparticles of endothelial origin although platelet-derived microparticles also mediate some of them. For this reason, most of the studies have focused on microparticles of endothelial origin as possible biomarkers of endotelial-dysfunction in patients with vascular disease. In this regard, when compared with classical markers of endothelial activation, endothelial derived microparticles appear to be more robust predictor of the incidence of coronary events [79]. For instance, it has been shown that circulating endothelial microparticles correlated positively with the extent and severity of coronary stenosis at angiography in patients with coronary syndromes [80].

It has been also observed that pharmacological treatment affects microparticle formation. While statins impair endothelial microparticle formation, aspirin seems not to affect microparticle formation, and others such as ticlopidine, abciximab, or cilostazol induced reduction in the number of circulating microparticles [81, 82]. Therefore, analysis of circulating microparticles could represent a useful tool in monitoring the efficacy of antihypertensive treatments.

Increasing evidence indicates that changes in plasma levels of microparticles of different cellular origins might be used as surrogate markers of vascular alterations, as those that occur during hypertension. However, there are still many questions of whether circulating levels of endothelial microparticles are the cause or result of endothelial dysfunction, and more studies will be needed. Thus, due to their procoagulant, prothrombotic, and proinflammatory effects on vasculature, microparticles could modulate the cross-talk between the cellular elements of the coagulative, thrombotic, and inflammatory systems through the transfer of different signaling molecules and receptors of their cellular origin to other cell types. Therefore, the study of circulating microparticles could be considered as novel therapeutic target in cardiovascular diseases. In this regard, novel proteomic approaches represents a new interesting tool for the study of the concrete microparticle composition, facilitating the identification of active components and clarifying their involvement in the development of diseases. In this context, the first proteomic studies analyzing the proteomic pattern of platelet [83], red blood cells [84], and endothelial cells-derived microparticles have already appeared [85].

4.4. Epigenetics and Lifestyle. Despite the considerable knowledge gained in recent years on the human genome, there are many questions regarding the mechanisms of inheritance and the mechanisms involved in hypertension and cardiovascular diseases. Nowadays, is fully accepted that the development of diseases is very directly involved with both genetic and epigenetic alterations.

In this regard, it is well known that genes are expressed or not depending on various factors such as chromatin and certain biochemical conditions, such as methylation of DNA and modification of histones. The science that studies all these factors is called epigenetics. It is important to realize that epigenetic processes are natural and essential for many body functions, but if they occur improperly they can cause serious adverse health effects, and hence the relevance of epigenetics in the study of human disease.

Epigenetics studies the interaction of DNA and its expression with the environment. It consists in the study of the inheritance of gene expression patterns that are not determined simply by the genetic sequence of each individual. It includes the study of any process that alters gene activity without changing DNA sequence and leads to changes that can be transmitted to daughter cells. We can say that epigenetics acts as "interlocutor" with the genetics and environment, helping to explain the action of lifestyle on the genes. It also describes the mechanisms that allow cells to respond quickly to environmental changes, thus providing a clear link between genes and the environment around them.

Hypertension is an arterial wall disease that together with smoking, high cholesterol, diabetes, overweight, and sedentary lifestyle is one of the main modifiable risk factor that leads to the development of cardiovascular diseases. Environmental factors such as diet, stress, and inactivity directly affect the incidence of this pathology, but it has also been established that stress in utero may program the later development of the disease. To date, the cardiovascular effects of early nutritional changes have been largely investigated following maternal undernutrition or protein restriction [86]. In this regard, interestingly, studies have shown that in maternal low-protein diet rat model, administration of angiotensin converting enzyme inhibitors or angiotensin receptor antagonists in early life can prevent the development of hypertension [87]. Epigenetic analysis demonstrated that the proximal promoter of the AT1b gene in the adrenal is significantly undermethylated. In vitro studies showed that the expression of this gene is highly dependent on promoter methylation, suggesting a link between fetal insults to epigenetic modification of genes and ultimately leading to the development of hypertension. Similarly, the methylation pattern of a serine protease inhibitor gene in human placenta is shown to be a marker for preeclampsia-associated hypertension.

The hallmark of hypertension in the elderly is increased vascular resistance. The usual therapeutic approach to the elderly hypertensive patient should generally consist of a reduction in salt and caloric intake and an increase in aerobic exercise. It has been demonstrated the effectiveness of modifications in the lifestyle to reduce blood pressure in aging patients. For instance, the Nonpharmacologic Interventions in the Elderly trial (TONE) demonstrated that with small reduction in salt or corporal weight, it is possible to reach a significantly reduction of blood pressure levels [88]. In this sense, epigenetics studies could provide new information about the effect of the environmental factors that are involve in the development of cardiovascular diseases.

Nowadays, most of epigenetic studies are being conducted in the area of oncology, which are getting plenty of evidence linking epigenetic processes in cancer development. However, in the cardiovascular area, there is a great deal of untapped information. Therefore, epigenetics offer a promising avenue of investigation of the mechanisms involved in the development and evolution of cardiovascular diseases.

5. Summary

In the elderly population hypertension is a significant determinant of cardiovascular risk, and nowadays, it is well known that is closely associated with the incidence of vascular events. The development of vascular endothelial dysfunction is thought to be critical in the development of the vascular dysfunctionality observed in hypertension. In recent years, new molecular mechanisms such as telomere shortening, dysfunction of progenitor cells, increase of deleterious microparticles, and epigenetics alterations have appeared as possible targets to improve the knowledge of this pathology. Knowing more in depth the critical molecular mechanisms underlying the vascular dysfunctionality associated to hypertension may provide novel interventional treatments for promotion of cardiovascular health in older persons.

Author's Contribution

P. J. Mateos-Cáceres and J. J. Zamorano-León share the authorship of the revision.

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Review Article

Cultural Considerations: Pharmacological and Nonpharmacological Means for Improving Blood Pressure Control among Hispanic Patients

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Cardiovascular disease is a leading cause of morbidity and mortality in the United States, and its prevention and treatment remain a priority for the medical community. Ethnic variations account for some differences in the prevalence of hypertension and blood pressure (BP) control rates among Hispanics, indicating the need for culturally appropriate management models. Aggressive treatment strategies are key to achieving optimal BP control in high-risk Hispanic patients. Hypertension in this ethnic group continues to be a major health concern. Of note, when provided access to comprehensive care, Hispanics demonstrate similar response rates to treatment as the majority of non-Hispanic whites. This highlights the importance of effective, culturally responsive hypertension management among high-risk Hispanic patients for achieving observable, positive health outcomes.

1. Introduction

In the United States, cardiovascular disease is a leading cause of morbidity and mortality; therefore, prevention and treatment remain a priority for the medical community [1]. Though each ethnic group and segments of the populations are affected by cardiovascular disease, it has been observed that socioeconomic and racial factors are strongly correlated with health. Hypertension awareness often accounts for minor differences in blood pressure (BP) control between Hispanics and non-Hispanics, resulting in the need for culturally appropriate education and management models [2].

2. Acculturation, Language, and Hypertension

In the United States, researchers note that factors such as modernization, education, and structural assimilation were correlated with favorable BP profiles [3]. The prevalence of hypertension among Hispanic Americans appears to increase with the process of acculturation and is inversely correlated with socioeconomic status [4]. Indeed, acculturation and language proficiency in this ethnic group can be directly correlated with the incidence of diabetes and associated morbidities, which have implications for cardiovascular health [5].

For example, among Mexican Americans, acculturation and age are strong predictors of hypertension as opposed to economic status [6]. Based on these findings, Mexican American women who are English proficient and had healthcare coverage were more likely to be screened for heart disease [7]. This assertion is confirmed by Sundquist and Winkleby [8], who found that risk of cardiovascular disease is highest for US-born Spanish-speaking individuals, intermediate for US-born English-speaking individuals, and lowest for individuals of Mexican origin. In spite of increased awareness on the part of both patients and their primary care providers, Spanish-speaking patients continue to have higher rates of hypertension, LDL cholesterol, and fasting blood glucose, when compared to acculturated, or English-speaking Hispanics [9]. US-born Mexican Americans are

more likely to obtain BP screenings than their Mexican counterparts, highlighting the need for clinicians to carefully note a patients' country of origin and other sociodemographic risk factors, such as lower levels of education [10].

3. Hispanic Identity

Hispanic and Latino individuals are the largest minority in the US population at over 15 percent. This ethnic group exhibits a great degree of genetic, physiologic, and socioeconomic variability.

Due to the complexity of this group, intracultural variability for the treatment of hypertension in Hispanics deems greater appreciation. Findings suggest that within this "single" ethnic group, there are differences in disease prevalence and complications and in access to health care. For example, Getaneh et al. [11] report that Dominican Americans have a higher incidence of diabetes than Mexican Americans.

Lin et al. [12] reported that the incidence of hypertension was 66 percent among Puerto Rican men and 73 percent among Dominican men, compared with 69 percent for non-Hispanic white men. Also, Hispanic Americans of Caribbean descent have a hypertension profile similar to that of African Americans [13].

4. Prevention and Patient Awareness

Awareness is a key in combating hypertension, which is often described as the "silent disease." It has been found that Mexican American hypertensive subjects had significantly poorer BP control than non-Hispanic white hypertensive subjects. This trend is often attributed to low hypertension awareness among Hispanics when compared with their counterparts in other ethnic groups [13].

The most effective way to ensure good health is to emphasize a healthy, preventative lifestyle. Prevention behaviors can be taught in childhood and actively practiced through adolescence and into young adulthood. Increasingly, adolescents are at risk for developing insulin resistance and worsened cardiovascular disease risk factors [14].

Such risk factors set the stage for obesity, which is placing young people at risk for diabetes and hypertension [14]. Hispanics have been shown to have a 21 percent greater prevalence of obesity compared with non-Hispanic whites [15]. This trend among adolescents suggests prevention and health literacy beginning should be emphasized at a very early age by way of school-based and community-based prevention strategies. Such strategies can directly impact health outcomes and academic performance [16]. Because diabetes tends to be diagnosed in Mexican Americans at younger ages, it is important to screen this population at earlier timepoints (i.e., adolescence) for hypertension. In addition, African Americans and Mexican Americans have the lowest rates of BP control though under treatment [17]. Specifically, it has been reported that among patients with hypertension, medication use was lower in Hispanics (45%) than in non-Hispanic whites (54%) [18]. These high rates indicated a need for educational campaigns to raise awareness.

5. Incidence of Hypertension in Hispanics

Although historically, Mexican Americans' prevalence for heart disease and hypertension has been lower than among their counterparts in the general population, there has been an increase since 1993 making it the leading cause of death among Mexican Americans [10, 19]. This increasing incidence is partly indicative of a failure to prevent cardiovascular disease through management and education [20].

Although BP control and cholesterol levels have improved for adults with cardiovascular disease and diabetes, in general, differences in disease control with respect to ethnicity and age have not decreased, with hypertension control remaining higher among non-Hispanic whites [21]. This demonstrates that, with respect to demographic trends, the overall incidence of hypertension among Mexican Americans continues to be a matter of concern for public health, with severely adverse outcomes seen in 6 percent of the Mexican American older population [22].

6. Medications and Treatment

The findings from ALLHAT (antihypertensive lipid lowering treatment to prevent heart attack trial) demonstrate that Hispanic participants had equivalent or superior BP control compared with non-Hispanics in a clinical trial setting where patients with hypertension possessed equal access to medical care. In this trial, medication was also provided at no cost. Compared with non-Hispanic whites, Hispanic whites had a 20 percent increased likelihood of achieving BP control than non-Hispanic whites, after adjusting for multiple factors that predict BP control [23].

Hispanic Americans have higher rates of cardiac morbidity. As a result, researchers have suggested that angiotensin-converting enzyme inhibitors (ACEIn) and angiotensin II receptor blockers (ARBs) may be particularly useful in the Hispanic population owing to the ability of RAAS inhibitors to protect against end-organ damage caused by hypertension [24].

The effectiveness of proper medication regimens should not be underestimated among Hispanic patients. It has been noted that the use of antihypertensive regimens resulted in superior BP control and fewer cardiovascular events in Hispanic women compared with non-Hispanic white women [25]. Furthermore, it has been found that adherence to treatment was better among blacks (83.7%) and Hispanics (83%) than among whites (78.4%) [26].

Several large trials continue to explore this important line of inquiry. The ongoing telmisartan alone and in combination with ramipril global endpoint trial (ONTARGET) [27] study suggests that high-risk patients benefit from combination therapy. In the INVEST (international verapamil-trandolapril study) trial, no significant differences were noted between verapamil and atenolol-based strategies for the primary outcome of death and nonfatal

myocardial infarction or stroke by ethnicity [28]. The INVEST researchers discovered that Hispanics, in particular, had a lower risk of adverse cardiovascular outcomes than non-Hispanics. A third study, the VALUE (valsartan long-term use evaluation) trial, found no differences by ethnicity between valsartan- and amlodipine-based therapies for the composite cardiac outcome [29]. Moreover, the INCLUSIVE study demonstrated that combination therapy led to substantial decreases in systolic BP among Hispanic patients [30].

The efficacy of the ACE and ARB combinations has been demonstrated in many studies. ACE and ARB agents each have their own pharmacologically relevant profiles, including different efficacy profiles for BP control [31]. There may be unwanted side effects, such as angioedema, which may be associated with some ARBs [32].

Some studies have suggested that primary care providers should aim for more aggressive treatment of their hypertensive patients, regardless of ethnicity [26]. Compliance with JNC prescribing guidelines and more aggressive increase of medication dosages when indicated can improve rates of hypertension control and reduce the racial differences in hypertension outcomes [26]. Overall, the control rates of hypertension among Mexican Americans have increased significantly over a period of 5 years and have even been described as "encouraging" [19].

7. Comorbidities and Quality of Life in Hispanics with Hypertension

Comorbidity rates and mortality related to hypertension may be higher among individuals in the Hispanic community. For elderly patients, hypertension and its associated comorbidities present special challenges. It has been found that there is a direct correlation between age, the severity of the hypertension, and cognitive decline among Mexican Americans aged 65 years or older [33]. Lower extremity functional limitation (LEFL) is one of the comorbidities associated with suboptimal prescribing in hypertension [34]. In addition, it has also been noted that psychological effects caused by hypertension and the need for daily management can lead to a decreased quality of life [35].

8. Choosing the Right Treatments for Hypertension and Comorbidity Management

Targeted efforts to increase the use of ACE inhibitors or ARBs have been shown to improve quality of care for high-risk patients, regardless of ethnicity.

Several practical clinical management strategies have been found effective in improving clinical outcomes. For example, because nonadherence was found to be correlated with having BP checked in an emergency room, changing the locus of care for hypertension from emergency rooms to primary care may improve outcomes [36]. Another strategy, the dietary approaches to stop hypertension (DASH) combination diet, may be an effective strategy for preventing and treating hypertension, particularly in high-risk populations [37].

9. Special Considerations for Hispanic Women

It has been demonstrated that Hispanic women exhibit less favorable risk profiles for hypertension than non-Hispanic women [38]. Among younger, perimenopausal women, African American and Hispanic women exhibited the lowest rates of control for hypertensive risk factors [39], and hypertension control rates continue to be subobtimal for Hispanic women aged 60 years or older [40]. However, Hispanic women continue to have better treatment and control rates for hypertension than Hispanic men (Table 1).

10. Promotoras and Community Health Workers

The Hispanic community has a tradition of relying upon community health workers, also known as promotoras, to help improve the health of individuals in the community. For example, The Salud para su Corazón-HRSA initiative was successful in the development of infrastructure directed at supported promotoras de salud workforce in the US-Mexico border region [41]. Reductions in salt and cholesterol intake were shown to improve through promotora intervention [41]. A diabetes self-management education program can be effectively implemented in community settings for glycemic control [42]. In looking at community-based prevention, intervention was found to significantly increase the number of women meeting national recommendations for fruit and vegetable consumption [43].

Community-health workers also play a vital role in addressing the needs of rural patients. Optimization of healthcare delivery is needed for Hispanics who live in rural areas and who tend to be at higher risk for hypertension and less responsive to primary and specialty care compared with their urban counterparts [44]. The delivery of rural healthcare to patients with hypertension requires new strategies such as programs targeting therapeutic inertia, home-based monitoring of BP, and internet-based communication programs [45].

11. Innovative Strategies for Treatment and Prevention

Continuing care and lifestyle modification are practical, effective means of controlling hypertension among Hispanics. It has been shown that effective, culturally appropriate interventions result in increased adherence to lifestyle and diet modification [46].

One approach that has been suggested is a community-academic partnership, which enabled the successful recruitment, intervention, and assessment of Hispanics at risk for diabetes [47]. While this approach was adopted with the goal of reducing the risk of diabetes, its methods can perhaps be applied to patients with hypertension to achieve BP control. Another suggested intervention, the use of senior centers

Table 1: Percentage of noninstitutionalized US adults with hypertension* and, among those with hypertension, estimated percentage of persons who are aware of‡, treated for§, and in control of their condition¶, by sex, race/ethnicity, and age group—United States, 1999–2002.

Characteristic**	Hypertension prevalence % (95% CI‡‡)	Awareness of condition % (95% CI)	Under current treatment % (95% CI)	Condition controlled % (95% CI)
Sex				
Men	27.8 (24.9–29.7)	59.4 (55.8–63.1)	45.2 (40.9–49.6)	27.5 (23.7–31.3)
Women	29.0 (27.3–30.8)	69.3 (61.7–77.0)	56.1 (29.2–63.1)	35.5 (28.4–42.7)
Race/Ethnicity				
White, non-Hispanic	27.4 (25.3–29.5)	62.9 (57.3–68.5)	48.6 (44.1–53.1)	29.8 (25.7–34.0)
Black, non-Hispanic	40.5 (38.2–42.9)	70.3 (64.9–75.9)	55.4 (51.2–59.6)	29.8 (25.2–34.5)
Mexican American	25.1 (23.1–27.1)	49.8 (40.4–59.2)	34.9 (27.5–42.3)	17.3 (10.7–23.8)
Age group (yrs)				
20–39	6.7 (5.3–8.2)	48.7 (38.8–58.7)	28.1 (20.1–36.1)	17.6 (11.6–23.7)
40–59	29.1 (25.9–32.4)	73.5 (69.1–77.90	61.2 (57.1–65.2)	40.5 (36.4–44.5)
≥60	65.2 (62.4–68.0)	72.4 (70.0–74.7)	65.6 (61.9–69.3)	31.4 (28.7–34.2)
Total¶¶	**28.6 (26.8–30.4)**	**63.4 (59.4–67.4)**	**45.3 (45.3–52.8)**	**29.3 (26.0–32.7)**

* Had a blood pressure measurement ≥140 mm Hg systolic or ≥90 mm Hg diastolic or took antihypertensive medication.
‡ Told by a health-care professional that blood pressure was high.
§ Took antihypertensive medication.
¶ Hypertension levels <140 mm Hg systolic and <90 mm Hg diastolic.
** All characteristic estimates (excluding age group) are age adjusted [15].

as an intervention point for offering behavioral counseling and implementing lifestyle changes, has resulted in reduced systolic BP and increased adherence [48]. Church-based interventions may be a way to reduce stroke [49]. Culturally appropriate community-based interventions, such as those designed to engage individuals in physical activity while also increasing their awareness of risk factors, can impact clinical outcomes [50]. Cultural adaptation strategies, such as Spanish-language intervention models leading to lifestyle-based management programs, may also be effective [51].

Family-based interventions to raise awareness about hypertension can be effective, especially if they are administered through school-based programs that can educate both parents and children. In fact, it has been demonstrated that school-based programs are effective and correlated with reductions in BP among adult family members [52].

Nursing care management programs can also be clinically effective as well as cost effective in a medically indigent, culturally diverse population and provide an immediate benefit to a high-risk population [53]. Pharmacists play an important role in community-based screenings and in identifying high-risk individuals for cardiac disease [54]. To combat the increasing risk of hypertension and diabetes in increasingly younger groups, school-based interventions have been developed and implemented in Southwestern states [55].

12. Conclusions

Innovative, aggressive, timely treatment, with support in a community-based context, is needed. Interventions to reduce disparities in cardiovascular outcomes should consider the need to intensify drug therapy among all high-risk populations, as the aggressiveness of treatment strategies is key to achieving optimal BP control in high-risk patients. Although hypertension continues to be a major health concern for Hispanics, when these patients are given access to effective care, they demonstrate the same responsiveness to treatments as the majority of non-Hispanic white Americans.

These findings highlight the importance of effective, culturally responsive hypertension management in high-risk Hispanic patients for achieving observable, positive health outcomes.

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Clinical Study

Management of Hypertension in the Elderly Patient at Abidjan Cardiology Institute (Ivory Coast)

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Background. Since the treatment of hypertension is beneficial for the elderly, we have undertaken this study that aims to evaluate the management of hypertension in elderly patient in Côte d'Ivoire. *Methods*. A retrospective study was conducted among 854 hypertensive elderly patients of Abidjan Cardiology Institute who were followed for a minimum of one year, between January 2000 and December 2009. *Results*. The patients mean age was 73.1 ± 5.3 years, and 59% were women. At the first presentation, it was mostly systolic-diastolic hypertension (51.8%) and isolated systolic hypertension (38.5%). Mean blood pressure was 169.4 ± 28.4 mmHg for systolic, 95.3 ± 15.7 mmHg for diastolic, and 74.1 ± 22.8 mmHg for pulse pressure. Pulse pressure was ≥60 mmHg in 80.4%. According to the European Guidelines stratification of the cardiovascular risk-excess attributable to high blood pressure, 82.1% of the sample had a very high added risk. The pharmacological therapy was prescribed in 93.5%. More than 66% of patients were receiving ≥2 antihypertensive drugs including fixed-dose combination drugs. The most common agents used were diuretics (63.5%) followed by angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in 61.3%. The most common agents used for monotherapy were calcium antagonists. When ≥2 drugs were used, diuretics and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers were the most common. Blood pressure control was achieved in 42.6%. *Conclusion*. The control of elderly hypertension can be effective in Sub-Saharan Africa. He required at least two antihypertensive drugs to meet the recommended blood pressure target.

1. Introduction

Hypertension is an important worldwide public-health challenge because it is one of the most common chronic conditions [1, 2]. The prevalence of hypertension in Sub-Saharan Africa is between 12.5 and 26.9% [3]. In 2005 the World Health Organization stepwise approach to surveillance of noncommunicable diseases risk factors established prevalence of hypertension in Côte d'Ivoire to 21.7% [4].

Hypertension is a major risk factor for cardiovascular (CV) disease [5–7]. It remains an important cause of coronary heart disease, cerebrovascular disease, peripheral artery disease, and heart failure [8].

Age is the most powerful risk factor for hypertension, death, and cardiovascular death [9]. The worldwide increase in the elderly population (age ≥ 65 years) is associated with concurrent increases in prevalence of systemic hypertension and morbidity and mortality from vascular complications of hypertensive disease [10].

Recently, numerous large clinical trials have provided evidence of the benefits of reducing BP in the elderly. Meta-analysis of clinical trials showed that treatment of hypertension in older adults is as beneficial as that in younger adults [11, 12]. It is well established now that the treatment of hypertension in elderly patient was associated with a reduction in the rate of fatal or nonfatal stroke, a reduction in the rate of death from stroke, a reduction in the rate of death from any cause, a reduction in the rate of death from cardiovascular causes, and a reduction in the rate of heart failure [12, 13].

There are few Sub-Saharan African data about management of hypertension in elderly. It was in this context that we undertook the present study at Institute of Cardiology of Abidjan, the single university hospital managing

cardiovascular diseases in Côte d'Ivoire. This study aims to describe characteristics, risk factors, treatment and control of blood pressure of elderly hypertensive patients.

2. Methods

We undertook a retrospective descriptive study involving patients seen at the outpatient clinics of the Institute of Cardiology of Abidjan. The study period spans 10 years, between January 2000 and December 2009. The study population was hypertensive elders (aged at least 65 years) with a regular followup at the Institute of Cardiology of Abidjan within one year. This series includes patients who had been on an initial treatment upon referral to our center. Data were collected from the information contained in medical records.

We used the definition and classification hypertension standards of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) [7]. We have separated the systolic-diastolic hypertension from isolated systolic hypertension and from isolated diastolic hypertension. Pulse pressure has been considered pathological when it was ≥60 mmHg. The data collected were age, sex, blood pressure at initial presentation and during the followup (one month, 2 months, 3 months, 6 months, 1 year or last presentation), the coexistence of other cardiovascular risk factors, the impact of hypertension, and the treatment modalities. The following additional CV risk factors were document when present: current smoking, dyslipidaemia, diabetes, and obesity. Obesity was defined by a body mass index over 30 kg/m^2. Waist circumference was recorded when available. Dyslipidaemia was defined according to our biochemistry laboratory standard when the level of total cholesterol was >2 g/dL, LDL-cholesterol >1.4 g/dL, or HDL-cholesterol <0.4 g/L. Diabetic patients were informed and treated for diabetes as per standard clinical practice. New diabetic patients detected at Institute of Cardiology of Abidjan were diagnosed based on the standard value in our laboratory, fasting plasma glucose >1.26 g/dL on repeated measurement. The overall management of diabetes was coordinated by the individual patient's physician and not by the Cardiology staff of Institute of Cardiology of Abidjan. The assessment of the impact of hypertension has systematically included electrocardiogram and plasma creatinine. All strokes were documented by a brain computerized tomography scan imaging. Echocardiogram was frequently performed, and the results were included in the data collection. Finally, when other tests were seldom performed (e.g., albuminuria, microalbuminuria, the fundscopy, and 24-hour ambulatory blood pressure), they were not used for analysis.

The ESH and ESC categorization of total risk as low, moderate, high, and very high added risk has the merit of simplicity and was, therefore, chosen for risk stratification [7]. In addition, we focused on the evolution of blood pressure during followup. Blood pressure control was defined as a treated blood pressure <140 mmHg systolic and <90 mmHg diastolic and was ascertained by direct measurement of blood pressure.

Table 1: Population distribution according to the classification of blood pressure, the other cardiovascular risk factor, and target organ damage at first presentation.

Clinical data	%
Classification of blood pressure	
Controlled blood pressure	9.2
Systolic and diastolic hypertension (51.8%)	
Grade1 hypertension	4.8
Grade 2 hypertension	14.7
Grade 3 hypertension	32.3
Isolated systolic hypertension (38.5%)	
Grade1 hypertension	16.8
Grade 2 hypertension	12.7
Grade 3 hypertension	9
Isolated diastolic hypertension	0.5
Other cardiovascular risk factor	
Dyslipidemia	56%
Diabetes	18.6
Smoking	23.7
Obesity	33.8
Abnormal pulse pressure	80.4
Organ damage	
No organ damage	36.3
One organ damage	
Cardiovascular	37.9
Neurological	9.8
Renal	2.7
More than one organ damage	
Cardiovascular + renal	8.5
Cardiovascular + neurological	3.1
Renal + neurological	0.6
Cardiovascular + neurological + renal	1.1

Data analysis was conducted using IBM SPSS Statistics 17 software. Univariate analysis was performed for significant associations. A P value of ≤ 0.05 was considered for statistical significance.

3. Results

During the study period, 2575 hypertensive Black Africans patients have had a regular follow-up of at least one year. Among these patients, 849 were elderly subjects. The mean age was 73.1 ± 5.3 years (range 65–98 years), 59% were female. At first presentation blood pressure was inappropriately controlled in 90.8% patients.

It was mostly systolic-diastolic hypertension (51.8%) and isolated systolic hypertension (38.5%). Diastolic hypertension was observed in 0.5% (Table 1). Mean blood pressure was 169.4 ± 28.4 mmHg for systolic, 95.3 ± 15.7 mmHg for diastolic, and 74.1 ± 22.8 mmHg for pulse pressure. Blood pressure of men was not significantly different from that of women (Table 2). Pulse pressure was ≥60 mmHg in

Table 2: Type of drugs used.

Type of drug	%
One drug (33.1%)	
Calcium antagonists	36.3
RAS blockers	32
Diuretics	16
β-blockers	10.7
CAS	5
Two drugs (53.8%)	
RAS blockers + Diuretics	69.8
β-blockers + Diuretics	8.5
β-blockers + Calcium antagonists	7.4
Diuretics + Calcium antagonist	5.5
RAS Blockers + Calcium antagonists	3.5
RAS Blockers + β-blockers	3.5
CAS + (diuretics or RAS blockers or calcium antagonist or β-blockers)	1.8
Three drugs (11%)	
RAS blockers + Diuretics + Calcium antagonists	51.7
RAS blockers + Diuretics + β-blockers	18.4
Diuretics + β-blockers + Calcium antagonists	17.2
RAS blockers + β-blockers + Calcium antagonists	2.3
Other using CAS	10.4
Four drugs (2.2%)	
RAS blockers + Diuretics + Calcium antagonists + β-blockers	58.8
RAS blockers + Diuretics + Calcium antagonists+ CAS	35.3
RAS blockers + Diuretics + β-blockers+ CAS	5.9

RAS blockers: angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, CAS: Centrally acting sympatholytics.

Table 3: Change in blood pressure for all patients.

Blood pressure (mmHg)	First presentation	Last presentation	P
SBP	169.4 ± 28.4	153.5 ± 26.1	<0.001
DBP	95.3 ± 15.7	87.1 ± 14.3	<0.001
PP	74.1 ± 22.7	66.5 ± 19.9	<0.001

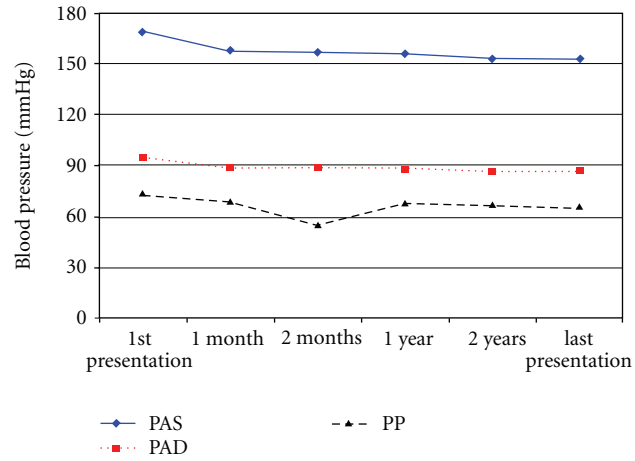

Figure 1: Changes in blood pressure during followup.

80.4%. Overall, patients were diagnosed with hypertension for an average of 4 ± 6.7 years (range 1–47) at the time of their initial assessment in our clinics. The mean follow-up duration in ICA was 3 ± 1.8 years (range 1 to 18 years).

Diabetes was found in 18.6% of patients. It was type 2 in 61.4%. At least one target organ damage was observed in 50%. Isolated cardiac complications were the most frequent (37.9%). The cardiovascular risk factors other than hypertension and the results of target organ damage are reported in Table 1. Habitual alcohol consume was found in 28.4%.

Echocardiography was performed in 50.2%. The recorded anomalies were a left ventricular diastolic dysfunction (39.2%), hypertensive cardiomyopathy (32.1%) and minor lesions (slight valve regurgitation, valvular sclerosis, valvular calcification) (19.6%).

Application of the cardiovascular risk stratification according to the European Guideline for the management of arterial hypertension identified a very high added risk in 82.1%, a high added risk in 4.8%, a moderate add risk in 7.5% and a low add risk in 5.7%.

In addition to lifestyle changes, 93.5% of patients received antihypertensive drugs (Table 2). Of those on treatment for high blood pressure, the most common agents used were diuretics in 63.5%, followed by blockers of the renin-angiotensin system (RAS) in 61.3% (either angiotensin converting enzyme inhibitors or angiotensin receptor blockers), calcium antagonists (31.6%), β-blockers (19%), and centrally acting sympatholytics (4.5%). Antihypertensive drugs were used in monotherapy or combination (Table 3). As a monotherapy, the most prescribed drug class was calcium antagonists (36.3%), followed by RAS blocker (32%). Polytherapy (more than 2 antihypertensive drugs including fixed-dose combination drugs) was used for 67% of patients on treatment for hypertension. The most common combination of drugs among those taking 2 agents was RAS blockers plus diuretics (69.8%).

Diabetic patients as well as those with kidney failure have received significantly more RAS-blockers for the treatment of hypertension than other patients ($P = 0.03$ for diabetic and $P = 0.04$ for renal failure).

Between the first and the last visit, blood pressure decreased significantly (Table 3). It was for systolic blood pressure by 15.9 mmHg, diastolic blood pressure by 8.2 mmHg, and pulse pressure by 7.6 mmHg. Hypertension was controlled in 42.6% of patients.

Figure 1 shows changes in blood pressure during followup. The sex ($P = 0.88$), age ($P = 0.48$), duration of treatment of hypertension ($P = 0.13$), the number of consultation ($P = 0.13$), and the duration of hypertension ($P = 0.27$) did not influence the control of blood pressure. Hypertension

Table 4: Change in blood pressure by gender.

	Blood pressure (mmHg)	Male	Female	P
First presentation	SBP	171 ± 28.6	168.3 ± 28.3	0.28
	DBP	95 ± 16.3	95.4 ± 15.3	0.39
	PP	76 ± 23.3	72.9 ± 22.3	0.24
Last presentation	SBP	155.4 ± 27.1	152.2 ± 25.4	0.88
	DBP	87.9 ± 14.9	86.5 ± 13.9	0.89
	PP	67.4 ± 19.5	65.7 ± 20.2	0.03
Control rate		39.2	45.0	0.88

DBP: Diastolic blood pressure, PP: Pulse pressure, SBP: Systolic blood pressure.

was best controlled with multiple drugs therapy (1.7 drugs for controlled patients as compared to 1.4 for to uncontrolled patients, $P < 0.001$). Pulse pressure was significantly lowered in females ($P = 0.03$) (Table 4).

4. Discussion

This study found that a significant proportion of patients (33%) who visit the ICA are elderly. In the elderly a significant part of hypertension is represented by systolic hypertension. Increased arterial stiffness may increase cardiovascular morbidity and mortality because of an elevation of systolic blood pressure (SBP), which raises left ventricular afterload, and because of a decrease in diastolic blood pressure (DBP), which alters coronary perfusion [14]. These elderly patients have a high pulse pressure (PP). Elevated PP is a powerful independent predictor of cardiovascular end points in the elderly [15–18].

According to Skurnick et al. [19], the PP levels of women were lower than those of men in early adulthood and higher in older ages. But in our study, although the difference was not statistically significant, the PP of men was higher than women's PP. Moreover, under hypertension treatment, the PP of women had significantly regressed compared to men's.

Cardiovascular risk of our patients was very high in most cases. As has been previously described, it is suggested that Black Africans present more severe forms of arterial hypertension and a greater risk of target organ damage [20–23]. Overall, uncontrolled blood pressure remains the main factor for target organ damage more frequently in Sub-Saharan Africa compared to western countries [24].

The main benefits of antihypertensive treatment are blood pressure lowering per se, largely independent of the drugs employed. Diuretics, β-blockers, calcium antagonists, and RAS blockers can adequately lower blood pressure, significantly improving cardiovascular outcome [25]. Several properties of the thiazide-type diuretics have led to them being recommended as first-line therapy in older adults with uncomplicated stage 1 hypertension. At low doses (<25 mg/day of hydrochlorothiazide or equivalent), these agents have been demonstrated in randomized controlled trials to reduce mortality, stroke, and cardiovascular events in the older hypertensive population [26]. There is good synergy with agents of different classes (RAS-blockers and calcium antagonists) and most importantly in the elderly; these drugs preferentially lower SBP relative to DBP. In our study, diuretics have been widely prescribed. In our environment, the added benefit to of diuretics is their low cost. RAS-blockers were also widely prescribed because of comorbidities such as diabetes, left ventricle hypertrophy or kidney failure, situations that required a preferential indication of RAS-blockers. Furthermore, HYVET [12] recommended the addition of a RAS-blocker in the event of insufficient control of BP. The RAS-blocker diuretic combination was by far the most used in our study.

In monotherapy, calcium antagonists were the most prescribed. Calcium antagonists have shown effectiveness in lowering BP in the older hypertensive patient. Significant reductions in stroke risk in older hypertensive patients were demonstrated in the Systolic Hypertension Europe and China Trials [27, 28]. Furthermore, results from patients with very high cardiac risk enrolled in ACCOMPLISH trial demonstrated the superiority of an ACEI-calcium antagonists (amlodipine) combination over an ACE-thiazide combination with regard to a decrease in cardiovascular events despite comparable BP-lowering effects [29].

In most cases, combination therapy was required for our patients. According to Aronow [30] if blood pressure is more than 20/10 mmHg above the target BP, treatment should be initiated with two antihypertensive drugs. In our study, hypertension was best controlled with multiple drugs therapy. One should certainly not hesitate to use more than one antihypertensive drug even in elderly patients if the target blood pressure is not reached. Particular attention must be given to eventual side-effects in elderly population. Control rate of hypertension (42.6%) was acceptable in our Sub-Saharan African context.

5. Study Limitation

There is no information on treatment tolerance, particularly on orthostatic hypotension occurrence in the elderly often polymedicated patients. This limit is due to the retrospective nature of our study. Also in these elderly patients with high cardiovascular risk, it would be interesting to describe cardiovascular events occurred during the year-long or more followup. Furthermore, the control rate of hypertension obtained does not reflect the reality of the management of hypertension in Côte d'Ivoire. There is certainly a bias due to the method of recruitment of our population. Patients who were regularly monitored for at least one year showed probably best treatment adherence.

6. Conclusion

Despite the classical reduced life expectancy in Sub-Saharan African population because of various illnesses, numerous elderly people exist. One must deal with the specific health

needs of the elderly. Their blood pressure is characterized by the frequency of isolated systolic hypertension. Elderly hypertensive patients have a very high cardiovascular risk. Diuretics as recommended were the drugs most prescribed. The control rate of hypertension was significant, mostly at the cost of combination therapy.

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Review Article

Antihypertensive Treatment in the Elderly and Very Elderly: Always "the Lower, the Better?"

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Arterial hypertension (HT) is age dependent and, with the prolongation of life expectancy, affects more and more elderly people. In the elderly, HT is a risk factor for organ damage and cardiovascular (CV) events. Both pharmacologic and nonpharmacologic reduction of blood pressure (BP) is associated with a corresponding decrease in systolic-diastolic or isolated systolic HT. Clinical trials have shown that BP lowering is associated with a decrease in stroke and other CV events. Therefore, BP reduction *per se* appears more important than a particular class of antihypertensive drugs. The benefit of antihypertensive treatment has been confirmed up to the age of 80 years, remaining unclear in the octogenarians. The benefit in lowering diastolic BP between 80 and 90 mmHg is well established, while that of lowering systolic BP below 140 mmHg requires further confirmations.

The lifespan increase during the last 30 years has resulted in a remarkable raise in the world population of people aged ≥65 years [1]. Arterial hypertension (HT) is age dependent and, with the prolongation of life expectancy, affects more and more elderly people [2]. Approximately over 80% of the elderly have HT, mainly isolated systolic hypertension (ISH), defined in the European guidelines as systolic blood pressure (BP) ≥ 140 mmHg and diastolic BP < 90 mmHg [3]. ISH is an age-related condition, as systolic BP increases with advancing age, while diastolic remains unchanged or even decreases after the sixth decade of life [4]. This phenomenon produces a progressive increase in pulse pressure (PP) [5]. PP, the difference between systolic and diastolic BP, reflects the work increase due to systolic energy [6, 7].

In clinical practice, the decision to treat an elderly with HT depends on the answers to the following three questions

(i) Is HT a risk factor for stroke and cardiovascular (CV) events?

(ii) Does non-pharmacologic and pharmacologic treatment reduce the risk of these events?

(iii) Which is the target to achieve in the elderly hypertensives?

The aim of this paper is to answer these questions, particularly focusing the discussion on whether the paradigm "the lower, the better" maintains a prognostic role in elderly and very old hypertensives.

In clinical trials completed before 1985, elderly hypertensive subjects were not included or represented a little component of the population under investigation [8]. At the beginning of the 90s, when the first epidemiological evidences documented the prognostic role of systolic BP [9, 10], many trials were performed in elderly hypertensives (Table 1). On the basis of the evidence provided by these trials, HT is now considered a well-established risk factor for stroke and CV disease in elderly people, and its treatment is considered as mandatory.

Table 1: Efficacy of the antihypertensive treatment in stroke and cardiovascular events in different trials performed in the elderly.

Trial	Mean age at randomization (years)	Subjects enrolled	Mean BP at randomization (mmHg)		Drug treatment	Mean followup (years)	Stroke Reduction (%)	CV events reduction (%)
			SBP	DBP				
Coope/Warrender	68	884	196	99	Atenolol; Bendrofluazide	4,04	−30	—
EWPHE	72	840	183	101	HCTZ; Triamterene; Methyldopa	8	NS	−27
HYVET	84	3845	173	91	Indapamide; Perindopril	2	−30	−34
MRC-HT	70	4396	185	91	Atenolol; HCTZ; Amiloride	5,8	−31	−35
SHEP	72	4716	170	77	Chlorthalidone	4,5	−36	−32
STONE	67	1632	180	90	Nifedipine (Long-acting)	2,5	−57	−60
STOP-HTN	76	1627	195	94	Atenolol; HCTZ; Amiloride; Metoprolol; Pindolol	5	−47	−40
Syst-China	67	3000	171	86	Nitrendipine; Captopril; HCTZ	2	−38	−37
Syst-Eur	70	4695	174	85	Nitrendipine; Enalapril; HCTZ	2	−42	−31

SBP: systolic blood pressure; DBP: diastolic blood pressure; EWPHE: European Working Party on High blood pressure in the Elderly trial; HYVET: hypertension in the very elderly; MCR: *Medical Research Council Hypertension Trial;* SHEP: systolic hypertension in the elderly; STONE: Shanghai Trial of Hypertension in the Elderly; STOP-HTN: Swedish Trial in Old Patients with Hypertension; Syst-China: systolic hypertension in China; Syst-Eur: Systolic Hypertension in Europe; NS: not significant; HTCZ: hydrochlorothiazide.

In the elderly hypertensives, antihypertensive treatment is commonly recommended, but with high caution due to alterations in drug distribution and disposal, to presumptive changes in homeostatic CV control and to the quality of life that is typical of this age class. The randomized, controlled trials of antihypertensive treatment in the elderly have shown benefits comparable to those observed in younger or middle-aged subjects. Not only this, but, as the baseline CV risk is higher in the elderly, the absolute benefit of treatment (expressed as number of events prevented per 1000 patient-years) is even higher in the elderly. However, most of the hypertensives enrolled in clinical trials were <80 years old.

The first evidence that antihypertensive treatment is also useful in subjects aged ≥80 years is that published in 1999 by Gueyffier et al., concerning a subgroup of 1,670 very old subjects taking part of the INdividual Data ANAlysis of antihypertensive intervention trials (INDANA) [11]. In this meta-analysis, antihypertensive therapy led to a reduction in stroke (−33%), CV morbidity (−22%), and heart failure (−39%). No significant effect was demonstrated for coronary events, and when the effect of treatment on fatal and nonfatal stroke was analyzed separately the benefit was limited to the nonfatal only. Ten years later, similar results were partially confirmed in the Hypertension in the Very Elderly Trial (HYVET) over 3,845 subjects aged ≥80 years and having high systolic BP [12], where all subjects were randomly assigned to placebo or active treatment with indapamide and perindopril was added in individuals who failed to meet the target BP of 150/80 mmHg. At two years of followup, mean BP was 15/6 mmHg lower in subjects receiving active treatment than in those receiving the placebo, a difference that was associated with significant reduction of death from stroke, both fatal and non-fatal (−30%), cardiovascular disease (−23%), and heart failure (−64%).

In the HYVET, a 21% reduction of the risk of overall mortality was also observed with active treatment. Nevertheless, the results of Bejan-Angoulvant's meta-analysis did not support those of the HYVET, showing comparable overall mortality in treated and untreated patients [13]. This discrepancy was outlined in the recent joint consensus developed by the American College of Cardiology Foundation and the American Heart Association [14]. The subjects enrolled in the HYVET were in good physical and mental condition and had low rate of previous CVD and therefore were not representative of very elderly.

Systolic HT (≥140 mmHg) and pulse HT (≥80 mmHg) [6] characterise the pressure profile of elderly hypertensives. It is therefore only natural that the intervention trials were

focused on reducing systolic BP. The current ESH/ESC guidelines recommend reducing systolic BP below 140 mmHg in grade 1-2 hypertensives having low-to-moderate total CV risk. Nevertheless, whether this recommendation also applies to elderly and very old subjects is unproved by outcome trials. In all trials [15–22] but one [23], elderly hypertensives randomized to more active treatment had lower incidence of CV events, but in no trial the systolic target (<140 mmHg) was reached. The ACCOMPLISH [24] and the INVEST [25] studies showed no difference in antihypertensive effects when comparing drug treatment in subjects of age ≥80 or <80 years, implicitly supporting the opportunity to treat very old subjects. Nevertheless, the Japanese Trial to Assess Optimal Systolic (JATOS) blood pressure in elderly hypertensive patients over-65–85-year-old subjects, (JATOS) demonstrated that a more strict BP control did not provide further benefit in reducing stroke, heart disease, vascular disease, and renal failure [23] and even showed a negative result on CV events suggesting a possible deleterious effect of intensive BP control in elderly hypertensives. This is not peculiar of old subjects, being in agreement with the results of the ACCORD trial [26] that showed no additional benefit of BP reduction—but only an increase in drug-related adverse effects in—high-risk patients with diabetes mellitus ≥55 years when targeting systolic at 120 rather than 140 mmHg. In addition, observational data from INVEST in hypertensive patients with coronary artery disease showed a J-curve pattern for adverse outcomes at on-treatment systolic BP of 135 mmHg in patients aged 70 to 79 years and at 140 mmHg for those aged ≥80 years. This is not a new notation, as some retrospective analyses of intervention studies suggested [27] with exceptions [17–22] a J-curve trend of the risk of myocardial infarction in relation to treated BP. Also in a posthoc analysis of the EWPHE [15] it appears that in elderly hypertensives under active treatment total mortality had a U-shaped trend in relation to systolic BP, with a nadir about 150 mmHg, whereas total mortality increased gradually with decreasing DBP from the upper tertile of 98 mmHg (these results were partially flawed by the fact that a U-shaped trend with a nadir at 95 mmHg was also found in the patients taking placebo, so that conclusive inferences cannot be drawn from this retrospective analysis). Finally, in the Hypertension Optimal Treatment (HOT) study [28], where 30% of the hypertensives were older than 65 years, it was found that the optimal BP for the lowest incidence of CV events was 138 mmHg for systolic and 83 mmHg for diastolic, with no significant improvement in CV end-points when BP was led to lower levels. The intention-to-treat analysis revealed a comparable pattern in the incidence of CV events in the adults and in the older patients, suggesting that optimal BP reductions are similar and independent of age.

Therefore, no trial evidence supports the guidelines recommendation to achieve a systolic target <140 mmHg in elderly subjects; in particular systolic values <130 and diastolic <65 mmHg should probably be avoided in the elderly.

In conclusion, particular attention should be paid to antihypertensive treatment of elderly hypertensives, which constitute a large, growing, and vulnerable part of general population. There is no doubt that antihypertensive treatment is justified by medical evidence. The assumption "the lower systolic BP, the lower the risk" is adequate for stroke and heart failure. Despite this, the best meta-analysis showed no clear results in decreasing total mortality by forcing antihypertensive treatment in very old subjects. In the randomized-controlled trials, elderly hypertensives were treated with diuretics, β-blockers, dihydropyridines calcium channel blockers, and converting-enzyme inhibitors. However, monotherapy normalizes BP in only 40–50% of cases, and therefore a combination of two or more drugs is often required to achieve the recommended BP goals. The most reasonable strategy is to start with a thiazide diuretic as first-line therapy and to optimize the maximal antihypertensive therapy with two drugs in low doses. The JNC, the WHO/ISH, and ESH/ESC guidelines recommend lowering BP in elderly hypertensives below 140/90 mmHg. In this respect there are sufficient data that a diastolic BP between 80 and 90 mmHg is associated with a clear benefit, except in case of coronary heart disease where a mortality increase was observed reducing diastolic BP below 80 mmHg.

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Review Article

Biochemical and Molecular Aspects of Vascular Adrenergic Regulation of Blood Pressure in the Elderly

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Hypertension, orthostatic hypotension, arterial insufficiency, and atherosclerosis are common disorders in the elderly that lead to significant morbidity and mortality. One common factor to these conditions is an age-related decline in vascular beta-adrenergic receptor-mediated function and subsequent cAMP generation. Presently, there is no single cellular factor that can explain this age-related decline, and thus, the primary cause of this homeostatic imbalance is yet to be identified. However, the etiology is clearly associated with an age-related change in the ability of beta-adrenergic receptor to respond to agonist at the cellular level in the vasculature. This paper will review what is presently understood regarding the molecular and biochemical basis of age-impaired beta-adrenergic receptor-mediated signaling. A fundamental understanding of why β-AR-mediated vasorelaxation is impaired with age will provide new insights and innovative strategies for the management of multiple clinical disorders.

1. Introduction

1.1. Clinical Relevance. Life expectancy has increased during the past century, and this has led to a dramatic increase in the aging population. The number of Americans over 65 is expected to double from the years 2000 to 2030: in 2000, there were 34.8 million over the age of 65 (12% of the population), and in 2030, it is predicted that there will be 70.3 million in this age group (representing 20% of the population) [1]. This change in population dynamics presents substantial medical issues, as aging is a primary independent risk factor for development of cardiovascular disorders. The fact that aging contributes to cardiovascular morbidity is not novel. Sir William Osler (1849–1919), one of the founders of Johns Hopkins University Hospital, stated in his textbook that, "Longevity is a vascular question... a man is only as old as his arteries." From a strictly aging/vascular perspective, numerous recent articles have described changes in anatomical and histological properties with age (e.g., see [2]) as well as biophysical alterations, such as with changes in pulse wave velocity with age (as described in [3]). However, one possibility to consider is that these aforementioned changes are likely due to aging-mediated alterations in the molecular and biochemical factors that determine vascular tone.

Vascular tone is regulated by both the intimal (endothelial) and medial (vascular smooth muscle) layers as well as through interlayer interactions. Age-related changes in the structure and function of each layer is well documented [4, 5]. Smooth muscle cells represent the major arterial cell population, and these cells highly express adrenergic receptors that mediate smooth muscle tone. Thus, adrenergic receptors are important regulators of cardiovascular physiology. Although all three beta adrenergic receptor (β-AR) subtypes, β1, β2, and β3, are found in vascular smooth muscle cells, the β2-AR subtype is by far the most highly expressed [6]. Of specific relevance to this paper is that the vascular β2-AR exhibits an age-related decline in signaling with advancing age that leads to impaired vasorelaxation. In contrast, the intrinsic ability for vascular muscle contraction is generally maintained throughout the aging process [7]. This change is important, because it may allow for multiple age-associated clinical conditions such as

hypertension, arterial insufficiency, orthostatic hypotension, and arteriosclerosis. The underlying change is hypothesized to be a decrease in β-AR-stimulated cAMP production. Therefore, conditions associated with altered cAMP production are likely affected. To this end, the β-AR is a target for many medications prescribed to the elderly [8] and are used to manage hypertension, angina, postmyocardial infarction risk, congestive heart failure, glaucoma, tremor, arrhythmias, and chronic obstructive pulmonary disorders [9].

1.2. Basic Science Relevance. Beta-AR-mediated signal transduction pathways are well described, but new discoveries continue to impart complexity (see [10] and following sections). At present, no change in any one factor in the β-AR signal cascade has been identified to fully explain the impaired β-AR vascular function observed with aging. Instead, the cause of the change is likely multifactorial. This notion is supported due to intricate nature of β-AR signaling and two biochemical findings: first is that expression of β2-AR does not change with age [11], and secondly, although drugs that activate β-ARs do *not* elicit complete vasorelaxation with advancing age, drugs that act on proteins postreceptor in the signaling cascade *do* [12]. That is, the physiologic factors that mediate vasorelaxation cannot completely dilate blood vessels with advancing age; however, the molecular and cellular/anatomic machinery—postreceptor—remains fully functional.

2. Contraction/Relaxation Vascular Pharmacodynamics

2.1. Mechanisms of Vascular Contraction/Relaxation. Vascular tone is physically established in the medial layer of blood vessels, which is almost entirely composed of vascular smooth muscle cells. Numerous agents (epinephrine, norepinephrine, acetylcholine, angiotensin II, nitric oxide, etc.) function through their cognate receptors localized at vascular smooth muscle, and/or endothelial cells and influence an elaborate network of signal transduction pathways that yields homeostatic control [13]. The molecular mechanisms regulating smooth muscle contraction and relaxation are beyond the scope of this paper; however, excellent reviews are found elsewhere [14, 15].

2.2. Vascular β-AR Signaling. In blood vessels, the β-AR signal transduction cascade mediates smooth muscle vasorelaxation. Activation of the β-AR stimulates the dissociation of the G protein, Gαs, from the $\beta\gamma$ subunit. The G protein $\beta\gamma$ subunit can also affect various membrane and/or organelle channels whose action can rapidly alter the ionic milieu of the cell. After uncoupling from the β-AR, Gαs becomes activated by exchanging GDP for GTP. The activated form of Gαs triggers adenylyl cyclase to convert ATP into cAMP [16]. Two molecules of this second messenger bind one regulatory subunit of protein kinase A (PKA). Structurally, PKA is a tetrameric kinase made up of regulatory and catalytic subunit dimers. Functionally, PKA is a multipurpose kinase that controls numerous cellular events by phosphorylating protein targets. PKA is distributed to multiple discrete intracellular compartments via the function of A-kinase anchoring proteins (AKAP) [17]. β-AR activation also initiates G protein receptor kinase (GRK) function. GRKs are a family of kinases that phosphorylate, β-ARs [18]. Phosphorylated β-ARs are targets for still another group of proteins, the β-arrestins that desensitize β-ARs and mediate internalization, which leads to receptor recycling and/or degradation. In addition, β-arrestins can serve as scaffolds and adaptors for other kinases such as extracellular signal-regulated kinase (ERK), Src, and Raf that regulate several cellular pathways that result in the activation of MAP kinases [19].

Identifying a possible locus for the age-related decline in β-AR function has proven elusive due to the complexity of this cascade. Three subtypes of the β-AR (β1-AR, β2-AR, and β3-AR) are found in vascular smooth muscle cells [20]. Also, at least nine different isoforms of adenylyl cyclase have been identified [21, 22], along with at least six GRK [23], three arrestin [24], and multiple types of AKAP [25] isoforms are known to exist. Similarly, multiple Gαs-modifying proteins are also known to alter β-AR signaling [26]. Therefore, to understand the mechanism(s) of impaired β-AR function with age, recent research has focused on proteins that interact with the β-AR, directly or indirectly, that may be critical for optimal receptor signaling. Investigations on age-related changes in various modifications to the β-AR, such as phosphorylation-mediated desensitization, scaffolding proteins that form postreceptor signalosomes, or proteins that directly interact and affect β-AR function may provide insight to explain the change.

3. Age-Related Changes in Vascular Function

The initial observation of an aging effect on vasorelaxation was made in the early 1970s involving analysis of vascular smooth muscle pharmacodynamics in general. Blood vessels from 6-month-old animals relaxed 90% less to isoproterenol as compared to blood vessels from 1-month-old animals [27, 28]. To explain this physiologic change, biochemical analysis found that both basal- and isoproterenol-mediated cAMP synthesis significantly declined in isolated aorta with advancing age. This was in contrast to adenylyl cyclase and phosphodiesterase activity that was essentially unaffected by age. From these results, it was concluded that the decreased ability of isoproterenol to elevate intracellular cAMP concentration, and thus relax aortas from older rats was predicated by an "upstream" change in the β-AR itself, rather than a "downstream" change specific to adenylyl cyclase [29]. From these initial observations, numerous researchers have evaluated the aging vasculature in an attempt to uncover the mechanism of this change in β-AR function with age. As described above, the β-AR signaling cascade is multifaceted, including numerous protein factors, each of which exists with multiple subtypes. The following is a discussion of what is currently known regarding the mechanism of the age-related change in β-AR function, organized in a sequential manner, starting upstream with the β-AR itself and continuing through the cascade as we currently understand it.

3.1. Beta-Adrenergic Receptors. Presently, three distinct subtypes of the β-AR have been identified in mammals, (β1-AR, β2-AR, and β3-AR [20]: crystalline structures (including affect of agonist occupancy) have recently been described [30]. Most of the literature demonstrates that the primary β-AR subtype in the vasculature is the β2-AR [31], but both β1-AR and β3-AR are present and mediate vasorelaxation [32]. The overall distribution, and relative proportion, of each β-AR subtype varies across vascular beds [33, 34]. These three β-AR subtypes work in concert to alter vascular tone in a complementary manner, as they all couple to Gαs and promote cAMP production [35].

The vascular adrenergic receptor subtypes behave differently after exposure to agonist. Both β1-AR and β2-AR desensitize with activation due to the function of GRKs, PKA, as well as other kinases and/or factors [36, 37]. Interestingly, agonist exposure to the β2-AR also initiates the transformation of its G protein-coupling selectivity from Gαs to Gαi [38]. This phenomenon has been documented in the heart [39] and multiple cultured cell lines [40]. When the β2-AR is linked to Gαi, one cellular event that occurs is an inhibition of adenylyl cyclase activity that is manifested as a reduction of intracellular cAMP concentration [41]. There are no data to suggest that β1-AR changes its Gα protein subtype coupling preference. In contrast, the β3-AR does not appear to undergo desensitization, as it lacks regulatory phosphorylation sites for GRKs, PKA, or other kinases [42]. This characteristic may allow for prolonged signaling compared to β1-AR- and β2-AR-mediated effects. Although expression levels of the three adrenergic receptor types is differential, with β2 being the most predominant subtype, and β3 being the least expressed, patterns of function could be altered with pathology. For instance, under maintained stimulation, β1-AR is predicted to desensitize, β2-AR is predicted to desensitize and further inhibit cAMP production through its linkage to Gαi [43], and β3-AR is predicted to possibly represent a functional alternative for cAMP production [6].

We have evaluated whether an agonist-mediated change in β2-AR/G protein coupling observed in the heart could explain the age-related change in vasorelaxation [12]. Using pertussis toxin (pertussis toxin irreversibly ADP ribosylates and inactivates Gαi) to block the coupling of activated β2-AR to Gαi in aortae isolated from Fischer 344 rats of increasing age, it was found that this treatment did not alter the age-related decline in relaxation. However, a population of β2-AR coupled to Gαi was found, as pertussis toxin treatment improved β2-AR-mediated vasorelaxation in aortae for all ages in equal proportion. Changes in vascular β3-AR function with aging are unknown. However, left ventricular function and age-related heart failure were highly correlated with β3-AR expression in rats [44]. These findings suggest that further investigation is warranted to characterize AR subtype expression patterns and β3-AR function throughout the vasculature.

Because the β2-AR is the most highly expressed subtype in the vasculature, much interest is the finding that β2-AR sensitivity substantially declines with age [45]. Results found that in aortic preparations from 1-month-old animals, 64% of the β-ARs were in the high affinity state. This compared to 40%, and 0% high affinity β-ARs for 6- and 24-month-old animals, respectively. To explain these results, age-related changes in the content of β2-AR bound to Gαs was examined: β2 AR : Gαs complexes were found *only* in aortic preparations from 1-month-old animals. These data strongly suggest that there is a substantial decline in high-affinity β2-AR with advancing age. This change did not appear to be related to a decline in the presence of β-ARs at the membrane (further confirmed [11]) or caused by a switch in G protein coupling as occurs in cardiac tissue [12].

Another interesting possibility to explain the age-related decline in β2-AR signaling is the possibility that β-AR can form hetero- and homodimers, and this could alter signaling fidelity. Mercier et al. [46] showed that β-ARs likely exist as either β1-AR : β1-AR homodimers, or β1-AR : β2-AR heterodimers, and they suggested that changes in the overall cellular configuration of monomers, heterodimers, and homodimers could be altered by agonist as well as disease state, and this finding was supported by Lavoie et al. [47]. Also, β1-AR : β2-AR heterodimers have been shown to exhibit distinct functional and pharmacological properties, resulting in enhanced signaling efficiency in response to agonist stimulation and optimizing β-adrenergic modulation of contractility in cardiomyocytes [48]. However, controversy exists as to whether β-AR dimerization occurs in cardiovascular tissue. A report by Ianoul et al. [49] that used higher-fidelity imaging techniques suggested that β1-AR and β2-AR may be localized in two different populations of microdomains in cardiomyocytes, an observation inconsistent with the existence dimers. Of additional interest is a recent report by LaRocca et al. [50] that showed, also in cardiomyocytes, that β2-AR form heterodimers with the chemokine receptor type 4 (CXCR4) and this interaction negatively regulated isoproterenol-mediated β2-AR signaling by altering β2-AR sensitivity. Following from these studies, we evaluated whether CXCR4 activity modulation could alter β-AR-meditated vasorelaxation. Using aortae isolated from 2-month-old Fischer 344 rats, it appeared that CXCR4 activation inhibited, and CXCR4 blockade improved the vasorelaxant effect of isoproterenol (Figure 1). We also have found that Fischer 344 aortic vascular smooth muscle expresses CXCR4. Determination of age-related changes in CXCR4-mediated alterations in β-AR-stimulated vasoreactivity, CXCR4 expression, and the interaction between β2-AR and CXCR4 are underway.

3.2. G Proteins. The age-related change in β2-AR signaling appears to caused by changes in receptor sensitivity, and changes in G protein expression or function could manifest this physiology. Interestingly, as with β-AR expression, Gαs expression similarly remains unchanged [52]. However, its function appears to be age impaired, as direct Gαs activation-mediated cAMP production by was reduced in aortae isolated from old rats [53]. Our lab further characterized this observation by finding a marked decline in cholera toxin catalyzed ADP ribosylation labeling of Gαs without a decline in the expression [54], suggesting some age-related alteration in G protein structure/function. We have also

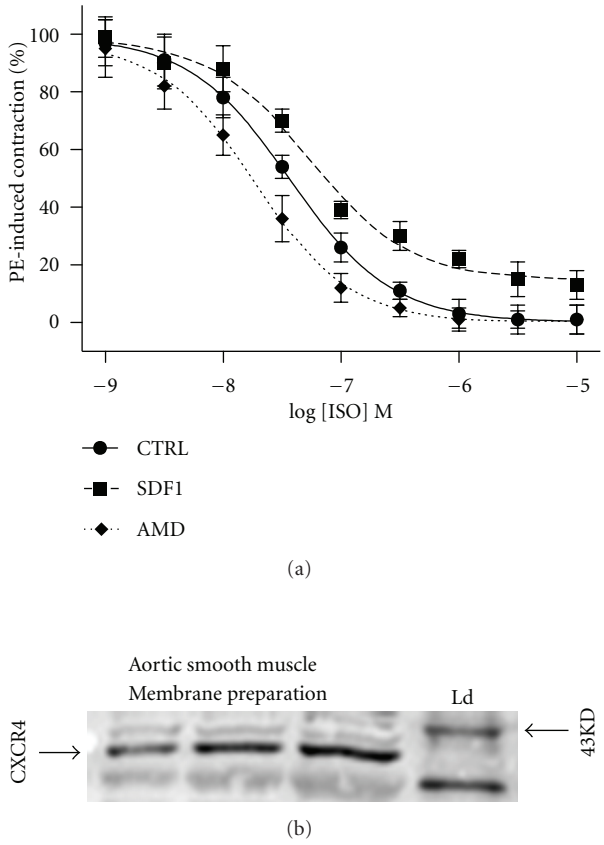

Figure 1: Vascular smooth muscle and chemokine receptor subtype 4 (CXCR4). (a) Aortae from 2-month-old animals ($n = 5$) were isolated and mounted on an apparatus to measure vascular reactivity as described [12]. Vessels were exposed to three treatments. The control (CTRL) treatment was that vessels were contracted with phenylephrine (PE) and allowed to stabilize (approximately 10 minutes) that was followed with relaxation stimulated by increasing doses of isoproterenol (ISO). The stromal cell derived factor (SDF1; ligand for the CXCR4 receptor also known as CXCL12) treatment was similar except that after the PE-mediated contraction stabilized, 100 ng/mL SDF1 was added. Following a 5-minute SDF1 incubation, relaxation was stimulated by increasing doses of ISO. SDF1 did not alter the tone produced by PE alone. The AMD-3100 (AMD; a CXCR4 specific antagonist) treatment occurred with a 45 minute, 10 μM AMD incubation preceding the PE-mediated contraction and stabilization (10 minutes), which was followed by relaxation stimulated by increasing doses of ISO. AMD treatment did not effect PE-mediated contraction as compared to CTRL. Also conducted, but not shown, is that addition of AMD blocked the effect of SDF1 thereby implicating a direct effect of CXCR4 on impairing β-AR-mediated vasorelaxation. Data are expressed as percent of PE-induced contraction. The doses for AMD, and SDF1 were used as per LaRocca et al. [50]. (b) Aortic smooth muscle medial layers were homogenized, and membrane-specific fractions were prepared for western blotting as described [51]. Increasing concentrations (5 μg, 10 μg, and 20 μg; as determined with BCA analysis) of total protein extracts were loaded in each lane. A specific antibody for CXCR4 (Abcam; Cambridge, Mass, USA) was used to visualize expression of CXCR4 that is predicted to locate at approximately 39 kilodaltons (kD). Shown also is a size-indicating ladder (Ld).

found that cholera toxin-mediated relaxation in aortic rings decreased with advancing age [7]. Further evidence that Gαs function is altered with advancing age in the vasculature is from a study where it was attempted to reverse age-related declines in β-AR-mediated vasorelaxation by expressing a constitutively activated mutant of Gαs (Gαs-Q227L) into aorta from 6-month-old Fisher 344 rats. In that study [55], aorta that expressed Gαs-Q227L exhibited enhanced isoproterenol-stimulated vasorelaxation, and both basal- and isoproterenol-stimulated cAMP production was increased. Therefore, Gαs may undergo some age-related change that inhibits its ability to become activated via the action of an agonist-occupied receptor. In support of a functional change in Gαs with age is the identification of a regulator of G protein signaling (RGS)/GTPase activating protein (GAP) that functions on Gαs [26] called RGS-PX1. Age-related enhanced RGS-PX1 activity could impair β-AR signaling without changes in β-AR or Gαs expression as agonist exposure would not initiate vasorelaxation as Gαs signaling would be quenched due to the high RGS/GAP activity of RGS-PX1. At present, RGS-PX1 has not been evaluated within an aging paradigm. In total, the decline in β-AR-mediated vasorelaxation and cAMP accumulation observed in old vessels could be caused by a change in the function *but not* expression of Gαs.

Another possible explanation for the decline in β-AR-mediated signaling could be an increase in Gαi function, as this G protein subunit inhibits adenylyl cyclase activity and thus cAMP production. Also, the β2-AR, the predominant receptor species in vascular smooth muscle, has been shown in cardiomyocytes to rapidly link to Gαi after agonist activation, and it is PKA-phosphorylated [38]. We actually found a slight decline in pertussis toxin labeling of Gαi with age [54]. Also, a 30% decrease in G$\alpha i_{1\&2}$ protein content between 6- and 24-month-old aortic preparations has been documented [52]. Age-related changes in G$\beta\gamma$ could also affect β-AR-mediated signaling. G$\beta\gamma$ has been shown to either stimulate or inhibit adenylyl cyclase activity in the presence of activated Gαs [56]. G$\beta\gamma$ also affects numerous plasma and organelle membrane-localized ion channels, thereby affecting the net polarity and potential for tonal changes of vascular smooth muscle [57]. However, we have found no age-related changes in the expression of G$\beta\gamma$ subunit [54].

3.3. Adenylyl Cyclase, Protein Kinase A, cAMP, and Phosphodiesterases. As discussed, the fundamental change in blood vessels from older animals is a pronounced inability to relax to β-AR stimulation. This decline is directly correlated to an inability to synthesize appreciable concentrations of cAMP. However, old vessels do maintain the ability to relax entirely, as acetylcholine-, forskolin-, and nitrate-mediated vasorelaxation is complete [58]. Therefore, a probable protein candidate for the impairment is Gαs (as discussed previous) or G protein receptor kinase (see following). The classical effector of Gαs is adenylyl cyclase. Forskolin directly activates adenylyl cyclase, and thus stimulates cAMP production. Because forskolin stimulates blood vessels from young and

old animals to relax completely, and to accumulate cAMP equally, it is generally thought that adenylyl cyclase function does not change with advancing age. Our results further support that adenylyl cyclase activity is maintained across aging [59]. However, the adenylyl cyclase family contains nine different isoforms, each with discrete tissue distribution [60]. Perhaps more importantly, each isoform is differentially regulated by various factors. For instance, calcium (at relevant intracellular concentrations) stimulates adenylyl cyclase subtype-1, and subtype-8 but inhibits subtype-3 and subtype-9. Interestingly, Zhang et al. have demonstrated that the predominant adenylyl cyclase isoforms in vascular smooth muscle are of the calcium-sensitive variety [61]. Therefore, a possible explanation for impaired receptor-mediated-cAMP production is not with the cyclase itself, but rather the interaction between cyclase and another, critical and age-affected, cellular factor that could regulate intracellular calcium sequestration.

Another line of reasoning would be that adenylyl cyclase activity is unchanged across age, but cAMP processing is altered. Therefore, changes in physiology could be due to age-related changes in the processing and degradation of cAMP through phosphodiesterases. We have determined that there are no age-related changes in general phosphodiesterase inhibitor-mediated vasorelaxation using 3-isobutyl-1-methylxanthine (IBMX), a nonspecific phosphodiesterase subtype inhibitory agent [62]. However, others [63] found that using a low dose of IBMX caused impaired cAMP accumulation in blood vessel preparation from older rats. The role of phosphodiesterases in mediating age-related changes in cAMP concentration is presently underevaluated. There are multiple phosphodiesterase subtypes, each that may have differential expression or activity [64]. Also, only recently have drugs specific to individual isoforms have become available. To that end, it has recently been shown that the vasodilator pathway associated with phosphodiesterase III is likely unchanged with aging in humans [65].

3.4. G Protein Receptor Kinases and Arrestins. β-AR desensitization is initiated by phosphorylation of the receptor, which is followed by its uncoupling from its signaling cascade. The kinases PKA, GRK, and others phosphorylate β-ARs [37]. Phosphorylated β-ARs are targets for another family of proteins that mediate uncoupling/desensitization, the arrestins [24]. Therefore, arrestins function in concert with GRKs to attenuate intracellular signaling [66, 67]. To date, six different GRKs have been identified. Of interest, GRK-2, GRK-3, and GRK-5 (GRK-2 and GRK-3 are also known as β-AR kinases: β-ARK-1 and β-ARK-2, resp.) target β-ARs and are highly expressed in the cardiovascular system [23].

Evidence shows that GRKs are important regulators of pathology in humans [68]. Significant increases in GRK activity and expression have been observed in ventricles of failing human hearts [69]. The progression of Alzheimer's disease has also been associated with enhanced GRK function in fibroblasts taken from human skin [70]. Relating specifically to GRK function and the vasculature, cultured vascular smooth muscle cells have been shown to express GRK-2 both within the cytoplasm and at the membrane [71], and a transgenic mouse that overexpressed GRK-2 in a vascular-specific manner has been developed [72]. These mice exhibited attenuated β-AR-mediated cAMP production and vasorelaxation. Also, overexpression caused elevations in resting blood pressure and was accompanied by an increase in vascular thickening, suggesting a decline in cAMP generation.

An age-related change in GRK activity or expression in vascular tissue would implicate GRKs in the age-related decline in β-AR mediated vasorelaxation. Only a few studies have been performed to assess age-related changes in GRKs. No changes in GRK activity or GRK-2 and 5 expression were observed in lymphocytes of aged humans [73]. However, expression of soluble GRK-2 increased with maturation in thoracic aortic preparations from Fischer 344/Brown Norway rats [11]. We have also examined age-related changes in GRKs [51]. In aorta from aged Fischer 344 rats, total GRK activity increased nearly 2.1-fold. In the soluble (cytosolic) fraction, GRK-2 expression increased nearly 3.6-fold, GRK-3 expression increased approximately 3.8-fold, and β-arrestin expression increased approximately 1.6-fold. In the membrane fraction, GRK-2 expression increased approximately 1.5-fold, GRK-3 expression increased nearly 2.1-fold, while there was not an age-related change in the expression of GRK-5. These data suggest that a critical feature of age-related impaired β-AR signaling may be imparted through an increase in total pool of GRK that could be explained by either increased expression, or decreased degradation [74]. This increased pool could allow for enhanced targeting of these receptor kinases to the membrane, and hence the β-AR. Whether β-ARs from aged vessels have increased phosphorylated residues, and thus enhanced desensitization is yet to be established. Also, the mechanism for the enhanced expression of GRKs with advancing age is likewise yet to be explained but is an active interest of our lab.

3.5. Scaffolding. β-AR signaling depends on the interaction between numerous proteins. Therefore, β-AR-mediated function requires appropriate localization (cytoplasmic versus membrane) and organization (to allow efficient and rapid interaction with one another) of these proteins. Therefore, recent research has focused on "scaffolding proteins," which are intracellular proteins that compartmentalize multiple related signaling molecules to specific intracellular domains. This theory has replaced the classical "random collision-coupling theory" of signal transduction [75]. The β-AR signaling cascade is anchored within the plasma membrane by the scaffolding protein caveolin [76]. β_2-ARs [77, 78], numerous G-proteins (including Gαs) [79, 80], adenylyl cyclase (numerous isoforms) [80–82], and GRKs 2, 3, and 5 [83] all localize in caveolin-rich domains of the cell membrane.

Age-related changes in caveolin have recently been demonstrated revealing tissue-specific changes in expression [84]. Also, our results with Fischer 344 rat aortic tissue show that the expression of caveolin-1 decreases with advancing age [85]. An age-related change in caveolin expression could

easily alter the milieu of proteins within a β-AR signaling pocket, and thereby alter signaling. Indeed, Carman et al. [83] found that GRK activity is inhibited when GRK is bound to caveolin-1. Our lab has shown that with advancing age, the interaction between caveolin-1 and GRK2 substantially declines [85]. Therefore, both the scaffolding and protein activity-modulating functions of caveolin may be compromised with advancing age in the vasculature.

Other reports implicate caveolin as a regulator of vascular function [86]. Razani and Lisanti [87], and Drab et al. [88] produced caveolin-1 null mice and found that these animals exhibited impaired aortic steady-state maximal tension induced by phenylephrine (an α-AR agonist). Also, acetylcholine-mediated (nitric oxide-dependent) vasorelaxation was similarly altered in null animals. Finally, caveolin-1 null mice displayed hyperproliferation in certain cell types, suggesting (but not documented) a decline in cAMP production. Changes in β-AR-, cAMP-, or age-mediated effects in the caveolin-1-null mice have yet to be evaluated. However, these data from transgenic animals clearly indicate that caveolin is an important modulator of vascular function.

3.6. Receptor Cross-Talk and Ion Channels. A potentially interesting phenomenon observed in molecular signaling is receptor cross-talk events. Cross-talk between Gαq-linked receptors and β-ARs have been observed. Activation of PKC by Gαq-linked-agonists directed GRKs to the membrane, enhancing β-AR phosphorylation and desensitization [89]. Also, it has been shown that GRK-2 is more effective at desensitizing β-ARs after its activation by PKC [90]. Finally, antisense technologies have been used to knockout PKC expression and function; these studies determined that this manipulation produced enhanced β-AR agonist-induced desensitization rather than the expected attenuation result. In addition, these authors subsequently found that this effect was linked to phosphatase activity [91]. These findings suggest that PKC might also be involved with β-AR resensitization through interaction with a phosphatase. Therefore, phosphorylation/dephosphorylation and desensitization/resensitization of β-ARs can be induced from a number of stimuli including angiotensin II.

In terms of vascular β-AR being altered by receptor cross-talk are *in vitro* studies showing that angiotensin II enhanced β-AR-mediated cAMP production in cultured aortic vascular smooth muscle cells [61, 92, 93] as well as in preglomerular microvascular smooth muscle cells [94, 95]. In terms of vasorelaxation being affected was a study that found that angiotensin II can enhance cAMP-mediated vasorelaxation via angiotensin II-type 1-receptors (AT_1) [96]. We examined the interaction among aging, β-AR-mediated vasorelaxation, and angiotensin II [62]. Our results showed that this effect of angiotensin II on agonist-mediated vasorelaxation was limited to young (6-week-old) or adult (6-month-old) rats, was absent in aged (12- and 24-month-old) animals, and was mediated by angiotensin II-type 1 receptors. Angiotensin II appeared to amplify vasorelaxation in aorta from 6-week and 6-month-old animals via enhanced production of cAMP. The mechanisms involved with angiotensin II enhanced, β-AR-mediated signaling are unknown but may involve adenylyl cyclase, Gαs, or calcineurin. Further study may show that aging may effect a factor common to both angiotensin II and β-AR signaling pathways or that aging may impair cross-talk between these two receptor pathways.

A final interesting aspect of age-related changes in β-AR-mediated signaling is understanding the role of various ion channels; it is well understood that the function of numerous ion channels is responsible for determining membrane potential [97]. The effect of isoproterenol on the ionic milieu of aortic vascular smooth muscle cells was characterized [98]. Results determined that isoproterenol functioned by inducing hyperpolarization via activating ATP-sensitive potassium channels (K_{ATP}). They also determined that the isoproterenol/K_{ATP}-mediated hyperpolarization was impaired in smooth muscle cells from older rats. However, the effect of direct activation of K_{ATP} was unchanged between young and old groups. Therefore, their data fit well with what has been previously known about the age-related changes in β-AR signaling—the alteration appears to be localized proximal to adenylyl cyclase and may involve changes in the β-AR itself or in its ability to couple to other regulatory molecules.

3.7. Endothelium-Localized β-AR/VSM Interactions. A controversial topic is the endothelium-mediated effect on the age-related change in β-AR function. It is clear that age-related changes in the endothelium occur [99], and there are endothelium-localized β-AR [100]. It is also well accepted that removal of endothelium reduces the effect of isoproterenol on vasorelaxation in a variety of isolated arteries and veins from different species, including humans [100]. Data show that endothelial cells have binding sites for β-AR ligands [101] and that isoproterenol increases nitric oxide synthase activity in these cells. Compatible with these findings is that inhibition of nitric oxide synthase modestly decreased relaxation to β-AR agonists [102]. Therefore, endothelium- and vascular smooth muscle-mediated function may be additive in that β-AR-mediated vasorelaxation appears to be induced via both nitric oxide-mediated pathways (endothelial), and cAMP-mediated pathways (vascular smooth muscle) [103].

In terms of aging, β-AR vasorelaxation is initiated in both endothelial and vascular smooth muscle cells. However, [104] found that the endothelial component did not change with age, whereas the vascular smooth muscle component did. They did identify an age-specific, endothelium-dependent effect in that vascular tone appeared to be mediated through an endothelium-derived hyperpolarizing factor (tetraethylammonium-sensitive K+ channels) that was increased with advancing age. Age-related changes in membrane polarization are also discussed previously where K_{ATP}-mediated hyperpolarization was found to be impaired in vascular smooth muscle cells from older rats [98]. Our lab has also produced data in support of a role for changes in polarization in mediating the age-related change in β-AR-mediated vasorelaxation. When comparing

the effect of age on isoproterenol-mediated vasorelaxation on phenylephrine- versus KCl-contracted aorta, vessels contracted with phenylephrine relaxed to a substantially higher degree that those contracted with KCl, although the age-effect was maintained [7]. One interpretation of this result is that with advancing age, isoproterenol-mediated signaling pathways involve an increased role for K+ channels. Further support that the aging change in β-AR signaling is vascular smooth muscle-, rather than endothelium-dependent is that other agents that initiate vasorelaxation through vascular smooth muscle localized G protein-coupled receptors (adenosine, parathyroid hormone) also show impaired vasorelaxation with age [105, 106]. Therefore, the age-related change is likely due to a factor common to all vascular smooth muscle-localized G protein-coupled receptors, such as GRK (see above discussion), while a nonage-related endothelial dependent component contributes to β-AR-stimulated vasorelaxation in general.

4. Summary and Perspectives

Hypertension, orthostatic hypotension, arterial insufficiency, atherosclerosis, and restenosis are common disorders in the elderly that lead to significant morbidity and mortality. These clinically significant conditions all may have a common feature in that they are associated with and age-related change in β-AR signaling. Impaired β-AR-mediated vasorelaxation with age is observed throughout species and arterial beds, and in aged vascular tissue, β-ARs are desensitized. One cellular process that changes with age that modulates β-AR sensitivity is phosphorylation by GRK-2. But, there are multiple other protein factors that may modulate β-AR function with aging. Similarly, there are multiple factors that may modulate GRK function [107]. Therefore, the overall complexity of the molecular pathways creates difficulties in isolating a single therapeutic target. Regardless, a large and growing segment of the general population are age 65 or older, and this percentage will continue to rise. Optimal care of this population is a priority for clinicians, and better understanding of this age-related change in the vasculature will allow for innovative strategies for the management of multiple disorders. Findings will be applicable to other tissues and disease states where β-AR signaling is altered (such as in the kidney and liver [108], heart [109], lung [110], and brain [111].

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Review Article

Hypertension in the Elderly

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Background. The incidence of hypertension in the Western countries is continuously increasing in the elderly population and remains the leading cause of cardiovascular and morbidity. *Methods*. we analysed some significant clinical trials in order to present the relevant findings on those hypertensive population. *Results*. Several studies (SYST-EUR, HYVET, CONVINCE, VALUE, etc.) have demonstrated the benefits of treatment (nitrendipine, hydrochrotiazyde, perindopril, indapamide, verapamil, or valsartan) in aged hypertensive patients not only concerning blood pressure values but also the other important risk factors. *Conclusion*. Hypertension is the most prevalent cardiovascular disorder in the Western countries, and the relevance of receiving pharmacological treatment of hypertension in aged patients is crucial; in addition, the results suggest that combination therapy—nitrendipine plus enalapril—could have more benefits than those observed with the use of nitrendipine alone.

1. Introduction

Hypertension remains the first cause of cardiovascular risk and mortality worldwide, and, in people aged 65 or older, it has been duplicated in relation to four decades before. Also population aged 80 or older is increasing; the prevalence of hypertension in this group of people is above 60% and continues to grow. It is well known that hypertension is *per se* associated to other risk factors such as overweight, obesity (46.8%), tobacco abuse, or hypercholesterolemia (45.4%) [1]. It is estimated that during the next years, 75% of the medical practice will be aimed at the geriatric age group. Today, everybody wishes to reach elderly without ailments or clinical disorders that could seriously alter his quality of life. Hypertension is one of the main medical problems affecting the elderly. Pharmacological therapeutics is especially aimed at studying that very common medical condition. During the last years, and before the final findings of the Syst-Eur were published [2], the general medical opinion considered not to decrease blood pressure values in order to avoid possible ischemic events and poor oxygenation of the trigger organs (brain, myocardium, kidney, and visual organ). This strong belief within the medical community raised the question of whether or not aged people should receive pharmacological treatment similarly to other younger patients. This scientific question was raised at the beginning of the 90s about hypertensive people aged 60–79. Until then, many clinicians thought that it was harmful to normalize blood pressure values of aged hypertensive people because of the hypothetical danger of ischemic events in the trigger organs and, then, the possibility to provoke serious cardiovascular complications.

2. Methods

However, the results of the *Systolic Hypertension in Europe trial* (*Syst-Eur*), where our group has actively participated, clearly proved the benefits of hypertensive treatment versus placebo, in contrast to the nihilistic attitude to leave the disease to itself. The significant results of the Syst-Eur trial are based on the research and the ten-year followup of 4,227 patients from 23 European countries. The protocol of this trial has been described in detail before [2]. These findings demonstrated (1) a reduction in cardiac mortality in the group of patients treated with antihypertensive agents (nitrendipine, enalapril, and hydrochlorothiazide); (2) a lower incidence of stroke, angina pectoris, and myocardial infarction in the group receiving active treatment;

(3) a decrease in the incidence of dementia in this group. The potential reduction up to 50% of dementia episodes after treatment with antihypertensive agents was based on the use of nitrendipine (dihydropyridine calcium antagonist) as the first drug with an important role in increasing the longevity of the elderly all over the world; these findings also showed that the nonpharmacological intervention in this disease must not be neglected [3, 4]. The results of the Syst-Eur trial suggest that combination therapy of nitrendipine plus enalapril could be interesting in a better prognosis of hypertensive patients [5]. In conclusion, the benefits of the antihypertensive treatment in patients with hypertension aged 60 or older revealed a reduction in the cases of stroke and cardiovascular events, which has been confirmed by other studies and meta-analysis of the last years.

3. Results

Also, it is well-known that life expectancy is rising around the world which is related to an increased risk of developing dementia; this is becoming a major public health problem. The Syst-Eur study showed that randomized patients actively treated presented a lower incidence of dementia up to 50% (from 7.7 to 3.8 cases every 1000 patients/yr) (21 cases versus 11 cases; $P = 0.05$) compared to the group treated with placebo.

Based on the placebo group, we can extrapolate that five-year treatment of 1,000 patients with isolated systolic hypertension could prevent 19 cases of dementia [6]. Therefore, the conclusive results of the Syst-Eur trial showed that physicians (internists, cardiologists, primary care, endocrinologists, and others) should treat hypertension drastically in aged patients and try to reach blood pressure values similar to those recommended in younger populations ($\leq$130/80 mmHg); these values should be lower when patients have also diabetes ($\leq$125/75 mmHg).

On the other hand, several observations suggested that calcium antagonists could have a specific neuroprotective effect. It is well known that both in vascular and mixed or degenerative dementias the values of the minimental state examination (MMSE) are less decreased in patients treated with nimodipine than in those treated with placebo. Brain aging is accompanied by alterations of intracellular calcium regulation, which leads to several cellular disorders, resulting in cellular death. Disorders of calcium homeostasis are related to the brain's aging process and the Alzheimer's disease. Antihypertensive treatment and reduction in blood pressure levels decrease the risk of developing dementia in aged patients, which is an important finding for the public healthcare system; calcium antagonists (nitrendipine and nimodipine) can have a specific neuroprotective effect. Important advances have been achieved relating physiopathological, pathogenetic, and therapeutic mechanisms of arterial hypertension. However, few studies have been made until now including the treatment of hypertension in patients aged 80 or older. These significant results led the researchers to investigate whether the benefits of the Syst-Eur trial could be extrapolated to patients aged 80 or older. However, empiric therapy is not adequate to this important pathology. The question was the *primum movens* of the HYVET study (Hypertension in the Very Elderly Trial), which was designed to provide a clear, definitive, and scientific answer to the treatment of hypertension in individuals older than 80 years.

The adequate control of these patients is greatly important for the general practitioners, internists, geriatrists, and other specialists, since hypertension together with other chronic conditions such as diabetes, hypercholesterolemia, and obesity are the main pathogenetic factors of cardiovascular disease, which is today the first cause of morbidity and mortality in the Western countries. The risks and benefits of treating hypertensive patients were studied in the HYVET trial, in which our group participated actively. The pilot study was carried out in 1,283 patients and was supported by the British Heart Foundation. Three different therapies were designed: (1) no treatment; (2) low-dose diuretic-based regimen (hydrochlorothiazide 12.5–25 mg daily); (3) an angiotensin-converting enzyme inhibitor (lisinopril 5 mg or enalapril 10 mg), following accurate inclusion and follow-up clinical criteria, and quality of results and procedures carried out according to protocol. The cases studied (1,283 patients) were recruited from several European countries (Bulgaria, Spain, Romania, UK, Poland, Finland, Lithuania, Ireland, Greece, and Serbia) [7, 8]. This study demonstrated that treating 1,000 patients per year, 19 cases of stroke could be prevented (nine of them nonfatal stroke). The good results of the study led to continue the investigation ("Main HYVET Trial") as international randomized double-blind trial.

Around 5,000 patients were included in the study. In conclusion, HYVET trial demonstrated the benefits of reducing blood pressure values in patients aged 80 or older and provided clear evidences about the need to treat hypertension in this growing population; this has become very important in the clinical practice and therapeutic guides [9, 10]. For many years, physicians have had the mistaken idea that hypertension was a result of ageing and that treatment was not necessary and no common criteria existed about the therapy on these cases; some proposed no treatment, others suggested low-dose diuretics, and others recommended the use of other pharmacological groups (angiotensin-converting enzymes inhibitors, calcium channel blocker, or angiotensin-II receptor antagonists). It is well established that hypertension is frequently associated with several cardiovascular risk factors, such as obesity, hypercholesterolemia, diabetes, tobacco abuse, and others. This fact led to carry out new clinical trials including hypertensive population with other cardiovascular events, like CONVINCE (Controlled Onset Verapamil Investigation of Cardiovascular Endpoints) study; this is a double-blind, randomized, multicentre, international trial which compared two initial treatments [11].

At the beginning, physicians could choice the treatment with hydrochlorothiazide (HCTZ) or atenolol, and the possibility to add controlled-onset extended-release verapamil, if necessary. The protocol permitted an increase of the doses or the number of drugs until reaching values lower than 140/90 mmHg. A total of 16,602 patients were included in the study selected from 15 countries and 661 centres. The mean age of the patients was 65.6 ± 7.4 years. The main risk factors

Table 1: main clinical trials on hypertensive patients.

Acronym	Patients	Age	Drugs
ACTION	7.665	63.5*	Nifedipine GITS
ALLHAT	40.000	≥55 years	Chortalidone, amlodipine, lisinopril, doxazosin, pravastatin
ELITE	722	≥65	Losartan, captopril
HOT	18.790	50–80	Felodipine, hydroclorotiazide, atenolol, ACEI
INSIGH	6.321	55–80	Nifedipine, amiloride
SYST-EUR	4.227	60–79	Nitrendipine, enalapril, hydroclorotiazide
$ANBP_2$	6.000	65–84	Enalapril versus $\beta\beta$/$\alpha\beta$/diuretic/antiCa^{++}
CAPP	7.000	25–66	Captopril versus $\beta\beta$/diuretics
LIFE	9.193	55–85	Losartan versus atenolol
NORDIL	10.881	50–69	Diltiazem versus $\beta\beta$/diuretic
PROGRESS	6.000	64*	Perindopril. Indapamide
CONVINCE	16.602	>55	Verapamil** versus/atenolol/hydroclorotiazide
VALUE	14.400	>50	Valsartan, amlodipine
HYVET	2.100	>80	Indapamide, perindopril

* Median Age; ** Verapamil Slow Release.

of the participants were overweight (BMI ≥ 28.5/m^2, 50.4%); dyslipemia, 31.3%; tobacco abuse 22.6%; diabetes, 19.8%, and in a lower incidence others such as known vascular disease, left ventricular hypertrophy, previous myocardial infarction, transient cerebral ischaemia, and so forth. Results showed a similar efficiency in the reduction of the cardiovascular disease with the calcium antagonist agents than with diuretics and beta blockers agents [12].

There have been many therapeutic advances since the development of reserpine and phenobarbital as therapeutic agents, more than five decades ago. However, despite the excellent advances of the last years, hypertension continues to be the main factor of complication and cardiac death not only in the Western population, mostly present as cerebral infarction and coronary heart disease. At the moment, the number of patients with controlled hypertension is under 25% all over the world and this could be due to the following reasons: (1) a difficult access to the healthcare system, (2) the lack of symptoms of hypertension, (3) the side effects of the antihypertensive agents, (4) the presence of other risk factors (obesity, tobacco abuse, diabetes, hypercholesterolemia, etc.), (5) the concomitance of other associated noncardiovascular diseases (pneumopathy, digestive disorders, and osteoarticular disorders), and (6) the difficulty in adjusting dosage.

Despite the therapeutic advances, uncontrolled hypertension is a growing problem in the developed countries and populations having easy access to the healthcare system. Unfortunately, not all the hypertensive patients receive treatment when the values of the diastolic blood pressure are 90–95 mmHg, specially, when only systolic blood pressure values between 140–160 mmHg are considered. Therefore, the aim to reach values ≤130 mmHg is still far away. This is a very important problem, since in hypertensive people brain alterations secondary to vascular diseases lead to intellectual impairment and a worse quality of life of these patients [13, 14].

The ACTION study [15] was carried out in 7,665 patients (mean age 63.5 years) randomly assigned to treatment with nifedipine GITS (gastrointestinal therapeutic system) and 3,840 patients treated with placebo. The study demonstrated that after addition of nifedipine GITS to the conventional treatment of angina pectoris, no effect was observed on major cardiovascular event-free survival, and it reduced the need to perform angiography and coronary interventions. Table 1 shows some findings (number of patients, age, and drugs used) on clinical trials in aged hypertensive people.

4. Conclusion

Hypertension is a very important disorder in aged people and is associated with higher risk of cardiovascular morbidity and mortality. The fact of reducing blood pressure values decreases the risk for cardiac death as well as neurological, metabolic, and musculoskeletal system sequelae in aged people. Therefore, the aim of the antihypertensive treatment must be to reduce cardiovascular risks and to maintain an adequate quality of life and good functional capacity in these patients.

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