Reducing stressed blood volume with levosimendan

presenting data from

Hemodynamic Evaluation of Levosimendan in PH-HFpEF

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Disclosures:

- Chief Medical Officer, Tenax Therapeutics
  - Tenax has the license for levosimendan in North America

Background: PH-HFpEF

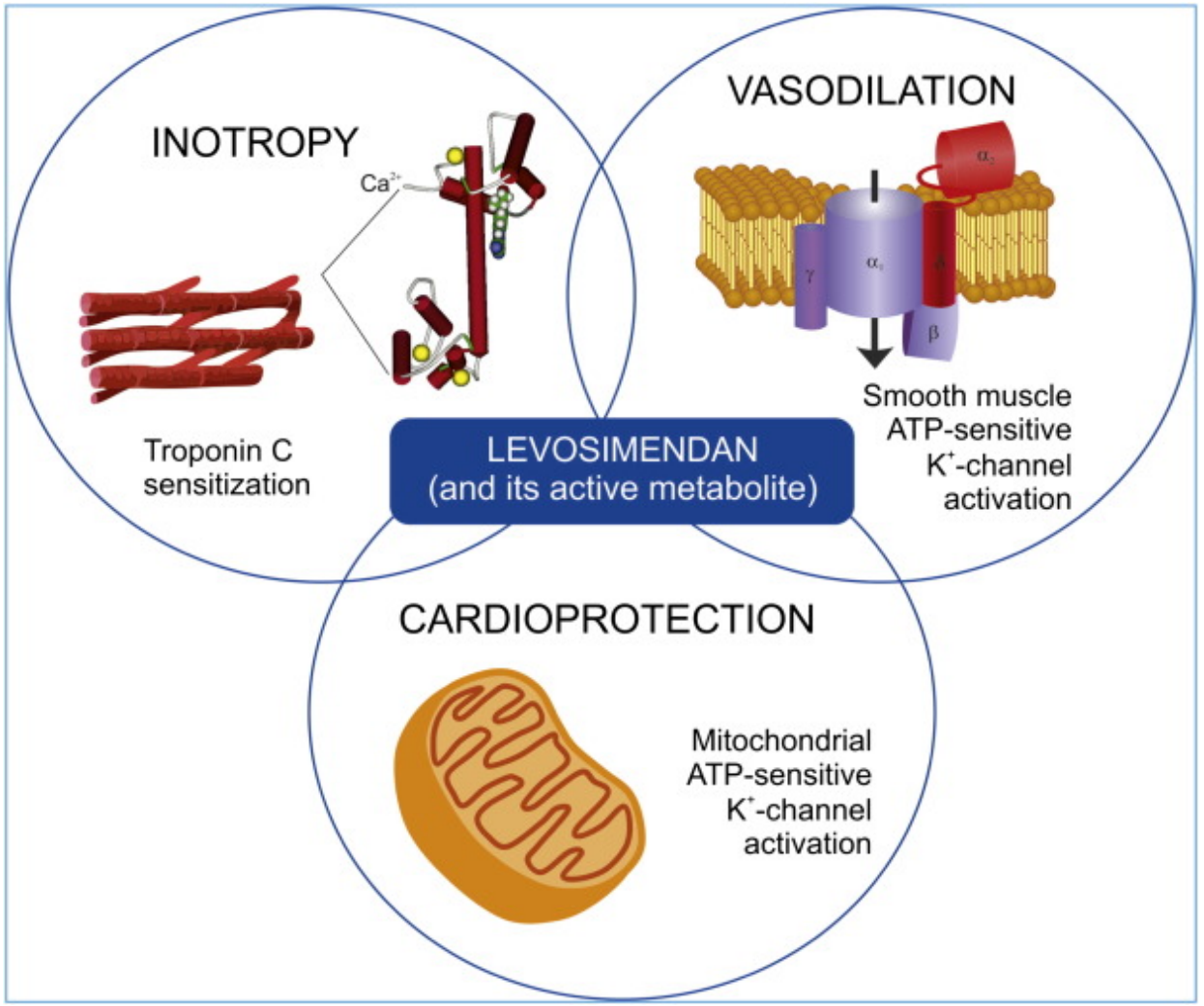
- HFpEF affects ~50% of all patients with HF
- Approximately 70% of patients with HFpEF have PH, and ~30% have RVD
- PH-HFpEF represents a more severe phenotype
  - Higher risk of death compared to HFpEF without PH
  - Poorer outcomes compared to WHO Group 1 PH, with no treatments even suggested by the guidelines
- 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

Background: Levosimendan

- Inotropic properties due to Ca++ sensitization of troponin C
- K+ATP channel activator
  - Direct vasodilatory action of vascular smooth muscle
  - Selectivity for different arterial and venous circulations
  - Potential for mitochondrial protection from ischemia-reperfusion injury



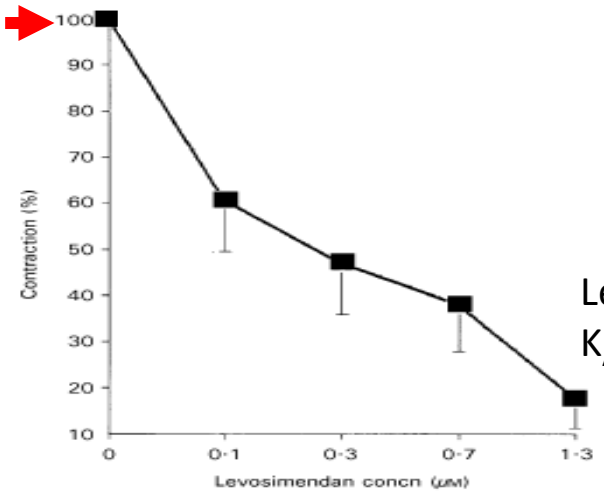
Why the K+ ATP activator properties of levosimendan are important in pulmonary hypertension

- Downregulation of K+ channel activity is considered the hallmark of pulmonary hypertension
  - K+ channels control PASMCs and PAECs
  - K+ channels regulate pulmonary venous tone
- Downregulation of K+ channels occur in animal models of PH and in human disease
- K+ channels are involved in the transition of the pulmonary circulation to a proliferative vascular phenotype

Mondéjar-Parreño G, Cogolludo A, Perez-Vizcaino F. Potassium (K^+) channels in the pulmonary vasculature: Implications in pulmonary hypertension Physiological, pathophysiological and pharmacological regulation. Pharmacol Ther. 2021 Sep;225:107835.

Levosimendan has Vasodilating Effects on Human Portal Vein

NE preconditioned Portal Vein



Levosimendan
K_{ATP} Activator

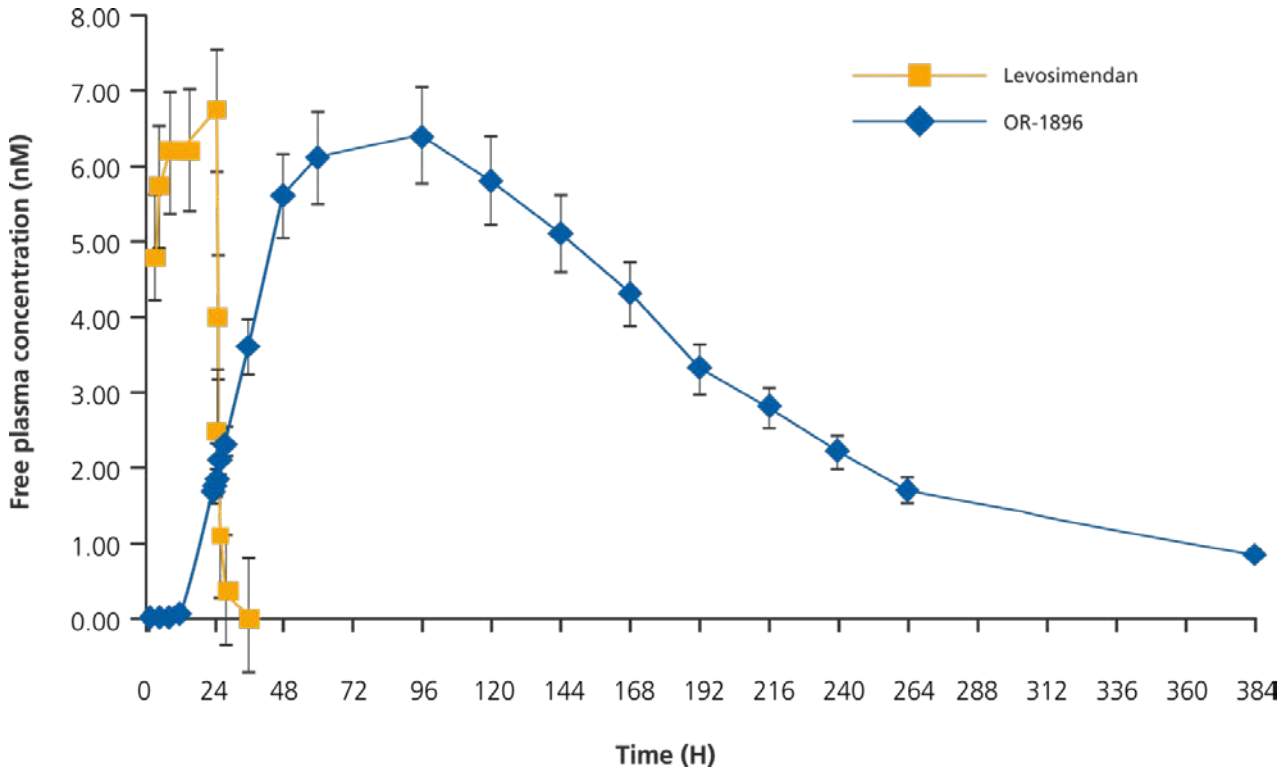
Figure 2. Effect of 1·5 μM ▲ and 15 μM ● glibenclamide on the relaxations induced by cromakalim (A, ■) and levosimendan (B, ■) in noradrenaline-precontracted human portal vein. Magnitude of contractions was expressed as percent of noradrenaline-induced tone. Data represent mean values ± s.e.m of 7 independent 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.

Pataricza, 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.

Levosimendan and Active Metabolite OR-1896:

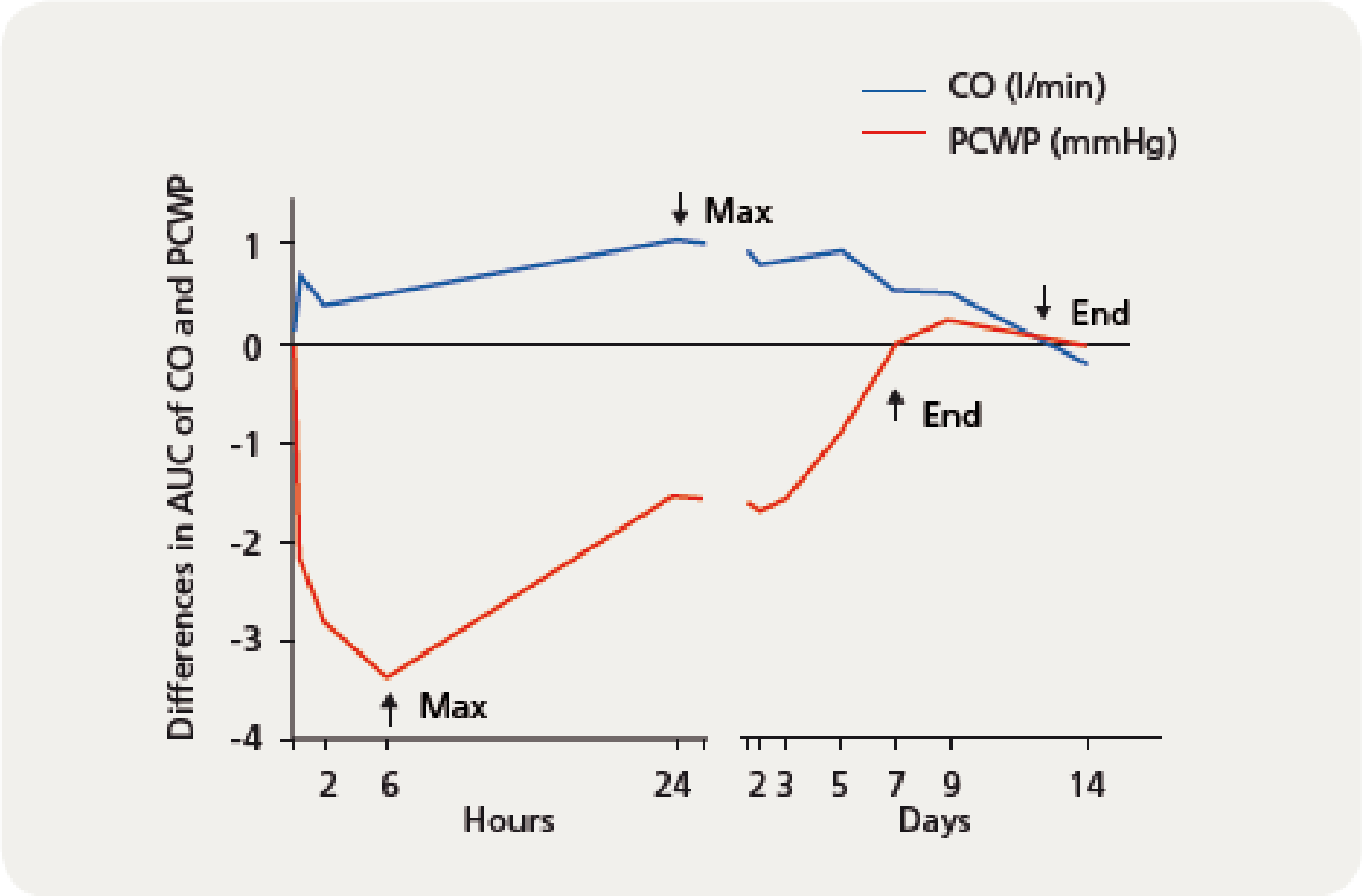
similar effects provide sustained efficacy over 7 days

- Levosimendan currently only for intravenous use.
- Approved for ADHF in the ICU.
- Administered as a 24-hour infusion.



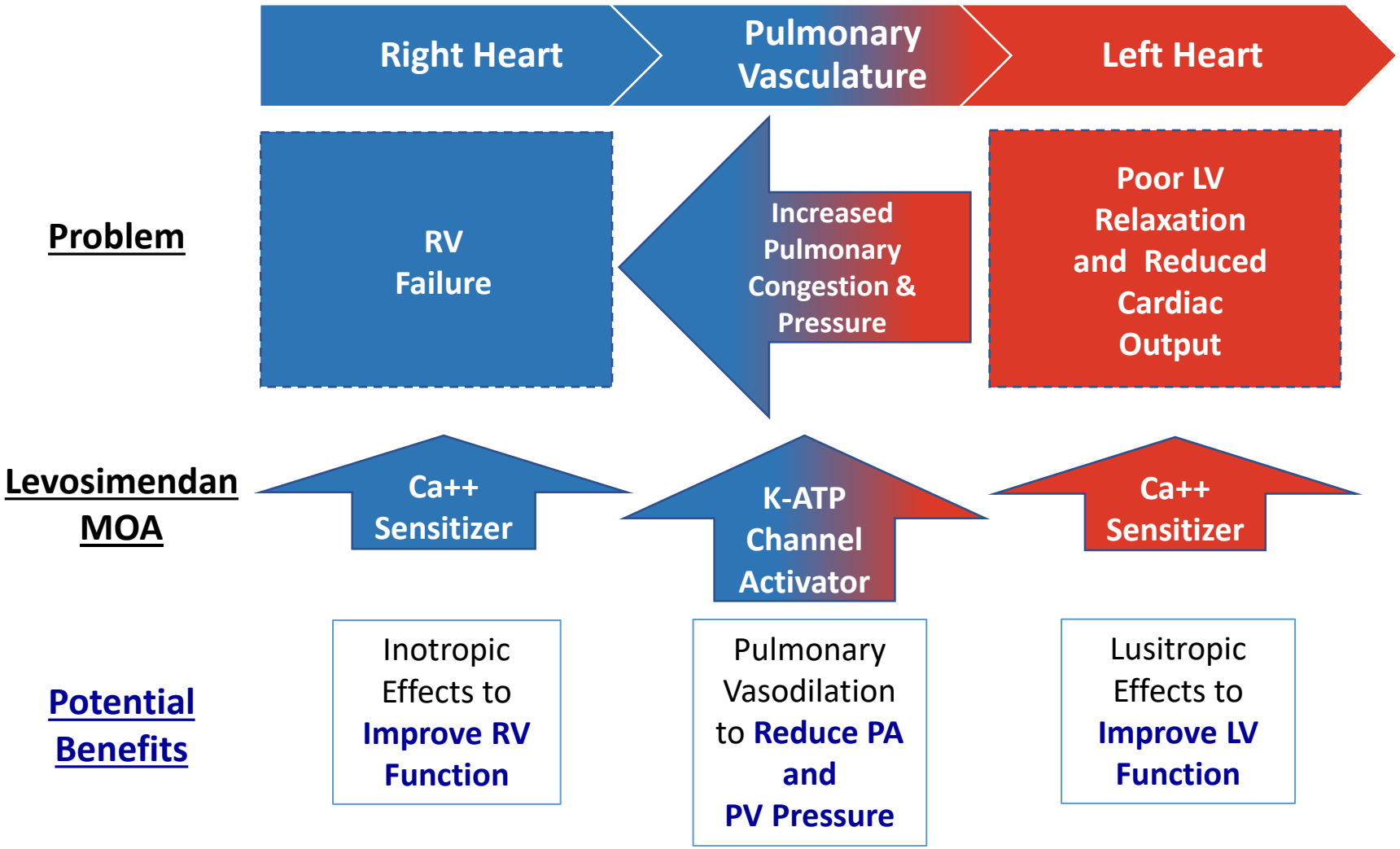
Kivikko *et al. Int J Clin Pharm & Ther* 2002;**40**:465

Changes in cardiac output and PCWP over time from levosimendan



Lilleberg et al. *Eur J Heart Fail* 2007;**9(1)**:75-82

Mechanistic Rationale for Levosimendan in PH-HFpEF – Inotrope or Vasodilator?



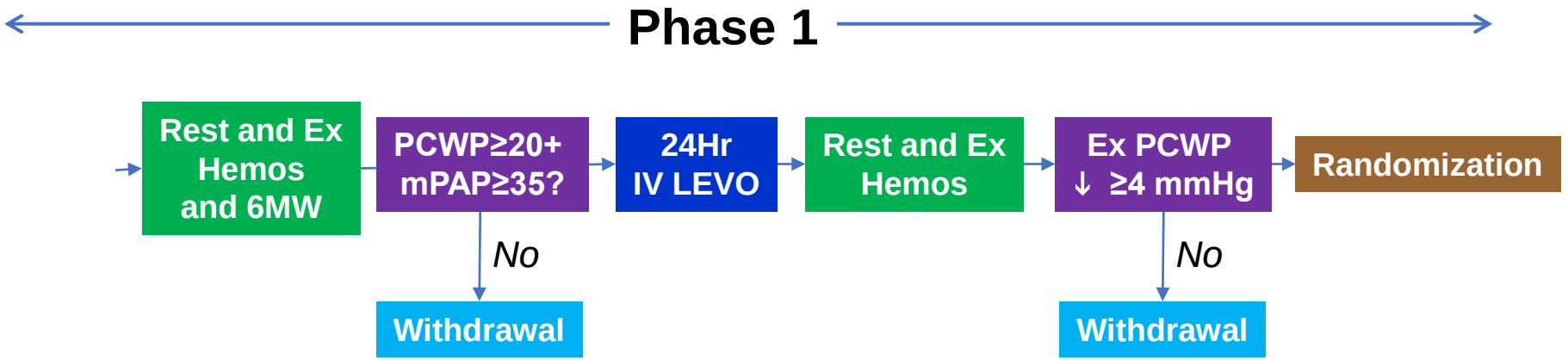
HELP Study

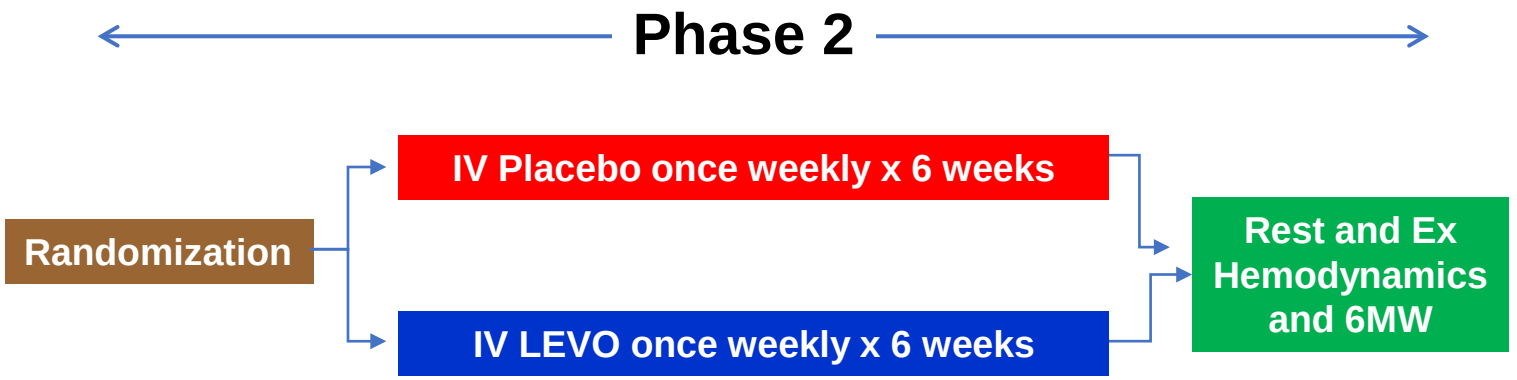
Hemodynamic **E**valuation of **L**evosimendan in **P**H-HFpEF

- WHO Group 2 PH-HFpEF (EF≥40%)
- NYHA class II-III symptoms
- PCWP≥20 and mPAP≥35 mmHg
- Two phases to the trial
  - Phase 1: Open label assessment (exercise RHC) of 24-hour infusion of levosimendan
  - Phase 2: Randomized double-blinded 6 weeks of levosimendan home infusion
    - Enriched enrollment of responders (defined as ≥4mmHg fall in exercise PCWP)
    - The long half-life of OR-1896 supports that once/week infusions would provide sustained effectiveness

HELP Study

Hemodynamic Evaluation of Levosimendan in PH-HFpEF





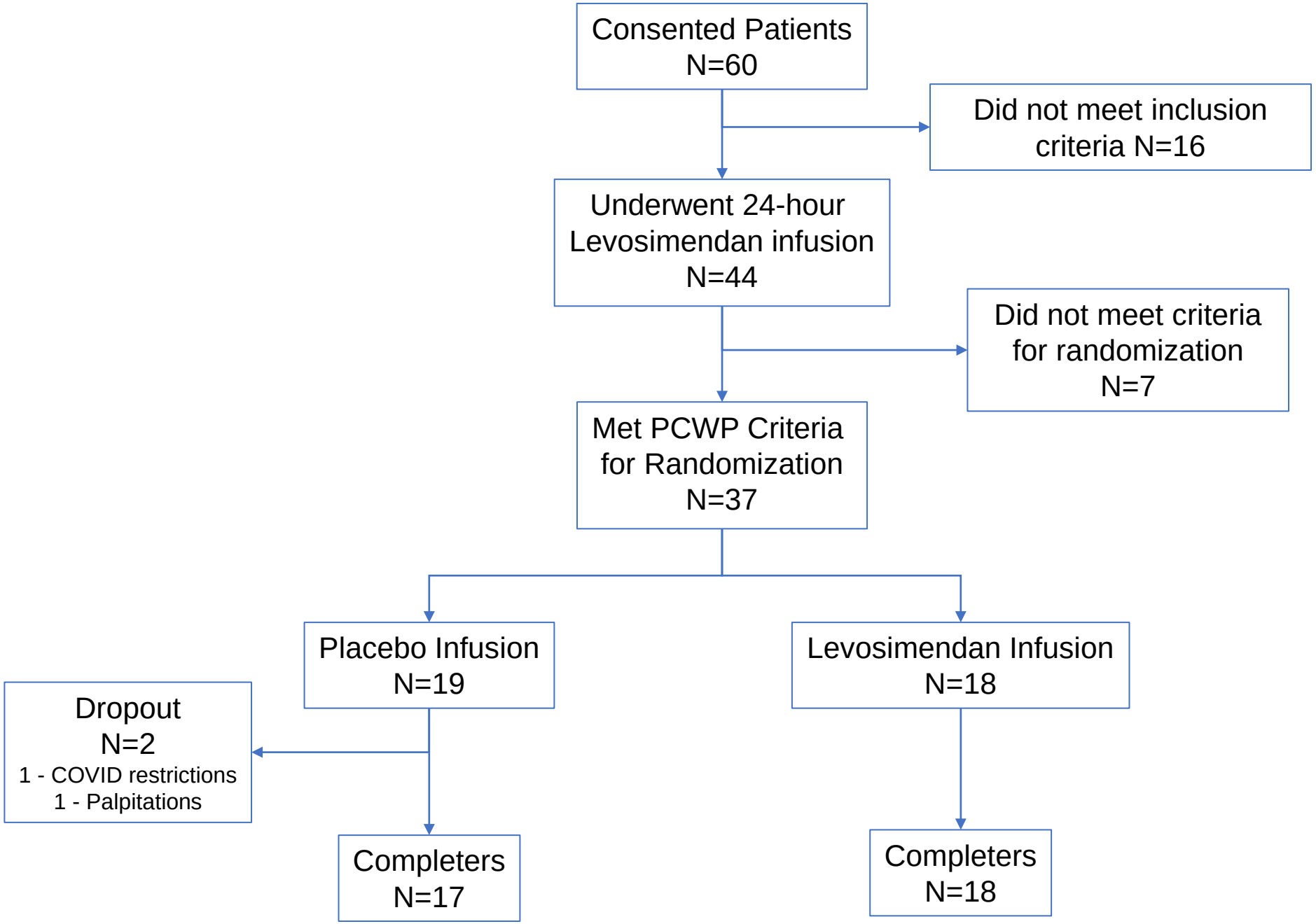
HELP Study

Trial Endpoints

- Primary

  Change in PCWP at 25 W exercise at 6 weeks

- Secondary
  - Change in 6-minute walk distance
  - Change in CVP, PCWP, mPAP, CI, PVR at rest and with exercise


Consented Patients
N=60
Did not meet inclusion criteria N=16
Underwent 24-hour Levosimendan infusion
N=44
Did not meet criteria for randomization
N=7
Met PCWP Criteria for Randomization
N=37
Placebo Infusion
N=19
Levosimendan Infusion
N=18
Dropout
N=2
1 - COVID restrictions
1 - Palpitations
Completers
N=17
Completers
N=18

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

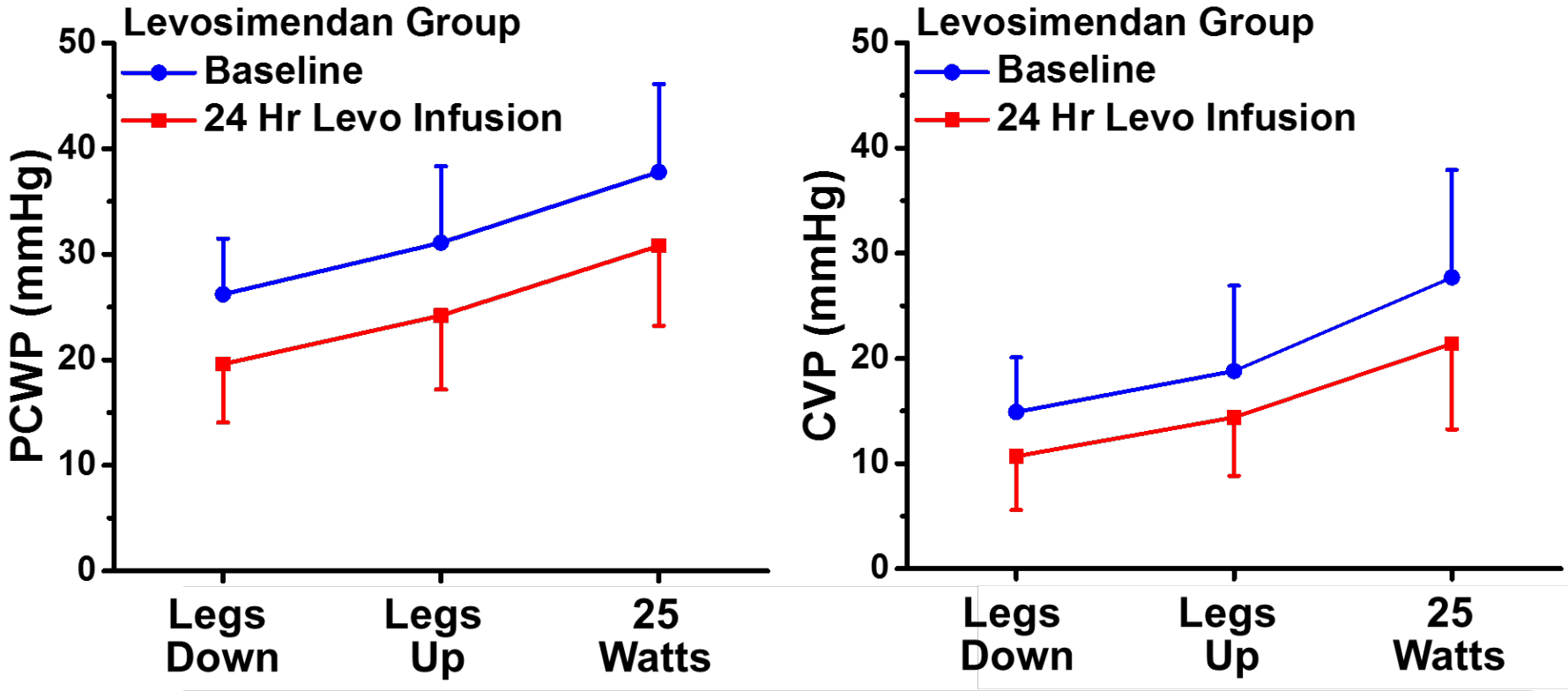
Hemodynamics at Baseline

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

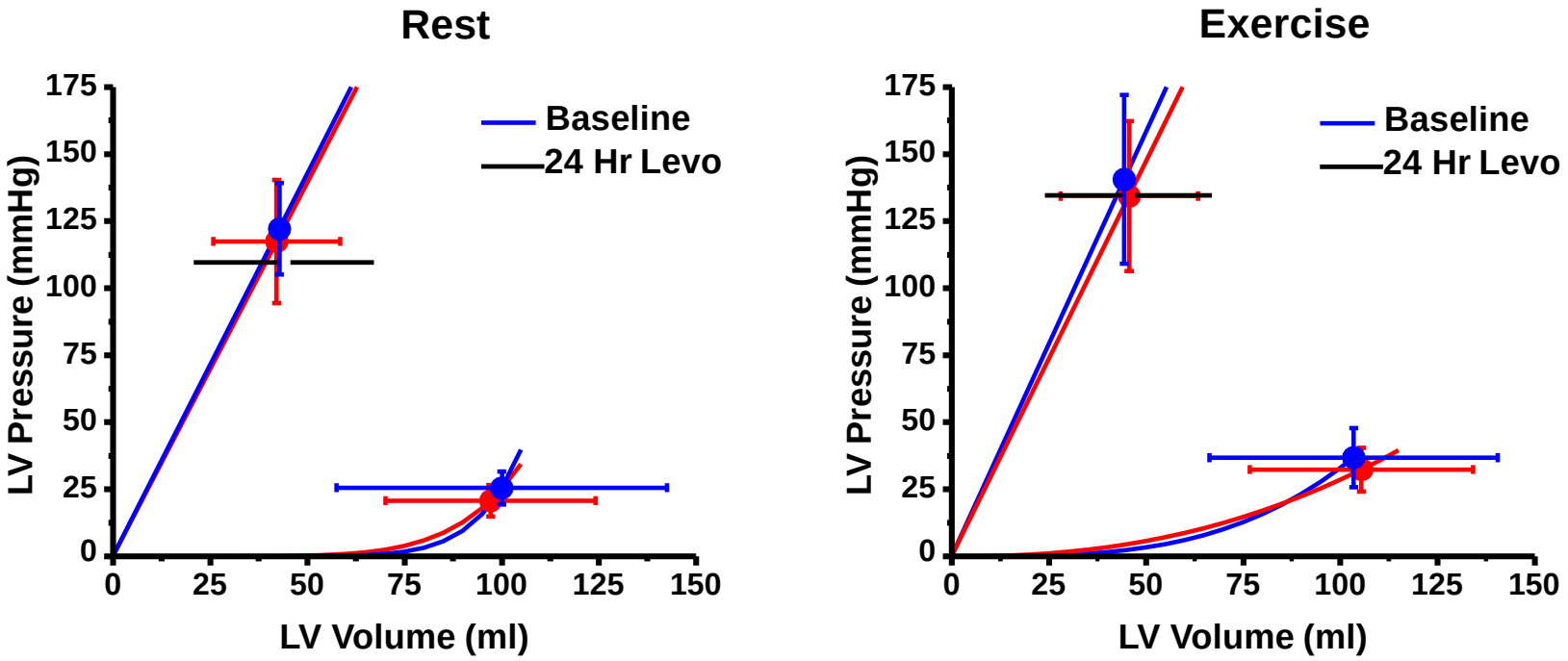
Baseline vs Post 24-Hour Levosimendan Infusion



All values between baseline and 24 hr LEVO infusion p<0.01

Burkhoff, Daniel, et al. "Levosimendan Improves Hemodynamics and Exercise Tolerance in PH-HFpEF: Results of the Randomized Placebo-Controlled HELP Trial" *Journal of the American College of Cardiology: Heart Failure* Vol. x No. x pp xx-xx; April 2021

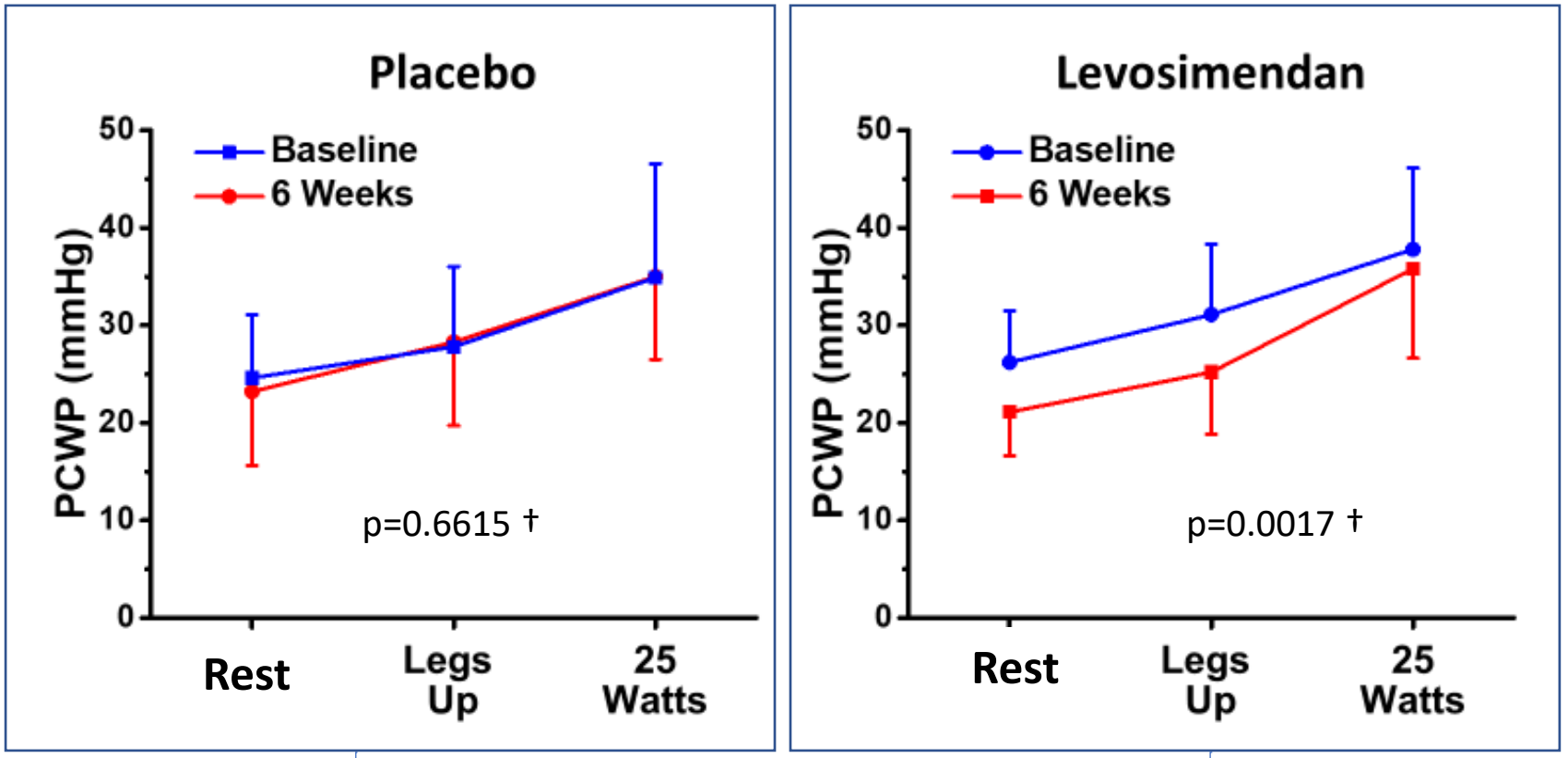
Baseline vs post 24-hour Levosimendan Infusion on LV contractility



(No significant difference in cardiac index with levosimendan at rest or with exercise)

PCWP Endpoint

Baseline versus 6 Weeks

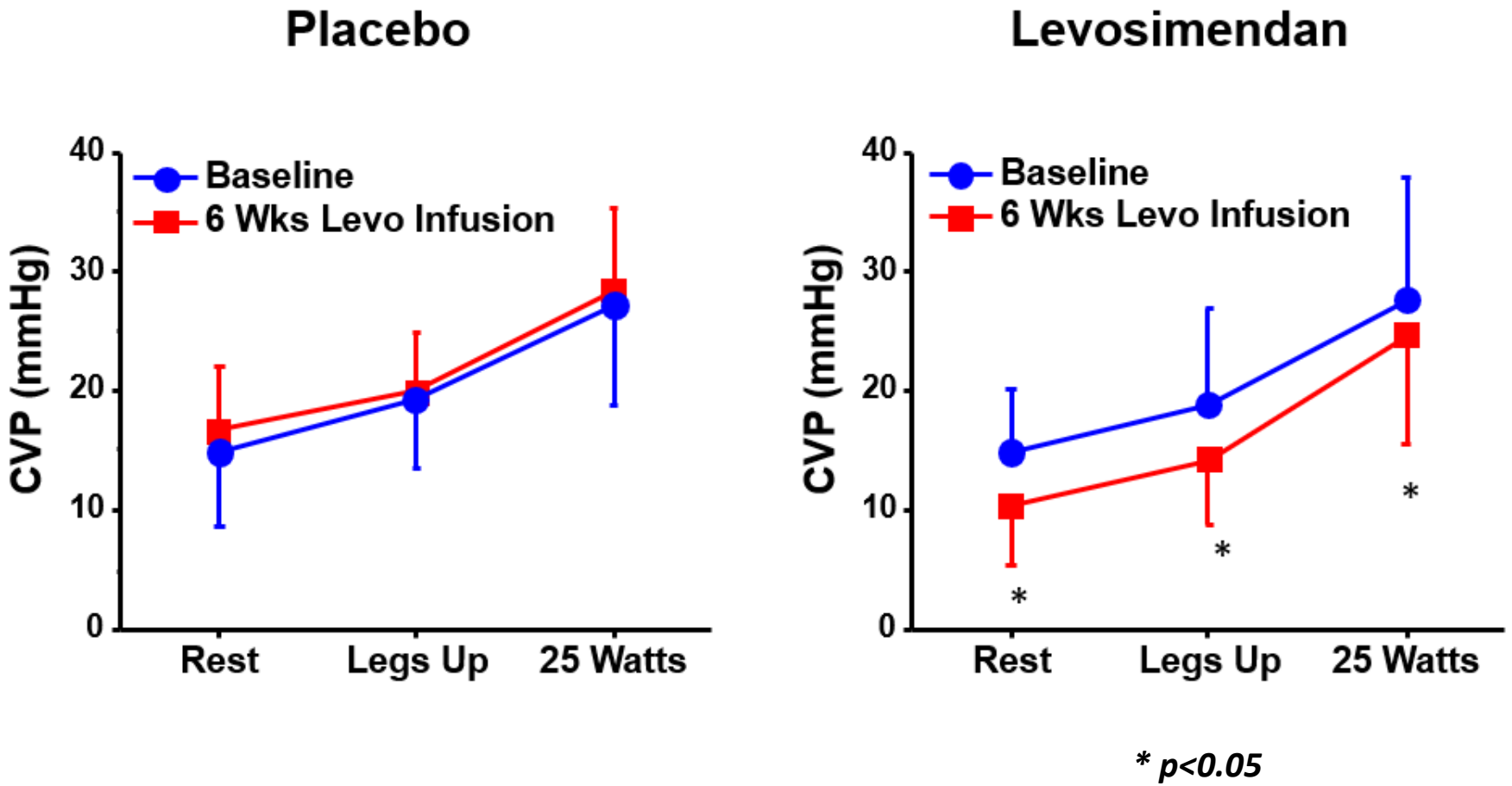


Levosimendan effect on PCWP across positions significant vs placebo

† Tested in a mixed effect model using treatments as factors and position as a random effect

CVP Endpoint

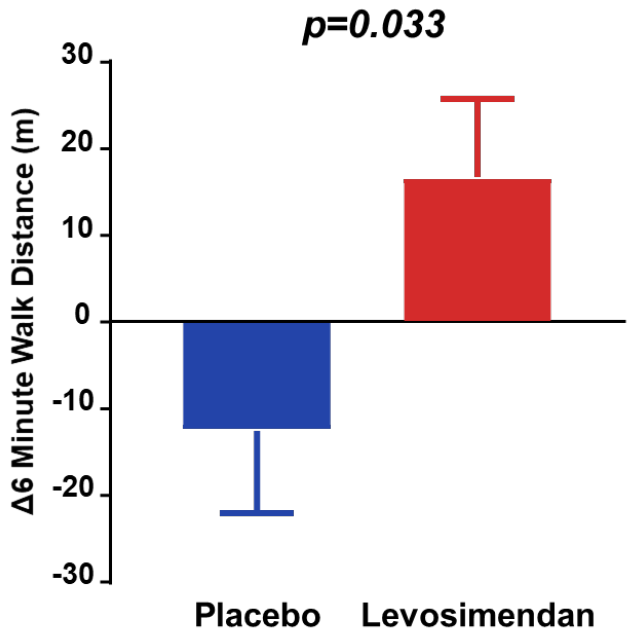
Baseline vs. 6 weeks



** p<0.05*

Weekly Levosimendan Dosing Improves Exercise Capacity in PH-HFpEF Patients

Effects on 6 minute walk distance



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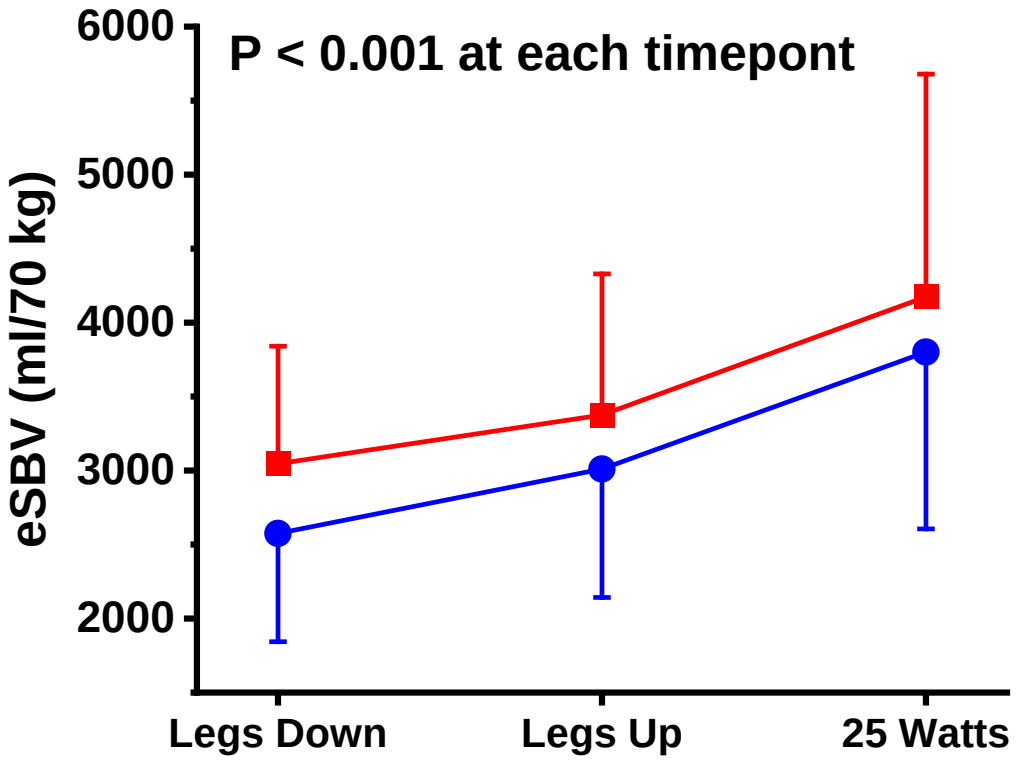
Safety

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

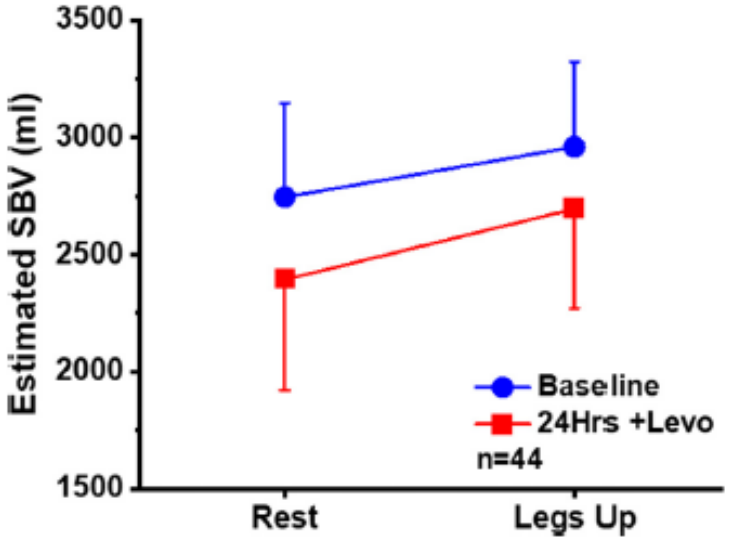
All p > 0.05

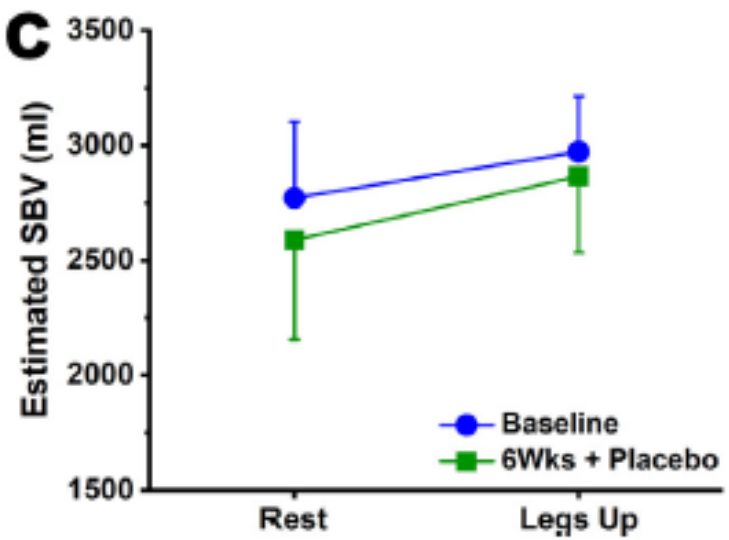
*comparison of 72 hr ambulatory ECG monitoring between baseline and week 5

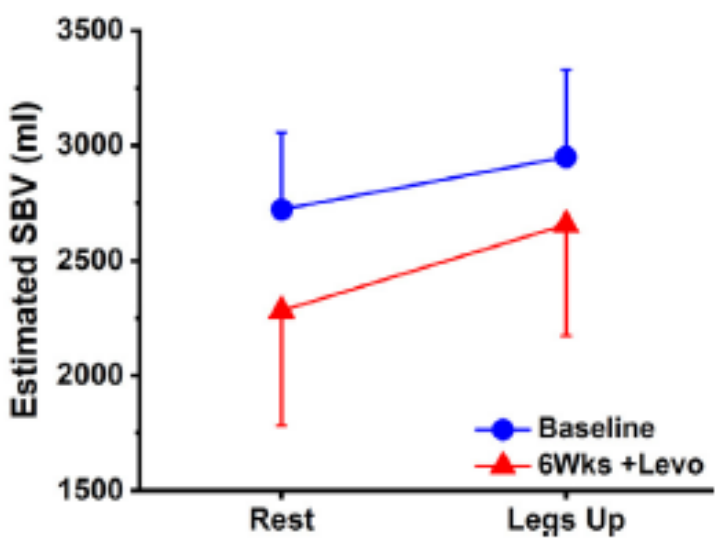
Baseline vs 24 hour Levosimendan Infusion on Estimated Stressed Blood Volume



Baseline vs 6 weeks of Levosimendan on Estimated Stressed Blood Volume







Brener MI, Hamid NB, Sunagawa K, Borlaug BA, Shah SJ, Rich S, Burkhoff D. Changes in Stressed Blood Volume with Levosimendan in Pulmonary Hypertension from Heart Failure with Preserved Ejection Fraction: Insights Regarding Mechanism of Action From the HELP Trial. J Card Fail. 2021 Sep;27(9):1023-1026.

Conclusion

- Levosimendan causes a significant fall in PCWP and CVP during rest and exercise in patients with PH-HFpEF
- Long term (6 weeks) use of levosimendan produced a significant improvement in 6MW
- The mechanism of action appears to be a reduction in stressed blood volume from splanchnic dilation via the K^+_{ATP} activator properties of levosimendan
  - There was no evidence to suggest that positive inotropic effects were a factor