ABSTRAKTER PRESENTERT PÅ *RESEARCH SYMPOSIUM* PÅ NCS' VINTERMØTE

C-type natriuretic peptide signalling through NPR-B enhances the β_1-AR signalling both in non-failing and failing rat hearts

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Atrial (ANP), B-type (BNP) and C-type (CNP) natriuretic peptide levels are increased in heart failure. Natriuretic peptides mediate their effects through natriuretic peptide receptors (NPRs), ANP and BNP preferentially through NPR-A and CNP through NPR-B. NPRs are membrane bound guanylyl cyclases that increase cyclic GMP (cGMP) production when activated. Increased cGMP levels may have beneficial cardiovascular effects through protein kinase G. In contrast, we have previously shown that NPR-B stimulation by CNP enhances β_1-adrenoceptor (β_1-AR) mediated signalling in failing hearts through inhibition of phosphodiesterase 3 (PDE3). This cardioexcitatory influence is longstanding and is thus probably detrimental in the failing heart. However, a comparison of the PDE3 inhibitory effect of NPR-B signalling in non-failing and failing hearts was not elucidated. We now demonstrate that CNP through NPR-B is able to potently inhibit PDE3 and thus increase cAMP signalling in non-failing as in failing hearts. This was evident from a marked ability of CNP to potentiate the inotropic and lusitropic responses to β_1-AR stimulation in left ventricular strips. This conserved mechanism may enhance detrimental β_1-AR effects during pathological remodelling, and may contribute to the development of the failing cardiac phenotype.

Osteoprotegerin and the Risk of Recurrent Events in Patients with Non-ST elevation Acute Coronary Syndromes (NSTE-ACS): Observations from MERLIN-TIMI 36

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Introduction: Osteoprotegerin (OPG) is a glycoprotein belonging to the tumor necrosis factor (TNF) receptor super family. OPG has been implicated as a mediator in bone turnover as well as in arterial calcification and atherogenesis. Recent studies suggest that OPG is also associated with long term adverse prognosis and mortality in patients with acute coronary disease.

Hypothesis: We hypothesized that OPG would be useful for risk assessment of recurrent coronary events and cardiovascular mortality in patients presenting with Non ST-elevation Acute Coronary Syndromes (NSTE-ACS).

Methods: Plasma levels of OPG were measured at baseline in 4,463 patients with NSTE-ACS randomized to ranolazine or placebo in the MERLIN-TIMI 36 trial. Patients were followed for an average of one year. We assessed the risk of CV death, myocardial infarction (MI) and development of new or worsening heart failure (HF) within 30 days and one year of follow up. Endpoints were adjudicated by a blinded clinical events committee.

Results: During a median follow-up time of 348 days, 206 patients died of CV-causes. The concentration of OPG at baseline was strongly associated with both 30 days and 1 year CV mortality. After adjustment for conventional risk markers, including TIMI risk score covariates, history of HF, creatinine clearance <60 ml/min, gender, body mass index, BNP and CRP. OPG

concentrations remained a significant predictor of CV mortality after 30 days (HR (95% CI): 2.32 (1.29-4.16); p=0.005) and 1 year (HR (95% CI): 1.85 (1.32-2.59); p<0.0001). Baseline levels of OPG were also an independent predictor of new or worsening HF at 30 days (2.25 (95% CI: 1.38-3.69; p=0.001)) and 1 year (HR of 1.81 (1.26-2.58) p=0.001). There was no significant association between OPG levels and MI in multivariable analysis.

Conclusions: OPG is strongly and independently associated with 30 days and 1 year risk of CV mortality and HF development after NSTE-ACS. As no independent relationship between OPG levels and MI was observed, myocardial dysfunction may be a more important stimulus for OPG production than ischemia in ACS.

Enhanced mitochondrial respiration in liver and kidney following cardiogenic shock – an experimental study in pigs.

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Objectives: Multiple organ dysfunction syndrome (MODS) following cardiogenic shock (CS) has poor prognosis. It is not known if mitochondrial function and viability are key players in the onset of MODS. We hypothesized that low cardiac output following myocardial ischemia would cause mitochondrial dysfunction in liver and kidney.

Methods: 13 closed-chest pigs were employed. The animals were anesthetized and mechanically ventilated. CS was induced by left coronary microembolization (n=7) and compared to sham operated animals (n=6). The animals were observed in CS for 14 ± 3 (mean ± SD) hours after coronary microembolization. At the end of the experiment tissue biopsies were harvested and mitochondria were isolated from liver, kidney and the left ventricle for assessment of respiratory function in an oxygraph.

Results: In liver and kidney mitochondria, using glutamate + malate as substrates, state 2, state 3 and state 4 respiration were significantly enhanced in the CS group. Mitochondrial viability and efficiency in the liver and kidney were maintained, evident by an unaltered respiratory control ratio (RCR) and ADP/O-ratio. In intermyofibrillar mitochondria (IFM) isolated from the ischemic left ventricle, both RCR and ADP/O-ratio were impaired.

Conclusion: Compensatorily enhanced respiration in both liver and kidney mitochondria were evident in our model of cardiogenic shock without inotropic and vasoactive drug support. These findings suggest that the intrinsic organ and cellular regulatory responses are compensatory and protective even after several hours of global hypoperfusion.

Mitochondrial DNA (mtDNA) damage during myocardial ischemia – marker or maker of injury?

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Background: Myocardial injury can lead to activation of the innate immune system through unknown mechanisms. Mitochondria are evolutionary endosymbiots and might contain bacterial molecular motifs, potentially leading to inflammatory response upon injury. We hypothesize that mtDNA is damaged and released during myocardial ischemia-reperfusion.

Materials, methods: Mouse hearts were isolated and perfused with induced global ischemia and reperfusion (n=10). Perfusates and hearts were collected for mtDNA extraction and the amount released and extent of mtDNA damage was assessed by quantitative (q)PCR.

Patients with acute STEMI (n=20) or stable angina (SAP, n=10) were treated successfully with PCI. Blood samples were collected immediately before PCI (only SAP group), and serially after revascularization. mtDNA was analyzed by qPCR.

Results: Ischemic-reperfused mouse hearts had an increase of mtDNA damage (p=0,01)

and mtDNA was released into the perfusate (p=0,0015).

Patients undergoing STEMI had increased mtDNA release 3 hours after PCI (p<0,01). There was a correlation between infarct size and mtDNA release (p=0,01).

Conclusion: Ischemia-reperfusion leads to mtDNA damage and leakage of mtDNA into the circulation.

Stress-induced arrhythmias caused by reduction of ankyrin B

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Background: Patients with mutations in the ankyrin B (ank B) encoding gene are at increased risk of experiencing various cardiac brady- and tachyarrhythmias, and sudden cardiac death. Ank B is an intracellular structural polypeptide anchoring a macromolecular complex in cardiac myocytes, consisting of the Na/K-ATPase (NKA), the Na/Ca-exchanger (NCX) and the IP_3-receptor. Heterozygous ank B knockout mice (ank B KO) exhibit long QT-syndrome 4 (ank B syndrome) and have an increased risk of stress-induced afterdepolarizations, extrasystoles and sudden cardiac death.

Objective: Investigate the mechanism leading to cardiac arrhythmias in ank B KO mice.

Results: The cardiac myocytes from ank B KO exhibited increased tendency to produce Ca waves (a type of cellular arrhythmia) during betaadrenergic stimulation. These Ca waves propagated at a higher velocity in ank B KO than wildtype. These findings can be explained by a higher sarcoplasmatic reticulum (SR) Ca content in ank B KO, especially during betaadrenergic stimulation. The increased SR Ca content in ank B KO could at least partly be explained by increased L-type Ca current. Furthermore, preliminary data indicate disrupted interaction between the NKA and the NCX in ank B KO. This could also contribute to increased SR Ca content since NCX might not remove cytosolic Ca efficiently. Combined with an increased L-type Ca current, this will promote SR Ca filling.

Conclusion: Reduced expression of ank B increases the propensity for arrhythmogenic Ca waves during betaadrenergic stress by limiting the Ca extrusion through NCX from the cardiac myocyte.

Compartmentation of the cGMP signal: CNP and BNP cause differential functional responses in failing myocardium

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Natriuretic peptides (NPs) are used as biomarkers in heart failure (HF) as they increase with severity of the disease. C-type natriuretic peptide (CNP) and brain natriuretic peptide (BNP) activate NPR-B and NPR-A receptors, respectively. Earlier studies have shown that CNP elicits a direct negative inotropic response (NIR) through the cGMP - protein kinase G pathway.

In this study we investigated cGMP increase and functional responses to CNP and BNP and the regulation by phosphodiesterases (PDEs) in isolated ventricular cardiomyocytes and muscle strips from Wistar rats with HF.

CNP and BNP both increased cGMP levels, but only CNP caused a NIR and a positive lusitropic response. Preincubation with BNP did not affect the CNP-induced NIR. cGMP measurements indicated that NPR-A and NPR-B stimulation involved different cGMP compartments. Both BNP- and CNP-induced cGMP increase is regulated by PDE2, 3 and 5 but a NIR to BNP was not revealed, even in an attempt to abolish compartmentation by the presence of combined PDE2, 3 and 5 inhibition. Inhibiton of PDE2 with EHNA or PDE5 with sildenafil did not affect functional effects of CNP, despite that EHNA caused a profound inhibitory effect on cGMP PDE activity in cardiomyocytes and thus significantly enhanced CNP-mediated cGMP levels. The presence of the PDE3 inhibitor cilostamide increased the NIR and the postive lusitropic response to CNP despite only a marginal cGMP increase.

In conclusion, there is a strong functional compartmentation of the cGMP signal indicating different roles of BNP and CNP in the pathophysiology of HF.

Pregnancy protects against antiangiogenic and fibrogenic effects of Angiotensin II in rat hearts

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Aim: To investigate the difference between physiological and pathological cardiac remodelling induced, respectively, by pregnancy and angiotensin (Ang) II, and to test the hypothesis that pregnancy protects against Ang II effects. Methods: Female Wistar rats, pregnant (n = 12) and non-pregnant (n = 12), were implanted with mini-pumps containing saline (sham) or 150 ng kg)1 min)1 Ang II. Ten days later echocardiography and blood pressure measurement were performed. Expression of 22 genes was assessed using RT-PCR. Microscopic sections of LV were prepared to determine collagen content (Sirius Red staining), vessel density (b-actin immunolabelling) and myocytes diameter (Toluidine Blue). Results: Heart weight (HW) was increased in Ang II treated groups compared with their controls. Furthermore, HW of Ang II treated pregnant rats (1.0 ± 0.03 g) was higher than that in non-pregnant sham (0.7 ± 0.02 g), pregnant (0.8 ± 0.01 g) and Ang II treated non-pregnant (0.8 ± 0.02 g) rats. Relative LV wall thickness showed similar pattern. Aortic pressure was significantly increased in Ang II groups. Collagen content was increased in Ang II (4.0 ± 0.5%) compared with sham (1.5 ± 0.1%) but reduced again when treated rats were pregnant (2.8 ± 0.4%). Vessel density was reduced by 47.8% after Ang II treatment in non-pregnant and by only 13.9% in pregnant rats. Gene expression analysis showed increased expression of atrial natriuretic factor (ANF), brain natriuretic peptide (BNP), anykrin repeat domain-containing protein 1 (Ankrd-1), protein kinase C-a and -d and tumour suppressor gene TP53 (p53) in Ang II treated groups and upregulation of ANF, BNP and Ankrd-1 remained when pregnancy was combined with Ang II. Pregnancy reduced expression of: a-myosin heavy chain, tumour necrosis factor-a, p53, endothelial nitric oxide synthase and inducible nitric oxide synthase. Conclusion: Pregnancy seems to counteract the detrimental effects of Ang II on fibrosis and angiogenesis in heart. In addition, pregnancy and Ang II lead to partly opposite changes in the expression of some genes important for heart function.

Abnormal glucose regulation and risk of fatal coronary artery disease by gender: long term follow-up in the HUNT 1 Study

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Aim To assess mortality from coronary artery disease (CAD) by gender in subjects with impaired glucose regulation (IGR), newly diagnosed diabetes (NDM) and known diabetes (KDM) compared to subjects with normal glucose regulation (NGR).

Methods From the HUNT1 cohort, originating in 1984-86, we included 47951 subjects ≥ 40 years, with a valid assessment of glucose regulation status defined according to WHO. All participants were linked to the Cause of Death Registry at Statistics Norway up to 2004. Deaths caused by CAD were defined by ICD-codes. Hazard ratios (HR) for CAD mortality were adjusted for age, BMI, hypertension, previous cardiovascular disease, exercise and smoking and compared by gender using Cox regression analysis.

Results HR for fatal CAD in subjects with IGR were 1.2 (0.8-1.9) in women and 1.2 (0.9-1.6) in men, in subjects with NDM 1.6 (1.2-2.2) in women and 1.4 (1.1.-1.9) in men and in subjects with KDM 2.5 (2.1-2.8) in women and 1.8 (1.6-2.1) in men. Using women as the reference, HRs in men were stepwise reduced from 2.1 (2.0-2.3) in the NGR group, 1.8 (1.0-3.3) in the IGR group, 1.6 (1.0-2.5) in the NDM group, to 1.2 (1.0-1.5) in the KDM group.

Conclusions NDM and KDM were stronger predictors of fatal CAD in women than in men. IGR was not a significant predictor of fatal CAD in either sex. However, when comparing HRs in genders, the presence of IGR attenuated the traditional gender gap in CAD mortality, which was further weakened in subjects with diabetes mellitus.

Increased relative wall thickness – a marker of subclinical cardiac target organ damage in African diabetic patients

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Introduction: Diabetes and hypertension are associated with increased prevalence of abnormal left ventricular (LV) geometry in African-Americans. However, limited data is available on subclinical cardiac target organ damage in African diabetic patients living in Sub-Saharan Africa.

Aim: To assess prevalence and covariates of abnormal LV geometry in type1 and type 2 diabetic out-patients attending Muhimbili National Hospital in Dar Es Salaam, Tanzania.

Methods: Cardiovascular risk assessment and echocardiography was performed in 184 patients, 62 type 1 and 122 type 2 diabetics, mean age 44 years, 61% women. LV hypertrophy was taken as LV mass index >116 g/m^2 in men and >104 g/m^2 in women. Relative wall thickness (RWT) was calculated as LV posterior wall thickness/end diastolic radius ratio at end-diastole and considered increased if ≥0.43. LV geometry was defined from LV mass index and RWT in combination.

Results: Type 2 diabetics had higher prevalence of hypertension (83 vs 18%) and abnormal LV geometry (75% vs 39 %), both p<0.001. In both groups concentric remodelling was the most prevalent type of abnormal LV geometry (Table 1). In univariate analysis, RWT was associated with higher age, blood pressure, LV mass and higher BMI and with lower eGFR, transmitral early velocity, early diastolic mitral annular tissue velocity (E'), LV end diastolic volume and midwall fractional shortening (all p<0.05). In multivariate linear regression among Type 1 diabetics, higher RWT (multiple R^2= 0.743, p < 0.001) was independently associated with higher age (ß = 0.27, p = 0.007), lower stress corrected midwall shortening (scMWS) (ß = -0.47, p < 0.001) and lower LV end diastolic volume (ß = -0.64, p < 0.001). Using the same regression model among patients with Type 2 diabetes, higher RWT (R^2 = 0.667, p < 0.001) was independently associated with lower scMWS (ß = -0.51, p < 0.001), lower LV end diastolic volume (ß = -0.37, p < 0.001), higher diastolic blood pressure (ß = 0.13, p = 0.029) and higher E/E' ratio (ß = 0.14, p = 0.048). No independent association was found with renal function, diabetes control or obesity.

Conclusion: Abnormal LV geometry is common both in type 1 and type 2 diabetics. Increased RWT is primarily associated with both systolic and diastolic dysfunction among type 2 diabetics but only systolic dysfunction among type 1 diabetics.

Table 1. Prevalence of LV geometric patterns in type 1 and type 2 diabetic patients

	Normal**	Concentric remodelling (NS)	Eccentric LV hypertrophy (NS)	Concentric LV hypertrophy**
Type 1 diabetes n (%)	37 (60.1)	20 (32.8)	3 (4.9)	1 (1.6)
Type 2 diabetes n (%)	27 (25)	48 (44.4)	4 (3.7)	29 (26.9)

***p < 0.001, NS = not significant*

The Prognostic Impact of HDL-Cholesterol for Coronary Heart Disease Is Independent of Physical Fitness: A 28 year follow-up of apparently healthy men

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Objectives: To test the hypothesis that physical fitness (PF) does not influence the prognostic impact of high density lipoprotein cholesterol (HDL) for coronary heart disease (CHD) and also CHD-, cardiovascular disease- (CVD) and all-cause-death.

Background: High density lipoprotein cholesterol and PF have both been shown to predict CVD, particularly CHD. Improved PF is associated with increased

HDL and may possibly explain the benefit of HDL.

Methods: HDL was measured 1979-1982 in 1357 healthy men aged 44-69 years followed up to 28 years and, PF was measured using bicycle exercise test. Hazard ratios (HR) adjusted for age, smoking, systolic blood pressure, and total cholesterol and further for PF between quartiles of HDL were calculated using Cox proportional-hazard modelling. A possible interaction between HDL and PF was tested using separate analyses for our main endpoint, CHD, for men with *age adjusted PF* above and below median.

Results: The highest quartile of HDL was associated with lower risk of CHD (angina pectoris, non-fatal myocardial infarction and CHD-death), CHD-, CVD- and all-cause-death compared to the lowest quartile, HR=0.57 (95% CI 0.43-0.74), 0.54 (0.35-0.83), 0.63 (0.45-0.87) and 0.80 (0.65-0.99), respectively. Adjustments for PF did not change the results except for all-cause-death which was not significantly different between HDL quartiles. Beneficial effects of HDL were similar above and below median age adjusted PF.

Conclusions: HDL is a strong predictor of long-term risk of CHD, CHD-death and CVD-death in healthy middle aged men. Physical fitness has no impact on the ability of HDL to predict CVD.

Neutralization of circulating interleukin-18 reduces diastolic dysfunction

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Background: Both in patients with COPD and in experimental animal models, chronic hypoxia and pulmonary hypertension have been linked with left ventricular diastolic dysfunction. At the same time, there is evidence of increased circulating levels of interleukin-18.

Aim: To establish a method for neutralization of IL-18 *in vivo* by administration of IL-18 binding protein (IL18-BP), and to investigate whether inhibition of IL-18 during hypoxia exposure is beneficial for the heart.

Methods and Results: C57Bl/6 mice received intraperitoneal injections of IL-18BP every 48 hours. ELISA showed stable circulating levels of IL-18BP at various time points. We also showed that IL-18BP reduces LPS-induced production of IFN-*xx in vivo*. To investigate the effect of IL-18 neutralization during alveolar hypoxia, mice (n=20) were exposed to hypoxia (10 % oxygen). IL-18BP was administrated according to the established protocol (n=10), while the control group received PBS (n=10). After seven days, echocardiography revealed a decrease in mitral deceleration velocity (27.9 ± 1.1 vs 31.9 ± 0.6 m/s, p=0.01) in the animals receiving IL-18BP, indicating improved diastolic function. Both alterations in Ca^{2+}-handling proteins and extracellular matrix were investigated as possible mechanisms of improved diastolic function.

Conclusion: Our data indicate that IL-18 neutralization reduces left ventricular diastolic dysfunction after chronic hypoxia exposure, possibly through effects on Ca^{2+}-handling proteins.

Cardiac dysfunction in Juvenile Dermatomyositis – a case control study

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Objective: To compare cardiac function in patients with Juvenile Dermatomyositis (JDM) with matched controls, and examine associations between pathological ECG, echocardiographic abnormalities and disease variables in JDM patients.

Methods: Fifty-nine JDM patients aged median 21.5 years (6.7-55.4) examined 16.8 years (2-38) after disease onset, were compared with 59 age- and sex-matched controls. 12-channel ECG and echocardiography, including early diastolic transmitral flow/tissue velocity (E/E') as a marker for diastolic dysfunction, were performed with colour coded Tissue Doppler and analyzed blinded to patient information. Possible diastolic dysfunction was defined as E/E' >mean +2SD (E/E'>9.5) of the matched control values. Disease activity and damage were assessed by clinical examination at follow-up and chart review.

Results: Possible diastolic dysfunction was found in 13 (22%) patients vs. 0 controls (p<0.001). Ten patients presented with pathological ECG compared to 4 controls (p=0.054). Previous or

current hypertension was found in 12 patients vs. 0 controls (P<0.001). Among the patients, pathological ECG was found in 6/13 patients with vs. 4/44 without elevated E/E' (p=0.002); and systolic BP was correspondingly 132mmHg ±24 vs. 112mmHg ±18 in the groups (p=0.012). E/E' correlated with cumulative organ damage assessed at follow-up (r_{sp} 0.41, p=0.001) and disease activity at 1-year (r_{sp} 0.56, p<0.001), which also predicted elevated E/E' after controlling for age and gender. During disease course, 12% of JDM patients developed pericarditis.

Conclusion: Only JDM patients and no controls had subclinical left ventricular diastolic dysfunction; the patients with elevated E/E' also had high prevalence of pathological ECG and hypertension. High disease activity one year post diagnosis, predicted high E/E' at follow up. The findings suggest that subclinical heart disease is related to the systemic nature of JDM.

Exercise echocardiography and maximal oxygen uptake in HTx recipients

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Background: Patients with ortothopic heart transplantation (HTx) have limited exercise capacity despite normal systolic left ventricular (LV) function. Reduced exercise capacity is often associated with diastolic dysfunction and increased LV filling pressure (LVFP). Thus, we investigated LV diastolic and systolic reserve capacity, and whether diastolic function could explain the variation in exercise capacity in these patients.

Methods: 52 HTx recipients, 38 men, with age (mean ± SD) 51.7 ± 15.7 years with no signs of rejection or cardiac failure were investigated 4.1 ± 2.2 years after HTx by ergometric stress echocardiography (GE Vingmed, Vivid 7) and maximal exercise test. Colour-tissue Doppler images and transmitral flow were recorded at rest and during semi-supine bicycle exercise (n= 33) in increments of 25W every 2 minutes until muscular fatigue and/or dyspnea. Maximal exercise capacity test (n=51) was performed on a treadmill with a ramp protocol.

Results (Table): Mitral annular early diastolic (e') and systolic velocity (s') increased by 80 ± 45% and 47 ± 27%, respectively from semi-supine rest to the highest load (126± 22 W, Borg 16 ± 2). Both E and e' increased significantly during exercise, whereas E/e' (an indicator of LV filling pressure) was unchanged. Mean VO_{2peak} was 27.7 ± 6.3 ml/kg/min (84% of normal values). VO_{2peak} correlated with e' at rest (r = 0.422, p= 0.003), but not with e' during exercise.

Conclusion: Patients with HTx have a preserved diastolic and systolic reserve. Exercise capacity in HTx patients was related to diastolic function, but not to filling pressure.

	Supine	Semi-supine			
	Rest	Rest	50W	Highest load	p-ANOVA
HR (bpm)	82 ± 12	88 ± 13	109 ± 11*	133 ± 14*†	p<0.001
e' (cm/s)	8.0 ± 1.7	7.5± 1.5	10.5 ± 2.0*	13.1 ± 2.6*†	p<0.001
E/e'	8.9 ± 2.6	9.3 ± 2.2	9.8 ± 3.4	9.3 ± 2.4	p=0.49
s' (cm/s)	5.7± 1.2	6.4 ± 1.5	7.6 ± 1.6*	9.1 ± 1.8*†	p<0.001
Displacement (mm)	9.4 ± 1.9	9.0 ± 1.5	11.2 ± 1.7*	11.6 ± 1.5*	p<0.001

*Mean ± SD. *p<0.01 vs semi-supine rest. † p<0.01 vs 50W. All tests Bonferroni corrected. E- early diastolic transmitral flow velocity, e'- mitral annular early diastolic velocity, s'- mitral annular systolic velocty. Both e' and s' were averaged from lateral, septal, anterior and inferior mitral annular velocities.*

Increased mean pulmonary artery pressure (mPAP) during exercise in COPD patients with normal mPAP at rest is accompanied by reduction in pulmonary artery compliance and lack of reduction in pulmonary vascular resistance.

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Background: The majority of COPD patients have normal resting mean pulmonary artery pressure (mPAP). The aim of the present study was to investigate if these patients show abnormal pulmonary pressure rise during exercise.

Methods: 112 patients (47 % male), in age 63±7 (mean ± SD) years with smoke associated COPD, and normal LV function, were included. Right heart catheterization at rest and during supine bicycle exercise

was performed to exhaustion. End expiratory mPAP, mean pulmonary arterial wedge pressure (mPCWP) and cardiac output (CO) were measured. Pulmonary vascular resistance (PVR) was calculated as (mPAP-mPCWP) / CO. Pulmonary artery compliance (PAC) was calculated as stroke volume / pulse pressure.

Results: 74 patients had normal mPAP at rest (18 ± 3 mmHg), which increased to 37 ± 7 mmHg ($p < 0.01$) during max effort (Wattmax 35 ± 21). CO increased from 5.2 ± 1.0 to 10.8 ± 3.0 L/min ($p<0.01$) and stroke volume increased from 71.2 ± 16.7 to 98.7 ± 24.2 ml/beat ($p<0.01$) There was a significant decrease in PAC from rest 4.0 ± 1.5 to exercise 3.0 ± 1.2 ($p= <0.01$).There was no significant change in PVR (exercise 2.1±1.1 vs. 1.9±0.9 wu at rest). There was a significant correlation between PACmax and PVRmax ($r=0.7$, $p<0.01$) and between PACmax and mPAPmax ($r= 0.5$ ($p<0.01$).

Conclusion: We have demonstrated a significant mPAP elevation on exercise at low workload, which was accompanied by a reduction in PAC and a lack of reduction in PVR. These findings might support the existence of an early clinical phase of pulmonary hypertension in patients with COPD and normal mPAP at rest. ■