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_2Rec) is associated with adverse outcomes in severe heart failure.[2,3]

In heart failure, VO_2Rec increases proportionally with reduction in exercise cardiac output (CO).[2]

Neither VO_2Rec 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_2Rec proportionally with improvements in other measures of cardiac performance in patients with symptomatic oHCM.
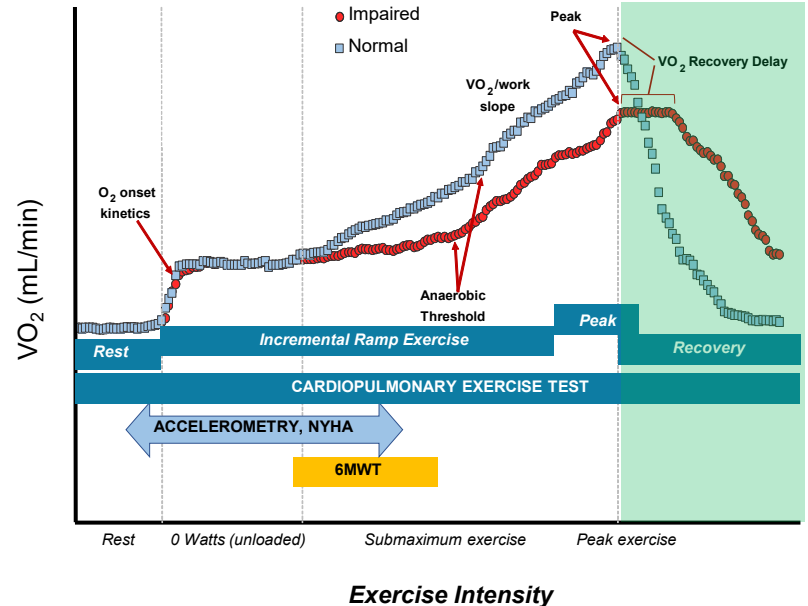
6MWT, 6-minute walk test; NYHA, New York Heart Association; VO_2, oxygen uptake.
1. Lewis GD, et al. *Circ Heart Fail* 2022;15(3):e008970; **2.** Bailey CS, et al. *JACC Heart Fail* 2018;6(4):329-39;
3. Cohn-Solal A, et al. *Circulation* 1995;91(12):2924-32.

METHODS AND MATERIALS

SEQUOIA-HCM Trial (NCT05186818):
282 participants with oHCM were randomized to aficamten or placebo plus background therapy

142 were randomized to aficamten

140 were randomized to placebo

Participants were treated for 24 weeks and underwent exercise testing at baseline and **Week 24**

or

Primary CPET endpoint:
• Change in pVO_2

Secondary CPET endpoints:
• VO_2 at Cardio
• V_E/VCO_2
• Exercise duration
• METS
• Circulatory power
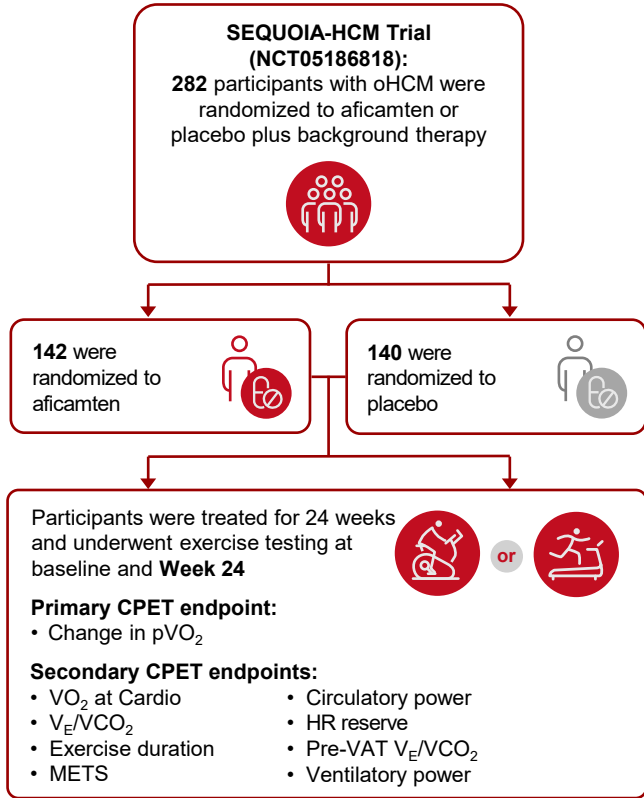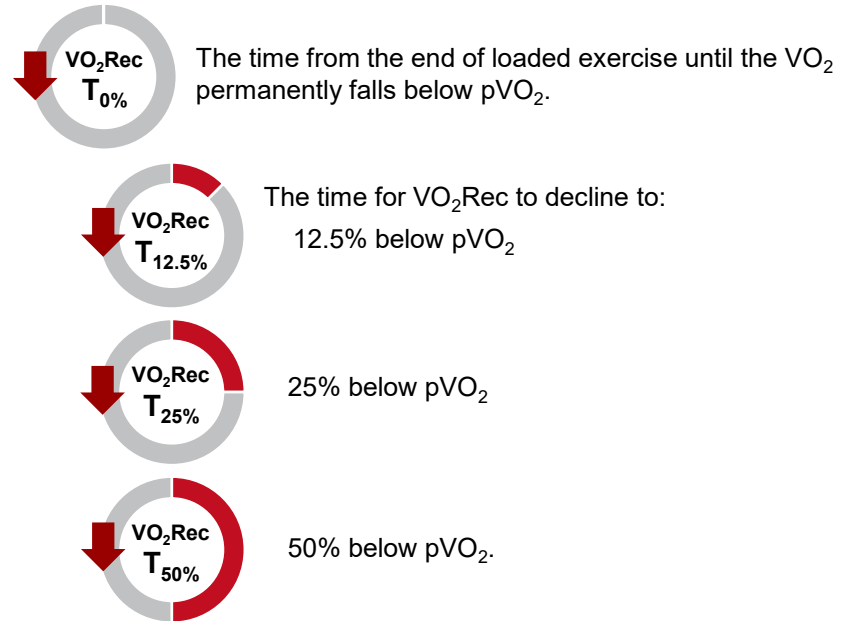• HR reserve
• Pre-VAT V_E/VCO_2
• Ventilatory power

Characterization of post-exercise VO_2Rec patterns was prespecified as an exploratory analysis in SEQUOIA-HCM.

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

VO_2Rec $T_{0\%}$ The time from the end of loaded exercise until the VO_2 permanently falls below pVO_2.

VO_2Rec $T_{12.5\%}$ The time for VO_2Rec to decline to:
  12.5% below pVO_2

VO_2Rec $T_{25\%}$ 25% below pVO_2

VO_2Rec $T_{50\%}$ 50% below pVO_2.

AT, aerobic threshold; HR, heart rate; METS, metabolic equivalent; pVO_2, peak VO_2; VAT, ventilatory anerobic threshold; V_E, minute ventilation; VCO_2, carbon dioxide uptake.
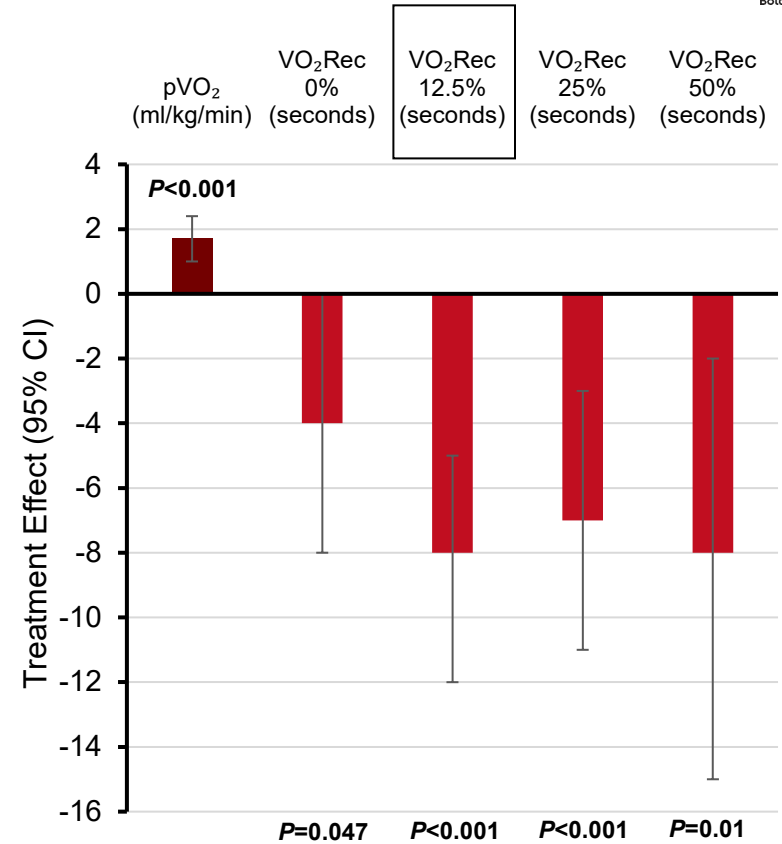**4.** Coats CJ, et al. *J Am Coll Cardiol HF* 2024;12:199-215; **5.** Maron M et al, *N Engl J Med* 2024;390:1849-61.
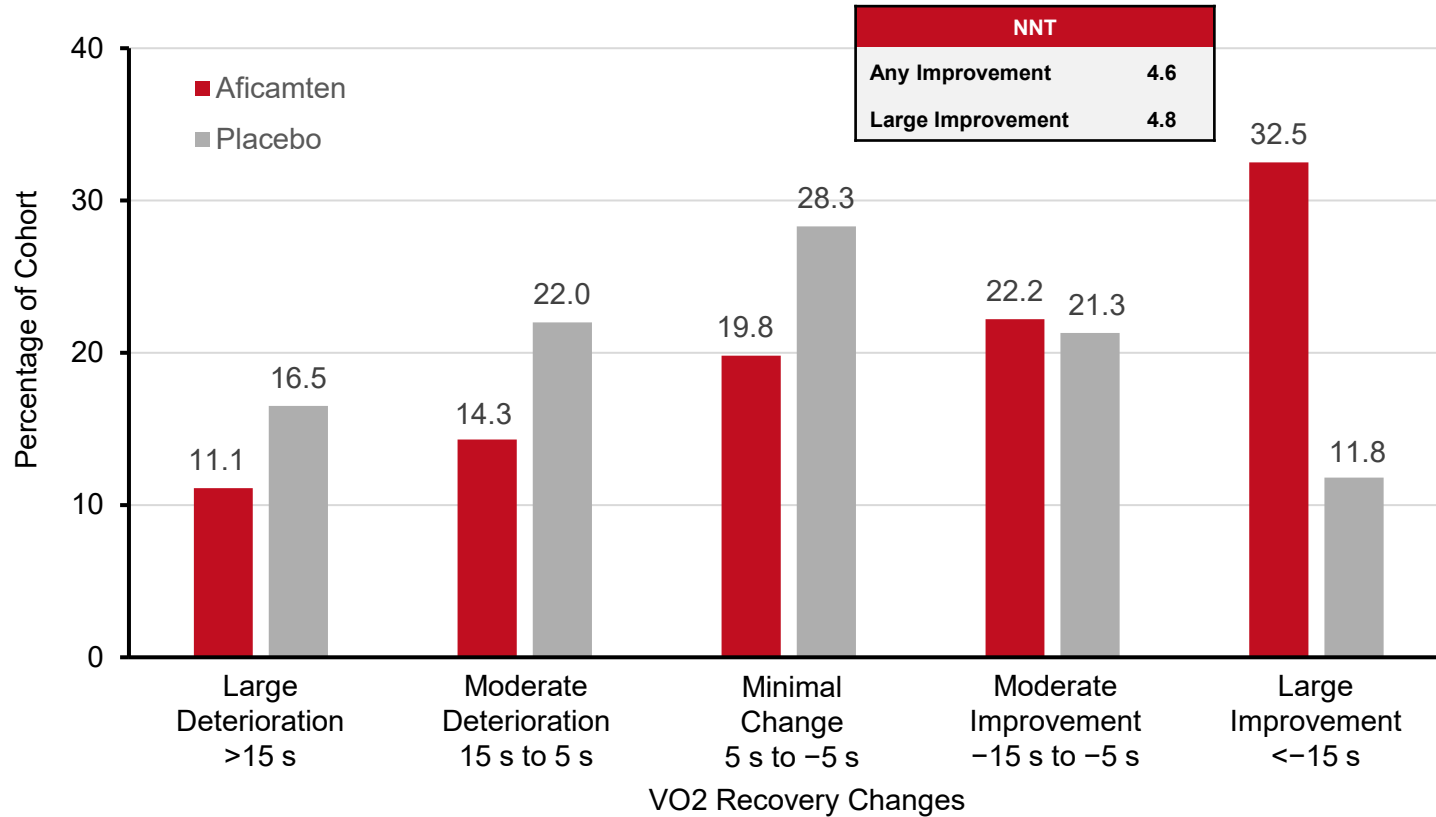
RESULTS

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.

BL, baseline; BMI, body mass index; hs-cTnI, high-sensitivity cardiac troponin I; IQR, interquartile range; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; LVOT-G, left ventricular outflow tract gradient; NT-proBNP, N-terminal pro B-type natriuretic peptide.

RESULTS: VO$_2$Rec Responder Analysis in SEQUOIA-HCM

NNT, number needed to treat. Responder analyses of clinically meaningful changes in VO$_2$Rec T$_{12.5\%}$ with aficamten vs placebo at 24 weeks.

RESULTS

- In participants treated with aficamten, a decrease in $VO_2Rec\ T_{12.5\%}$ from baseline to Week 24 was associated with decreases in:
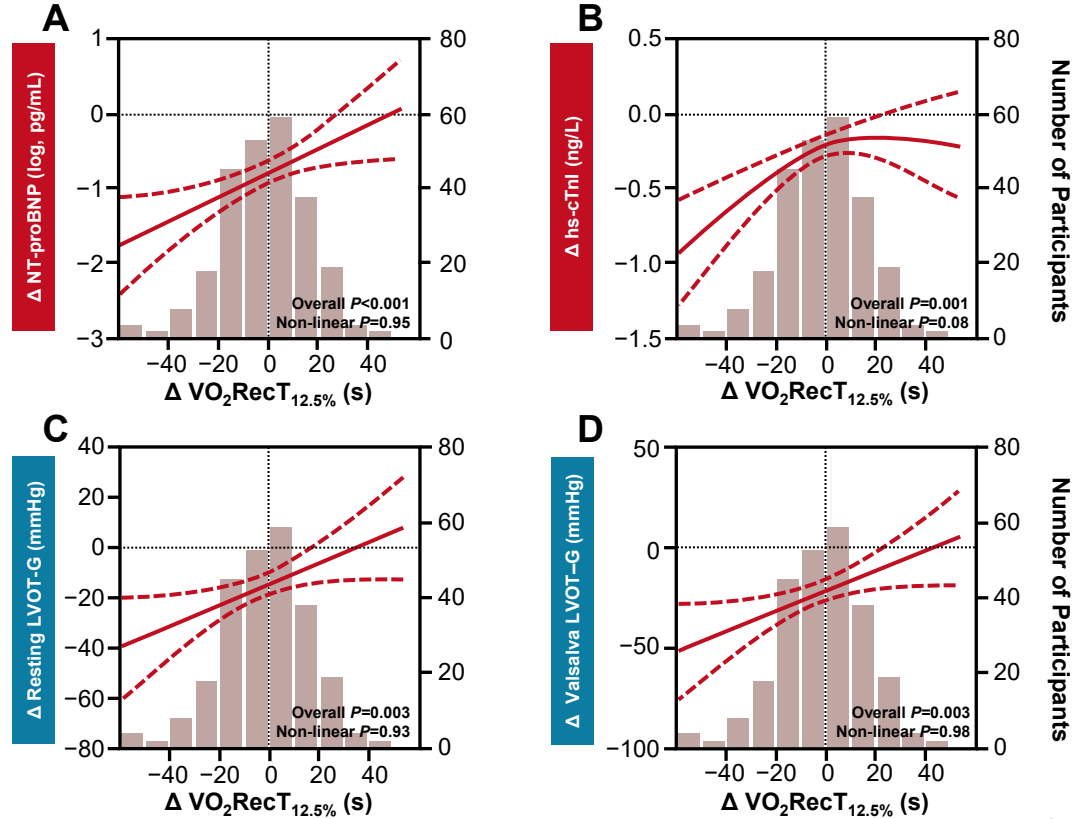
  A: NT-proBNP concentration

  B: hs-cTnI concentration

  C: Resting LVOT-G

  D: Valsalva LVOT-G

- VO_2Rec decreased proportionately with improvements in cardiac performance.

Solid (dashed) lines show the association (95% CIs) between changes from baseline to Week 24 in $VO_2Rec\ T_{12.5\%}$ and cardiac biomarkers (A and B) or LVOT-G (C and D).

CONCLUSIONS

- This study is the first to comprehensively characterize VO_2Rec in oHCM and to demonstrate its modifiability with aficamten.

- With aficamten treatment, VO_2Rec ($T_{12.5\%}$) 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_2Rec $T_{12.5\%}$ supports its inclusion in routine CPET protocols for evaluating cardiac performance during exercise, and potentially as a clinical trial endpoint.

ACKNOWLEDGMENTS