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

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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 les 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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