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Exercise Systolic Blood Pressure at Moderate Workload is Linearly Associated with Coronary Disease in Healthy Men: No Threshold Level for Increased Risk

Exercise Systolic Blood Pressure at Moderate Workload is Linearly Associated with Coronary Disease Risk in Healthy Men

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Abbreviations: SBP, systolic blood pressure; CV, cardiovascular; CHD, coronary heart disease; ECG, electrocardiography/electrocardiogram; bpm, beats per minute; SBP100W, peak exercise SBP during 100W workload; SBPmax, systolic blood pressure under maximal workload; SD: standard deviation; HR: hazard ratio; $VO2_{max,}$ maximal oxygen uptake.

Abstract

There is no consensus on the definition of an exaggerated increase in systolic blood pressure (SBP) during exercise. The aim was to explore a potential threshold for exercise SBP associated with increased risk of coronary heart disease (CHD) in healthy men, using repeated exercise testing.

2,014 healthy Caucasian male employees were recruited into the Oslo Ischemia Study during early 1970s. At follow-up seven years later, 1,392 men were still considered healthy. A bicycle exercise test at 100W workload was performed at both visits. Cox regression analyses were performed with increasing cut-off levels of peak SBP during 100W workload (SBP100W) from 160 mmHg to 200 mmHg, adjusted for cardiovascular risk factors and physical fitness. Participants with SBP100W below cut-off level at both baseline and first follow-up were compared to participants with SBP100W equal to or above cut-off level at both visits.

Compared to participants with SBP100W below all cut-off levels between 165-195 mmHg, CHD risk was increased amongst participants with SBP100W equal to or above cut-off at all levels. There was no evidence of a distinct threshold level for CHD risk, and the relation between SBP100W and CHD appears linear.

When investigating exercise SBP at moderate workload measured at two exercise tests in healthy middle-aged Caucasian men, there is increasing risk of coronary disease with increasing exercise SBP independent of SBP at rest. The association is linear from the low range of exercise SBP and there is no sign of a distinct threshold level for increased coronary disease risk.

Introduction

Previous studies have shown an association between exercise systolic blood pressure (SBP) and cardiovascular (CV) disease (1). The risk of CV disease and mortality has been investigated with increasing follow-up time (2-4), with particular interest regarding coronary heart disease (CHD) (5), showing an association between exaggerated exercise SBP and increased risk. The association may, however, be confounded by other CV risk factors. Exercise SBP has predicted future hypertension in normotensive individuals (6-8), and low-intensity exercise has revealed masked hypertension (9). Further, exaggerated exercise SBP is associated with increased risk of hypertensive end-organ damage in well-treated patients assessed with office blood pressure (10, 11), suggesting additional prognostic information from exercise SBP beyond the traditional CV risk factors.

There is no current consensus on the definition of a pathological increase in SBP during exercise (1, 12). Definitions of exaggerated exercise SBP are often arbitrary (13, 14), exemplified by the use of age- and sex-specific 90^{th} or 95^{th} percentiles (7, 15) or ≥210 mmHg for men and ≥190 mmHg for women (9, 16, 17). The observation of exaggerated SBP under exercise has limited clinical relevance until evidence and consensus on definition and treatment thresholds for exercise blood pressure is made (15). Hence, the purpose of the present study was to thoroughly study the relationship between a sustained elevation of exercise SBP at moderate workload, and CHD risk, by testing our previous hypothesis (18) that there could be a distinct threshold level above which exercise SBP indicates increased CHD risk. Studies on exercise SBP and CV risk have usually been performed with single measurements only, except for a previous work of ours that showed an increased risk of CHD

with an increase in exercise SBP over time (19). In the present study we further investigate the use of multiple exercise tests, using tests from baseline and first follow-up after seven years, to investigate the effects of sustained elevation of exercise SBP in participants who remained healthy over a significant timespan.

Methods

During 1972-75, 2014 Caucasian men aged 40-59 years, living in Oslo, Norway, gave their informed consent to participate, and were included into the Oslo Ischemia Study. They were then followed until January 1st 2007. The participants were employees from five companies, representing both office and factory workers, and had to be free from chronic diseases or disorders, including CV disease and diabetes mellitus, and without pharmacologically treated hypertension. They also had to be free of any other long-term pharmacological treatment, and be fit enough to perform an exercise test on a stationary ergometer bicycle. In the present study, only participants remaining healthy and fulfilling the second exercise test at first follow-up visit seven years later were included. Further details on selection methods and exclusion criteria for this cohort have been presented earlier (20, 21). Due to the sensitive nature of our dataset, the dataset will not be made available. In dire needs, this may be discussed with the Corresponding author.

Follow-up, Exercise Testing and Endpoints

After initial enrolment in 1972, three follow-up visits were performed, in 1979-82, 1989-90 and 1994-95 (Figure 1). A postal questionnaire was sent to survivors, inquiring about diseases and medication, of which 99% responded. In 1995-96 and 2005-07, hospital medical records and data from the Norwegian Cause of Death Registry were cross-matched. Lengths of hospital admissions and up to three diagnoses for each stay were registered, with particular

focus on registration of CV disease, pulmonary disease, diabetes mellitus and cancer. No participant was lost to follow-up.

At each of the four visits, identical disease history assessment, clinical examination and supplementary investigations were performed, consisting of chest x-ray, spirometry, blood sample laboratory testing, resting electrocardiography (ECG) and resting supine blood pressure. Auscultatory blood pressure was measured with a mercury column sphygmomanometer after five minutes of supine rest in a quiet room. The second measurement of a total of three measurements was used, as this was the lowest measurement (2, 3). Non-invasive blood pressure measurements were deemed sufficient for SBP due to its high reproducibility in this cohort (2). Investigations were performed between 7:30 and 10 a.m. after 12 hours of fasting. Participants had to be free from intercurrent illness; otherwise exercise testing and investigations were postponed at least 14 days. Questionnaires were used to collect information on previous medical history, family history of CHD, and also symptoms of angina pectoris. Further details on the investigations have previously been published (22).

The exercise test at each visit was performed under ECG monitoring on a stationary bicycle with ergometer and adjustable resistance. The test was initiated at 100W, and the workload was increased by 50W every sixth minute until near exhaustion. The participants continued until next increase when 90% of predicted maximal heart rate based on age was reached, or when reaching 10 beats per minute more than 90% of predicted maximal heart rate. If exhaustion or symptoms or ECG signs of cardiac ischemia occurred, the test was terminated. SBP during exercise was measured manually using a mercury sphygmomanometer and performed every second minute throughout the test. The highest SBP measured during the initial six minutes of the exercise test (SBP100W) was used in the multivariate analyses in the present study. SBP at maximal workload (SBPmax) for each

participant was also obtained, and represents the maximal SBP during the whole test in almost all participants.

The endpoint was the first occurrence of CHD, including angina pectoris and fatal and non-fatal myocardial infarction, defined in accordance with diagnostic criteria at the time of diagnosis. Angina pectoris was defined as having a written diagnosis in the hospital records, in combination with documented ischemia on ECG and/or use of short- or long-acting nitrates.

Statistical Methods

For the purpose of the present analysis, only participants considered healthy at both Visit 1 (1972-75) and Visit 2 (1979-82) were included. As the aim of the study was to investigate threshold levels for increased risk of CHD, we performed stepwise incremental analyses with cut-off level increasing from 160 mmHg to 200 mmHg with increments of 5 mmHg. Participants were divided into groups defined by SBP100W at Visit 1 and Visit 2 (Figure S1). Group 1 includes participants with SBP100W *below* cut-off level at both Visit 1 and Visit 2. Group 3 includes participants with SBP100W *equal to or above* cut-off level at both Visit 1 and 2, and Group 2 includes participants with SBP100W equal to or above cut-off level at only one of the two visits, regardless of which. To investigate the risk of CHD, we performed Cox regression analyses adjusted for age, resting SBP, total serum cholesterol, smoking status and family history of CHD. We also performed additional analyses adjusting for physical fitness. Physical fitness was defined as total workload during the exercise test measured in kilojoules divided by body weight. Due to the increases in cut-off levels, the number of participants in each group successively changed in each analysis, as Group 1 expanded and Group 3 diminished.

An alternative and supplementary way of examining the existence of thresholds was performed by first subdividing the cohort into groups of increasing SBP100W at Visit 2 and then evaluate the increase in CHD with increasing SBP100W, using the lowest group with cut-off at 165 mmHg as reference. The rest of the participants were divided into groups of SBP100W of 10 mmHg. The rationale for this grouping, which was guided by a histogram of the SBP100W values, was to make larger groups of participants in order to increase the statistical power. The same multivariate analysis as described above was then performed with this grouping. Hazard ratios for CHD were plotted against SBP100W to investigate whether there was a linear association between SBP100W and CHD risk. SBP100W was also used in the above-mentioned Cox regression analysis as a second-degree term, making a polynomial function of second degree, in order to further investigate linearity.

The multivariate tests are two-sided, and significance was defined as $\alpha \leq 0.05$. Differences in baseline variables were tested with Chi-square test for categorical data and Students *t*-test for continuous variables. Variance is presented as standard deviation (SD). Statistical analyses were performed with JMP 13.0.0, SAS Institute Inc. (Cary, NC, United States).

Results

Of the 2,014 participants, 1,392 participants were able to complete the initial six minutes of the exercise tests at Visits 1 and 2 and were still healthy and not on any long-term pharmacological treatment at both visits. The 622 participants excluded where not considered healthy at Visit 2 (n=607) or did not complete the exercise test at Visit 1 (n=15), hence not included in this study. Baseline characteristics for this cohort of 1,392 participants have been presented earlier (19, 22) (Table 1). Mean age of the participants at Visit 2 was 56.5 (SD 5.4) years, mean resting blood pressure 131/84 (SD 18/10) mmHg and their serum cholesterol

averaged 6.4 mmol/l. One-third of the participants were smokers at Visit 2, which was a small, but significant reduction since enrolment into Oslo Ischemia Study. There were also significant, but marginal, differences in other baseline parameters. The time from Visit 2 until end of follow-up was 28 years, and median follow-up time was 20.8 years. During follow-up, 452 events of the combined endpoint of CHD occurred, of which 186 were fatal events. There were a total of 715 deaths during follow-up.

As cut-off level was adjusted in incremental steps, the number of participants in each group differed at each step (Table 2). There was also increasing mean SBP100W at each step, hence, Group 3 was always compared with increasing mean SBP100W in Group 1 (Table 2).

When performing the stepwise multivariate analyses adjusting for Visit 2 variables, there was a significant increase in risk of CHD in Group 3 compared to Group 1 at all levels from 165 until 195 mmHg (Table 3, Figure 2, Table S1). HR ranged between 1.3 and 3.0 (mainly between 1.3 and 1.6). The analyses were also performed with cut-off level at 150 and 155 mmHg, as presented in Online Supplement, Table S1 and S2, but the number of participants in Group 1 was too low to justify inclusion in our discussion. When including physical fitness in the multivariate analyses, the same pattern occurred, with only minor differences in HR. In the multivariate analyses, resting SBP became insignificant when including SBP100W. Also SBP at maximal workload (SBPmax) lost its significant impact in a combined analysis with SBP100W. SBPmax and SBP100W appear to be widely correlated, but SBP100W has far greater impact in the multivariate analyses. The same analyses were also performed with variables from Visit 1 (Table S2 and Table S3), giving essentially the same results, and only minor differences in HR. When including high-density lipoprotein cholesterol levels, fasting blood glucose, development of diabetes mellitus and body mass index in the multivariate analyses, separately, only minor changes occurred (data not shown).

The analyses showed no sign of a distinct threshold level regarding increased risk of CHD. Additional analyses on SBP100W suggest a linear association between exercise SBP and CHD risk. Also when SPB100W was used in the multivariable Cox analysis as a second-degree term, the results did not reveal any threshold level. Further analyses showed increasing risk of CHD when comparing groups of 10 mmHg increments of SBP100W with a larger group in the low range of SBP100W at Visit 2, representing an arbitrary group of low exercise SBP (Table S4). This analysis also suggests a linear relationship (Figure S2). When performing these analyses with Visit 1 parameters, the results are in line with previous results of this study; the comparisons were not statistically significant at all levels.

Discussion

In the present study, we aimed to investigate the existence of a threshold level for exercise SBP at moderate workload, above which there is an association between exercise SBP and elevated risk of CHD in healthy middle-aged Caucasian men. We compared presumed healthy males with sustained elevation of exercise SBP during a seven-year, disease-free period, with men with repeated exercise SBP measurements below a given cut-off. When the predictive power of an elevated SBP at moderate work-load was tested at increasing cut-off levels, exercise SBP was a strong, independent predictor of CHD at all levels, with an approximately linearly increasing effect.

Our additional analysis comparing elevated SBP100W against an arbitrarily defined group of 'normal exercise SBP' provides evidence in line with the rest of the results of this study. The two main analyses in this study complement each other and support in different ways the finding of what appears to be a linear relationship between exercise SBP at moderate workload and CHD, supporting the hypothesis of an inexistence of thresholds. To our knowledge, this has not been demonstrated before. Our results support the usefulness of SBP

as a strong predictor for CHD, as SBP measured with two different methods independently predicts CHD in the same cohort of healthy people. The finding of a linear association differs from previous research suggesting a threshold level for increased risk with high exercise SBP (3, 18, 22)

In our analyses, the association between resting SBP and CHD becomes non-significant when including SBP100W. This is also the exact point of our meticulous selection of disease-free, normotensive participants in this study. By excluding participants with pharmacologically treated hypertension at two examinations with a rather long observation time in between, we aimed to eliminate the confounding effect of hypertension, thereby enabling us to investigate exercise SBP. The observation period also makes it possible to investigate participants without other subclinical CV disease. The excluded participants had significantly higher levels of risk factors (data not shown) and also presented with CV disease shortly after Visit 1 (22).With a homogenous and normotensive cohort, it is not surprising that SBP at rest does not manage to impact the CHD risk in the different groups in our study. We believe that exercise SBP is a subtle predictor, often becoming clinically insignificant when comparing to strong risk factors like heritage, resting blood pressure, smoking and cholesterol, and also after end-organ damage from hypertension already has occurred. We have shown increased CV risk at exercise blood pressure around 200 mmHg (3, 4, 23), and most recently as low as 180 mmHg (22). The established risk factors for CHD usually show linearly increasing risk, without distinct thresholds. The design of the present study permitted such analysis also for SBP100W, and the finding that even lower values herald adverse prognosis, may be clinically important. The seven-year observation period is based on the design of Oslo Ischemia Study, and shorter observation periods, or none, may prove sufficient if exercise SBP is implemented in clinical practice. Bicycle exercise tests are extensively used worldwide during ECG stress tests in CHD assessments. The exercise test in our study was

designed specifically for Oslo Ischemia Study and differs from today's protocol. Therefore, the use of exercise SBP in clinical risk assessment must await the development of standardized protocols.

Like resting SBP, exercise SBP at maximal workload, SBPmax, which in almost all of the participants represented the maximal SBP during the exercise test, loses impact in combination with SBP100W. Still, all of these variables are highly correlated (data not shown), and one should be careful to imply loss of impact of other SBP measurements based on this study solely.

Exaggerated exercise SBP has been correlated to sub-clinical hypertension, including masked hypertension (9, 15, 24, 25). In our study, we have selected participants without hypertension through seven years of observation. Considering that, as well as the statistical adjustment for resting SBP, the risk of CHD is increased. Exercise SBP enables further risk estimations beyond the well-known risk factors, and also predicts end-organ damage in treated hypertensive patients reaching treatment target (8). One may therefore argue that elevated exercise SBP is not merely a sign of sub-clinical hypertension, but may instead be considered an entity of its own, namely 'exercise hypertension'. Still, many of the same underlying mechanisms may be common for essential hypertension and 'exercise hypertension'. Research from our group has previously shown a correlation between increasing moderate-exercise SBP and total vascular resistance, indicative of structural changes in resistance vasculature (26, 27), and also changes in vasodilation of larger arteries have been shown in participants with exaggerated SBP during exercise (28), contributing to the hypothesis that many of the same mechanisms are underlying both forms of high blood pressure. The theory regarding endothelial dysfunction is supported by more recent research (29) and a recent review article (30), in which also dysfunction in the renin-angiotensin-aldosterone pathway is present with increased levels of angiotensin II during exercise (31).

Even though forearm vasculature, endothelial dysfunction and renin-angiotensin-aldosterone pathway dysfunction represent an oversimplified surrogate of central arterial stiffness, it is likely that arterial stiffness play a significant role in the association between exercise SBP and CHD, as it is well known that arterial stiffness is a major contributor to hypertension (32). The clinical relevance of separating these two presentations of high SBP becomes apparent when it comes to treatment. There is overwhelming evidence regarding treatment of essential hypertension, whereas high exercise SBP has no recommendations regarding treatment, although it is often empirically regarded a sign of sub-clinical hypertension, and treated thereafter. Future research may focus on intervention on exercise SBP, in order to investigate the optimal level of exercise SBP and whether intervention results in reduced risk of CHD.

In our study, physical fitness is defined as total workload in kilojoules during the test divided by body weight. The rationale for adjusting for this variable has been discussed in detail before (4); physical fitness makes a significant impact on CV risk prediction in our cohort (4, 33, 34). The standard for measuring exercise capacity and fitness is maximal oxygen uptake ($VO2_{max}$). Given the equipment available at the time of the exercise tests, possible application in routine clinical practice and correlation to $VO2_{max}$ (33), our definition of physical fitness appears to be the best possible measure in our study. The exercise test was not performed until utmost exhaustion, which might underestimate actual exercise capacity, possibly greater in fit than unfit participants. This might have underestimated the protective benefits of being fit on the predictive value of exercise SBP.

The novelty of this study is that when able to select healthy participants, and data from two exercise tests, as well as performing an exercise test in a highly standardized situation with the same level of physical activity, exercise SBP is strongly associated with CHD. The moderate workload used in this study, may very well correspond to physical activity performed during the day, as running to the bus, walking in stairs, housekeeping etc. A

hypertensive response to this physical stressor will not necessarily be revealed during rest in seated or supine position. Nonetheless, it will contribute to the overall 'hypertensive load' and hence contribute to the CHD risk.

The main limitation of this study is its observational design. Neither can the results be directly used in risk estimation in women, very young or elderly patients nor patients of other ethnicities. The adjustments are also only made with baseline variables, and development of the known risk factors such as resting SBP, cholesterol or smoking habits during follow-up has not been taken into account, and may therefore confound our results. The investigation of temporal changes beyond the initial seven years in other cardiovascular risk factors, as well as exercise SBP, would further enlighten the association found in our study. Our measurements are performed manually and non-invasive. The use of invasive methods would probably increase the accuracy of our measurements, and also provide reliable diastolic blood pressure during exercise, though with uncertain benefit. Previous studies on this cohort presents excellent reproducibility of exercise SBP (2), and we believe that the high accuracy of the SBP measurements in this study rather strongly contributed to the visualizing of the present findings with two SBP taken in the same study as independent predictors of CHD. High-density lipoprotein cholesterol (HDL) has shown a strong and inverse correlation to CHD in this cohort earlier (35), but was not included in our main analyses. When additionally investigating the impact of HDL in our study, there were only minor changes in risk suggesting a small protective effect of high levels of HDL (data not shown). Also when adjusting for development of diabetes mellitus (n=139) and body mass index through 28 years of follow-up, there is only a negligible effect on the results (data not shown). We have a moderate number of participants in our study, and when divided into groups, the numbers and subsequent power for statistical analyses decrease further. This renders the study susceptible to the play of chance, and our results do not reach statistical significance at certain levels, as

exemplified by the result of the analyses with cut-off at 160 mmHg and 200 mmHg. The study compensates for this by its long follow-up and relatively large number of events. The overall lethality from CHD (26%) was as expected for this population. The definition of CHD and myocardial infarction has in some degree changed during the follow-up period, and may have influenced our results. Nonetheless, the detection and criteria for myocardial infarction have generally become more sensitive, and the assessment of CHD has for years been fairly standardized amongst Norwegian physicians. Hence this may at best result in an underestimation of the impact on CHD risk implied by exercise SBP.

Conclusion

When investigating exercise SBP at moderate workload measured at two exercise tests in healthy middle-aged Caucasian men, there is increasing risk of CHD with increasing exercise SBP. Exercise SBP appears to be strongly associated with CHD, independent of SBP at rest and other CV risk factors. The association is linear from the low range of exercise SBP and there is no sign of a distinct threshold level for increased CHD risk, further strengthening SBP as a predictor for CHD.

Perspectives

Increased risk of CHD has been acknowledged only at very high blood pressures during moderate workload. The results of our study are the first to imply increased risk from the normotensive range, hence providing rationale for performing studies on intervention on normotensive men with a hypertensive response to moderate exercise.

Sources of Funding

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Conflicts of Interest

Outside the present work, SEK has received ad hoc honoraria for lecturing from Bayer, Merck KGaA, Merck & Co., Sanofi, and Takeda, and honoraria from Takeda for study committee work within the past three years. EP has received speaking honoraria from Pfizer. JB holds a full time position as epidemiologist in AstraZeneca. KG has received lecture honoraria from Bayer, Boehringer, MSD, Novo Nordisk. The other authors declare no conflicts of interest.

References

1. Keller K, Stelzer K, Ostad MA, Post F. Impact of exaggerated blood pressure response in normotensive individuals on future hypertension and prognosis: Systematic review according to PRISMA guideline. Adv Med Sci. 2017;62:317-29

2. Mundal R, Kjeldsen SE, Sandvik L, Erikssen G, Thaulow E, Erikssen J. Exercise blood pressure predicts cardiovascular mortality in middle-aged men. Hypertension. 1994;24:56-62.

3. Kjeldsen SE, Mundal R, Sandvik L, Erikssen G, Thaulow E, Erikssen J. Supine and exercise systolic blood pressure predict cardiovascular death in middle-aged men. J Hypertens. 2001;19:1343-8.

4. Mariampillai JE, Engeseth K, Kjeldsen SE, Grundvold I, Liestol K, Erikssen G, et al. Exercise systolic blood pressure at moderate workload predicts cardiovascular disease and mortality through 35 years of follow-up in healthy, middle-aged men. Blood Press. 2017;26:229-36.

5. Mundal R, Kjeldsen SE, Sandvik L, Erikssen G, Thaulow E, Erikssen J. Exercise blood pressure predicts mortality from myocardial infarction. Hypertension. 1996;27:324-9.

6. Holmqvist L, Mortensen L, Kanckos C, Ljungman C, Mehlig K, Manhem K. Exercise blood pressure and the risk of future hypertension. J Hum Hypertens. 2012;26:691-5.

7. Singh JP, Larson MG, Manolio TA, O'Donnell CJ, Lauer M, Evans JC, et al. Blood pressure response during treadmill testing as a risk factor for new-onset hypertension. The Framingham heart study. Circulation. 1999;99:1831-6.

8. Tsumura K, Hayashi T, Hamada C, Endo G, Fujii S, Okada K. Blood pressure response after two-step exercise as a powerful predictor of hypertension: the Osaka Health Survey. J Hypertens. 2002;20:1507-12.

9. Schultz MG, Hare JL, Marwick TH, Stowasser M, Sharman JE. Masked hypertension is "unmasked" by low-intensity exercise blood pressure. Blood Press. 2011;20:284-9.

10. Tanaka S, Masuda T, Kamada Y, Hamazaki N, Kamiya K, Ogura MN, et al. Excessive SBP elevation during moderate exercise discriminates patients at high risk of developing left ventricular hypertrophy from hypertensive patients. J Hypertens. 2018;36:1291-8.

11. Mottram PM, Haluska B, Yuda S, Leano R, Marwick TH. Patients with a hypertensive response to exercise have impaired systolic function without diastolic dysfunction or left ventricular hypertrophy. J Am Coll Cardiol. 2004;43:848-53.

12. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial

hypertension of the European Society of Cardiology and the European Society of Hypertension. J Hypertens. 2018;36:1953-2041.

13. Le VV, Mitiku T, Sungar G, Myers J, Froelicher V. The blood pressure response to dynamic exercise testing: a systematic review. Prog Cardiovasc Dis. 2008;51:135-60.

14. Lorbeer R, Ittermann T, Volzke H, Glaser S, Ewert R, Felix SB, et al. Assessing cutoff values for increased exercise blood pressure to predict incident hypertension in a general population. J Hypertens. 2015;33:1386-93.

15. Schultz MG, La Gerche A, Sharman JE. Blood Pressure Response to Exercise and Cardiovascular Disease. Curr Hypertens Rep. 2017;19:89.

16. Lauer MS, Levy D, Anderson KM, Plehn JF. Is there a relationship between exercise systolic blood pressure response and left ventricular mass? The Framingham Heart Study. Ann Int Med. 1992;116:203-10.

17. Lauer MS, Pashkow FJ, Harvey SA, Marwick TH, Thomas JD. Angiographic and prognostic implications of an exaggerated exercise systolic blood pressure response and rest systolic blood pressure in adults undergoing evaluation for suspected coronary artery disease. J Am Coll Cardiol. 1995;26:1630-6.

18. Mariampillai JE, Engeseth K, Kjeldsen SE, Prestgaard EE, Gjesdal K, Liestol K, Erikssen J, Bodegard J, Grundvold I, Skretteberg PT. Exercise Systolic Blood Pressure at Moderate Workload: Which Threshold Level Predicts Coronary Heart Disease in Healthy, Middle-aged Men? J Hypertens. 2018;35:e30.

19. Skretteberg PT, Grundvold I, Kjeldsen SE, Engeseth K, Liestol K, Erikssen G, et al. Seven-year increase in exercise systolic blood pressure at moderate workload predicts long-term risk of coronary heart disease and mortality in healthy middle-aged men. Hypertension. 2013;61:1134-40.

20. Erikssen J, Enge I, Forfang K, Storstein O. False positive diagnostic tests and coronary angiographic findings in 105 presumably healthy males. Circulation. 1976;54:371-6.

21. Sandvik L, Erikssen J, Thaulow E, Erikssen G, Mundal R, Rodahl K. Physical fitness as a predictor of mortality among healthy, middle-aged Norwegian men. New Engl J Med. 1993;328:533-7.

22. Mariampillai JE, Prestgaard EE, Kjeldsen SE, Liestol K, Engeseth K, Erikssen J, et al. SBP above 180 mmHg at moderate exercise workload increases coronary heart disease risk in healthy men during 28-year follow-up. J Hypertens. 2019;37:949-55.

23. Mariampillai JE, Engeseth K, Kjeldsen SE, Grundvold I, Liestol K, Erikssen G, et al. Exercise systolic blood pressure ≥ 190 mmHg at moderate workload predicts coronary heart disease in healthy, middle-aged men. J Hypertens. 2015;33 Suppl 1:e28.

24. Kramer CK, Leitao CB, Canani LH, Ricardo ED, Pinto LC, Gross JL. Blood pressure responses to exercise in type II diabetes mellitus patients with masked hypertension. J Hum Hypertens. 2009;23:620-2.

25. Kayrak M, Bacaksiz A, Vatankulu MA, Ayhan SS, Kaya Z, Ari H, et al. Exaggerated blood pressure response to exercise--a new portent of masked hypertension. Clin Exp Hypertens. 2010;32:560-8.

26. Fossum E, Hoieggen A, Moan A, Rostrup M, Kjeldsen SE. Insulin sensitivity is related to physical fitness and exercise blood pressure to structural vascular properties in young men. Hypertension. 1999;33:781-6.

27. Fossum E, Hoieggen A, Moan A, Rostrup M, Nordby G, Kjeldsen SE. Relationship between insulin sensitivity and maximal forearm blood flow in young men. Hypertension. 1998;32:838-43.

28. Stewart KJ, Sung J, Silber HA, Fleg JL, Kelemen MD, Turner KL, et al. Exaggerated exercise blood pressure is related to impaired endothelial vasodilator function. Am J Hypertens. 2004;17:314-20.

29. Thanassoulis G, Lyass A, Benjamin EJ, Larson MG, Vita JA, Levy D, et al. Relations of exercise blood pressure response to cardiovascular risk factors and vascular function in the Framingham Heart Study. Circulation. 2012;125:2836-43.

30. Kim D, Ha JW. Hypertensive response to exercise: mechanisms and clinical implication. Clin hypertens. 2016;22:17.

31. Shim CY, Ha JW, Park S, Choi EY, Choi D, Rim SJ, et al. Exaggerated blood pressure response to exercise is associated with augmented rise of angiotensin II during exercise. J Am Coll Cardiol. 2008;52:287-92.

32. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. European heart journal. 2006;27(21):2588-605.

33. Engeseth K, Prestgaard EE, Mariampillai JE, Grundvold I, Liestol K, Kjeldsen SE, et al. Physical fitness is a modifiable predictor of early cardiovascular death: A 35-year follow-up study of 2014 healthy middle-aged men. Eur J Prev Cardiol. 2018;25:1655-63.

34. Prestgaard E, Mariampillai J, Engeseth K, Erikssen J, Bodegard J, Liestol K, et al. Change in Cardiorespiratory Fitness and Risk of Stroke and Death. Stroke. 2018. E-pub ahead of print

35. Skretteberg PT, Grundvold I, Kjeldsen SE, Erikssen JE, Sandvik L, Liestol K, et al. HDL-cholesterol and prediction of coronary heart disease: modified by physical fitness? A 28-year follow-up of apparently healthy men. Atherosclerosis. 2012;220:250-6.

Novelty and Significance

1) What is new?
    - When using sustained elevation of exercise systolic blood pressure after seven years of disease-free observation, elevated exercise systolic blood pressure is a strong predictor of coronary heart disease and with an approximately linearly increasing effect over the studied SBP interval.
    - The association is independent of the classical cardiovascular risk factors including systolic blood pressure at rest, and also physical fitness.
2) What is relevant?
    - This study paves the way for future interventional trials seeking to investigate the potential of intervention on exercise hypertension in order to decrease risk of coronary heart disease
3) Summary
    - In the present study, we have investigated the association between elevated exercise systolic blood pressure and coronary heart disease in a selected cohort of healthy, middle-aged, Caucasian men performing repeated exercise tests on 100W workload. We found a strong and linear association between exercise systolic blood pressure and coronary heart disease, and the association is independent of classical cardiovascular risk factors including systolic blood pressure at rest. The results provide evidence for increased risk at far lower exercise systolic blood pressure than earlier acknowledged.

Figure legends

Figure 1.

Flowchart showing follow-up surveys from the Oslo Ischemia Study (left) and the present study (right). SBP100W: peak exercise systolic blood pressure at 100W workload.

Figure 2.

Hazard ratio with 95 % confidence interval for coronary heart disease in Group 3 (SBP100W equal to or above cut-off level at both surveys) compared to Group 1 (SBP100W below cut-off level at both surveys) at each level of SBP100W from 160 mmHg to 200 mmHg, adjusting for age, resting systolic blood pressure, total serum cholesterol, smoking status and physical fitness at Visit 2, and family history of coronary heart disease obtained at Visit 1. SBP100W: peak exercise systolic blood pressure at 100W workload; n: number of participants in Group 3 at current threshold level. CI: confidence interval. *p-value ≤0.05; **p-value ≤0.01; ***p-value ≤0.001.

Online Supplement, Figure S1.

Grouping of participants based on SBP100W at Visit 1 and Visit 2. SBP100W: peak systolic blood pressure at 100W workload.

Online Supplement, Figure S2.

Hazard ratios for each Group 1-6 with Group 1 as reference in a multivariate analysis adjusting for age, resting systolic blood pressure, total serum cholesterol, smoking status and physical fitness at Visit 2, and family history of coronary heart disease obtained at Visit 1.

SBP100W: peak exercise systolic blood pressure at 100W workload; n: number of participants (%). Dotted line represents linear regression line.

Table 1. Baseline Characteristics

All participants, n=1392	Visit 1	Visit 2 (Baseline)	P-value
Age, years (SD)	49.2 (5.4)	56.5 (5.4)	<0.0001
SBP at rest, mmHg (SD)	127.3 (15.7)	130.7 (17.7)	<0.0001
SBP100W, mmHg (SD)	177.3 (21.9)	180.3 (25.4)	<0.0001
Family history of CHD, % (SD)*	21.0 (0.4)	21.0 (0.4)	N/A
Current smokers, n (%)	546 (39.2)	452 (32.5)	<0.0001
Serum cholesterol, mmol/l (SD) †	6.6 (1.2)	6.4 (1.2)	<0.0001
Physical fitness, kJ/kg (SD)	1.5 (0.6)	1.4 (0.6)	<0.0001
Maximal SBP, mmHg (SD)	213.7 (20.7)	216.9 (23.9)	<0.0001
Resting DBP, mmHg (SD)	85.6 (9.2)	84.1 (10.2)	<0.0001
Resting heart rate, bpm (SD) ‡	60.9 (9.4)	62.9 (10.2)	<0.0001
Fasting blood glucose, mmol/l (SD)§	4.4 (0.5)	N/A	N/A
Body mass index, kg/m^2 (SD)	24.4 (2.6)	24.7 (2.7)	<0.0001

Values are presented as number (%) or mean (standard deviation (SD)). Comparisons between Visit 1 and Visit 2 variables are tested with Chi-square test for smoking and Students *t*-test for the other variables. *Data collected at Visit 1 only. † n= 1390 at Visit 2. ‡ n= 1391. § n=1382.

Table 2. Mean Peak Systolic Blood Pressure at 100W Workload (SBP100W) in Each Group at Every Cut-off Level of SBP100W

	Group 1	Group 2	Group 3
SBP100W 160 mmHg, n (%)	124 (8.9)	229 (16.5)	1039 (74.6)
Visit 1, mmHg (SD)	145.8 (7.4)	160.0 (12.7)	184.9 (19.0)
Visit 2, mmHg (SD)	144.8 (8.2)	160.0 (15.8)	189.1 (21.9)
SBP100W 165 mmHg, n (%)	213 (15.3)	309 (22.2)	870 (62.5)
Visit 1, mmHg (SD)	150.4 (8.7)	164.6 (13.2)	188.4 (18.2)
Visit 2, mmHg (SD)	149.0 (9.6)	165.4 (15.6)	193.2 (21.0)
SBP100W 170 mmHg, n (%)	300 (21.6)	325 (23.3)	767 (55.1)
Visit 1, mmHg (SD)	153.7 (9.5)	166.8 (13.5)	191.0 (17.6)
Visit 2, mmHg (SD)	152.0 (10.2)	170.0 (15.6)	195.9 (20.6)
SBP100W 175 mmHg, n (%)	448 (32.2)	366 (26.3)	578 (41.5)
Visit 1, mmHg (SD)	157.5 (10.3)	171.8 (14.1)	196.1 (16.6)
Visit 2, mmHg (SD)	156.0 (11.2)	177.2 (16.5)	201.1 (19.7)
SBP100W 180 mmHg, n (%)	547 (39.3)	350 (25.1)	495 (35.6)
Visit 1, mmHg (SD)	159.7 (11.1)	174.6 (14.6)	198.7 (16.2)
Visit 2, mmHg (SD)	158.4 (11.9)	180.5 (16.1)	204.4 (19.1)
SBP100W 185 mmHg, n (%)	673 (48.3)	341 (24.5)	378 (27.2)
Visit 1, mmHg (SD)	162.1 (11.9)	178.9 (15.0)	202.9 (15.7)
Visit 2, mmHg (SD)	161.3 (13.1)	185.7 (15.9)	209.3 (18.3)
SBP100W 190 mmHg, n (%)	784 (56.3)	306 (22.0)	302 (21.7)
Visit 1, mmHg (SD)	164.3 (13.0)	181.6 (14.9)	206.8 (14.9)
Visit 2, mmHg (SD)	163.5 (13.9)	191.6 (16.0)	212.4 (18.1)
SBP100W 195 mmHg, n (%)	897 (64.4)	274 (19.7)	221 (15.9)

Visit 1, mmHg (SD)	166.2 (13.8)	186.7 (16.3)	210.7 (14.4)
Visit 2, mmHg (SD)	166.2 (15.3)	196.0 (16.0)	217.8 (17.0)
SBP100W 200 mmHg, n (%)	992 (71.3)	230 (16.5)	170 (12.2)
Visit 1, mmHg (SD)	167.8 (14.5)	190.6 (16.5)	214.5 (13.9)
Visit 2, mmHg (SD)	168.5 (16.4)	200.9 (17.5)	220.9 (16.9)

Mean peak systolic blood pressure at 100W workload at Visit 1 and 2 for each group at each cut-off level. SD: standard deviation.

Table 3. Multivariate Analysis Comparing Group 1, 2 and 3 at Different Cut-off Levels

Cut-off level of SBP100W	Group 1 (SBP100W <cut-off level at both Visit 1 and 2)	Group 2 (SBP100W ≥cut-off level at one Visit)	Group 3 (SBP100W ≥cut-off level at both Visit 1 and 2)	p-value, compared to Group 1: Group 2; Group 3
160 mmHg	1.00	1.31 (0.84-2.10)	1.25 (0.84-1.94)	0.23; 0.29
165 mmHg	1.00	1.41 (0.99-2.04)	1.40 (1.00-1.99)	0.06; 0.05
170 mmHg	1.00	1.44 (1.05-1.98)	1.50 (1.11-2.04)	0.02; 0.007
175 mmHg	1.00	1.05 (0.80-1.38)	1.45 (1.11-1.87)	0.72; 0.006
180 mmHg	1.00	1.09 (0.84-1.41)	1.41 (1.09-1.83)	0.53; 0.009
185 mmHg	1.00	1.08 (0.84-1.38)	1.41 (1.08-1.83)	0.54; 0.01
190 mmHg	1.00	1.20 (0.93-1.54)	1.64 (1.25-2.15)	0.15; 0.0004
195 mmHg	1.00	1.09 (0.82-1.40)	1.35 (1.00-1.81)	0.51; 0.05
200 mmHg	1.00	1.31 (1.00-1.69)	1.28 (0.93-1.75)	0.05; 0.13

Hazard ratio and p-values comparing Group 1, 2 and 3 in a multivariate analysis adjusting for family history of coronary heart disease and Visit 2 values of age, resting systolic blood pressure, serum cholesterol, smoking status and physical fitness. SBP100W: peak exercise systolic blood pressure at 100W workload.