



#AHA24

MODIFIABILITY OF POST-EXERCISE OXYGEN UPTAKE RECOVERY PATTERNS: A SUBSTUDY OF THE SEQUOIA-HCM RANDOMIZED TRIAL

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BACKGROUND/OBJECTIVE



Cardiopulmonary exercise testing (CPET) enables objective assessment of all stages of exercise.¹



Prolonged post-exercise oxygen uptake recovery (VO_2 Rec) is associated with adverse outcomes in severe heart failure.^{2,3}



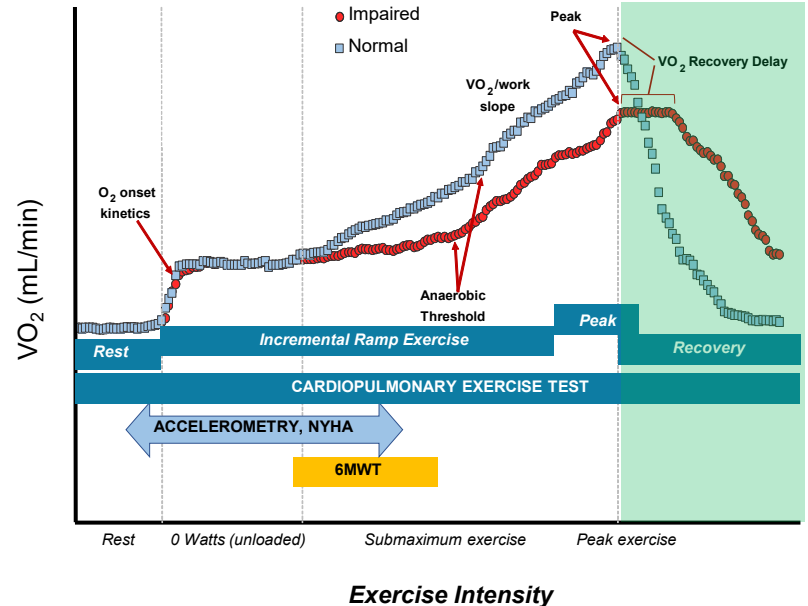
In heart failure, VO_2 Rec increases proportionally with reduction in exercise cardiac output (CO).²



Neither VO_2 Rec nor its potential modifiability with cardio-specific interventions have been characterized in obstructive hypertrophic cardiomyopathy (oHCM).



Hypothesis: aficamten, a next-in-class cardiac myosin inhibitor, reduces VO_2 Rec proportionally with improvements in other measures of cardiac performance in patients with symptomatic oHCM.

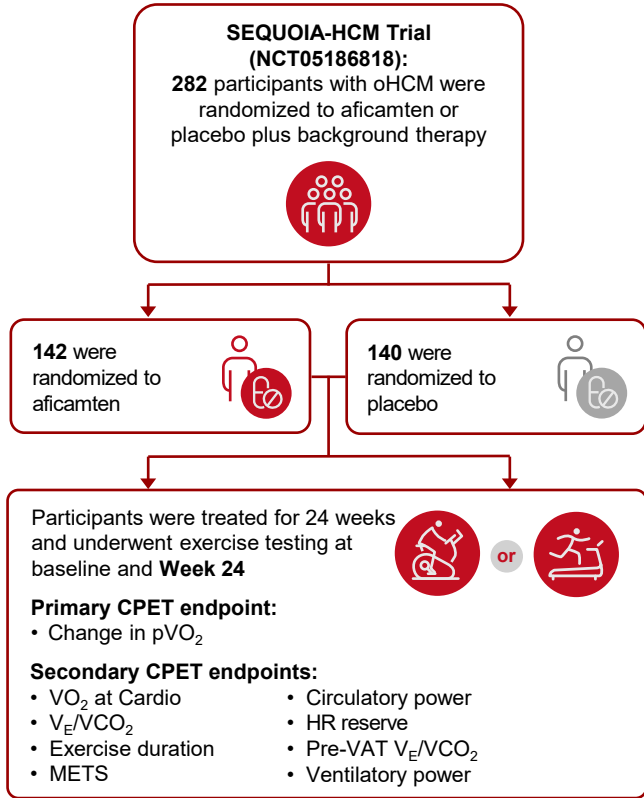


6MWT, 6-minute walk test; NYHA, New York Heart Association; VO_2 , oxygen uptake.

1. Lewis GD, et al. *Circ Heart Fail* 2022;15(3):e008970; 2. Bailey CS, et al. *JACC Heart Fail* 2018;6(4):329-39;

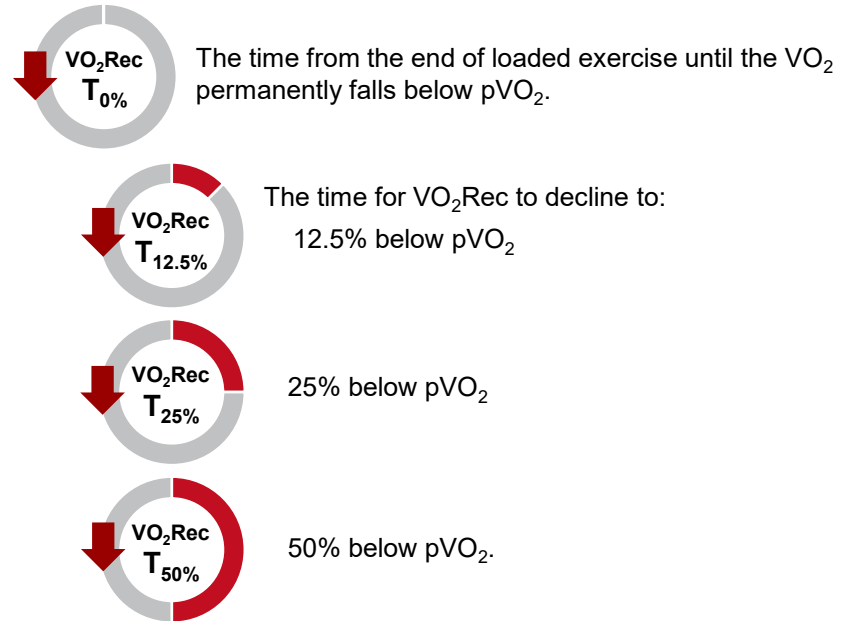
3. Cohn-Solal A, et al. *Circulation* 1995;91(12):2924-32.

METHODS AND MATERIALS



Characterization of post-exercise VO_2 Rec patterns was prespecified as an exploratory analysis in SEQUOIA-HCM.

- Recovery was defined as the period beginning when the workload was removed.



AT, aerobic threshold; HR, heart rate; METS, metabolic equivalent; pVO_2 , peak VO_2 ; VAT, ventilatory anaerobic threshold; V_E , minute ventilation; VCO_2 , carbon dioxide uptake.

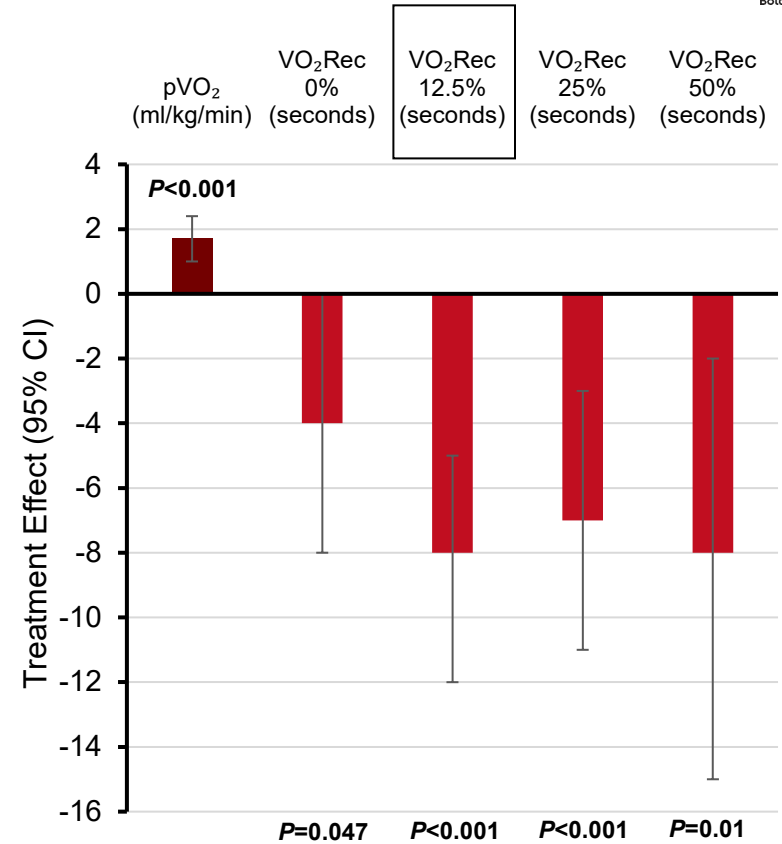
4. Coats CJ, et al. *J Am Coll Cardiol HF* 2024;12:199-215; 5. Maron M et al, *N Engl J Med* 2024;390:1849-61.

RESULTS

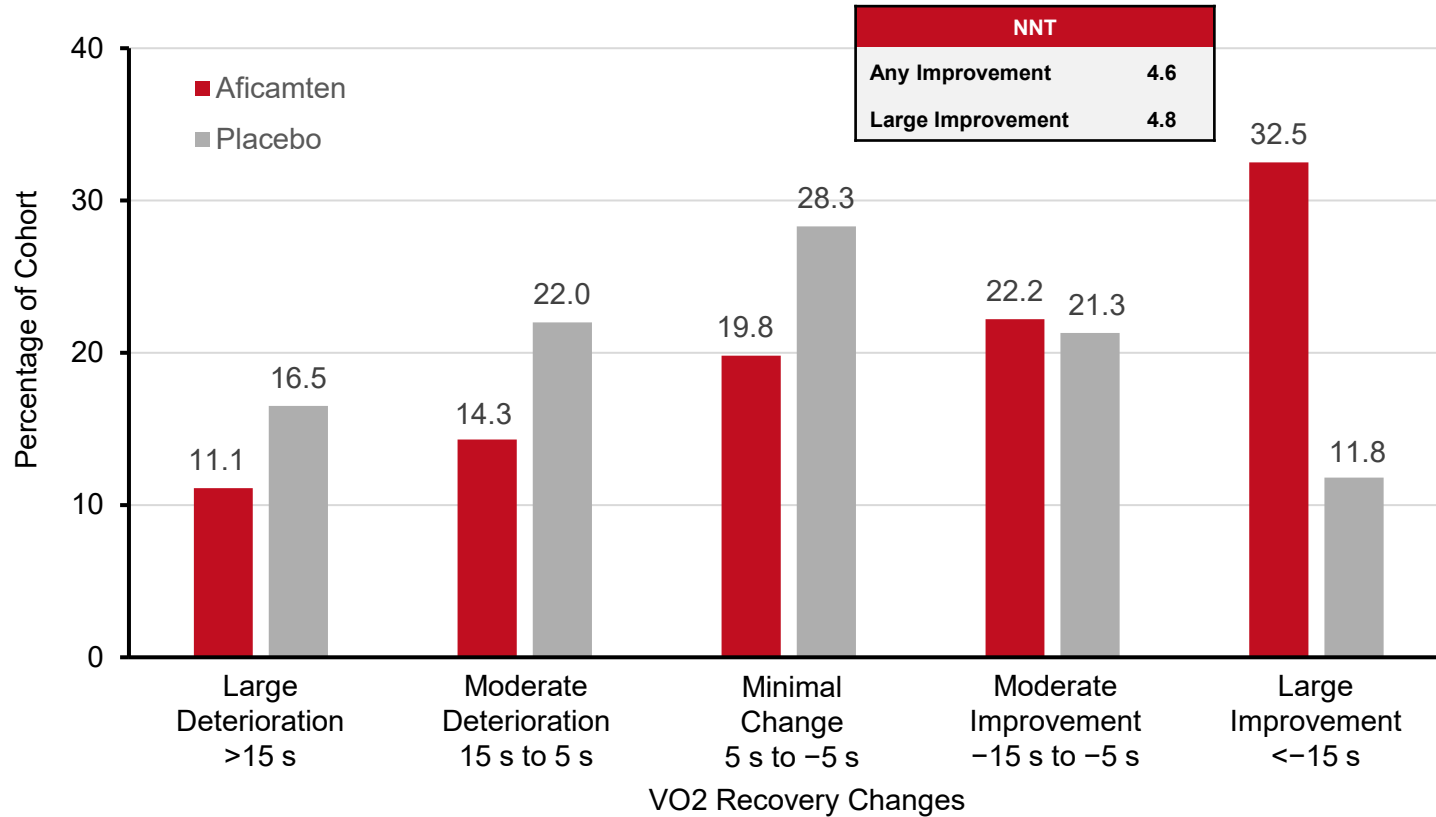
BL characteristics of participants in SEQUOIA-HCM

	All N=282	Aficamten n=142	Placebo n=140
Age, y	59.1 ± 12.9	59.2 ± 12.6	59.0 ± 13.4
Female, n (%)	115 (40.8)	56 (39.4)	59 (42.1)
BMI, kg/m ²	28.1 ± 3.7	28.0 ± 3.8	28.2 ± 3.7
pVO ₂ , (mL/kg/min)	18.5 ± 4.5	18.4 ± 4.4	18.6 ± 4.5
NYHA functional class, n (%)			
II	214 (75.9)	108 (76.1)	106 (75.7)
III/IV	68 (24.0)	34 (23.9)	34 (24.0)
Resting LVOT-G, mmHg	55 ± 29	55 ± 32	55 ± 27
Valsalva LVOT-G, mmHg	83 ± 32	83 ± 33	83 ± 32
NT-proBNP, median [IQR], pg/mL	788 [346, 1699]	818 [377, 1630]	692 [335, 1795]
hs-cTnI, median [IQR], ng/L	12 [8, 27]	13 [8, 34]	12 [8, 25]
KCCQ-CSS	75 ± 18	76 ± 18	74 ± 18
pVO ₂ , (mL/kg/min)	18.5 ± 4.5	18.4 ± 4.5	18.6 ± 4.6
Post-exercise VO ₂ Rec			
VO ₂ Rec 0%, s (n)	18.0 ± 20	19 ± 20	17 ± 19
VO ₂ Rec 12.5%, s (n)	45.1 ± 21.3	45 ± 20	45 ± 22
VO ₂ Rec 25%, s (n)	68.5 ± 24.1	66 ± 21	70 ± 27
VO ₂ Rec 50%, s (n)	116.0 ± 35.0	115 ± 32	116 ± 38

Values are means ± SD, unless otherwise shown.



RESULTS: VO₂Rec Responder Analysis in SEQUOIA-HCM



NNT, number needed to treat. Responder analyses of clinically meaningful changes in VO₂Rec T_{12.5%} with aficamten vs placebo at 24 weeks.

RESULTS

- In participants treated with aficamten, a decrease in $VO_2\text{Rec } T_{12.5\%}$ from baseline to Week 24 was associated with decreases in:

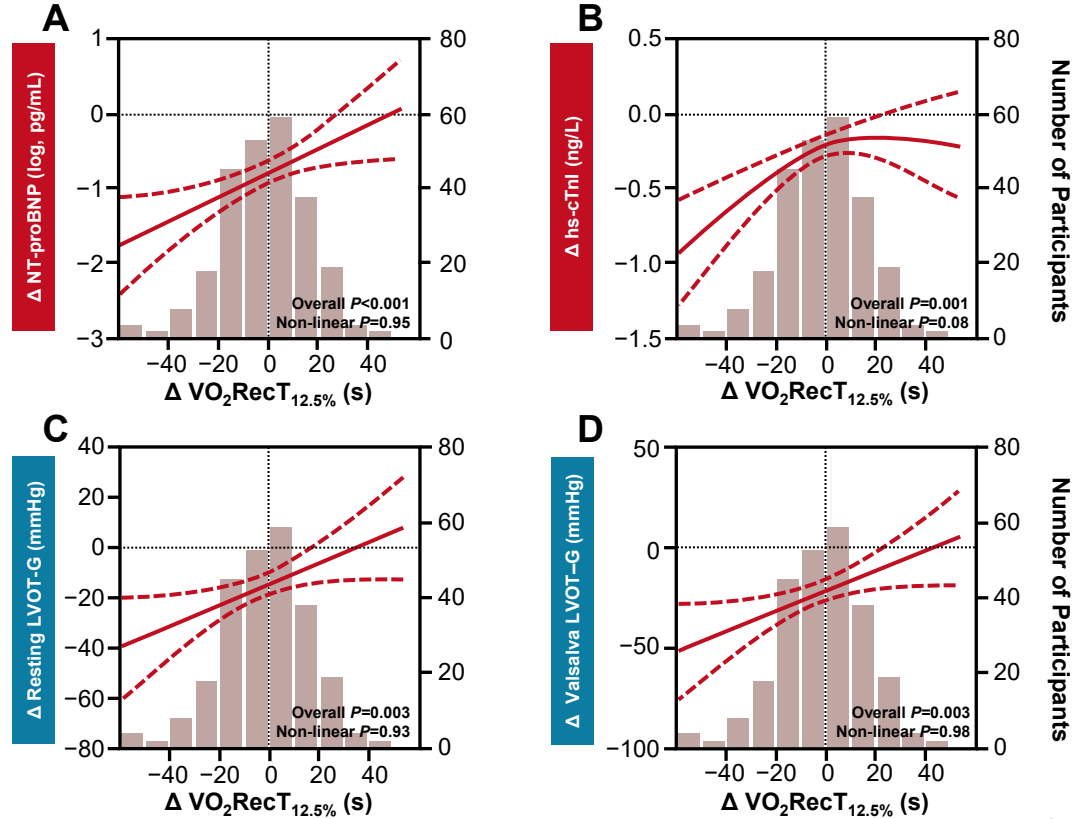
A: NT-proBNP concentration

B: hs-cTnI concentration

C: Resting LVOT-G

D: Valsalva LVOT-G

- $VO_2\text{Rec}$ decreased proportionately with improvements in cardiac performance.



Solid (dashed) lines show the association (95% CIs) between changes from baseline to Week 24 in $VO_2\text{Rec } T_{12.5\%}$ and cardiac biomarkers (A and B) or LVOT-G (C and D).

CONCLUSIONS

- This study is the first to comprehensively characterize $VO_2\text{Rec}$ in oHCM and to demonstrate its modifiability with aficamten.
- With aficamten treatment, $VO_2\text{Rec}$ ($T_{12.5\%}$) decreased proportionally and in parallel with other clinically important metrics of improved cardiac function (NT-proBNP, hs-cTnI, LVOT-G) assessed at rest.
- Identifying cardiac-specific parameters that are easily measured during non-invasive CPET is crucial for characterizing the impact of effective therapeutic cardiac interventions.
- The simplicity and relevance of $VO_2\text{Rec}$ $T_{12.5\%}$ supports its inclusion in routine CPET protocols for evaluating cardiac performance during exercise, and potentially as a clinical trial endpoint.

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