Average Heart Rate, Atrial Fibrillation and R-on-T Ventricular Ectopy in 24h Holter Recordings Predict All-Cause Mortality in Healthy Middle-aged Men

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Abstract

Ambulatory ECG recordings contain unique information about heart rate dynamics and arrhythmias. However, little is known about the long-term prognostic value in healthy persons. Here we present results of a 22-year follow-up study in 153 apparently healthy men, age at inclusion 52±6 [40-60] years.

In the Holter ECG we determined type and incidence of arrhythmias, minimal, averaged and maximal heart rate (HRmin, HRav, HRmax), averaged standard deviation of normal-to-normal beat intervals (SDNN), standard deviation of the normal-to-normal beat interval averages (SDANN), % successive normal-to-normal beat interval differences exceeding 50 ms (pNN50), and low-frequency heart rate variability in normalized units (LFnu). All cause mortality risk factors were computed by a Cox proportional hazards model.

During follow-up 27 persons died. Significantly ($P<0.05$) elevated relative risk (RR) was found for atrial fibrillation (RR = 13.8), R-on-T ventricular ectopic beats (RR = 7.0), Hrav (RR = 5.6) and pNN50 (RR = 3.4).

1. Introduction

A 24h electrocardiogram (Holter ECG) contains unique dynamic information about heart rate and arrhythmias not found in brief resting ECG recordings. Multiple studies were done to demonstrate the prognostic value of Holter ECGs in diseased persons; contrastingly, the prognostic value of Holter ECGs in healthy subjects is only little studied. This white spot on the map is caused by a number of reasons. When mortality risk is studied, e.g., in middle-aged subjects, the required follow-up period is relatively long, and to our knowledge prospective long-term follow-up studies with 24h ambulatory ECGs recorded in healthy persons are virtually nonexistent. Retrospectively, it can be attempted to identify healthy 24h ECGs amongst the diagnostic recordings routinely made in an outpatient clinic. The problem here is that even when the patient appears to have no detectable abnormalities or disease, the ECG remains suspect because of referral bias. A final option is to use data of older studies, e.g., originally done for the purpose of obtaining reference values, and do the follow-up retrospectively. In the case that the original tapes still exist and are of sufficient technical quality, reprocessing can be considered, e.g., to add heart rate variability parameters to the study when these had originally not been computed.

Here we present the results of a restrospective long-term follow-up study, including reprocessing, on the basis of a set of ambulatory ECG recordings made in 1978-1980 in the course of a research project intended to investigate the prevalence of arrhythmias in the normal active population.

2. Methods

Data collection for this study was done between July 1978 and December 1980. All study participants were active male employees of a financial institution in the Amsterdam area. They had no history of heart disease, and had no anginal complaints. None of these subjects used beta-blocking agents, or antianginal, antiarrhythmic, or antihypertensive medication. Hypertensive systolic / diastolic readings were accepted as long the subject was not medically treated for hypertension. All subjects had a normal physical examination and a normal resting ECG according to the Minnesota criteria (accepted abnormalities: QRS axis deviations of -30° to -90° or of +90° to +120°, non-diagnostic ST-segment and T-wave abnormalities). A blood sample was taken to determine total serum cholesterol. Height and weight were measured for computation of the body mass index (BMI), and the subjects completed a questionnaire including items regarding general health, smoking behavior, medical history and use of medication.

2.1. Holter recording and initial analysis

Ambulatory 24h ECG recordings (bipolar modified V1 and modified V5 leads) were made by means of a 2-channel Oxford Medilog portable ECG recorder with clock track. A full-time Holter technician, using the Oxford Medilog-1 system, analyzed the recordings. Tapes with less than 20 hours of analyzable signal were excluded from the study. Write-outs were made of all

detected arrhythmias, to be confirmed and further studied by the supervising cardiologist (VMC).

Presence/absence of the following arrhythmias was noted: isolated supraventricular extrasystoles, runs of supraventricular extrasystoles, atrial flutter, atrial fibrillation, nodal rhythm, 1st degree AV block, 2nd degree AV block, 3rd degree AV block, 1-10 ventricular extrasystoles, >10 ventricular extrasystoles, multifocal ventricular extrasystoles, bigeminal ventricular ectopy, doublets of ventricular extrasystoles, runs of ventricular extrasystoles, R-on-T ventricular ectopy.

2.2. Holter reanalysis

We recenly decided to reanalyze the original recordings for the computation of heart rate variability (HRV) parameters. First, we explored the technical option of using a Holter analyzer able to read and interpret the Oxford clock track. This is needed for time linearization (as a compensation for recording and play back speed fluctuations and for tape stretch). It appeared that current Oxford analyzers couldn t handle this clock track any more. Also, attempts to read the tapes by means of an Oxford playback module connected to a Marquette Holter system failed. It was then decided to digitize the clock signal with the ECG and to develop software to linearize time in a later processing stage.

All Oxford cassette tapes, originally recorded at 2 mm/s tape speed, were re-analyzed as stranger tapes on a Marquette Mars 8000 Holter Analyzer. In this modality, the Marquette playback device reads the tape at a fixed speed of 1 mm/s. Basically, the Oxford recordings are seen by the Marquette Analyzer as three channel recordings: channels 1 and 2 are the original Oxford ECG channels, and channel 3 is the original Oxford clock track (a 60 Hz fixed amplitude sine wave). As the Marquette Analyzer uses channels 1 and 2 for the actual analysis, while channel 3 is only displayed, the Oxford clock track was not interfering with the analysis procedure.

Using the standard Marquette analysis software and interactive procedures, most tapes could reliably be converted into a beat annotation stream (obviously with time a factor two stretched). Tapes with inferior signal quality, possibly deteriorated by ageing, were excluded from further analysis. Next, the beat annotation stream plus the complete 3-channel signal, digitized at 128 Hz, were exported to a PC for subsequent time linearization (correction for possible variations in recording or play back speeds).

The time linearization procedure was as follows. First, describing the clock signal as a series of zeniths and nadirs, all successive zeniths and the sample numbers thereof were located and stored. A zenith was defined as a sample value larger or equal than its direct neighbours. By definition, the distance between two adjacent zeniths is 1/60 s. Without time distortion, this corresponds to 2 * 128/60 = 4.266 samples (the factor two is due to the Oxford-Marquette tape speed differences, 128 is the Marquette sampling rate). Some tape stretching and some fluctuations in the recording or playback speed were allowed, however, when adjacent zeniths differed <4 or >10 sample points, a disconinuity in time was signalled. When adjacent zeniths were 4-10 samples apart time was considered continuous.

Then, the sample numbers corresponding to the times-of-occurrence of all beats were computed from the beat annotation stream, and series of uninterrupted beats were forged as long as time was continuous. When the total amount of continuous annotation stream was less than 960 minutes (16 hours), the tape was considered as non-representative for a full day, and excluded from analysis.

Finally, the actual times-of-occurrence of all beats were determined by interpolation between two adjacent zeniths in the clock signal, after which the following heart rate and heart rate variability parameters were computed (time window: 5 minutes): minimal / average / maximal heart rate (HRmin / HRav / HRmax = minimum / average / maximum of all heart rates computed for each 5-minute time window), standard deviation of the averaged intervals between normal beats as computed for each 5-minute time window (SDANN), average of the standard deviations of the intervals between normal beats as computed for each 5-minute time window (SDNN), averaged percent successive intervals between normal beats differing >50 ms (pNN50), averaged low-frequency heart rate variability in normalized units as computed in each 5-minute time window (LFnu)[1].

2.3. Follow up

Follow up was done in 2001 and 2002. The national registry of the causes of death in The Netherlands is held by Statistics Netherlands (Centraal Bureau voor de Statistiek, Den Haag). Severe restrictions imposed by the Dutch privacy law practically block the possibility to query this database for individual death causes. As a consequence, our follow up study has all cause mortality as endpoint.

2.4. Statistics

The risk factors smoking, hypertension, overweight and hypercholesteremia were dichotomized at >0 cigarettes / day, systolic blood pressure > 140 mmHg, diastolic blood pressure >95 mmHg, BMI > 27.8 kg/m^2, and total serum cholesterol > 8 mmol/l, respectively. Arrhythmias were already categorical variables. Heart rate and heart rate variability parameters (HRmin, HRav, HRmax, SDANN, SDNN, pNN50, LFnu) were dichotomized according to their median values.

Finally, multivariate Cox regression procedures (SPSS, method = ENTER) were done for the following groups of variables: 1) age and risk factors; 2) age, risk factors, arrhythmias; 3) age, risk factors, HRV; 4) age,

risk factors, arrhythmias, HRV. To be entered in the multivariate regression, the arrhythmia and HRV factors had to have *P*-values < 0.10 in an univariate Cox regression. These selected variables were: average heart rate (*P*=0.07), atrial fibrillation (*P*<0.001) and R-on-T ventricular extrasystoles (univariate *P*=0.06).

Table 1. Study population overview (N=153)

Variable	Mean±SD	Unit
Age	51.4±5.6	y
BMI	24.3±2.4	kg/m^2
Systolic blood pressure	133.6±13.9	mmHg
Diastolic blood pressure	82.4±9.0	mmHg
Total serum cholesterol	6.3±1.0	mmol/l
HRmin	55.9±7.4	bpm
HRav	72.6±8.4	bpm
HRmax	113.8±15.2	bpm
SDANN	0.13±0.04	s
SDNN	0.056±0.015	s
PNN50	10.0±8.0	%
LFnu	72.0±8.5	nu

Table 2. Overview of risk factors and arrhythmias. SVES/VES = (supra-)ventricular extrasystoles.

Variable	Present	%
Smoker	57	37.3
Hypertension	38	24.8
Overweight	11	7.2
Hypercholesteremia	7	4.6
Isolated SVES	125	81.7
Runs of SVES	33	21.6
Atrial flutter	1	0.7
Atrial fibrillation	2	1.3
Nodal rhythm	7	4.6
1st degree AV block	1	0.7
2nd degree AV block	4	2.6
3rd degree AV block	0	0
1-10 VES	96	62.7
>10 VES	21	13.7
Multifocal VES	48	31.4
VES in bigeminy	6	3.9
VES in doublets	12	7.8
VES in runs	0	0
VES R-on-T	9	5.9

3. Results

The original 1978-1980 study comprised of 300 subjects with ambulatory ECG recordings that were fully analyzed as to arrythmia incidence. Follow-up duration was 21.8±0.6 years, 52 subjects (17.7%) died during this period, and 7 subjects (2.3%) were lost to follow-up.

Reliable reanalysis for computation of heart rate variability was possible in 153 cases (the remaining cassettes could not be used because of inferior signal quality or insufficient data after the time linearization procedure had been executed) and consitute the study group. Descriptive statistics of this group are given in Tables 1 and 2. During the follow-up period 27 subjects (17.6%) of this study group died.

The significant variables in the multivariate Cox regression procedures for age and risk factors; for age, risk factors and arrhythmias; for age, risk factors and HRV; and for age, risk factors, arrhythmias and HRV are summarized in Tables 3-6, respectively.

Table 3. Significant variables in the multivariate Cox regression procedure for age and risk factors.

Variable	Rel. Risk & 95% Conf. Interval	*P*-value
Smoker	3.1 [1.4-6.9]	0.005

Table 4. Significant variables in the multivariate Cox regression procedure for age, risk factors and arrhythmias. Because of the low number of cases with atrial fibrillation (2) we give here the univariate results for this variable.

Variable	Rel. Risk & 95% Conf. Interval	*P*-value
Smoker	3.2 [1.3-7.6]	0.008
Atrial fibrillation	13.8 [3.2-59.2]	0.001
VES R-on-T	7.0 [1.8-27.5]	0.005

Table 5. Significant variables in the multivariate Cox regression procedure for age, risk factors, and HRV.

Variable	Rel. Risk & 95% Conf. Interval	*P*-value
Age	1.1 [1.0-1.2]	0.044
Smoker	2.7 [1.2-6.4]	0.021
HRav	6.2 [1.6-23.9]	0.008

Table 6. Significant variables in the multivariate Cox regression procedure for age, risk factors, arrhythmias and HRV. Because of the low number of cases with atrial fibrillation (2) we give here the univariate results for this variable.

Variable	Rel. Risk & 95% Conf. Interval	*P*-value
Overweight	3.8 [1.0-14.5]	0.049
Atrial fibrillation	13.8 [3.2-59.2]	0.001
VES R-on-T	8.4 [1.8-38.3]	0.006
HRav	5.6 [1.4-21.9]	0.014

4. Discussion

This restrospective follow-up study, done 22 years after an ambulatory ECG recording was made in 153 apparently healthy middle aged men showed that occasionally observed arrhythmias in this population have predictive value for all-cause mortality: elevated relative risks were found for artial fibrillation (univariate relative risk 13.8) and for ventricular ectopic beats of the R-on-T type (multivariate relative risk 7.0 / 8.4). Also, elevated relative risks were found for average heart rate (multivariate relative risk 6.2 / 5.6).

The arrhythmia factors that had prognostic value (atrial fibrillation, R-on-T ventricular ectopy) were based on the original analysis of the ambulatory recordings that had been done more than 20 year ago. Recent reanalysis of these cassettes yielded one new prognostic factor, that of average heart rate. Though this may be regarded as important added value, one may question why there were no heart rate variables identified as risk factors. The best answer we can provide is that we may have set our quality levels in various stages of the reanalysis too high. This caused a lot of data loss: only 153 of the original number of 300 recordings could be analyzed, and in these 153 recordings a substantial amount of data was not used because of the discontinuities that resulted from the time linearization procedure.

The recruitment of apparently healthy subjects is obviously not a standard procedure. E.g., an exercise test would have added more certainty about the possible presence of ischemic heart disease in our study group. The definition of apparent health is also subject to changes in time. E.g., high blood pressure values at intake were tolerated as long as the subjects were not treated for hypertension. Part of these high readings may have been caused by the white coat effect, but part may have been real hypertension, that now would have been medically treated. However, according to statistical comparison with the general Dutch population of similar age and gender, our study group appeared to have a mortality ratio (observed/expected deaths) of 0.51 (95% confidence interval 0.35-0.70). This relative good health is attributable to the healthy worker effect : by selecting subjects from active working people most invalidating and large part of not yet diagnosed diseases are excluded.

The high relative risks associated with atrial fibrillation, R-on-T ventricular ectopy and average heart rate are to be interpreted in the setting of the study group. As the mortality rate in healthy middle aged persons is low, serious risk of dying must necessarily reflect into a substantial relative risk. Also, the results for atrial fibrillation and R-on-T ventricular ectopy should be interpreted with care because they are based on small numers: only 2 subjects had episodes of atrial fibrillation (both subjects died), and 9 had R-on-T ventricular extrasystoles (4 subjects died).

To our knowledge our study is unique, as there are no follow-up studies on the basis of ambulatory ECG recordings in healthy subjects, with all-cause mortality as endpoint, that can be used as a reference. Studies in random samples of the population, like those of Engström and colleagues [2], Mäkikallio and colleagues [3], cannot be used as comparative material, because such groups are not free of disease. Molgaard and colleagues [4,5] performed an 8-year follow-up study in 245 apparently healthy subjects (163/82 male/female, mean age 54 [40-79]), but did not present all-cause mortality statistics.

As our study had to be restricted to the end point of all cause mortality it is difficult to speculate about the involved mechanisms of death; arrhythmias (risk factors: atrial fibrillation and R-on-T ventricular ectopy) and abnormal sympathetic cardiac control (risk factors: average heart rate) are likely to play a role. The prognostic value of ambulatory recordings in an apparently healthy population deserves more attention than has been payed to it until now.

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