24-hour Levosimendan Infusion Decreases Biventricular Filling Pressures at Rest and Exercise in PH-HFpEF

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For the HELP Study Investigators

TEACH

Cardiovascular Research Foundation

Disclosures

- I, Daniel Burkhoff, that my institution, the Cardiovascular Research Foundation, has received research grant support from TENAX related to the conduct of this study.

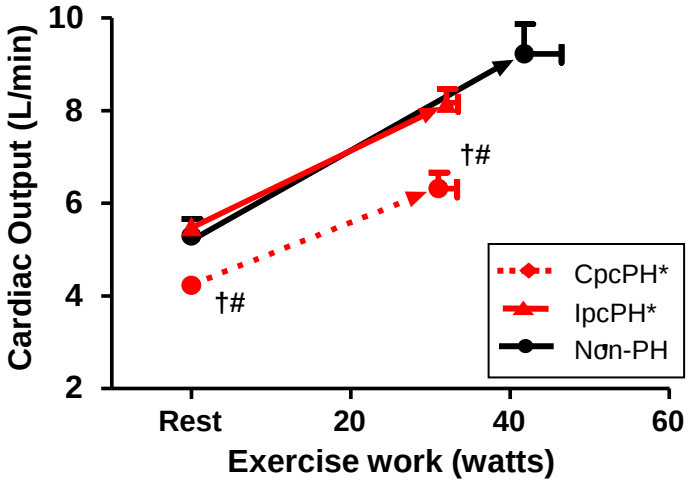
Background

- HFpEF affects ~50% of all patients with HF, no unequivocally proven effective treatment
- Approximately 70% of patients with HFpEF have PH, and ~30% have RVD
- PH-HFpEF represents more severe phenotype
  - Higher risk of death compared to HFpEF without PH
  - Poorer outcomes compared to WHO Group 1 PH, but no established treatment
- RV Dysfunction is common in PH-HFpEF and contributes to right-sided congestion

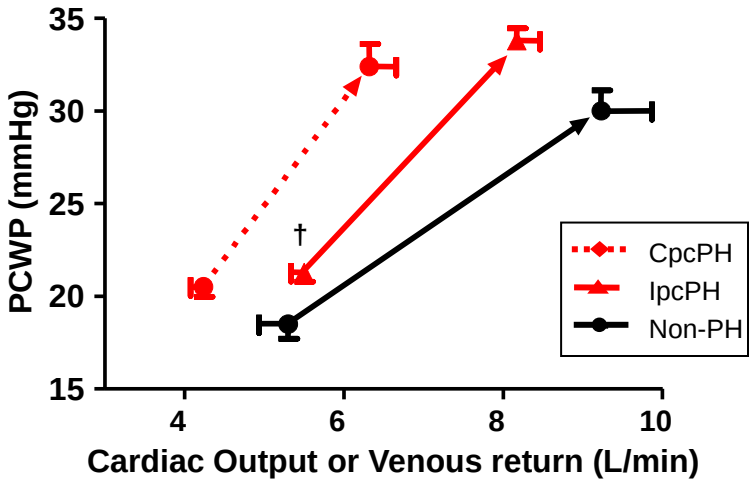
Vanderpool…Simon *JAMA Cardiol* 2018

Wijeratne…Archer *Circ Cardiovasc Qual Outcomes* 2018

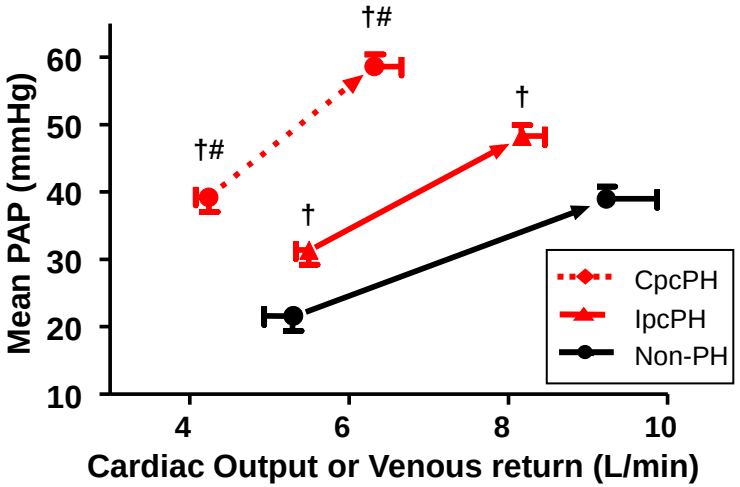
Exercise Hemodynamics Severely Deranged in PH-HFpEF



CO increases less in HFpEF patients with combined pre- and post-capillary PH (*CpcPH) than in patients with isolate post-capillary PH (*IpcPH)



For a given CO, PCWP is significantly higher in PH-HFpEF and in HFpEF patients with post-capillary PH or no PH

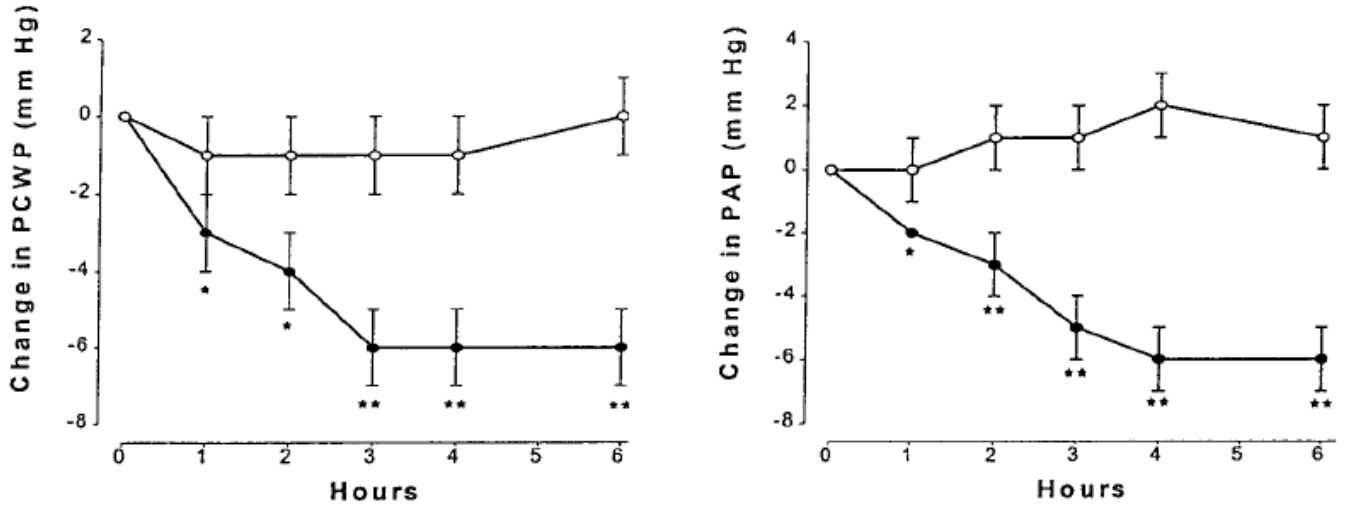


For a given CO, mean PAP is significantly higher in PH-HFpEF and in HFpEF patients with post-capillary PH or no PH

PH-HFpEF patients have lower CO and higher PCWP at rest and exercise compared to HFpEF patients with post-capillary PH or no PH

Levosimendan (LEVO)

- Combined Ca sensitizer, K_{ATP} channel activator, PDE3 inhibitor
  —Inodilator
- LEVO is known to decrease pulmonary pressures in patients with severe heart failure and reduced LVEF.



Acute hemodynamic and clinical effects of levosimendan in patients with severe heart failure

Slawsky…Smith *Circulation* 2000

HELP Study

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

Study conducted in 2 phases:

- **Phase 1: Open label 24-hour Levo infusion testing effects of LEVO 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 LEVO

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

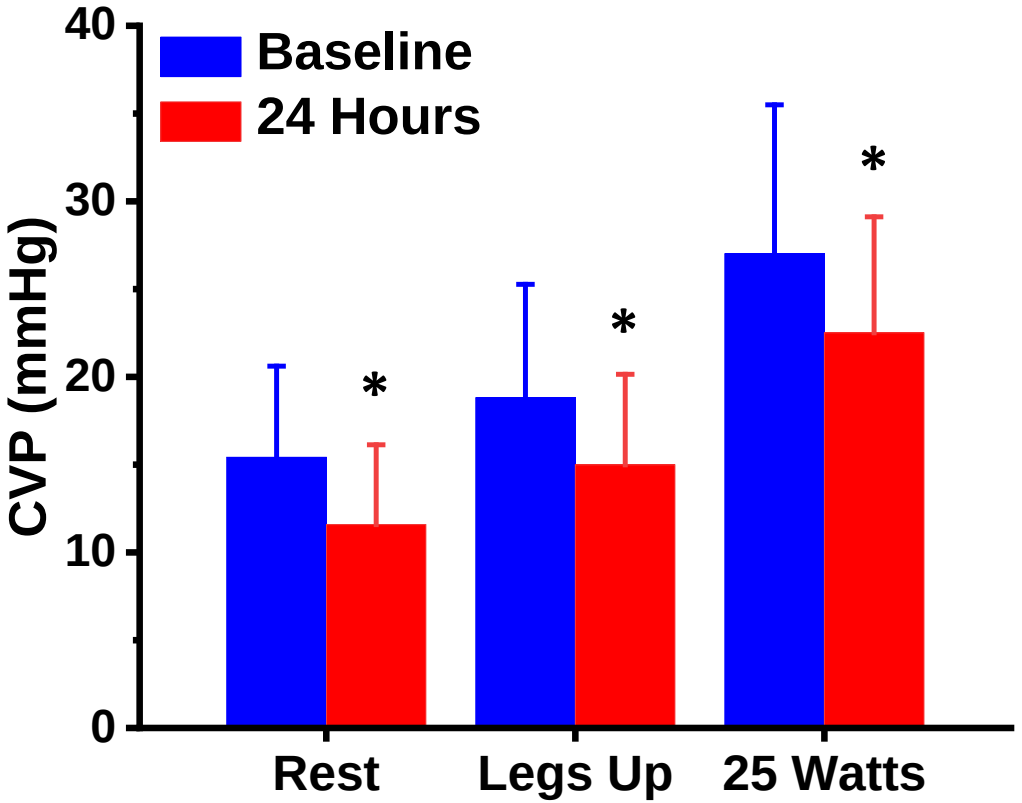
Study population: HFpEF with PH

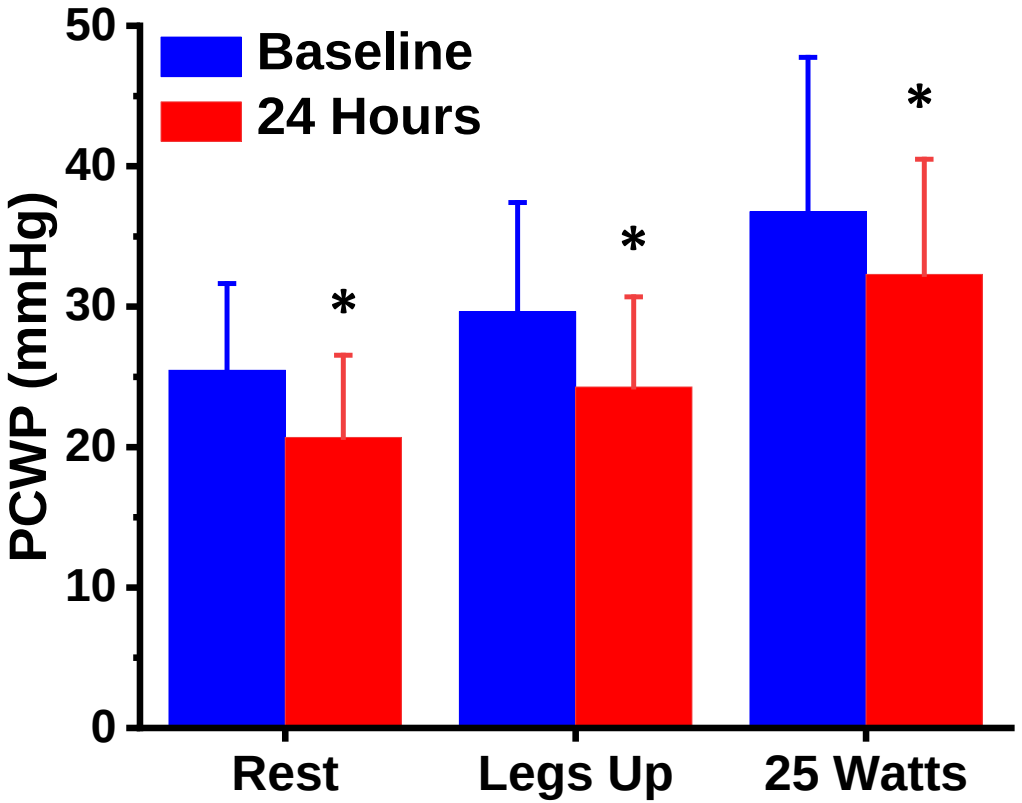
- Group 2 PH due to HF with EF≥40%
- NYHA class II-III symptoms
- PCWP≥20 *and* mPAP≥35 mmHg
- Key exclusion criteria
  - Coronary disease unless negative perfusion scan
  - Significant mitral and aortic valve disease
  - SBP<100 mmHg
  - Other causes of PH (lung, congenital)
  - Planned transplant or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

Key Baseline Characteristics

Characteristic	N=44 Patients
Age (years)	69.0 ± 9.1
Gender, n (% male)	17 (38.6)
BMI (kg/m²)	35.1 ± 8.9
Medical History	
Atrial Fibrillation (history)	34 (77.3)
HTN, n (%)	26 (59.1)
CAD, n (%)	13 (29.5)
CKD, n (%)	11 (25.0)
Obstructive Sleep Apnea, n (%)	28 (63.6)
COPD, n (%)	9 (20.5)
NYHA, n (%)	
II	6 (13.6)
III	38 (86.4)
Vital Signs	
HR	73.1 ± 15.0
SBP	129.5 ± 16.6
DBP	69.0 ± 10.5
RR	17.0 ± 2.1
6-Minute Walk (meters)	284.6 ± 106.2
Echocardiogram	
LVEF	58.2 ± 8.8
LA Dimension	91.8 ± 38.5
TAPSE	1.74 ± 0.37

Baseline vs 24 hour Levosimendan Infusion: Impact on CVP and PCWP*





*All values differ between baseline and 24-hours LEVO infusion by paired t-test

Summary of Overall Hemodynamic Effects of 24-hour Levosimendan Infusion

	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)*
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**

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
- In the already-reported Phase 2 results, these findings were associated with increased 6-minute hall walk following 6 weeks of once-weekly LEVO infusions
- Further studies are warranted to investigate the longer-term impact of LEVO in treatment of PH-HFpEF

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HELP INVESTIGATORS

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