



## Exercise-induced ST depression in an asymptomatic population without coronary artery disease

Anna Carlén, Mikael Gustafsson, Meriam Åström Aneq & Eva Nylander

To cite this article: Anna Carlén, Mikael Gustafsson, Meriam Åström Aneq & Eva Nylander (2019) Exercise-induced ST depression in an asymptomatic population without coronary artery disease, Scandinavian Cardiovascular Journal, 53:4, 206-212, DOI: [10.1080/14017431.2019.1626021](https://doi.org/10.1080/14017431.2019.1626021)

To link to this article: <https://doi.org/10.1080/14017431.2019.1626021>



© 2019 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group



Accepted author version posted online: 30 May 2019.  
Published online: 13 Jun 2019.



Submit your article to this journal [↗](#)



Article views: 478



View related articles [↗](#)



View Crossmark data [↗](#)

ORIGINAL ARTICLE



## Exercise-induced ST depression in an asymptomatic population without coronary artery disease

Anna Carlén<sup>a</sup> , Mikael Gustafsson<sup>b</sup> , Meriam Åström Aneq<sup>a</sup>  and Eva Nylander<sup>a</sup> 

<sup>a</sup>Department of Clinical Physiology and Department of Medical and Health Sciences, Linköping University, Linköping, Sweden;

<sup>b</sup>Department of Cardiology and Department of Medical and Health Sciences, Linköping University, Linköping, Sweden

### ABSTRACT

**Objectives.** Exercise electrocardiogram (ExECG) in low risk populations frequently generates false positive ST depression. We aimed to characterize factors that are associated with exercise-induced ST depression in asymptomatic men without coronary artery disease. **Design.** Cycle ergometer exercise tests from 509 male firefighters without imaging proof of significant coronary artery disease were analysed. Analysed test data included heart rate at rest before exercise, and workload, blood pressure, heart rate, ST depression and ST segment slope at peak exercise. ST depression of  $>0.1$  mV was considered significant (ST<sub>dep</sub>). With a mean follow-up of  $6.1 \pm 1.7$  years, medical records were reviewed for cardiovascular diagnoses, hyperlipidemia and diabetes. Logistic regression analysis was used for risk assessment. **Results.** In total, 22% had ST<sub>dep</sub> in  $\geq 1$  lead. Subjects with ST<sub>dep</sub> were older than those with normal ExECG ( $p < .001$ ). Downsloping ST<sub>dep</sub> was more common in extremity leads (9%) than in precordial leads (2%). ST<sub>dep</sub> was categorized according to location (precordial/extremity) and slope direction into eight categories. Larger age-adjusted heart rate increase predicted ST<sub>dep</sub> in seven categories ( $p < .05$ ). Age-adjusted peak heart rate correlated with ST<sub>dep</sub> in five categories, predominantly where the ST slope was positive. Peak blood pressure and exercise capacity were both associated with ST<sub>dep</sub> in few categories. We found no association between ST<sub>dep</sub> and hypertension, hyperlipidemia or diabetes (all  $p > .05$ ). **Conclusions.** In asymptomatic men with a physically demanding occupation and no coronary artery disease, both age and heart rate response were associated with ST depression, whereas common cardiovascular risk factors, blood pressure response and exercise capacity were not.

### ARTICLE HISTORY

Received 6 December 2018

Revised 1 April 2019

Accepted 27 May 2019

### KEYWORDS

Stress test; false positive; electrocardiography; heart rate; ST segment deviation; firefighters; low risk

### Introduction



Exercise testing has the dual purpose of assessing physical capacity and evaluating cardiovascular health. In the periodic evaluation of Swedish firefighters, exercise ECG (ExECG) to maximal exhaustion is mandatory, with the aim to detect subclinical signs of cardiovascular disease [1]. The aerobic capacity of firefighters is higher than in the general population. They are also disqualified from duty if their medical health deteriorates. Therefore a firefighter cohort presumably consists of individuals with better than average health and a lower than average risk for disease. However, we have previously found the prevalence of exercise-induced ST depression - one of the cornerstones in ExECG interpretation for identification of coronary artery disease (CAD) - to be around 20% in a firefighter cohort [2]. Yet the IHD event rate was only 2% during follow-up, which illustrates the interpretational challenge in differentiating true from false positive ST changes in this firefighter cohort as well as in any asymptomatic population with low pre-test probability [3].

The clinical significance of exercise-induced ST segment deviations in apparently healthy subjects has been under

debate for several decades. An increase in long-term risk for myocardial infarction or future need for coronary artery bypass grafting has been seen with risk factor adjusted ST depression in healthy middle-aged men, acknowledging a possible prognostic value [4]. Nevertheless, due to the low prevalence of disease in asymptomatic populations, the positive predictive value of a positive test response in low-risk individuals is poor, which limits the diagnostic value [5]. Multiple studies have evaluated both the diagnostic and prognostic capacity of ST depression in relation to CAD [6,7]. The cause of ST depression in the absence of CAD as well as its relation to cardiovascular risk factors and test-derived variables such as heart rate (HR), blood pressure (BP) and exercise capacity, remains to be further investigated.

### Aim

We aimed to evaluate factors that characterize and potentially contribute to exercise-induced ST depression in asymptomatic men without objective evidence of CAD. Bearing those factors in mind during ExECG in low-risk

**CONTACT** Anna Carlén  [anna.carlen@liu.se](mailto:anna.carlen@liu.se) 

© 2019 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited, and is not altered, transformed, or built upon in any way.

individuals, an improved understanding of the test results might be possible.

## Material and methods

### Study population

Screening ExECGs performed 2004–2010 were previously studied in a cohort of 521 male firefighters, analysing their ECG response in relation to the incidence of CAD during follow-up. The recruitment procedure has been described in detail elsewhere [2]. The follow-up included review of medical records until 2015, in search for 1) cardiac imaging studies (coronary angiography, myocardial scintigraphy, cardiac magnetic resonance imaging and coronary computed tomography), and 2) registered diagnoses related to the circulatory system according to the International Classification of Diseases coding (I00–I99), as well as diabetes (E10, E11, E14) and hyperlipidemia (E78) [8]. Each diagnose was registered the first time it occurred for each individual.

From the initial cohort, 12 subjects were identified with ischemic heart disease based on significant stenosis at angiography or exercise-induced ischemia at scintigraphy, and those were excluded from further analysis in the present study. No additional cases of acute myocardial infarction or sudden cardiac death were found. Subjects assigned the diagnosis “chronic ischemic heart disease” (I25) were not excluded if both history and imaging were negative. We thereby intended to reduce work-up bias and avoid incorrect CAD classification in asymptomatic firefighters referred for cardiac evaluation due to ST depression at the screening ExECG. The study sample hence consisted of 509 male firefighters without imaging or diagnostic proof of significant CAD neither before the analysed test nor during 6.1 ± 1.7 years follow-up.

### Cycle ergometer test

A PC-based ExECG system (Welch Allyn Cardioperfect 1.6.3) was used for all tests. This system was connected to an ergometer bicycle (Monark E839, Vansbro Sweden) to control load, and to the wearable ECG recorder. The exercise tests were carried out as incremental ramp tests with a continuous increase by 1 W every 3 seconds until exhaustion, either starting with 6 minutes at 200 W or 250 W followed by immediate conversion to ramp test, or as ramp protocol during the entire test.

Workload and 12-lead ECG were monitored continuously during all tests and BP was measured every 3 minutes. The same cardiologist supervised all tests. Firefighters with exercise tests abnormalities such as arrhythmias, pathological BP response and ST segment deviations, were routinely referred for further cardiologic evaluation.

### Exercise ECG variables

Tests where the ECG had abnormalities that could hamper the interpretation of the ST analysis were excluded in a

previous test selection step [2]. Exclusion criteria for resting ECGs were bundle branch block and software-identified left ventricular hypertrophy, if manual assessment verified secondary ST-T changes. Tests with exercise-induced arrhythmia or intermittent conduction disorders were also excluded, together with tests performed by pacemaker carriers, and tests with insufficient signal quality. The total exclusion rate from the main firefighter study database was 5%.

The most recent test was selected if a subject had performed multiple ExECGs during the inclusion period. From the selected tests, peak workload ( $P_{\text{peak}}$ ; W) and peak BP ( $BP_{\text{peak}}$ ; mmHg) were registered; the latter refers to the latest BP measured during exercise.  $BP_{\text{peak}}$  lower than two standard deviations below the average  $BP_{\text{peak}}$  for the cohort were manually checked and excluded if registered >3 minutes before end of exercise. From the 12-lead ECG, ST data were analysed in all leads except V1 and aVL. ST values (60 milliseconds from the J-point, ST60;  $\mu\text{V}$ ) were collected from rest and from peak exercise, and was calculated as the median value of the first three measurements during sitting rest and the last three during pedalling respectively. ST depression was defined at peak exercise. If ST60 was negative at rest, ST depression was calculated as additional negative deflection at peak exercise compared to rest. Also, the slope of the ST segment and peak HR ( $HR_{\text{peak}}$ ; beats/min) were evaluated at peak exercise. ST depression  $\geq 0.1$  mV was considered significant ( $ST_{\text{dep}}$ ) and the ST slope was classified as downsloping if  $\leq 0$   $\mu\text{V/s}$ . The HR span ( $HR_{\text{span}}$ ; beats/min) was calculated as difference between  $HR_{\text{peak}}$  and HR at rest sitting on the bicycle. We analyzed target HR achievement as percentage of age-predicted maximum HR according to the Tanaka formula [9].

### Statistics

SPSS statistical software (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY, USA) was used for analyses. Student's t-test was used for comparison of continuous data and Chi-squared test was used for comparison of categorical data. Binary logistic regression analysis for single and multiple variables was used to assess association between cardiovascular diagnoses, test derived variables and exercise-induced  $ST_{\text{dep}}$ . Odds ratios (OR) with 95% confidence interval (CI) were reported from the binary logistic regression analysis.

### Results

We studied 509 asymptomatic male firefighters with no history of myocardial infarction. The average exercise capacity was  $279 \pm 39$  W, 97% reached  $\geq 85\%$  of age-predicted maximum HR. None of the test subjects reported exertional chest pain. Anthropometrics of the study sample, and basic test data are presented in Table 1.

In this cohort, 8% had gone through cardiac imaging studies during the inclusion period or follow-up, with negative result for exercise-induced ischemia or with none or

less than 50% coronary artery lumen reduction. The remaining firefighters had not presented clinical symptoms or exercise test abnormalities that motivated additional imaging studies, neither earlier in their career nor during the follow-up period of  $6.1 \pm 1.7$  years. During follow-up there were six deaths, none of them due to CAD.

According to medical records, 7% of subjects had either a cardiovascular diagnosis, hyperlipidemia or diabetes registered prior to the examined test. Diagnoses of established risk factors for CAD (hypertension, hyperlipidemia and diabetes) were all infrequent. Hypertension was diagnosed in 2% while the diagnoses diabetes mellitus and hyperlipidemia occurred in 1% each. None of the other identified diagnoses was more frequent (Appendix 1).

### Prevalence and characteristics of ST depression

At the end of exercise, ST<sub>dep</sub> in at least one lead was present in 22%. The slope of the ST segment and the location of the affected lead(s) were used for further sub-classification of the ECG response into eight categories, each labelled with a Roman numeral, I–VIII (Figure 1).

In 15%, ST<sub>dep</sub> was found in a precordial lead and in 11%, ST<sub>dep</sub> was present in two or more consecutive precordial leads. A negative slope of precordial ST<sub>dep</sub> was however less frequent than 2%.

**Table 1.** Anthropometrics and basic test data.

	Mean	SD	Range
<b>Anthropometrics</b>			
Age, years	46	11	21–68
Height, cm	181	6	162–199
Weight, kg	86	10	60–127
BMI, kg/m <sup>2</sup>	26	3	19–36
<b>Basic test data</b>			
P <sub>peak</sub> , W	279	39	188–467
HR <sub>peak</sub> , beats/min	171	13	130–200
%HR <sub>pred</sub> , %	97	6	76–120
BP <sub>peak</sub> , mmHg	203	23	140–290

BMI: body mass index; P<sub>peak</sub>: peak workload; HR<sub>peak</sub>: peak heart rate; %HR<sub>pred</sub>: achievement of age-predicted maximum HR; BP<sub>peak</sub>: peak blood pressure.

ST<sub>dep</sub> in one or two leads was less common in extremity leads than in precordial leads, but extremity lead ST<sub>dep</sub> more often had a negative slope (Figure 1).

One out of ten subjects (10%) had at least one lead with downsloping ST<sub>dep</sub> by the end of exercise.

Subjects with ST<sub>dep</sub> in any lead at the end of exercise were significantly older compared to those who did not develop ST<sub>dep</sub> ( $49 \pm 9$  vs.  $45 \pm 11$  years,  $p < .001$ ). Similarly, subjects who developed ST<sub>dep</sub> in any precordial lead or in two consecutive precordial leads were significantly older compared to those who did not ( $p < .001$ ). Among all other categories, the mean age of subjects who developed ST<sub>dep</sub> was consistently higher than in those who did not, although not significantly so (Figure 2).

Age was an independent predictor of any-lead ST<sub>dep</sub> as well as one- and two-lead precordial ST<sub>dep</sub> (all OR > 1.0,  $p < .001$ ).

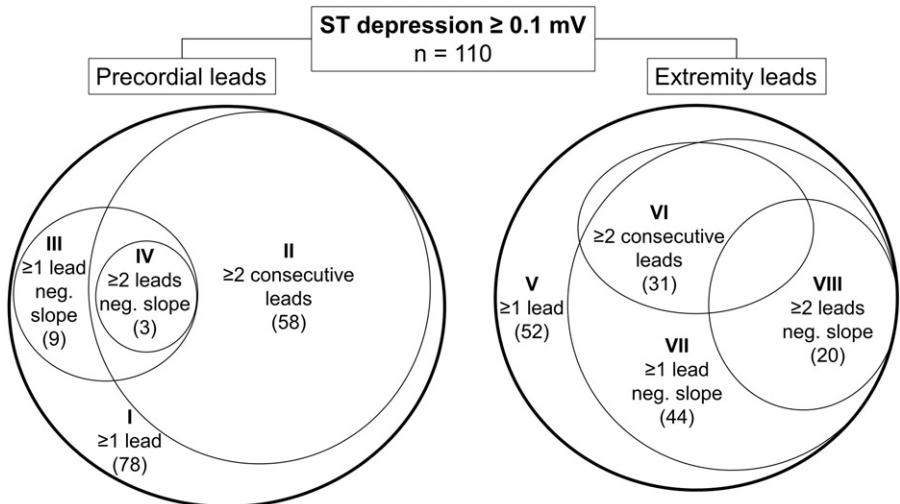
### Test related variables and ST depression

Relations between test-derived parameters and exercise-induced ST<sub>dep</sub> were analysed for precordial (Table 2) and extremity (Table 3) leads. A large HR<sub>span</sub> predicted ST<sub>dep</sub> in the majority of ST depression categories, both in absolute numbers and after adjustment for age,  $p < .05$  or lower. High age-adjusted HR<sub>peak</sub> was also associated with ST<sub>dep</sub> in several categories, whereas unadjusted HR<sub>peak</sub> consistently lacked such association.

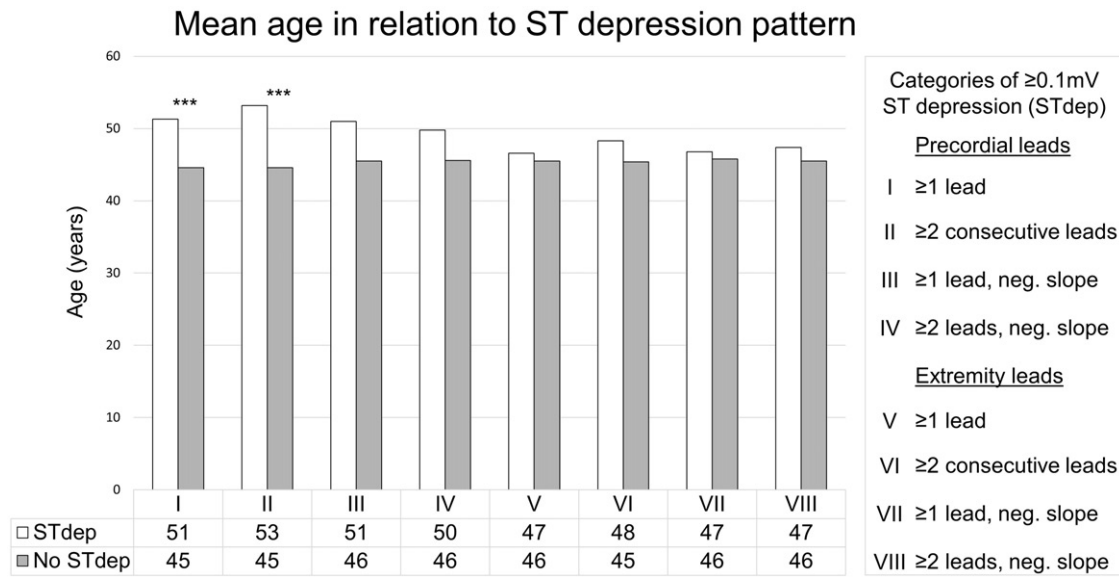
In general, low BP<sub>peak</sub> tended to be associated with ST<sub>dep</sub>, but risk estimates were not significant. However, in precordial leads there was a significant association between high end-exercise BP and downsloping ST<sub>dep</sub> (Table 2).

Low end-exercise workloads were associated with precordial ST<sub>dep</sub>, but it was not significantly so after adjustment for age (Table 2).

Multivariable analysis, including combination of factors did not add significant predictors.



**Figure 1.** Frequency (n) of  $\geq 0.1$  mV ST depression at the end of exercise, categorized by location and morphology. Each category was labelled with a Roman numeral and numbers in parenthesis refer to number of subjects within each category. Subjects may be represented with ST depression in both precordial and extremity leads. The circles do not have exact proportional dimensions.



**Figure 2.** Mean age in relation to ST depression pattern. The different patterns analysed are defined on the right hand side of the figure. ST<sub>dep</sub> = ST depression  $\geq 0.1$  mV. \*\*\* $p < .001$ .

**Table 2.** Association between test-derived variables and  $\geq 0.1$  mV ST depression in precordial leads, expressed as odds ratio (OR) with 95% confidence interval (CI).

	I: 1 precordial lead OR (95% CI)	II: 2 consecutive precordial leads OR (95% CI)	III: 1 precordial lead, neg. slope OR (95% CI)	IV: 2 precordial leads, neg. slope, OR (95% CI)
<b>Unadjusted</b>				
HR <sub>peak</sub>	1.01 (0.99–1.03)	1.00 (0.98–1.02)	1.01 (0.96–1.06)	1.01 (0.92–1.10)
HR <sub>span</sub>	1.02* (1.00–1.04)	1.02* (1.00–1.04)	1.04 (0.99–1.08)	1.01 (0.94–1.09)
BP <sub>peak</sub>	1.00 (0.99–1.01)	1.00 (0.99–1.01)	1.04*** (1.02–1.07)	1.04* (1.00–1.08)
P <sub>peak</sub>	0.99** (0.98–1.00)	0.98*** (0.97–0.99)	1.01 (1.00–1.03)	0.98 (0.95–1.02)
<b>Age-adjusted</b>				
HR <sub>peak</sub>	1.07*** (1.04–1.10)	1.06*** (1.03–1.09)	1.04 (0.98–1.11)	1.03 (0.93–1.15)
HR <sub>span</sub>	1.03*** (1.02–1.05)	1.04*** (1.02–1.07)	1.05* (1.00–1.11)	1.02 (0.94–1.11)
BP <sub>peak</sub>	0.99 (0.98–1.00)	0.99 (0.98–1.01)	1.04*** (0.02–1.07)	1.04 (1.00–1.08)
P <sub>peak</sub>	1.00 (0.99–1.01)	0.99 (0.98–1.00)	1.02* (1.00–1.04)	0.99 (0.95–1.02)

Roman numerals refer to patterns of ST depression as categorized in Figure 1. Only pure ramp tests are included in the analysis of P<sub>peak</sub>. HR<sub>peak</sub>: peak heart rate; HR<sub>span</sub>: heart rate span between sitting rest and peak exercise; BP<sub>peak</sub>: peak blood pressure; P<sub>peak</sub>: peak workload.

\* $p < .05$ ; \*\* $p < .01$ ; \*\*\* $p < .001$ .

Downsloping ST<sub>dep</sub> in at least one lead, independent of its location, was significantly associated with age-adjusted high P<sub>peak</sub> (OR 1.01, CI 1.00–1.02), high HR<sub>peak</sub> (OR 1.03, CI 1.00–1.06) as well as a large HR<sub>span</sub> (OR 1.03, CI 1.01–1.05), all  $p < .05$ .

### Cardiovascular risk factors

Neither diagnosed hypertension, hyperlipidemia, nor diabetes was associated with exercise-induced ST<sub>dep</sub> in this study sample, for any of the ST<sub>dep</sub> categories, neither raw nor age-adjusted. Analysis of combination of risk factors did not add significant predictors either.

### Discussion

Exercise-induced ST depression of at least 0.1 mV in one or several leads was found in every five subjects in this cohort

of asymptomatic firefighters with no CAD. In about 50% of these, the ST<sub>dep</sub> was horizontal or downsloping. Both age and HR response were associated with ST<sub>dep</sub>, whereas common cardiovascular risk factors, BP response and exercise capacity were not.

In a clinical setting, evaluation of the exercise test usually includes a compound of exercise capacity, BP and HR responses, subjective symptoms and ECG analysis during exercise and recovery. Out of those, the ST segment reaction is the most important and objectively verifiable parameter for evaluation of ischemic heart disease, and by far the most assessed parameter in studies of the diagnostic accuracy of the ExECG. Exercise-induced ST depression in the absence of ischemic heart disease is a false positive test result. The present study was designed to characterize exercise-induced ST depression in subjects without CAD.



**Table 3.** Association between test-derived variables and  $\geq 0.1$  mV ST depression in extremity leads, expressed as odds ratio (OR) with 95% confidence interval (CI).

	V: 1 extremity lead OR (95% CI)	VI: 2 consecutive extremity leads OR (95% CI)	VII: 1 extremity lead, neg. slope OR (95% CI)	VIII: 2 extremity leads, neg. slope OR (95% CI)
<b>Unadjusted</b>				
HR <sub>peak</sub>	1.02 (0.99–1.04)	1.02 (0.99–1.05)	1.01 (0.99–1.04)	1.03 (1.00–1.07)
HR <sub>span</sub>	1.03* (1.01–1.05)	1.03 (1.00–1.05)	1.02* (1.00–1.04)	1.05** (1.01–1.08)
BP <sub>peak</sub>	1.00 (0.99–1.01)	0.99 (0.97–1.00)	0.99 (0.98–1.01)	0.99 (0.97–1.01)
P <sub>peak</sub>	1.00 (1.00–1.01)	1.00 (0.99–1.01)	1.01 (1.00–1.01)	1.00 (0.99–1.01)
<b>Age-adjusted</b>				
HR <sub>peak</sub>	1.03* (1.00–1.06)	1.05** (1.01–1.09)	1.02 (0.99–1.05)	1.06* (1.01–1.11)
HR <sub>span</sub>	1.03** (1.01–1.05)	1.03** (1.01–1.06)	1.03* (1.01–1.05)	1.05** (1.02–1.09)
BP <sub>peak</sub>	1.00 (0.99–1.01)	0.99 (0.97–1.00)	0.99 (0.98–1.01)	0.99 (0.97–1.01)
P <sub>peak</sub>	1.01 (1.00–1.01)	1.00 (0.99–1.01)	1.01 (1.00–1.02)	1.00 (0.99–1.02)

Roman numerals refer to patterns of ST depression as categorized in Figure 1. Only pure ramp tests are included in the analysis of P<sub>peak</sub>.

HR<sub>peak</sub>: peak heart rate; HR<sub>span</sub>: heart rate span between sitting rest and peak exercise; BP<sub>peak</sub>: peak blood pressure; P<sub>peak</sub>: peak workload.

\* $p < .05$ ; \*\* $p < .01$ ; \*\*\* $p < .001$ .

In asymptomatic subjects and athletes, screening with ExECG typically yields a relatively low frequency of positive test results. In a review analysing athletes, the mean prevalence of positive ExECG (defined as 0.1 mV horizontal or downsloping ST depression, in most studies analysis restricted to precordial leads) was 5% in a subgroup of athletes aged 35–60 years. The calculated positive predictive value (PPV) was poor (6%), reflecting a low prevalence of underlying cardiac disease [10]. The prevalence of horizontal or downsloping ST depression in the present study was similar, 2% in precordial leads and 10% when all leads were considered. Although firefighters are not athletes by definition, physical training is necessary to maintain the required aerobic capacity. Therefore, the fitness of firefighters is generally better than in the general population and comparison to recreational athletes is motivated. In fact, smaller studies comparing master athletes and sedentary subjects have indicated a higher incidence of false positive ST depression in athletes [11,12]. The underlying mechanisms are not fully understood, but increased left ventricular mass with secondary repolarization abnormalities has been suggested [10].

### Heart rate

We found that a large HR<sub>span</sub> was associated with ST<sub>dep</sub>. In healthy subjects, a progressive decrease of the J-point amplitude is often seen with increasing exercise, concurrent with a marked rise of the ST segment slope [13]. At high HR, depression of the ST junction may be due to atrial repolarization occurring slightly after ventricular depolarization, instead of simultaneously, thus coinciding with the beginning of the ST segment, with a depressing effect. An isolated rapidly upsloping ST segment (without significant ST depression at ST80), has even shown to be associated with reduced long-term risk for ischemic heart disease compared to a normal exercise ST segment morphology [14].

Interestingly, unadjusted HR<sub>peak</sub> per se was not associated with ST<sub>dep</sub> in this study, but only so after adjustment for age. Healthy subjects with a high HR<sub>peak</sub> ‘despite’ higher age, might hence be more prone to develop ST<sub>dep</sub> than those who reached a lower HR<sub>peak</sub>. Speculatively, this might be due to a reduced coronary flow reserve at peak exercise with high HR in the older subjects. In young subjects, high HR was not as likely to explain any ST<sub>dep</sub> as in older individuals.

### Cardiovascular risk factors

Firefighters who presented with precordial ST<sub>dep</sub> in one or several leads were significantly older than their colleagues who did not. That may indicate that pathological processes accumulate over time and contribute to an abnormal ST segment response, although not necessarily caused by significant luminal reduction of the coronary arteries. In this cohort, neither hyperlipidemia, diabetes, hypertension nor combinations of them were significantly associated with ST<sub>dep</sub>, suggesting that other mechanisms could be relevant in this type of population.

In one study of patients with exertional angina but angiograms with no or less than 50% stenosis, a pathological ExECG was more common in those who had coronary microvascular dysfunction [15]. Although coronary microvascular dysfunction is a phenomenon more often seen in women [16], it could be a possible cause of ST segment depression in the asymptomatic subjects in our cohort, however microvascular dysfunction was not assessed with the main imaging modalities analyzed during follow-up in this study [17].

Massie et al. found that exercise-induced ST depression in the absence of CAD was more common in hypertensive men than in normotensive, risk factor-matched controls, especially in case of left ventricular hypertrophy [18]. That study was conducted in high risk men, as opposed to the

low prevalence of diagnosed cardiovascular risk factors in our cohort, which may explain why no such association was seen in our cohort. ST depression in patients with severe left ventricular hypertrophy has been explained by e.g. reduced coronary artery flow reserve [19].

An exaggerated BP response during exercise is a known risk factor for future resting hypertension in healthy asymptomatic persons [20,21]. A hypertensive response at moderate exercise intensity is furthermore shown to be an independent risk factor for cardiovascular events and mortality in patients without significant CAD [22]. At the same time, athletes tend to reach higher peak exercise BP compared to healthy controls [11]. Thus, high end-exercise BP can be seen as both a presumably healthy pattern and one that is not. A high BP<sub>peak</sub> was in our study associated with ST<sub>dep</sub> in two of the sub classification categories, including precordial lead(s) downslowing ST<sub>dep</sub> (Table 2).

### Other causes to ST depression

In addition to ischemia and parameters already mentioned above, some additional factors not assessed in this study have also been suggested to affect the ST segment response, including hyperventilation, serum electrolyte concentrations, anaemia and certain therapeutic drugs (digoxin, tricyclics, antiarrhythmic drugs etc.) [23].

### Limitations

The current study is based on data from a clinical database, following clinical guidelines for exercise testing but not strictly adhered to a study protocol. This might have implications on the collection of data, such as the time point for measurement of BP<sub>peak</sub> and how close to maximal exhaustion the tests are driven. Medical record derived diagnoses for hypertension, diabetes and hyperlipidemia instead of measurements/blood samples could potentially have underestimated the actual frequency of disease.

As in nearly all studies on myocardial ischemia, coronary angiography was not done in all subjects in our cohort. Instead, referral was most likely related to the result of the ExECG, hence constituting a possible work-up bias. To reduce its potential effect we have included cardiac imaging studies from a longer follow-up and not only directly related to the ExECG.

The associations between ST<sub>dep</sub> and test related variables found in the logistic regression analysis in the present study were, although statistically significant, in general modest.

### Conclusion

Age-adjusted HR<sub>peak</sub> was associated with end-exercise ST<sub>dep</sub> in physically active men without CAD. Notably, neither high BP response nor established cardiovascular risk factors were associated with ST<sub>dep</sub> in this cohort. Whether the effect of age and HR on exercise-related changes is electrophysiological or secondary to microvascular or structural myocardial variations remains to be further elucidated.

### Acknowledgements

We thank Malin Huss and Anette Gylling, research nurses, Department of Cardiology, Linköping University Hospital, Sweden and Olof Malm, assistant, Department of Clinical Physiology, Linköping University Hospital, Sweden, for their assistance with the collection of medical record data. We also thank Lars Valter, statistician, County Council of Östergötland, Sweden for advice on statistical methodology.

### Disclosure statement

The authors have nothing to declare.

### Funding

This work was supported by the County Council of Östergötland, Sweden, under Grants number [LIO-711261] and ALF grant [700731].

### ORCID

Anna Carlén  <http://orcid.org/0000-0001-9196-7820>  
Mikael Gustafsson  <http://orcid.org/0000-0002-3756-207X>  
Meriam Åström Aneq  <http://orcid.org/0000-0002-2693-0949>  
Eva Nylander  <http://orcid.org/0000-0001-9510-5558>

### References

- [1] The Swedish Work Environment Authority. The Swedish Work Environment Authority's Statute Book, Occupational Medical Supervision AFS 2005:06. Stockholm: Elanders Gotab; 2005.
- [2] Carlen A, Nylander E, Astrom Aneq M, et al. ST/HR variables in firefighter exercise ECG - relation to ischemic heart disease. *Physiol Rep*. 2019;7:e13968.
- [3] Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J*. 2013;34:2949–3003.
- [4] Bodegard J, Erikssen G, Bjornholt JV, et al. Symptom-limited exercise testing, ST depressions and long-term coronary heart disease mortality in apparently healthy middle-aged men. *Eur J Cardiovasc Prev Rehabil*. 2004;11:320–327.
- [5] Lauer M, Froelicher ES, Williams M, et al. Exercise testing in asymptomatic adults: a statement for professionals from the American Heart Association Council on Clinical Cardiology, Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention. *Circulation*. 2005;112:771–776.
- [6] Gianrossi R, Detrano R, Mulvihill D, et al. Exercise-induced ST depression in the diagnosis of coronary artery disease. A meta-analysis. *Circulation*. 1989;80:87–98.
- [7] Kurl S, Laukkanen JA, Tuomainen TP, et al. Association of exercise-induced, silent ST-segment depression with the risk of stroke and cardiovascular diseases in men. *Stroke*. 2003;34:1760–1765.
- [8] World Health Organization. International Statistical Classification of Diseases and Related Health Problems 10th Revision 2016 [cited 2018 Oct 25]. Available from: <http://apps.who.int/classifications/icd10/browse/2016/en>
- [9] Tanaka H, Monahan KD, Seals DR. Age-predicted maximal heart rate revisited. *J Am Coll Cardiol*. 2001;37:153–156.
- [10] van de Sande DA, Breuer MA, Kemps HM. Utility of exercise electrocardiography in pre-participation screening in asymptomatic athletes: a systematic review. *Sports Med*. 2016;46:1155–1164.
- [11] Pigozzi F, Spataro A, Alabiso A, et al. Role of exercise stress test in master athletes. *Br J Sports Med*. 2005;39:527–531.

- [12] Katzel LI, Fleg JL, Busby-Whitehead MJ, et al. Exercise-induced silent myocardial ischemia in master athletes. *Am J Cardiol.* 1998;81:261–265.
- [13] Wolthuis RA, Froelicher VF, Hopkirk A, et al. Normal electrocardiographic waveform characteristics during treadmill exercise testing. *Circulation.* 1979;60:1028–1035.
- [14] Hodnesdal C, Prestgaard E, Erikssen G, et al. Rapidly upsloping ST-segment on exercise ECG: a marker of reduced coronary heart disease mortality risk. *Eur J Prev Cardiol.* 2013;20:541–548.
- [15] Ong P, Athanasiadis A, Hill S, et al. Coronary microvascular dysfunction assessed by intracoronary acetylcholine provocation testing is a frequent cause of ischemia and angina in patients with exercise-induced electrocardiographic changes and unobstructed coronary arteries. *Clin Cardiol.* 2014;37:462–467.
- [16] Zijlstra LE, Bootsma M, Jukema JW, et al. Chest pain in the absence of obstructive coronary artery disease: a critical review of current concepts focusing on sex specificity, microcirculatory function, and clinical implications. *Int J Cardiol.* 2019;280:19–28.
- [17] Di Franco A, Lanza GA, Di Monaco A, et al. Coronary microvascular function and cortical pain processing in patients with silent positive exercise testing and normal coronary arteries. *Am J Cardiol.* 2012;109:1705–1710.
- [18] Massie BM, Szlachcic Y, Tubau JF, et al. Scintigraphic and electrocardiographic evidence of silent coronary artery disease in asymptomatic hypertension: a case-control study. *J Am Coll Cardiol.* 1993;22:1598–1606.
- [19] Houghton JL, Carr AA, Prisant LM, et al. Morphologic, hemodynamic and coronary perfusion characteristics in severe left ventricular hypertrophy secondary to systemic hypertension and evidence for nonatherosclerotic myocardial ischemia. *Am J Cardiol.* 1992;69:219–224.
- [20] Allison TG, Cordeiro MA, Miller TD, et al. Prognostic significance of exercise-induced systemic hypertension in healthy subjects. *Am J Cardiol.* 1999;83:371–375.
- [21] Manolio TA, Burke GL, Savage PJ, et al. Exercise blood pressure response and 5-year risk of elevated blood pressure in a cohort of young adults: the CARDIA study. *Am J Hypertens.* 1994;7:234–241.
- [22] Schultz MG, Otahal P, Cleland VJ, et al. Exercise-induced hypertension, cardiovascular events, and mortality in patients undergoing exercise stress testing: a systematic review and meta-analysis. *Am J Hypertens.* 2013;26:357–366.
- [23] Fleg JL, Gerstenblith G, Zonderman AB, et al. Prevalence and prognostic significance of exercise-induced silent myocardial ischemia detected by thallium scintigraphy and electrocardiography in asymptomatic volunteers. *Circulation.* 1990;81:428–436.

## Appendices

**Appendix 1.** Cardiovascular diagnoses, diabetes mellitus and hyperlipidemia diagnosed before the analysed exercise test, according to reviewed medical records. Codes within parenthesis refer to the World Health Organization International Classification of Diseases.

Diagnoses	Frequency, % (n)
Chronic ischemic heart disease (I25)	1% (3)
Hypertension (I10, I11, I15)	2% (9)
Aortic or mitral valve disease (I34, I35)	1% (4)
Cardiac failure (I50)	0% (1)
Atrial fibrillation/flutter (I48)	1% (6)
Tachyarrhythmia (I47)	0% (2)
Other cardiac arrhythmias (I49)	0% (2)
Pericarditis (I30)	0% (1)
Myocarditis (I40)	0% (1)
Ischemic brain disease (I63)	0% (1)
Aortic aneurysm (I71)	1% (3)
Peripheral arterial disease (I73)	0% (1)
Venous disease (I80, I83, I86)	1% (6)
Diabetes mellitus (E11, E14)	1% (6)
Hyperlipidemia (E78)	1% (5)