# A Music-Guided Home-Based Claudication Rehabilitation Program

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## ABSTRACT

**Background:** We previously demonstrated that using rhythmic auditory stimulation (RAS) to accentuate the beat and increase the tempo of music immediately increased walking distance and distracted from pain in patients with claudication. We hypothesized that it would be feasible to tailor a home-based walking exercise program using rhythm-controlled RAS-enhanced music, and that this would improve total distance walked during a 6-minute walk test distance (6MWD).

**Methods:** This study was designed as a feasibility study in patients with lifestyle limiting claudication. We enrolled 12 participants (8 men, 8 black, age =  $65.4 \pm 7.8$  y, ankle brachial index =  $0.59 \pm 0.17$ ) in an RAS-enhanced, music-guided, home-based walking program, 3 times per week for 60 min per session. Repeated-measures mixed modeling with unstructured covariance matrix and robust standard errors were used to assess within-group treatment differences over time.

**Results:** At 6 weeks, 6MWD increased by 48 m ( $P \le 0.001$ ). At 12 weeks, similar patterns were noted, with an increase of 41 m in total walking distance (P=0.001). Subjective measures of physical function were significantly improved. Exercise adherence was 89%.

**Conclusion:** It is feasible to design a home-based exercise program for claudication by using the rhythmic and distractive properties of music to guide, facilitate, and progress exercise while maintaining a high level of adherence. *Journal of Clinical Exercise Physiology*. 2019;8(3):102–107.

Keywords: home-based exercise, peripheral artery disease, walking

## INTRODUCTION

Patients with peripheral artery disease (PAD) claudication pain deteriorate from a reduction in walking mobility to a complete loss of independence (1). Although supervised exercise rehabilitation programs improve functional status and are a Class I Recommendation (2), they are still limited in availability. Home-based PAD rehabilitation programs can be beneficial (3–5) but are challenging because patients typically stop walking prematurely and take prolonged rest periods because of claudication pain (6). This makes it difficult to obtain higher walking intensities and walking duration as is typical during supervised exercise rehabilitation. Motivation to maintain adherence to home-based exercise is

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FIGURE 1. Conceptual Model. Based on current guidelines, walking exercise training for claudication is performed to a level of moderate claudication levels (2 to 3 on the 1 to 5 claudication pain scale) within 7 to 10 min followed by a rest period until all claudication pain has dissipated (about 3 min) after which walking is resumed once again. This process is repeated for 45 to 60 min at least 3 times per week. By enhancing the rhythm and tempo of music we can increase walking speed (intensity). By using preferred music, we can distract from claudication pain. This combination enables us to increase the intensity of a given exercise training bout, reduce rest time, extend the duration of the exercise session, and provide an optimal exercise prescription.

typically lower than for supervised exercise (6), reducing adherence and resulting in less than optimal outcomes (7).

Listening to preferred music leads to dopamine and endogenous opioid secretion in the brain, thus reducing pain symptoms (9,10). Moreover, the use of rhythmic patterns entrain movement (8–11). This rehabilitative technique is known as rhythmic auditory stimulation (RAS). The motor response (i.e., walking) is subconsciously adapted to synchronize with the rhythm of the music (12,13). Enhancing the beat (RAS) and altering the tempo of music provide natural stimuli to speed up walking cadence. RAS music has been shown to distract from pain, enabling patients with claudication to walk further (see Figure 1) (14).

The purpose of this study was to examine the feasibility and effect of a 12-week RAS, music-enhanced, rhythm-controlled, home-based walking exercise program on walking ability in patients with claudication due to PAD. We hypothesized that it would be feasible to tailor a home-based walking exercise program using rhythm-controlled RAS-enhanced music and that this program would result in improved total distance walked during a 6-minute walk test (6MWT).

## METHODS

## Study Design

This was a feasibility study in which patients with lifestyle limiting claudication participated in a 12-week, home-based, RAS-enhanced, music-guided rehabilitation program.

## Sample

English-speaking participants (>18 years) with claudication due to PAD were recruited via directed mailing from 2 large metropolitan hospitals in the midwestern United States. Institutional Review Board approval was obtained at both sites. All patients provided informed consent prior to any study procedures. The presence of PAD was confirmed via a resting ankle brachial index of < 0.90 (15). Exclusion criteria were ischemic foot ulceration, exercise capacity limited because of conditions other than claudication, class III-IV heart failure, peripheral or myocardial revascularization within the previous 6 months, contraindications to exercise per American College of Sports Medicine (16), or inability to hear music.

## Procedure

Participants came to the laboratory 2 times at baseline and then for follow-up at 6 and 12 weeks. During the first visit, preferred walking cadence (steps/minute) was determined by having the participant walk at their usual, preferred walking speed for 30 seconds. Participants then completed a practice 6MWT to limit any learning effect (14). The 6MWT is a valid and reliable method for evaluating walking distance in patients with claudication (17). Subjective walking ability was assessed using the Walking Impairment Questionnaire (18), Peripheral Artery Disease Quality of Life Questionnaire (PADQOL) (19), PROMIS Mobility, PRO-MIS Pain-interference, and PROMIS Profile 57 (20). Participants were given an accelerometer (Actigraph GTX3; Actigraph Corporation, Pensacola, FL) to wear on their hips for 7 d to determine volume of daily physical activity (21). Participants also selected types of music that they did and did not enjoy listening to.

During the second visit, a second 6MWT was completed. This 6MWT was used as the baseline measure and follow-up measure at 6 and 12 weeks. RAS was not used during the 6MWT. The Actigraph GTX3 was collected, and the intervention was explained.

## **Exercise Intervention**

Participants were instructed to exercise at home, 3 times per week, progressively increasing the duration from 30 to 60 min over 12 weeks. The exercise program followed standard guidelines for exercise rehabilitation for claudication (2,22). Participants performed walking to a level of mild-moderate claudication pain (i.e., 2 to 3 on the 1 to 5 claudication pain scale) within 10 min, followed by resting until the claudication pain dissipated, followed by resumption of walking. Participants walked on their own in the community that they live in. We worked closely with each individual to identify places to walk in their community (e.g., mall walking, parks, Chicago trail system). Participants did not use treadmills during the study.

#### **RAS-Enhanced Music**

Participants were given an iPod loaded with playlists that consisted of RAS-enhanced music within their preferred genres. The playlist was altered using the Audacity® software so that the tempo of the music was increased to a tempo 10 to 15 beats per min higher than the patient's usual walking cadence (steps per minute). The bass of the music was enhanced to accentuate the rhythm (i.e., RAS-enhancement). Participants were instructed on how to use the playlist and headphones and walk to the beat of the music. Each participant was provided with numbered playlists that represented an increase in exercise intensity and duration (i.e., playlists with 2% to 5% increase in tempo). Participants were notified during the biweekly phone calls when they should switch to the new playlist to progress the exercise program. Each playlist was developed to allow for a progressive increase in exercise intensity (i.e., a warm-up tempo), followed by an overload phase (i.e., an overload tempo), and a cool down phase (i.e., a cool-down tempo).

#### **Exercise Adherence**

Participants used a Fitbit tracker for assessment of adherence. Step counts were synced automatically, and data were transmitted to an associated deidentified Fitbit account. Using the Fitbit, an exercise session was documented as completed, and adherence percentages were calculated in days per week exercised divided by recommended days x 100 (4).

## **Statistical Analysis**

Measures of central tendency were used to describe the sample. We developed a repeated-measures mixed model with unstructured covariance matrix and robust standard errors to assess within-group treatment differences over time. Pearson correlations were used to assess associations between change in walking distance and subjective measures of physical function and pain interference.

#### TABLE 1. Demographics (n=11).

Variable	Mean	Mean SD	
Age	65.4	4 7.8	
Pack/years	36.5	21.5	
Mean ABI	0.59	0.19	
Charlson score	3.0	1.9	
Weight (Kg)	84.7	12.5	
Height (cm)	178	8.5	
BMI (Kg·m <sup>-2</sup> )	26.0	5.2	
Variable	n	%	
Male	8	73	
Female	3	27	
White	4	36	
Black	7	64	
Diabetes	10	63	
CAD	2	18	
HTN	8	73	
Dyslipidemia	8	73	
PTA	3	3 27	
Smoking	7	64	
Medication	n	%	
Aspirin	5	45	
Antihypertensives	9 82		
Statin drug	7 64		
Antiplatelet	3	3 27	
Cilostazol	1 9		
Beta-blocking agent	4 36		

ABI = Ankle brachial index; BMI = body mass index; CAD = coronary artery disease; HTN = hypertension; PTA = previous percutaneous peripheral revascularization; SD = standard deviation; Antihypertensives = use of antihypertensive agent; Beta-blocking agent = use of beta-adrenergic blocking agent; Charlson score = Charlson comorbidity score (higher number: more comorbidities); Diabetes = type 2 diabetes; Pack/years = smoking in pack years; Smoking = currently smoking; White = non-Hispanic White.

## RESULTS

We enrolled 12 participants (8 men, 8 black, age= $65.4\pm7.8$  y, ankle brachial index =  $0.59\pm0.17$ ; Table 1). One participant was lost to follow-up and was subsequently excluded from all analyses. There were no adverse events related to the exercise rehabilitation program.

## Walking Distance

At 6 weeks, total walking distance increased by 48 m ( $P \le 0.001$ ), and functional claudication distance increased by 46 m (P = 0.13). At 12 weeks, distance increased by 41 m

TABLE 2. Rhythmic auditory stimulation rehabilitation.						
Variable	Baseline (n=11)	6-wk (n=11)	12-wk (n= 11)	MM B-6	MM B-12	
6MWT distance (m)						
Distance	339±84	387±62	380±70	< 0.001	0.001	
OCD	130±89	166±107	170±107	0.18	0.14	
FCD	310±123	356±106	353±111	0.13	0.13	
WIQ						
Distance	25±21	39±31	33±29	0.11	0.29	
Speed	35±13	50±25	43±24	0.07	0.32	
Stairs	54±26	57±30	67±25	0.60	0.13	
PADQOL						
Physical function	28±21	34±26	39±25	0.10	0.03	
PROMIS						
Physical function	42.1±6.9	42.7±5.5	44.8±5.6	0.77	0.04	
Pain interference	57.1±6.7	55.2±8.6	54.1±6.9	0.40	0.09	

6MWT = 6-minute walking test; B-6 = baseline to six-week follow-up; B-12 = baseline to 12-week follow-up; FCD = functional claudication distance; MM = repeated-measures mixed-model with unstructured covariance matrix and robust standard errors to assess within-group treatment differences over time RAS group only; OCD = onset to claudication distance; PADQOL = Peripheral Artery Disease Quality of Life Questionnaire; PROMIS = Patient-Reported Outcomes Measurement Information System; WIQ = Walking Impairment Questionnaire.

(P=0.001, Table 2), and 43 m in functional claudication distance (P=0.13).

## **Daily Physical Activity**

Daily physical activity expenditure, measured via actigraphy, increased from 239 to 260 Kcal•d<sup>-1</sup>, and the daily actigraphy step count increased from 2,589 steps to 3,480 steps per day.

## **Self-Reported Outcomes**

The PADQOL physical function limitation due to symptoms was improved by 11 units (P=0.03), and the PROMIS profile physical function was improved by 3 units (P=0.04). The PROMIS measures indicated a trend for reduction in pain interference (P=0.09). Change in claudication onset distance was strongly correlated with exercise adherence (r=0.87, P<0.001), and reduced pain-interference (r=-0.61, P<0.02).

## **Exercise Adherence and Satisfaction**

Participants completed a mean of 32 of the 36 (89%) prescribed home exercise training bouts. They were satisfied with the intervention and with the home-based exercise program (mean  $8.3\pm1.6$ ; Likert scale 0 to 10; 0=not satisfied to 10=extremely satisfied) and indicated that they enjoyed exercising to music very much (mean  $8.8\pm1.7$ , Likert scale 0 to 10; 1=not at all to 10=very much). No participants expressed a dislike of the RAS-music.

## DISCUSSION

We report that an RAS-enhanced, music-guided, homebased walking program for patients with claudication

improved 6MWT distance and subjective physical function. The observed increase in walking distances of 41 to 48 m is considered a large, clinically meaningful improvement (23) comparable to supervised exercise training rehabilitation (reported range 15 to 44 m). These findings support other home-based exercise training programs with increases of 20 to 40 m (3-5,24,25). Those home-based exercise training programs used weekly, structured, supervised exercise sessions and included extensive weekly cognitive-behavioral interventions, education, and support for a total of 90 min per week for 6 months or biweekly in-person meetings for 12 weeks. This constitutes a staff-intensive program and places a significant burden on patients, who need to attend weekly or biweekly hour-long classes. The HONOR trial compared the use of wearable technology (i.e., Fitbit) and telephone coaching to usual care and reported no difference in outcomes at 9 months (7). Investigators surmised that patients limited their exercise because of pain and that participants in the intervention group may not have increased their walking exercise. Our study results suggest that an intervention using RAS-enhanced music to guide and facilitate the home-based exercise program may increase home walking while distracting from claudication pain. We acknowledge that the Actigraph GTX3 captures total daily physical activity, and not only exercise training; therefore, the increase in energy expenditure could be caused by a spontaneous increase in physical activity in the RAS-walking group. There was no change in ratings of peak perceived exertion from baseline to follow-up testing at 6 and 12 weeks during the six-minute walk, suggesting that improvements in walking distance were caused by an increase in physical fitness levels and not level of exertion. This was supported by a nonsignificant decrease in peak exercise heart rate.

Adherence to the home-based exercise program was similar to those using in-person visits and cognitive-mediated interventions (4,5). Thus, this study demonstrated the feasibility of using an RAS-enhanced music-guided exercise training program to improve walking ability in patients with PAD.

## Limitations

This study was not designed to determine efficacy but to gain experience with the intervention methodology. We did not use a device to measure steps per minute. Future studies should assess regular step count using a device such as a stepwatch. The use of the Fitbit for adherence determination has only been validated for use in the general population. (26,27) Since the Actigraph GTX3 devices were mailed back after the participant's last research visit, we did not ask participants about reasons for nonadherence. Participants in the

#### REFERENCES

- 1. Widener JM. Peripheral arterial disease and disability from NHANES 2001-2004 data. J Vasc Nurs. 2011;29(3):104-12.
- Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, Fleisher LA, Fowkes FGR, Hamburg NM, Kinlay S, Lookstein R, Misra S, Mureebe L, Olin JW, Patel RAG, Regensteiner JG, Schanzer A, Shishehbor MH, Stewart KJ, Treat-Jacobson D, Walsh ME. 2016 AHA/ ACC guideline on the management of patients with lower extremity peripheral artery disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017;69(11):1465-508.
- Gardner AW, Parker DE, Montgomery PS, Blevins SM. Stepmonitored home exercise improves ambulation, vascular function, and inflammation in symptomatic patients with peripheral artery disease: a randomized controlled trial. J Am Heart Assoc. 2014;3(5):e001107.
- Gardner AW, Parker DE, Montgomery PS, Scott KJ, Blevins SM. Efficacy of quantified home-based exercise and supervised exercise in patients with intermittent claudication: a randomized controlled trial. Circulation. 2011;123(5): 491-8.
- McDermott MM, Liu K, Guralnik JM, Criqui MH, Spring B, Tian L, Domanchuk K, Ferrucci L, Lloyd-Jones D, Kibbe M, Tao H, Zhao L, Liao Y, Rejeski WJ. Home-based walking exercise intervention in peripheral artery disease: a randomized clinical trial. JAMA. 2013;310(1):57-65.
- Al-Jundi W, Madbak K, Beard JD, Nawaz S, Tew GA. Systematic review of home-based exercise programmes for individuals with intermittent claudication. Eur J Vasc Endovasc Surg. 2013;46(6):690-706.
- McDermott MM, Spring B, Berger JS, Treat-Jacobson D, Conte MS, Creager MA, Criqui MH, Ferrucci L, Gornik HL, Guralnik JM, Hahn EA, Henke P, Kibbe MR, Kohlman-Trighoff D, Li L, Lloyd-Jones D, McCarthy W, Polonsky TS, Skelly C, Tian L, Zhao L, Zhang D, Rejeski WJ. Effect of a home-based exercise intervention of wearable technology and telephone coaching on walking performance in peripheral artery disease: the HONOR randomized clinical trial. JAMA. 2018;319(16):1665-76.

#### CONCLUSION

We conclude that it is feasible to design a purposeful homebased exercise rehabilitation program for claudication by using the rhythmic and distractive properties of music to guide, facilitate, and increase the exercise while maintaining a high level of adherence.

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- Navratilova E, Porreca F. Reward and motivation in pain and pain relief. Nat Neurosci. 2014;17(10):1304-12.
- Nozaradan S, Peretz I, Mouraux A. Selective neuronal entrainment to the beat and meter embedded in a musical rhythm. J Neurosci. 2012;32(49):17572-81.
- Salimpoor VN, Benovoy M, Larcher K, Dagher A, Zatorre RJ. Anatomically distinct dopamine release during anticipation and experience of peak emotion to music. Nat Neurosci. 2011;14(2):257-62.
- Tsai HF, Chen YR, Chung MH, Liao YM, Chi MJ, Chang CC, Chou KR. Effectiveness of music intervention in ameliorating cancer patients' anxiety, depression, pain, and fatigue: a metaanalysis. Cancer Nurs. 2014;37(6):E35-50.
- Lim I, van Wegen E, de Goede C, Deutekom M, Nieuwboer A, Willems A, Jones D, Rochester L, Kwakkel G. Effects of external rhythmical cueing on gait in patients with Parkinson's disease: a systematic review. Clin Rehabil. 2005;19(7): 695-713.
- 13. Thaut MH, Demartin M, Sanes JN. Brain networks for integrative rhythm formation. PLoS One. 2008;3(5):e2312.
- Bronas UG, Everett S, Steffen A, Briller J, Hannan M, Hernandez A, Collins E. Rhythmic auditory music stimulation enhances walking distance in patients with claudication: a feasibility study. J Cardiopulm Rehabil Prev. 2018;38(4): E1-5.
- 15. Aboyans V, Criqui MH, Abraham P, Allison MA, Creager MA, Diehm C, Fowkes FG, Hiatt WR, Jönsson B, Lacroix P, Marin B, McDermott MM, Norgren L, Pande RL, Preux PM, Stoffers HE, Treat-Jacobson D; American Heart Association Council on Peripheral Vascular Disease; Council on Epidemiology and Prevention; Council on Clinical Cardiology; Council on Cardiovascular Nursing; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Surgery and Anesthesia. Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association. Circulation. 2012;126(24): 2890-909.
- 16. Pescatello LS, Arena R, Riebe D, Thompson PD. ACSM's guidelines for exercise testing and prescription. 9th ed.

Downloaded from https://prime-pdf-watermark.prime-prod.pubfactory.com/ at 2025-06-02 via free access

Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins; 2014.

- McDermott MM, Ades PA, Dyer A, Guralnik JM, Kibbe M, Criqui MH. Corridor-based functional performance measures correlate better with physical activity during daily life than treadmill measures in persons with peripheral arterial disease. J Vasc Surg. 2008;48(5):1231-7.
- Sagar SP, Brown PM, Zelt DT, Pickett WL, Tranmer JE. Further clinical validation of the walking impairment questionnaire for classification of walking performance in patients with peripheral artery disease. Int J Vasc Med. 2012;2012:10.
- Treat-Jacobson D, Lindquist RA, Witt DR, Kirk LN, Schorr EN, Bronas UG, Davey CS, Regensteiner JG. The PADQOL: development and validation of a PAD-specific quality of life questionnaire. Vasc Med. 2012;17(6):405-15.
- 20. Hays RD, Spritzer KL, Amtmann D, Lai JS, Dewitt EM, Rothrock N, Dewalt DA, Riley WT, Fries JF, Krishnan E. Upper-extremity and mobility subdomains from the Patient-Reported Outcomes Measurement Information System (PROMIS) adult physical functioning item bank. Arch Phys Med Rehabil. 2013;94(11):2291-6.
- Kelly LA, McMillan DG, Anderson A, Fippinger M, Fillerup G, Rider J. Validity of actigraphs uniaxial and triaxial accelerometers for assessment of physical activity in adults in laboratory conditions. BMC Medical Phys. 2013;13(1):5.
- 22. Bronas UG, Hirsch AT, Murphy T, Badenhop D, Collins TC, Ehrman JK, Ershow AG, Lewis B, Treat-Jacobson DJ, Walsh ME, Oldenburg N, Regensteiner JG; CLEVER Research Group. Design of the multicenter standardized supervised

exercise training intervention for the claudication: exercise vs endoluminal revascularization (CLEVER) study. Vasc Med. 2009;14(4):313-21.

- Perera S, Mody SH, Woodman RC, Studenski SA. Meaningful change and responsiveness in common physical performance measures in older adults. J Am Geriatr Soc. 2006;54(5): 743-9.
- 24. McDermott MM, Ades P, Guralnik JM, Dyer A, Ferrucci L, Liu K, Nelson M, Lloyd-Jones D, Van Horn L, Garside D, Kibbe M, Domanchuk K, Stein JH, Liao Y, Tao H, Green D, Pearce WH, Schneider JR, McPherson D, Laing ST, McCarthy WJ, Shroff A, Criqui MH. Treadmill exercise and resistance training in patients with peripheral arterial disease with and without intermittent claudication: a randomized controlled trial. JAMA. 2009;301(2):165-74.
- 25. McDermott MM, Ferrucci L, Tian L, Guralnik JM, Lloyd-Jones D, Kibbe MR, Polonsky TS, Domanchuk K, Stein JH, Zhao L, Taylor D, Skelly C, Pearce W, Perlman H, McCarthy W, Li L, Gao Y, Sufit R, Bloomfield CL, Criqui MH. Effect of granulocyte-macrophage colony-stimulating factor with or without supervised exercise on walking performance in patients with peripheral artery disease: the PROPEL randomized clinical trial. JAMA. 2017;318(21):2089-98.
- 26. Takacs J, Pollock CL, Guenther JR, Bahar M, Napier C, Hunt MA. Validation of the fitbit one activity monitor device during treadmill walking. J Sci Med Sport. 2014;17(5):496-500.
- 27. Noah JA, Spierer DK, Gu J, Bronner S. Comparison of steps and energy expenditure assessment in adults of fitbit tracker and ultra to the actical and indirect calorimetry. J Med Eng Technol. 2013;37(7):456-62.