

Pulmonary Vascular Response to Exercise in Heart Failure with Reduced Ejection Fraction and Pulmonary Hypertension

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activation also depends on Iron availability reflecting the molecular links between oxygen homeostasis and iron metabolism. HIF1 causes overexpression of Interleukin 6 which has been linked to development of pulmonary hypertension in animal models. Elevated levels of Interleukin 6 increase hepcidin release from liver which is a master regulator of iron metabolism. Elevated levels of hepcidin decrease serum which in turn can further activate HIF1 α . **Materials and Methods:** Iron deficiency (ID), defined by raised levels of soluble transferrin receptor (sTfR) in conjunction with iron studies were investigated in 140 patients with PH. Iron studies were also correlated to Interleukin-6 levels. IL-6 levels were independently evaluated in 90 consecutive pts. Iron data and IL-6 levels were related to 6 minute walk distance (6MWD), hemodynamics from the right heart catheterization, oxygen requirements and NYHA functional class at the time of blood sampling. Pts were classified according to WHO classification for PH. Survival status was gathered for both iron deficiency and IL-6 levels on march 15, 2014 and survival time was calculated individually for each pt from blood sampling to censoring, death or lung transplantation. **Results:** ID is present in a majority of pts with PH (69%) and is associated with lower 6MWD (232 vs 312 meters, $p=0.03$), higher O₂ requirement (2.3 vs 1.1 liter, $p=0.02$) and worse NYHA class (2.9 vs 2.4, $p=0.0003$) compared to iron sufficient pts respectively. There was no significant difference in hemodynamics. The cumulative incidence of all cause death or need for lung transplantation was 36% in iron deficiency group compared to 16% in iron sufficient group respectively at a median follow up period of 23 months ($p=0.04$). Iron deficient pts had higher IL-6 levels compared to iron sufficient patients. (16 vs 8 ng/ml). Serum IL-6 levels were overall elevated in 76% of the pts with a mean level of 16 pg/ml compared to 1.9 pg/ml in group with normal IL-6 (normal range 0-3 pg/ml). There was no statistically significant difference in hemodynamics, 6 MWD, O₂ requirements and NYHA class. At a median follow up of 21 months, the incidence of death/lung transplantation was 32% compared to 14% in group with and elevated and normal IL-6 levels respectively ($p=0.03$). There was a linear correlation between IL-6 levels and mortality. **Conclusion:** Iron deficiency and inflammation is present in a majority of patients with pulmonary hypertension and correlates with worse survival at 2 years of follow up. There is a linear correlation between IL-6 levels and mortality. IL-6 is a better biomarker compared to traditional risk factors and should be used to risk stratify patients with PH.

009

Inorganic Nitrate Supplementation Improves Exercise Capacity in Subjects with HF with Preserved EF - A Pilot Study

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Introduction: Reduced exercise capacity is the hallmark of HF with preserved EF (HFpEF). Inorganic nitrate (NO₃⁻) supplementation is a novel method to enhance hypoxic nitric oxide (NO) release and has been shown to increase exercise efficiency in healthy subjects. **Methods:** This was a randomized, double blind crossover trial comparing a single dose of nitrate-rich concentrated beetroot juice (NO₃⁻ BR, containing 12 mmol NO₃⁻) to an otherwise identical nitrate-depleted juice (placebo, PB) among 20 subjects (17 men and 3 women) with HFpEF. Subjects underwent maximal cardiopulmonary exercise testing on a graded exercise protocol. The primary endpoint was exercise efficiency (ratio of work performed to O₂ consumed). Pre-specified secondary endpoints included: the change in peak O₂ consumption (VO₂), change in total work performed, and change in systemic vascular resistance (SVR) with exercise. Data were analyzed using paired t tests or a non-parametric equivalent (Wilcoxon signed rank test) as appropriate. All subjects provided written informed consent. **Results:** Seventeen subjects completed both study visits. Mean age was 66±9 years, with 16 (94%) of subjects having NYHA Class II/III symptoms. NO₃⁻ BR supplementation significantly increased serum nitrate (503 versus 49 pmole/mg, $P<0.001$) and nitrite (299 vs. 46 pmole/mg, $P<0.001$) 2 hours after ingestion. Efficiency did not change with NO₃⁻ BR supplementation ($P=0.67$) due to concurrent increases in peak VO₂ achieved (12.6 vs. 11.6 mL/min/m²; $P=0.003$) and total work performed (55 kJ vs. 49kJ, $P=0.04$). Anaerobic threshold increased with NO₃⁻ supplementation (7.59 vs. 7.05 mL/min/m²; $P=0.015$). SVR at peak exercise was lower (9.67 vs. 11.25 Wood Units; $P=0.005$), whereas cardiac output was greater (12.1 L/min vs. 10.8 L/min, $P=0.037$) with NO₃⁻ supplementation. There were no significant differences in the arterial-venous O₂ difference

between NO₃⁻ and placebo. **Conclusion:** NO₃⁻ supplementation results in parallel increases in peak VO₂ and total work, resulting in unchanged efficiency. The mechanism of increased VO₂ was an increase in cardiac output, presumably from hypoxic vasodilation resulting in lower SVR at peak exercise.

010

Pulmonary Vascular Response to Exercise in Heart Failure with Reduced Ejection Fraction and Pulmonary Hypertension

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Background: Pulmonary vascular response patterns to exercise have not been studied extensively in symptomatic heart failure with reduced ejection fraction (HFrEF) and pulmonary hypertension (PH). **Methods:** Consecutive, symptomatic HFrEF patients ($n=40$), with mean pulmonary arterial pressure >25 mmHg, pulmonary capillary wedge pressure >15 mmHg, and cardiac index <2.5 L/min/m², received protocol-driven titrated sodium nitroprusside (SNP) and diuretics to reach mean arterial blood pressure 65-75 mmHg and pulmonary capillary wedge pressure <15 mmHg, after which they performed a supine bicycle test. Afterwards, SNP was gradually withdrawn, renin-angiotensin system blockers uptitrated, and hydralazine added to maintain hemodynamic targets. Subsequently, bicycle testing was repeated. **Results:** Prior to therapy, thirteen (33%) versus twenty-seven patients (67%) presented with pulmonary vascular resistance (PVR) lower versus higher than 3.5 Wood Units, respectively (post-capillary versus mixed PH). After decongestion, mean pulmonary arterial pressure normalized (<25 mmHg) in 44% post-capillary versus 20% mixed PH patients, and PVR decreased to 2.6±1.2 versus 3.1±0.8 Wood Units in both groups, respectively. Under SNP administration versus oral therapy, an exercise-induced PVR increase above 3.5 Wood Units was noticed in five (13%) versus nineteen patients (48%), respectively (Figure 1). Such exercise-induced PVR increase was associated with a 39% (32-57%) decrease in right ventricular stroke work index, which was also significantly attenuated by SNP (P -value=0.028; Figure 2). **Conclusions:** Even after thorough decongestion and under afterload reduction, PH secondary to HFrEF is only completely reversible in a minority of patients. Moreover, almost half of them demonstrate an exercise-induced PVR increase, associated with impaired right ventricular stroke work index, which might be ameliorated by nitric oxide donor support.

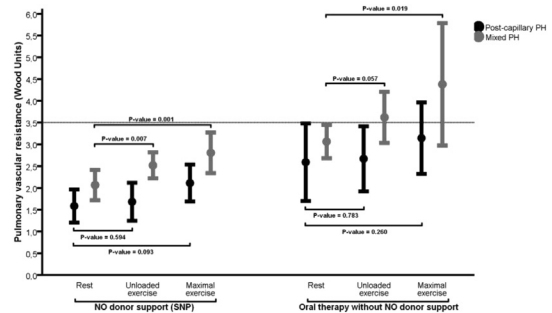


Figure 1.

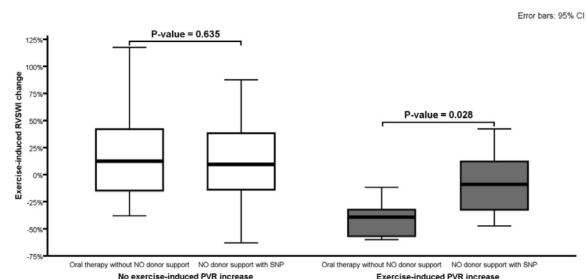


Figure 2.