ORIGINAL RESEARCH

Temporal Reduction in Chronotropic Index Predicts Risk of Cardiovascular Death Among Healthy Middle-Aged Men: a 28-Year Follow-Up Study

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***Background*—**Chronotropic index is a standardized measure of heart rate (HR) increment during exercise that reflects the combined effects of age, resting HR, and physical fitness. Low chronotropic index has been reported to predict disease and death. We tested whether temporal change in chronotropic index over 7 years influenced risk of cardiovascular death through up to 28 years.

***Methods and Results*—**Chronotropic index was calculated ([achieved maximal HR−resting HR]/[age-predicted maximal HR−resting HR]) after a symptom-limited bicycle ECG exercise test in 1420 healthy men at 2 examinations 7 years apart, in 1972 and 1979. Events of cardiovascular death were registered by manual scrutiny of all participants' hospital charts and the Norwegian Cause of Death Registry. The participants were divided into quartiles of temporal change in chronotropic index, with quartile one having the most negative value. Cox proportional hazard regression models were used to estimate risks and adjusted for classical cardiovascular risk factors. Incidence of cardiovascular death was 310 (22%) during median of 21 years of follow-up. After multivariable adjustment, and comparison with quartile four (mean +0.11), quartiles one (−0.16), two (−0.04), and three (+0.02) were associated with hazard ratios 1.50 (95% CI 1.10–2.05), 1.10 (0.79–1.53), and 1.04 (0.74–1.45) for cardiovascular death. Results remained robust also after exclusion of 31 participants with exercise ECG-induced signs of coronary ischemia.

***Conclusions*—**Temporal reduction in chronotropic index was associated with increased long-term risk of cardiovascular death and might be a clinically important predictor when assessing risk in healthy individuals over a longer time. **(*J Am Heart Assoc*. 2016;5: e004555 doi: 10.1161/JAHA.116.004555)**

Key Words: all-cause death prediction • cardiovascular outcomes • chronotropic index • exercise testing • heart rate • physical exercise • risk prediction

Cardiovascular diseases remain leading causes of severe morbidity and death worldwide.[1] In preventive cardiology, improved cardiovascular prediction is important in order to choose appropriate risk-modifying strategies. Risk predictors derived from exercise testing have gained interest and are now important complements to classical risk factors, such as smoking, blood pressure, and cholesterol.[2–5] One established exercise-derived cardiovascular predictor is the chronotropic index ([achieved maximal heart rate−resting heart rate]/[age-predicted maximal heart rate−resting heart rate]), which is a standardized measure of heart rate (HR) change during exercise that reflects the combined effects of age, resting HR, and physical fitness (PF).[6] Measured HR increment during exercise, which is incorporated in the chronotropic index formula, is shown to be associated with cardiovascular death[6–8] and its predictive ability is influenced by PF.[9] Temporal changes in PF-related or exercise-derived parameters such as resting HR and exercise systolic blood pressure have been reported to predict cardiovascular disease and death.[5,10] Despite inevitable individual changes in resting HR, maximal HR, and PF over time,[11–13] the prognostic impact of temporal change in chronotropic index on cardiovascular death risk has not been studied before.

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Accompanying Tables S1 through S4 are available at http://jaha.ahajournals.org/content/5/12/e004555/DC1/embed/inline-supplementary-material-1.pdf

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The main aim of the present work was to study the possible association between temporal change in chronotropic index over 7 years and risk of future cardiovascular death among 1420 apparently healthy middle-aged men. Second, we tested the possible association between temporal change in chronotropic index and risk of all-cause death. Finally, we aimed to investigate whether there was an interaction between change in chronotropic index and PF that validated investigation of associations between chronotropic index and end points within subgroups of men according to their PF level.

Methods

Study Population

The present study included a population of 1420 men in the Oslo Ischemia Study who fulfilled our criteria for studying the possible prognostic impact of change in chronotropic index on cardiovascular death and all-cause death (Figure 1). The Oslo Ischemia Study consists of 2014 apparently healthy men aged 40 to 59 years recruited from 5 governmental institutions in Oslo during the years 1972–1975.[14] All men gave their informed consent before inclusion. Further details about selection procedures and exclusion criteria have been presented elsewhere.[14–16] All participants underwent standardized clinical examinations, blood tests, chest radiograph, resting ECG, and symptom-limited bicycle exercise ECG tests at inclusion (Survey 1, 1972–1975) and identical examination in the years 1979–1982 (Survey 2). Family history of coronary heart disease, including angina pectoris, nonfatal/fatal myocardial infarction among parents or siblings, was registered in questionnaires. To be included in the present study, the men had to be healthy at both Survey 1 and Survey 2. The study was approved by the regional committee for medical and health research ethics (REK).

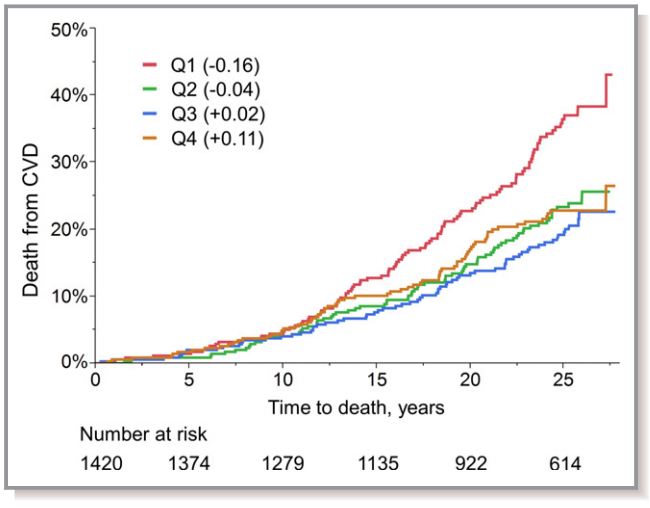

Figure 1. Cardiovascular death in quartiles of men according to 7-year change in chronotropic index. Kaplan–Meier plot exhibiting death from cardiovascular disease in percent (*y*-axis) during 28 years of follow-up (*x*-axis) in quartiles (Q1–Q4) by 7-year change in chronotropic index among 1420 healthy middle-aged men. CVD, cardiovascular disease.

Examinations

Resting HR was counted manually during 60 s measured with a stopwatch after a standardized period of supine rest. All participants performed a standardized bicycle exercise ECG test and were examined by the same physician (J.E.) at both surveys. The initial workload was 6 minutes at 100 W, increased by 50 W every 6 minutes. The exercise tests were continued until a HR of at least 90% of the maximal predicted HR was reached unless specific symptoms or signs necessitated a premature termination.[17] If an individual seemed physically fit despite his reaching 90% of maximal predicted HR +10 bpm at the end of 1 load, he was encouraged to continue as long as possible on the next load, ie, maximally for an additional 6 minutes on a higher load.[6] Exercise testing was repeated within 2 weeks in 130 of the participants and showed high reproducibility for HRs and working capacity between the 2 tests, within ±5% in 90% of the men, and within ±10% in all of them. HR was measured every second minute throughout the test. Peak exercise HR was recorded from ECG just before termination of the test. Chronotropic index was calculated ([achieved maximal HR−resting HR]/[age-predicted maximal HR−resting HR]). Age-predicted maximal HR was calculated according to Tanaka et al (208−0.7×age).[18] PF was defined as the total bicycle exercise work (Joules), calculated as the sum of work at all workloads divided by body weight (kg). Further details about HR and PF measurements have also been presented previously.[15,16]

Follow-Up

Morbidity and mortality data were consecutively obtained from 2 clinical surveys in 1989–1990 (Survey 3), and 1994–1995 (Survey 4), 1 questionnaire survey in 1987, and 2 nationwide searches of patient records from all Norwegian hospitals in 1995–1996 and in 2005–2008 with permission from relevant authorities. Mortality data were obtained from the Norwegian Cause of Death Registry and validated through scrutiny of medical records. All morbidity and mortality data are complete up to January 1, 2007, and none of the participants were lost to follow-up.

End Points

The main end point in the present study was cardiovascular death, consisting of fatal myocardial infarction, sudden

cardiac death, fatal stroke (cerebral infarction or hemorrhage), and death from pulmonary embolism or aortic disease. The secondary end point was death from any cause.

Statistical Methods

All statistical calculations were performed using SAS JMP 9 software. Kendall rank tests were used to assess correlation (trend) between 7-year change in chronotropic index quartiles and clinical characteristics of participants. The risks of end points in change in chronotropic index-quartiles were estimated by Kaplan–Meier plots and tested with log-rank tests. Cox proportional-hazard modeling was used when calculating hazard ratios and observation time started at Survey 2. Significant variables in univariate analyses ($P<0.05$) were entered into multivariable analysis, and a final prediction model was reached by stepwise backward variable selection. We chose to keep chronotropic index at Survey 1 in all adjustment models because it forms the baseline level for change in chronotropic index. Hazard ratios for end points were then examined after bivariable adjustment for baseline chronotropic index and age; and then multivariable adjustment for baseline chronotropic index, age, smoking status, total cholesterol, resting systolic blood pressure and PF, as well as smoking cessation between Survey 1 and Survey 2 and family history of coronary heart disease. Statistical interactions between change in chronotropic index and change in PF were tested by adding the interaction term of these variables in the regression models. The same adjustment models and interaction analyses were used for both end points to obtain comparable results. Models were also tested for both endpoints after exclusion of 31 men who exhibited ischemia during the exercise test by developing ST-depressions of more than 2 mm or chest pain.[2,19] The same change in chronotropic index quartile-limits from the total material was also used for the group of 1389 men with no signs of ischemia at Survey 2 exercise test. Sensitivity analyses of other potential predictors of cardiovascular death and all-cause death were also performed (see Results section).

Results

Characteristics of Participants

At Survey 1, the 1420 men were on average 49.3 years, had a body mass index of 24.4, and 567 (40%) were current smokers. Mean resting HR was 61 beats per minute (BPM), and mean maximal HR was 165. Mean resting HR increased with 2 beats per minute, and mean maximal HR decreased with 7 beats per minute from Survey 1 to Survey 2. Smoking cessation, Survey 1 and 2 PF, 7-year change in PF, Survey 2 maximal HR, and Survey 2 chronotropic index were correlated with increasing chronotropic index. The relationship between temporal changes in chronotropic index and PF was further studied with a scatterplot analysis exhibiting a correlation coefficient of 0.34 (Figure 2). Survey 1 percentage of smokers, serum cholesterol, and chronotropic index were inversely correlated with increasing chronotropic index. There was no correlation between body mass index or change in body mass index and increasing chronotropic index (Table 1).

End Points

Crude incidence of cardiovascular death among the 1420 men was 310 (21.8%) during up to 27.7 years (median 20.8) comprising 29 536 person-years of follow-up after Survey 2. Crude incidence of all-cause death was 740 (52.1%). The incidences of cardiovascular death and all-cause death were inversely correlated with change in chronotropic index (Table 1).

Hazard Ratios for Death

Change in chronotropic index and classical cardiovascular risk factors were significant and independent predictors of cardiovascular death and all-cause death after multivariable adjustment (Tables 2 and S1). Crude risks of cardiovascular death increased with negative changes in chronotropic index-quartiles as shown in Figure 1. After multivariable adjustment and comparison with quartile four (mean +0.11), quartile one (−0.16) was associated with hazard ratio 1.50 (95% CI 1.10–

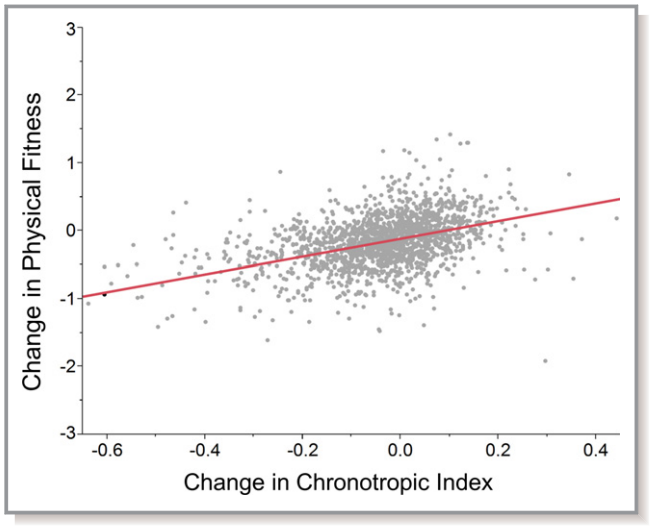

Figure 2. Relationship between temporal changes in chronotropic index and physical fitness. Scatterplot exhibiting the relationship between temporal change in chronotropic index (*x*-axis) and physical fitness in kJ/kg (*y*-axis). Two outliers ($x=0.07$, $y=4.16$) and ($x=-0.16$, $y=-5.06$) are not shown due to the scaling of the axes. Correlation coefficient, $R=0.34$.

Table 1. Characteristics of Participants in Quartiles According to 7-Year Change in Chronotropic Index

	Q1	Q2	Q3	Q4	*P* Value
N	355	355	355	355	Kendall
Age, y	50.2 (5.4)	48.6 (5.3)	48.6 (5.2)	49.7 (5.4)	0.3177
BMI, kg/cm^2	24.5 (2.4)	24.3 (2.7)	24.4 (2.7)	24.2 (5.4)	0.1834
ΔBMI, kg/cm^2	0.25 (1.49)	0.33 (1.23)	0.17 (1.23)	0.26 (1.21)	0.6838
Serum cholesterol, mmol/L	6.7 (1.3)	6.6 (1.2)	6.5 (1.1)	6.6 (1.2)	0.0254
Systolic blood pressure, mm Hg	128 (16)	128 (16)	126 (16)	128 (16)	0.2653
Resting heart rate 1, BPM	62 (11)	61 (9)	60 (9)	62 (9)	0.7157
Maximal heart rate 1, BPM	164 (13)	166 (13)	166 (13)	162 (14)	0.0314
Resting heart rate 2, BPM	63 (10)	63 (10)	61 (9)	65 (11)	0.0924
Maximal heart rate 2, BPM	144 (14)	157 (12)	162 (12)	168 (12)	<0.0001
Physical fitness 1, kJ/kg	1.45 (0.60)	1.60 (0.60)	1.61 (0.56)	1.46 (0.56)	0.0076
Physical fitness 2, kJ/kg	1.10 (0.55)	1.43 (0.60)	1.52 (0.57)	1.50 (0.65)	<0.0001
ΔPhysical fitness, kJ/kg	−0.35 (0.42)	−0.17 (0.33)	−0.09 (0.34)	0.04 (0.44)	<0.0001
Smoking, n (%)	171 (48)	133 (37)	135 (38)	128 (36)	0.0024
Smoking cessation, n (%)	38 (10)	33 (9)	49 (13)	51 (14)	0.0034
Family history CHD, n (%)	62 (18)	82 (24)	67 (19)	80 (23)	0.5033
Cardiovascular death, n (%)	102 (29)	73 (21)	65 (18)	70 (20)	<0.0001
All-cause death, n (%)	236 (66)	177 (50)	149 (42)	178 (50)	<0.0001
Chronotropic index 1	0.93 (0.10)	0.93 (0.10)	0.93 (0.10)	0.90 (0.11)	0.0067
Chronotropic index 2	0.77 (0.12)	0.89 (0.10)	0.94 (0.10)	1.00 (0.11)	<0.0001
ΔChronotropic index (mean)	−0.16	−0.04	0.02	0.11	<0.0001
ΔChronotropic index (range)	−0.60 to −0.08	−0.08 to −0.01	−0.01 to 0.05	0.05 to 0.44	

Values are mean with SD in parentheses or n, number, with percent in parentheses of characteristics of men in quartiles according to 7-year change in chronotropic index. Δ represents 7-year change of the denoted parameter. BMI indicates body mass index; BPM, beats per minute; CHD, coronary heart disease.

2.05) for cardiovascular death. When using the most negative change in chronotropic index-quartile, quartile one, as reference, and quartiles two, three, and four were all associated with hazard ratios 0.73 (0.54–0.99), 0.69 (0.50–0.94), and 0.67 (0.49–0.91) for cardiovascular death (Table 3).

Crude risks of all-cause death increased with more negative temporal changes in chronotropic index-quartiles. After multivariable adjustment and comparison with quartile four, quartile one was associated with hazard ratio 1.35 (1.10–1.64) for all-cause death. When using the most negative change in chronotropic index-quartile, quartile one, as reference, quartiles two, three, and four were associated with hazard ratios 0.78 (0.64–0.95), 0.67 (0.54–0.82), and 0.74 (0.61–0.91) for all-cause death (Table S2).

Sensitivity Analyses and Statistical Interaction

In the subgroup of 1389 men with no detectable ischemia at Survey 2 exercise ECG tests, the incidence of cardiovascular death and all-cause death were 295 (21.2%) and 715 (51.5%), respectively. The most negative change in chronotropic index-category (mean −0.16) was associated with 41% and 34% increased multivariable adjusted risk of cardiovascular death and all-cause death, respectively, compared with the largest change in chronotropic index-category (mean +0.11) (Table S3).

Several other possible predictors of cardiovascular death, including systolic blood pressure at 100 W workload, fasting blood glucose, triglycerides, radiograph-measured relative heart volume, forced expiratory volume at 1 s, hemoglobin level, resting HR, maximal HR, body mass index, and temporal change in body mass index, were introduced into a complete multivariable analysis model to evaluate potential impact on cardiovascular death prediction. However, none of these variables had significant impact on the prediction model (Table S4).

We found no statistical interaction between chronotropic index, temporal change in chronotropic index and PF, or temporal change in PF (data not shown) and hence, no stratification by PF level was validated.

Table 2. Impact of Predictors of Cardiovascular Death

	Univariable HR	Multivariable HR	χ^2	*P* Value
Age	2.09 (1.86–2.35)	2.37 (1.60–3.57)	19.9	<0.0001
Systolic blood pressure	1.35 (1.20–1.51)	1.31 (1.16–1.48)	18.7	<0.0001
Smoker, y/n	1.42 (1.13–1.77)	1.56 (1.20–2.03)	10.9	0.0010
Cholesterol	1.26 (1.13–1.39)	1.19 (1.07–1.33)	9.8	0.0018
Δ Chronotropic index	0.80 (0.70–0.91)	0.83 (0.72–0.95)	7.0	0.0080
Family history CHD, y/n	1.47 (1.13–1.89)	1.42 (1.09–1.83)	6.5	0.0108
Smoking cessation	0.62 (0.41–0.89)	0.70 (0.47–1.02)	3.4	0.0659
Body mass index	1.16 (1.03–1.30)	1.08 (0.96–1.23)	1.7	0.1928
Chronotropic index	0.90 (0.80–1.02)	0.47 (0.12–1.71)	1.3	0.2549
Maximal heart rate	0.90 (0.80–1.03)	2.08 (0.51–9.34)	1.0	0.3164
Resting heart rate	1.03 (0.91–1.15)	0.94 (0.81–1.09)	0.6	0.4412
Physical fitness	0.87 (0.76–0.99)	1.00 (0.86–1.16)	<0.1	0.9670

Values are hazard ratios (HR) of 1 SD increase in baseline value for continuous variables, and HR for yes vs no for baseline status of nominal variables, 95% CI in parentheses. Ranked by χ^2 in multivariate model with all possible predictors included. BMI indicates body mass index; CHD, coronary heart disease.

Discussion

We investigated a possible association between temporal changes in chronotropic index, measured by repeated symptom-limited bicycle exercise ECG tests, and long-term (up to 28 years) risks of cardiovascular death and all-cause death among 1420 apparently healthy middle-aged men followed for more than 29 000 person-years. We confirmed that chronotropic index measured immediately before the start of follow-up (at Survey 2) was a significant long-term predictor of cardiovascular death after adjustment for PF and classical cardiovascular risk factors, whereas baseline measurements of chronotropic index (at Survey 1) had no prognostic value for cardiovascular death. For all-cause death, however, both present and previous chronotropic index measurements are of prognostic value using the same adjustment models. The new finding was that temporal change in chronotropic index was an independent long-term predictor of cardiovascular death after adjustment for PF and classical cardiovascular risk factors. Similar findings were detected when separately assessing all-cause death risks. The results remain robust after exclusion of a limited number of participants with signs of myocardial ischemia on exercise ECG tests.

Potential Pathophysiological Mechanisms

Baseline values of chronotropic index and PF were correlated inversely with change in chronotropic index, and change in PF increased with increasing change in chronotropic index. Smoking elevates resting HR, slows HR increase during

Table 3. Hazard Ratios for Cardiovascular Death in Quartiles According to 7-Year Change in Chronotropic Index, n=1420

	Q1	Q2	Q3	Q4
N	355	355	355	355
Crude cardiovascular death, n (%)	102 (29)	73 (21)	65 (18)	70 (20)
Bivariable adjusted HR				
Q4 as reference	1.68 (1.24–2.30)	1.22 (0.88–1.71)	1.07 (0.76–1.50)	1
Q1 as reference	1	0.73 (0.54–0.98)	0.63 (0.46–0.87)	0.59 (0.44–0.81)
Multivariable adjusted HR				
Q4 as reference	1.50 (1.10–2.05)	1.10 (0.79–1.53)	1.04 (0.74–1.45)	1
Q1 as reference	1	0.73 (0.54–0.99)	0.69 (0.50–0.94)	0.67 (0.49–0.91)

Values are hazard ratios for cardiovascular death with 95% CI in parentheses. Bivariable adjusted for baseline age and chronotropic index. Multivariable adjusted for baseline values of chronotropic index, physical fitness, age, systolic blood pressure, smoking status, and total serum cholesterol as well as family history of coronary heart disease and smoking cessation between Survey 1 and Survey 2.

exercise, and impairs the ability to reach age-predicted maximal HR,[20,21] and physical exercise lowers resting HR.[11] However, resting HR at Survey 1 and 2 were not different among the change in chronotropic index-quartiles, whereas maximal HR at both Survey 1 and 2 were. Smoking cessation was most frequent in the highest change in chronotropic index-quartile. Adjustment for smoking cessation did not alter the results and other lifestyle changes, such as increased physical exercise, may also contribute. Maximal HR, which is not modifiable by endurance training, and is highly age dependent and genetically determined,[6] was inversely correlated with chronotropic index at Survey 1 and correlated with Survey 2 chronotropic index and change in chronotropic index. Subclinical cardiovascular disease can cause exercise intolerance and failure to reach maximal HR. Still, excluding 31 men who exhibited signs of coronary ischemia at the Survey 2 exercise test only weakened the results marginally.

We previously showed that HR reserve (the difference between maximal HR and resting HR) predicts cardiovascular death and showed that HR reserve and PF interact on cardiovascular risk prediction. After stratifying the same study population included in the present study by low, intermediate, or high PF, the predictive abilities of HR reserve were confined to the group of men with low physical fitness.[9] We found no statistical interaction between chronotropic index or temporal change in chronotropic index and PF and hence, no stratification by PF level was validated. Chronotropic index is, however, a standardized measure of HR increment during exercise that reflects the combined effects of age, resting HR, and physical fitness. Similar to HR reserve, the chronotropic index reflects the complex interaction between the autonomic nervous system and the cardiovascular system during exercise. We have discussed this relationship in more detail elsewhere.[9]

Clinical Relevance

Our past and previous results add to the growing amount of evidence that autonomic imbalance, as revealed by measurement of resting HR, maximal HR during exercise, HR reserve, or chronotropic index during exercise, is an important death risk predictor.[3,6,13,22–24] Resting and maximal HR are easily measured during exercise testing and allows self-assessment during rest and endurance training using commonly available HR monitoring equipment such as watches or smart-phone applications. Chronotropic index can then be calculated by a simple formula and results can be logged to assess temporal changes. Our results suggest that a reduction in chronotropic index as time progresses is associated with increased death risk.

Equally interesting, the results also indicate that a temporal increase in chronotropic index is associated with reduced long-term death risk. This finding encourages change to a healthier lifestyle with cessation of smoking and start of regular physical exercise. Such changes can, in the absence of relevant morbidity, influence the ability to reach maximal HR, lower resting HR, and modify classical cardiovascular risk factors such as blood pressure and cholesterol level.[20,21] It is possible that use of temporal change in chronotropic index and other markers of autonomic imbalance could improve the accuracy of cardiovascular death risk prediction, for example, by reclassifying individuals for medium to low or high cardiovascular death risk.[3,6,7,9,22]

Strengths of the Study

The present study is prospective in design, and all data sets are complete with none lost to follow-up. We have no work-up bias, and all event data are on the basis of complete hospital records and cause-specific death records. All men were healthy and free of drugs, and the study group has not interfered with treatment in case of disease. The reproducibility of our exercise data was verified by re-examination of 130 participants within 2 weeks. PF, as defined in the present study (total exercise capacity divided by body weight), has been shown to be highly correlated with maximum oxygen uptake, which is the most accepted measure of PF.[25,26]

Limitations

Predicted maximal HR may underestimate true maximal HR in middle-aged and older persons.[27] We cannot rule out that this and intravariability in exercise capacity and response in some individuals could have influenced the results. Our cohort consists of middle-aged white men who were healthy and employed full-time at inclusion, and our findings cannot necessarily be generalized to individuals of other ages, ethnicities, or sex. Only those who stayed healthy and free of medical treatment between Survey 1 and Survey 2 were included in our study. As a result of this, our findings cannot be applied in the setting of significant comorbidities and/or chronic drug use.

Conclusions

We have shown that a temporal reduction in chronotropic index is associated with increased long-term risk of cardiovascular death. Chronotropic index is derived from a normal exercise test, and our data suggest that repeated measurements might become a clinically important tool when assessing cardiovascular preventive strategies in healthy individuals followed in the routine clinical practice.

Sources of Funding

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Disclosures

Dr Kjeldsen received honoraria from Bayer, MSD, and Takeda. Dr Bodegard holds a full-time position as epidemiologist with AstraZeneca. The other authors have no conflicts of interest.

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SUPPLEMENTAL MATERIAL

Table S1. Impact of predictors of all-cause death

	Univariable HR	Multivariable HR	X2	P
Smoker, y/n	1.68 (1.47-1.94)	1.72 (1.46-2.03)	38.6	<0.0001
Age	2.03 (1.88-2.19)	1.89 (1.47-2.43)	27.6	<0.0001
Δ Chronotropic index	0.79 (0.72-0.86)	0.81 (0.75-0.89)	19.7	<0.0001
Systolic blood pressure	1.18 (1.09-1.27)	1.19 (1.09-1.29)	16.3	<0.0001
Smoking cessation	0.61 (0.48-0.77)	0.69 (0.54-0.87)	9.61	0.0019
Physical fitness	0.80 (0.73-0.87)	0.89 (0.81-0.99)	4.8	0.0287
Cholesterol	1.15 (1.07-1.23)	1.08 (1.01-1.17)	4.6	0.0314
Family history CHD, y/n	1.14 (0.96-1.36)	1.15 (0.96-1.37)	2.2	0.1392
Resting heart rate	0.98 (0.91-1.06)	0.95 (0.86-1.05)	0.9	0.3380
Chronotropic index	0.79 (0.72-0.86)	0.86 (0.37-1.95)	0.1	0.7263
Maximal heart rate	0.84 (0.77-0.91)	1.04 (0.43-2.62)	<0.1	0.9410
Body mass index	1.04 (1.95-1.12)	0.99 (0.92-1.07)	<0.1	0.8474

Values are hazard ratios (HR) for all-cause death of one standard deviation increase in baseline value for continuous variables, and HR for yes vs. no for baseline status of nominal variables, 95% confidence interval in parenthesis. Ranked by chi square in multivariate model with all listed possible predictors included. CHD: Coronary heart disease.

Table S2. Hazard ratios for all-cause death in quartiles according to 7-year change in chronotropic index, n = 1420

	Q1	Q2	Q3	Q4
N	355	355	355	355
All-cause death, n (%)	236 (66%)	177 (50%)	149 (42%)	178 (50%)
Bivariable adjusted HR				
Q4 as reference	1.59 (1.30-1.93)	1.19 (0.96-1.47)	0.97 (0.77-1.20)	1
Q1 as reference	1	0.75 (0.62-0.91)	0.61 (0.50.0.75)	0.63 (0.51-0.77)
Multivariable adjusted HR				
Q4 as reference	1.35 (1.10-1.64)	1.05 (0.85-1.30)	0.90 (0.72-1.12)	1
Q1 as reference	1	0.78 (0.64-0.95)	0.67 (0.54-0.82)	0.74 (0.61-0.91)

Values are hazard ratios for CV death with 95 per cent confidence intervals in parenthesis. Bivariable adjusted for baseline age and chronotropic index. Multivariable adjusted for baseline values of chronotropic index, physical fitness, age, systolic blood pressure, smoking status and total serum cholesterol as well as family history of coronary heart and smoking cessation between Survey 1 and Survey 2.

Table S3. Hazard ratios for death in quartiles according to 7-year change in chronotropic index in men with no detectable ischemia at Survey 2, n = 1389

End points	Q1	Q2	Q3	Q4
CV death	1.41 (1.02-1.93)	1.03 (0.74-1.45)	1.01 (0.72-1.43)	1
All-cause death	1.34 (1.09-1.64)	1.08 (0.87-1.34)	0.92 (0.74-1.15)	1

Values are hazard ratios for death with 95 per cent confidence intervals in parenthesis after multivariable adjustment for baseline values of chronotropic index, physical fitness, age, systolic blood pressure, smoking status and total serum cholesterol as well as family history of coronary heart and smoking cessation between Survey 1 and Survey 2. CV: Cardiovascular.

Table S4. Impact of predictors of CV death, full multivariable model

	Multivariable HR	X2	P
Age	2.21 (1.47-3.36)	15.3	<0.0001
Smoker, y/n	1.64 (1.26-2.13)	13.0	0.0003
Cholesterol	1.19 (1.06-1.34)	8.4	0.0038
Smoking cessation	0.58 (0.38-0.86)	7.2	0.0073
Systolic blood pressure	1.21 (1.03-1.41)	5.6	0.0178
Δ Chronotropic index	0.84 (0.73-0.97)	5.6	0.0178
Family history CHD, y/n	1.38 (1.05-1.79)	5.4	0.0196
Fasting blood glucose	1.11 (0.99-1.23)	3.3	0.0711
Δ Body mass index	1.12 (0.98-1.27)	2.7	0.0987
Systolic BP 100W	1.11 (0.94-1.31)	1.6	0.2044
Body mass index	1.07 (0.93-1.24)	1.0	0.3085
Resting heart rate	0.92 (0.79-1.08)	1.0	0.3093
Chronotropic index	0.54 (0.14-2.07)	0.8	0.3845
Maximal heart rate	1.73 (0.40-7.96)	0.6	0.4676
Relative heart volume	1.03 (0.90-1.16)	0.2	0.6808
Physical fitness	0.98 (0.82-1.15)	0.1	0.7817
Triglycerides	0.98 (0.87-1.09)	0.1	0.7405
FEV1	1.01 (0.88-1.16)	<0.1	0.8596
Haemoglobin level	1.01 (0.90-1.15)	<0.1	0.8269

Values are hazard ratios (HR) of one standard deviation increase in baseline value for continuous variables, and HR for yes vs. no for baseline status of nominal variables, 95% confidence interval in parenthesis. Δ is temporal change in the denoted variable, FEV1 is forced expiratory volume at one second, CHD is coronary heart disease, Systolic BP 100W is systolic blood pressure at 100 Watts workload. Variables are ranked by chi square in a multivariate model with all possible predictors included.