Chronotropic Response to Exercise Testing and the Risk of Stroke

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Although the chronotropic response to exercise testing, defined as an inadequate heart rate response to incremental exercise to volitional fatigue, is associated with adverse cardiovascular outcomes, it remains unclear whether this response is related to the future risk of cerebrovascular events. We tested the hypothesis that the chronotropic response to exercise is associated with an increased risk of stroke in a general population. This prospective study was based on a population sample of 2,036 men aged 42 to 60 years in the Kuopio Ischemic Heart Disease cohort study. Chronotropic response to exercise was defined as the percentage of chronotropic index ([maximum heart rate − resting heart rate] / [220 − age − resting heart rate] × 100). Incident strokes were obtained from the Finnish national hospital discharge registry. During a median 27-year follow-up, 343 incident stroke (289 ischemic and 66 hemorrhagic) events occurred. Twelve events were diagnosed as both ischemic and hemorrhagic stroke. Comparing the bottom versus top quintile of chronotropic reserve, there was an increased risk of stroke (hazard ratio [HR] 1.73, 95% confidence Interval [CI]: 1.09 to 2.75) and ischemic stroke (HR 1.72, 95% CI, 1.04 to 2.85), but not hemorrhagic stroke (HR 2.23, 95% CI, 0.77 to 6.46) in analyses that adjusted for potential risk factors. These results suggest that an impaired chronotropic response to exercise is independently associated with a higher risk of total and ischemic stroke events in middle-aged men. The role of chronotropic incompetence during exercise testing as a potential prognostic indicator for stroke risk needs further investigation. **(Am J Cardiol 2021;143:46−50)**

An impaired chronotropic response to exercise testing or chronotropic incompetence, defined as an inadequate heart rate response to incremental exercise, is commonly used as an indicator of cardiac autonomic dysfunction as well as impaired exercise capacity.[1] Chronotropic incompetence has also been shown to be independently associated with subsequent cardiovascular events and a heightened risk of cardiovascular mortality in asymptomatic subjects as well as patients with cardiovascular disease (CVD).[2-4] However, it remains unclear whether the attenuated heart rate response to exercise is related to the risk of subsequent cerebrovascular events in the general population. Because individuals with an impaired chronotropic response to exercise have higher levels of cardiovascular risk factors and impaired cardiac autonomic function, which also explain the increased risk of stroke,[5,6] it is possible that the chronotropic response to exercise may herald incident stroke. We tested the hypothesis that the chronotropic response to exercise is associated with an increased risk of stroke in a general population, independent of potential risk factors and exercise capacity.

Methods

The Kuopio Ischemic Heart Disease risk factor prospective cohort study was designed to investigate risk factors (blood-based biomarkers and lifestyle characteristics) for CVD and related health outcomes over time. The population sample systematically underwent baseline examinations between March 1984 and December 1989.[4] Of 3,433 randomly selected men, 198 were excluded because of death (n = 84), serious disease (n = 65), or migration (n = 49), leaving 3,235 eligible to participate in the study. Of the 3,235 eligible men, 2,682 volunteered to participate, 186 did not respond to the invitation, and 367 declined to give informed consent. Among 2,682 men, we excluded 514 men who did not have resting heart rate and/or maximal heart rate and 132 men with incomplete data on exercise test variables and those with a previous history of stroke. The derivation of the analytic sample is described in Figure 1. We analyzed data on 2,036 men (age 42 to 60 years), who had resting and maximal heart rate determined by exercise testing and who met the eligibility criteria for

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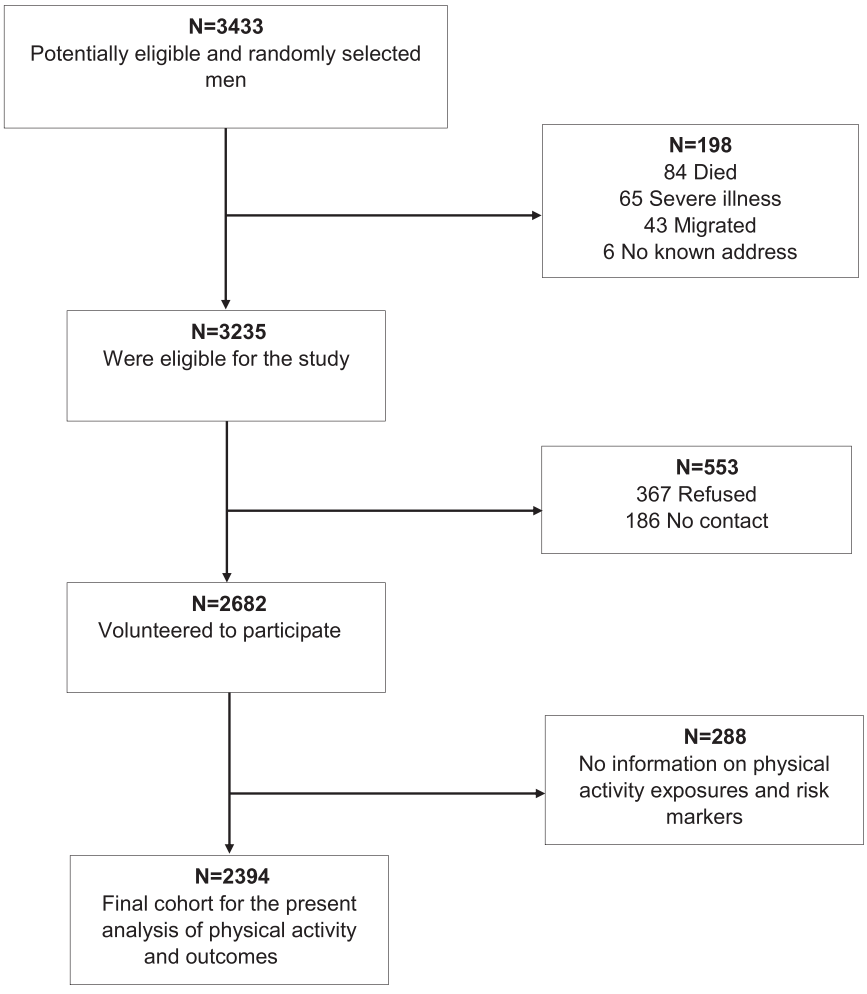

Figure 1. Flowchart of the study.

stroke outcomes in the present study. The study protocol was approved by the Research Ethics Committee of the University of Eastern Finland, Kuopio, Finland, which complies with the Helsinki Declaration. Each participant provided written informed consent.

Resting blood pressure was measured using a random-zero sphygmomanometer in the seated position following 5 and 10 minutes of quiet rest. Body mass index (BMI) was computed as the ratio of weight in kilograms to the square of height in meters. Smoking habits, 12-month physical activity history, diagnosis of chronic diseases, medications, socioeconomic status (SES) and related demographic and/or lifestyle information were obtained by a self-administered questionnaire. SES was based on a summary index that combined several measures of living. The combined SES index ranged from 0 to 25, with higher values indicating lower SES. Detailed methods for measurement of these variables and the collection of blood samples have been previously described.[7]

We employed a computerized exercise electrocardiogram and metabolic measurement system (Medical Graphics, St. Paul, Minnesota) during progressive exercise testing to volitional fatigue on an electrically braked cycle ergometer. The standardized testing protocol included a 3-minutes warm-up at 50 W, followed by 20 W/min increases in workload with the direct assessment of peak oxygen uptake (VO_{2peak}). Heart rate was measured using resting electrocardiogram, at the end of each 60-second interval during cardiopulmonary exercise testing, and at peak exercise. Maximal heart rate was defined as the highest attained value for heart rate at maximal exercise. Heart rate reserve was calculated as maximal heart rate − resting heart rate. Then, chronotropic reserve was defined as the percentage of chronotropic index ([maximum heart rate − resting heart rate] / [220 − age − resting heart rate] × 100).[8] Chronotropic incompetence was defined as the failure to achieve 80% of chronotropic index.[9] Participants were divided into quintiles according to chronotropic index.

Incident stroke outcomes were obtained through the Finnish Monitoring Trends and Determinants in Cardiovascular Diseases stroke registry. Information on incident strokes was derived from computerized linkage to the national hospital discharge registry. Diagnostic information was collected from hospitals and classified by a neurologist with diagnostic criteria identical to the Finnish Monitoring Trends and Determinants in Cardiovascular Diseases criteria. Additional information regarding the diagnostic classification of strokes has been previously described.[10]

Skewed variables (*e.g.* alcohol consumption, physical activity and C-reactive protein) were natural logarithm (log_e) transformed to achieve normality. Data were presented as mean (standard deviation) or median (interquartile range) and n (%) for continuous and categorical variables, respectively. Cox proportional hazards regression was employed to determine the hazard ratios (HRs) and 95% confidence intervals (CIs) of the exercise heart rate response to the incidence of stroke using an unadjusted model and multivariable models that included age, body mass index, systolic blood pressure, smoking, alcohol intake, CVD history, anti-hypertensive medication, beta blockers, dyslipidemia agents, C-reactive protein, creatinine, physical activity, SES, diabetes, family history of CVD, atrial fibrillation and VO_{2peak}. These variables were selected based on their previously established role as potential confounders. Cumulative hazard curves for stroke outcomes comparing quintiles of chronotropic reserve were plotted. The log rank test was used to test whether there was a difference between the survival times of the different quintiles. Statistical significance was set at $p < 0.05$, and analyses were conducted using the SPSS 22.0 (SPSS, Armonk, New York).

Results

Baseline characteristics of study participants are listed in Table 1. The prevalence of chronotropic incompetence (<80%) was 28.6% (n = 582). During a median 27-year follow-up, 343 incident stroke (289 ischemic stroke and 66 hemorrhagic stroke) events occurred. Twelve events were diagnosed as both ischemic and hemorrhagic stroke. Table 2 shows the risk of stroke by quintiles of chronotropic reserve. The unadjusted HR (95% CI) for risk of incident stroke events in the lowest versus the highest chronotropic reserve quintile were 2.42 (95% CI, 1.74 to 3.37) for stroke, 2.59 (95% CI, 1.80 to 3.74) for ischemic stroke and 1.98 (95% CI, 0.96 to 4.08) for hemorrhagic stroke, respectively. These associations remained robust when adjusted for established risk factors and directly measured exercise capacity. Comparing the bottom versus top quintile of chronotropic reserve, there was an increased risk of stroke (HR 1.73, 95% CI, 1.09 to 2.75) and ischemic stroke (HR 1.72, 95% CI, 1.04 to 2.85), but not hemorrhagic stroke (HR 2.23, 95% CI, 0.77 to 6.46) (Table 2). Figure 2 shows the Kaplan-Meier curves for stroke outcomes according to quintiles of chronotropic reserve during follow-up (p value for log rank test < 0.001).

Table 1
Baseline characteristics of study participants (n = 2,036)

Characteristics	Mean (standard deviation) or median (Interquartile range) or n (%)
Resting heart rate (bpm)	63 (11)
Maximal heart rate (bpm)	154 (25)
Chronotropic incompetence index (%)	88 (23)
Age (years)	53 (5)
Alcohol consumption (g/week)	31.4 (6.1-93.1)
Anti-hypertensive medications	419 (20.6%)
Beta-blockers	342 (16.8%)
Dyslipidemia medications	13 (0.6%)
Current smoking	661 (32.5%)
History of CVD	739 (36.3%)
Diabetes mellitus	106 (5.2%)
Family history of CVD	992 (48.7%)
Physical activity	281 (148-475)
Body mass index (kg/m^2)	26.9 (3.6)
Systolic blood pressure (mmHg)	134 (17)
Diastolic blood pressure (mmHg)	89 (11)
Peak oxygen uptake (ml/kg/min)	30.2 (8.0)
Socioeconomic status	8.54 (4.24)
Total cholesterol (mg/dl)	228.2 (41.7)
High-density lipoprotein cholesterol (mg/dl)	49.8 (11.6)
Fasting glucose (mg/dl)	86.5 (21.9)
C-reactive protein (mg/l)	1.30 (0.71-2.47)
Creatinine (umol/l)	89.6 (20.6)

Discussion

The novel findings of the present study were that a blunted chronotropic response to maximal cardiopulmonary exercise testing was associated with an increased risk of total and ischemic stroke in a general population of middle-aged men. The association was independent of conventional and emerging cardiovascular risk factors including exercise capacity. To our knowledge, this is the first study to evaluate the potential relationship of chronotropic incompetence with the risk of stroke and its subtypes.

Our findings are consistent with a previous report that showed chronotropic incompetence to be independently associated with the incidence of cerebrovascular disease in elderly patients with diabetes.[11] Other studies have reported an association between autonomic nervous system dysfunction (as measured by decreased heart rate variability) and an increased risk of stroke.[6,12] Our results extend these previous studies in two important ways. First, impaired heart rate reserve during exercise testing, used as a marker of autonomic dysfunction, was associated with an increased risk of subsequent total and ischemic stroke events. Second, the increased risk of stroke associated with impaired heart rate reserve was independent of several potential risk factors including exercise capacity, which is strongly related to chronotropic incompetence;[1] previous studies did not account for the role of.[6,11,12] Accordingly, the heart rate response during peak or symptom-limited exercise testing can be used to provide a simple index of autonomic dysfunction, suggesting that chronotropic incompetence may have the potential to be incorporated into future stroke risk assessment algorithms in clinical practice.

Several mechanistic pathways may underlie the association between impaired heart rate reserve and the increased risk of incident stroke. The chronotropic response to exercise is associated with carotid artery atherosclerosis,[8] which may reflect decreased sensitivity of carotid baroreceptor reflex to regulate cerebral blood flow and thus parallel lesion development in the cerebrovascular bed.[13] Chronotropic incompetence is commonly associated with an impaired exercise capacity and cardiac autonomic dysfunction. Thus, it has been suggested that the increased risk of stroke in individuals with an impaired chronotropic response to exercise may be attributed, at least in part, to a

Table 2
Hazard ratios (HRs) and 95% confidence intervals (CIs) for incident stroke outcomes by quintiles of chronotropic reserve

Total stroke	Events/Total (343/2,036)	Unadjusted HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Q 1 (≤70)	88/413	2.42 (1.74-3.37)	.001	1.73 (1.09-2.75)	.021
Q 2 (71-87)	77/369	2.06 (1.47-2.89)	.001	1.44 (0.97-2.14)	.070
Q 3 (88-97)	69/405	1.31 (0.93-1.85)	.129	1.15 (0.79-1.69)	.455
Q 4 (98-105)	50/399	0.95 (0.65-1.39)	.801	0.97 (0.65-1.45)	.856
Q 5 (≥106)	59/450	1 (ref)		1 (ref)	
Ischemic stroke	Events/Total (289/2,036)				
Q 1 (≤70)	75/413	2.59 (1.80-3.74)	.001	1.72 (1.04-2.85)	.036
Q 2 (71-87)	62/369	2.08 (1.43-3.05)	.001	1.32 (0.85-2.05)	.211
Q 3 (88-97)	58/405	1.40 (0.95-2.05)	.090	1.17 (0.77-1.78)	.464
Q 4 (98-105)	47/399	1.13 (0.76-1.70)	.545	1.13 (0.74-1.74)	.562
Q 5 (≥106)	47/450	1 (ref)		1 (ref)	
Hemorrhagic stroke	Events/Total (66/2,036)		.		.
Q 1 (≤70)	17/413	1.98 (0.96-4.08)	.143	2.23 (0.77-6.46)	.140
Q 2 (71-87)	17/369	1.96 (0.95-4.04)	.115	2.06 (0.84-5.05)	.112
Q 3 (88-97)	15/405	1.28 (0.61-2.70)	.391	1.45 (0.61-3.42)	.401
Q 4 (98-105)	8/399	0.69 (0.29-1.67)	.909	0.95 (0.36-2.48)	.914
Q 5 (≥106)	13/450	1 (ref)		1 (ref)	

Adjusted for age, body mass index, systolic blood pressure, smoking, alcohol intake, CVD history, antihypertensive medication, beta blockers, dyslipidemia agents, C-reactive protein, creatinine, physical activity, socioeconomic status, diabetes, atrial fibrillation, family history of CVD and VO_{2peak}.

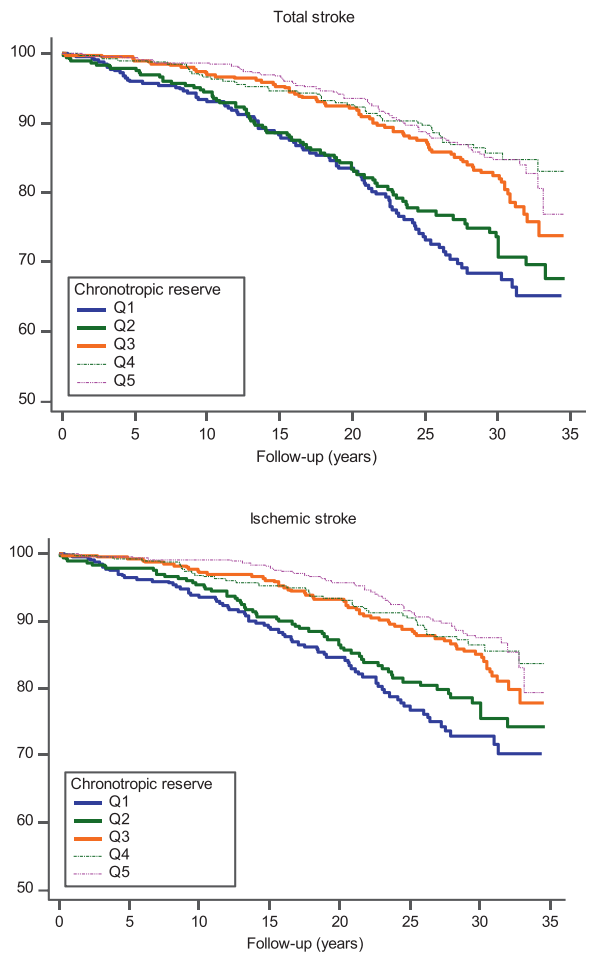

Figure 2. Kaplan-Meier curves for stroke outcomes according to quintiles of chronotropic reserve during follow-up (p value for log rank test < 0.001)

reduced exercise capacity and cardiac autonomic dysfunction, which are significant cardiovascular risk factors. However, we found that the association between an impaired chronotropic response to exercise and stroke remained significant, even after adjusting for exercise capacity. Therefore, the impairment of cardiac autonomic function, as reflected by chronotropic incompetence, may independently contribute to the increased risk of incident stroke. Heart rate increases linearly during progressive exercise due to increases in sympathetic activity coupled with concomitant decreases in parasympathetic stimulation. Therefore, an impaired heart rate response to exercise could be explained by a heightened level of vagal control, reduced sympathetic drive during exercise, or both.[5] Sympathetic activity may play a critical role in cerebral autoregulation and blood pressure. Activation of the sympathetic system influences regulation of cerebral blood flow and cerebral metabolism, while cholinergic activity may be important for maintaining or augmenting cerebral perfusion during exercise in humans.[14] Thus, autonomic nervous system imbalance (attenuated sympathetic activation) caused by sympathetic-vagal dysregulation during exercise may impair cerebral autoregulation.[15] However, additional research regarding the relation between chronotropic incompetence and incident stroke as well as the potential pathways underlying this association is clearly needed. Limitations of the present investigation include using a study population that comprised exclusively of middle-aged Caucasian men, and the inability to explore heart rate variability and changes in the chronotropic response to exercise testing over time. Future research is needed to confirm our findings in women and other races/ethnicities. In addition, chronotropic response is dependent on the duration of exercise testing, but we did not have data on this variable.

In conclusion, an abnormal chronotropic response to peak or symptom-limited exercise testing in middle-aged men is independently associated with an increased risk

of stroke, including its ischemic subtypes, over a median 27-year follow-up. The identification of chronotropic incompetence during exercise testing as a bonafide prognostic indicator for stroke risk needs further investigation and, if confirmed, has the potential to be incorporated into future stroke risk assessment algorithms in clinical practice.

Authors' Contributions

Sae Young Jae: conceptualization, writing original draft preparation. Kevin Heffernan: conceptualization, writing original draft preparation. Sudhir Kurl: methodology, data acquisition Setor K. Kunutsor: Reviewing and Editing. Barry A. Franklin: reviewing and editing. Kai Savonen: data acquisition, supervision. Jari A. Laukkanen: methodology, supervision.

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Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.12.042.

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