

# Norske abstrakter/postere på EuroPrevent 2008

## **Exercise-induced abnormal pulmonary arterial pressure response in adolescents and adults with atrial or ventricular septal defect.**

**T Moller, E Pettersen, K Peersen, PM Fredriksen, H Holmstrøm, E Thaulow (Tønsberg, Oslo).**

**Introduction:** The European Heart Survey on Congenital Heart Disease described follow-up data in 902/634 adult patients with isolated atrial or ventricular septal defect (ASD or VSD). The reported prevalence of pulmonary hypertension was 18% in both closed ASD and closed VSD which was surprisingly high. However, the study recruited patients from specialised centres with a selection towards difficult cases. Our study aims to examine a representative population-based group of young patients with isolated ASD or VSD. The main focus is pulmonary hypertension or its postulated precursor, abnormal pulmonary pressure response (AR) during exercise.

**Methods:** The study comprises 49 patients with either isolated VSD or ASD, whose defects were assumed hemodynamically insignificant or surgically closed early in life. The patients were recruited among all patients born between 1982 and 1993 from two regions in Norway. They are matched against 62 healthy controls with same age and gender. Cardiovascular exercise testing (treadmill protocol) and echocardiography at rest and during supine cycling (target heart rate 160-min) are performed.

**Results:** Treadmill testing showed normal (Gaussian) distribution of agecorrected maximal oxygen uptake (VO<sub>2</sub>peak) for both groups expressed by VO<sub>2</sub>peak Z-score related to a Norwegian normal standard. Highly endurance-trained volunteers with a Z-score > 2 were excluded. There was a significant lower mean Z-score of VO<sub>2</sub>peak in the patient group (-1.65, -5.2 to 1.3) as compared to the normally trained controls (mean -0.12, -4.5 to 1.8). Echocardiography showed a significant lower right ventricular performance measured by tricuspid annular plane systolic excursion (TAPSE) (p<0.001, means patient/control 18.4/23.0 [-6.1,-3.0]). There

were no cases of pulmonary hypertension at rest in the patient group. Exercise echocardiography rendered assessable registrations of tricuspid regurgitation jet velocity in 45/49 patients and in 60/62 controls. 20 of 45 patients (44%) and 11/60 controls (18%) had PAP above 40mmHg during exercise. Eight patients (18%) but only one control (2%) had PAP above 50mmHg during exercise. The PAP did not differ between genders and no correlation was found between TAPSE and PAP.

**Conclusion:** Young patients with small untreated or surgically closed isolated ASD or VSD have lower exercise capacity and lower right ventricular performance than healthy individuals. About one out of five patients has pathologic pulmonary pressure load above 50mmHg during exercise. The long-term implications of these findings have to be investigated.

## **Soleus gene expression in exercise trained and sedentary rats with inborn high or low aerobic capacity.**

**A Bye, M Langaas, MA Høydal, D Catalucci, OJ Kemi, L Koch, SL Britton, O Ellingsen, U Wisløff (Trondheim, Milano, Glasgow, Ann Arbor).**

**Purpose:** Aerobic capacity is a strong predictor of cardiovascular mortality. To determine the relationship between inborn aerobic capacity and soleus gene expression we examined genome-wide gene expression in soleus muscle of rats artificially selected for high- and low running capacity (HCR and LCR, respectively) over 16 generations. The artificial selection of LCR caused accumulation of risk factors of cardiovascular disease similar to the metabolic syndrome seen in man, whereas HCR had markedly better cardiac and vascular functions. We also studied alterations in gene expression in response to exercise training in the two groups, since accumulating evidence indicates that exercise has profound beneficial effects on the metabolic syndrome.

**Methods:** Soleus gene expression of both sedentary and exercise trained HCR and LCR was characterized by microarray- and gene ontology analysis.

Results: Although HCR and LCR had an inborn 347 % difference in running capacity, only three genes were found differentially expressed in the soleus muscle between the two groups. Up-regulation of the mitochondrial enzyme leucyl-transferRNA synthetase (LARS2) was found in the sedentary LCR. Increased expression of LARS2 has been associated with a mitochondrial DNA mutation linked to maternally inherited diabetes and mitochondrial dysfunction. In line with our findings, a growing body of evidence suggests that LCR have compromised mitochondrial function. After exercise training, 58 genes were altered in the soleus muscle of HCR, in contrast to only one in the LCR group. This suggests that animals born with different levels of fitness respond different to the same type of exercise training. Adaptations to exercise in HCR seemed to be associated with increased lipid metabolism and fatty acid elongation in the mitochondria. Also, genes associated with the fatty acid metabolizing peroxisomes, seemed to be central in the adaptation to exercise. The same subunit of the mitochondrial cytochrome c oxidase (COX), a marker of mitochondrial biogenesis, was found significantly up-regulated by exercise in both HCR and LCR. As a result of this adaptation, the muscle is able to increase its aerobic energy-producing capacity and endurance work capacity.

Conclusion: The results indicate that (i) LCR might have mitochondrial dysfunction, which may be a contributing factor of the low inborn aerobic capacity, (ii) animals born with different levels of fitness respond different to the same exercise program.

### **Cardiac SERCA2 function is essential for aerobic capacity and response to exercise training.**

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Purpose: Aerobic fitness is closely linked to function of sarco-endoplasmic reticulum Ca<sup>2+</sup> ATPase (SERCA2) and cardiomyocyte contractile function, in both healthy and failing hearts. In a new mouse model of progressive heart failure, deletion of the Serca2 gene in cardiac myocytes is induced by tamoxifen administration (SERCA2 KO). SERCA2 KO mice develop severe congestive heart failure within 7 weeks after Serca2 deletion.

Control mice with floxed alleles (SERCA2 FF) are unaffected. Our hypothesis was that aerobic capacity, measured as maximal oxygen uptake (VO<sub>2</sub>max) is reduced in both sedentary and trained SERCA2 KO mice.

Methods: Two studies were performed. To assess aerobic capacity, sedentary groups of either control or SERCA2 KO animals underwent daily testing of VO<sub>2</sub>max from day 5 before knockout through day 14 after knockout. To determine whether the training response is altered in the SERCA2 KO mice, a four week training program, starting two weeks after knockout, was set up. Animals were either subjected to exercise training or remained sedentary. Exercise training was performed as treadmill running in intervals, 8 min at 85-90% of VO<sub>2</sub>max, interspersed with 2 min at 40--50%, for 1 hour, five days per week.

Results: In the first study, aerobic capacity in sedentary SERCA2 KO mice transiently decreased to a nadir 50%--70% below baseline 3--5 days after knockout, before reverting to baseline values. In the second study, VO<sub>2</sub>max fell by 50% after 4 weeks of exercise training in the SERCA2 KO mice, although running speed was maintained. Echocardiography showed dilation of the left atrium in SERCA2 KO. Increased heart and lung weights as well as pulmonary congestion were consistent with congestive heart failure in both training and sedentary SERCA2 KO mice.

Conclusion: After ablation of the Serca2 gene, aerobic capacity declines in parallel with the reduction of SERCA2 protein in the myocardium of sedentary and exercising mice. Response to exercise training is altered in SERCA2 KO animals compared to control mice. Thus, normal SERCA2 function in the heart seems essential to sustain cardiac function and aerobic capacity.

### **Moderate altitude conditions may cause hypoxia and abnormal pulmonary arterial pressure response at rest and during exercise in patients with atrial or ventricular septal defect.**

*T Moller, PM Fredriksen, H Holmstrøm, J Hallen, E Thaulow (Tønsberg, Oslo). Introduction: Hypoxia and abnormal pulmonary pressure response*

(AR) during exercise have been observed in healthy individuals. AR has been shown to corre-

late with susceptibility to high altitude pulmonary edema. It is not known whether moderate altitude can cause or augment these abnormal reactions in numerous patients with minor or surgically closed ventricular septal defect (VSD) or atrial septal defect (ASD) that might have caused increased pulmonary vascular reactivity early in life.

**Methods:** 11 patients with ASD or VSD (10/11 surgically closed, age 14 to 25 yrs) were examined by echocardiography at rest and during supine cycling at sea level. The patients then rested in a low-pressure chamber for 2 hours at 2500 meters/8200 feet altitude. Oxygen saturation (SpO<sub>2</sub>), right ventricular performance and pulmonary arterial peak systolic pressure (PAP) were monitored. Exercise echocardiography was repeated before descent.

**Results:** During exercise at sea level 3 patients showed abnormal PAP response > 40mmHg (44 to 56), none had hypoxia (mean 98.6%). After 120 minutes resting at moderate altitude mean PAP increased from 24mmHg at sea level to 32 mmHg, 3 patients showed PAP increase above 40mmHg (43 to 45), mean SpO<sub>2</sub> had fallen to 94% (88 to 98). During altitude exercise mean PAP raised to 49 mmHg, 9 patients showed PAP > 40mmHg (41 to 63), mean oxygen saturation dropped to 81%, in 3 patients SpO<sub>2</sub> decreased below 80% (68 to 79). 2 of these patients had simultaneously hypoxia and pressure increase above 50 mmHg. No patient had symptoms beyond dizziness at rest or fatigue during altitude exercise.

**Discussion:** Moderate altitude simulates the atmospheric condition in mountainous areas or in pressurised commercial airplanes. Like many other people patients with closed VSD or ASD may be exposed to these conditions for hours (airplane), days or months or even permanently (mountains) with or without physical strain. It is commonly assumed that patients without shunts between pulmonary and systemic circulation would not show major hypoxia or changes in pulmonary vascular resistance.

**Conclusion:** There might be a significant risk of hypoxia and pulmonary hypertensive reaction in patients with minor or surgically closed ASD or VSD when exposed to moderate altitude. Exercise in altitude seems regularly to provoke or augment abnormal pulmonary vascular resistance despite surgical repair early in life.

## Accelerated decline in maximal oxygen uptake with ageing in long term endurance cross-country skiers. A 28 to 30 year follow-up study.

**J Grimsmo, H Arnesen, S Mæhlum (Feiring, Oslo)**

**Objectives:** Age-related decline in maximal oxygen uptake (VO<sub>2</sub>max) is well documented. Most of the studies are cross-sectional. Longitudinal data are rare, but some studies have described the decline in VO<sub>2</sub>max with increasing age in different age groups of endurance-trained men. However, the results differ substantially. The aim of this study was to assess longitudinal changes in maximal oxygen uptake during almost three decades of ageing in two different age groups of long-time highly active cross-country skiers.

**Methods:** The population was previously studied in 1976 and consisted of 122 long-time active, highly trained cross-country skiers belonging to three preselected age groups. Out of the initial 122 men 37 (30.3%) had died at follow-up. Of the 86 still living 78 responded (90.7%). Thirtytwo (91%) from the youngest (age group I: 53--62 years; mean 58.7±2.3) and 36 (75%) from the middle age group (age group II: 71--79 years; mean 74.5±2.5) participated in a maximal exercise retest 28--30 years after.

**Results:** Only 6 subjects, (2 in group I and 6 in group II), were not training any more. Among all subjects the annual decline in VO<sub>2</sub>peak was 0.81 ml/kg/min in group I and 0.82 in group II in absolute values. Thirty subjects in age group I and 25 in age group II achieved the criteria for VO<sub>2</sub>max. The results are shown in table 1. **Conclusion:** Age group II had a significant accelerated decline in VO<sub>2</sub>max with ageing in relative values, but not in absolute values, compared two the younger age group I, because of the lower values in VO<sub>2</sub>max at baseline in the older group. The decline in maximal oxygen uptake was greater than reported in most other longitudinal studies. This study shows that the annual decline in VO<sub>2</sub>max is greater in these endurance trained men than reported in the literature for sedentary men, but that they still have a VO<sub>2</sub>max far above normal values for men at the same age.

## Increase in exercise training one year after the participation in a 4-week comprehensive cardiac rehabilitation programme: a case-control study

**OE Borstad, G Skoglund, CM Stenbakken, J Grimsmo (Fering).**

**Objectives:** One of the goals of cardiac rehabilitation is to get the participants to exercise lifelong. The aim of this study was to assess to what extent exercise training is maintained after a follow-up of 1 year in patients participating in a cardiac rehabilitation program (CRP) versus patients not participating.

**Methods:** Ninety-eight participants under the age of 62 were included into the intervention group (IG). During the 4-week-rehabilitation-stay they participated in 35 different exercise lessons and were maximal exercise tested before and after CRP. They were given advise how to continue to train at home. Seventy-nine participated in the follow-up study. The control group (CG) was draught out from patients from treated at the same time as IG. They were matched by gender, age, social status and procedure ('PCI' or 'CABG'). Both IG and CG underwent a maximal exercise test after one year and answered questionnaires about training. Group characteristics are shown in table 1.

**Results:** At follow up IG had unchanged body mass index (BMI) from baseline and there was no difference between IG and CG groups (mean 29,0 kg/cm<sup>2</sup> vs. 28,4; NS). Only 2 subjects in IG reported that they did not exercise at follow-up versus 10 before CRP. In CG 8 subjects did not exercise one year after treatment. IG significantly increased self-reported training time in hours from baseline to follow-up (2.9±2.3 vs. 4.4±2.2; p=0.0001) but they did not exercise harder than before (p=0.3). They reported both significantly more training hours per week (4.4±2.2 vs. 3.4±2.2; p=0.0001) and harder training (p=0.0001) than CG. No significant difference was found between the groups in VO<sub>2</sub>max in ml/kg/min after one year (29.0±7.7 vs. 27.3±6.3; p=0.1). However, IG significantly increased VO<sub>2</sub> max from start of CRP (27.0±6.5) to one year after (p=0.0001), but they had a decline from the end of CRP (30.3±7.6; p=0.001).

**Conclusion:** One year after CRP the participating subjects exercised harder and more hours per week than the control group, but we did not find any

difference between the groups in maximal oxygen uptake.

Table 1

	IG after 1 year	CG after 1 year	p
Female/ male	10/69	13/80	NS
Age in years	53,1±6,1	55,3±5,3	0,01
CABG/ PCI	32/47	36/57	NS

Group characteristics.

## Aerobic interval versus standard group exercise training after myocardial infarction.

**T Moholdt, IL Aamot, A Støylen, T Stølen, I Granoien, T Hole, L Brattbakk, T Graven, U Wisløff, S Slørdahl (Trondheim, Ålesund, Levanger)**

**Purpose:** To determine the effect of group exercise training versus high intensity interval treadmill training upon peak oxygen uptake (VO<sub>2</sub>- peak) in myocardial infarction (MI) patients. Based on data from three hospitals in Norway, we wanted to compare usual care with an alternative exercise training model.

**Methods:** 107 MI patients referred to hospital based rehabilitation were randomised to standard group exercise training (n=71) or an interval treadmill protocol (n=36) in a 2:1 manner. Patients were recruited 2--12 weeks post MI. All patients were asked to meet for organized exercise training two times per week for 12 weeks and to exercise once weekly on their own. VO<sub>2</sub>peak was measured at baseline and again after 12 weeks. Patients randomised to group exercise participated in the usual exercise training program at the hospitals. The intensity of their exercise was supervised using heart rate monitors. The group exercise differed somewhat between the three hospitals. For the treadmill exercise patients each training sessions consisted of four times four minutes intervals at 85--95% of HRpeak with lower intensity periods in between.

**Results:** Eleven of the group training patients and five of the treadmill patients dropped out, so 91 patients were included in the analysis. VO<sub>2</sub>peak increased significantly in both groups, from 32.4 (SD 6.7) to 34.4 (SD 7.8) ml/min/kg (6.8%) in the group exercise training group and from 31.3 (SD 5.5) to 35.6 (SD 8.3) ml/min/kg (13,8%) in the treadmill group (both p<0.0001). The treadmill group had a statistical significantly larger increase (p=0.005). Also when analysed as intention to threat, the treadmill group had a larger increase (p=0.02).



Conclusion: High intensity interval treadmill training was more effective than the group exercise training after myocardial infarction. The results of this study may have implications on future organization of cardiac rehabilitation.

## Significant difference in maximal heart rate in fit and unfit boys.

**EA Skaug, AB Johnsen, U Wisløff, O Ellingsen (Trondheim ).**

Introduction: Previous studies indicate that fit persons have lower maximal heart rate compared to unfit individuals, but the literature is conflicting. The aim of the present study was to determine maximal heart rate in the 25% best fit (highest VO<sub>2</sub>max/peak) compared to the 25% most unfit (lowest VO<sub>2</sub>max/peak) from a population of 600 healthy Norwegian adolescents.

Methods: 600 healthy adolescents (278 boys and 322 girls) between 13 and 19 years old were included from a middle school and a neighbouring college in a small city in Norway. Systolic and diastolic blood pressure, weight and height were measured, and all went through a limited interview with a physician. All included performed a 10 minute warm-up before VO<sub>2</sub>m/p (VO<sub>2</sub>max/peak) and maximal heart rate was measured during an individualized treadmill protocol. 277 boys and 312 girls reached VO<sub>2</sub>m/p.

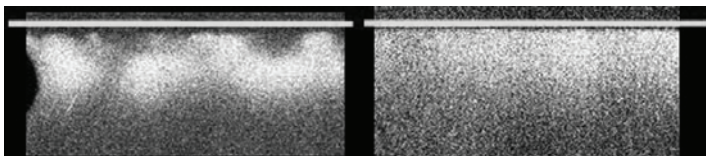
Results: Mean maximal heart rate was found to be 203±7 for unfit boys, 198±8 for fit boys, 199±8 for unfit girls, and 199±7 for fit girls. Mean VO<sub>2</sub>m/p for unfit boys were 50.0±4.4 ml/kg/min, for fit boys 72.5±4.3 ml/kg/min, for unfit girls 40.2±4.0 ml/kg/min, and for fit girls 58.0±4.3 ml/kg/min. Using the 1-way ANOVA we found the difference in maximal heart rate between unfit and fit boys to be significant (p<0.005) Conclusions: The fit boys had a significant lower maximal heart rate compared to the unfit boys. 61% of the fit boys had a VO<sub>2</sub>m/p higher than 70 ml/kg/min, and were considered to be athletes (6% had a VO<sub>2</sub>m/p higher than 80 ml/kg/min). Among the unfit boys we found 42% with VO<sub>2</sub>m/p lower than 50 ml/kg/min (which in Norway is considered to be the "mean" value for a 20 year old man). 28% of the fit girls had a VO<sub>2</sub>m/p higher than 60 ml/kg/min, and 36% had a lower than 40 ml/kg/min. So there were overall more homogeneity among the girls, and a greater difference between the two groups of boys compared. This

can explain why we did not find a correlation in the girls. Physical exercise or genetic basis may be the reason for the difference we found in the boys, but this is still unclear.

## Calcium handling in atrial myocytes: effects of exercise training and heart failure.

**T Skoglund, R Rosbjorgen, T Stolen, MA Høydal, U Wisløff (Trondheim)**

Background: The dependence of cardiac function on the contribution of atria becomes increasingly important with age and exercise. In place of the T-tubules, which is a central structure for normal excitation-contraction coupling in LV-myocytes, atrial cells have prominent SR elements, which have been described as 'Z-tubules'. The lack of T-tubules in atrial myocytes means that depolarization provokes calcium signals that largely originate around the periphery of the cells. To engage the contractile machinery, the calcium signal must propagate centripetally deeper into the cells. At present nothing is known about the effect of exercise training upon calcium handling in atrial cells. The aim of the present study was to study the calcium transients in single atrial myocytes from rats with post-infarction heart failure and study the effect of exercise training. Methods: Single atrial cells from rats with post-infarction heart failure (controls, interval-trained and moderately trained) loaded with the Ca<sup>2+</sup> indicator, fluo-3. The Ca<sup>2+</sup>-transients were studied using confocal line-scan. Results and Conclusion: The method for studying atrial calcium handling is now established, and in ventricular cells, we observed a near synchronous SR Ca<sup>2+</sup> release throughout the cell results in a horizontal band of fluorescence in a linescan image transverse to the longitudinal axis of the cell. In contrast, the rise in [Ca<sup>2+</sup>]<sub>i</sub> was asynchronous in atrial cells (figure, horizontal line indicate action potential). Quantitative data comparing the adaptation to aerobic interval training, moderate continuous exercise in rats with post-infarction heart failure will be available before May 2008. - Atrial (left) and LV Ca<sup>2+</sup> transient



**Exercise-induced abnormal pulmonary arterial pressure response in young athletes. Normal physiology or precursor of endothelial damage? T Moller, K Peersen, PM Fredriksen, H Holmstrøm, E Thaulow (Tønsberg, Oslo).**

Introduction: Pulmonary arterial pressure (PAP) is considered to remain nearly unchanged during exercise. Earlier studies have shown an abnormal rise in PAP during exercise in endurance-trained professional athletes.

Methods: A group of 68 healthy volunteers (age 14 to 25 yrs) were studied by cardiopulmonary exercise testing, echocardiography at rest and during supine cycling with target heart rate 160-min. Eight individuals with extremely high (>2 SD) maximal oxygen uptake were defined as highly endurance-trained athletes (ETA). Their data were compared to 16 age- and gender-matched normal trained individuals (NTI).

Results: At rest, right ventricular performance as measured by tricuspid annulus plane systolic excursion (TAPSE) was equal in both groups (mean 23/23). Exercise peak systolic PAP raised above 500mmHg in 6 of 8 ETA (mean 48, median 55, range 17 to 66) but only in 1 (511mmHg) of 16 matched NTI (mean 31, median 31). The difference is statistically significant (p=0.008 [-28.8,-4.8]).

Discussion: The mechanism of abnormal PAP elevation in high cardiac output situations may be due to pulmonary blood flow beyond dilative capacity in the pulmonary vascular system. Pressure levels above 355mmHg are commonly considered to damage pulmonary endothelium and to be a possible precursor of permanent pulmonary hypertension. Young athletes with abnormal PAP response may have high pressure load in their pulmonary vessels several hours a day for years while maintaining their endurance training program.

Conclusion: Non-professional highly endurance-trained individuals show abnormal pulmonary pressure response during exercise. The common definition of normal range in pulmonary arterial pressure may have to be reconsidered.

**Limited relationship between blood pressure and VO2max in a healthy, adolescent population.**

*S Aspenes, U Wisløff (Trondheim)*

Purpose: There exists an inverse relationship between adolescent fitness and CVD risk factors, and prospective studies have demonstrated how adolescent's fitness is inversely associated with adult CVD risk factors. Most studies use an estimate of maximal oxygen uptake (VO2max), and investigations of true VO2max and CVD risk factors is sparse. The purpose of the present study was to determine whether there is a close relationship between blood pressure and VO2max in a healthy adolescent population.

Methods: 612 healthy participants between 13 and 20 years were included from a middle school and a college in Nord-Trøndelag, Norway. Height, weight and blood pressure was measured using standard procedures and VO2max measured during an individualized treadmill protocol.

Results: 501 participants reached VO2max. Independent samples t-test revealed a significant difference (p<0.01) in diastolic blood pressure between the lowest and highest female quartile of VO2max. No other differences were found.

Conclusion: Regarding former studies the significant difference in diastolic blood pressure between first and fourth quartile of VO2max is not surprising. However, it is surprising that a similar difference is not evident for any other parameter. It should be noted that the first female quartile is closest to former investigations. There is no reason to believe any systematic bias occurred regarding these elevated VO2max-values. Thus, in a healthy, fit adolescent population there is only a limited relationship between VO2max and blood pressure.

*Characteristics and findings*

	Female	Male
N	251	250
Age	16.7±1.8	16.6±1.9
Height (cm)	166.0±6.1	176.2±9.1
Weight (kg)	57.9±9.0	67.9±14.6
BMI	21.0±2.8	21.7±3.4
Systolic BP	124±12	133±13
Diastolic BP	78±8	78±9
VO2max	49.6±7.3	61.5±8.9
1. quartile	41.1±3.4	50.2±4.3
4. quartile	59.4±4.3	72.8±4.3

*VO2max in mL • kg-1 • min-1.*

## Exercise induced vasodilatation in healthy males identifies individual at high risk.

**T Wethal, T Omland, R Røysland, J Kjekshus (Oslo)**

**Purpose:** Flow mediated vasodilatation involves a NO sensitive mechanism of endothelial cells. Reduced arterial vasodilatory capacity is a marker of coronary heart disease. Most methods to evaluate endothelial dysfunction are invasive. The aim was to investigate if exercise in combination with non-invasive methodology is related to endothelial and inflammatory markers, and thus able to identify individuals at a high risk.

**Methods:** Post ischemic hyperemia after 5 minutes of arterial occlusion was examined before and after a bicycle test (15 minutes at 150 watt) with the use of strain-gauge plethysmography (measuring peak reactive hyperemia in the forearm) and peripheral arterial tonometry (measuring pulse waves in the index finger relative to the contra-lateral index finger; PAT hyperemia ratio) in 30 healthy males. A low PAT hyperemia ratio or a low peak reactive hyperemia reflects endothelial dysfunction. Blood samples were analyzed for inflammatory and endothelial biomarkers (von Willebrand factor (vWF), high-sensitivity CRP (hs-CRP), tumor necrosis factor receptor inhibitor (TNFRI), osteoprotegrin (OPG), asymmetric dimethylarginine (ADMA), P-selectin, Interleukin 8 and 10 (IL-8 and 10)).

**Results:** Except from a correlation between peak reactive hyperemia before exercise and ADMA ( $r=-0.45$ ,  $p=0.015$ ) there were no correlations between PAT hyperemia ratio and peak reactive hyperemia with any of the endothelial and inflammatory markers. A low peak reactive hyperemia before the bicycle test resulted in a high percentage post exercise increase in the peak reactive hyperemia ( $r=-0.72$ ,  $p<0.001$ ). The percentage post exercise increase in peak reactive hyperemia correlated positively with ADMA ( $r=0.53$ ,  $p=0.003$ ), IL-10 ( $r=0.43$ ,  $p=0.019$ ), OPG ( $r=0.41$ ,  $p=0.026$ ) and sTNFRI ( $r=0.37$ ,  $p=0.046$ ) and showed inverse negative correlation with the PAT hyperemia ratio before activity ( $r=-0.35$ ,  $p=0.056$ ). Individuals with a large PAT hyperemia ratio before exercise did not obtain further maximal reactive hyperemic activation after physical exercise.

**Conclusions:** A high percentage increase in peak reactive hyperemia after a bicycle test seems to be an indicator of endothelial dysfunction and inflammation as this percentage was related to both

enhanced levels of ADMA, OPG, sTNFRI and partly to a low PAT hyperemia ratio before exercise. The associated increase in IL-10 may suggest a general activation of the immune system. A simple exercise performance in combination with non-invasive strain-gauge plethysmography may be effective to reveal endothelial dysfunction, and thus identify individuals at high risk.

## Determination of endothelial function and cardiovascular risk scores.

**T Wethal, T Omland, R Røysland, J Kjekshus (Oslo)**

**Purpose:** Reduced arterial vasodilatory capacity characterizes endothelial function in individuals prone to coronary heart disease. Detection by invasive methods is unpractical for routine clinical use. The aim was to study the relation between different non-invasive methods and their association with a) traditional risk factors by the use of Euro-score and Framingham risk score and b) newer biochemical biomarkers for cardiovascular disease in apparently healthy males. We hypothesize that the non-invasive methods will relate differently to the risk scores and the biomarkers because these non-invasive methods reflect different parts of the vasculature.

**Methods:** Strain-gauge plethysmography and peripheral arterial tonometry were compared in 30 healthy males. Forearm blood flow (peak reactive hyperemia) and registered pulse waves in the index finger corrected for the contra-lateral index finger (PAT hyperemia ratio) were determined after 5 minutes of arterial occlusion. A calibrated proprietary tonometer of radial artery waveforms in 24 healthy males at rest was used to calculate large (C1) and small artery elasticity (C2). Blood samples were analyzed for i) pro-inflammatory markers (high-sensitivity CRP (hs-CRP), serum tumor necrosis factor receptor inhibitor (sTNFRI), osteoprotegrin (OPG), P-selectin, Interleukin 8), ii) the anti-inflammatory marker Interleukin 10 and iii) markers of endothelial dysfunction (von Willebrand factor, asymmetric dimethylarginine (ADMA)). Framingham risk score and Euro-score were calculated for each male.

**Results:** C2 was negatively associated to Framingham score ( $r=-0.56$ ,  $p=0.005$ ) and Euro-score ( $r=-0.57$ ,  $p=0.005$ ) while C1 correlated negatively with Euro-score ( $r=-0.42$ ,  $p=0.047$ ). Peak reactive hyperemia correlated negatively with ADMA ( $r=-0.45$ ,  $p=0.015$ ). Euro-score correlated with OPG

( $r=0.47$ ,  $p=0.010$ ), sTNFRI ( $r=0.39$ ,  $p=0.035$ ) and vWF ( $r=0.37$ ,  $p=0.049$ ).

Conclusion: Pulse wave analysis is more closely related to traditional risk factors in healthy males as measured by Euro-score and Framingham risk score which reflects that atherosclerosis is a process developing in conducting arteries. Peak reactive hyperemia had no direct relation to these scores as strain-gauge plethysmography measures the function of the resistance vessels where no atherosclerosis takes place in the absence of diabetes mellitus, but where ADMA is an important regulator of NO-production. sTNFRI and OPG (associated with the development of heart failure) and vWF (marker of endothelial dysfunction) were associated with Euro-score in healthy males.

## Increasing the predictive and discriminative ability of a risk prediction model

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Purpose: The many known risk factors of Ischemic heart disease (IHD) increase the opportunity to predict the absolute risk of IHD. There is however lack of knowledge concerning which ones that are sufficient to predict a substantial amount of individuals who will develop IHD. The aim was to develop a stepwise risk prediction model and to determine the model's predictive and discriminative ability.

Methods: This study included 19,999 participants from The Tromsø Study III. Using a Cox-regression model with competing risk, models that were able to predict ten-year absolute risk of fatal and non-fatal IHD were developed. Explanatory variables were added in a stepwise approach starting with data assessed through questionnaires (Q), then data from simple examinations (E) and finally data from blood samples (B). Furthermore the ability of a model consisting only of sex, age and data from blood samples was determined. Using the area under the ROC-curve (AUROC), Brier Score and Integrated Discrimination Improvement (IDI) the ability of the model in each of the steps was determined.

Table 1 The predictive and discriminative ability of the models.

Men		Obs.	Exp.	Brier	P*	AUROC	IDI**	P***
IHD	Q	277	289.3	0.0283		0.8296		
	Q+E	277	296.3	0.0278	>0.1	0.8493	0.0138	<0.0001
	Q+E+B	277	299.1	0.0273	<0.02	0.8705	0.0230	<0.0001
	B	314	334.2	0.0286		0.8446		
	B+E	314	339.0	0.0284	>0.48	0.8562	0.0101	0.0006

\*Comparison of Brier Scores from previous and actual model. \*\*Mean difference in risk between cases and non-cases in the previous and actual model. \*\*\*Test whether IDI differs from 0.

Results: When assessing the predictive ability using Brier Score we found no significant improvement when adding more variables except when adding blood samples to the model for IHD in men (Table 1). The Discriminative ability was assessed using AUROC and IDI and showed a general improvement in discrimination with increasing number of explanatory variables.

Conclusion: The risk prediction models showed good predictive and discriminative ability in all of the three steps. Increasing the number of explanatory variables by adding a new group of variables increases the discriminative but not the predictive ability.

## Physical activity level and self rated mental health among employees of the western region of Sweden and social insurance offices

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Purpose: The relationship between a physical active lifestyle and health is in many aspects well-known. It has been suggested that the level of physical activity (PA) is associated with mental health but more evidence from larger studies is still needed. The primary aim was to explore in a cross-sectional setup the relationship between the level of PA and self rated mental health in a large population as a part of an ongoing longitudinal study.

Method: A postal questionnaire to a representative sample of employees (health care  $n=5300$ ) and Social Insurance offices (SIO) ( $n=700$ ) in western Sweden was used. This represents the baseline



measurements of an on-going longitudinal study on work-related factors, lifestyle and stress-related mental health problems. The response rate was 61% and 3692 individuals were included in this part of the study. The Hospital Anxiety Depression scale (HAD) and Shirom-Melamed-Burnout Questionnaire (SMBQ) was used for measuring prevalence of anxiety, depression and burnout. The physical activity level was evaluated, using a 4 graded scale (Grade 1: Sedentary; Grade 2: light physical activity; Grade 3: moderate physical activity and Grade 4: vigorous physical activity). Grade 3 and 4 were emerged, as few individuals (2.7%) scored grade 4. Non-parametric test (Kruskal Wallis) was used to discriminate differences between groups, and a p-value of <0.05 was considered significant.

**Results:** Fifteen percent of the participants reported their activity level as sedentary (grade 1), 53% as grade 2 and 32% as grade 3-4. Significantly higher percent of individuals in the sedentary group were classified with probable depression (10%) and 23% with probable anxiety according to HAD. This is to compare with the grade 2 group (3% depression and 12% for anxiety) and the grade 3-4 group (2% depression and 10% anxiety)  $p < 0,01$  Individuals who reported a sedentary activity level expressed the highest mean SMBQ score (3,75 (SD 1,3)), followed by the grade 2 group (3,09 (SD 1,2)), and the grade 3-4 group (2,76 (SD 1.26)  $p < 0,01$ .

**Conclusion:** The majority of individuals in this survey reported at least a couple of hour's activity per week, but still 15% may be classified as sedentary. The physical activity level is positively associated with better self rated mental health, however causality can not be evaluated using this cross sectional design. A longitudinal follow-up study is therefore currently undertaken, to specifically look at the predictive power of the PA-level for development of stress related mental ill-health.

## Higher aortic valve velocities in heterozygous familial hypercholesterolemia patients compared to controls

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**Purpose:** Epidemiological studies have established a relationship between LDL-cholesterol and aortic valve disease; however clinical studies regarding the prevalence of aortic valve disease in heterozygous familial hypercholesterolemia (FH) patients have been conflicting.

**Methods:** Aortic valve velocities were examined in patients with familial hypercholesterolemia heterozygous for known mutations in the LDL receptor gene and matched controls. Persons with known atherosclerotic disease were excluded. Aortic valve velocities were recorded with continuous Doppler and averaged over three cardiac cycles and measured blinded off-line. Inflammation was evaluated using standard blood sample tests including a wide range of cytokines and chemokines analysed using Multiplex technology (data not shown).

**Results:** 140 patients were examined including 72 cases and 68 controls. In the total group there were 67 women (48%), and the average age ( $\pm$ SD) was  $43 \pm 12$  years. The body mass index was  $26 \pm 5$  kg/m<sup>2</sup>, and the systolic blood pressure was  $117 \pm 16$  mmHg. The group contained 29 current smokers (21%). The most common mutations in the FH group was D200N (18%), C210G (17%), del exon 11--14 and Elverum (both 14%). Of the FH patients, 89% were on statin treatment. Differences between case and controls are shown in Table 1.

**Conclusion:** Aortic valve velocities were higher in FH patients compared with age matched controls and this could indicate a higher prevalence of degenerative aortic valve disease in this group even if the difference is small. The LDL-cholesterol level was not increased in the FH group using statins, but the HDL-cholesterol was significantly lower compared to the controls. However, the levels of sensitive CRP were not different in the two groups.

Table 1

	FH case	Control	P-value
Age (years)	42.7 (11.9)	44.0 (11.8)	0.559
Body mass index (kg/m <sup>2</sup> )	27.2 (5.2)	24.6 (3.5)	0.001
LDL-cholesterol (mmol/l)	3.8 (1.8)	3.3 (1.0)	0.056
HDL-cholesterol (mmol/l)	1.1 (0.2)	1.3 (0.2)	0.002
Sensitive CRP (mg/l)	2.4 (4.7)	1.9 (2.7)	0.501
Aortic valve velocity (m/s)	1.3 (0.2)	1.2 (0.2)	0.025

Comparison of FH case and controls given as means and (standard deviations) with level of significance.