Tenax Investor R&D Webinar

NOVEMBER 18, 2020

4:30 – 5:30 PM EST

Safe Harbor Statement

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Tenax Investor Webinar Agenda

- **Objective:**
  - **Scientific experts will share their perspectives regarding the unmet needs of PH-HFpEF patients and the relevance of the HELP Study results.**

- **Topics:**
  - **Why PH-HFpEF Represents an Important Unmet Medical Need? (Stuart Rich)**
    - What is PH-HFpEF?
    - What is the unmet need and current treatment?
  - **What is the Mechanism of Action for Levosimendan in PH-HFpEF? (Dan Burkhoff)**
    - What does the 24-Hr open-label HELP Study data tell us about how levosimendan is working?
  - **What Clinical Data Exists for Levosimendan in PH-HFpEF? (Barry Borlaug)**
    - What does the randomized placebo-controlled phase of the Help Study tell us ?
      - What is the hemodynamic evidence?
      - What is the clinical evidence?

- **Format**
  - **Presentations (10 min each)**
  - **Q&A ALL (20 mins)**
  - **Closing Comments**

PH-HFpEF Experts

Stuart Rich, MD

- Professor of Medicine, Northwestern University Feinberg School of Medicine
- Director, Pulmonary Vascular Disease Program, Bluhm Cardiovascular Institute
- Previous FDA Cardio-Renal Advisory Committee Member
- Recognized Global Pulmonary Hypertension Expert

Northwestern Medicine
Feinberg School of Medicine

Daniel Burkhoff, MD, PhD

- Director Heart Failure, Hemodynamics and MCS Research at the Cardiovascular Research Foundation
- Adjunct Associate Professor of Medicine, Columbia University

Columbia University
Cardiovascular Research Foundation

Barry Borlaug, MD

- Professor of Medicine, Mayo Clinic
- Chair for Research, Division of Circulatory Failure,
- Department of Cardiovascular Medicine, Mayo Clinic

MAYO CLINIC

TENAX THERAPEUTICS

Northwestern Medicine®

The Unmet Need in PH-HFpEF

Stuart Rich, MD
Professor of Medicine,
Northwestern University Feinberg School of Medicine
Bluhm Cardiovascular Institute

Common Questions Regarding PH-HFpEF

Most common questions asked from potential investors:

QUESTION: How do you pronounce PH-HFpEF?

ANSWER: Pulmonary hypertension from heart failure with preserved ejection fraction

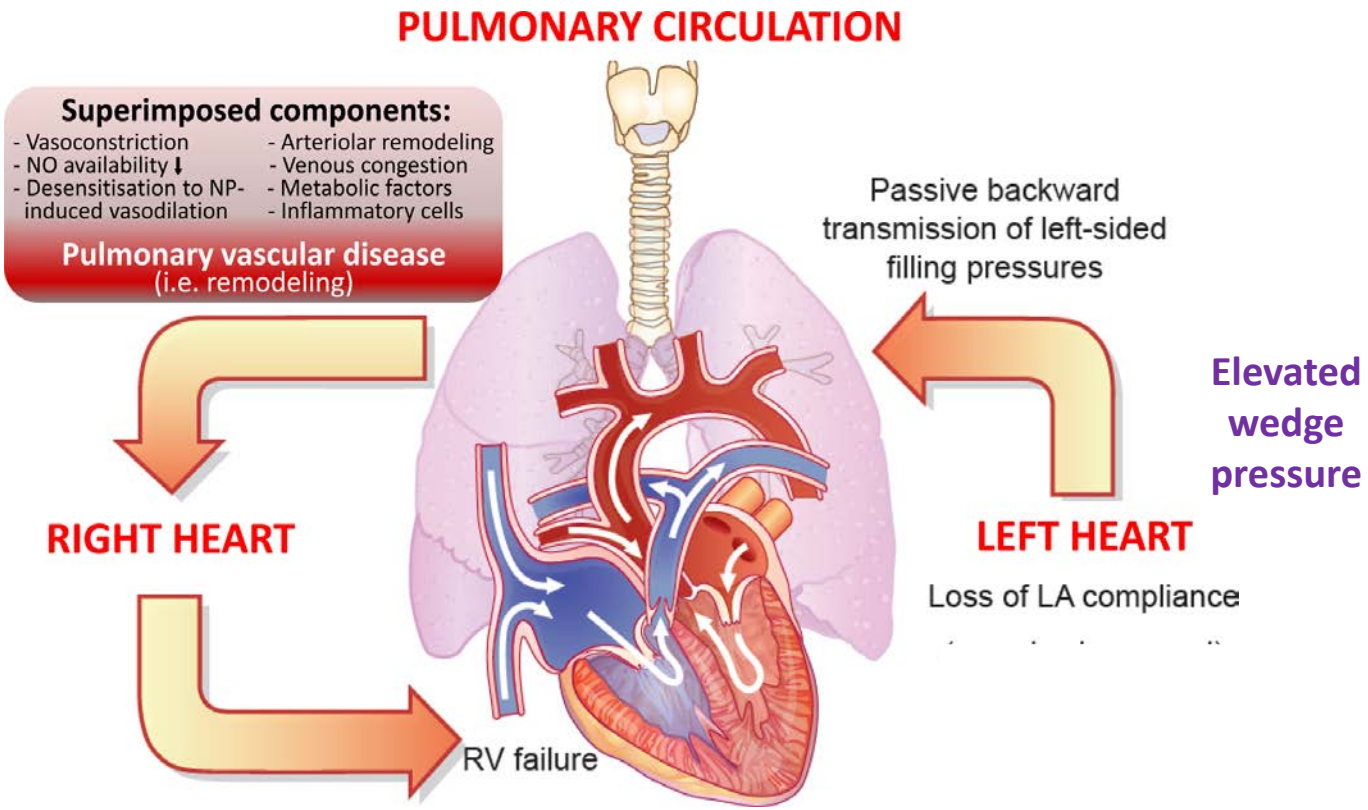
QUESTION: What is PH-HFpEF?

ANSWER: See the next slide

Heart Failure Concepts

- Heart failure is a condition where the heart fails to adequately provide blood to the body.
- Different ways the heart can fail:
  - Forward (systolic) heart failure
    - The heart isn't contracting well during heartbeats (a squeezing problem)
    - Generally from an injury to the heart muscle such as heart attack, or intrinsic muscle damage (cardiomyopathy).
  - Backward (diastolic) failure
    - The heart isn't able to relax normally between beats (a filling problem)
    - Generally from loss of compliance (e.g. stiffness) causing the blood to engorge the pulmonary veins.
    - Commonly referred to as HFpEF

Cardiopulmonary Interaction and Pathobiology of Pulmonary Hypertension in Left Ventricular Heart Failure

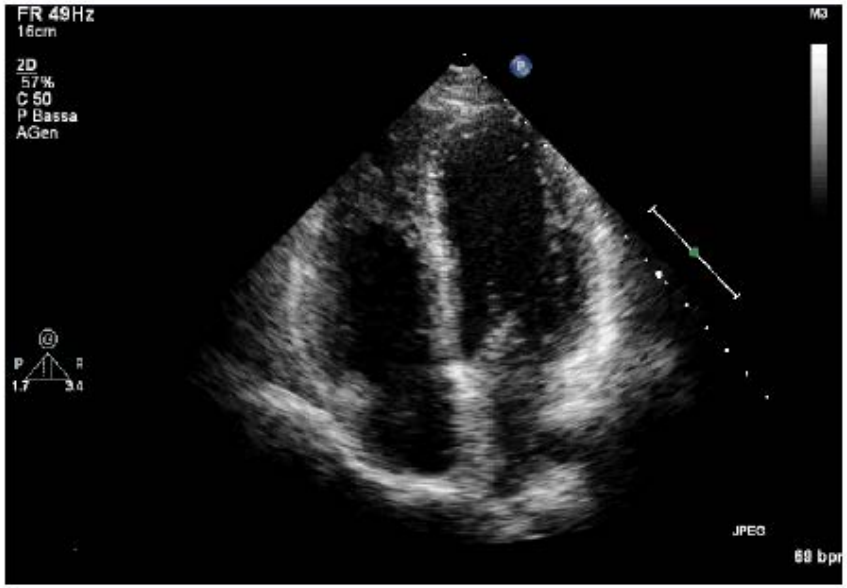


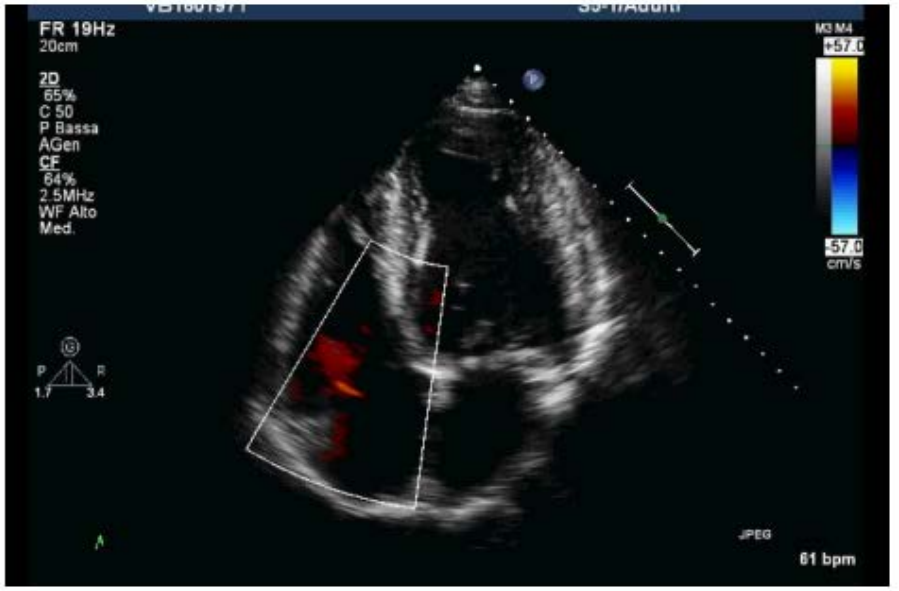
Eur Heart J, Volume 37, Issue 12, 21 March 2016, Pages 942–954,

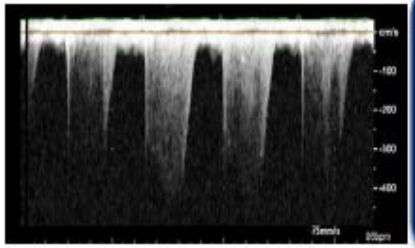
Pulmonary Hypertension from Heart Failure with Preserved Ejection Fraction

- A condition where HFpEF triggers a reaction in the lung resulting in pulmonary hypertension
- How does it present?
  - Shortness of breath and swelling of the ankles
  - The pulmonary hypertension causes right heart failure
- How is it diagnosed?
  - An echocardiogram will confirm the pulmonary hypertension
  - A cardiac catheterization will confirm the HFpEF
    - An elevated pulmonary capillary wedge pressure is the **critical** abnormality

PAH vs. PH-HFpEF

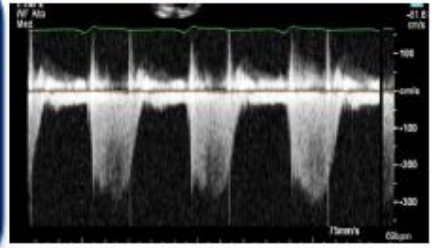






PASP=58 mmHg
Mean PAP=40 mmHg
PCWP=11 mmHg
TPG=34 mmHg

PASP=60 mmHg
Mean PAP=42 mmHg
PCWP=21 mmHg
TPG=25 mmHg

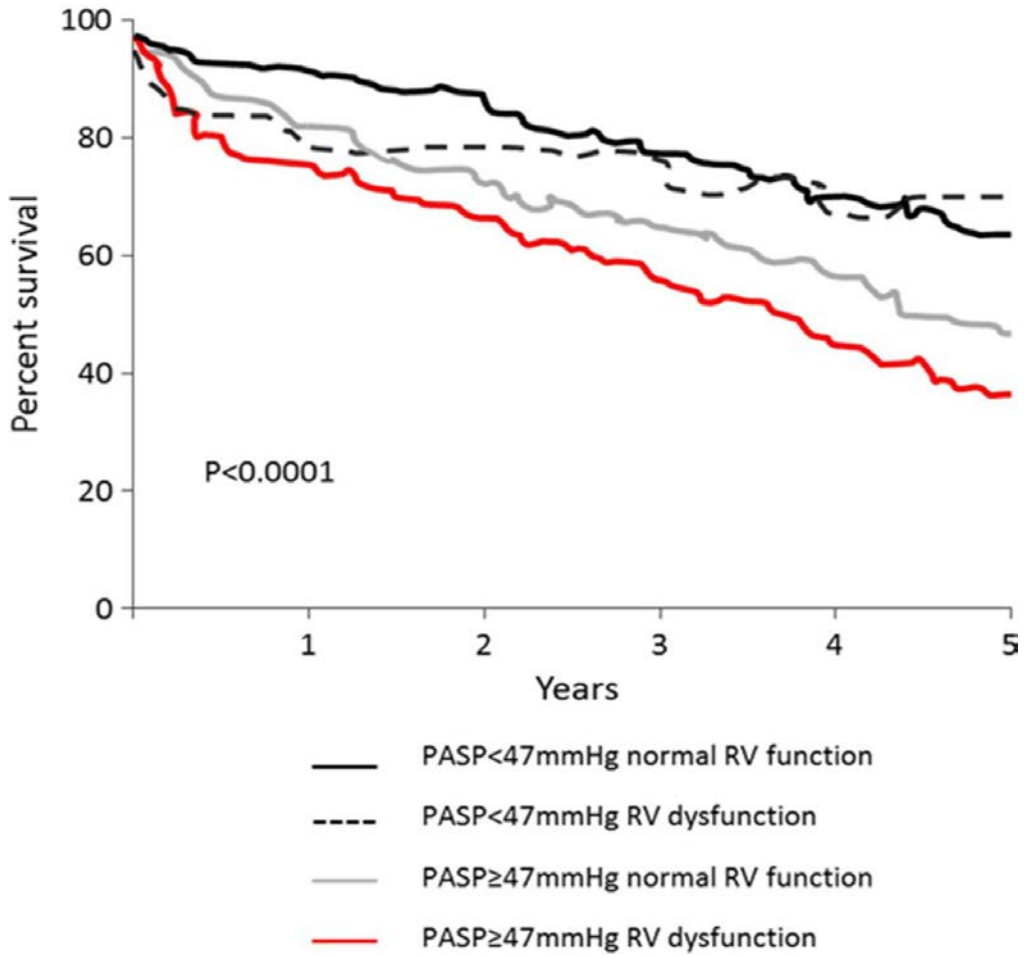


Pulmonary Hypertension from Heart Failure with Preserved Ejection Fraction

- WHO Group 2 Pulmonary Hypertension
  - Accounts for almost 50% of PH patients seen in PH specialty clinics
  - Estimated prevalence > 1,500,000 US patients
- Patients similar to PAH in:
  - Symptoms
    - Severe limits on exercise tolerance
  - Survival
    - 56% at 5 years

PH-HFpEF Patients have Poor Outcomes

PH-HFpEF + RV Dysfunction is Associated with Highest Mortality



PH-HFpEF Patients Normal RV

PH-HFpEF Patients w/ RV Dysfunction

Right ventricular systolic function in subjects with HFpEF: a community based study. (2011): A17407.

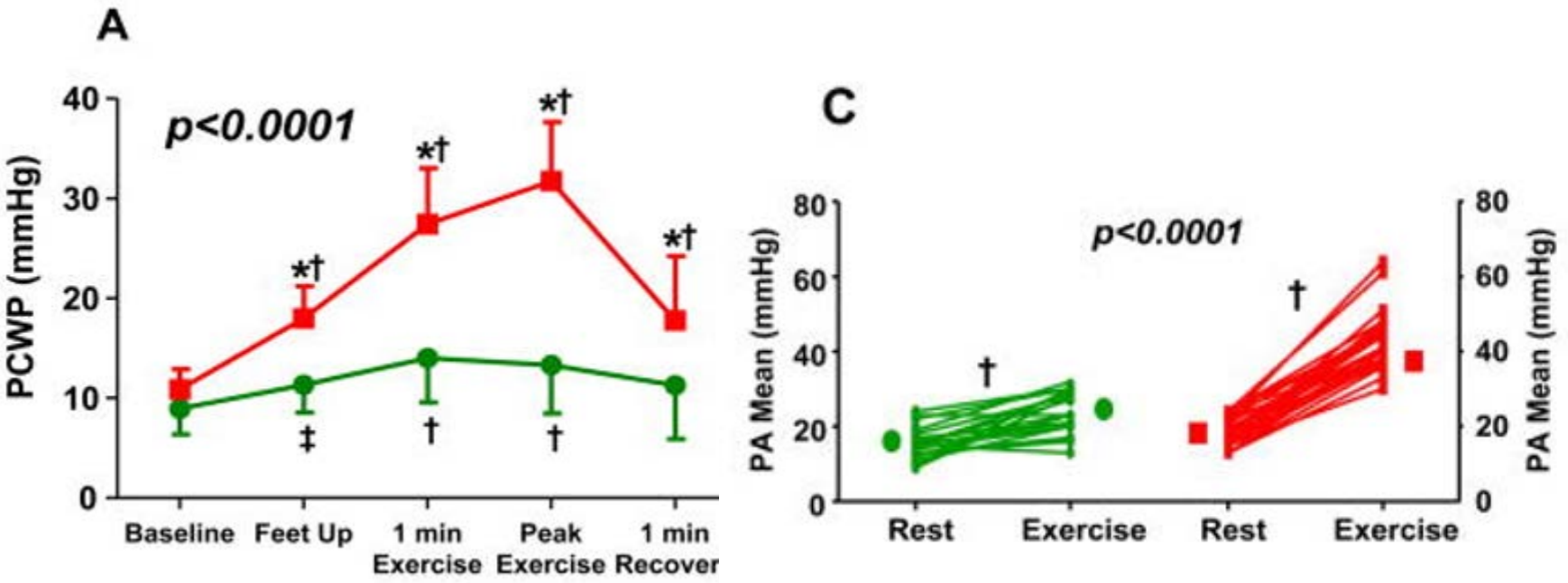
The Current Effective Treatments for PH-HFpEF

- None
  - Every clinical trial using pulmonary vasodilators and heart failure treatments in PH-HFpEF has failed!
  - ***The current unmet medical need is extraordinary.***

Features the Ideal Treatment for PH-HFpEF is a Drug that:

- Lowers PCWP at rest **and** during exercise
- Maintains or lowers pulmonary artery pressure (PAP) at rest **and** exercise
- Improves patient functional/exercise capacity

Exercise Hemodynamics in the Diagnosis of PH-HFpEF



Normal

PH-HFpEF

Circ Heart Fail. 2010 3:588-95.

Conclusions

- PH-HFpEF is a debilitating and fatal disease which is becoming increasingly common
- There is no therapy currently available that is effective
- For a treatment to be effective it must lower the pulmonary wedge pressure at rest and with exercise.
- PH-HFpEF is a disease with a serious unmet medical need.

Potential Mechanism of Action for Levosimendan in PH-HFpEF

An analysis Based on the HELP Study 24 Hour Data

Daniel Burkhoff
Director
Heart Failure, Hemodynamics and MCS Research
Cardiovascular Research Foundation

TEACH

Cardiovascular Research Foundation

HELP Study

Prospective, multicenter study of Levosimendan in patients with PH-HFpEF

Study conducted in 2 phases:

Phase 1: Open label 24-hour Levosimendan infusion testing effects of Levosimendan on resting and exercise hemodynamics

Phase 2: Double-blind, placebo controlled, once-weekly LEVO infusion for 6 weeks with primary endpoint of PCWP at 25 Watts supine cycle exercise

(Hemodynamics from both phases read in a blinded core lab)

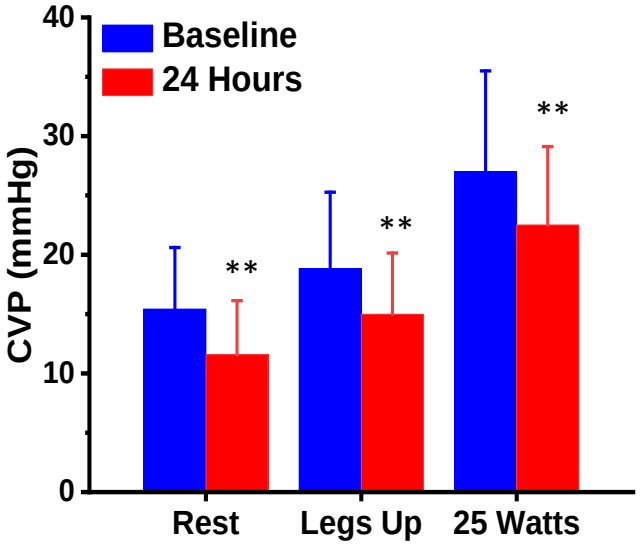
Phase 1 of HELP Study: 24-hour Open Label Levosimendan

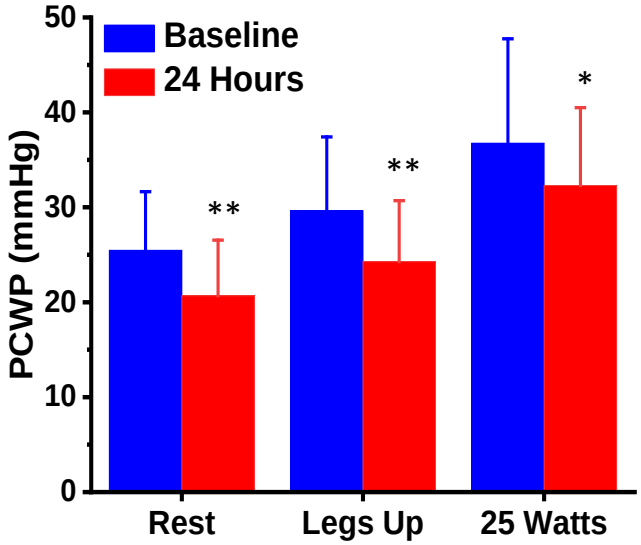
Hypothesis: LEVO administration can improve hemodynamics at rest and during exercise in PH-HFpEF, with effects mediated by its vasodilatory and inotropic effects

Objective: Determine the effects of LEVO at rest and during supine cycle exercise in patients with PH-HFpEF on:

- Cardiac filling pressures (CVP, PCWP)
- Vascular resistance (SVR, PVR)
- Cardiac output
- LV and RV contractility

Baseline vs 24 hour Levosimendan Infusion Changes in CVP and PCWP





All values highly significant between baseline and 24 hours Levosimendan Infusion

**** P≤ 0.001**

*** P ≤ 0.01**

Acute (24 hours) effects of Open-Label levosimendan (n=44)

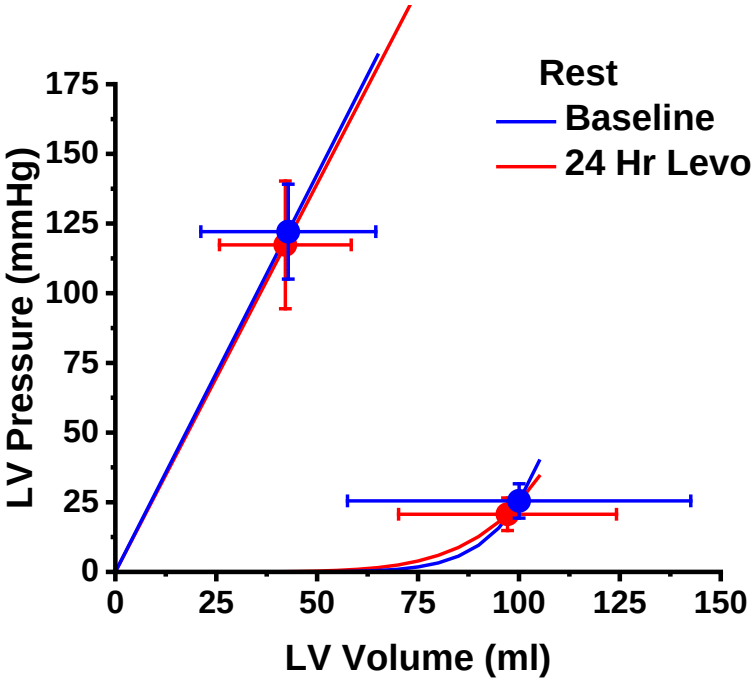
	Baseline, mean (SD)			Δ24Hr, mean (95% CI)		
Parameter	**Legs Down**	**Legs Up**	**25 Watts**	**Legs Down**	**Legs Up**	**25 Watts**
HR (bpm)	69.6 (16.4)	71.0 (15.9)	86.3 (18.0)	+5.7 (2.9,8.4)*	+6.7 (3.6,9.7)*	+4.8 (0.2,9.3)*
CVP (mmHg)	15.5 (5.2)	18.9 (6.5)	27.1 (8.6)	-3.9 (-5.3,-2.6)*	-3.3 (-4.8,-1.7)*	-4.7 (-6.8,-2.6)*
PAS (mmHg)	64.9 (18.4)	73.5 (18.2)	89.5 (22.1)	-6.4 (-9.7,-3.1)*	-6.2 (-9.6,-2.8)*	-2.4 (-7.2,2.4)
PAD (mmHg)	29.0 (6.3)	32.8 (7.4)	41.2 (9.9)	-3.0 (-5.0,-1.1)*	-3.4 (-5.6,-1.3)*	-3.1 (-5.7,-0.4)*
PA Mean (mmHg)	41.0 (9.3)	46.4 (9.6)	57.3 (13.3)	-4.2 (-6.4,-1.9)*	-4.3 (-6.6,-2.1)*	-2.7 (-5.9,0.4)
PCWP (mmHg)	25.7 (6.3)	29.7 (7.8)	36.8 (11.3)	-4.9 (-7.0,-2.9)*	-5.3 (-7.3,-3.3)*	-3.9 (-6.8,-0.9)*
AoS (mmHg)	135.0 (18.8)	138.4 (18.7)	155.7 (34.7)	-4.7 (-12.2,2.8)	-1.4 (-8.5,5.7)	-7.2 (-17.5,3.1)
CI (L/min/M2)	2.5 (0.8)	2.6 (0.9)	3.2 (1.1)	0.1 (-0.0,0.3)	0.1 (-0.0,0.3)	0.2 (-0.0,0.4)
SVR (Wood Units)	15.5 (4.2)	15.3 (5.2)	12.5 (5.6)	-1.1 (-2.2,0.0)	-0.4 (-1.8,1.0)	-1.0 (-2.7,0.8)
PVR (Wood Units)	3.3 (2.6)	2.7 (1.6)	3.6 (2.9)	-0.1 (-0.6,0.3)	0.2 (-0.3,0.7)	0.0 (-0.4,0.5)

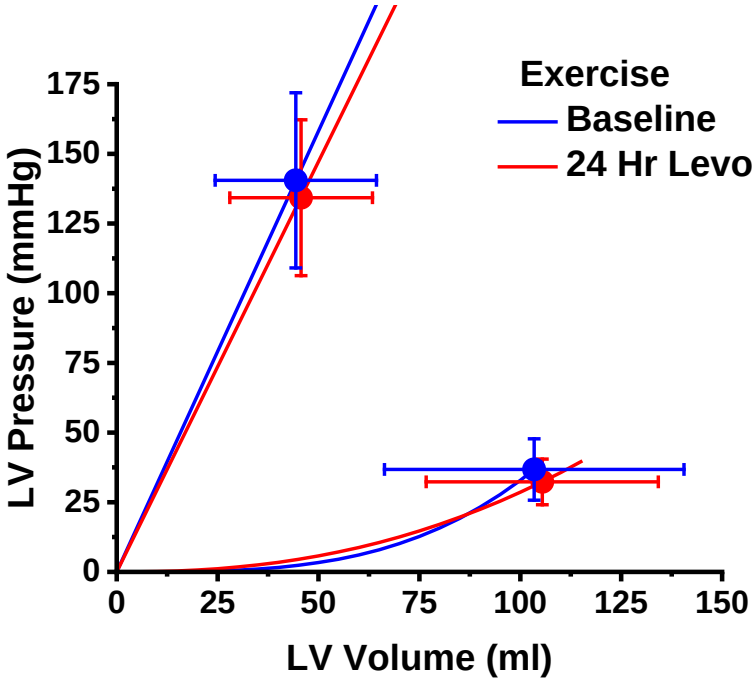
***85% of patients exhibited a ≥4 mmHg decrease of PCWP**

†Numbers in red denote changes that are statistically significantly changes from baseline (p<0.05)

No significant effect on intrinsic LV Systolic or Diastolic properties detected by noninvasive pressure-volume analysis

Baseline vs 24-hour Levosimendan Infusion



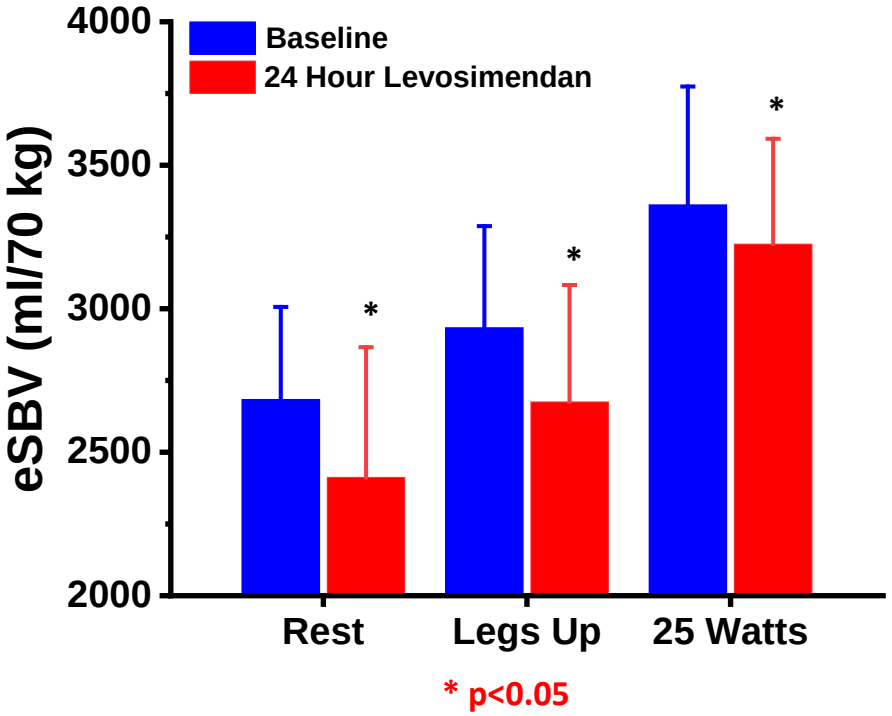


Possible Mechanism of Action: Venodilation

- In the absence of effects on myocardium, systemic and pulmonary arterial properties, simultaneous reductions of CVP and PCWP suggest that a primary mechanism may included venodilation.
- Venodilation can be indexed by a reduction of stressed blood volume (SBV)
- SBV is the portion of the total blood volume pool in excess of the amount of blood required to just start developing pressure within the vasculature
- SBV cannot be measured, but can be estimated using numerical computational methods

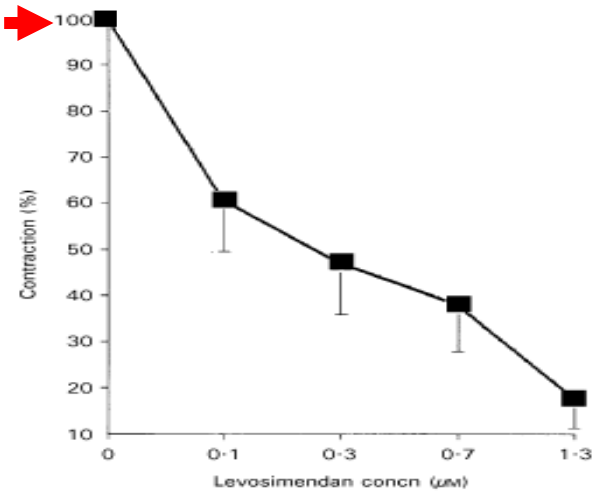
Impact of Levosimendan on Estimated Stressed Blood Volume

Baseline vs 24 hour Levosimendan Infusion



Levosimendan has Venodilating Effects through its K_{ATP} Channel Effects

NE preconditioned
Portal Vein



Glibenamide
(K_{ATP} Channel Blocker)

Levosimendan
K_{ATP} Activator

Figure 2. Effect of 1·5 μM ▲ and 15 μM ● glibenclamide on the relaxations induced by cromakalim (A, ■) and levosimendan (B, ■) in noradrenaline-precontracted human portal vein. Magnitude of contractions was expressed as percent of noradrenaline-induced tone. Data represent mean values ± s.e.m of 7 independent experiments in the case of cromakalim and 6 in the case of levosimendan. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ compared with cromakalim or levosimendan alone; †† $P < 0.01$, ††† $P < 0.001$ compared with 1·5 μM glibenclamide treatment.

Patariczа, János, et al. "Comparison of the vasorelaxing effect of cromakalim and the new inodilator, levosimendan, in human isolated portal vein." *Journal of pharmacy and pharmacology* 52.2 (2000): 213-217.

Conclusions

- **In a group of PH-HFpEF patients, 24-Hour LEVO infusion at 0.1 ug/kg/min:**
  - Decreased resting and exercise:
    - CVP, PCWP, PAP (by 3-6 mmHg)
  - Increased HR
  - Did not impact (at rest or exercise):
    - Arterial pressure, CO, systemic or pulmonary vascular resistances
- **Primary mechanism may be mediated by K_{ATP} channel activation causing venodilation**

Levosimendan Improves Hemodynamics and Submaximal Exercise Capacity in PH-HFpEF: *Primary Results from the HELP-PH-HFpEF Multicenter Randomized Controlled Trial*

Barry A. Borlaug, Daniel Burkhoff, Sanjiv J. Shah, Ronald Zolty, Ryan J. Tedford, Thenappan Glipalamide, Roham Zamanian, Jeremy A. Mazurek, Jonathan D. Rich, Marc A. Simon, Stuart Rich

Disclosure

Financial Relationships

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Mesoblast, AstraZeneca, Novartis, Corvia

Advisory Board/Consulting:

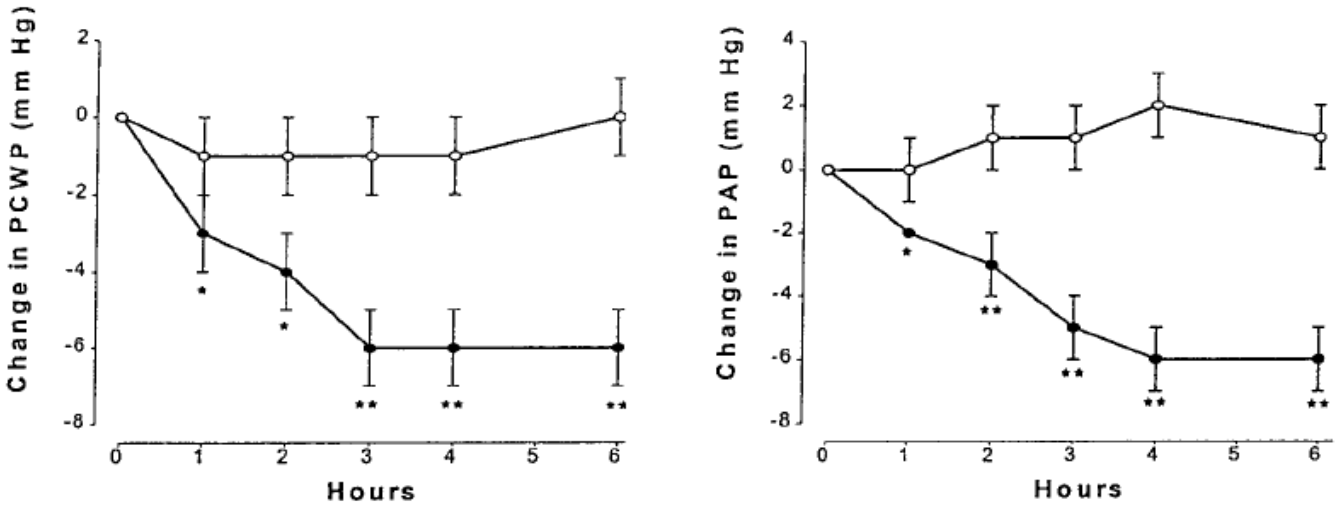
Aria, Actelion, Boehringer-Ingelheim, Imbria, Janssen, Merck, Novartis, Lilly, Novo Nordisk, Pfizer, and VADovations.

Background

- ~50% of all patients with HF have HFpEF, no unequivocally proven effective treatment
- PH is common in HFpEF
- PH-HFpEF represents more severe phenotype
  - Poorer exercise capacity
  - Higher risk of hospitalization & death
- ↑PCWP at rest and during play central role in pathophysiology

Levosimendan (LEVO)

- Combined Ca sensitizer + K_{ATP} channel activator
- Approved in >60 countries for decompensated HFrEF



- $t_{1/2}$ for LEVO is ~1 hour, but its active metabolite (OR-1896) has $t_{1/2}$ ~75 hours enabling once weekly dosing

Slawsky…Smith *Circulation* 2000

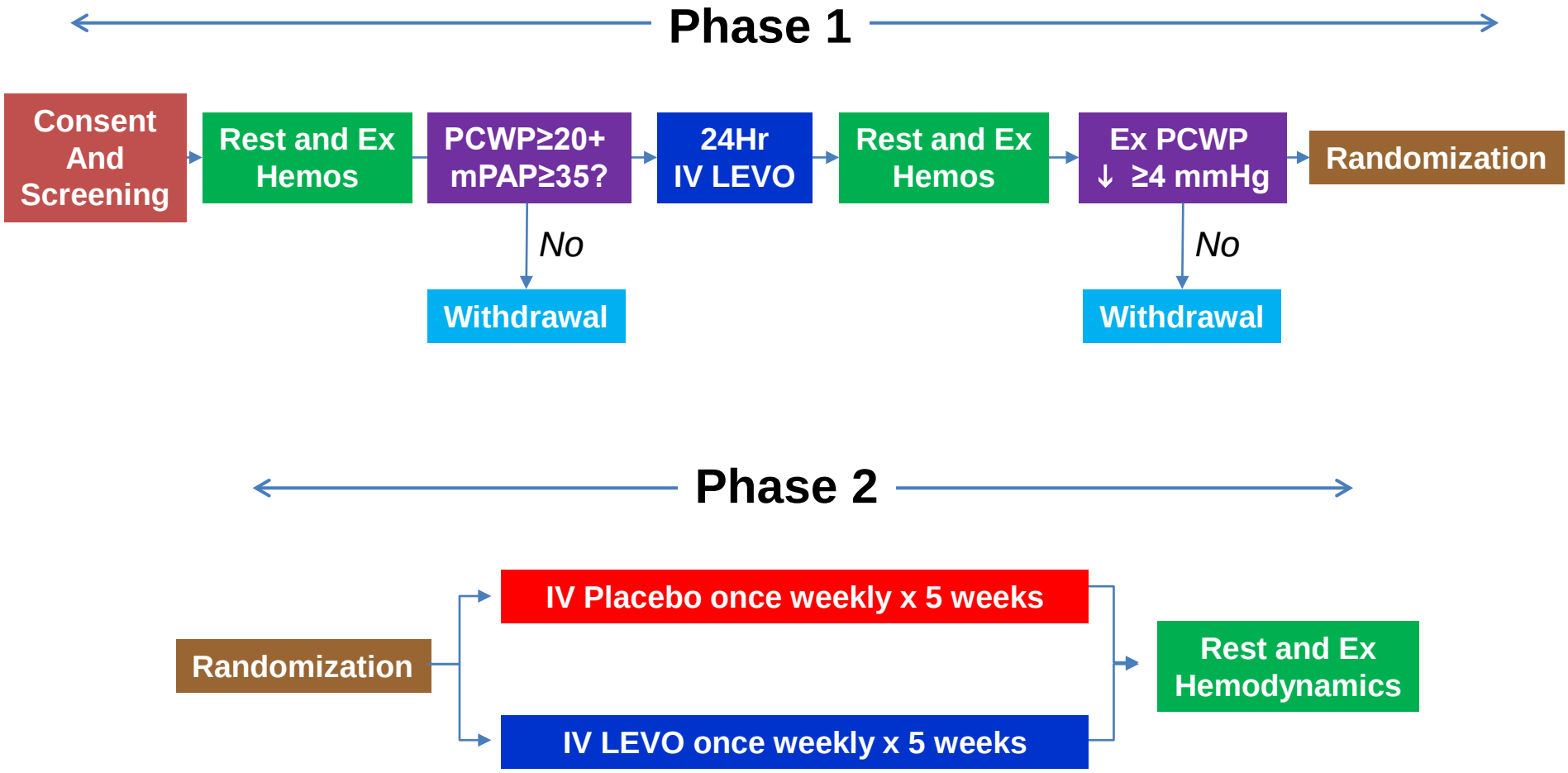
Hypothesis

- As compared to placebo, 6 weeks treatment with once weekly home infusion of IV LEVO will reduce pulmonary capillary wedge pressure (PCWP) at rest and during exercise, and improve exercise capacity

Study population: HFpEF with PH

- Group 2 PH due to HF with EF≥40%
- NYHA class II-III symptoms
- PCWP≥20 *and* mPAP≥35 mmHg
- Key exclusion criteria
  - Coronary disease unless negative perfusion scan
  - Significant mitral and aortic valve disease
  - SBP<100 mmHg
  - Other causes of PH (lung, congenital)
  - Planned transplant or cardiac surgery

Study Design: Randomized, double-blind, placebo controlled trial



Trial Endpoints

- Primary

  Change in PCWP at 25 W exercise at 6 weeks

- Secondary
  - Change in 6 minute walk distance
  - Change in PCWP incorporating rest, PLR and exercise using a mixed effect model with repeated measures (post hoc)

Baseline Characteristics

Characteristic	Placebo (n=19)	Levo (N = 18)
Age (years)	67 (11)	69 (8)
Women (%)	68	56
White (%)	84	89
BMI (kg/m^2)	33.0 (7.2)	35.6 (9.2)
Atrial fibrillation (%)	63	89

Mean values (SD) or % shown

All p > 0.05

Baseline Characteristics

Characteristic	Placebo (n=19)	Levo (N = 18)
NYHA class II/III (%)	16/84	11/89
6 minute walk distance (m)	280 (85)	290 (127)
Ejection fraction (%)	59 (8)	58 (7)

Mean values (SD) or % shown

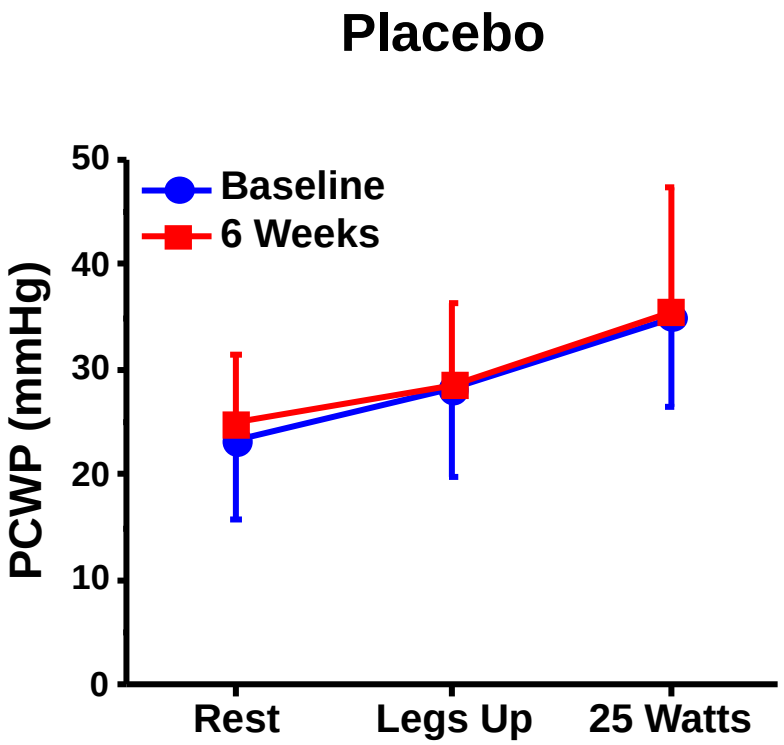
All p > 0.05

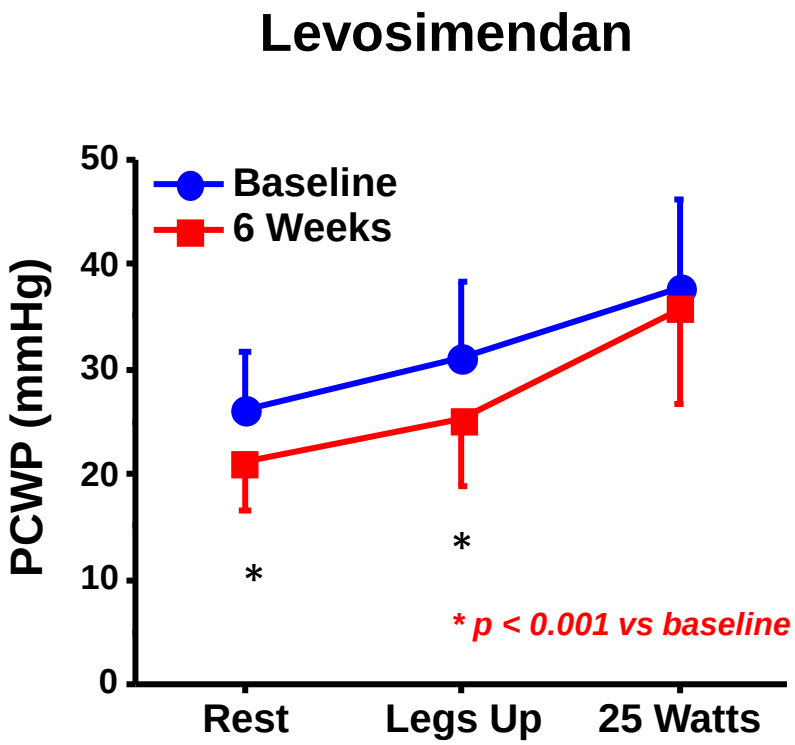
Hemodynamics at Baseline

Characteristic	Placebo (n=19)	Levo (N = 18)
Right atrial pressure (mmHg)	17 (5)	15 (5)
Mean PA pressure (mmHg)	42 (11)	41 (9)
PCWP (mmHg)	25 (7)	26 (5)
Cardiac index (l/min/m^2)	2.3 (0.6)	2.7 (1.0)
PVR (WU)	4.1 (3.6)	2.7 (1.5)

Mean values (SD) or % shown

All p > 0.05

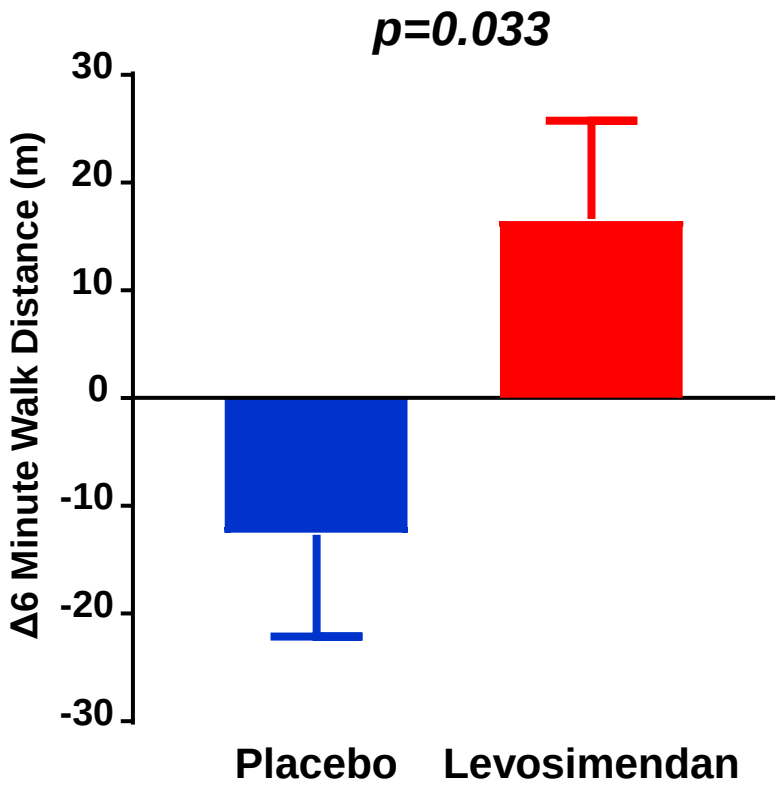




Primary Endpoint ex PCWP (-1.4 mmHg, 95% CI, -7.7 to 4.8, p=0.65)

Mixed-effect repeated measure regression analysis: -3.9±2.0 mmHg as compared to placebo (p=0.047)

Effects on 6 minute walk distance



Safety

Characteristic	Placebo (n=18)	LEVO (n=19)
Discontinued study drug	2	0
PICC Line Infection	0	2
Arrhythmia	0	0
Worsening HF	1	2
Stroke	0	0
Syncope	0	0
SAE - Death	0	0

All p > 0.05

Conclusions

- As compared to placebo, once weekly treatment with levosimendan did not reduce the primary endpoint of PCWP during exercise in PH-HFpEF
- Levosimendan reduced PCWP across rest and exercise stages
- Levosimendan improved 6 minute walk distance
- These data support conduct of a Phase 3 trial of levosimendan in PH-HFpEF

Thank you for your attention

- Daniel Burkhoff MD PhD, Cardiovascular Research Foundation, New York, NY
- Barry A. Borlaug MD, Mayo Clinic, Rochester, MN
- Sanjiv J Shah MD, Northwestern University, Chicago, IL
- Ronald Zolty MD, University of Nebraska Medical Center, Omaha, NE
- Ryan J. Tedford MD, Medical University of South Carolina, Charleston, SC
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- Gregory D. Lewis MD, Mass General Hospital, Boston, MA
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