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RESEARCH LETTER

Association of oxygen uptake at ventilatory threshold with risk of incident hypertension: A long-term prospective cohort study

Running title: Anaerobic threshold and incident hypertension

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Peak oxygen uptake (peak VO$_2$) has been suggested as a causal risk factor for future hypertension. Oxygen uptake at ventilatory threshold (VO$_2$ at VT), is a proxy for peak VO$_2$, but its relationship with incident hypertension has not been previously investigated. VO$_2$ at VT was determined at baseline during submaximal exercise testing using respiratory gas analyzers in the Kuopio Ischemic Heart Disease cohort of 1,360 middle-aged men without hypertension, and its relationship with incident hypertension risk was assessed. During a median follow-up of 25.1 years, there were 217 incident cases of new onset hypertension. This study suggested that in middle-aged Caucasian men, VO$_2$ at VT is inversely associated with future risk of hypertension.

Peak oxygen uptake (VO$_2$), a measure of cardiorespiratory fitness (CRF), is considered the gold standard index of aerobic capacity.$^1$ Peak VO$_2$ has been consistently shown to be inversely and independently associated with incident cardiovascular disease (CVD) as well as CVD mortality.$^2,^3$ Emerging evidence from large-scale epidemiological cohorts also demonstrate peak VO$_2$ to be consistently associated with future hypertension risk and it has been suggested to be a causal risk factor.$^4$ Hypertension is an established risk factor for CVD and is included in the standard cardiovascular risk assessment panel.$^6$ Oxygen uptake at ventilatory threshold (VO$_2$ at VT), another cardiopulmonary exercise testing (CPX) parameter and often referred to as the anaerobic threshold, is assessed at submaximal levels of CPX.$^7$ VO$_2$ at VT is considered as a measure of cardiovascular fitness and a reliable index of aerobic capacity,$^1$ and has been suggested to be protective of fatal cardiovascular outcomes as well as all-cause mortality.$^8$ Previous findings have suggested VO$_2$ at VT to be a suitable proxy for peak VO$_2$.$^8$ Though peak VO$_2$ is a gold standard measure of aerobic capacity, some individuals are unable to achieve this VO$_2$ level due to exercise-related limitations such as musculoskeletal problems. In such instances, VO$_2$ at VT, which can be assessed safely at submaximal exercise levels, may be used as a suitable replacement for the assessment of maximal VO$_2$. To our knowledge, the nature of the relationship between VO$_2$ at VT and future hypertension risk in general populations has not been previously investigated. We aimed to assess the nature and magnitude of the association between VO$_2$ at VT and incident hypertension using the
established Kuopio Ischemic Heart Disease (KIHD) population-based cohort comprising healthy middle-aged men from eastern Finland.

Participants in the study were men aged 42-61 years recruited into the Kuopio Ischemic Heart Disease (KIHD) study, a prospective epidemiologic study of the incidence of cardiovascular and other related outcomes among Finnish adults. The institutional review board of the University of Eastern Finland approved the study, and each participant provided written informed consent. Detailed description of blood sample collection, physical measurements, as well as measurements of covariates have been reported previously. VO\textsubscript{2} at VT as well as peak VO\textsubscript{2} were assessed using a respiratory gas exchange analyzer (Medical Graphics, MCG, St. Paul, Minnesota), of which details have been reported in a recent report. Incident hypertension was defined as a physician diagnosis of hypertension, systolic blood pressure (SBP) ≥ 140 mm Hg and/or diastolic BP ≥ 90 mm Hg, or use of anti-hypertensive medication (beta-blockers, calcium channel blockers, diuretics or angiotensin-converting-enzyme inhibitor/angiotensin receptor antagonists). All physicians or evaluators who assessed follow-up events were blinded to baseline data. All BP measurements including follow-up data were measured under standardized conditions. Baseline BP measurements were assessed after a supine rest of 5-minutes and were measured three times in a supine position, once in standing position, and twice in sitting position with 5-minute intervals, and the arithmetic mean of all available measurements was taken. Incident hypertension was ascertained through record linkage to the National Hospital Discharge Registry and the Social Insurance Institution of Finland register, which contains information on the reimbursement of expenses for antihypertensive medication. There were no losses to follow-up. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using Cox proportional hazard models. All statistical analyses were conducted using Stata version 14 (Stata Corp, College Station, Texas).

The mean age of participants at study entry was 52 [standard deviation (SD), 5] years. The baseline mean (SD) level of VO\textsubscript{2} at VT was 24.57 (6.13) ml/kg/min and the corresponding level as metabolic equivalent was 7.02 (1.75). There were weak to moderate inverse correlations of VO\textsubscript{2} at VT with several
risk markers. Significant positive correlations were observed with peak VO$_2$ ($r = 0.90$), high-density lipoprotein cholesterol (HDL-C) ($r = 0.26$) and physical activity ($r = 0.14$). Similar correlations were observed for peak VO$_2$ with several risk markers including HDL-C ($r = 0.28$) and physical activity ($r = 0.15$). During a median follow-up of 25.1 (interquartile range, 19.4-26.9) years, 217 new onset hypertension cases were recorded. The age-adjusted HR (95% CIs) per unit increase in VO$_2$ at VT for hypertension was 0.95 (0.93-0.97), which remained unchanged on further adjustment for systolic blood pressure, smoking status, history of diabetes mellitus, family history of hypertension, total cholesterol, HDL-C, alcohol consumption, and physical activity 0.95 (0.93-0.98). VO$_2$ at VT was strongly and positively correlated with peak VO$_2$. Alternatively, comparing the top versus bottom quartile of VO$_2$ at VT, the corresponding age-, multivariate-, and multivariate plus peak VO$_2$-adjusted HRs (95% CIs) for hypertension were 0.50 (0.33-0.76), 0.51 (0.33-0.78), and 1.31 (0.66-2.60) respectively (Table 1). To put the strength of the association of VO$_2$ at VT with risk of hypertension into context, direct comparisons were made to the association of peak VO$_2$ with risk of hypertension. Similarly, peak VO$_2$ was inversely and independently associated with hypertension risk as shown in Table 1. This association remained significant after further adjustment for VO$_2$ at VT.

Based on this population-based prospective cohort study of apparently healthy middle-aged Finnish men without a history of hypertension at baseline, we have shown an inverse association between VO$_2$ at VT and future hypertension risk, which was independent of several established risk factors and other potential confounders; however, the association was dependent on peak VO$_2$. Consistent with previous findings, VO$_2$ at VT was strongly and positively correlated with peak VO$_2$. VO$_2$ at VT was shown to be strongly and positively correlated with peak VO$_2$. In contrast, an analysis in the same set of participants showed the inverse association between peak VO$_2$ and hypertension risk to be stronger and was also independent of VO$_2$ at VT; which suggests that peak VO$_2$ is a stronger risk indicator for hypertension risk than VO$_2$ at VT.
To our knowledge, no previous study has evaluated the prospective association VO$_2$ at VT with risk of hypertension, therefore we are unable to compare the current results with previous work. However, given that VO$_2$ at VT is strongly correlated with peak VO$_2$, with both parameters being measures of aerobic capacity$^1,7,10$, the current results are in line with previous reports that have demonstrated peak VO$_2$ to be associated with the risk of developing future hypertension$^4,5$.

It has been reported that VO$_2$ at VT is more strongly correlated with endurance compared with peak VO$_2$.$^{11}$ Though there has been emerging evidence on the potential application of CPX parameters in clinical practice,$^7$ their use in general population settings have not been well established. VO$_2$ at VT can be assessed safely at submaximal exercise levels, unlike peak VO$_2$ which can be difficult to assess sometimes as a maximal exercise level needs to be achieved.$^{12}$ Though peak VO$_2$ remained the best indicator of hypertension risk, our findings do suggest that VO2 at VT could be used as a proxy marker when peak VO$_2$ cannot be achieved due to other limitations.

Our report is the first prospective evaluation of the association between VO$_2$ at VT and the risk of future hypertension. Other strengths include the well-established cohort and long-term follow-up. The assessment of VO$_2$ at VT during exercise test may have potential applications in clinical settings such as the detection of at risk patients. However, our results cannot be generalized to women and other populations. In addition, we could not correct for regression dilution because of absence of repeat measurements of VO$_2$ at VT, which could have underestimated our associations. Thus, further studies are needed to clarify the role of VO$_2$ at VT as a risk assessment tool for adverse cardiovascular outcomes such as hypertension.

In conclusion, VO$_2$ at VT is inversely associated with future risk of hypertension in middle-aged Caucasian men. The prognostic value of VO$_2$ at VT for future hypertension deserves further study.
CONFLICT OF INTEREST

The authors declare no conflict of interest.
REFERENCES


### Table 1. Associations of VO\textsubscript{2} at VT and peak VO\textsubscript{2} with incident hypertension

| VO\textsubscript{2} at VT and incident hypertension | Model 1 | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|
| | Hazard ratio (95% CI) | P-value | Hazard ratio (95% CI) | P-value | Hazard ratio (95% CI) | P-value |
| Per unit (ml/kg/min) | 217 / 1,360 | 0.95 (0.93-0.97) | < 0.001 | 0.95 (0.93-0.98) | < 0.001 | 1.02 (0.96-1.07) | 0.551 |
| Per 1 MET | 217 / 1,360 | 0.83 (0.77-0.91) | < 0.001 | 0.84 (0.76-0.92) | 0.003 | 1.06 (0.88 - 1.28) | 0.551 |
| Quartile 2 (20.32-24.03) | 72 / 340 | 1.06 (0.75-1.50) | 0.748 | 1.01 (0.71-1.44) | 0.943 | 1.40 (0.94-2.08) | 0.101 |
| Quartile 3 (24.04-28.35) | 47 / 340 | 0.66 (0.45-0.97) | 0.036 | 0.72 (0.49-1.08) | 0.111 | 1.24 (0.75-2.07) | 0.399 |
| Quartile 4 (28.36-52.21) | 40 / 340 | 0.50 (0.33-0.76) | 0.001 | 0.51 (0.33-0.78) | 0.002 | 1.31 (0.66-2.60) | 0.436 |
| P-value for trend | | < 0.001 | | < 0.001 | | 0.538 |

| Peak VO\textsubscript{2} and incident hypertension | Model 1 | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|
| | Hazard ratio (95% CI) | P-value | Hazard ratio (95% CI) | P-value | Hazard ratio (95% CI) | P-value |
| Per unit (ml/kg/min) | 217 / 1,360 | 0.95 (0.93-0.97) | < 0.001 | 0.95 (0.93-0.97) | < 0.001 | 0.94 (0.89-0.98) | 0.005 |
| Per 1 MET | 217 / 1,360 | 0.82 (0.77-0.88) | < 0.001 | 0.83 (0.77-0.90) | < 0.001 | 0.80 (0.68-0.93) | 0.005 |
| Quartile 2 (27.44-32.22) | 64 / 340 | 0.83 (0.59-1.17) | 0.285 | 0.81 (0.57-1.16) | 0.250 | 0.84 (0.57-1.24) | 0.380 |
| Quartile 3 (32.26-36.94) | 51 / 340 | 0.58 (0.40-0.85) | 0.004 | 0.62 (0.42-0.91) | 0.014 | 0.66 (0.40-1.08) | 0.101 |
| Quartile 4 (36.97-65.40) | 35 / 340 | 0.36 (0.24-0.55) | < 0.001 | 0.38 (0.24-0.59) | < 0.001 | 0.42 (0.21-0.86) | 0.018 |
| P-value for trend | | < 0.0001 | | < 0.0001 | | 0.022 |

Model 1: Adjusted for age
Model 2: Model 1 plus systolic blood pressure, smoking status, history of diabetes mellitus, family history of hypertension, total cholesterol, high-density lipoprotein cholesterol, alcohol consumption, and physical activity
Model 3: Model 1 plus peak VO\textsubscript{2} (for VO\textsubscript{2} at VT) or VO\textsubscript{2} at VT (for peak VO\textsubscript{2})

VO\textsubscript{2} at VT, oxygen uptake at ventilatory threshold
1 MET is equivalent to 3.5 ml/kg/min of oxygen uptake at ventilatory threshold