

# BILATERAL CONCENTRIC HEEL RAISE TEST: A NOVEL FUNCTIONAL ENDPOINT FOR EARLY STAGE CLINICAL TRIALS IN PERIPHERAL ARTERY DISEASE (PAD)

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## ABSTRACT

- Background:** Patients with peripheral artery disease (PAD) and claudication experience reproducible symptoms of leg pain during walking exercise. The symptom of claudication is due to exercise-induced ischemia of the muscles in the legs, most commonly in the calf muscles, limiting both walking distance and functional exercise capacity. Peak exercise performance during a standardized graded treadmill test is often used as the primary endpoint in clinical trials. The present report describes the experience and reproducibility of a novel heel raise test of muscle function and claudication-limited exercise performance in patients with PAD and claudication.
- Methods:** In a multi-center trial, 61 patients performed standing bilateral heel raises at 0.5 Hz until reaching calf muscle fatigue at three visits separated by 1 week. Ankle plantarflexion was monitored and recorded using a wireless goniometer. The number of heel raises, total work performed, time to the onset of claudication, and maximal exercise time were assessed.
- Results:** All patients (mean age: 67.3 ± 9.2 yrs) experienced claudication symptoms during heel raise testing. The mean number of heel raises to maximal claudication at the first baseline was 36.0 ± 23.1 repetitions. The mean time to intolerable claudication pain was 78.4 ± 48.14 seconds. The mean heel raise work index was 145.76 ± 74.31 kg-m. The Intra-class correlations were 78.7%, 76.3%, and 75.2% for heel raises, time, and total work, respectively.
- Conclusion:** The bilateral concentric heel raise test is a simple, specific, and reliable method for assessing muscle performance in patients with claudication. The use of the heel raise test in early phase “proof of concept” clinical trials may facilitate demonstration of clinical efficacy in patients with claudication without requiring treadmill procedures.

## INTRODUCTION

- Patients with peripheral artery disease (PAD) and claudication experience reproducible symptoms of leg pain during walking exercise.
- The symptom of claudication is due to the exercise-induced ischemia-perfusion mismatch of the muscles in the legs. Claudication pain is most commonly experienced in the calf muscles, limiting both walking distance and functional exercise capacity.
- Peak exercise performance measured as maximal walking time during a standardized graded treadmill test is the gold standard for assessing functional exercise capacity in PAD and is often used as the primary endpoint in clinical trials.
- Because of the local metabolic and hemodynamic perturbations in patients with claudication, it was assumed that a simple test of repeated bilateral heel raises would: 1) elicit leg claudication pain symptoms and 2) provide a functional assessment for symptom-limited muscular strength and fatigue.
- The present report describes the experience and reproducibility of a novel heel raise test of muscle function and claudication-limited exercise performance in patients with PAD and claudication.

## OBJECTIVES

- To determine the baseline characteristics and variance of the bilateral heel raise test among patients with PAD
- To determine the variance and intra-class correlation coefficients of heel raise test parameters among three repeated baseline measurements

## METHODS

- As part of a multi-center trial, the bilateral heel raise test was employed to assess symptom-limited muscle strength and fatigue at three visits, each separated by 1 week.
- Test instrumentation consisted of an electro-mechanical goniometer, handheld data processor, personal computer, and automated data collection software (Figure 1).
- The lateral aspect of the ankle on the dominant leg was instrumented with an electro-mechanical goniometer to assess ankle angle position and range of motion (Noraxon U.S.A., Inc., Scottsdale, AZ) (Figure 2).
- Ankle plantar flexion was monitored and recorded using the goniometer-handheld processor connected to a PC-based data collection system (Figure 3 inset).
- Patients were positioned standing in a clinic doorway and instructed to perform heel raises at the frequency as directed by a metered, audible cue (1 heel raise every other second ~ 0.5Hz) (Figure 3).
- Subjects reported the onset of claudication symptoms, and the test was performed to intolerable/maximal claudication pain and fatigue.
- The total number of heel raises, time, and a calculated index of work performed were assessed from the beginning of test to the onset of claudication and to maximal exercise.
- An index of work performed was calculated:
  - Heel Raise Work Index (HRWI) = (sinθ \* foot length) \* body mass
- The number of heel raises were defined as the number of heel raises achieving or exceeding 20 degrees of ankle plantar flexion (Figure 4).
- A mixed-effects model was employed (fixed effect of Visit and random intercepts for patients) to determine the intra-class coefficient (ICC) and evaluate potential differences among pre-treatment means of the repeated heel raise tests.

## METHODS (CONTD.)

Figure 1

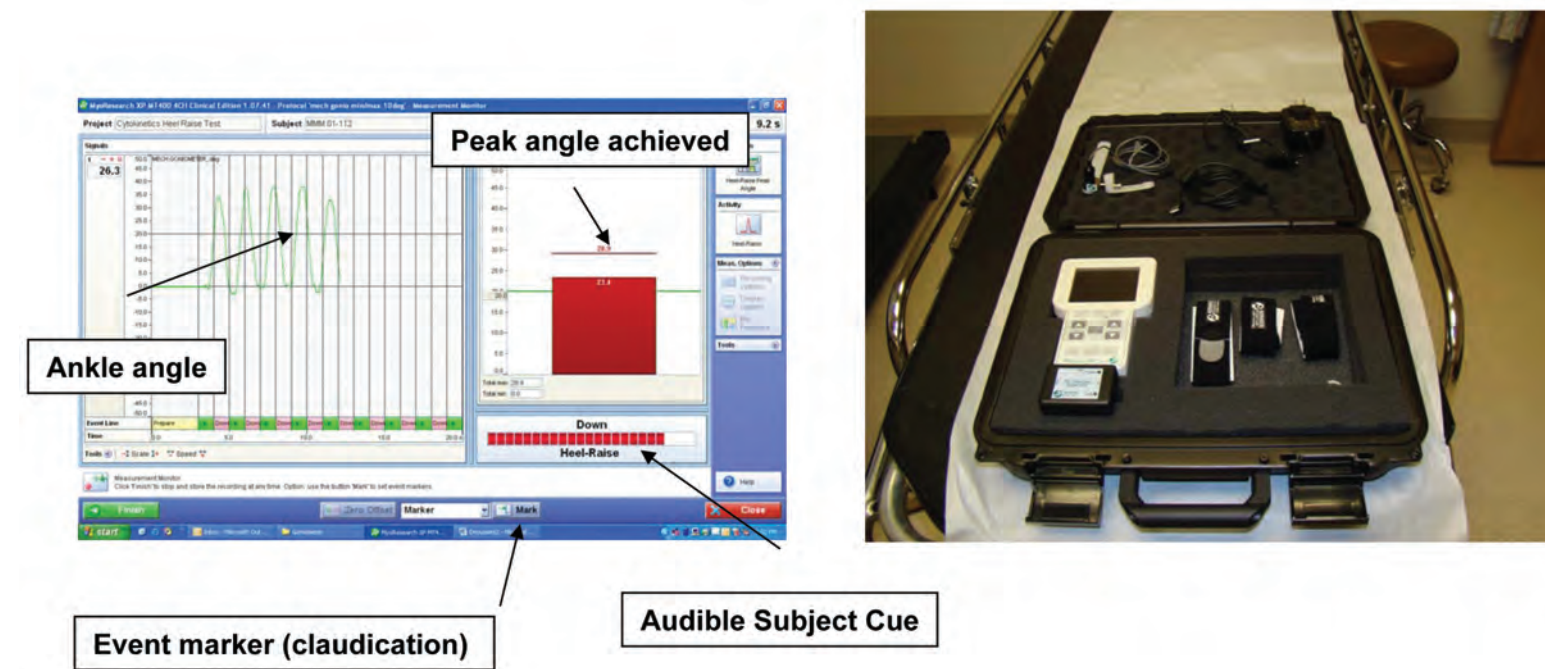


Figure 2

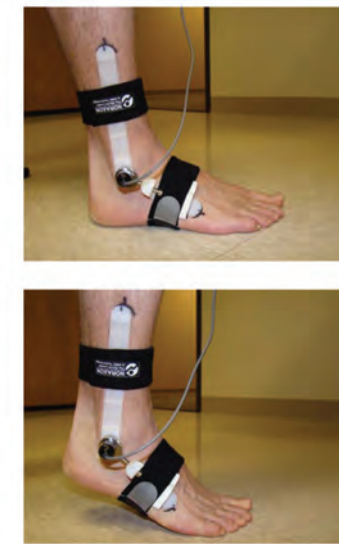


Figure 3



Figure 4: Example tracing of heel raise data obtained from test

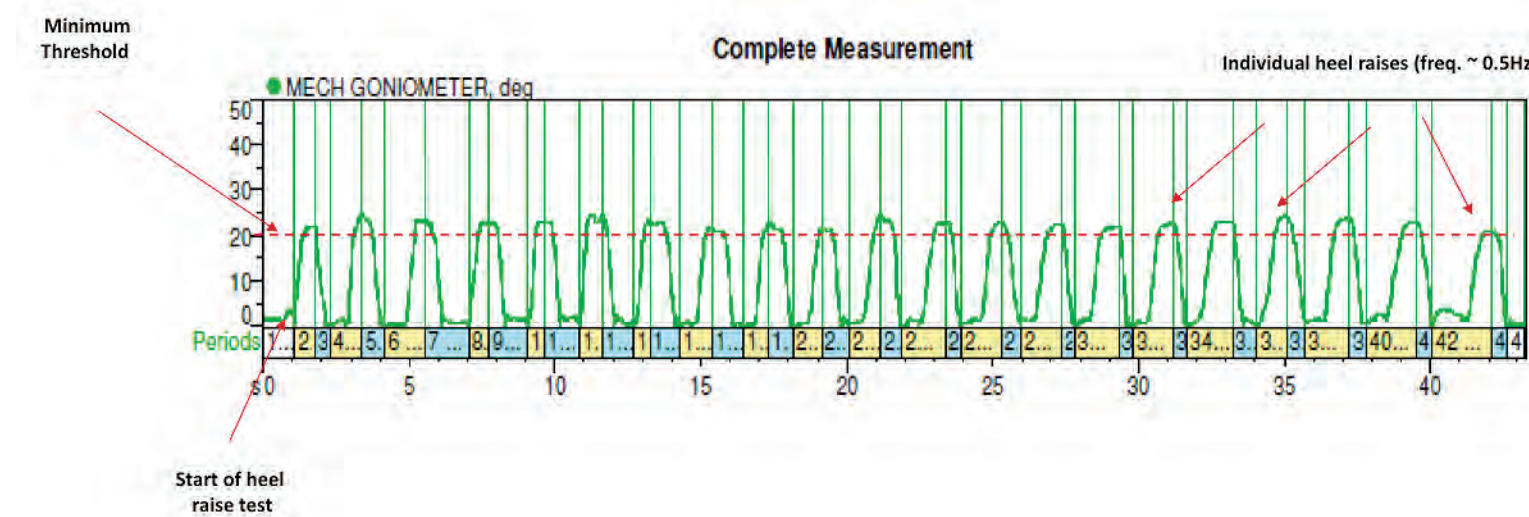
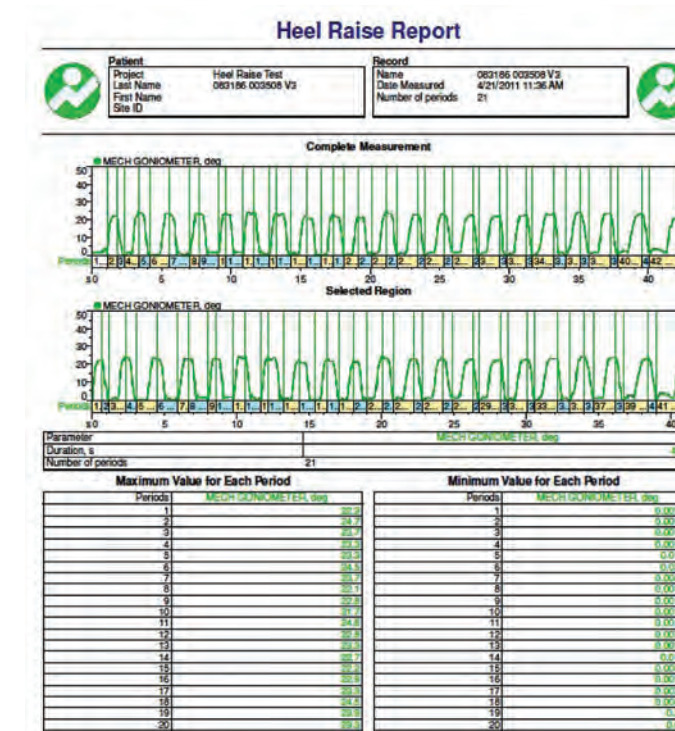


Figure 5: Sample report of heel raise test data



## RESULTS

Demographics N = 61 *Mean ± SD unless noted	
Age (Yrs)	67.3 ± 9.2
Weight (Kg)	76.96 ± 17.30
Currently smoking (%)	39.3%
Male (%)	85.2%

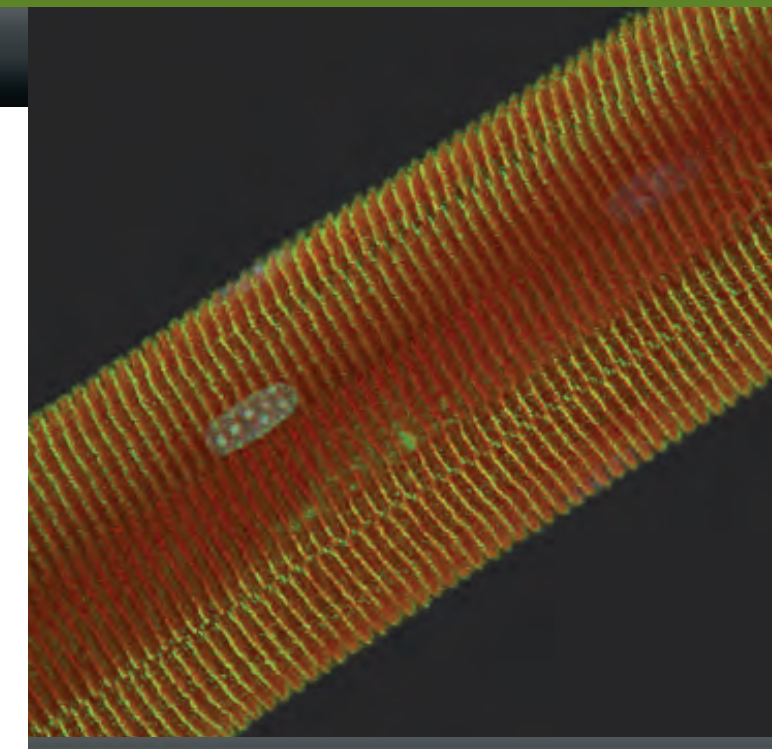
Intra-Class Correlation Coefficients	
Time to Claudication Onset	79.2%
Number of Repetitions to Claudication Onset	78.4%
Work Performed to Claudication Onset	72.2%
Time to Intolerable Claudication or Calf Muscle Fatigue	78.7%
Number of Repetitions to Intolerable Claudication or Calf Muscle Fatigue	76.3%
Work Performed to Intolerable Claudication or Calf Muscle Fatigue	75.2%

Heel Raise Test parameter by Visit				
Least squares mean ± SE	Visit 1	Visit 2	Visit 3	P-value*
Time to Claudication Onset (s)	44.2 ± 2.3	41.3 ± 2.3	44.2 ± 2.3	0.0972
Number of Repetitions to Claudication Onset (#)	20.8 ± 1.1	20.7 ± 1.1	22.5 ± 1.1	0.0527
Work Performed to Claudication Onset (kg-m)	86.7 ± 5.0	85.9 ± 5.0	96.8 ± 5.2	0.0155
Time to Intolerable Claudication or Calf Muscle Fatigue (s)	78.4 ± 6.0	70.9 ± 6.1	75.3 ± 6.2	0.1806
Number of Repetitions to Intolerable Claudication or Calf Muscle Fatigue (#)	36.0 ± 2.9	34.5 ± 2.9	36.9 ± 3.0	0.3361
Work Performed to Intolerable Claudication or Calf Muscle Fatigue (kg-m)	146.01 ± 9.68	142.39 ± 9.74	153.09 ± 9.95	0.5261

\* Comparison of least squares means computed by mixed effects model for differences between Visits

## CY 4022 INVESTIGATORS

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## CONCLUSIONS

- Bilateral heel raises performed according to a specified protocol elicited claudication pain in test subjects and provided a functionally relevant, easy-to-deploy, and cost effective measure of calf muscle endurance and fatigue in patients with PAD.
- The parameters assessed from a single bilateral concentric heel raise test demonstrated modest reliability among baseline measurements across a 3-week period in patients with PAD and claudication.
- The use of the heel raise test in early phase “proof-of-concept” clinical trials may facilitate demonstration of clinical efficacy in patients with claudication without requiring treadmill procedures.
- Comparison of bilateral heel raise tests with standardized treadmill testing will be needed to establish this test as a surrogate endpoint that parallels the current gold standard for functional exercise testing in the PAD population.

