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High blood pressure at old age : The Leiden 85 plus study

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High blood pressure at old age

The Leiden 85 plus study

Thomas van Bommel



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High blood pressure at old age

The Leiden 85 plus study

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in 1969

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Aan Annemarie, Lucas en Marit

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CHAPTER 1

Introduction

The last decades have shown an increasing interest in treatment of high blood pressure. Copious amounts of data have been published on the mortality and morbidity risks of high blood pressure. [1] Overall these data have resulted in an increasing awareness of the deleterious effects of only modest elevation of blood pressure on morbidity and mortality. Moreover, treatment of high blood pressure resulted in substantial benefits in terms of reduced morbidity and mortality. [2-6] This has resulted in official guidelines about treatment for hypertension that have become stricter with every decade. However, most of the evidence has been generated from middle-aged people. Only a few trials have included people of 80 year and older. [7-9] Looking at the results in detail within that age group the evidence is not robust. Given the increasing lifespan worldwide, physicians are confronted with many elderly patients over eighty. Hence, there is an increasing urge to generate more knowledge in regard to the effects of high blood pressure in the elderly.

Even in ancient times, high blood pressure has been recognized as a potential health threat. In the Yellow Emperor's Classics of Internal Medicine, the following answers were given to the plain questions of the emperor of China, 2600 B.C [10]:

"The blood current flows continuously in a circle and never stops."

"When the heart pulse beats vigorously and the strokes markedly prolonged, the corresponding illness makes the patient unable to speak."

"If too much salt is used in food, the pulse hardens."

More than 4000 years elapsed before William Harvey in 1628 proved the circulation of the blood; still later the sequence of hypertension, cerebral haemorrhage, and aphasia was recognized. [11] A hundred years later, Stephen Hales managed to measure systolic arterial blood pressure and the effect of haemorrhage on arterial blood pressure. [12] He also determined that the capillary arteries were the site of the chief peripheral resistance. The latter observation remains a basic concept in modern human physiology. In the early nineteenth century it became possible to measure blood pressure with a mercury manometer; it was used until 1896 when Scipione Riva-Rocci of Turin designed the first clinically acceptable sphygmomanometer. [13] In 1905 Korotkoff reported the now standard clinical procedure on the auscultatory method of determining systolic and diastolic blood pressure. [14]

At the beginning of the twentieth century there were three schools of thought with reference to the pathogenesis of hypertension. [15] First, the school of Bright that believed that essential hypertension was due to renal disease. [16] In 1827 Bright associated hardness and fullness of the pulse with albuminuria, edema and hypertrophy of the left ventricle with contracted kidneys. Thus, Bright introduced the concept of renal disease at the base of cardiovascular disease. Second, the school of Gull and Sutton believed that primary generalized arteriocapillary fibrosis caused contracted kidneys and left ventricular hypertrophy causing hypertension. [17] Hence regarding hypertension as the result of widespread vascular disease. Third, the school of Huchard and Allbutt making the statement that hypertension could occur without renal disease. [18,19] Years before, Mahomed had already published his clinical observation showing that high arterial blood pressure could exist without albuminuria. [20] Due to his untimely death, it wasn't until Huchard and Allbutt's finding that it was more widely established that arteriosclerosis and hypertension were independently associated diseases. These concepts were evaluated further in the early thirties of the 20th century mainly after Goldblatt could make dogs hypertensive after constricting their renal arteries. [21] In 1940, this resulted in the discovery of renin and finally in the discovery of the renin-angiotensin system. Nowadays many forms of secondary hypertension have been acknowledged, but the most frequent diagnosis remains essential hypertension. Though the pharmacological treatment has expanded explosively, still no definite pathophysiological process has been recognized as the sole determinant of essential hypertension.

Although high blood pressure was known to have deleterious effects on health, the ultimate prognosis was considered to be different according to the underlying cause of hypertension. For example, in 1953 the arteriosclerotic form of hypertension in the elderly associated with arteriosclerosis of the large vessels, e.g. resulting in a wide pulse pressure, was supposed to have a benign prognosis. [22] Presently this is recognized as a common, but by no means, benign form of hypertension and referred to as isolated systolic hypertension. [23] Up to the late seventies of the 20th century only diastolic blood pressure was considered to be detrimental and was used to classify subjects who suffer from hypertension. [24] Later on, systolic blood pressure became recognized as an even stronger predictor of morbidity and mortality than diastolic blood pressure. Presently, goal levels of systolic blood

pressure should be attained lower than 140 mmHg and for individuals with renal disease and diabetes even lower than 130 mmHg, irrespective of age. [23]

According to the recent guidelines, hypertension has a very high prevalence amongst elderly. [23] In the Framingham study one could discern the average diastolic and systolic blood pressure increased up to the sixth decade resulting in a prevalence of hypertension up to 40% at the age of sixty. [25,26] From that point on the systolic blood pressure continued to rise up to the eighth decade, however the diastolic blood pressure started to decline.

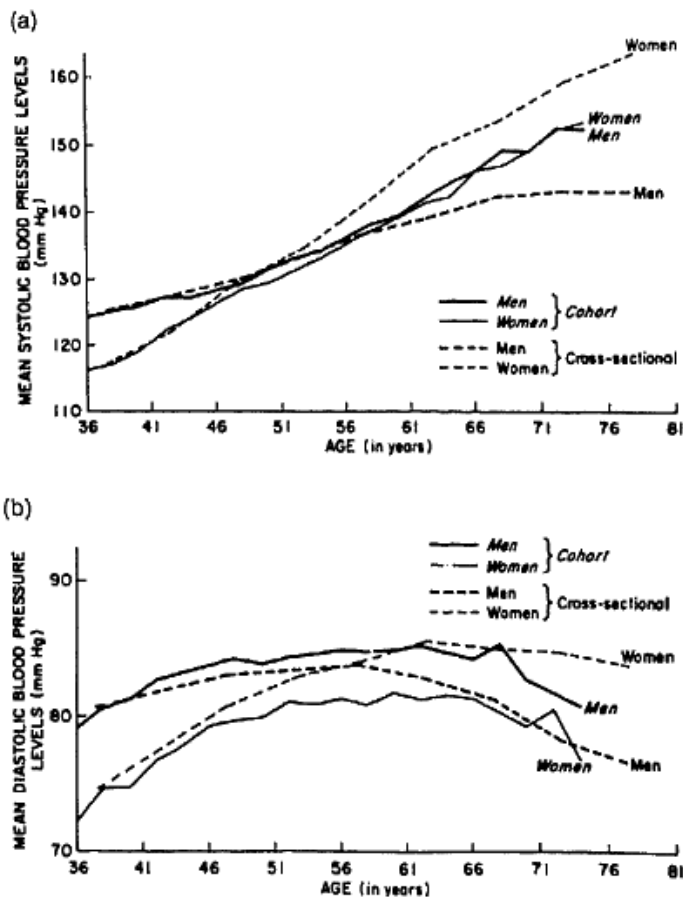


Figure 1. Average age trends in (a) systolic and (b) diastolic blood pressure levels for men and women based on cross-sectional (dotted lines) and longitudinal (cohort, unbroken lines) data on participants in the Framingham Study. [26]

In another report the prevalence of hypertension reached 60% in persons aged 85 and over. [27] Given this high prevalence, many are reluctant in accepting the strict criteria for high blood pressure at middle age for people at old age, as most of the population eventually will fulfil these criteria.

It is argued that a high blood pressure at old age might have a different effect on health compared to same levels of blood pressure in the middle aged. This has been proven for other cardiovascular risk factors also. For example in persons aged 85 years and older total cholesterol levels were no longer related to mortality. [28] Additionally observational data have shown that high blood pressure in elderly persons; above 80 years is no longer a risk factor for mortality. [27, 29, 30] Placebo-controlled clinical trials are not conclusive. Few subjects older than 80 years are included in these studies [2-6, 8]. An open-randomised trial has been published with patients exclusively over eighty years old. [7] In the treated group there was a non-significant increase in mortality that completely nullified the significant reduction in strokes. In contrast, the HYVET study, a placebo controlled double blind trial in persons aged 80 years and older, was prematurely stopped after safety analysis showed excess mortality in the placebo group. [9]

The differences in outcome between the observational and interventional studies at old age versus younger age are difficult to understand. In younger subjects the observational studies are in line with the intervention studies. A high blood pressure is related with greater mortality/morbidity and lowering high blood pressure reduces the mortality/morbidity. It is counterintuitive that high blood pressure at old age suddenly appeared not to be a risk factor; even more, that treatment of high blood pressure at old age may prove harmful. Possibly the elderly, as a group, are not so heterogeneous compared to the middle aged people. Treatment of high blood pressure in more diseased elderly might have more harmful effects compared to treatment in less diseased elderly. In younger age groups who are more vascular diseased, it has been reported that treatment for high blood pressure resulting in low diastolic blood pressure might give excess morbidity and mortality as well. [31, 32] In this thesis we have explored the predictive value of blood pressure and the possible underlying mechanism for the above-mentioned contradictory findings. This thesis consists of a general

introduction, a prognosis part, an etiological insight part, a general discussion and a summary.

Prognosis:

Is high blood pressure at older age associated with adverse outcomes, including cardiovascular mortality, renal failure and cognitive decline?

Etiological insights:

What is the association between blood pressure and cardiac function at older age?

We have used data of the Leiden 85-plus Study and the Rotterdam Study. The Leiden 85-plus Study was a prospective population-based study of all 85 years old inhabitants of Leiden, The Netherlands.[33] Between September 1997 and September 1999 all 705 members of the 1912 to 1914-birth cohort in the city of Leiden were asked to participate in this study in the month after their 85th birthday. There were no selection criteria related to health or demographic characteristics. At baseline, 85 year old participants were visited at their place of residence. During these visits blood pressure was measured twice, an electrocardiogram recorded, a face-to-face interview taken and performance tests were conducted. The participants were annually visited up to age 90 years old. At this age, a sample was invited to the study-centre for an echocardiographic examination. The collected data provided unique opportunities to examine population wise the effects of blood pressure at old age.

The Rotterdam Study is a large, prospective, population-based cohort study conducted in all inhabitants aged 55 and older of Ommoord, a district of Rotterdam, The Netherlands. [34] Of 10,275 eligible subjects, 7,983 (77.7%) participated in the baseline examinations between 1990 and 1993 (mean age 71.2±25.2, range 55–106). All participants were interviewed at home and visited the research centre for further examinations. At the fourth survey (2002–2004), cognitive function was extensively assessed using a dedicated neuropsychological test battery.

In the first part three studies on prognosis of blood pressure are presented. Chapter two presents the association between blood pressure at age 85 years and mortality in the following 5 years. Chapter three presents the association between

blood pressure and creatinine clearance at the age of 85 years up to the age of 90 years. Chapter four describes the association between blood pressure and cognitive function over time. In the second part, three etiological oriented studies are presented. Chapter five describes the prevalence of cardiac valve dysfunction in participants aged 90 years. Chapter six describes the association between blood pressure and cardiac function at the age of 90 years. Chapter seven studies the possible connection between the autonomous nervous system and mortality in subjects 85 years and older. The eighth chapter contains a general discussion of the preceding studies chapters and their possible implications for care of older people with high blood pressure. The ninth chapter reveals the summary in English and Dutch.

References

1. Prospectives Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903-13
2. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. *JAMA* 1991;265:3255-64
3. Dahlöf B, Lindholm LH, Hansson L, Scherstén B, Ekblom T, Wester P-O. Morbidity and mortality in the swedish trial in old patients with hypertension. *Lancet* 1991;338:1281-5
4. Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *Lancet* 1997;350:757-64
5. Liu L, Wang JG, Gong L, Liu G, Steassen JA. Comparison of active treatment and placebo in older chinese patients with isolated systolic hypertension. *J Hypertens* 1998;16:1823-9
6. Staessen JA, Gasowski J, Wang JG, et al. Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. *Lancet* 2000;355:865-72
7. Bulpitt CJ, Beckett NS, Cooke J, et al. Results of the pilot study for the hypertension in the very elderly trial. *J Hypertens* 2003;21:2409-17
8. Gueyffier F, Bulpitt C, Boissel JP, et. al. Antihypertensive drugs in very old people: a subgroup meta-analysis of randomised controlled trials. *Lancet* 1999;353:793-6
9. Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med*; 2008; 358:1887-98.
10. The Yellow Emperor's Classics of Internal Medicine. Translated by Ilza Veith. Wiliams & Wilkins, 1949
11. Robert Willis M.D. The works of William Harvey M.D. Anatomical Essay on the Motion of the Heart and Blood in Animals. (Translated from Latin to English) London Sydenham Society. 1847
12. Hales S: Statical Essays: Containing Haemastaticks; or, an Account of Some Hydraulick and Hydrostatical Experiments Made on the Blood and Blood-Vessels of Animals. Ed. 1, London, W. Innys, R. Manby, and T. Woodward, 1733, vol. II.
13. Riva-Rocci S. Un Nuovo sfigmomanometro. *Gazz Med Torino* 1896;47:981
14. Korotkoff NS. On methods of studying blood pressure. *Izv VoennomedAkad* 1905;11:365

15. Wakerlin GE. From bright toward light: The story of hypertension research. *Circulation* 1962;26:1-6
16. Bright R. Reports of medical cases. Selected with a view of illustrating the symptoms and cure of diseases by a reference to morbid anatomy. London, Longman, Rees, Orme. Brown and Green. 1827
17. Gull WW, Sutton HG. On the pathology of the morbid state commonly called chronic Bright's disease with contracted kidney ('Arterio-capillary fibrosis'). *Med Chir Trans* 1872; 55:273-326
18. Huchard H. *Maladies du Coeur et des vaisseaux*. Paris, Doin 1889
19. Allbutt TC. Senile plethora or high arterial pressure in elderly persons. *Trans Hunterian Soc* 1896; 96:38-57
20. Mahomed FA: The etiology of Bright's disease and the pre-albuminuric stage. *Med Chir Trans* 1874; 57:197-228
21. Goldblatt H, Lurch J, Hanzal RF, Summerville WW. The production of persistent elevation of systolic blood pressure by means of renal ischemia. *J Experim Med* 1934; 59:347-381
22. Hoobler SW. Treatment of hypertension in the elderly patient. *J Am. Geriatrics. Society* 1954;2:108-113
23. The task force for the management of arterial hypertension of the European society of hypertension and of the European society of cardiology. 2007 Guidelines for the management of arterial hypertension. *J Hypertension* 2007;25:1105-1187
24. Report of the Joint National Committee on detection, evaluation and treatment of high blood pressure: a cooperative study. *JAMA* 1977;237:255-261
25. Franklin SS, Gustin IV W, Wong ND, Larson MG, Weber MA, Kannel WB, et al. Hemodynamic patterns of age-related changes in blood pressure. The Framingham heart study. *Circulation* 1997;96:308-15
26. Vokonas PS, Kannel WB, Cupples LA. Epidemiology and risk of hypertension in the elderly: the Framingham study. *J Hypertens* 1988;6(suppl 1):S3-S9
27. Boshuizen HC, Izaks GJ, Van Buuren S, Ligthart GJ. Blood pressure and mortality in elderly people aged 85 and older. *BMJ* 1998;316:1780-4
28. Weverling-Rijnsburger AW, Jonkers IJ, van Exel E, Gussekloo J, Westendorp RG. High-density versus low-density lipoprotein cholesterol as the risk factor for coronary artery disease and stroke in old age. *Arch Intern Med* 2003;163:1549-54
29. S Rastas, Pirtillä T, Viramo P, Verkkoniemi A, Halonen P, Juva K, et al. Association between blood pressure and survival over 9 years in a general population aged 85 and older. *J Am Geriatr Soc* 2006;54:912-18

30. Heikinheimo RJ, Haavisto MV, Kaarela RH, Kanto AJ, Koivunen MJ, Rajala SA. Blood pressure in the very old. *J Hypertens* 1990;8:361-7
31. Fagard RH, Staessen JA, Thijs L, Celis H, Bulpitt CJ, de Leeuw PW, Leonetti G, Tuomilehto J, Yodfat Y. On-treatment diastolic blood pressure and prognosis in systolic hypertension. *Arch Int Med* 2007;167:1884-91
32. Messerli FH, Mancia G, Conti CR, Hewkins AC, Kupfer S, Champion A, Kolloch R, Benetos A, Pepine CJ. Dogma deputed: Can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? *Ann Intern Med* 2006;144:884-893
33. Bootsma-van der Wiel A, van Exel E, de Craen AJ, et al. A high response is not essential to prevent selection bias. Results from the Leiden 85-Plus Study. *J Clin Epidemiol* 2002;55:1119-25
34. Hofman A, Breteler MMB, van Duijn CM, et al. The Rotterdam Study: objectives and design update. *Eur J Epidemiol* 2007;22:819-829.

FIRST PART

Prognosis

CHAPTER 2

In a population-based prospective study no association between high blood pressure and mortality after age 85 years.

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J Hypertension 24:287-292, 2006

Abstract

Objective: To study the impact of a history of hypertension and current blood pressure on mortality in the oldest old.

Design: An observational population-based cohort study.

Setting: Community city of Leiden, the Netherlands.

Participants: Five hundred and ninety-nine inhabitants of the birth-cohort 1912-1914 were enrolled on their 85th birthday. There were no selection criteria related to health or demographic characteristics.

Interventions: The mean follow-up was 4.2 years. The medical histories were obtained from general practitioners. Medication histories were obtained from the participant's pharmacist. Blood pressure was measured twice at baseline.

Main outcome measures: All cause and cardiovascular mortality.

Results: Five hundred and seventy-one participants were included, 39.2% had a history of hypertension. During follow-up 290 participants died, 119 due to cardiovascular causes. Compared to participants without a history of hypertension, those with a history of hypertension had increased mortality from cardiovascular causes [relative risk (RR) 1.60, confidence interval (CI) 1.06-2.40] but equal mortality from all causes (RR 1.19, CI 0.91-1.55). High blood pressure at baseline (age 85) was not a risk factor for mortality. Baseline blood pressure values below 140/70 mmHg (n=48) were associated with excess mortality, predominantly in participants with a history of hypertension.

Conclusion: In the oldest old, high blood pressure is not a risk factor for mortality, irrespective of a history of hypertension. Blood pressure values below 140/70 are associated with excess mortality.

Introduction

The role of high blood pressure as a risk factor for morbidity and mortality in the oldest old is still subject to debate, despite the fact that people aged 85 years and older often have a history of hypertension [1-9]. The relatively scarce observational data in people aged 80 years and over are contradictory, showing either an increased risk or an inverse relationship for high blood pressure with mortality [4-8].

Some of the different results found might be due to the differences between current blood pressure and former blood pressure [5]. Normal blood pressure in the face of a longstanding history of hypertension might have a considerable different impact on prognosis than high blood pressure without a history of hypertension.

Placebo-controlled clinical trials are also inconclusive, because hardly any subjects older than 80 years are included in these studies [2,10-14]. The only study designed for people older than 80 years reported a reduced risk for strokes but an increased total mortality rate in the actively treated group [2]. Those findings could be arguments for clinicians to be reluctant to treat high blood pressure in old age.

The aim of the present study was to disentangle the relationship between a positive history of hypertension and current blood pressure in very old men and women participating in the population-based Leiden 85-plus Study. With this study we elaborate on the previous findings in the former cohort of the Leiden 85-plus Study, showing that elevated blood pressure was associated with better survival in this age group [4].

Methods

Study population

The Leiden 85-plus Study is a prospective population-based study of all 85-year old inhabitants of Leiden, The Netherlands. The study design and characteristics of the cohort have been described in detail previously [15,16]. In short, between September 1997 and September 1999 all 705 members of the 1912 to 1914-birth cohort in the city of Leiden were asked to participate in the month after their 85th birthday. There were no selection criteria related to health or demographic characteristics.

At baseline, 85-year old participants were visited three times at their place of residence to administer extensive data on health, functioning and well-being. In addition, a medical history was obtained from participant's general practitioner or nursing home physician, and information on the use of medication was obtained from participant's pharmacist. Participants gave oral informed consent and for people who were severely cognitively impaired, a guardian gave informed consent. The Medical Ethics Committee of the Leiden University Medical Center approved the study.

History of hypertension and baseline blood pressure

The definition of a positive history of hypertension was fulfilled when at baseline the diagnosis hypertension could be obtained from the medical records. This was assessed independently of the baseline blood pressure (age 85 years).

An experienced research nurse measured blood pressure twice at baseline with a mean interval of 2 weeks. Blood pressure was measured in seated position after at least 5 min of rest and no vigorous exercise during the preceding 30 min. The cuff was inflated to 30 mmHg above the pressure after the disappearance of the radial pulse. The systolic value was measured at the onset of Korotkoff phase 1 and the diastolic value was measured at the onset of Korotkoff phase 5. For the analysis of blood pressure we used the mean of the measured systolic values and the mean of the measured diastolic blood pressures.

Mortality

All participants were followed for mortality up until the censor date (1 April 2004). Shortly after the civil registry reported the death of a participant, the general practitioner or nursing home physician was interviewed to obtain the specific cause of death. Two senior specialists of internal medicine determined the primary causes of death by consensus without knowledge of medical history and the research aims. Primary causes of death were classified according to the tenth version of the International Classification of Diseases (ICD-10) [17] and were divided into two groups: cardiovascular mortality (ICD-codes I00-I99, I20-I25 and I60-I69) and non-cardiovascular mortality (all other ICD-codes).

Demographic and clinical characteristics

At baseline, a research nurse collected information concerning the demographic characteristics. Low education was defined as primary school only. At baseline the Mini-Mental State Examination (MMSE) was administered to screen for cognitive impairment [18]. Disability in basic activities of daily living (ADL) and instrumental activities of daily living (IADL) were assessed with the Groningen Activity Restriction Scale [19]. The presence of cardiovascular disease was defined as a previous history of cerebrovascular accident, angina pectoris, myocardial infarction, peripheral vascular disease or an electrocardiogram revealing myocardial ischaemia or infarction (Minnesota codes 1-1, 1-2, 1-3, 4-1, 4-2, 4-3, 5-1, 5-2 and 5-3) [20]. The presence of chronic disease was defined as a previous history of diabetes, Parkinson's disease, chronic obstructive pulmonary disease, arthrosis, or malignancies. Angiotensin converting enzyme inhibitors, angiotensin-1 receptor blockers, thiazide diuretics, dihydropyridin calcium channel blockers or β -blockers with the exclusion of sotacor, were classified as antihypertensive drugs.

Baseline blood pressure categories

According to national and international guidelines, we categorized the participants for both systolic and diastolic blood pressure in three clinically relevant groups, namely a systolic blood pressure lower than 140 mmHg (normal blood pressure), 140-159 mmHg (hypertension stage 1) and 160 mmHg and over (hypertension stage 2) [21]. For diastolic blood pressure we used lower than 70 mmHg (low blood pressure), 70-89 mmHg (normal blood pressure) and 90 mmHg and over (hypertension stage 1 and 2) [7,21].

Statistical analysis

Distributions of categorical clinical characteristics were compared with chi-squared tests, and continuous data were compared with independent t-tests. Mortality risks and 95% confidence intervals for participants with hypertension versus those without a history of hypertension were estimated in a Cox proportional-hazards model. We adjusted the mortality risks for gender, number of used antihypertensive medications and the presence of cardiovascular disease, because these determinants were differently distributed in the participants with and without a history of hypertension. The association between all-cause mortality and systolic and diastolic blood pressure was first visualized by use of Kaplan-Meier analyses, and differences were tested by log-rank tests. Mortality risks and 95% confidence intervals depending on systolic and diastolic blood pressure were estimated in a Cox proportional-hazards model. We adjusted the mortality risks for gender, use of antihypertensive medication and the presence of cardiovascular disease. To estimate the absolute risks of mortality, mortality rates and corresponding 95% confidence intervals were calculated by life tables for strata of systolic and diastolic blood pressure. All analyses were performed with SPSS version 12.01 (SPSS Inc., Chicago, Illinois, USA).

Results

Of the 705 eligible participants, 14 died before they could be enrolled and 92 refused to participate, resulting in a cohort of 599 participants (87% response). In the present analyses we included only the 571 participants for whom two measurements of blood pressure at baseline were available.

At baseline, 224 participants (39.2%) had a history of hypertension according to the medical records of their general practitioner or nursing home doctor. The history of hypertension was equally distributed for gender and education (Table 1). There were no differences in daily functioning (both ADL and IADL), cognitive function and the presence of chronic diseases for those with and without a history of hypertension (Table 1). Participants with a history of hypertension more often had a history of cardiovascular disease compared to participants without a history

of hypertension (71 versus 58%, chi-squared $P \leq 0.001$). Some 62% ($n=138$) of the participants with a history of hypertension used one or more antihypertensive drugs. Specific medications that were used included (combinations of) β -blockers ($n=57$, 41%), thiazide diuretics ($n=55$, 40%), dihydropyridin calcium channel blockers ($n=36$, 26%), angiotensin converting enzyme inhibitors and angiotensin-1 receptor blockers ($n=45$, 33%). Of the participants without a history of hypertension, some 20% used one or more of the aforementioned drugs for other diagnosis, as was verified by the general practitioners.

For participants with a history of hypertension, the mean baseline systolic blood pressure was 157.3 mmHg [standard deviation (SD) 18.3] versus 153.7 mmHg (SD 19.1) in those without a history of hypertension (independent t-test, $P = 0.03$). In total, 210 participants (36.8 %) had a systolic blood pressure at age 85 of 160 mmHg or higher. The mean diastolic blood pressure at age 85 was 77.0 mmHg (SD 9.9) in participants with a history of hypertension versus 75.8 mmHg (SD 9.2) in those without a history of hypertension (independent t-test, $P = 0.01$). In total, 48 participants (8.4 %) had a mean diastolic blood pressure above 90 mmHg at age 85.

Table 1 Clinical characteristics at baseline of 571 participants at age 85 years, according to a history of hypertension.

	History of Hypertension	
	Present ($n=224$)	Absent ($n=347$)
Females	160 (71%)	221 (64%)
Low education (%)	151 (68%)	219 (64%)
ADL independency (%)	105 (47%)	154 (45%)
IADL independency (%)	56 (25%)	91 (26%)
Cognitive function		
MMSE > 27 points (%)	78 (35%)	124 (36%)
MMSE < 19 points (%)	34 (15%)	58 (17%)
Mean systolic blood pressure (SD) (mmHg)	157.3 (18.3)*	153.7 (19.1)
Mean diastolic blood pressure (SD) (mmHg)	77.0 (9.9)*	75.8 (9.2)
History of chronic disease (%) †	131 (59%)	200 (58%)
History of cardiovascular disease (%) ‡	160 (71%)**	200 (58%)

ADL, basic activities of daily living; IADL, instrumental activities of daily living; MMSE, Mini-Mental State Examination; SD, standard deviation. * independent t-test $P \leq 0.03$, **chi-squared, $P \leq 0.001$, † Including diabetes, Parkinson's disease, chronic obstructive pulmonary disease, arthritis (including rheumatoid arthritis and polymyalgia rheumatica), and malignancies. ‡ Including cerebrovascular accident, angina pectoris, myocardial infarction, peripheral vascular disease or an electrocardiogram revealing myocardial ischaemia or infarction.

During a median follow-up of 4.2 years, 290 participants died. One hundred and nineteen participants died from cardiovascular causes and 164 from non-cardiovascular causes; causes of death could not be obtained for 7 participants. Participants with a history of hypertension did not have an increased all-cause mortality risk compared to those without a history of hypertension [adjusted relative risk (RR) 1.19, 95% confidence interval (CI) 0.91-1.55], but they did have a 1.6-fold increased cardiovascular mortality risk (95% CI 1.06-2.40). There was no association between a history of hypertension at age 85 years and non-cardiovascular mortality (Table 2).

Table 2 Mortality risks depending on history of hypertension at age 85 years.

	History of hypertension	
	Present (<i>n</i> =224)	Absent * (<i>n</i> =347)
All causes († 290)	1.17 (0.90-1.53)	1
Cardiovascular († 119)	1.54 (1.03-2.32)	1
Non-cardiovascular († 164)	0.97 (0.68-1.39)	1

Mortality risks and corresponding 95% confidence intervals were estimated with Cox proportional hazards model adjusted for gender, number of antihypertensive medications and presence of cardiovascular disease. † Observed Number of deaths; * Reference category; *n* = number of participants.

Figure 1 presents the cumulative mortality depending on categories of systolic and diastolic blood pressure at baseline. A significantly gradual inverse relation appeared between all-cause mortality and systolic blood pressure. Participants (*n*=129) with a diastolic blood pressure at baseline below 70 mmHg had a higher all-cause mortality compared to those in the other two categories of diastolic blood pressure.

Table 3 presents the all-cause mortality risks dependent on categories of systolic and diastolic blood pressure at baseline, adjusted for gender, number of antihypertensive medications and presence of cardiovascular disease. Compared to participants with a systolic blood pressure between 140 and 159 mmHg and a diastolic blood pressure between 70 and 89 mmHg (reference group) a 2.3-fold increased mortality risk was found for participants with a blood pressure lower than 140/70 mmHg (95% CI 1.61-3.38).

No association between high blood pressure and mortality.

2

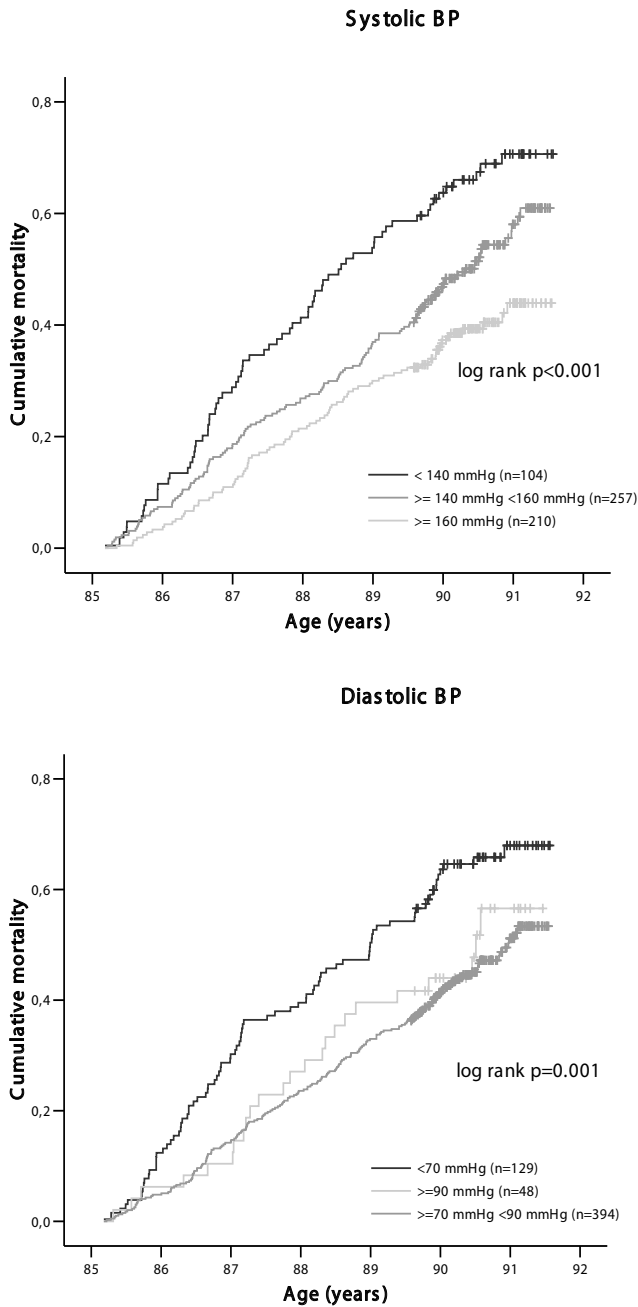


Figure 1: Cumulative all cause mortality depending on systolic and diastolic blood pressure at age 85.

Table 3: Number of participants rates (number of deaths) and relative risks (RR) for all cause mortality dependent on categories of systolic and diastolic blood pressure at baseline.

Diastolic BP (mmHg)	Systolic BP (mmHg)		
	< 140	140 - 159	≥ 160
<i>< 70</i>			
No. participants (no. deaths)	48 (40)	68 (37)	13 (7)
RR (95% CI)	2.33 (1.61-3.38)	1.04 (0.71-1.53)	1.14 (0.52-2.46)
<i>70 – 89</i>			
No participants (no. deaths)	56 (31)	180 (93)	158 (58)
RR (95% CI)	1.19 (0.79-1.79)	1*	0.66 (0.47-0.92)
<i>≥ 90</i>			
No participants (no. deaths)	0	9 (6)	39 (18)
RR (95% CI)		1.65 (0.72-3.78)	0.82 (0.50-1.36)

BP, blood pressure. Mortality risks and corresponding 95% confidence intervals (CI) were estimated with Cox proportional-hazards model adjusted for gender, number of antihypertensive medications and presence of cardiovascular disease. *, Reference category.

To investigate whether poor general health might be confounding this result an additional adjustment for the presence of chronic diseases, MMSE, ADL and IADL was performed. The increased mortality risk for participants with a blood pressure lower than 140/70 mmHg remained significant (RR 1.51, 95% CI 1.03-2.23). For participants with a systolic blood pressure equal to and higher than 160 mmHg and a diastolic blood pressure between 70 and 89 mmHg, a survival benefit was found compared to the reference group (RR 0.66, CI 0.47-0.92). However, after the additional adjustment for poor general health, this survival benefit disappeared (RR 0.73, 95% CI 0.52-1.02).

The absolute mortality rates dependent on blood pressure at age 85 stratified for the history of hypertension are presented in Table 4. In both strata, all-cause mortality was highest for participants with low blood pressure (systolic blood pressure below 140 mmHg or diastolic blood pressure below 70 mmHg) and most pronounced in participants with a history of hypertension and a low systolic blood pressure. In the group of participants with a systolic blood pressure lower than 140 mmHg, participants with a history of hypertension had a significant higher all-cause mortality rate (29.1 per 100 person years, 95% CI 19.4-38.9) compared to those without a history of hypertension (14.6 per 100 person years, 95% CI 9.9-19.3).

Table 4 Absolute mortality rates dependent on blood pressure at baseline stratified for a history of hypertension at age 85 years.

	Systolic BP	History of hypertension		Diastolic BP	History of hypertension	
		Present	Absent		Present	Absent
All cause	< 140	29.1 (19.4-38.9)*	14.6 (9.9-19.3)	< 70	19.6 (12.1-27.1)	17.5 (13.0-21.9)
	140-159	13.1 (9.2-16.9)	12.5 (10.0-15.1)	70-89	11.7 (9.2-14.3)	9.9 (8.0-11.9)
	≥ 160	8.6 (6.0-11.3)	9.2 (6.4-11.9)	≥ 90	11.2 (4.9-17.6)	12.7 (4.8-20.6)
Cardiovascular	< 140	12.0 (5.7-18.3)	6.3 (3.2- 9.4)	< 70	9.8 (4.5-15.1)	6.0 (3.4-8.7)
	140-159	7.1 (4.3-10.0)*	3.4 (2.1-4.7)	70-89	5.9 (4.1-7.8) *	3.5 (2.4-4.7)
	≥ 160	4.4 (2.5-6.3)	4.1 (2.3-6.0)	≥ 90	4.7 (0.1-8.8)	4.2 (0.0-8.4)
Non-cardiovascular	< 140	17.1 (9.6-24.7)*	7.9 (4.4-11.4)	< 70	9.8 (4.5-15.1)	10.8 (5.5-14.4)
	140-159	5.6 (3.1-8.2)	8.6 (6.5-10.7)*	70-89	5.5 (4.2-7.8)	6.1 (4.6-7.6)
	≥ 160	4.0 (2.2-5.8)	5.0 (3.0-7.1)	≥ 90	6.6 (1.7-11.4)	8.5 (2.6-14.3)

BP blood pressure in mmHg. Data are presented as number of deaths per 100 observed person years at risk and corresponding 95% confidence intervals. * $P < 0.05$, present versus absent history of hypertension within stratum of blood pressure.

Within the participants with blood pressures lower than 140/70 mmHg at baseline, the amount of cardiovascular disease was not uniformly divided. Of the 48 participants, 16 had a positive history of hypertension. Cardiovascular disease was present in 14 (87.5%) participants with a history of hypertension compared to 18 (56.3%) of the 32 participants without a history of hypertension (chi squared, $P = 0.03$).

Discussion

The main finding of this prospective population-based study was, that at the age of 85 years and over, high blood pressure was not associated with increased mortality, independently of the history of hypertension. Moreover, subjects with low systolic and diastolic blood pressure had an increased mortality risk.

Except for the lowest range of blood pressures, we did not find a relationship between blood pressure and mortality in participants aged 85 years and over, despite the fact that a history of hypertension remained a risk factor for cardiovascular mortality in this age group. This is different from reports in younger age groups, where those with the highest blood pressure are at the highest mortality risk [1,10-13,22]. The finding that low blood pressure is associated with an increased mortality risk in the oldest old corroborates with earlier results from the Leiden 85-plus Study and other reports [4-6,8,23,24].

The crude results from both cohorts of the Leiden 85-plus Study are similar. Both studies showed a higher mortality for participants in the low blood pressure group. However, in the present study the higher mortality was especially apparent for the participants with a history of hypertension. Secondly, in the present study systolic and diastolic blood pressure were analysed together in blood pressure categories according to international guidelines [21]. This was done because a low diastolic blood pressure in the presence of a high systolic blood pressure might have a different aetiology and thus prognosis, e.g. high atherosclerotic burden, than the same low diastolic blood pressure with a low systolic blood pressure, e.g. heart failure [25]. This was confirmed by the finding that a low diastolic blood

pressure is only harmful in the presence of a low systolic blood pressure in the very old.

How can we explain the results? Hypertension is a well-known risk factor for heart failure. Possibly, longstanding hypertension leads to preclinical heart failure that might lower actual blood pressure and therefore could be partly responsible for our finding [26]. Nevertheless, it cannot be excluded that blood pressure-lowering therapy contributed to the inverse relation between low blood pressure and mortality risk.

The strength of the present study is that it seems to reflect the history of elderly individuals with different levels of blood pressure, given the population-based character, the 87% enrolment of the 85-year-olds and the small number of individuals who were lost to follow-up. Its weakness is that it relies on a baseline assessment of blood pressure. Another possible weakness might be the lack of uniformity for a positive history of hypertension. It could be that the general practitioners used variable criteria for a former diagnosis of hypertension. Moreover, because of the observational nature of the data, we cannot exclude that residual confounding is at play and therefore we are not able to draw final conclusions on causality.

From the present study, the clear message is that in the oldest old, blood pressure is not a predictor for mortality, again except for those participants with a blood pressure lower than 140/70 mmHg. Our finding supports the general clinical feeling that at old age a blood pressure lower than 140/70 mmHg is relatively rare; in the present cohort only 8.4 % of the participants had blood pressures lower than 140/70 mmHg. This is in sharp contrast to younger age groups where these ranges of blood pressures are considered to be normal. The finding that blood pressures higher than 140/70 mmHg are found not to be associated with mortality risk in the oldest old might have important clinical implications. Moreover, a blood pressure below 140/70 mmHg in the general population of oldest old identifies a new high-risk subgroup. The therapeutic consequences of these findings are unknown and have to be explored in future. The fact that a history of hypertension remains a risk factor for cardiovascular mortality in old age, independent of the current blood pressure, further complicates clinical decision-making.

References

- 1 Prospectives Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903-13
- 2 Bulpitt CJ, Beckett NS, Cooke J, et al. Results of the pilot study for the hypertension in the very elderly trial. *J Hypertens* 2003;21:2409-17
- 3 Gueyffier F, Bulpitt C, Boissel JP, et. al. Antihypertensive drugs in very old people: a subgroup meta-analysis of randomised controlled trials. *Lancet* 1999;353:793-6
- 4 Boshuizen HC, Izaks GJ, Van Buuren S, Ligthart GJ. Blood pressure and mortality in elderly people aged 85 and older. *BMJ* 1998;316:1780-4
- 5 Lernfelt B, Svanborg A. Change in blood pressure in the age interval 70-90. Late blood pressure peak related to longer survival. *Blood Pressure* 2002;11:206-12
- 6 Heikinheimo RJ, Haavisto MV, Kaarela RH, Kanto AJ, Koivunen MJ, Rajala SA. Blood pressure in the very old. *J Hypertens* 1990;8:361-7
- 7 Glynn RJ, Chae CU, Guralnik JM, Taylor JO, Hennekens CH. Pulse pressure and mortality in old persons. *Arch Int Med* 2000; 160:2765-72
- 8 Rajala S, Haavisto M, Heikinheimo R, Mattila K. Blood pressure and mortality in the very old. *Lancet* 1983; 322:520-1
- 9 Vasan RS, Beiser A, Seshadri S, et al. Residual lifetime risk for developing hypertension in middle-aged women and men. The Framingham heart study. *JAMA* 2002;287:1003-10
- 10 Dahlöf B, Lindholm LH, Hansson L, Scherstén B, Ekblom T, Wester P-O. Morbidity and mortality in the swedish trial in old patients with hypertension. *Lancet* 1991;338:1281-5

- 11 SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. *JAMA* 1991;265:3255-64
- 12 Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *Lancet* 1997;350:757-64
- 13 Liu L, Wang JG, Gong L, Liu G, Steassen JA. Comparison of active treatment and placebo in older chinese patients with isolated systolic hypertension. *J Hypertens* 1998;16:1823-9
- 14 Hansson L, Lindholm LH, Ekblom T, et al. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the swedish trial in old patients with hypertension-2 study. *Lancet* 1999;354:1751-6
- 15 Bootsma-van der Wiel A, van Exel E, de Craen AJ, et al. A high response is not essential to prevent selection bias. Results from the Leiden 85-Plus Study. *J Clin Epidemiol* 2002;55:1119-25.
- 16 Exel E, Gussekloo J, Houx P, et al. Atherosclerosis and cognitive impairment are linked in the elderly. The Leiden 85-plus Study. *Atherosclerosis* 2002;165:353-9.
- 17 WHO, Geneva. International Statistical Classification of Diseases and Related Health Problems 1994.
- 18 Tombaugh TN, McIntyre NJ. The Mini-Mental State Examination: A comprehensive review. *J Am Geriatrics Soc* 1992;40:922-35.
- 19 Kempen GI, Miedema I, Ormel J, Molenaar W. The assessment of disability with the Groningen Activity Restriction Scale. Conceptual framework and psychometric properties. *Soc Sci Med* 1996;43:1601-10.

- 20 Macfarlane PW, Latif S. Automated serial electrocardiogram comparison based on the Minnesota code. *J Electrocardiol* 1996;29 suppl:29-34.
- 21 Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the joint national committee on prevention detection and treatment of high blood pressure. *JAMA* 2003; 289:2560-72
- 22 Staessen JA, Gasowski J, Wang JG, et al. Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. *Lancet* 2000;355:865-72
- 23 Askari M, DK Kiely, Lipsitz LA. Is pulse pressure a predictor of cardiovascular complications in a frail elderly nursing home population. *Aging Clin Exp Res* 2004;16:206-11
- 24 Glynn RJ, Field TS, Rosner B, Hebert PR, Taylor JO, Hennekens CH. Evidence for a positive linear relation between blood pressure and mortality in elderly people. *Lancet* 1995;345:825-9
- 25 Sutton-Tyrrell K, Alcorn HG, Wolfson Jr SK, Kelsey SF, Kuller LH. Predictors of carotid stenosis in older adults with and without isolated systolic hypertension. *Stroke* 1993;24:355-61
- 26 Himmelmann A. Hypertension: an important precursor of heart failure. *Blood pressure* 1999;8:253-60

CHAPTER 3

Prospective study of the effect of blood pressure on renal function in old age; The Leiden 85-plus Study

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Abstract

High blood pressure is associated with decline of renal function. Whether this is true for very old people largely is unknown. Therefore, the study assessed the effect of blood pressure on creatinine clearance over time in very old participants. A total of 550 inhabitants (34% men) of Leiden, The Netherlands, were enrolled in a population-based study at their 85th birthday and followed until death or age 90. Blood pressure was measured twice at baseline and at age 90 years. Creatinine clearance was estimated annually (Cockcroft-Gault formula). The mean creatinine clearance at baseline was 45.4 ml/min (SD 11.5). Systolic blood pressure was not associated with changes in creatinine clearance during follow-up. Those with diastolic blood pressure below 70 mmHg had an accelerated decline of creatinine clearance (1.63 ml/min/year) compared with those with diastolic blood pressures between 70 and 79 mmHg (1.21 ml/min/year; $P = 0.01$), 80 to 89 mmHg (1.26 ml/min/year; $P = 0.03$), and higher than 89 mmHg (1.38 ml/min/year; $P = 0.32$). Participants with a decline in systolic blood pressure during follow-up had an accelerated decline of creatinine clearance compared with those with stable blood pressures (1.54 ml/min/year [SE 0.09] versus 0.98 ml/min/year [SE 0.09]; $P < 0.001$). Similar results were found for a decline in diastolic blood pressure (1.54 ml/min/year [SE 0.10] versus 1.06 ml/min/year [SE 0.08]; $P < 0.001$). In the oldest individual, high blood pressure is not associated with renal function. In contrast, low diastolic blood pressure is associated with an accelerated decline of renal function. The clinical implications of these findings have to be studied.

Introduction

An old age, renal function will be compromised as a result of progressive loss of glomeruli and decline in renal blood flow [1], especially in those with persistent high blood pressure [2]. Because blood pressure increases with age, this implicates a possible double strike for creatinine clearance in the oldest individual [3].

In contrast with younger populations, in the oldest individuals, the association among high blood pressure, mortality and renal function is not straightforward. The available data suggest that blood pressure lowering above 80 years does not lower overall mortality [4,5]. Data on the effect of blood pressure on morbidity such as renal function are relatively scarce in the oldest individuals [6-8]. One longitudinal report associated blood pressure and renal function in a considerable group of very old Japanese individuals [7]. In that report, high blood pressure was related to an excess decline of serum creatinine. However, an important drawback was the use of serum creatinine for estimation of renal function. In addition, selection bias could have been induced as a result of exclusion of 40% of the participants, who did not attend the reexamination after 3 years.

Although blood pressure lowering in individuals over 80 years might not lower mortality, it is unknown if a high blood pressure might be deleterious for renal function. To investigate whether high blood pressure still is a risk factor for decline in renal function in the oldest individuals, we prospectively studied the effect of blood pressure on changes of creatinine clearance over time in a population-based study of the general population of the oldest individuals.

Materials and Methods

Study population

The Leiden 85-plus Study is a prospective population-based study of all 85-year-old inhabitants of Leiden, The Netherlands. The study design and characteristics of the cohort were described in detail previously [9,10]. In short, between September 1997 and September 1999 all 705 members of the 1912 to 1914-birth cohort in the city of Leiden were asked to participate in the month after their 85th birthday. There were no selection criteria related to health or demographic characteristics. Participants were followed until death or the age of 90. At baseline and yearly thereafter, 85-year-old participants were visited at their place of residence. During these visits, participants were weighed, blood pressure was measured, a venous blood sample was drawn, an electrocardiogram was recorded and face-to-face interviews and performance tests were conducted. Information on the medical history was obtained by standardized interviews of the participant's treating physicians. In addition, information on the use of medication was obtained from the participant's pharmacist. Participants gave informed consent; for people who were severely cognitively impaired, a guardian gave informed consent. The Medical Ethics Commission of Leiden University approved the study.

Blood pressure

At baseline and at age 90 years, blood pressure was measured twice, with a mean intervening period of 2 weeks. Blood pressure was measured, using a mercury sphygmomanometer, in the seated position after at least 5 min of rest and no vigorous exercise the preceding 30 min. The systolic value was measured at Korotkoff sound 1, and the diastolic value was measured at Korotkoff sound 5. For the analysis of blood pressure, we used the mean of the measured systolic and diastolic values. For the analysis of pulse pressure, we used the mean systolic minus the mean diastolic blood pressure. Data are presented according to four strata of systolic blood pressure (<140, 140 to 149, 150 to 159, and \geq 160 mmHg), four strata of diastolic blood pressure (<70, 70 to 79, 80 to 89, and \geq 90 mmHg), and quartiles of pulse pressure. The change of systolic and diastolic blood pressure between ages 85 and 90 was categorized into 3 groups: Declining (\geq 10-mmHg decrease), stable (<10-mmHg increase or <10-mmHg decrease) and increasing (\geq 10-mmHg).

Creatinine clearance

At entry and at yearly intervals thereafter, both the serum creatinine concentration and bodyweight were measured. Creatinine was fully automatically measured according to the Jaffé method (Hitachi 747; Hitachi, Tokyo, Japan). The creatinine clearances were estimated yearly with the Cockcroft-Gault formula as follows [11]:

$$\text{Creatinine clearance} = \frac{(140 - \text{Age}) \times \text{weight (kg)} \times 1.23}{\text{serum creatinine } (\mu\text{mol/l})} \times (0.85 \text{ if female})$$

Demographic and clinical characteristics

At baseline, a research nurse collected information concerning the demographic characteristics. The presence of cardiovascular disease was defined as a previous history of cerebrovascular accident, angina pectoris, myocardial infarction, peripheral vascular disease (including a history of arterial grafting, endarterectomy and angioplasty) or an electrocardiogram revealing myocardial ischemia or infarction (Minnesota codes 1-1, 1-2, 1-3, 4-1, 4-2, 4-3, 5-1, 5-2 and 5-3) [12]. The presence of chronic disease was defined as a history of diabetes, Parkinson's disease, chronic obstructive pulmonary disease, osteoarthritis, or malignancies. Antihypertensive drugs were classified as usage of angiotensin converting enzyme inhibitor, angiotensin-1 receptor blocker, thiazid diuretic, dihydropyridin calcium channel blocker or β -blocker with the exclusion of Sotacor. We had data on use of anti-hypertensive medication at the ages of 85 and 86.

Statistical analyses

Data were presented as percentages for clinical characteristics and as the mean with standard deviation for continuous variables. The differences in mean creatinine clearances between the categories of blood pressure at baseline were compared with independent *t* test. The associations over time between creatinine clearance (ml/min) and categories of diastolic and systolic blood pressure were analyzed with a linear mixed model. The creatinine clearance was the dependent factor. The outcome was the effect on the change in creatinine clearance of the interaction between time and categories of blood pressure. This analysis models the change over time by computing the rate of change for each participant on the basis of all data for that individual adjusted for gender and other possible confounders.

Then the rate of changes for the entire group and the individual deviation from the group rate are computed. This model analyzes the unique effects of individual predictors adjusted for all other fixed and random predictors, accounts for the correlation among repeated measurements on the same participant, and is unaffected by randomly missing data. To investigate the effects of missing data due to mortality, we repeated all analyses with exclusion of participants who died within the first year of follow-up and repeated all analyses with inclusion only of surviving participants who participated up to age 90 years.

An additional analysis was done to examine the effect of a decline in systolic and diastolic blood pressure between ages 85 and 90 on the decline of creatinine clearance in participants who were alive at age 90. The associations between the groups of blood pressure and creatinine clearance were analyzed with a linear mixed model. All analyses were done with software SPSS version 12.0 (SPSS, Inc. Chicago, IL).

Results

Of the 705 eligible participants, 14 died before they could be enrolled and 92 refused to participate, resulting in a cohort of 599 participants (87 % response). Only one blood pressure measurement was available for 27 participants, serum creatinine at baseline was missing in 11 participants and body weight in 11 participants. Thus, in these analyses we included 550 participants (Table 1). During follow up, 34 participants declined further participation and 243 participants died (Figure 1). At age 86, 36 participants had started antihypertensive medication and 54 had stopped antihypertensive medication. There were no significant associations between the categories of diastolic and systolic blood pressure and changes of use of antihypertensive medication between ages 85 and 86 years (data not shown).

Table 1: Baseline characteristics of 550 participants aged 85 years.

Females		363 (66%)
History of hypertension		218 (40%)
Antihypertensive treatment		201 (37%)
Mean diastolic blood pressure (mmHg [SD])		76.9 (9.4)
Mean systolic blood pressure (mmHg [SD])		155.6 (18.4)
Mean pulse pressure (mmHg [SD])		78.7 (15.2)
Number of cardiovascular disease ^a	0	203 (37%)
	1	210 (38%)
	2	105 (19%)
	>=3	32 (6%)
No history of chronic diseases ^b		227 (41%)
Diagnosis of diabetes		87 (16%)

^a Including history of peripheral vascular disease, cerebrovascular accident, angina pectoris, myocardial infarction, or an electrocardiogram revealing myocardial ischemia or infarction,

^b History of diabetes, Parkinson's disease, chronic obstructive pulmonary disease, osteoarthritis, or malignancies.

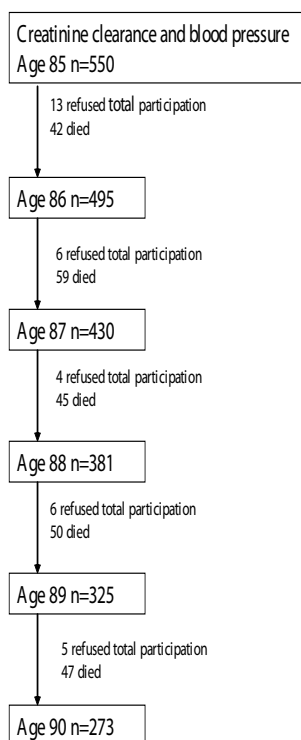


Figure 1: Number of participants during the study period.

At baseline the mean creatinine clearance was 45.4 ml/min (standard deviation [SD] 11.5 ml/min). Females had a 2.19 ml/min (standard error [SE] 1.04 ml/min) lower creatinine clearance compared with men ($P < 0.035$). During follow-up, the overall decline in creatinine clearance was 1.31 ml/min per year (SE 0.06, $P < 0.001$). At baseline, four participants had end-stage renal failure, defined as a creatinine clearance less than 15 ml/min. During follow-up, three participants progressed to end-stage renal failure: Two at age 89 years and one at age 90 years.

At baseline, creatinine clearance was correlated with the presence of cardiovascular disease. For every additional cardiovascular disease, creatinine clearance was 2.05 ml/min (SE=0.54, $P < 0.001$) lower. During follow-up, creatinine clearance declined with an extra 0.21 ml/min per year (SE 0.07, $P = 0.002$) over the normal annual decline for every additional manifestation of cardiovascular disease. A history of hypertension and diabetes (Table 2) was not associated with the decline of renal function either at baseline or during follow-up.

At baseline, creatinine clearance was not dependent on systolic blood pressure or pulse pressure (all comparisons between groups, $P > 0.18$). In contrast, diastolic blood pressure at baseline was significantly associated with creatinine clearance: Creatinine clearances were significantly lower in the two lowest categories (<70 and 70 to 79 mmHg) of diastolic blood pressure (43.8 ml/min [SE 0.98], 44.7 ml/min [SE 0.77]) compared with the two highest categories (80 to 89 and ≥ 90 mmHg) of diastolic blood pressure (47.5 ml/min [SE 0.97], 46.5 ml/min [SE 1.61]; $P = 0.005$). The associations among systolic, diastolic blood pressure and pulse pressure versus creatinine clearance were similar in men and women (data not shown).

Table 2: Additional change in creatinine clearance (ml/min) per year during follow-up until death or the age of 90, according to the number of cardiovascular diseases, the history of hypertension, and the history of diabetes at baseline in 550 participants^a.

	Crude model		Adjusted model	
	ml/min (SE)	P-value	ml/min (SE)	P-value
Number of cardiovascular diseases ^b	-0.21 (0.07)	0.002	-0.21 (0.07)	0.002
History of hypertension ^c	-0.12 (0.12)	0.31	-0.12 (0.12)	0.30
History of diabetes mellitus ^c	-0.18 (0.17)	0.27	-0.18 (0.17)	0.27

^aAnalyses with linear mixed model with estimates plus Standard Errors (SE) of the mean. Crude model: adjusted for gender. Adjusted model: adjusted for gender and use of antihypertensive medication at age 85 and 86.

^bChange per additional number (range: 0 to 5) of cardiovascular diseases present.

^cChange according to positive history versus negative history of hypertension and diabetes.

Relations between baseline blood pressure and changes in renal function over time were similar to those observed at the cross-sectional analyses. There was no association between baseline systolic blood pressure or pulse pressure and the annual decline of creatinine clearance (Figure 2). However, baseline diastolic blood pressure lower than 70 mmHg was associated with a significantly accelerated decline of creatinine clearance during follow-up when compared to higher diastolic blood pressures (Figure 2). These findings remained similar after exclusion of 42 participants who died within the first year of follow-up. The restricted analyses for 273 surviving participants who participated up to 90 years did also not change the significant association between low diastolic blood pressure and an accelerated decline of creatinine clearance. The yearly decline in creatinine clearance was -1.58 ml/min for 53 participants with baseline diastolic blood pressure < 70 mmHg (reference group), -1.13 for 70 to 79 mmHg ($n = 112$, $P = 0.006$), -1.13 for 80 to 89 mmHg ($n = 82$, $P = 0.01$), and -1.30 ($n = 26$, $P = 0.24$) for > 89 mmHg.

During follow-up a low diastolic blood pressure was consistently associated with an accelerated decline of creatinine clearance in those with and those without cardiovascular disease at baseline (data not shown). Stratification according to the median of creatinine clearance at baseline did not reveal a different effect of blood pressure on creatinine clearance over time (data not shown).

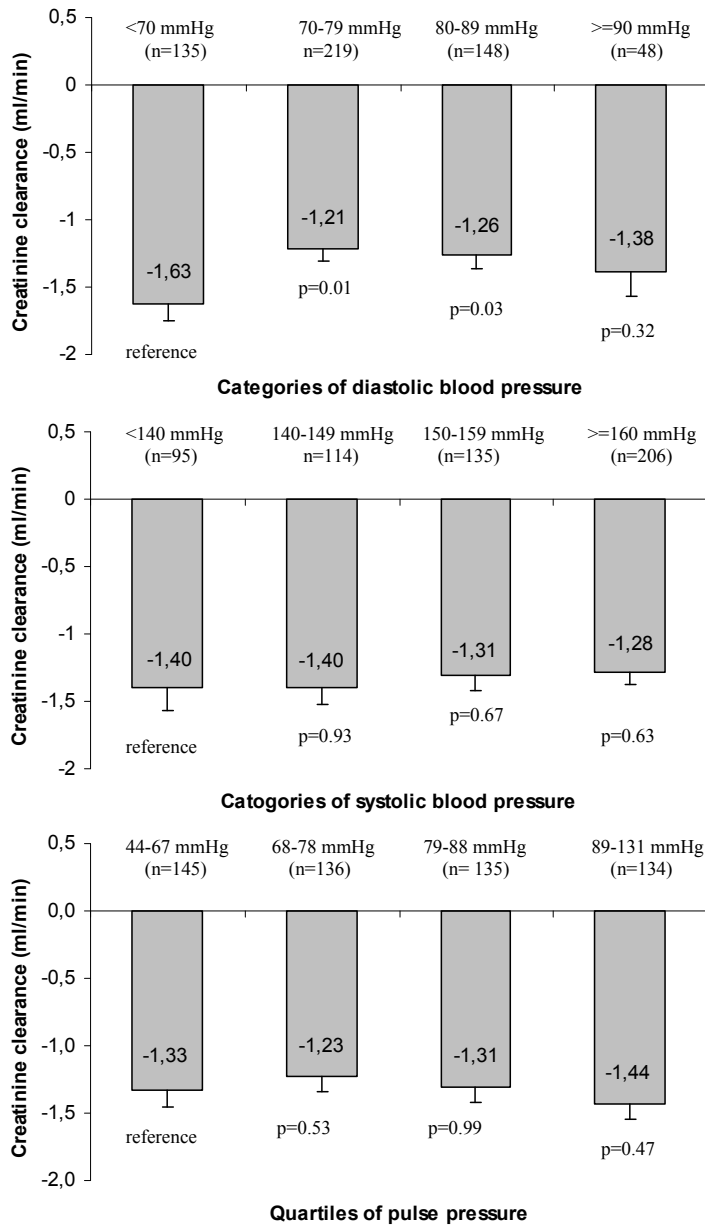


Figure 2. Yearly decline of creatinine clearance depending on categories of blood pressure and pulse pressure. Analyses with linear mixed model with estimates plus standard errors of the mean. Adjusted for gender, cardiovascular disease, chronic disease and use of antihypertensive medication at age 85 and 86 year. Diastolic blood pressure was adjusted for systolic blood pressure and vice versa. P-values reflecting the differences in additional annual decline compared to the reference category.

Figure 3 presents the annual decline of creatinine clearance in survivors up to 90 year according to the change of blood pressure from age 85 up to 90. Those with a decline in systolic blood pressure had an accelerated decline of creatinine clearance -from age 85 up to 90- compared with those with a stable systolic blood pressure (1.54 ml/min/year [SE 0.09] versus 0.98 ml/min/year [SE 0.09]; $P < 0.001$). Those with a decline in diastolic blood pressure had an accelerated decline of creatinine clearance -from age 85 up to 90- compared with those with a stable diastolic blood pressure also (1.54 ml/min/year [SE 0.10] versus 1.07 ml/min/year [SE 0.08]; $P < 0.001$). There were no associations between the presence of chronic disease, cardiovascular disease, history of hypertension or usage of antihypertensive medication at baseline and a decline versus an increase in systolic or diastolic blood pressure between 85 and 90 year (data not shown).

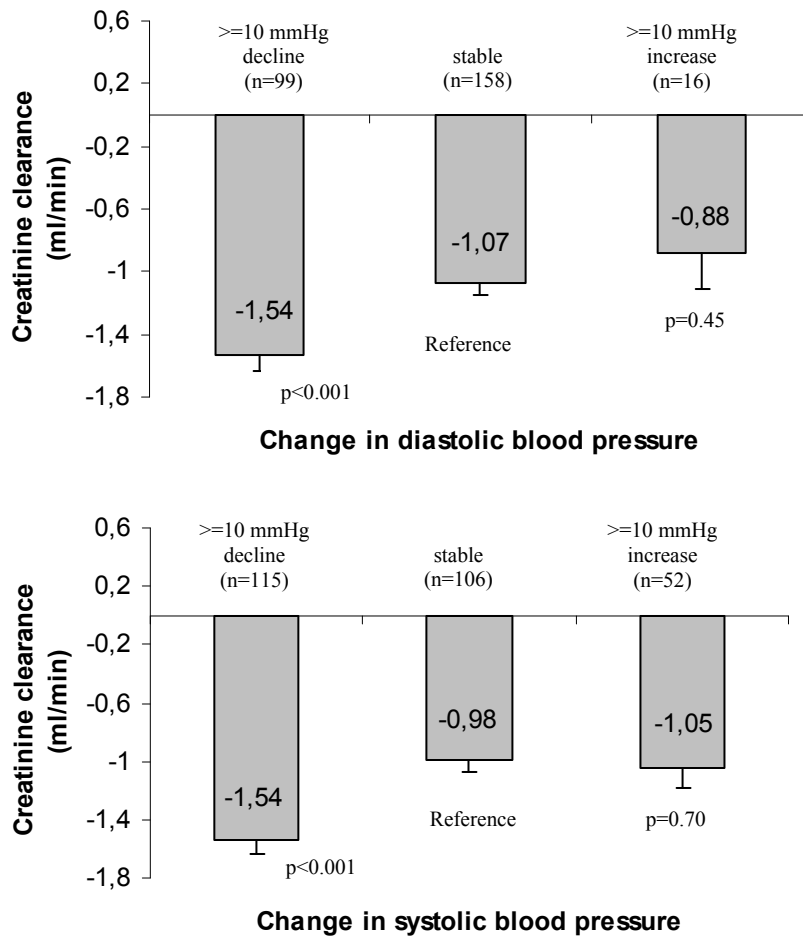


Figure 3: Annual decline of creatinine clearance in 273 survivors up to 90 year depending on a decline, stable or increase in systolic and diastolic blood pressure in-between age 85 to age 90. Analyses with linear mixed model with estimates plus standard errors of the mean. Adjusted for gender and use of antihypertensive medication at age 85 and 86. P-values reflecting the differences in additional annual decline compared to the reference category.

Discussion

In our prospective, population based study of the oldest individuals, we found no association between high systolic blood pressure and decline of creatinine clearance during follow-up. Strikingly, a diastolic blood pressure below 70 mmHg preceded an accelerated decline of creatinine clearance during follow-up. Moreover, a decline in systolic and diastolic blood pressure from ages 85 up to 90 was related to an accelerated decline of creatinine clearance.

In younger age groups, the deleterious effect of elevated diastolic and systolic blood pressure on renal function is beyond doubt [13]. Up to an average age of 72 year, harmful effects of systolic blood pressure on renal function has been reported [14]. Intervention trials have shown that blood pressure lowering prevents renal failure, independently of renal function at baseline [15]. Therefore, it is surprising that we could not find an association between elevated blood pressure (diastolic and systolic) and creatinine clearance in our elderly participants. To date, only one published longitudinal study with a considerable amount of very old participants has shown that high blood pressure was associated with a decline of creatinine clearance [7]. However, renal function was estimated with two measurements of serum creatinine three years apart. In older people, serum creatinine is less reliable as an estimate for renal function due to progressive loss of muscle mass [1,16]. In addition, only 60% of the participants who attended the first examination were reexamined after three years, possibly inducing selection bias. We did find an annual decline of renal function of 1.3 ml/min/year and also gender differences in creatinine clearances, both in line with the literature [17-20]. In addition, a strong association with cardiovascular disease and creatinine clearance existed at baseline and during follow-up [21]. Therefore, we do think that our data are reliable and representative for the oldest individuals.

How can we explain the effect of a low diastolic blood pressure on creatinine clearance over time and the accelerated decline in creatinine clearance that is associated with a decline in blood pressure? Possibly, a low diastolic blood pressure in the ninth decade is a reflection of a decline in blood pressure in the years before. The underlying mechanism of the accelerated decline of creatinine clearance might be chronic hypoperfusion of the kidneys. The vulnerability of the

kidney in the elderly could be related due to an impaired autoregulatory response of the renal arteries in the presence of atherosclerosis.

Different from in middle age, high blood pressure in elderly has been associated with an increased, equal, or even decreased mortality [22-24]. Within our prospective cohort study, high blood pressure was not related to an increased mortality risk after age 85 years [25]. In addition, it is not established whether hypertension should be treated in the very old. A meta-analysis of treated participants of 80 years and older included in hypertension trials had inconsistent results [5]. A placebo-controlled trial for treatment of hypertension in people above 80 year is still running [26]. The pilot study did not show a survival benefit for treatment; even worse, a non-significant trend towards excess mortality was found in the treated group [4]. However, some beneficial effect was seen on the reduction of strokes. Given these considerations, our finding that an elevated blood pressure is not a risk factor for decline of renal function in the oldest old is of interest.

Because our data are from a prospective population-based study with a high response rate and virtually no dropouts during follow-up, we were able to observe the impact of blood pressure on renal function of the oldest individuals in the population at large. Another strength is that we measured blood pressure twice and assessed the creatinine clearance yearly for a period of 5 years. Although the estimation of creatinine clearance with the Cockcroft-Gault formula is not the gold standard to measure renal function, this is a very widely used and validated method for estimation of the creatinine clearance [11,16,17,19]. Because we did not have reliable data on clinical heart failure, this might have influenced our results. The linear mixed model that was used is an accurate model that can handle at random missing data. Participants who die probably will not die at random. However, our results remained similar in the additional analyses without the participants who died within the first year and also in the restricted analyses for survivors up to age 90 years. These additional analyses show that our results are unlikely to be influenced by underlying survivor bias.

In contrast with younger age groups, elevated systolic and diastolic blood pressure did not influence the annual decline in renal function in the oldest individuals. A diastolic blood pressure lower than 70 mmHg and a decline in systolic or diastolic

blood pressure between ages 85 and 90 was related to an accelerated decline of creatinine clearance over time. Clinical implications of these findings have to be studied more in depth.

References

- 1 Epstein M. Aging and the kidney. *J Am Soc Nephrol* 7:1106-22, 1996
- 2 Klag MJ, Whelton PK, Randall BL, et al. Blood pressure and end-stage renal disease in men. *N Engl J Med* 334:13-8, 1996
- 3 Franklin SS, Gustin WBS, Wong ND, et al. Hemodynamic patterns of age-related changes in blood pressure. The Framingham-heart study. *Circulation* 96:308-15, 1997
- 4 Bulpitt CJ, Beckett NS, Cooke J, et al. Results of the pilot study for the hypertension in the very elderly trial. *J Hypertens* 21:2409-17, 2003
- 5 Gueyffier F, Bulpitt C, Boissel JP, et. al. Antihypertensive drugs in very old people: a subgroup meta-analysis of randomised controlled trials. *Lancet* 353:793-6. 1999
- 6 Lindeman RD, Tobin JD, Shock NW. Association between blood pressure and the rate of decline in renal function with age. *Kidney International* 26:861-8, 1984
- 7 Ishida K, Ishida H, Narita M, et al. Factors affecting renal function in 119,985 adults over three years. *Q J Med* 94:541-50, 2001
- 8 Voyaki SM, Staessen JA, Thijs L, et al. Follow-up of renal function in treated and untreated older patients with isolated systolic hypertension. *J Hypertens* 19:511-9, 2001
- 9 Bootsma-van der Wiel A, van Exel E, de Craen AJ, et al. A high response is not essential to prevent selection bias. Results from the Leiden 85-Plus Study. *J Clin Epidemiol* 55:1119-25, 2002
- 10 Exel E, Gussekloo J, Houx P, et al. Atherosclerosis and cognitive impairment are linked in the elderly. The leiden 85-plus Study. *Atherosclerosis* 165:353-9, 2002
- 11 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 16:31-41, 1976
- 12 Macfarlane PW, Latif S. Automated serial electrocardiogram comparison based on the Minnesota code. *J Electrocardiol* 29 suppl:29-34, 1996
- 13 Hsu C, McCulloch CE, Darbinian J, Go AS, Iribarren C. Elevated blood pressure and risk of end-stage renal disease in subjects without baseline kidney disease. *Arch Int Med* 165:923-928, 2005
- 14 Young JH, Klag M, Muntner P, Whyte JL, Pahor M, Coresh J. Blood pressure and decline in kidney function: Findings from the systolic hypertension in the elderly program (SHEP). *J Am Soc Nephrol* 13:2776-82, 2002

- 15 Maschio G, Alberti D, Janin G, et al. Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. *N Engl J Med* 334:939-45, 1996
- 16 Friedman JR, Norman DC, Yoshikawa TT. Correlation of estimated renal function parameters versus 24-hour creatinine clearance in ambulatory elderly. *J Am Geriatr Soc* 37:145-9, 1989
- 17 Coresh J, Brad CA, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third national health and nutrition examination survey. *Am J Kidney Dis* 41:1-12, 2003
- 18 Lindeman RD, Tobin J, Shock NW. Longitudinal studies on the rate of decline in renal function with age. *J Am Geriatr Soc* 33:278-85, 1985
- 19 Fehrman-Ekholm I, Skeppholm L. Renal function in the elderly (>70 years old) measured by means of iohexol clearance, serum creatinine, serum urea and estimated clearance. *Scand J Urol Nephrol* 38:73-7, 2004
- 20 Vidt DG. Renal disease and renal artery stenosis in the elderly. *Am J Hypertens* 11:46S-51S, 1998
- 21 Salive ME, Jone CA, Guralnik JM, Agodoa LY, Pahor M, Wallace RB. Serum creatinine levels in older adults: relationship with health status and medications. *Age and Ageing* 24:142-50, 1996
- 22 Boshuizen HC, Izaks GJ, Van Buuren S, Ligthart GJ. Blood pressure and mortality in elderly people aged 85 and older. *BMJ* 316:1780-4, 1998
- 23 Lernfelt B, Svanborg A. Change in blood pressure in the age interval 70-90. Late blood pressure peak related to longer survival. *Blood Pressure* 11:206-12, 2002
- 24 Staessen JA, Gasowski J, Wang JG, et al. Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. *Lancet* 355:865-72, 2000
- 25 Bommel T, Gussekloo J, Westendorp RGJ, Blauw GJ. In a population-based prospective study, no association between high blood pressure and mortality after age 85 years. *J Hypertension* 24:287-292, 2006
- 26 Bulpitt CJ, Fletcher AE, Amery A, et al. Hypertension in the very elderly trial (HYVET) protocol for the main trial. *Drugs Aging* 18:151-64, 2001

CHAPTER 4

The Effect of Age on the Association Between Blood Pressure and Cognitive Function Later in Life

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Abstract

Objectives:

To determine the prospective relationship between blood pressure (BP) and cognitive function across a wide age range.

Design:

Prospective population-based cohort study.

Setting:

The Rotterdam Study and the Leiden 85-plus Study.

Participants:

Three thousand seventy-eight men and women, initial age 55 to 84 from the Rotterdam Study and 276 men and women, initial age 85, from the Leiden 85-plus Study.

Measurements:

Systolic BP (SBP) and diastolic BP (DBP) were measured at baseline, cognitive function was assessed at the end of follow-up using a dedicated neuropsychological test battery. The association between baseline BP levels and cognitive function later in life was assessed in 10-year age groups in the Rotterdam Study and in 85-year-olds of the Leiden 85-plus Study.

Results:

In the youngest participants (<65), SBP and DBP were not associated with cognitive function 11 years later. For persons aged 65 to 74, higher baseline SBP and DBP were related to worse cognitive function 11 years later. In contrast, in older age (≥ 75), higher SBP and DBP seemed to be related to better cognitive function at the end of follow-up. This effect appeared strongest in the highest age group (85 years).

Conclusion:

High BP was associated with greater risk of cognitive impairment in persons younger than 75 but with better cognitive function in older persons. Age-specific guidelines for BP management are needed, because the current directive that “lower is better” may not apply to BP levels in the very old.

Introduction

Data on the relationship between BP and cognitive function are not consistent, notwithstanding a large number of studies that have investigated the relationship. [1] Most studies report that higher BP levels at middle age relate to cognitive impairment later in life,[2–5] but results on the relationship between higher BP in older age and later cognitive function are conflicting. Some studies have shown a negative effect of higher BP on cognitive function,[6,7] whereas others have not. [8,9] These findings may suggest that age influences the relationship between BP and cognitive function. If this suggestion is correct, it might have consequences for BP management, especially in very old people. Earlier evidence of beneficial effects of BP lowering on cognitive function in older people[10] could not be replicated in recent studies,[11] despite the fact that stroke risk was significantly lower in those studies. Therefore, the effect of age on the relationship between baseline BP and cognitive function later in life was examined over a wide range of age groups in two prospective population-based studies (the Rotterdam Study and the Leiden 85-plus Study). It was hypothesized that the relationship between BP and cognitive function changes with age. Whereas high BP is a risk factor for cognitive impairment at middle age, it might have beneficial effects in old age.

Methods

Populations

The Rotterdam Study is a large, prospective, population-based cohort study conducted in all inhabitants aged 55 and older of Ommoord, a district of Rotterdam, The Netherlands.[12] The medical ethics committee of the Erasmus University of Rotterdam approved the study, and informed consent was obtained from all participants. Of 10,275 eligible subjects, 7,983 (77.7%) participated in the baseline examinations between 1990 and 1993 (mean age 71.2 ± 25.2 , range 55–106). All participants were interviewed at home and visited the research center for further examinations. At the fourth survey (2002–2004), cognitive function was extensively assessed using a dedicated neuropsychological test battery.

The Leiden 85-plus Study is a prospective population-based cohort study of 85-year-old inhabitants of Leiden, The Netherlands. The medical ethics committee of the Leiden University Medical Centre approved the study, and informed consent was obtained from all participants. Between September 1997 and September 1999, all 705 inhabitants of Leiden born between 1912 and 1914 were contacted within a month after their 85th birthday; 599 (85.07%) agreed to participate. From age 85 to 90, annual neuropsychological tests were performed during home visits.

Study Sample

In the Rotterdam Study, the sample for this study was restricted to the 6,502 participants aged 55 to 85 with BP measurements at baseline because of the limited number of participants aged 85 and older with follow-up examinations 11 years later ($n=4$). Of these 6,502 participants, 3,424 (52.7%) did not participate in the fourth survey; 63.7% had died, 29.4% refused the in-person examination or were too ill to visit the research center, and 6.9% could not be contacted. The proportion of participants who did not participate in the fourth survey increased with age, from 30.9% for age 55 to 64 to 54.4% for age 65 to 74 to 87.8% for age 75 to 84. The study sample therefore consisted of 3,078 participants with baseline BP measurements and cognitive measurements 11 years later.

In the Leiden 85-plus Study, BP was measured in 572 participants at age 85; 276 of these underwent neuropsychological testing 5 years later at age 90. Of the remaining 296 individuals (51.7%) who did not participate at age 90, 87.5% had died, and 12.5% refused to participate.

Blood Pressure

In both study samples, systolic BP (SBP) and diastolic BP (DBP) were measured twice at baseline using a sphygmomanometer after 5 minutes of seated rest. The averages of two measurements were used in the analyses. In the Rotterdam Study, the two measurements were separated by a count of the pulse rate. In the Leiden 85-plus Study the two measurements were 2 weeks apart.

Cognitive Function

Global cognitive function was measured in both cohorts using the Mini-Mental State Examination (MMSE; range 0–30, lower scores indicating worse cognitive

function).[13] Only a serial 7s question was used, not the WORLD-backward version. In addition, a dedicated neuropsychological test battery was used to assess executive function and memory. Executive function was assessed using the abbreviated Stroop Test part 3[14] and the Letter Digit Substitution Task (LDST) [15] in both cohorts and the Word Fluency Test (WFT)[16] in the Rotterdam Study only. Memory was assessed using the 15-Word Learning Test (15-WLT) immediate and delayed recall[17] in the Rotterdam Study and the 12-Picture Learning Test (12-PLT) immediate and delayed recall[18] in the Leiden 85-plus Study. Dutch-translated and -validated versions were used for all neuropsychological tests. MMSE score was used as a measure of global cognitive function. In the Leiden 85-plus Study, executive function and memory were not assessed in participants with a MMSE score of 18 points or lower (n=74) because it was assumed that the tests lack reliability and validity in subjects with severe cognitive impairment. These participants were assigned to the lowest quartile of the distribution to reflect their impaired state of cognitive function.

Additional Measurements

In both study populations, education was measured at baseline and dichotomized into primary education or less versus more than primary education. Antihypertensive drug use was determined at baseline during the home interview (Rotterdam Study) or through pharmacy records (Leiden 85-plus). Smoking status, alcohol intake, history of stroke, history of diabetes mellitus, and history of cardiovascular disease were assessed at baseline.

Statistical Analysis

The association between baseline BP and cognitive function later in life was examined using linear regression models, with BP as independent and cognitive test score as dependent variable. All analyses were adjusted for age (Rotterdam Study only), sex, and education level. Additional adjustments were made for the use of antihypertensive drugs, smoking status, alcohol intake, history of stroke, history of diabetes mellitus, and history of cardiovascular disease. Analyses were conducted using the SPSS statistical package (release 11.1; SPSS, Inc., Chicago, IL).

Results

Table 1 shows the baseline characteristics of participants who did and did not undergo cognitive testing at the follow-up examination for both cohorts. In both studies, the percentage of women was higher, and their proportion increased with age. The level of education was lower in older age (in those who originated from earlier birth cohorts). Average SBP increased and DBP decreased with age, although DBP was highest in the oldest old. The percentage of participants with a history of stroke, diabetes mellitus, or cardiovascular disease increased with age, as did the use of antihypertensive treatment.

In the Rotterdam Study, participants without cognitive assessment at follow-up were older and less educated and had higher SBP and DBP and worse cognitive function at baseline than the participants included in the analyses. This was seen similarly for all age groups from age 55 to 85. In the oldest old (Leiden 85-plus Study), participants who did not undergo cognitive testing at the follow-up examination had lower SBP and DBP and concurrent worse cognitive function at baseline than the participants included in the analyses. In both samples, participants who were not included in the analyses more often had a history of stroke, diabetes mellitus, or cardiovascular disease than participants in the study samples.

Figure 1 shows the effect of age on the association between baseline BP and cognitive function later in life. Individuals up to 65 years of age showed in general little decline in cognitive function over the 11-year follow-up period, and neither baseline SBP nor DBP was related to cognitive function 11 years later. In individuals aged 65 to 74, higher SBP and DBP at baseline were related to worse cognitive function 11 years later. With older baseline age, the effect of BP on cognitive function seemed to invert; in individuals aged 75 and older, higher SBP and DBP at baseline were related to better cognitive function 11 years later, although in the Rotterdam Study, the number of people in this age group was small, and consequently results were not significant for the majority of tests. This effect was even stronger in the highest age group (85 years, subjects from the Leiden 85-plus Study), with higher SBP and DBP related to better cognitive function 5 years later. The shift from risk to benefit of high BP from age 65 to 85 years was observed for all neuropsychological tests (Figure 1).

Table 1. Baseline Characteristics of Study Samples and Participants without Follow-up Examination

Characteristic	Rotterdam Study										Leiden 85-plus Study	
	Total sample		Age groups				75-84 yrs		85 years		Study Sample	No follow-up
	Study Sample	No follow-up	55-64 yrs	65-74 yrs	75-84 yrs	75-84 yrs	Study Sample	No follow-up	Study Sample	No follow-up		
Number	3078	3424	1772	791	1126	1341	180	1292	276	296		
Age, mean ± SD	64.5 ± 6.0	71.6 ± 7.8	60.2 ± 2.8	60.7 ± 2.8	69.1 ± 2.7	70.3 ± 2.8	77.8 ± 2.3	79.6 ± 2.8	85	85		
Female, %	59.1	58.3	58.4	54.9	58.8	54.4	67.8	64.4	72.1	61.8		
Low level of education, %	27.9	44.1	23.8	32.9	31.6	40.4	44.9	55.3	62.0	68.3		
Use of antihypertensive drugs, %	23.9	37.1	20.2	25.9	27.4	37.4	39.1	43.6	36.2	35.8		
SBP, mmHg, mean ± SD	135 ± 20	143 ± 23	131 ± 20	135 ± 21	139 ± 20	144 ± 22	140 ± 19	147 ± 24	158 ± 18	153 ± 19		
DBP, mmHg, mean ± SD	74 ± 11	74 ± 12	74 ± 11	76 ± 11	73 ± 11	74 ± 12	71 ± 11	72 ± 13	78 ± 9	75 ± 10		
MMSE-score, mean ± SD	28.1 ± 1.5	26.9 ± 2.9	28.2 ± 1.4	27.7 ± 2.1	28.0 ± 1.5	27.4 ± 2.2	27.7 ± 1.6	26.0 ± 3.7	25.7 ± 4.3	22.4 ± 7.2		
Ever smoking, %	67	66	69	78	65	70	50	54	43	52		
Alcohol intake, U/day ± SD	1.3 ± 1.8	1.3 ± 2.0	1.4 ± 1.9	1.5 ± 2.2	1.3 ± 1.8	1.3 ± 2.0	0.8 ± 1.2	0.9 ± 1.6	0.8 ± 0.8	1.0 ± 0.9		
History of stroke, %	1	4	1	2	1	4	3	7	7	13		
History of diabetes mellitus, %	6	14	5	7	7	15	10	17	13	19		
History of cardiovascular disease, %	18	40	15	25	21	36	25	52	56	68		

SBP = systolic blood pressure; DBP = diastolic blood pressure; MMSE = Mini-Mental State Examination
SD = standard deviation

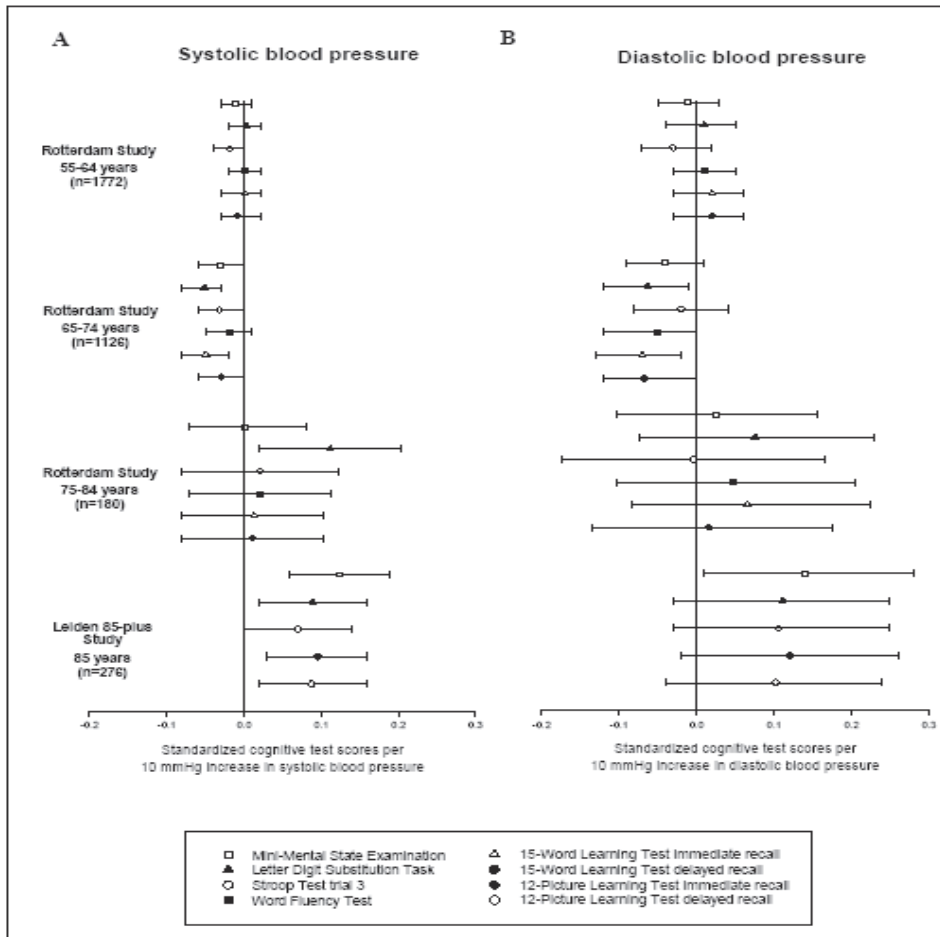


Figure 1. The effect of age on the association of baseline blood pressure and cognitive function later in life. Symbols represent the mean standardized cognitive test scores and 95% confidence intervals per 10 mmHg increase in systolic (A) and diastolic (B) blood pressure. For graphical reasons, the estimates for the Stroop test were inverted because a higher Stroop score reflects worse cognitive function. Analyses were adjusted for age (Rotterdam Study only), sex and level of education.

Additional adjustments for the use of antihypertensive drugs, smoking status, alcohol intake, history of stroke, history of diabetes mellitus, or history of cardiovascular disease did not markedly change any of these results (data not shown).

Discussion

These data show that age has an important effect on the relationship between BP and cognitive function later in life. In participants younger than 75, higher SBP and DBP were associated with worse cognitive function 11 years later. This relationship reversed in older participants, in whom higher SBP and DBP at baseline were associated with better cognitive function later in life.

The detrimental effect of higher BP levels on cognitive performance in middle-aged people is well established,[2–5] and the results from the analyses in the 65- to 74-year age group in the Rotterdam Study sample were consistent with these previous findings. The mechanisms behind this association may involve atherosclerotic changes in large and hyaline degeneration in small cerebral vessels, ischemic brain lesions, and disturbances in endothelial or brain cell permeability,[1–5] although in the oldest-old participants in the Rotterdam Study, high BP at baseline was related to better cognitive function later in life, and when the analyses were replicated in the 85-year-old participants of the Leiden 85-plus Study sample, similar results were found.

In the current study, participants with low BP and good cognitive function at baseline were more likely to be included in the study sample than participants with higher BP and worse cognitive function at baseline. One might expect that this selective attrition could have influenced the results, especially in the oldest age group of the Rotterdam Study, in which a large proportion (87.8%) of the participants who were present at baseline were not available at follow-up. Although selective attrition may have attributed to the formation of a selective group of survivors in the oldest age group of the Rotterdam Study, this does not necessarily diminish the importance of the findings that, in this group of individuals, high BP was related to better cognitive function later in life.

The results on the relationship between BP and cognitive function from the Leiden 85-plus Study, with data available on the oldest old (aged 85 years), confirmed those from the Rotterdam Study. Although the proportion of participants in the Leiden 85-plus sample who were not available at follow-up was also considerable (51.72%), these participants had predominantly lower BP levels and worse cognitive function than those included in the analyses. This concurs with previous findings that high BP is not a risk factor for mortality in the oldest old.[19,20]

Although the observations cannot be interpreted that BP management should be changed in old individuals, they underscore the need for further elucidation of risks and benefits of BP lowering therapy in the oldest old.

The previous studies that associated higher BP in middle-age with worse cognitive function later in life[2–5] suggested that antihypertensive treatment might prevent or delay the onset of impaired cognitive function, but data from randomized clinical trials on the beneficial effects of antihypertensive treatment on cognitive function are not consistent.[7,10,21–23] From these earlier studies, only the Syst-Eur trial,[10] which studied the effect of treatment with nitrendipine with the possible addition of enalapril and hydrochlorothiazide on incidence of dementia, showed benefit that could not be replicated in the Hypertension in the Very Elderly Trial (HYVET).[11] This large, double-blind, placebo-controlled trial included 3,336 participants aged 80 and older and showed that antihypertensive treatment with indapamide with the option of perindopril did not reduce incidence of dementia.[11] Although the short follow-up, owing to the early termination of the trial, could have affected this result, the alternative explanation is that there is no clear benefit in correspondence with the observational data presented here. Alternatively, the use of the relatively insensitive Mini-Mental State Examination as an outcome measure for cognitive impairment or decline could also have contributed to the inconsistent findings in clinical trials. Another explanation is that the oldest old in whom impaired cognitive function is most prevalent were underrepresented in these studies.

It is tempting to speculate why BP lowering is consistently associated with a lower risk of stroke, whereas this benefit is not reflected in consistent preservation of cognitive function. Although counterintuitive, the aggregated data from the observational and experimental studies suggest that, in the oldest old, higher BP may have also have a benefit with respect to cognitive function, possibly through

the necessity of maintaining adequate cerebral perfusion.[24–26] Local regulation of cerebral blood flow tightly regulates cerebral perfusion over a wide range of BP.[27] A combination of myogenic and neurogenic mechanisms mediates this autoregulation of cerebral blood flow.[28] With older age, basal cerebral blood flow decreases, possibly caused by impaired cerebral autoregulation through atherosclerosis or endothelial dysfunction.[29,30] In the oldest old, higher BP may therefore be required to prevent cerebral hypoperfusion and preserve cognitive function. Individuals with greater risk of morbidity and mortality are present in the population-based prospective studies but are less likely to be included in randomized clinical trials. Participants of the HYVET[11] who were randomized to placebo had a mortality risk less than half that of the general population, indicating the recruitment of relative healthy people into the trial.

The current study had several strengths. Data on BP and cognitive function were available from two independent Dutch prospective population-based studies. These two cohorts are complementary and allowed the association between BP level and cognitive function from age 55 onward to be examined. The dedicated neuropsychological test batteries that were used in both studies were comparable and assessed several cognitive domains, including global cognitive function, executive function, and memory. Some of the participants in the oldest age group (Leiden 85-plus Study) could not undergo all the cognitive tests that were available because of their severely impaired cognitive status (MMSE score \leq 18). Rather than excluding these persons from the analyses, the information on the cognitive status of these participants that was available (MMSE score) was used to infer their scores on the other cognitive tests.

There were also some limitations. The associations between BP and cognitive function were based on the assessment of BP at baseline and the measurement of cognitive function 11 years (Rotterdam Study) or 5 years (Leiden 85-plus Study) later. The difference in follow-up length between the two study samples warrants some caution in the comparison and interpretation of the results, because the Rotterdam Study results are based on 11 years of follow-up, compared with 5 years of follow-up in the Leiden 85-plus Study. Despite the long follow-up periods, extension of these periods may have revealed even stronger associations between baseline BP and cognitive function later in life, because the effect of BP on cognitive function is thought to be long-term.[1] This may especially play a role up to the age of 65, for which the follow-up period may just have been too short.

However, a longer follow-up, especially in older age, would also lead to further dropout of participants and consequently to limited statistical power, as well as the potential of survival bias.

In conclusion, this study shows that the relationship between baseline BP levels and cognitive function later in life differs across age groups. Although there is not a clear age cut-off at which the relationship between BP and cognitive function later in life inverts, there seems to be a gradual shift with age from high BP being a risk factor for cognitive impairment to high BP potentially helping to preserve cognitive function in the oldest old, presumably through maintaining perfusion pressure. The data illustrate that it should not simply be assumed that advice to 65-year-olds on target BP should be the same as advice to 85-year-olds and underscore the need for further elucidation of risks and benefits of BP lowering therapy in the oldest old.

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Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

References

1. Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. *Lancet Neurol* 2005;4(8):487-499.
2. Singh-Manoux A, Marmot M. High blood pressure was associated with cognitive function in middle-age in the Whitehall II study. *J Clin Epidemiol* 2005;58(12):1308-1315.
3. Elias MF, Wolf PA, D'Agostino RB et al. Untreated blood pressure level is inversely related to cognitive functioning: the Framingham Study. *Am J Epidemiol* 1993;138(6):353-364.
4. Kilander L, Nyman H, Boberg M et al. Hypertension is related to cognitive impairment: a 20-year follow-up of 999 men. *Hypertension* 1998;31(3):780-786.
5. Launer LJ, Masaki K, Petrovitch H et al. The association between midlife blood pressure levels and late-life cognitive function. The Honolulu-Asia Aging Study. *JAMA* 1995;274(23):1846-1851.
6. Waldstein SR, Giggey PP, Thayer JF et al. Nonlinear relations of blood pressure to cognitive function: the Baltimore Longitudinal Study of Aging. *Hypertension* 2005;45(3):374-379.
7. Tzourio C, Anderson C, Chapman N, et al. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. *Arch Intern Med* 2003;163(9):1069-1075.
8. Herbert LE, Scherr PA, Bennett DA, et al. Blood pressure and late-life cognitive function change: a biracial longitudinal population study. *Neurology* 2004;62:2021-2024.
9. Tervo S, Kivipelto M, Hänninen T, et al. Incidence and risk factors for mild cognitive impairment: a population-based three-year follow-up study of cognitive healthy subjects. *Dement Geriatr Cogn Disord* 2004;17:196-203.
10. Forette F, Seux ML, Staessen JA, et al. Prevention of dementia in randomized double-blind placebo-controlled systolic hypertension in Europe (Syst-Eur) trial. *Lancet* 1998;352:1347-1351.
11. Peters R, Beckett N, Forette F, et al. Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. *Lancet Neurol* 2008;7(8):683-689.
12. Hofman A, Breteler MMB, van Duijn CM, et al. The Rotterdam Study: objectives and design update. *Eur J Epidemiol* 2007;22:819-829.
13. Folstein MF, Folstein SE, McHugh PR. «Mini-mental state». A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*

- 1975;12(3):189-198.
14. Golden CJ. Identification of brain disorders by the stroop color and word test. *J Clin Psychol* 1976; 32:654-658.
 15. Lezak MD, Howieson DB, Loring DW. *Neuropsychological assessment*, 4th ed. New York, NY:Oxford University Press, 2004.
 16. Welsh KA, Butters N, Mohs RC, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part V. A normative study of the neuropsychological battery. *Neurology* 1994;44(4):609-614.
 17. Brand N, Jolles J. Learning and retrieval rate of words presented auditorily and visually. *J Gen Psychol* 1985;112(2):201-210.
 18. Houx PJ, Shepherd J, Blauw GJ, et al. Testing cognitive function in elderly populations: the PROSPER study. PROspective Study of Pravastatin in the Elderly at Risk. *J Neurol Neurosurg Psychiatry* 2002;73:385-389.
 19. Mattila K, Haavisto M, Rajala S et al. Blood pressure and five year survival in the very old. *BMJ* 1988;296:887-889.
 20. van Bommel T, Gussekloo J, Westendorp RGJ et al. In a population-based prospective study, no association between high blood pressure and mortality after age 85 years. *J Hypertens* 2006;24:287-292.
 21. SHEP Cooperative Research group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. *JAMA* 1991;265(24):3255-3264.
 22. Lithell H, Hansson L, Skoog I, et al. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. *J Hypertens* 2003;21(5):875-886.
 23. Prince MJ, Bird AS, Blizard RA, et al. Is the cognitive function of older patients affected by antihypertensive treatment? Results from 54 months of the Medical Research Council's trial of hypertension in older adults. *BMJ* 1996;312(7034):801-805.
 24. Ruitenberg A, Skoog I, Ott A, et al. Blood pressure and risk of dementia: results from the Rotterdam study and the Gothenburg H-70 Study. *Dement Geriatr Cogn Disord* 2001;12(1):33-39.
 25. Ruitenberg A, den Heijer T, Bakker SL, et al. Cerebral hypoperfusion and clinical onset of dementia: the Rotterdam Study. *Ann Neurol* 2005;57(6):789-794.
 26. Spilt A, Weverling-Rijnsburger AWE, Middelkoop HAM, et al. Late-onset dementia: structural brain damage and total cerebral blood flow. *Radiology* 2005;236:990-995.

27. Paulson OB, Strandgaard S, Edvinsson L. Cerebral autoregulation after age 85 years. *Cerebrovasc Brain Metab Rev* 1990;2:161-192. *Journal of Hypertension* 2006;24:287-292.
28. van Mook WNKA, Rennenberg RJMW, Schurink GW, et al. Cerebral hyperperfusion syndrome. *Lancet Neurology* 2005;4:877-878.
29. Buijs PC, Krabbe-Hartkamp MJ, Bakker CJ, et al. Effect of age on cerebral blood flow: measurement with ungated two-dimensional phase-contrast MR angiography in 250 adults. *Radiology* 1998;209:667-674.
30. Kamper AM, Spilt A, de Craen AJM et al. Basal cerebral blood flow is dependent on the nitric oxide pathway in elderly but not in young healthy men. *Exp Geront* 2004;39:1245-1248.

SECOND PART

Etiology

CHAPTER 5

Low blood pressure in the very old, a consequence of imminent heart failure.

The Leiden 85-plus Study

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Abstract

Low blood pressure in the very old has been associated with organ dysfunction and excess mortality but the underlying mechanism has yet to be elucidated. We hypothesized that cardiac dysfunction contributes to low blood pressure in the very old. We invited a convenience sample consisting of 82 participants all aged 90 years from a population based cohort study in the very old. Blood pressure was measured twice and all but one underwent echocardiography to assess cardiac dimensions and functional cardiac parameters. Some 47 participants were free from hemodynamically significant valvular disease and were included in the present analyses. There were low values for mean cardiac output (2.04 l/min/m², SE 0.40) and mean stroke volume (31.4 ml/m², SE 7.7). For every 10-mmHg decrease in systolic blood pressure, cardiac output was 0.09 L/min/m² lower (SE 0.04, p=0.019) and stroke volume was 1.58 ml/m² lower (SE 0.68, p=0.024). Mean left ventricular ejection fraction was normal and 2.39% (SE 1.16, p=0.046) higher for each 10-mmHg decrease in systolic blood pressure. Mean left ventricular dimensions were normal but the E/A ratio was reduced (0.68, SD 0.21), indicating diastolic dysfunction. In conclusion, among the oldest old, low systolic blood pressure correlates with low cardiac output. Systolic ventricular function is not impaired.

Introduction

There is a wide range of observational data on the relation between blood pressure and mortality in the very elderly but the outcomes are not unanimous. [1-6]. Some of the studies have shown the expected correlation between high blood pressure and increased mortality risk [6]. Some, however, did not find these associations [2-4]. Moreover, others reported the mortality risk to be higher in those with a relatively low blood pressure [1,5, 7]. In line with these unexpected findings we have recently shown low blood pressure to be associated with organ failure, for example loss of renal function [8].

In general, both diastolic and systolic blood pressure gradually increases up to middle age. From the sixth decade onwards, in most people, diastolic blood pressure tends to decrease, whereas the systolic blood pressure further increases [9]. This increase in 'pulse pressure' is generally interpreted as a consequence of arterial stiffening. At very old age, however, systolic blood pressure eventually decreases again and it is this decline in systolic blood pressure that is associated with a worse prognosis [1, 10].

If low blood pressure at very old age was a reflection of cardiac dysfunction, the increased mortality risk in those with low blood pressure would be easier to understand. To evaluate whether cardiac dysfunction may in part underlie the lower blood pressure in the very old we performed a comprehensive transthoracic echocardiographic examination in a population-based sample of older people all aged 90 years.

Material and Methods

Study population

The Leiden 85-plus Study is a prospective population-based study of all 85-year old inhabitants of Leiden, The Netherlands. The study design and characteristics of the cohort were described in detail previously [11,12]. In short, between September 1997 and September 1999 all 705 members of the 1912 to 1914-birth

cohort in the city of Leiden were asked to participate in the month after their eighty-fifth birthday. There were no selection criteria related to health or demographic characteristics. At baseline and yearly thereafter, the 85-year old participants were visited at their place of residence up to age 90 years. During these visits blood pressure was measured, a venous blood sample drawn, an electrocardiogram recorded and face-to-face interviews and performance tests conducted. At 90 years of age, participants were invited for an echocardiographic examination.

All participants in the study gave informed consent, and when people were severely cognitively impaired, a guardian provided informed consent. The Medical Ethics Commission of the Leiden University Medical Center approved the study.

Echocardiography

All patients were imaged in the left lateral decubitus position using a commercially available system (Vingmed system /Vivid Seven; General Electric-Vingmed, Milwaukee, WI, USA). Images were obtained using a 3.5-MHz transducer at a depth of 16 cm in the parasternal (standard long and short axis) and apical views (two- and four-chamber images, long-axis view). The left ventricular dimensions (end-systolic and end-diastolic diameter) were determined from parasternal M-mode acquisitions; fractional shortening and left ventricular ejection fraction were derived [13]. Left ventricular stroke volume (assessed from pulsed-wave Doppler flow through the left ventricular outflow tract times the cross-sectional area of the outflow tract) and cardiac output (stroke volume times heart rate) were calculated. Left ventricular dimensions, stroke volume and cardiac output were subsequently corrected for body surface area.

The mitral inflow (assessed by pulsed-Doppler echocardiography, with the sample placed at the tip of the mitral leaflets) was used to assess the peak velocity of the early rapid filling wave (E) and late filling wave (A); the E/A ratio was used as a marker of diastolic function. The presence and severity of mitral and aortic regurgitation were graded semi-quantitatively from colour-flow Doppler images obtained from the conventional parasternal long-axis, apical four-chamber and apical long-axis views [14-16]. To avoid the influence of significant valvular disease in the relations between echocardiographic measurements and blood pressure, participants with hemodynamically significant valvular disease were excluded from the analyses.

Blood pressure

Blood pressure was measured twice with an interval of two weeks. Blood pressure was measured, using a mercury sphygmomanometer, in seating position after at least five minutes rest without having performed vigorous exercise during the preceding 30 minutes. The systolic value was measured at the onset of phase 1, and the diastolic value was measured at the onset of phase 5 of the Korotkoff sounds. For the analysis of blood pressure we used the mean of the assessed systolic values and diastolic values.

Demographic and clinical characteristics

At baseline, a research nurse collected information concerning the demographic characteristics. The Mini-Mental State Examination (MMSE) was administered to screen for cognitive impairment [17]. Disability in basic activities of daily living (ADL) was assessed with the Groningen Activity Restriction Scale (GARS) [18]. The presence of cardiovascular disease was defined as a previous history of cerebrovascular accident, angina pectoris, myocardial infarction, peripheral vascular disease or an electrocardiogram revealing myocardial ischaemia or infarction (Minnesota codes 1-1, 1-2, 1-3, 4-1, 4-2, 4-3, 5-1, 5-2 and 5-3) [19].

Statistical analysis

The clinical characteristics were presented with the mean and standard error for normal distributed, continuous variables and with the median and interquartile ranges for not normal distributed variables. Differences between participants were tested with the two-sided independent T-test, the Mann Whitney test and Chi-square test respectively. All associations between blood pressure and echocardiographic characteristics were analysed with linear regression and adjusted for gender. All analyses were performed with software SPSS version 12.0.

Results

Study population

Our initial cohort consisted of 599 participants (87% response) at age 85 years. Some 257 participants survived up to age 90 years on 1 April 2004 and were in principle eligible for the study. The study nurse invited a convenience sample consisting of 82 participants. All but one underwent echocardiography. The clinical characteristics of the study cohort and the 176 participants who did not undergo echocardiography are shown in table 1. Participants who underwent echocardiography had better cognitive function (higher MMSE scores) and less disability (lower ADL scores). They also had a significant higher systolic blood pressure.

Table 1: Clinical characteristics of participants aged 90 years

	Echocardiographic examination		
	Yes [n=81]	No [n=176]	p value
Female subjects [%]	66.7	76.1	0.11*
MMSE (IQR) [points] †	28 (26-29)	22 (16-27)	<0.001‡
ADL (IQR) [points] §	10 (9.0-13.5)	16.0 (10-24)	<0.001‡
History of cardiovascular disease [%]	48.1	55.1	0.30*
DBP (SE) [mmHg]	72.9 (8.9)	71.1 (9.9)	0.16¶
SBP (SE) [mmHg]	154.7 (16.0)	150.0 (18.8)	0.04¶

SE, Standard Error. IQR, Inter Quartile Range. †, Mini Mental State Examination. §, Activities in Daily Living. |, Including cerebrovascular accident, angina pectoris, myocardial infarction, peripheral vascular disease or an electrocardiogram revealing myocardial ischemia or infarction at age 85. ‡, *, Independent T-test. ‡, Mann Whitney test. ¶, Chi Square test. N, number of participants. DBP, Diastolic Blood Pressure. SBP, Systolic Blood Pressure.

Cardiac parameters

Some 20 participants had hemodynamically significant valvular disease. Blood pressure, both systolic and diastolic was not different between subjects with and without hemodynamically significant valvular disease (all $p > 0.06$). As functional parameters could not be assessed unequivocally: participants with hemodynamically significant valvular disease were excluded in the present analyses. An additional 14 participants were excluded because no reliable estimation of the left ventricular outflow could be assessed (not allowing for assessment of stroke volume). Table 2 shows the echocardiography findings of the

remaining 47 participants. The cardiac index (mean 2.04 L/min/m², SE 0.40) and stroke volume index (mean 31.4 ml/m², SE 7.7) were lower than considered normal [20,21]. Moreover, a low systolic blood pressure was significantly associated with lower stroke volume index. For every 10-mmHg lower systolic blood pressure, stroke volume index was 1.58 ml/m² (SE 0.68, p=0.024) lower (Figure 1a). The mean left ventricular ejection fraction was 66.9% (SE 10.8%) and for every 10-mmHg decrease of systolic blood pressure, ejection fraction was 2.39% (SE 1.16, p=0.046) higher (Figure 1b). Similar but nonsignificant associations were observed between diastolic blood pressure and functional characteristics of the heart. For every 10-mmHg decrease in diastolic blood pressure, stroke volume index was 1.54 ml/m² (SE 1.22, p=0.21) lower whereas ejection fraction was 3.59% (SE 2.04, p=0.09) higher.

Left ventricular end-diastolic and end-systolic dimensions were within reference values [20,21]. The left ventricular end-diastolic diameter was above 2.8 cm/m² in 21 participants and four participants had a diameter beneath 2.0 cm/m². The left ventricular end-systolic diameter was above 2.1 cm/m² in five participants and beneath 1.3 cm/m² in eight participants. The left ventricular dimensions were not related with diastolic or systolic blood pressure (all p>0.14). The average E/A ratio was low (mean 0.68, SE 0.22), indicating a high prevalence of diastolic dysfunction. However, the E/A ratio was not associated with systolic/diastolic blood pressure or cardiac output (all p>0.28).

Table 2: Echocardiographic characteristics in 47 participants without hemodynamically significant valvular disease.

	Mean (SE)	Range	Reference values
Cardiac Index [L/min/m ²]	2.04 (0.40)	1.24-2.80	2.4-4.0
SV Index [ml/m ²]	31.4 (7.7)	17.4-53.0	40-70
Heart rate [beats/min]	66.4 (10.8)	46-101	
LVEF [%]	66.9 (12.8)	32-87	
LVEDD Index [cm/m ²]	2.73 (0.49)	1.86-3.86	2.0-2.8
LVESD Index [cm/m ²]	1.70 (0.42)	0.58-2.59	1.3-2.1
E/A ratio	0.68 (0.21)	0.38-1.46	

LVEF, Left Ventricular Ejection Fraction. LVEDD, Left Ventricular End Diastolic Dimension corrected for BSA (Body Surface Area). LVESD, Left Ventricular End Systolic Dimension corrected for BSA. SV, Stroke Volume. BP, Blood Pressure. SE, Standard Error.

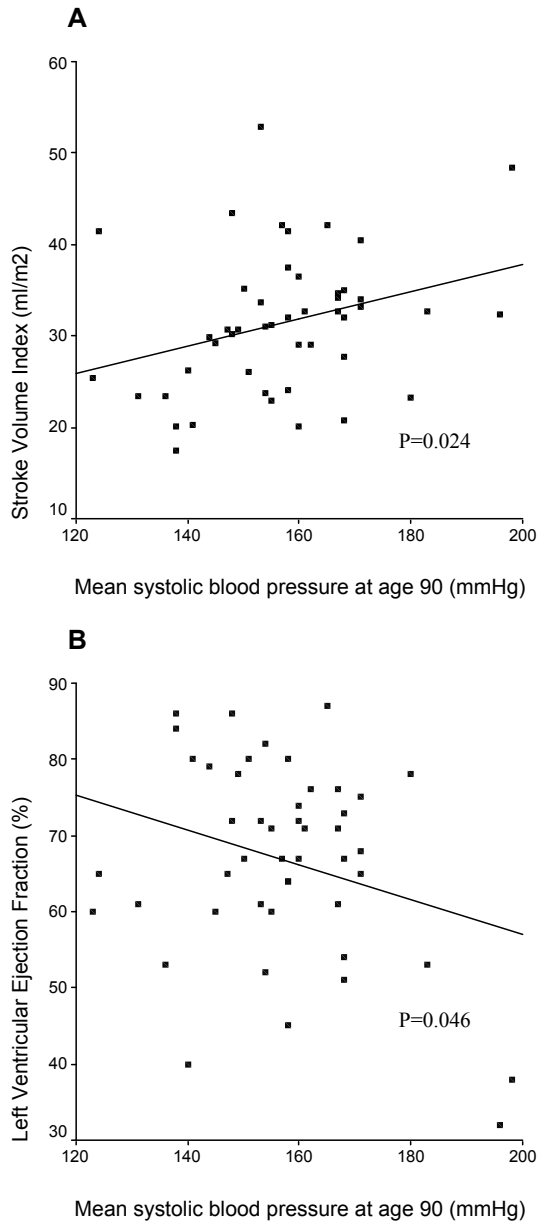


Figure 1: Cardiac performance dependent on systolic blood pressure. Analyses were done in 47 participants without hemodynamically significant valvular disease at age 90. P-values were obtained with linear regression analyses adjusted for gender.

Systemic parameters

A low systolic and diastolic blood pressure was associated with a lower cardiac index. For every 10-mmHg lower systolic blood pressure, cardiac index was 0.09 l/min/m² (SE 0.04, p=0.019) lower. For every 10-mmHg lower diastolic blood pressure, cardiac index was 0.12 l/min/m² (SE 0.06, p=0.06) lower. To study whether low blood pressure, which is associated with low stroke volume and low cardiac index, is appropriate on a systemic level, we have investigated the relation between stroke volume index and heart rate. Figure 2 displays that heart rates were significant higher in participants who had a lower stroke volume (p<0.001).

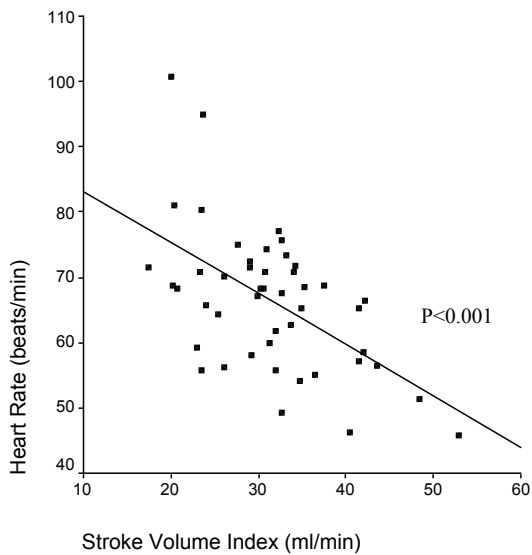


Figure 2: Systemic response to cardiac performance.

Analyses from 47 participants without hemodynamically significant valvular disease. P-values were obtained with linear regression analyses adjusted for gender.

Discussion

The main findings in our population-based study of nonagenarians consisted of fair evidence for an association between low systolic blood pressure and an impaired cardiac function. The cardiac index and the stroke volume index were on average below normal values and both were significantly and inversely related with systolic blood pressure. A low cardiac index and a low stroke volume index correlated with both, a low diastolic and a low systolic blood pressure. The left ventricular dimensions were mostly within normal values and were not related with diastolic or systolic blood pressure. Low blood pressure at very old age may thus reflect imminent heart failure, as defined by a diminished stroke volume and diminished cardiac output. It can be hypothesized that this association may, in part, underlies the association between low blood pressure and increased mortality [1,3-5].

There is only little data on routine echocardiographic examinations in very old people [22, 23]. These studies have highlighted the presence of impaired left ventricular systolic function and the prevalence of left ventricular hypertrophy among the elderly. Another study analysed cardiac parameters of all clinically performed normal echocardiography examinations among persons who are 90 years and older but did not relate outcomes with clinical signs and symptoms [24]. Only one earlier publication made a link with blood pressure and echocardiography in community dwelling elderly [25]. No association was found between left ventricular ejection fraction and decrease of systolic and diastolic blood pressure. Measurements of cardiac index and stroke volume were not reported. As left ventricular hypertrophy did predict a decrease in blood pressure, these results suggest that diastolic dysfunction is involved in the process of decline in blood pressure in older age [25].

Pathophysiological reasoning implies that low blood pressure results from either a normal or high cardiac output with concomitant low peripheral resistance or from a low cardiac output with a high peripheral resistance. We were not informed about the peripheral resistance in our participants but we found low cardiac output to be associated with lower systolic blood pressure, that is

impaired cardiac performance. The first physiological adaptation to compensate for a low stroke volume is an increase in heart rate, consequent on stimulation of the sympathetic nervous system via the baro-receptor reflex [26]. It seems unlikely that the elevated heart rate among the study participants has been consequent on autonomous sympathetic activation as under such circumstances, concomitant blood pressure would have been higher also. Therefore we reason that among the oldest old, an elevated heart rate is likely to be a systemic adaptation of cardiac dysfunction. Previously, we have reported on this same cohort that a higher heart rate on annual repeated electrocardiograms was predictive of mortality [27]. The data presented here, higher heart rates reflecting a compensatory response to impaired cardiac function, are an alternative biological explanation of our report.

In our sample the average stroke volume index and the E/A ratio were low: the findings together indicate a high prevalence of diastolic dysfunction [28], especially as significant valvular lesions were excluded. Hence, older people may have a stiff left ventricle with an impaired diastolic filling, which in turn may give a high left ventricular ejection fraction if the systolic function is not disturbed. The fact that in most people the left ventricular dimensions were within the normal range adds weight to our interpretation that systolic function is relatively intact, and left ventricular ejection fraction among very old participants may not provide a valid estimation of cardiac function. Although the E/A ratio is frequently used as an indicator of diastolic function, it is a limitation of our study that we have not assessed other measures of diastolic dysfunction.

One of the strengths of our study is the population-based character. However, the present analysis is limited due to the inclusion of relatively vital participants. The differences in general performance, cognitive performance (MMSE) and activities of daily living between the participants with versus those without an echocardiography underlined this bias towards health. Although the findings can thus not be applied to old people with ill health, one may argue that the adaptive responses as shown for those in good health, are exaggerated in those 90-year-old subjects who are less vital. The relatively small sample size prohibits us from identifying an optimal blood pressure at old age in the population at large.

Perspectives

The clinical consequences of these new unexpected echocardiographic findings have clinical significance. Physicians must be aware that a 'normal' blood pressures in the very old, for example non-hypertensive blood pressure values, does not guarantee a healthy cardiovascular state but may reflect cardiac dysfunction. Furthermore, the assessment of left ventricular ejection fraction only, to mark cardiac failure is insufficient as systolic function in old age is relatively conserved. Stroke volume index and cardiac output, together with heart rate, better identify older people at risk. Proper cardiac evaluation in those patients might open treatment modalities and hence improve prognosis.

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References

- 1 Lernfelt B, Svanborg A. Change in blood pressure in the age interval 70-90. Late blood pressure peak related to longer survival. *Blood Pressure* 2002;**11**:206-12
- 2 Boshuizen HC, Izaks GJ, Van Buuren S, Ligthart GJ. Blood pressure and mortality in elderly people aged 85 and older. *BMJ* 1998;**316**:1780-4
- 3 Rajalo S, Haavisto M, Heikinheimo R, Mattila K. Blood pressure and mortality in the very old. *Lancet* 1983; **322**:520-1
- 4 Heikinheimo RJ, Haavisto MV, Kaarela RH, Kanto AJ, Koivunen MJ, Rajala SA. Blood pressure in the very old. *J Hypertens* 1990;**8**:361-7
- 5 Bommel T, Gussekloo J, Westendorp RGJ, Blauw GJ. In a population-based prospective study no association between high blood pressure and mortality after age 85 years. *J Hypertens* 2006;**24**:287-292
- 6 Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;**360**:1903-13
- 7 Messerli FH, Mancia G, Conti CR, Hawkins AC, Kupfer S, Champion A, et al. Dogma deputed: Can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? *Ann Intern Med* 2006;**144**:884-893
- 8 T van Bommel, K Woittiez, GJ Blauw, F van der Sman-de Beer, FW Dekker, RGJ Westendorp, et al. Prospective study of the effect of blood pressure on renal function in old age: The Leiden 85-plus Study. *J Am Soc Nephrol* 2006; **17**:2561-2566
- 9 Franklin SS, Gustin IV W, Wong ND, Larson MG, Weber MA, Kannel WB, et al. Hemodynamic patterns of age-related changes in blood pressure. The Framingham heart study. *Circulation* 1997;**96**:308-15
- 10 Satish S, Zhang DD, Goodwin JS. Clinical significance of falling blood pressure among older adults. *J Clin Epidemiol* 2001;**54**:961-7
- 11 Bootsma-van der Wiel A, van Exel E, de Craen AJ, Gussekloo J, Lagaay AM, Knook DL, et al. A high response is not essential to prevent selection bias. Results from the Leiden 85-Plus Study. *Clin Epidemiol* 2002;**55**:1119-25.
- 12 Exel E, Gussekloo J, Houx P, de Craen AJ, MacFarlane PW, Bootsma-van der Wiel A, et al. Atherosclerosis and cognitive impairment are linked in the elderly. The Leiden 85-plus Study. *Atherosclerosis* 2002;**165**:353-9.
- 13 Isaaz K, Etchevenot G, Admant P, Brembilla B, Pernot C. A simplified normalized ejection phase index measured by Doppler echocardiography for the assessment of left ventricular performance. *Am J Cardiol* 1990;**65**:1246-5

- 14 Helmcke F, Nanda NC, Hsiung MC, Soto B, Adey CK, Goyal RG, et al. Colour Doppler assessment of mitral regurgitation with orthogonal planes. *Circulation* 1987;**75**:175-83
- 15 Perry GJ, Helmcke F, Nanda NC, Byard C, Soto B Evaluation of aortic insufficiency by Doppler colour flow mapping. *J Am Coll Cardiol* 1987;**9**:952-9
- 16 Weismann NJ, Tighe Jr JF, Gottdiener JS, Gwynne JT. An assessment of heart-valve abnormalities in obese patients taking dexfenfluramine, sustained-release dexfenfluramine, or placebo. Sustained-Release Dexfenfluramine Study Group. *N Engl J Med* 1998;**339**:725-32
- 17 Tombaugh TN, McIntyre NJ. The Mini-Mental State Examination: A comprehensive review. *J Am Geriatrics Soc* 1992;**40**:922-35.
- 18 Kempen GI, Miedema I, Ormel J, Molenaar W. The assessment of disability with the Groningen Activity Restriction Scale. Conceptual framework and psychometric properties. *Soc Sci Med* 1996;**43**:1601-10.
- 19 Macfarlane PW, Latif S. Automated serial electrocardiogram comparison based on the Minnesota code. *J Electrocardiol* 1996;**29**:29-34.
- 20 Feigenbaum. *Echocardiography*. Williams & Wilkins, Baltimore, Maryland, U.S.A. 1994
- 21 Marino P.L. *The ICU book*, second edition. Williams & Wilkins, Baltimore, Maryland, U.S.A. 1998
- 22 Raymond I, Pedersen F, Steensgaard-Hansen F, Green A, Busch-Sorensen M, Tuxen C, et al. Prevalence of impaired left ventricular systolic function and heart failure in a middle aged and elderly urban population segment of Copenhagen. *Heart* 2003;**89**:1422-9
- 23 Lindroos M, Kupari M, Heikkilä, Tilvis R. Echocardiographic evidence of left ventricular hypertrophy in a general aged population. *Am J Cardiol* 1994;**74**:385-90
- 24 Dokainish H, Gin K, Lee P, Jue J. Left ventricular filling patterns and pulmonary artery pressures in patients aged 90 to 100 years with normal echocardiography results. *J Am Soc Echocardiogr* 2003;**16**:664-9
- 25 Hakala SM, Tilvis RS. Determinants and significance of declining blood pressure in old age. *Eur Heart J* 1998;**19**:1872-8
- 26 Guyton AC. *Textbook of medical physiology*, eighth edition. W.B. Saunders company, Philadelphia, U.S.A. 1991
- 27 Bommel van T, Vinkers DJ, Macfarlane PW, Gussekloo J, Westendorp RGJ. Markers of autonomic tone on a standard ECG are predictive of mortality in old age. *Int J Cardiol* 2006;**107**:36-41

- 28 Aurigemma GP, Gaasch WH, Mclaughlin M, McGinn R, Sweeney A, Meyer TE. Reduced left ventricular systolic pump performance and depressed myocardial contractile function in patients >65 years of age with normal ejection fraction and high relative wall thickness. *Am J Cardiol* 1995;76:702-5

CHAPTER 6

Impact of valvular heart disease on daily living activity of nonagenarians: The Leiden 85-plus study

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Submitted

Abstract

Background: The present study evaluated the prevalence of significant valvular heart disease in community dwelling nonagenarians. In addition, we evaluated the impact of valvular heart disease on the ability to perform activities of daily living.

Methods: Nested within the Leiden 85-plus study, a population based follow-up study of the oldest old, a sample of 81 nonagenarians was recruited. The left ventricular (LV) dimensions, function and the presence and severity of heart valvular disease were evaluated by echocardiography. Significant valvular heart disease included any mitral or aortic stenosis severity, moderate or severe mitral regurgitation, moderate or severe aortic regurgitation and moderate or severe tricuspid regurgitation. Daily life activities were assessed using the Groningen Activity Restriction Scale (GARS).

Results: LV cavity diameters (end-diastolic diameter 47 ± 8 mm, end-systolic diameter 30 ± 8 mm) and systolic LV function (LV ejection fraction $66 \pm 13\%$) were within normal for the majority of the participants. Significant valvular disease was present in 57 (70%) individuals, with mitral regurgitation and aortic regurgitation as the most frequent valve diseases (49% and 28% respectively). The GARS score between individuals with and without significant valvular heart disease was similar (36.2 ± 9.2 vs. 34.4 ± 13.2 , $p=0.5$).

Conclusions: Nonagenarian, outpatient individuals have a high prevalence of significant valvular heart disease. However, no relation was observed between the presence of significant valvular heart disease and the ability to perform activities of daily living.

Introduction

The increasing life expectancy of the population in the Western countries has determined an increase of chronic diseases, with cardiovascular disease being one of the most prevalent pathologies.¹ The elderly individuals comprise a growing demographic subgroup characterized by a high frequency of cardiovascular risk factors and co-morbidities.² Furthermore, this subgroup of individuals is often excluded from randomized trials, resulting in important implications for clinical management.^{3,4} Particularly, data on the prevalence of valvular heart disease in very old individuals are scarce and based mostly on in-hospital series, introducing an important selection bias.^{4,7} In addition, the potential detrimental effect of valvular heart disease on the daily living activity is unknown.

Accordingly, the aim of the present study was twofold. First, the prevalence of significant valvular heart disease was evaluated in a group of outpatient individuals aged 90 years. Furthermore, the impact of significant valvular heart disease on the competence in different activities of daily living was studied. Significant valvular heart disease was defined according to the Euro Heart Survey on Valvular Heart Disease.⁴

Methods

Study protocol

The Leiden 85-plus Study is a prospective population-based study of all 85-year old inhabitants of Leiden, The Netherlands. The study design and characteristics of the cohort were described in detail previously.^{8,9} In short, between September 1997 and September 1999 all 705 members of the 1912 to 1914-birth cohort in the city of Leiden were asked to participate in the month after their 85th birthday. There were no selection criteria related to health or demographic characteristics. Participants were followed until death or the age of 90 years. At baseline and yearly thereafter, 85-year old participants were visited at their place of residence. During these visits blood pressure was measured, a venous blood sample drawn, an electrocardiogram recorded and face-to-face interviews and performance tests conducted. At 90 years of age, the participants were invited for an echocardiographic

examination. Participants gave informed consent and for individuals who were severely cognitively impaired, a guardian gave informed consent. The Medical Ethics Commission of Leiden University approved the study.

Clinical evaluation

Clinical status was evaluated in all individuals using the Groningen Activity Restriction Scale (GARS), 1-dimensional questionnaire that assess the performance in basic and instrumental activities of daily living (ADL and IADL).¹⁰ The score ranges from 18 to 90, higher scores indicating increasing disability. Cognitive function was assessed by the Mini-Mental State Examination (MMSE), with scores ranging from 0 to 30 points (optimal).¹⁰ Depressive symptoms were measured in those with MMSE > 18 points, using the 15-item Geriatric Depression Scale (GDS-15), with scores ranging from 0 (optimal) to 15 points.¹⁰ A GDS-15 score above 4 was considered to be poor. Furthermore, the cardiovascular history was recorded, including history of coronary artery disease (medical history of angina or myocardial infarction), bypass surgery, stroke, and peripheral vascular disease.⁹ Heart failure was defined as a positive response of the general practitioner to a specific question.

Blood pressure was measured twice with an interval of two weeks, using a mercury sphygmomanometer, in seating position after at least five minutes rest without having performed vigorous exercise during the preceding 30 minutes. We used the mean of the assessed systolic values and diastolic values.

Echocardiography

Transthoracic 2-dimensional echocardiography was performed in all individuals in the left lateral decubitus position. Images were obtained using a commercially available system equipped with a 3.5-MHz transducer (Vingmed system Vivid-5; General Electric-Vingmed, Milwaukee, WI, USA). Standard gray-scale and color Doppler images were acquired at a depth of 16 cm at the parasternal (standard long- and short-axis images) and apical views (2-, 4-chamber and apical long-axis images). Data were stored for further off-line analysis.

Left ventricular (LV) diameters, interventricular septal (end-diastolic) thickness and posterior wall (end-diastolic) thickness were measured from M-mode images obtained from the parasternal long-axis view, and LV ejection fraction was

derived using the Teichholz formula.¹¹ Left ventricular mass was calculated by the cube formula, using the correction formula proposed by Devereux *et al.*¹² Left ventricular mass was indexed by the body surface area. According to previous criteria, LV hypertrophy was defined by a LV mass index $> 110 \text{ g/m}^2$ in women and $> 134 \text{ g/m}^2$ in men.¹² Finally, left atrial dimension was calculated by measuring the anteroposterior diameter from M-mode recordings of the parasternal long-axis view.

Left ventricular diastolic function was evaluated by measuring the transmitral peak velocities (E-wave and A-wave) obtained from pulsed-wave Doppler recordings of the transmitral inflow velocity; from these velocities the E/A ratio derived as another marker of LV diastolic function.¹³

The valvular assessment included the evaluation of the function of the mitral, aortic and tricuspid valves. Color-Doppler echocardiography was performed after optimizing gain and Nyquist limit, and standard continuous and pulsed-wave Doppler recordings were acquired. Stenotic and regurgitant valve diseases were evaluated according to semiquantitative and quantitative methods recommended by the American Society of Echocardiography.^{13, 14} The severity of valvular stenosis was based on the valve area and the mean pressure gradient across the restrictive orifice.¹⁵ The mitral valve area was calculated by the pressure half-time and the aortic valve area was calculated by the continuity equation.^{13, 16} The mean pressure gradient across the restrictive orifice was estimated by averaging the instantaneous gradients obtained from continuous wave Doppler recordings.¹³ In addition, the severity of valvular regurgitation was determined on a qualitative scale and classified as mild (grade 1), moderate (grade 2) and severe (grades 3-4), according to the current ACC/AHA guidelines for the management of individuals with valvular heart disease.¹⁵ According to the Euro Heart Survey on Valvular Heart Disease, significant valvular disease was defined as any mitral or aortic stenosis severity, moderate or severe mitral regurgitation, moderate or severe aortic regurgitation.⁴ In addition, moderate or severe tricuspid regurgitation was considered as significant valvular heart disease. Finally, when tricuspid regurgitation was present, the pulmonary artery pressure was estimated using the modified Bernoulli equation.

Statistical analysis

Continuous variables are presented as mean \pm SD and categorical variables are presented as number and percentages. Differences between individuals with significant valvular disease and individuals without valvular disease were compared by the 2-tailed Student t-test, ANOVA, Mann-Whitney test and χ^2 -test for unpaired data, when appropriate. All statistical analyses were performed with software SPSS for Windows version 12.0 (SPSS, Inc., Chicago, IL). A p value <0.05 was considered statistically significant.

Results

Of the initial 705 eligible participants at the Leiden 85-plus study, 14 died before they could be enrolled and 92 refused to participate, resulting in a cohort of 599 participants who could be enrolled at age 85 (87% response). Some 277 participants survived up to age 90 years and were in principle eligible for the study. Among them, 81 outpatient individuals underwent echocardiography. The remaining 196 individuals were not able to visit the study center. Clinical and demographic characteristics are presented in Table 1. All individuals with echocardiographic examination were 90 years old (33% men). The majority of the individuals were in sinus rhythm (93%). The mean body surface area was 1,7 m² [SD \pm 0.7].

Table 1. Clinical and demographic characteristics

	Echocardiographic examination		
	Yes [n=81]	No [n=196]	p value
Females [%]	67	75	0.20*
Living independently [%]	78	55	<0.001*
ADL (IQR) [points]	10 (9-14)	16 (10-25)	<0.001‡
IADL (IQR) [points]	23 (17-29)	33 (25-36)	<0.001‡
GARS (IQR) [points]	33 (26-42)	49 (35-61)	<0.001‡
MMSE (IQR) [points]	28 (26-29)	22 (15-27)	<0.001‡
GDS-15 (>4) [%]	14.8	32	<0.001‡
History of cardiovascular disease [%]†	35	43	0.15*
History of heart failure [%]	19	17	0.82*
Diastolic blood pressure (SD) [mmHg]	73 (9)	71 (10)	0.17*
Systolic blood pressure (SD) [mmHg]	155 (16)	150 (19)	0.03*

SD, Standard Deviation. IQR, Inter Quartile Range. ADL, Activities in Daily Living. IADL, Instrumental Activities in Daily Living. GARS, Groningen Activity Restriction Scale. MMSE, Mini Mental State Examination. GDS-15, Geriatric Depression Scale. †, Including cerebrovascular accident, angina pectoris, myocardial infarction, peripheral vascular disease or an electrocardiogram revealing myocardial ischemia or infarction. *, Independent T-test. ‡, Mann Whitney test. N, number of participants.

Echocardiography

The echocardiographic characteristics of the study population are summarized in Table 2. The majority of the individuals showed normal LV dimensions and preserved systolic LV function. Seven (9%) individuals had LV systolic dysfunction (LV ejection fraction <50%). According to the previous definition, LV hypertrophy was present in 40 (51%) individuals, without differences between men and women (12 (44%) vs. 28 (55%), respectively; $p=0.5$). Mean anteroposterior diameter of the left atrium was 42 ± 9 mm. An enlarged left atrium (anteroposterior diameter > 40 mm) was present in 43 (53%) individuals. Evaluation of LV diastolic function demonstrated impaired LV relaxation in the majority of the individuals, reflected by an E/A ratio <1.

Data on heart valve study are presented in Table 3. Significant valvular disease was observed in 57 (70%) individuals. Significant left-sided valvular disease involving only one valve (mitral or aortic) was noted in 38 (47%) individuals, whereas 23 (28%) individuals had both the mitral and the aortic valves involved. Figure 1 shows the prevalence of significant valvular heart disease according to the diseased valve.

Mitral and aortic regurgitation were the most common valvular diseases diagnosed and no patient had mitral stenosis. Significant mitral regurgitation was observed in 39 (49%) individuals: 24 (30%) individuals had moderate mitral regurgitation and 15 (19%) individuals had severe mitral regurgitation. Significant aortic regurgitation was observed in 23 (28%) individuals: 17 (21%) individuals had moderate aortic regurgitation and 6 (7%) individuals had severe aortic regurgitation. Aortic stenosis was present in 14 (17%) individuals: 9 (11%) individuals had mild aortic stenosis, 4 (5%) individuals had moderate aortic stenosis and only 1 (1%) patient had severe aortic stenosis. Finally, moderate to severe tricuspid regurgitation was observed in 17 (21%) individuals, together with significant left-sided valvular heart disease. The mean (SD) pulmonary artery pressure in these individuals was 35 (\pm 7) mmHg.

Table 2. Left ventricular dimensions and function

	Mean [SD]
LV end-diastolic diameter (mm)	47 \pm 8
LV end-systolic diameter (mm)	30 \pm 8
Interventricular septum thickness (mm)	13 \pm 3
Posterior wall thickness (mm)	11 \pm 2
LV ejection fraction (%)	66 \pm 13
LV mass index (g/m ²)	126 \pm 37
Left atrium diameter (mm)	42 \pm 9
E/A ratio	0.7 \pm 0.2

81 participants included. LV = left ventricular. SD=Standard Deviation.

Table 3. Valvular heart disease in the study population

Mitral Valve	
- Mitral stenosis (%)	0 (0%)
- Mitral regurgitation (%)	59 (73%)
- Mild	20 (25%)
- Moderate	24 (30%)
- Severe	15 (19%)
Aortic Valve	
- Aortic stenosis (%)	14 (12%)
- Mild (mean $\Delta P < 25$ mmHg)	9 (11%)
- Moderate (mean $\Delta P 25 - 40$ mmHg)	4 (5%)
- Severe (mean $\Delta P > 40$ mmHg)	1 (1%)
- Aortic regurgitation (%)	38 (47%)
- Mild	15 (19%)
- Moderate	17 (21%)
- Severe	6 (7%)
Tricuspid valve	
- Tricuspid stenosis (%)	0 (0%)
- Tricuspid regurgitation (%)	25 (31%)
- Mild	8 (10%)
- Moderate	5 (6%)
- Severe	12 (15%)

81 participants included. ΔP = pressure gradient.

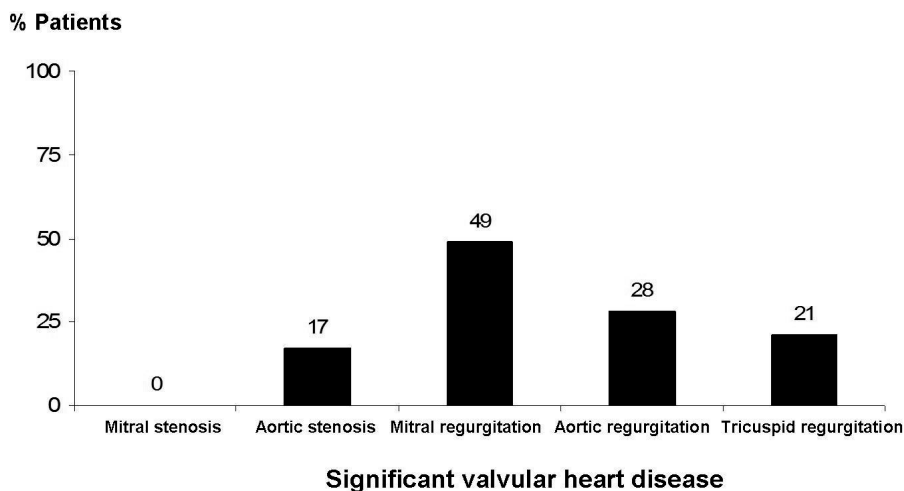


Figure 1. Prevalence of significant valvular heart disease according to the diseased valve.

Ability to perform activities of daily living and heart valvular disease

Differences in functional status as assessed by the GARS score were evaluated between individuals with and without significant valve disease. Patients with and without moderate or severe valvular heart disease showed comparable GARS score: 34.8 ± 13.4 vs. 34.8 ± 9.4 , $p = 0.97$. Furthermore, there were no differences in the GARS score between individuals without, one or two valves being significantly diseased ($p=0.6$) (Table 4).

Table 4. Relation between GARS score and significant valvular disease

	No valvular disease (N= 20)	Any valvular disease (N = 61)	One valve diseased (N = 38)	Two valve diseased (N = 23)
GARS score				
Mean (SD)	36.2 ± 9.2	34.4 ± 13.2 *	35.4 ± 14.4	32.7 ± 11.1 **

N=number of participants. * $p = 0.5$ vs. No valvular heart disease. † $p = 0.4$ one valve diseased vs. two valves diseased. ‡ ANOVA p -value = 0.6 No valvular disease vs. one and two valves diseased. SD=Standard Deviation.

Discussion

The findings in the current study illustrate that the majority of the nonagenarian outpatient individuals have normal LV cavity dimensions and normal systolic LV function on echocardiography. However, the prevalence of significant valvular disease is high, with mitral and aortic valve regurgitation being the most frequent valvular diseases. Nonetheless, the presence of significant valvular disease does not impact negatively on the functional status assessed with the GARS score.

Echocardiographic characteristics of the nonagenarian population

The nonagenarian outpatient population evaluated in the present study showed normal LV cavity dimensions and preserved systolic LV function. In contrast, diastolic LV function was characterized mostly by impaired LV relaxation. Several previous studies have reported similar findings in elderly individuals, with normal values of LV diameters and preserved systolic LV function, but with different grades of diastolic dysfunction.^{6, 17} As previously described, the aged-related changes in cardiac structure comprise a progressive increase in LV wall

thickness whereas LV diameters and systolic LV function remain unchanged.¹⁸ In addition, the increasing LV stiffness and collagen deposition that accompany the patient's aging, result in delayed LV relaxation and impairment of the early LV diastolic filling.¹⁸ All these changes were observed in the present study, with an increased LV mass index ($126 \pm 37 \text{ g/m}^2$) together with normal LV cavity diameters. Furthermore, various indices of diastolic dysfunction were abnormal (e.g. an E/A ratio <1 or an enlarged left atrium) indicating impaired LV compliance. However, all these structural and functional changes are strongly influenced by the presence of cardiovascular disease (i.e. coronary artery disease, valvulopathies or hypertension), the most common co-morbidity among the elderly individuals. Importantly, a high prevalence of valvular heart disease was observed in the present study population, with mitral and aortic valve regurgitation as the most frequent valvulopathies. Several contemporary series from Europe and the United States have demonstrated the relation between aging and the prevalence of degenerative valvular heart disease.^{4, 6, 7, 19} However, the true burden of valve disease remains still unclear since the majority of those series included in-hospital individuals or individuals referred for valvular surgery, introducing an important selection bias.^{4, 6, 7} Recently, Nkomo et al. demonstrated, in a community study including 3851 individuals older than 75 years, high absolute rates of significant valvular heart disease (11.7%), with mitral regurgitation and aortic stenosis being the most frequent valve diseases (7.1% and 4.6%, respectively).⁷ Furthermore, Sadiq et al. evaluated the distribution pattern of moderate to severe valve disease among 63 hospitalised centenarian individuals, a significant minority of them admitted because cardiovascular events (35%).⁶ In that study, aortic stenosis was the most prevalent valve disease (27%) followed by mitral regurgitation (22%) and aortic regurgitation (17%).⁶ Whereas in the aforementioned series the population comprised individuals with known valve disease or in-hospital individuals,^{6, 7} the present population consisted of clinically stable and mostly independently living nonagenarians from the general population. The high prevalence of valvular heart disease as observed in the present study when compared to previous studies is difficult to explain because of the different clinical characteristics. As previously described, aortic stenosis is characterized by poor clinical tolerance and, therefore, may determine higher hospital admission rates and higher prevalence of this particular valve disease in the inpatient-based series.

Impact of valvular disease on the ability in daily-life activities

In the current study, the competence in basic and instrumental activities of daily living was evaluated using the GARS score and related to the presence of valvular heart disease. Importantly, no differences in GARS score were observed between individuals with and without significant valve disease.

The relation between the impairments of basic activities of daily living and instrumental activities of daily living and cardiovascular co-morbidities has not been extensively studied.^{20, 21} Maugeri et al. related several parameters (e.g. walking speed, cognitive function, personal care) to systolic LV function in 170 individuals older than 70 years.²¹ The authors demonstrated significant functional disability in those individuals with heart failure, whereas individuals with preserved systolic LV function obtained better scores in the tests.²¹ In contrast, Formiga et al. evaluated the predictors of functional decline in 97 nonagenarians at 1 year follow-up and identified a history of stroke as an independent risk factor whereas the history of ischemic cardiomyopathy or heart failure were not related to functional decline.²⁰

The current study demonstrated that no relation existed between the ability in daily life activities and the presence of significant valvular heart disease. Of note, the preserved systolic LV function observed in the majority of the population could preclude us to find differences in functional status between individuals with and without significant valve disease. Additional large studies, including individuals with a broad range of systolic LV function, may provide more insight into the relation between the competence in daily life activities and the presence of valvular heart disease.

Study Limitations

The present study population represents a selected group of outpatient nonagenarians and therefore, the results may not apply to the general population of nonagenarians.

Although, the GARS score is a validated score reflecting the limitations in daily life other more physical tests might have been more appropriate to use. However, the GARS score gives a valuable insight in the limitations of daily life that was related to valve dysfunction. That there is no apparent difference in those with versus those without significant valve dysfunction is therefore remarkable.

Conclusions

The nonagenarian population has high prevalence of significant valvular heart disease, in the presence of preserved systolic LV function, without LV dilatation. The presence of significant valve disease did not impact negatively on the ability to perform activities of daily living. Therefore, in this age group one should be cautious before undertaking any medical intervention because of valvulopathy.

References

- (1) Aronow WS. Heart disease and aging. *Med Clin North Am* 2006 September;90(5):849-62.
- (2) Duncan AK, Vittone J, Fleming KC, Smith HC. Cardiovascular disease in elderly patients. *Mayo Clin Proc* 1996 February;71(2):184-96.
- (3) Detaint D, Sundt TM, Nkomo VT et al. Surgical correction of mitral regurgitation in the elderly: outcomes and recent improvements. *Circulation* 2006 July 25;114(4):265-72.
- (4) Iung B, Baron G, Butchart EG et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. *Eur Heart J* 2003 July;24(13):1231-43.
- (5) Aronow WS, Ahn C, Kronzon I. Prevalence of echocardiographic findings in 554 men and in 1,243 women aged > 60 years in a long-term health care facility. *Am J Cardiol* 1997 February 1;79(3):379-80.
- (6) Sadiq A, Choudhury M, Ali K et al. Echocardiographic characteristics in patients > or =100 years of age. *Am J Cardiol* 2007 December 15;100(12):1792-4.
- (7) Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet* 2006 September 16;368(9540):1005-11.
- (8) der Wiel AB, van EE, de Craen AJ et al. A high response is not essential to prevent selection bias: results from the Leiden 85-plus study. *J Clin Epidemiol* 2002 November;55(11):1119-25.
- (9) van EE, Gussekloo J, Houx P et al. Atherosclerosis and cognitive impairment are linked in the elderly. The Leiden 85-plus Study. *Atherosclerosis* 2002 December;165(2):353-9.
- (10) von Faber M, Bootsma-van der Wiel A, van Exel E, et al. Successful aging in the oldest old: Who can be characterized as successfully aged? *Arch Intern Med* 2001; 161: 2694-2700.
- (11) Teichholz LE, Kreulen T, Herman MV, Gorlin R. Problems in echocardiographic volume determinations: echocardiographic-angiographic correlations in the presence of absence of asynergy. *Am J Cardiol* 1976 January;37(1):7-11.
- (12) Devereux RB, Alonso DR, Lutas EM et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol* 1986 February 15;57(6):450-8.

- (13) Quinones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. *J Am Soc Echocardiogr* 2002 February;15(2):167-84.
- (14) Zoghbi WA, Enriquez-Sarano M, Foster E et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 2003 July;16(7):777-802.
- (15) Bonow RO, Carabello BA, Kanu C et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): developed in collaboration with the Society of Cardiovascular Anesthesiologists: endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *Circulation* 2006 August 1;114(5):e84-231.
- (16) Hatle L, Angelsen B, Tromsdal A. Noninvasive assessment of atrioventricular pressure half-time by Doppler ultrasound. *Circulation* 1979 November;60(5):1096-104.
- (17) Masugata H, Senda S, Goda F et al. Cardiac function as assessed by echocardiography in the oldest old > or = 90 years of age. *Int Heart J* 2007 July;48(4):497-504.
- (18) Gerstenblith G, Frederiksen J, Yin FC, Fortuin NJ, Lakatta EG, Weisfeldt ML. Echocardiographic assessment of a normal adult aging population. *Circulation* 1977 August;56(2):273-8.
- (19) Singh JP, Evans JC, Levy D et al. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). *Am J Cardiol* 1999 March 15;83(6):897-902.
- (20) Formiga F, Ferrer A, Perez-Castejon JM, Olmedo C, Pujol R. Risk factors for functional decline in nonagenarians: a one-year follow-up. The NonaSantfeliu study. *Gerontology* 2007;53(4):211-7.
- (21) Mauerger D, Testai M, Santangelo A et al. Cardiovascular aging and psychometric performances: correlations in a group of ultraseptagenarian elderly. *Arch Gerontol Geriatr* 2005 January;40(1):1-5.

CHAPTER 7

Markers of autonomic tone on a standard electrocardiogram are predictive of mortality in old age.

The Leiden 85-plus Study

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Abstract

Background

To investigate markers of autonomic tone on a standard electrocardiogram in relation to mortality in old age.

Methods

A total of 599 inhabitants of Leiden, the Netherlands, were enrolled in a population-based follow up study at their 85th birthday. Electrocardiograms were taken on entry and annually thereafter. ECGs were analysed automatically to determine four markers of autonomic tone, i.e. heart rate, the occurrence of ventricular extrasystoles and two time domain measures of heart rate variability. All participants were followed up for mortality.

Results

Participants with a heart rate in the highest quartile had a 1.8-fold increased total mortality risk (95% CI 1.0-3.4), but not an increased cardiovascular mortality risk. The occurrence of at least one ventricular extrasystole was related with a 2.3-fold increased total mortality risk (95% CI 1.3-3.9) and a 3.6-fold increased cardiovascular mortality risk (95% CI 1.6-8.2). In stratified analyses, the prognostic effect was confined to males. Both measures of heart rate variability were not related to mortality.

Conclusions

High heart rate and the occurrence of a ventricular extrasystole, both markers of sympathetic dominance, were predictive for mortality in old age. Two short-term measures of heart rate variability as measured on a standard 10 sec. electrocardiogram were not related to mortality, and hence may not reflect autonomic tone in old age.

Introduction

Altered autonomic activity resulting in sympathetic dominance leads to an excess of cardiovascular and non-cardiovascular mortality (1,2). The exact mechanism is not clear but among others, cardiac arrhythmias and accelerated atherosclerosis have been mentioned (3,4). Markers of autonomic activity are therefore of important prognostic value.

Heart rate and heart rate variability are the most common reflections of the balance of the parasympathetic/sympathetic nervous system (5). High heart rate (e.g. reflecting more sympathetic dominance) has repeatedly been associated with all cause, non-cardiovascular and cardiovascular mortality (6-12). Low heart rate variability (e.g. reflecting more sympathetic dominance), as measured on a 24-hour recording, has also been associated with all cause and cardiovascular mortality (13-15). For prognostic values the 5-min recording and the 24-hour recording have been recommended (15). However, a 10-second estimate of heart rate variability correlates highly with a similar estimate from a 5-min recording and the repeatability of the 5-min recording was found to be reasonable (16,17). Nevertheless, heart rate variability measured on a standard electrocardiogram has not been widely assessed and three population-based studies that have used such an approach showed conflicting results (18-20). In addition, these discordant findings are reinforced in a recent study in which the prognostic value of heart rate variability as measured on a standard electrocardiogram and on a 24-hour recording are compared; only the 24-hour recording had prognostic value (21).

A spontaneous increased sympathetic tone is involved in the genesis of ventricular extrasystoles (22). In addition a single ventricular extrasystole provokes a burst of sympathetic activity (23). Thus, ventricular extrasystoles are associated with an increased activity of sympathetic activity and, therefore, they can be used as a marker of sympathetic activity. The average of the absolute values of the beat-to-beat differences between normal consecutive RR intervals (AAD) has been shown to be a sensitive marker for parasympathetic activity (24). AAD is longer when parasympathetic influence is more prominent but its predictive value in clinical outcome studies has not been assessed as yet.

The aim of this study was to determine the association between mortality and markers of parasympathetic/sympathetic balance, i.e. heart rate, ventricular extrasystoles and two measures of heart rate variability as measured on the standard 10 seconds electrocardiogram.

Methods

Study population

The Leiden 85-plus Study is a prospective population-based study of all 85-year old inhabitants of Leiden, The Netherlands. The study design and characteristics of the cohort were described in detail previously (25, 26). In short, between September 1997 and September 1999 all 705 members of the 1912 to 1914-birth cohort were asked to participate in the month after their 85th birthday. There were no selection criteria related to health or demographic characteristics. At baseline, participants were visited three times at their place of residence. During these visits, face-to-face interviews were conducted and an electrocardiogram was recorded. During follow-up, an electrocardiogram was recorded yearly. Participants gave informed consent and for people who were severely cognitively impaired, their guardians gave informed consent. The Medical Ethics Commission of Leiden University approved the study.

Electrocardiogram

Standard 10 seconds electrocardiograms were recorded annually on a Siemens Sicard 440 and transmitted by telephone to the ECG Core Lab in Glasgow and analysed automatically (27). Only electrocardiograms with sinus rhythm were included in our analysis. In addition, all electrocardiograms with ectopic atrial rhythm, second- or third-degree AV-block, supraventricular or ventricular extrasystoles were excluded for assessment of heart rate and heart rate variability. Two measures of heart rate variability were studied, namely the standard deviation of the normal-to-normal RR-interval (SDNN), and the average of the absolute values of the beat-to-beat differences between normal consecutive RR intervals (AAD). Essentially, the onset of every QRS complex in the 10-second recording is determined and RR intervals are therefore calculated thereafter. For the analysis

of ventricular extrasystoles, only electrocardiograms with sinus rhythm and at least one ventricular extrasystole were analysed.

Mortality

All subjects were followed up for mortality till age 89 years. Shortly after the civil registry reported the death of a subject, the general practitioner or nursing home physician was interviewed to obtain the cause of death using a standardized questionnaire. Two senior specialists of internal medicine determined the primary causes of death by consensus according to the tenth version of the International Classification of Diseases (ICD-10) independent of ECG results (28). Primary causes of death were divided into two groups: cardiovascular mortality (ICD-codes I00-I99, I20-I25 and I60-I69) and non-cardiovascular mortality (all other ICD-codes).

Morbidity and demographic characteristics

At baseline, a research nurse collected information concerning the housing situation of each participant. The Mini-Mental State Examination (MMSE) was administered to screen for cognitive impairment (29). The presence of cardiovascular disease was defined as a positive medical history of cerebrovascular accidents, angina pectoris, myocardial infarction, peripheral vascular disease or an electrocardiogram revealing myocardial ischaemia or infarction (Minnesota codes 1-1, 1-2, 1-3, 4-1, 4-2, 4-3, 5-1, 5-2 and 5-3) (27).

Statistical analysis

Data are presented as percentages for clinical characteristics. Heart rate and heart rate variability were divided into quartiles, based on the distribution of all ECGs. Several ECGs per participant are included in this analysis. Mortality risks and 95% confidence intervals for both cardiovascular and non-cardiovascular mortality were estimated in a Cox proportional-hazards model including the data from the annual repeated electrocardiograms as time dependent covariates (30). For the analyses of the two heart rate variability measures, we have used heart rate as an additional time dependent covariate. The observed survival time was restricted to a period of a maximum of one year after the assessment of an electrocardiogram, or until age 89 years (date of censoring), or until the day of death as obtained from the civil registry.

Results

Of the 705 eligible participants, 14 died before they could be enrolled and 92 refused to participate, resulting in a cohort of 599 participants (87 % response). 204 (34%) participants were males and 395 participants (66%) were females. Signs or symptoms of cardiovascular disease were present in 62% of participants at baseline (23). The demographic characteristics of the 449 participants with an ECG showing sinus rhythm at baseline are given in table 1. During the 4-year follow up period subjects were observed for a total of 1906 person years. A total of 1822 ECGs were available for evaluation. 84 ECGs were missing because of technical problems.

Table 1: Clinical characteristics of participants at baseline.

	n= 449 (100%)
Male	31,6%
Living independently	84,6%
Good cognitive function*	64,1%
History of cardiovascular disease†	60,1%

* Mini Mental State Examination >24.

†Based on medical history and ECG findings.

During the follow-up, we observed 70 deaths of which 18 were caused by cardiovascular disease. When mortality risk was analysed dependent on heart rate for all participants, the participants in the highest quartile (heart rate of more than 74 per minute) had a 1.8-fold mortality risk from all causes (95% CI 1.0-3.4, $p=0.038$) and a 2.2 fold non-cardiovascular mortality risk (95% CI 1.0-4.9, $p=0.019$) when compared to the participants in the lowest quartile (heart rate less than 60 per minute). There was no increase in cardiovascular mortality dependent on heart rate (data not shown). When we stratified for gender, there seemed to be a trend towards a higher risk for all cause and non-cardiovascular mortality in males (table 2), whereas there was no association with heart rate and mortality in females (table 2). The estimates for heart rate and mortality risks were not different in participants with or without cardiovascular disease at baseline (data not shown). In addition, the estimates for heart rate and mortality risks were not different in participants with or without cognitive impairment (dichotomised on a MMSE value of 24 points, data not shown).

Table 2: Mortality risk dependent on quartiles of heart rate, stratified for gender.

	Quartiles of heart rate (beats per minute)			
	< 60	60 – 67	68 – 74	> 74
Males n=330				
All cause	1*	1.2 (0.3-4.4)	2.2 (0.7-7.2)	3.0 (1.0-9.1)†
Cardiovascular	1*	0.7 (0.07-8.0)	0.9 (0.08-10)	1.8 (0.3-13)
Non-cardiovascular	1*	1.5 (0.3-7.5)	3.1 (0.7-13)	3.8 (0.9-15)‡
Females n=812				
All cause	1*	0.8 (0.3-1.8)	0.8 (0.4-1.9)	1.3 (0.6-2.9)
Cardiovascular	1*	0.7 (0.2-2.9)	0.2 (0.02-1.8)	0.9 (0.2-3.5)
Non-cardiovascular	1*	0.8 (0.3-2.3)	1.2 (0.4-3.0)	1.6 (0.6-4.0)

Data presented as mortality risks (95% confidence intervals) from Cox proportional-hazards model with the quartiles of heart rate as time dependent covariate. Based on 1457 automatically included electrocardiograms with sinus rhythm, minus 315 manually excluded electrocardiograms with ventricular or supraventricular extrasystoles, ectopic atrial rhythm, second or third degree AV-block.

* Reference category; † p=0.058; ‡ p=0.062

In a similar analysis, as described above, all participants who had sinus rhythm and ventricular extrasystoles suffered a significant increased mortality risk from all causes (RR 2.3, CI 1.3-3.9) and from cardiovascular causes (RR 3.6, CI 1.6-8.2) as compared to the participants without a ventricular extrasystole. After we stratified for gender, the presence of ventricular extrasystoles was still predictive for all cause, cardiovascular and non-cardiovascular mortality in males (table 3). In females there was no association between mortality risk and the occurrence of ventricular extrasystole (table 3). The estimates for ventricular extrasystole and mortality risks were not different in participants with or without cardiovascular disease at baseline (data not shown). In addition, the estimates for ventricular extrasystole and mortality risks were not different in participants with or without cognitive impairment (dichotomised on a MMSE value of 24 points, data not shown).

In contrast to the analyses mentioned above, heart rate variability was not associated with all cause mortality or cardiovascular mortality (table 4). Stratification for gender did not change this lack of association (data not shown). As heart rate variability is dependent on heart rate, we adjusted for heart rate. However, after this adjustment heart rate variability still had no predictive value in relation to mortality (table 4).

Table 3: Mortality risk dependent on the presence of ventricular extrasystole, stratified for gender.

	No ventricular extrasystole	Ventricular extrasystoles
Males n=35		
All cause	1*	4.5 (2.3-9.0)
Cardiovascular	1*	6.4 (2.2-19)
Non-cardiovascular	1*	3.7 (1.5-9.2)
Females n=64		
All cause	1*	1.0 (0.4-2.7)
Cardiovascular	1*	1.8 (0.4-7.9)
Non-cardiovascular	1*	0.7 (0.2-2.7)

Data presented as mortality risks (95% confidence intervals) obtained from Cox proportional-hazards model with the presence of ventricular extrasystoles as time dependent covariate. Based on 1457 automatically analysed electrocardiograms with sinus rhythm, of which 99 had one or more ventricular extrasystoles. During follow-up 16 deaths (8 of cardiovascular disease) occurred among the participants who had sinus rhythm and ventricular extrasystoles.

* Reference category

Table 4: Mortality risk dependent on heart rate variability.

	Quartiles of heart rate variability			
	< 9.1 ms	9.1 – 14.9 ms	>14.9 – 26.4 ms	>26.4 ms
Crude				
All cause	1*	0.77 (0.42 – 1.4)	0.58 (0.30 – 1.1)	0.72 (0.39 – 1.4)
Cardiovascular	1*	0.60 (0.14 – 2.5)	0.96 (0.28 – 3.3)	0.99 (0.29 – 3.4)
Non-cardiovascular	1*	0.82 (0.47 – 1.6)	0.47 (0.21 – 1.1)	0.65 (0.31 – 1.3)
Adjusted for heart rate				
All cause	1*	0.85 (0.45 – 1.6)	0.66 (0.34 – 1.3)	0.87 (0.45 – 1.7)
Cardiovascular	1*	0.60 (0.14 – 2.6)	0.97 (0.27 – 3.5)	0.98 (0.32 – 4.2)
Non-cardiovascular	1*	0.92 (0.46 – 1.8)	0.56 (0.25 – 1.3)	0.83 (0.39 – 1.8)

Data presented as mortality risks (95% confidence intervals) obtained from Cox proportional-hazards model with the quartiles of heart rate variability as a time dependent covariate, adjusted for gender. Based on 1457 automatically included electrocardiograms with sinus rhythm, minus 315 manually excluded electrocardiograms with ventricular or supraventricular extrasystoles, ectopic atrial rhythm or second or third degree AV-block.

* Reference category

No association was found between AAD and all cause mortality or cardiovascular mortality (table 5). Stratification for gender did not change the lack of association (data not shown). As AAD is dependent on heart rate also, we adjusted for heart rate. However, after adjustment, AAD still had no predictive value (table 5).

Table 5: Mortality risk dependent on quartiles of the average of the absolute values of the beat-to-beat differences (AAD) between normal consecutive RR intervals.

	Quartiles of the absolute difference of the beat-to-beat variations			
	< 8,0 ms	8,0 – 13,6 ms	13,7 – 24,0 ms	> 24,0 ms
Crude				
All cause	1*	0.74 (0.37 – 1.5)	1.1 (0.58 – 2.0)	0.88 (0.46 – 1.7)
Cardiovascular	1*	1.1 (0.27 – 4.2)	1.0 (0.25 – 4.1)	1.6 (0.44 – 5.6)
Non-cardiovascular	1*	0.65 (0.30 – 1.4)	1.1 (0.54 – 2.1)	0.70 (0.32 – 1.5)
Adjusted for heart rate				
All cause	1*	0.86 (0.43 – 1.7)	1.4 (0.71 – 2.6)	1.2 (0.58 – 2.3)
Cardiovascular	1*	1.2 (0.28 – 4.7)	1.1 (0.27 – 4.9)	1.7 (0.43 – 6.8)
Non-cardiovascular	1*	0.77 (0.35 – 1.7)	1.4 (0.69 – 2.9)	1.0 (0.44– 2.3)

Data presented as mortality risks (95% confidence intervals) obtained from Cox proportional-hazards model with the quartiles of the absolute difference of the beat-to-beat variations as a time dependent covariate, adjusted for gender. Based on 1457 automatically included electrocardiograms with sinus rhythm, minus 315 manually excluded electrocardiograms with ventricular or supraventricular extrasystoles, ectopic atrial rhythm, second or third degree AV-block.

* Reference category

Discussion

This study has shown that ventricular extrasystoles as measured on a standard electrocardiogram, are predictive of cardiovascular and non-cardiovascular mortality in older men from the general population. Higher heart rate as measured on a standard 10 seconds electrocardiogram, seems to be predictive for all cause and non-cardiovascular mortality in older men from the general population also. However, neither heart rate variability nor AAD was predictive of cardiovascular or non-cardiovascular mortality in males or females.

The predictive value of heart rate variability, as measured on long-term electrocardiogram recording, for mortality is well established (13-15,31). In contrast, the predictive value of heart rate variability on a standard electrocardiogram is not clear. Three population-based studies have used a standard electrocardiogram for determining heart rate variability. The Rotterdam Study found an increased all cause mortality risk for all participants (mean age 69 years) in both the lowest and the highest quartile of heart rate variability compared with the third quartile

(18). Furthermore, mortality from cardiovascular causes was 2-fold increased among participants in the lowest and highest quartile. The Zutphen Study, which included only middle-aged men, found a 2-fold increased all cause mortality risk when the lowest and highest quartile of heart rate variability were compared (19). The two studies mentioned above did not correct for heart rate. It remains to be established whether the above found correlations remain after correction for heart rate. This reasoning is reinforced by the Bronx Aging Study (mean age 79 years) that did not find any difference in mortality between participants with high versus low heart rate variability (20). Heart rate variability as measured on a standard electrocardiogram at discharge of patients with an acute myocardial infarction had no predictive value for mortality, whereas heart rate variability measured on a 24-hour recording was highly predictive of cardiovascular mortality (21).

The prognostic value of AAD has not yet been established. As a sensitive marker of parasympathetic activity (16,24), we speculated that a more dominant parasympathetic activity is related with less cardiovascular mortality. However, we did not find a correlation between mortality and a longer AAD, i.e. more parasympathetic influence on a standard ECG recording.

The lack of prognostic information of the heart rate variability and AAD could mean that the parasympathetic / sympathetic balance in the general population of old people is not predictive of mortality. However, the association between heart rate and ventricular extrasystoles with overall mortality and cardiovascular mortality are at odds with this view. Heart rate is a reflection of the parasympathetic / sympathetic balance, a higher heart rate reflecting a dominance of the sympathetic nervous system. In line with this, various studies reported a high heart rate to be predictive of overall mortality, non-cardiovascular and cardiovascular mortality (6-12). Ventricular extrasystoles are another reflection of the activity of the sympathetic nervous system (22,23). The occurrence of three or more ventricular extrasystoles per hour on 24-hour ECG recordings in patients with a myocardial infarction predicted higher rates of mortality (32). Taken together, the data show that markers of parasympathetic/sympathetic balance –e.g. heart rate and the occurrence of a ventricular extrasystole- are predictive of mortality. The lack of prognostic value of heart rate variability and AAD as measured on a standard electrocardiogram could mean that they are not a reliable reflection of

the parasympathetic / sympathetic balance. The reason for this lack of association is not clear. It could well be, that in this age group, there is an increased heart rate variability due to different foci being involved in stimulating the atria, although in the main, we have been reported this as sinus rhythm. In other words, in this very elderly age group, there is an intrinsic increase in heart rate variability, which will mask any “impaired” heart rate variability. A concern might be that heart rate variability is more sensitive to the somewhat uncontrolled conditions in obtaining ECGs compared to ventricular extrasystoles. However, we found a prognostic effect of heart rate on mortality also, even though heart rate is known to be very sensitive to short term influences. Therefore, we think that the lack of association between heart rate variability and mortality is not due to conditions in where the ECGs were obtained.

Other studies did not correct for heart rate, but because we used only a short-term recording, the heart rate could potentially influence heart rate variability, i.e. with a lower heart rate, heart rate variability tends to be larger and vice versa. However, after adjustment for heart rate there was no material change in outcome. The short-term recording could also influence the results of AAD in the same manner, i.e. with a lower heart rate; there is a longer absolute difference of the beat-to-beat variation. But again, after adjustment for heart rate, no material change of outcome was noted.

As in other studies we see a difference in prognostic value of heart rate predominantly in males and less in females (6-12). As far as we know there is no good explanation for this phenomenon based upon biological differences between males and females. Suggestions in the literature of a protective effect of estrogens in females will not likely be the explanation for the difference found in our cohort. Other suggestions postulated a lower mortality risk for cardiovascular causes in females compared to males because of the absolute lower cardiovascular mortality. Although this could be partly true for middle-aged women, in our cohort more females died than men. In addition, our finding that prognostic value of heart rate for all cause mortality is higher than for cardiovascular mortality is of interest. It suggests that heart rate is an epiphenomenon of a more generalized process than cardiovascular disease alone. However, we do not know what the underlying process might be.

Within this population-based study of the oldest old, we were not able to correct for potential influences on the parasympathetic/sympathetic balance. ECG recording could be in the morning or the afternoon, no information of usage of caffeine is available, no information is available if there was physical effort shortly for ECG recording, and so forth. Therefore we did not correct for medication either, though numerous medications can influence the parasympathetic/sympathetic balance. We used the pragmatic view that whatever the cause of the findings on the ECG, modification of the parasympathetic/sympathetic balance is reflected in the overall survival.

Our study is very suitable for investigating the predictive value of the ECG characteristics, because we used a cohort of elderly without selection and had therefore a broad variation of persons and person characteristics. On the other hand the causality of our findings is more difficult to interpret. Another strength of our study is the multiple assessments of heart rate, ventricular extrasystoles and heart rate variability with a follow-up period of 1 year maximum. If heart rate variability deteriorates prior to an event the most recent ECG would be the one to investigate. This contrasts with other studies in which a single electrocardiogram has been associated with (very) long periods of follow-up, allowing misclassification to occur. A weakness of our study is that we did not have the ability to compare the heart rate variability as measured on a standard electrocardiogram with a 24-hour recording.

Sympathetic dominance as reflected in high heart rate and occurrence of ventricular extrasystoles is significantly associated with increased overall mortality. However, neither heart rate variability nor AAD was predictive of cardiovascular or non-cardiovascular mortality.

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References

- 1 Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. *Circulation* 1999;99:2192-217.
- 2 Curtis BM, O'Keefe JH Jr. Autonomic tone as a cardiovascular risk factor: the dangers of chronic fight or flight. *Mayo Clin Proc* 2002;77:45-54.
- 3 Meerson FZ. Stress-induced arrhythmic disease of the heart. Part 1 *Clin Cardiol* 1994;17:362-71.
- 4 Huikuri HV, Jokinen V, Syvanne M, Nieminen MS, Airaksinen KE, Ikaheimo MJ, et al. Heart rate variability and progression of coronary atherosclerosis. *Arterioscler Thromb Vasc Biol* 1999;19:1979-85.
- 5 Pomeranz B, Macaulay RJB, Caudill MA, Kutz I, Adam D, Gordon D, et al. Assessment of autonomic function in humans by heart rate spectral analysis. *Am J Physiol* 1985 (*Heart Circ Physiol* 17);248:H151-3
- 6 Kannel B, Kannel C, Paffenbarger Jr RS, Cupples LA. Heart rate and cardiovascular mortality: the Framingham study. *Am Heart J* 1987;113:1489-94.
- 7 Aronow WS, Ahn C, Mercado AD, Epstein S. Association of average heart rate on 24-hour ambulatory electrocardiograms with incidence of new coronary events at 48-month follow-up in 1311 patients (mean age 81 years) with heart disease and sinus rhythm. *Am J Cardiol* 1996;78:1175-6.
- 8 Dyer A, Persky V, Stamler J, Paul O, Shekelle RB, Berkson DM, et al. Heart rate as a prognostic factor for coronary heart disease and mortality: findings in three Chicago epidemiologic studies. *Am J Epidemiol* 1980;112:736-49.
- 9 Gillum F, Makuc DM, Feldman JJ. Pulse rate, coronary heart disease, and death: the NHANES I epidemiologic follow-up study. *Am Heart J* 1991;121:172-7.
- 10 Palatini P, Casiglia E, Julius S, Pessina AC. High heart rate. A risk factor for cardiovascular death in elderly men. *Arch Int Med* 1999;159:585-92.
- 11 Mensink GBM, Hoffmeister H. The relationship between resting heart rate and all-cause, cardiovascular and cancer mortality. *Eur Heart J* 1997;18:1404-10.
- 12 Benetos A, Rudnichi A, Thomas F, Safar M, Guize L. Influence of heart rate on mortality in a french population. Role of age, gender and blood pressure. *Hypertension* 1999;33:44-52.
- 13 American College of Cardiology cardiovascular technology assessment committee. Heart rate variability for risk stratification of life-threatening arrhythmias. *J Am Coll Cardiol* 1993;22:948-50.

- 14 Tsuji H, Venditti Jr FJ, Manders ES, Evans JC, Larson MG, Feldman CL, et al. Reduced heart rate variability and mortality risk in an elderly cohort. The Framingham heart study. *Circulation* 1994;90:878-83.
- 15 Task force of the European Society of Cardiology and the North American Society of pacing and electrophysiology. Heart rate variability. Standards of measurement, physiological interpretation and clinical use. *Circulation* 1996;93:1043-65.
- 16 Hamilton RM, Mckechnie PS, Macfarlane PW. Can cardiac vagal tone be estimated from the 10-second ECG? *Int J Cardiol* 2004;95:109-115
- 17 Murray PG, Hamilton RM, Macfarlane PW. Reproducibility of a non-invasive real-time measure of cardiac parasympathetic activity. *Physiol Meas* 2001;22:661-72
- 18 de Bruyne MC, Kors JA, Hoes AW, Klootwijk P, Dekker JM, Hofman A, et al. Both decreased and increased heart rate variability on the standard 10-Second electrocardiogram predict cardiac mortality in the elderly. The Rotterdam Study. *Am J Epidemiol* 1999;150:1282-8.
- 19 Dekker JM, Schouten EG, Klootwijk P, Pool J, Swenne CA, Kromhout D. Heart rate variability from short electrocardiographic recordings predicts mortality from all causes in middle-aged and elderly men. The Zutphen Study. *Am J Epidemiol* 1997;145:899-908.
- 20 Bernstein JM, Frishman WH, Jen Chang C. Value of ECG P-R and Q-Tc interval prolongation and heart rate variability for predicting cardiovascular morbidity and mortality in the elderly: the Bronx Aging Study. *Cardiology in the Elderly* 1997;5:31-41.
- 21 Klingenheben T, Zabel M, Hohnloser SH. Brief analysis of heart rate variability for determining prognosis in the post-myocardial infarct period: methodologically reliable alternative to long-term ECG? *Z Kardiol* 1998;87:128-33.
- 22 Stein KM, Karagounis LA, Markowitz SM, Anderson JL, Lerman BB. Heart rate changes preceding ventricular ectopy in patients with ventricular tachycardia caused by reentry, triggered activity, and automaticity. *Am Heart J* 1998;136:425-34.
- 23 Welch WJ, Smith MI, Rea RF, Bauernfeind RA, Eckberg DL. Enhancement of sympathetic nerve activity by single premature ventricular beats in humans. *J Am Coll Cardiol* 1989;13:1693-4.
- 24 Julu POO, Hondo RG. Effects of atropine on autonomic indices based on electrocardiographic R-R intervals in healthy volunteers. *J Neurol Neurosurg Psychiatry* 1992;55:31-5.
- 25 Bootsma-van der Wiel A, van Exel E, de Craen AJ, Gussekloo J, Lagaay AM, Knook DL et al. A high response is not essential to prevent selection bias. Results from the Leiden 85-Plus Study. *J Clin Epidemiol* 2002;55:1119-25.

- 26 Exel E, Gussekloo J, Houx P, de Craen AJ, Macfarlane PW, Bootsma- van der Wiel A, et al. Atherosclerosis and cognitive impairment are linked in the elderly. The leiden 85-plus Study. *Atherosclerosis* 2002;165:353-9.
- 27 Macfarlane PW, Latif S. Automated serial electrocardiogram comparison based on the Minnesota code. *J Electrocardiol* 1996;29 suppl:29-34.
- 28 International Statistical Classification of Diseases and Related Health Problems. Geneva: WHO; 1994.
- 29 Tombaugh TN, McIntyre NJ. The Mini-Mental State Examination: A comprehensive review. *J Am Geriatrics Soc* 1992;40:922-35.
- 30 Cox DR. Regression models and life tables. *J R Stat Soc Ser B Stat Methodol* 1972;74:187-220.
- 31 Dekker JM, Crow RS, Aaron RF, Hannan PJ, Liao D, Swenne CA, et al. Low heart rate variability in a 2-minute rhythm strip predicts risk of coronary heart disease and mortality from several causes. The ARIC study. *Circulation* 2000;102:1239-44.
- 32 Bigger JT Jr, Fleiss JL, Kleiger R, Miller JP, Rolnitzky LM. The relationship among ventricular arrhythmias, left ventricular dysfunction, and mortality in the 2 years after myocardial infarction. *Circulation* 1984;69:250-8.

CHAPTER 8

Discussion

The hazardous effect of high blood pressure in people of middle age is a well known fact. Moreover, there is ample evidence from randomised clinical trials that favour treatment of high blood pressure. In contrast, there is a substantial amount of observational data that high blood pressure in elderly people above age 80 years is not associated with excess morbidity and or mortality. [1-6] In order to explain these apparent discrepancy, there must be a threshold beyond which treatment of hypertension does not provide benefit. However, it is difficult to understand the nature of this threshold, as age alone is not likely to explain for the paradox. After all, physiological systems are not bound to age. In this chapter the results of our research in the Leiden 85-plus Study are used to disentangle these seemingly contradictory findings in the very old.

The first objective of this thesis was to explore the association between high blood pressure, morbidity and mortality in a very old population. A diagnosis of hypertension at age 85 years was predictive of a 50% higher cardiovascular mortality during a five years follow-up period.[7] Remarkable, this increased risk was independent of the actual blood pressure and known cardiovascular diseases at age 85 years. No association was found between high systolic or diastolic blood pressure and mortality (total or cardiovascular). Unexpectedly, low systolic blood pressure concordant with a low diastolic blood pressure was associated with a two-fold increased risk of total mortality. These observations were irrespective of gender, current cardiovascular diseases and usage of antihypertensive drugs. In chapter 3, the effect of blood pressure on renal function at old age was examined. [8] High systolic blood pressure was not associated with an accelerated decline of creatinine clearance. However, a decline in systolic and diastolic blood pressures over a five year period correlated with a 50% increased decline of creatinine clearance when compared to those with a stable blood pressure. Thus, at old age, high blood pressure was not a risk factor for renal dysfunction. In fact, a decrease of blood pressure at old age was associated with an increased decline of renal function.

In chapter 4 the relationship between baseline blood pressure and cognitive function later in life was examined across age groups from two independent population-based cohort studies. [9] Systolic and diastolic blood pressures were measured at baseline; cognitive function was assessed at the end of follow-up. In

the youngest age group (<65 years), systolic and diastolic blood pressures were not associated with cognitive function 11 years later. For persons aged 65-74 years, higher systolic and diastolic blood pressures at baseline were related to a decline in cognitive function 11 years later. In contrast, in older age (over 75 years) higher systolic and diastolic blood pressures were related with higher cognitive function 11 years later. This effect appeared to be strongest in the highest age group (85 years). Thus, the relation between baseline blood pressure levels and cognitive function later in life differs across age groups. High blood pressure increases the risk of cognitive impairment up to 75 years but may preserve cognitive function thereafter.

I conclude that high blood pressure is not related with excess mortality at age 85 years and over. High blood pressure has a preservative effect on creatinine clearance and finally high blood pressure seems to have a preservative effect on global cognition after age 75 years that is more pronounced after age 85 years. These observations point at a beneficial effect of high blood pressure in old age. The alternative hypothesis being that reversed causality is in play. Indeed, various chronic and cardiovascular diseases are associated with lower blood pressure and higher mortality rates. However, all the correlations reported here were corrected for the presence of cardiovascular and chronic diseases and the beneficial effects of high blood pressure still stand out. Moreover, reversed causality could explain for the relation between lower blood pressure and higher mortality risk, it is less likely to explain for the accelerated organ dysfunction that is described.

The second objective was to gain insight into the association between blood pressure and cardiac function at high age. Therefore, echocardiography examinations were performed in persons at 90 years of age. A first remarkable finding in the echocardiographic study was a high prevalence of significant mitral and aortic regurgitation. The combined prevalence of significant valvular disease was 70%. [Chapter 6] From a clinical perspective, it is noteworthy that our participants had little physical restrictions which points to limited impact of the valvular disease on the activities of daily living. As the echocardiographic examinations were not thorough enough to make a reliable estimation of the cardiac output in the presence of severe valvular abnormalities, we have used only

the echocardiographic examinations of subjects who were free from significant valvular abnormalities to examine the association between blood pressure and cardiac output. Overall, the mean cardiac index was low, as was the mean stroke volume and both were significantly correlated with systolic blood pressure. [10] A lower systolic blood pressure correlated with lower cardiac index and lower stroke volume. Left ventricular end-diastolic and left ventricular end-systolic dimensions were within reference values and were not related to blood pressure. The mean left ventricular ejection fraction was normal and positively associated with blood pressure. The average E/A ratio was low also, indicating a high prevalence of diastolic dysfunction. Heart rates were significantly higher in participants with a lower stroke volume, compared to those with a higher stroke volume.

To examine the role of the autonomic nervous system associating with mortality, annually conducted electrocardiograms were studied. [11] A diminished parasympathetic dominance as measured with low heart rate variability did not show an association between mortality. Higher heart rate and the occurrences of ventricular extrasystoles, both presentations of excess sympathetic activity, were associated with an increased mortality. The dominance of the sympathetic nervous system could be either a result of an autonomous decrease in parasympathetic activity or a systemic adaptation to an underlying process.

Taken together I conclude that systolic function was preserved but there was a high prevalence of diastolic dysfunction and a decreased cardiac index. A lower systolic blood pressure was associated with a lower cardiac index and higher heart rate. Moreover, an activated sympathetic nervous system was associated with an increased mortality. An integrated physiological explanation of these findings could lead to the following interpretation. To compensate for a diminished stroke volume, heart rate will increase consequent on stimulation of the sympathetic nervous system. The elevated heart rate that co-occurs with a lower cardiac index fits a systemic adaptation to cardiac dysfunction. Thus, in the populations of older people that we have studied, a lower systolic blood pressure will likely mark imminent heart failure.

The observational data that are presented in this thesis showed that high blood pressure (both systolic and diastolic) was not related with excess morbidity and mortality. On the other hand, low blood pressure was related with excess

morbidity and mortality. As earlier stated, it is difficult to imagine that there is a certain age after which high blood pressure is beneficial instead of harmful. However, if low blood pressure is the result of a decreased cardiac output it could facilitate general hypoperfusion and hence explain the hazardous effect of low blood pressure at old age. Mean blood pressure rises with age and systolic blood pressure continues to rise whereas from the fifth and sixth decade of life diastolic blood pressure tends to lower.[12,13] This phenomenon is explained by a stiffer vascular system, particularly of the aorta. It is logical that in light of generalised atherosclerosis and increased vascular resistance, blood pressure raises to compensate for a decline in perfusion of vital organs. In an aging population, the prevalence of generalised atherosclerosis will be higher and therefore the risk of hypoperfusion will be increased. The recently published HYVET trial, that had positive results of treating high blood pressure in persons above 80 years old, is at first sight incongruent with our hypothesis. [14] However, the participants in the HYVET trial had considerably less cardiovascular disease (12%) when compared to the general population of the same age [60%, Chapter 2, this thesis]. Additionally, the mortality risk was considerably less than expected for that age group. Here I put forward the hypothesis that it was the healthiest people that were recruited into the HYVET trial for whom a benefit has been proven. This fits with the original inclusion criterion to exclude people with isolated hypertension that results of arterial stiffening and atherosclerosis. At older age this is the most common form of hypertension. Therefore, the results support treatment of people over the age of eighty that do not suffer from significant cardiovascular disease. It is however, difficult to generalize these results to older people in the population at large amongst which the presence of generalised atherosclerosis is the rule rather than the exception.

It is tempting to speculate how to select the people at old age who will benefit from the treatment of high blood pressure. Most persons will not fulfil the inclusion criteria of the HYVET, especially persons with a high cardiovascular risk. This being the case, what selection criterion should be used to select a healthy elder person? Most likely those with a high blood pressure concordant with a normal cardiac output should be treated rigorously. Alternative those with a high blood pressure concordant with a low cardiac output should not be treated. Pulse wave velocity could be of value as well. A higher pulse wave velocity reflects a

stiffer vascular tree and therefore a higher risk of hypoperfusion when high blood pressure is being lowered. Once treatment is started, the following question is to what extent blood pressure should be lowered. What are the treatment goals? The international guidelines on treatment of hypertension propose to lower the blood pressure to the lowest possible values, but in any case systolic blood pressure should be lower than 140 mmHg. If these treatment goals would also suit the older population we should institute a far more aggressive treatment than is currently applied. But negative outcomes of intensive treatment of high blood pressure have been observed among middle-aged people with severe vascular disease. [15] In an aged population, it is expected that the hazardous effects of aggressive treatment of high blood pressure will be even more pronounced.

As reported in the HYVET study, mortality risk from stroke was considerably lower in the treated versus placebo group. As stroke is a major risk factor for cognitive decline one should expect in the treated group positive results for maintaining cognition. Remarkably, there was no benefit on cognition in the participants with versus those without treatment for hypertension. [16] Though the follow-up might have been too short to reveal an effect on cognition there could be an alternative explanation. In line with our hypothesis it could very well be that active treatment, in this apparently healthy cohort, induced cerebral hypoperfusion. The beneficial effect of the reduced stroke incidence might have been traded off with cerebral hypoperfusion, with as a result a negligible effect on cognition.

In conclusion, the population-based reports indicating lower mortality and morbidity risks in association with high blood pressure in the very old are robust and cannot be ignored. [1-9] The results of interventional trials, including the recent HYVET trial, provide a solid body of evidence also. [14] This thesis supports the notion that clinicians should not base treatment of high blood pressure in older people on cut-off levels only. Clinicians have to make a decision whether high blood pressure in a particular patient is appropriate or not. My hypothesis is that high blood pressure concordant with a low cardiac output should not be treated in contrast with high blood pressure concordant with a normal/high cardiac output. According to the Hippocratic Oath, clinicians have to prescribe medication for the good of their patients according to their best ability and judgment without

doing harm. For the time being, treatment of high blood pressure in the very old is a clinical challenge with little general rules and highly individualized. It goes without saying that, future randomised controlled trials should focus on the outcomes of blood pressure lowering stratified on levels of cardiac output and or generalized atherosclerotic burden.

References

- 1 Boshuizen HC, Izaks GJ, Van Buuren S, Ligthart GJ. Blood pressure and mortality in elderly people aged 85 and older. *BMJ* 1998;316:1780-4
- 2 Lernfelt B, Svanborg A. Change in blood pressure in the age interval 70-90. Late blood pressure peak related to longer survival. *Blood Pressure* 2002;11:206-12
- 3 Heikinheimo RJ, Haavisto MV, Kaarela RH, Kanto AJ, Koivunen MJ, Rajala SA. Blood pressure in the very old. *J Hypertens* 1990;8:361-7
- 4 Glynn RJ, Chae CU, Guralnik JM, Taylor JO, Hennekens CH. Pulse pressure and mortality in old persons. *Arch Int Med* 2000; 160:2765-72
- 5 Rajala S, Haavisto M, Heikinheimo R, Mattila K. Blood pressure and mortality in the very old. *Lancet* 1983; 322:520-1
- 6 Rastas S, Pirttilä T, Viramo P, et al. Association between blood pressure and survival over 9 years in a general population aged 85 and older. *J Am Geriatr Soc* 2006;54:912-8
- 7 Van Bommel T, Gussekloo J, Westendorp RGJ, Blauw GJ. In a population-based prospective study, no association between high blood pressure and mortality after age 85 years. *J Hypertension* 24:287-292, 2006
- 8 Van Bommel T, Woittiez K, Blauw GJ, van der Sman-de Beer F, Dekker FW, Westendorp RGJ, et al. Prospective study of the effect of blood pressure on renal function in old age: The Leiden 85-plus Study. *J Am Soc Nephrol* 2006; 17:2561-2566
- 9 Euser SM, van Bommel T, Schram MT, Gussekloo J, Hofman A, Westendorp RGJ, Breteler MMB. The effect of age on the association between blood pressure and cognitive function later in life. *J Am Geriatr Soc* 2009 Apr 21. [Epub ahead of print]
- 10 van Bommel T, Holman ER, Gussekloo J, Blauw GJ, Bax JJ, Westendorp RG. Low blood pressure in the very old, a consequence of imminent heart failure. The Leiden 85-plus Study. *J Hum Hypertens*. 2009 Jan;23(1):27-32.
- 11 Bommel van T, Vinkers DJ, Macfarlane PW, Gussekloo J, Westendorp RGJ. Markers of autonomic tone on a standard ECG are predictive of mortality in old age. *Int J Cardiol* 2006;107:36-41
- 12 Franklin SS, Gustin IV W, Wong ND, Larson MG, Weber MA, Kannel WB, et al. Hemodynamic patterns of age-related changes in blood pressure. The Framingham heart study. *Circulation* 1997;96:308-15
- 13 Vokonas PS, Kannel WB, Cupples LA. Epidemiology and risk of hypertension in the elderly: the Framingham Study. *J Hypertens Suppl*. 1988;6:S3-9.

- 14 Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med*; 2008; 358:1887-98.
- 15 Messerli FH, Mancia G, Conti CR, Hewkin AC, Kupfer S, Champion A, Kolloch R, Benetos A, Pepine CJ. Dogma disputed: can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? *Ann Intern Med* 2006;144(12):884-93
- 16 Peters R, Beckett N, Forette F, et al. Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind placebo controlled trial. *Lancet Neurol* 2008;7(8):683-689

CHAPTER 9

Summary

Chapter 1

This chapter contains a short review of the history of high blood pressure. The changing perspective in time of the hazardous effect of high blood pressure is highlighted. In the last 3 decades there has been an explosion in knowledge about high blood pressure. As a result of that treatment goals have been stricter and goal populations have been broader. However, the evidence of a hazardous effect of high blood pressure in the elderly is not robust and even contradictory compared to middle-aged people. To explore this possible contradiction this thesis has two aims. First it contributes to observational evidence between high blood pressure at older age and adverse outcomes, including cardiovascular mortality, renal failure and cognitive decline. Secondly, it tries to disentangle the association between blood pressure and cardiac function at older age.

Chapter 2

The aim of chapter 2 is to study the impact of a history of hypertension and current blood pressure on mortality in the most elderly. This study was part of the Leiden 85-plus Study, an observational population-based cohort study in the community city of Leiden, the Netherlands. Five hundred and ninety-nine inhabitants of the birth-cohort 1912-1914 were enrolled on their 85th birthday. There were no selection criteria related to health or demographic characteristics. The mean follow-up was 4.2 years. Five hundred and seventy-one participants were included, 39 % had a history of hypertension. During follow-up 290 participants died, 119 due to cardiovascular causes. Compared to participants without a history of hypertension, those with a history of hypertension had a 60% increased mortality risk from cardiovascular causes, but equal mortality risks from all causes. High blood pressure at age 85 years was not a risk factor for mortality irrespective of a history of hypertension. However, blood pressure values below 140/70 mmHg (n=48) at age 85 years were associated with excess mortality, predominantly in participants with a history of hypertension. Thus, in the most elderly, high blood pressure is not a risk factor for mortality, irrespective of a history of hypertension. Blood pressure values below 140/70 are associated with excess mortality.

Chapter 3

The aim of chapter 3 is to study the effect of blood pressure on creatinine clearance over time in very old participants. High blood pressure is associated with a decline in renal function. Whether this is true for very old people is largely unknown. This study was part of the Leiden 85-plus Study. For this study 550 subjects (34% men) were enrolled at their 85th birthday and followed until death or age 90. Blood pressure was measured twice at baseline and at age 90 years. Creatinine clearance was estimated annually (Cockcroft-Gault formula). The mean creatinine clearance at baseline was 45 ml/min. Systolic blood pressure was not associated with changes in creatinine clearance during follow-up. Those with diastolic blood pressure below 70 mmHg had a significant accelerated decline of creatinine clearance compared with those with higher diastolic blood pressure. Participants with a decline in systolic blood pressure during follow-up had a significant accelerated decline of creatinine clearance compared with those with stable blood pressures. Similar results were found for a decline in diastolic blood. Thus, in this study high blood pressure at older age is not associated with renal function. In contrast, low diastolic blood pressure is associated with an accelerated decline of renal function.

Chapter 4

The aim of this chapter is to determine the prospective relationship between blood pressure and cognitive function across a wide age range. This study was part of the Rotterdam Study and the Leiden 85-plus Study, both prospective population-based cohort studies.

Three thousand seventy-eight men and women, initial age 55 to 84 years from the Rotterdam Study and 276 men and women, initial age 85 years, from the Leiden 85-plus Study were included. Systolic blood pressure and diastolic blood pressure were measured at baseline; cognitive function was assessed at the end of follow-up using a dedicated neuropsychological test battery. In the youngest participants (<65 years), systolic and diastolic blood pressure were not associated with cognitive function 11 years later. For persons aged 65 to 74 years, higher baseline systolic and diastolic blood pressures were related to worse cognitive function 11 years later. In contrast, in older age (≥ 75 years), higher systolic and diastolic blood pressure seemed to be related to better cognitive function at the

end of follow-up. This effect appeared strongest in the highest age group (85 years). Thus, high blood pressure was associated with greater risk of cognitive impairment in persons younger than 75 but with better cognitive function in older persons.

Chapter 5

The aim of this study is to elucidate the underlying mechanism of the observational findings that low blood pressure in the very old is associated with organ dysfunction and excess mortality. We hypothesized that cardiac dysfunction contributes to low blood pressure in the very old. A sample of 82 participants all aged 90 years from the Leiden 85-plus Study, were invited. Blood pressure was measured twice and all but one underwent echocardiography to assess cardiac dimensions and functional cardiac parameters. Some 47 participants were free from hemodynamically significant valvular disease and were included in the present analyses. There were low values for mean cardiac output (2.0 l/min/m²) and mean stroke volume (31 ml/m²). For every 10-mmHg decrease in systolic blood pressure, cardiac output and stroke volume were significantly lower. Mean left ventricular ejection fraction was normal and higher for each 10-mmHg decrease in systolic blood pressure. Mean left ventricular dimensions were normal but the E/A ratio was 0.68 indicating diastolic dysfunction. In conclusion, among the most elderly, low systolic blood pressure correlates with low cardiac output while systolic ventricular function is not impaired.

Chapter 6

This study evaluates the prevalence of significant left-sided valvular heart disease in community dwelling nonagenarians. In addition, we evaluated the impact of valvular heart disease on the ability to perform activities of daily living. Nested within the Leiden 85-plus Study a sample of 81 nonagenarians was recruited. The left ventricular (LV) dimensions, function and the presence and severity of heart valvular disease were evaluated by echocardiography. Daily life activities were assessed using the Groningen Activity Restriction Scale (GARS). LV cavity diameters and systolic LV function were within normal for the majority of the participants. Significant valvular disease was present in 57 (70%) individuals, with mitral regurgitation and aortic regurgitation being mostly affected (73%

and 47% respectively). The GARS score between individuals with and without significant valvular heart disease was similar. In conclusion, the majority of the nonagenarians from the general population have significant valvular heart disease that does not affect the ability to perform activities of daily living.

Chapter 7

This study investigated markers of autonomic tone on a standard electrocardiogram in relation to mortality in old age. This study was part of the Leiden 85-plus Study. A total of 599 inhabitants were enrolled in a population-based follow up study at their 85th birthday. Electrocardiograms were taken on entry and annually thereafter. Electrocardiograms were analysed automatically to determine four markers of autonomic tone, i.e. heart rate, the occurrence of ventricular extrasystoles and two time domain measures of heart rate variability. All participants were followed up for mortality. For those participants with a heart rate in the highest quartile the total mortality risk was 1.8-fold increased. However, they had not an increased cardiovascular mortality risk. The occurrence of at least one ventricular extrasystole was related with a 2.3-fold increased total mortality risk and a 3.6-fold increased cardiovascular mortality risk. In stratified analyses, the prognostic effect was confined to males. Both measures of heart rate variability were not related to mortality. Thus, on a standard 10 sec. Electrocardiogram, high heart rate and the occurrence of a ventricular extrasystole, both markers of sympathetic dominance, were predictive for mortality in old age. Two short-term measures of heart rate variability as measured on a standard 10 sec. electrocardiogram were not related to mortality, and hence may not reflect autonomic tone in old age.

Chapter 8

This chapter reveals a general discussion about the hazardous effect of high blood pressure in the elderly. The population-based reports indicating lower mortality and morbidity risks in association with high blood pressure in the very old are robust and should not be ignored. However, the results of the only randomised double blind interventional trial done, is solid too. Possibly, high blood pressure concordant with a low cardiac output is a different entity compared with high blood pressure concordant with a normal/high cardiac output. This might explain that elderly with a limited amount of atherosclerosis / vascular disease will have

benefit from treatment of high blood pressure. In contrast, those with a huge amount of atherosclerosis / vascular disease might not benefit from treatment, due to decreased perfusion, especially in those persons with a decreased cardiac output. Clinicians have to make a decision whether the blood pressure in a particular patient is appropriate or not. Our hypothesis is that high blood pressure concordant with a low cardiac output should not be treated in contrast with high blood pressure concordant with a normal/high cardiac output. Therefore, at present, we propose that treatment of high blood pressure in the very old is not withheld but highly individualized. In our opinion, future research should focus on the relation between blood pressure and cardiac output.

CHAPTER 10

Samenvatting

Hoofdstuk 1

In dit hoofdstuk wordt kort de geschiedenis van hoge bloeddruk belicht. Met name zal het gewijzigde perspectief over de effecten van hoge bloeddruk door de eeuwen worden belicht. De laatste decennia is er een explosieve toename van kennis over hoge bloeddruk. Het gevolg daarvan is dat de behandelingsdoelen van hoge bloeddruk steeds strikter zijn geworden. Momenteel geldt bijna het credo hoe lager de bloeddruk hoe beter, onafhankelijk van de leeftijd. Problematisch is dat de meeste kennis van de effecten van hoge bloeddruk en de behandeling van hoge bloeddruk is opgedaan bij mensen van middelbare leeftijd. Bij mensen boven de 80 jaar is het bewijs dat hoge bloeddruk een risicofactor is voor de gezondheid verre van geleverd. Sterker nog, er zijn aanwijzingen dat een lagere bloeddruk bij ouderen juist een risicofactor voor ziekte en sterfte is. Dit proefschrift is geschreven om meer kennis te vergaren over de effecten van hoge bloeddruk bij ouderen. Het eerste doel van dit proefschrift is, om met behulp van observationele studies de gevolgen van hoge bloeddruk op sterfte, nierfunctie en cognitie te onderzoeken. Het tweede doel van dit proefschrift is om de samenhang tussen de bloeddruk en de hartfunctie nader te onderzoeken.

Hoofdstuk 2

In dit hoofdstuk is onderzocht of een voorgeschiedenis van hoge bloeddruk in relatie met de huidige bloeddruk een voorspeller is van vroegtijdig overlijden. Deze studie was onderdeel van de Leiden 85-plus studie, een observationale studie van alle inwoners van Leiden uit het geboortecohort 1912-1914. In totaal deden er 599 inwoners mee met de studie. Er waren geen selectie criteria met betrekking tot gezondheid of sociale omstandigheden. De gemiddelde duur dat de deelnemers werden gevolgd was 4,2 jaar. Van de 599 inwoners konden er 571 meedoen met deze studie, 39% had een medische voorgeschiedenis met hoge bloeddruk. Gedurende de studie overleden er 290 deelnemers, waarvan 119 ten gevolge van hart en vaatziekten. Vergeleken met de deelnemers zonder een medische voorgeschiedenis van hoge bloeddruk, hadden de deelnemers met een medische voorgeschiedenis van hoge bloeddruk een 60% verhoogd risico om te overlijden aan hart en vaat ziekten. De totale sterftetekans was overigens niet verschillend tussen beide groepen. Hoge bloeddruk vanaf een leeftijd van 85 jaar was niet voorspellend voor een verhoogde kans op sterven, onafhankelijk van een

voorgeschiedenis met hoge bloeddruk. Een bloeddruk lager dan 140/70mmHg (totaal 48 deelnemers) was wel voorspellend voor een verhoogde sterfte, en dan met name in de deelnemers met een voorgeschiedenis van hoge bloeddruk. Kortom, in deze studie bij 85 jarigen is een hoge bloeddruk niet voorspellend voor sterfte, een lage bloeddruk is dat wel.

Hoofdstuk 3

In dit hoofdstuk is de relatie tussen de nierfunctie en bloeddruk over de tijd onderzocht in ouderen mensen. Hoge bloeddruk is geassocieerd met een snellere daling van de nierfunctie. Of dat ook waar is in ouderen is onbekend. Deze studie maakte deel uit van de Leiden 85-plus studie. Uiteindelijk konden voor deze studie 550 deelnemers (34% mannelijk) van 85 jaar worden gevolgd tot overlijden of het bereiken van de leeftijd van 90 jaar. De bloeddruk werd gemeten op het 85^{ste} jaar en op het 90^{ste} jaar. De nierfunctie werd geschat met behulp de Cockcroft-Gault formule waarbij de kreatinine klaring kan worden berekend. De gemiddelde kreatinineklaring was 45ml per minuut. De bovendruk (systolische bloeddruk) was niet geassocieerd met de kreatinine klaring gedurende de studie. De deelnemers waarvan de onderdruk (diastolische bloeddruk) lager was dan 70 mmHg hadden een versnelde daling van de kreatinineklaring vergeleken met de deelnemers met een hogere diastolische bloeddruk. Deelnemers waarvan de systolische bloeddruk daalde tijdens de studie hadden ook een versnelde achteruitgang van de kreatinineklaring vergeleken met de deelnemers waarvan de bloeddruk gedurende de studie stabiel bleef. Dezelfde resultaten werden gezien bij de deelnemers waarvan de diastolische bloeddruk daalde gedurende de studie. Concluderend, in deze studie was een hoge bloeddruk bij ouderen mensen geen risicofactor voor een versnelde achteruitgang van de nierfunctie. Een lage bloeddruk, of een dalende bloeddruk was wel voorspellend voor een versnelde achteruitgang van de nierfunctie.

Hoofdstuk 4

Het doel van deze studie is om prospectief de relatie tussen cognitie en bloeddruk te onderzoeken in een qua leeftijd brede populatie. Deze studie maakt gebruik van de gegevens van de Rotterdam studie en de Leiden 85-plus studie, beide grote longitudinale bevolkingsonderzoeken. Vanuit de Rotterdam studie zijn

de gegevens van 3078 mannen en vrouwen met een leeftijd tussen de 55 en 84 jaar gebruikt. Vanuit de Leiden 85-plus studie zijn de gegevens van 276 mannen en vrouwen van 85 jaar gebruikt. De bloeddruk werd gemeten tijdens het begin van de studie en de cognitie tests werden aan het eind van de studie gemeten. In de deelnemers jonger dan 65 jaar was de bloeddruk niet geassocieerd met cognitie tests 11 jaar later. Bij de deelnemers tussen de 65 en 74 jaar was een hoge bloeddruk (systolisch en diastolisch) geassocieerd met een slechtere prestatie op de cognitie tests 11 jaar later. Bij de oudere deelnemers (75 jaar en ouder) was een hoge bloeddruk (systolisch en diastolisch) geassocieerd met een betere prestatie op de cognitie tests. Dit effect was het duidelijkst bij de oudste groep deelnemers van 85 jaar. Concluderend, hoge bloeddruk is geassocieerd met een in de toekomst slechtere prestatie op cognitie tests in mensen jonger dan 75 jaar, maar met betere prestaties op cognitie tests bij ouderen.

Hoofdstuk 5

Deze studie heeft als doel om het achterliggende mechanisme te ontrafelen achter de observaties dat een lage bloeddruk bij ouderen gepaard gaat met meer ziekte en hogere sterfte.

De hypothese was dat een lagere bloeddruk het gevolg zou zijn van hartfalen. Vanuit de Leiden 85-plus studie werden 82 deelnemers van 90 jaar onderzocht. De bloeddruk werd tweemaal gemeten en een echocardiografie van het hart werd gemaakt. Van 47 deelnemers waren de metingen betrouwbaar genoeg om te analyseren. De overigen deelnemers hadden ernstig kleplijden waardoor functionele parameters niet betrouwbaar gemeten konden worden.

De cardiac output was gemiddeld laag (2.0 l/min/m²), het slagvolume was ook gemiddeld laag (31 ml/m²). Voor elke 10 mmHg lagere systolische bloeddruk waren de cardiac output en het slagvolume significant lager. De gemiddelde ejectiefractie van de linkerkamer was normaal en hoger voor elke 10 mmHg lagere systolische bloeddruk. De dimensies van de linker hartkamer waren normaal, maar de E/A ratio was 0,68 dat duidt op een diastolische disfunctie. Concluderend, in deze groep ouderen is er een verband tussen een lage cardiac output en een lage systolische bloeddruk. Opvallend is dat de systolische functie van het hart intact lijkt te zijn.

Hoofdstuk 6

In deze studie is het voorkomen van kleplijden bestudeerd onder mensen van 90 jaar. Verder is er onderzocht of er een verminderd dagelijks functioneren bij deze ouderen samenhangt met significant kleplijden. Als een onderdeel van de Leiden 85-plus studie werden 81 deelnemers van 90 jaar gevraagd om mee te doen met deze substudie. De functie van het hart, de dimensies van de linker hartkamer en de aanwezigheid van kleplijden werden onderzocht met behulp van echocardiografie. Het dagelijks functioneren werd geëvalueerd met de "Groningen Activity Restriction Scale (GARS)". De dimensies van het hart en de systolische functie van de linkerkamer waren normaal in de meerderheid van de deelnemers. Significant kleplijden was aanwezig bij 57 (70%) van de deelnemers. Met name was er sprake van mitraalklep insufficiëntie (73%) en aortaklepinsufficiëntie (47%). De GARS score was niet verschillend tussen de deelnemers met en zonder significant kleplijden. Samenvattend, de meerderheid van de 90 jarigen in de bevolking heeft significant kleplijden. Opvallend is dat het kleplijden niet interfereert met het dagelijks functioneren.

Hoofdstuk 7

In deze studie werd onderzocht of op het standaard ECG van 10 seconden, markers van het autonome zenuwstelsel voorspellend waren voor sterfte bij ouderen. Deze studie was onderdeel van de Leiden 85-plus studie. In totaal werden 599 deelnemers gevolgd vanaf hun 85^{ste} verjaardag. Standaard ECG's werden jaarlijks gemaakt. De ECG's werden automatisch geanalyseerd op 4 markers van het autonome zenuwstelsel; hartfrequentie, de aanwezigheid van ventriculaire extrasystole en twee maten van hartritme variabiliteit. Alle deelnemers werden vervolgd tot hun 89^{ste} jaar of tot aan het overlijden. De deelnemers met de hoogste hartfrequentie hadden een 1,8 keer grotere kans om te overlijden vergeleken met de andere deelnemers. Opmerkelijk was dat de sterfte aan hart en vaatziekte wel gelijk was tussen beide groepen deelnemers. Indien er op het ECG een ventriculaire extrasystole aanwezig was, dan was de kans op sterfte 2,3 keer hoger en de kans op sterfte aan hart en vaatziekte 3,6 keer hoger vergeleken met de deelnemers die geen ventriculaire extrasystole op het ECG hadden. Deze hogere sterfte gold overigens alleen voor mannen. De beide maten van hartritme variabiliteit gemeten op een standaard ECG van 10 seconden hadden geen voorspellende waarde ten

aanzien van sterfte. Waarschijnlijk zijn deze maten bij ouderen niet de reflectie van de activiteit van het autonome zenuwstelsel.

Hoofdstuk 8

Dit hoofdstuk bevat een discussie over het al dan niet schadelijke effect van een hoge bloeddruk in ouderen. De observationele bevolkingsonderzoeken laten consequent zien dat bij ouderen de kans op sterfte en ziekte bij een hogere bloeddruk lager is dan bij een lagere bloeddruk. Maar de enige goed opgezette studie naar het effect van behandeling van hoge bloeddruk liet een voordeel zien van een bloeddruk verlagende behandeling. Misschien is het zo, dat de het niet zo zeer gaat om een hoge bloeddruk maar meer om de onderliggende fysieke gesteldheid van het hart- en vaatsysteem. Het zou kunnen dat een hoge bloeddruk samen met een verlaagde cardiac output een hele andere entiteit is dan een hoge bloeddruk met een normale cardiac output. Dat zou dan kunnen verklaren dat ouderen met maar weinig schade aan hart en vaten een positief effect hebben van een behandeling van hoge bloeddruk. Dit overigens in tegenstelling met ouderen die wel veel schade hebben aan hart en bloedvaten. Behandeling van een hoge bloeddruk van deze laatste groep ouderen zou kunnen leiden tot oversterfte ten gevolge van de behandeling. En deze oversterfte zou dan met name zichtbaar moeten zijn bij degene met een verlaagde cardiac output. De behandelende dokter zal een beslissing moeten maken of een bepaalde hoogte van bloeddruk bij een patiënt goed is of niet. Onze hypothese is dat een hoge bloeddruk die samen gaat met een verlaagde cardiac output niet zou moeten worden behandeld. Kortom, voorlopig, totdat er meer kennis is over de behandeling van hoge bloeddruk bij ouderen moet de behandeling daarvan niet worden onthouden maar wel sterk worden geïndividualiseerd. Naar onze mening zou verder onderzoek zich onder andere moeten richten op de relatie tussen de cardiac output en de bloeddruk.

List of publications

Black and blue . . . and unconscious. Van Onna M, van Bommel T, van Wensen E, Schaar C, Slis H, Spronk PE. *BMJ*. 2009; 22;339

The Effect of Age on the Association Between Blood Pressure and Cognitive Function Later in Life. Euser SM, van Bommel T, Schram MT, Gussekloo J, Hofman A, Westendorp RGJ, Breteler MB. *Journal of the American Geriatrics Society* 2009; 57:1232 - 1237

Low blood pressure in the very old, a consequence of imminent heart failure: the Leiden 85-plus Study. van Bommel T, Holman ER, Gussekloo J, Blauw GJ, Bax JJ, Westendorp RG. *J Hum Hypertens*. 2009;23:27-32

Severe hyponatraemia after DDAVP stimulation test in an adult patient. Posthouwer D, Rommes JH, van Bommel T, Schaar CG. *Haemophilia*. 2008;14:844-5

Rare oxygen, a rare way to diagnose Conn's syndrome. Greven WL, van Bommel T. *NDT Plus* 2008 1:427-428

Prospective Study of the Effect of Blood Pressure on Renal Function in Old Age: The Leiden 85-Plus Study. van Bommel T, Woittiez K, Blauw GJ, van der Sman-de Beer F, Dekker FW†, Westendorp RGJ, Gussekloo J. *J Am Soc Nephrol* 2006;17: 2561-2566.

In a population-based prospective study, no association between high blood pressure and mortality after age 85 years. Van Bommel T, Gussekloo J, Westendorp RGJ, Blauw G J. *Journal of Hypertension*. 2006;24:287-292

Markers of autonomic tone on a standard ECG are predictive of mortality in old age. Van Bommel T, Vinkers D, Macfarlane P, Gussekloo J, Westendorp RGJ. *International Journal of Cardiology* 2005;107: 36-41

List of publications

In an observational study elderly patients had an increases risk of falling due to home hazards. Van Bommel T, Vandenbroucke JP, Westendorp RGJ, Gussekloo J. J Clinical Epidemiology. 2005;58:63-67

Curriculum vitae

Thomas van Bommel werd op 5 september 1969 geboren te Arnhem. In 1987 werd het VWO-diploma behaald aan het Niels Stensen College te Utrecht. In datzelfde jaar werd aangevangen met de studie geneeskunde aan de Universiteit van Amsterdam. Het artsexamen werd behaald in 1994. Vanaf 1994 tot 1996 was hij werkzaam als arts assistent niet in opleiding tot internist in het St Lucas ziekenhuis in Amsterdam (Opleider dr.J.J.M.van Meyel). In 1996 werd aangevangen met de opleiding tot internist in het Leyenburg ziekenhuis te Den Haag (Opleider dr.J.C.M. van der Vijver). De opleiding werd in 2000 voortgezet in het Leids Universitair Centrum (Opleider Prof.dr.A.E. Meinders). In januari 2002 volgde de registratie als internist. Van 2002 tot 2005 was hij werkzaam als stafid bij de afdeling algemene interne geneeskunde, sectie ouderengeneeskunde (Hoofd Prof.dr.R.G.J.Westendorp), in deze periode werd tevens gestart met het in dit proefschrift beschreven onderzoek. Sinds oktober 2005 is hij werkzaam als internist-vasculair geneeskundige in de Gelre ziekenhuizen locatie Apeldoorn. Thomas van Bommel is getrouwd met Annemarie Huisman, samen hebben zij twee kinderen: Lucas (2000) en Marit (2002).

