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Peripheral artery disease (PAD) is an atherosclerotic disease that is associated with poor vascular function, walking impairment, and reduced quality of life. Land-based exercise therapy (LBET) is frequently recommended to improve walking and reduce symptoms. Recently, evidence has suggested that heated-water exercise therapy (HWET) is an effective intervention for PAD. How- ever, the efficacy of LBET versus HWET in PAD patients had not been elucidated. Therefore, we sought to compare effects of LBET with HWET on cardiovascular function, exercise tolerance, physical function, and body composition in PAD patients. PAD patients ($n$ = 53) were recruited and randomly assigned to a LBET group ($n$ = 25) or HWET group ($n$ = 28). The LBET group performed treadmill walking, whereas the HWET group performed walking in heated water for 12 wk. Leg (legPWV) and brachial-to-ankle arterial stiffness (baPWV), blood pressure (BP), ankle-brachial index (ABI), 6-min walking distance (6MWD), claudication onset time (COT), physical function, and body composition were assessed before and after 12 wk. There were significant group-by-time interactions ($P$ < 0.05) for legPWV, BP, 6MWD, COT, body composition, and resting metabolic rate (RMR). Both groups significantly reduced ($P$ < 0.05) legPWV, BP, and body fat percentage, and HWET measures were significantly lower than LBET measures. Both groups significantly increased 6MWD, COT, and RMR, and HWET group measures were

significantly greater than LBET measures. A time effect was noted for baPWV reduction in both groups ($P < 0.05$). These results suggest that both LBET and HWET improve cardiovascular function, exercise tolerance, and body composition, and HWET showed considerably greater improvements compared with LBET in patients with PAD.

**NEW & NOTEWORTHY** The results of this study reveal for the first time that although land-based exercise therapy is effective for reducing arterial stiffness and blood pressure in patients with peripheral artery disease (PAD), heated-water exercise therapy demonstrates greater benefits on vascular function. The greater improvements in muscular strength, time to onset of claudication, and exercise tolerance after heated-water exercise therapy may have clinical implications for improving quality of life in patients with PAD. The heated- water exercise therapy intervention demonstrated relatively higher exercise training adherence (~88%) compared with the land-based exercise intervention (~81%).

**KEYWORDS** atherosclerosis, aquatic exercise, pulse wave velocity, vascular disease

## INTRODUCTION

Peripheral artery disease (PAD) is estimated to affect nearly 200 million people worldwide, and the prevalence of PAD increases with age, affecting more than 20% of individuals over the age of 80 (63). PAD is a common atherosclerotic vascular disease, which includes a narrowing of the peripheral arteries supplying blood to the legs. This development of atherosclerosis associated with this condition results in impaired blood flow and oxygen delivery to the lower extremities (35). PAD is often characterized by vascular dysfunction and increased levels of arterial stiffness [pulse wave velocity (PWV)] (40), and atherosclerotic lesion formation is associated with increased arterial stiffness (78). We have previously reported that patients with PAD show increased levels of peripheral arterial stiffness that are specific to the lower extremity (56), and arterial stiffness contributes to increased blood pressure (BP) and a higher prevalence of adverse cardiovascular events such as myocardial infarction and stroke, although the causal role of arterial stiffness in these events is not entirely clear (2, 18, 40, 47). In fact,

elevated lower extremity PWV has been shown to reduce arterial blood flow to the lower extremity (69), be a major determinant of peripheral circulation (44), and contribute to leg symptoms such as claudication (71). Claudication, leg pain, is specifically known to impair walking ability, lower physical activity levels, and produce health-related quality-of-life scores lower than in patients with coronary artery disease and congestive heart failure (64, 82). Therefore, devising appropriate therapeutic interventions is in urgent need to improve arterial function, and targeting reductions in PWV while improving functional performance may be beneficial to improve overall quality of life in individuals with PAD.

Recent cumulating evidence supports the effectiveness of heated-water exercise therapy (HWET) as a rehabilitative and therapeutic strategy for individuals with cardiovascular mala- dies and functional limitations (10, 11, 16, 17, 26, 34, 59, 70). Because of the body's unique physiological responses to the heated-water stimulus, heated-water therapy can be incorporated to further enhance the benefits of exercise therapy. The heat increases circulating blood volume while decreasing pain and soft-tissue stiffness (36, 38). Additionally, the buoyancy component decreases weight-bearing stress (25), whereas drag can assist or resist movement that helps in muscle strengthening (25, 88). Furthermore, a number of cardiovascular adaptations have been reported after water immersion exercise therapy, including a greater decrease in catecholamine levels, sympathetic modulation, peripheral vascular resistance, and improvements in endothelial function and post-exercise hypo- tension when compared with land-based exercise therapy (LBET) (9, 29, 46, 52, 59, 60). We recently reported that beneficial cardiovascular adaptations occur from aquatic walking exercise in warm water (28 –30°C) (56). Considering the unique physiological responses and cardiovascular adaptations after exercise therapy in heated water, it is necessary to examine whether these adaptations provide greater benefits when compared with the adaptations in the clinically recommended LBET (commonly walking) as therapy for PAD. If HWET prevails as a more beneficial exercise modality, HWET may be a more ideal therapy for patients with PAD to better manage their pain and symptoms when compared with LBET. To our knowledge, no studies have investigated or compared the beneficial effects of HWET to LBET on PWV, BP, walking capacity, claudication onset

time (COT), and health-related quality of life in patients with PAD. This information may fill the gap in knowledge that must be addressed to optimize the current exercise treatments for PAD, potentially improving quality of life for these patients. Therefore, the aim of the current study was to investigate the effects of HWET compared with LBET on PWV, BP, ankle-brachial index (ABI), resting heart rate (HR), 6-min walking distance (6MWD), COT, muscular strength, physical function, resting metabolic rate (RMR), and body composition. We hypothesized that a HWET group would have greater improvements in PWV and BP compared with a traditional LBET group.

**METHODS**

*Participants.* Participants (mean age 65 ± 10, $n$ = 53) were recruited with flyers, referrals, and newspaper advertisements in a metropolitan city in South Korea at multiple community health centers, where the membership population was primarily female. Study allocation was determined randomly using a computerized random number generator (Fig. 1) to the HWET group or LET group. All participants were postmenopausal females (cessation of menses for >12 mo), sedentary, and classified as Fontaine stage II or III PAD with an ABI of $0.6 - 0.8$. Sedentary lifestyle was termed as taking part in <1 h/wk of regular exercise within the previous year. Exclusion criteria included stage IV PAD (tissue loss/gangrene), previous or pending revascularization procedure, hormone replacement therapy, current smoker (smoking within the previous 6 mo), and psychiatric conditions, as well as pulmonary, renal, and thyroid diseases. These exclusion criteria were incorporated to avoid potential secondary disease effects on the target population examined in this study. All exercise and experimental methods were conducted in accordance with approved protocols by the Institutional Review Board. All participants provided written, informed consent, and all procedures were performed in accordance with the Declaration of Helsinki. This study was registered with clinicaltrials.gov (NCT03849300).
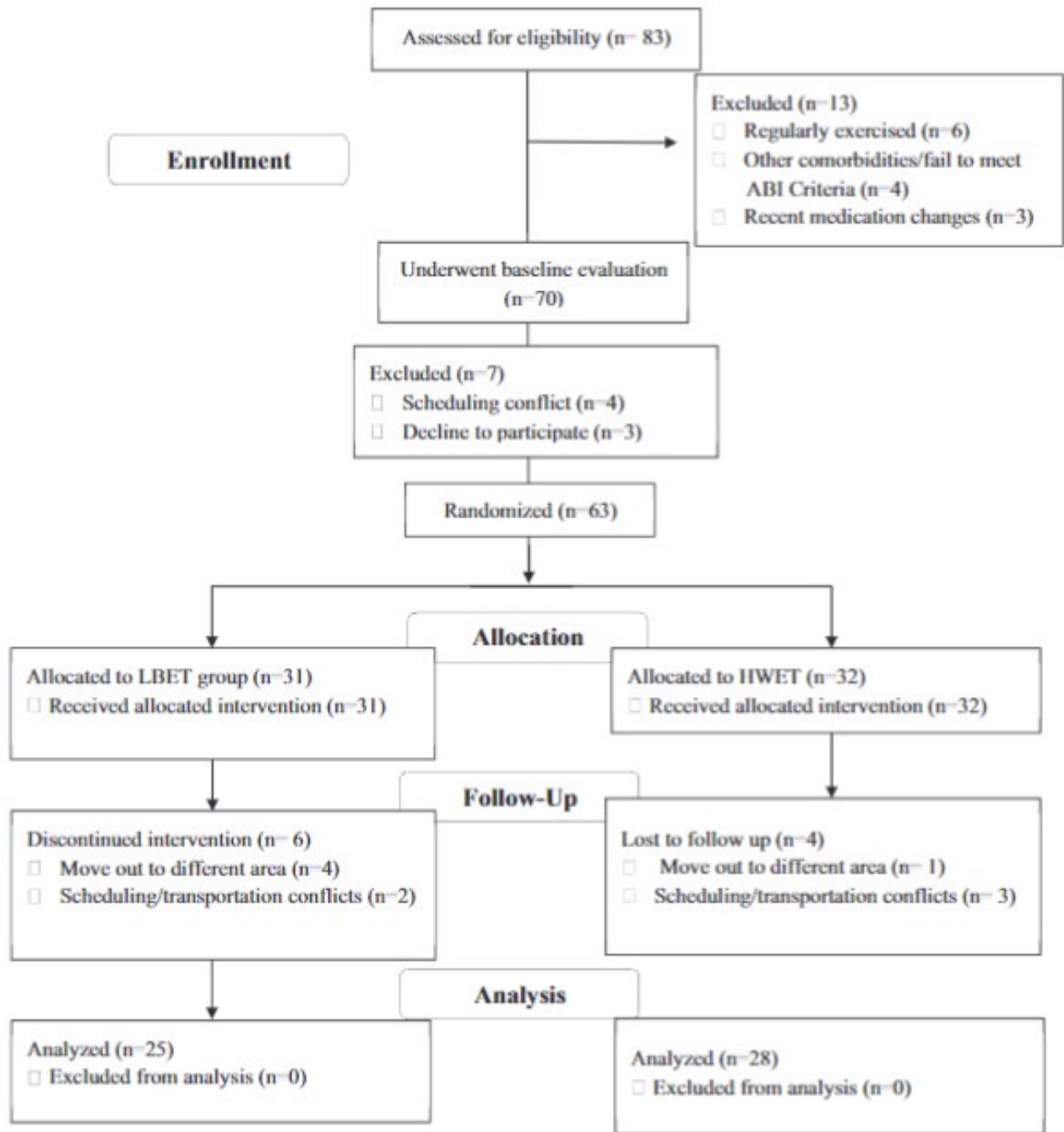
Fig. 1. Study allocation and flow. ABI, ankle- brachial index; HWET, heated-water exercise therapy; LBET, land-based exercise therapy.
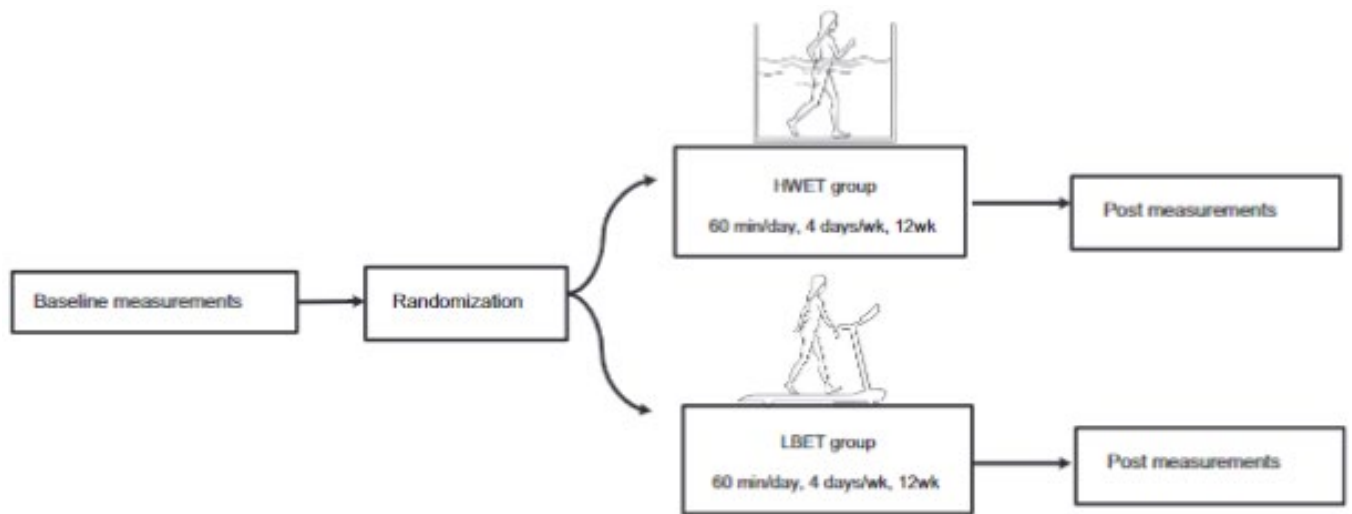
Fig. 2. Illustration of the study design for the heated-water exercise therapy (HWET; *n* = 28) and land-based exercise therapy (LBET; *n* = 25) groups.

*Study design.* A two-armed parallel experimental design was used (Fig. 2). Anthropometrics, vascular function, resting metabolic rate, walking capacity, COT, and muscular strength were assessed at baseline and after the 12 wk. All laboratory assessments were per- formed at the same time of day (8 AM, ± 1 h) following an overnight fast. All participants were asked to abstain from medications for >24 h before the baseline and post-exercise therapy measurements but continued taking medications throughout the exercise therapy proto- cols according to their physician instructions. After baseline measurements, participants were allocated randomly to the HWET group (*n* = 28) or the LBET group (*n* = 25). The HWET group participated in a supervised heated-water exercise therapy program for 12 wk. The LBET group participated in supervised treadmill therapy program for the same period of time. Both exercise groups were asked to refrain from altering dietary habits throughout the study period, and researchers obtained weekly diet logs from each participant to audit caloric intake. The exercise therapy sessions and experimental measures took place at the community centers. All participants were supervised by qualified trainers during exercise therapy sessions, and measurements were taken by experienced researchers who were blinded to participant randomization.

*Exercise programs.* The HWET group participated in a supervised heated-water exercise therapy program (Table 1) for 12 wk, 4 days/ wk, for 60 min/day. The 12-wk duration, exercise frequency, and intensity levels were programmed to be similar with previous water-based and land-based studies that demonstrated improvements in vascular function for older individuals and patients with PAD (3, 45, 54, 56, 87). Exercise sessions were performed in waist-to-chest-deep water (30 –31°C). HR was monitored using a standard chest strap Polar HR monitor (Polar Electro Oy, Kempele, Finland) during each exercise session to manage the appropriate training intensity level. Intensity was programmed using heart rate reserve (HRR) and Borg's revised rating of perceived exertion scale (RPE, 0 to 10 scale). HRR was calculated as (HRR = [%intensity desired X ($HR_{max}$ − $HR_{rest}$)] + $HR_{rest}$). Exercise intensity was increased every 4 wk: *weeks 1– 4* were at 50 – 60% HRR and 6 – 8 RPE, *weeks 5– 8* were at 60 –70% HRR and 6 – 8 RPE, and *weeks 9 –12* were at 70 – 85% HRR and 6 – 8 RPE. Exercise sessions were monitored by qualified trainers. Chest HR monitor

readings and RPE were checked every 5 min during the sessions. To maintain the appropriate intensity, if the HR or RPE was too low or too high according to the exercise program, the trainer encouraged participants to increase or decrease their effort during the session. The HWET program was divided into three components, including a warmup, main exercise section, and a cooldown. The warmup and cooldown included underwater stretching that emphasized major muscle groups and low-intensity gait training (forward, backward, and lateral movement) (3). The main exercises were performed for a total of 40 min. For the first 10 min of the main section, participants performed lower-limb movement patterns, including hip flexion/extension, hip abduction/adduction, and knee flexion/extension (3). The next 30 min of the main exercise session included water walking (3).

Table 1. *HWET program*

| Order | Exercise | Duration | Week | Intensity | Frequency |
|---|---|---|---|---|---|
| Warmup | Stretching | 10 min | | | |
| | Gait training | | | | |
| Main exercise | Hip flexion-extension | 10 min | 1-4 | 50-60% HRR; 6-8 RPE | 4 times/wk |
| | Hip abduction-adduction | | 5-8 | 60-70%; 6-8 RPE | |
| | Knee flexion-extension | | | | |
| | Water walking | 30 min | 9-12 | 70-85% HRR; 6-8 RPE | |
| Cooldown | Stretching | 10 min | | | |
| | Gait training | | | | |

HRR, heart rate reserve; HWET, heated-water exercise therapy; RPE, rating of perceived exertion.

The LBET group performed a supervised walking exercise program on a treadmill. The warmup and cooldown components included stretches similar to those in the HWET group, and the therapy program also lasted 12 wk, four times/wk, for 60 min/session (Table 2). The main exercise component consisted of simple movement patterns for 10 min that included low-intensity forward, backward, and lateral side-stepping movements on flat ground. The next 30 min included treadmill walking at the same intensity (HRR and RPE values) as in the HWET group. Target HRR and RPE

were achieved by adjusting the treadmill speed and incline grade. Participants with leg symptoms were encouraged to exercise to near-maximal leg symptoms until failure of walking.

Table 2. *LBET program*

| Order | Exercise | Duration | Week | Intensity | Frequency |
|---|---|---|---|---|---|
| Warmup | Stretching | 10 min | | | |
| | Gait training | | | | |
| Main exercise | Forward stepping | 10 min | 1-4 | 50-60% HRR; 6-8 RPE | 4 times/wk |
| | Backward stepping | | 5-8 | 60-70%; 6-8 RPE | |
| | Lateral stepping | | | | |
| | Treadmill walking | 30 min | 9-12 | 70-85% HRR; 6-8 RPE | |
| Cooldown | Stretching | 10 min | | | |
| | Gait training | | | | |

HRR, heart rate reserve; LBET, land-based exercise therapy; RPE, rating of perceived exertion.

*Anthropometrics.* Measurements of height, total body mass, and body composition were measured before and after 12 wk for the LBET and HWET groups. Height was measured using a standard stadiometer to the nearest 0.1 cm. Body composition was assessed using bioelectrical impedance analysis (BIA; InBody 230; Biospace, Seoul, South Korea). Total body mass (nearest 0.1 kg) and body fat (nearest 0.1%) were recorded. Body mass index (BMI) was calculated as body mass divided by the square of height (kg/m$^2$).

*Vascular function.* With participants in the supine position, ankle- brachial index (ABI) was recorded using the VP-2000 (OMRON Healthcare, Kyoto, Japan). Electrocardiogram (EKG) electrodes were placed on the forearms. BP cuffs with pulse wave sensors were wrapped around both arms (brachial artery) and ankles (posterior tibial artery). Measurements were recorded for 10 –30 s. Brachial-to- ankle pulse wave velocity (baPWV) was also recorded using the VP-2000, as previously described (89).

Femoral-to-ankle pulse-wave velocity (legPWV), a measurement of peripheral

arterial stiffness, was measured using applanation tonometry (TU-100 and VP-2000, OMRON Healthcare) (56). A tonometer was placed on the femoral artery, whereas the pulse wave sensor BP cuffs on the ankles and EKG electrodes remained in place from the ABI measurement. BP, EKG, and pulse waveforms were simultaneously recorded for 10 –30 s. Data analysis was performed according to the Clinical Application of Arterial Stiffness Task Force III (77).

Participants were then moved to a resting seated position. After 5 min of quiet sitting, the resting HR, systolic BP, and diastolic BP were measured in duplicate using radial artery palpation and an automated sphygmomanometer (BP-200; OMRON), respectively, before and after 12 wk of LBET and HWET. The average of the two measurements was recorded as the resting values. If the BP measurements differed by >5 mmHg, an additional measurement was taken, and the two readings that were the closest (differed by <2 mmHg) were averaged and recorded as the resting BP (58). The interclass correlation coefficient in our laboratory for systolic and diastolic BP calculated on two measurements is =0.97.

*Resting metabolic rate.* Resting metabolic rate (RMR) was calculated using a metabolic cart (OxyCon Pro; Viasys Healthcare, Conshohocken, PA). Subjects rested in the supine position on a padded table and were asked to breathe normally and to not fall asleep during the assessment. Measurements with the metabolic cart were per- formed for 30 min.

*Exercise tolerance and claudication assessment.* The 6-min walk test was used to determine 6-min walking distance or exercise tolerance. Participants were asked to walk as many laps as possible around a 60-meter track for 6 min. COT was measured during the 6-min walk test. Once the participants experienced any leg and/or foot pain during the walking test, they reported the pain to the trainers.

*Muscular strength.* Upper body muscular strength was quantified using a standard handgrip dynamometer to assess maximal isometric handgrip (JAMAR, Bolingbrook, IL). Measurements of the dominant hand were taken three times. The best value of the three trials was recorded as the hand grip strength value. Lower body muscular strength was quantified using leg extension one-repetition maximum (1RM) (Cybex 6000; Lumex, Albertson, NY). The 1RM was assessed using the dominant leg,

which was attained within five or fewer attempts. The highest weight lifted with proper form and full range of motion was recorded as the 1RM.

*Physical function.* Physical function was assessed collectively using physical function questionnaires from the Medical Outcomes Study Short-Form 36 General Health Survey (MOS SF-36) (83). This is a valid and reliable survey that is often used for patients with PAD (27, 30, 75, 83). Other parameters (i.e., not physical function domain) were not assessed using the MOS-SF 36.

*Statistical analysis.* The Shaprio-Wilk test was used to assess normality of the data. Independent $t$ tests were used to determine any baseline differences between the LBET and HWET groups. A two- way repeated-measure analysis of variance (ANOVA) [group (LBET and HWET) X time (pre- and post-12 wk)] was used to assess changes between pre- and post-LBET versus HWET within and between groups on the dependent variables. When a significant interaction was found, paired $t$ tests were used for post hoc comparisons. All analyses were performed using SPSS 24 (SPSS Inc. Chicago, IL). Statistical significance was set to $P < 0.05$. Data are presented as means ± SD. A power analysis calculation was used to determine whether the minimum sample size of 50 (25 in each group) would allow for the observation of a change of 3–5% between groups (LBET versus HWET) for legPWV with a power of 90% (4, 54).

## RESULTS

No participants in the LBET or HWET groups reported any unfavorable symptoms or adverse events resulting from either exercise therapy program. Baseline characteristics were not different between the LBET and HWET groups ($P > 0.05$; Table 3). Comorbidities included diabetes mellitus, hypertension, dyslipidemia, heart failure, and other conditions, including previous myocardial infarction, other cardiovascular anomalies (e.g., valve dysfunction, arrhythmias), and knee and/or hip arthritis, and participants were taking medications for their respective conditions and ailments (Table 4).There were significant group X time interactions ($P < 0.05$) for arterial stiffness, BP, RHR, 6-min walking distance, time to onset of claudication, leg strength, RMR, total body mass, and body fat percentage after 12 wk (Table 3 and Figs. 3 and 4).

After 12 wk of HWET, legPWV, baPWV, BP, RHR, total body mass, and body fat percentage significantly decreased ($P < 0.05$), whereas 6-min walking distance, time to onset of claudication, leg strength, and RMR significantly increased ($P < 0.05$) in HWET compared with LBET (Table 3 and Figs. 3 and 4). A time effect was noted in the LBET group for BP, legPWV, baPWV, and RHR, which significantly decreased ($P < 0.05$), whereas 6-min walking distance and leg strength significantly increased ($P < 0.05$) (Table 3 and Figs. 3 and 4). There were no significant changes ($P > 0.05$) in BMI, ABI, handgrip strength, or physical function scores after 12 wk (Table 3).

Table 3. *Participant characteristics before and after 12 wk of LBET (n = 25) or HWET (n = 28)*

| | LBET (*n* = 25) | | | HWET (*n* = 28) | | |
|---|---|---|---|---|---|---|
| | *Pre* | *Post* | *Δ* | *Pre* | *Post* | *Δ* |
| Age, yr | 60.0±10.0 | | | 60.0±9.0 | | |
| Height, cm | 158.8±4.6 | | | 156±5.8 | | |
| Body mass, kg | 56.5±5.7 | 53.5±7.8* | -3.0±2.1 | 55. ±7.4 | 53.9±8.5*† | -2.0±1.1 |
| BMI, kg/m² | 22.5±2.4 | 21.2±4.0 | -1.3±1.6 | 22.8±2.8 | 21.4±3.1 | -1.4±0.3 |
| Body fat, % | 29.7±3.6 | 28.7±6.1 | -1.0±2.5 | 30.5±3.9 | 28.5±5.2*† | -2.0±1.3 |
| Lean body mass, kg | 39.7±2.0 | 38.1±3.3 | -1.6±1.3 | 38.9±2.1 | 38.5±2.8 | -0.4±0.7 |
| ABI | 0.82±0.60 | 0.81±0.50 | -0.01±0.10 | 0.81±0.50 | 0.93±0.30 | 0.12±0.08 |
| RMR, kcal | 1222.0±40.0 | 1272.0±35* | 50.0±5.0 | 1211.0±56.0 | 1282.0±43*† | 71.0±13.0 |
| RHR, beats/min | 73.0±9.0 | 71.0±7* | -2.0±2.0 | 75. ±9.0 | 71.0±5*† | -4.0±4.0 |
| Systolic BP, mmHg | 135.0±16.0 | 129.0±10* | -6.0±6.0 | 134.0±12.0 | 126.0±9*† | -8.0±3.0 |
| Diastolic BP, mmHg | 88.0±9.0 | 85.0±10* | -3.0±1.0 | 88.0±10.0 | 84.0±8*† | -4.0±2.0 |
| Handgrip strength, kg | 26.0±4.0 | 27.0±5.0 | 1.0±1.0 | 25.0±4.0 | 26.0±3.0 | 1.0±1.0 |
| Leg strength, kg | 45.0±13.0 | 46.0±11* | 1.0±2.0 | 45.0±12.0 | 48.0±13*† | 3.0±1.0 |
| Physical function score, % | 47.0±29.0 | 53.0±25.0 | 6.0±4.0 | 46.0±30.0 | 55.0±27.0 | 9.0±3.0 |

Values are means ± SD. ABI, ankle-brachial index; BMI, body mass index; BP, blood pressure; HWET, heated-water exercise therapy; LBET, land-based exercise therapy; RHR, resting heart rate; RMR, resting metabolic rate. *$P < 0.05$, different from pre; †$P < 0.05$, different from LBET.

**DISCUSSION**

The objective of this investigation was to evaluate the effects of a 12-wk HWET intervention compared with a 12-wk LBET intervention on arterial stiffness, BP, RHR, walking performance, muscular strength, physical function, RMR, and body composition in individuals with PAD. We have several novel findings from this study. First, the present study confirmed that both HWET and LBET are useful exercise interventions to improve vascular function, body composition, and exercise tolerance in patients with PAD. Second, HWET improves vascular function and arterial health (primarily by improving arterial stiffness and BP) to a greater extent than those observed with LBET. Third, a greater improvement in walking performance, delayed COT, lower body strength, and reduced body fat percentage resulted after HWET when compared with the LBET intervention. The findings of this study suggest that HWET exercise therapy may be more effective than LBET as an intervention for improving arterial health, functional performance, and body composition in individuals with PAD.

*Vascular function.* It has been previously demonstrated that arterial stiffness can be reduced following aerobic exercise training in overweight adults, young adults with prehypertension, and patients with PAD (6, 42, 56). In this study, legPWV and baPWV significantly decreased following 12 wk of both LBET and HWET. Additionally, post-HWET legPWV was significantly lower than post-LBET legPWV after 12 wk, which suggests that HWET may be more effective for reducing leg arterial stiffness in this population. In accordance with our finding, Suntraluck et al. (68) showed that 12 wk of heated water immersion cycling can significantly reduce baPWV in older adults with type 2 diabetes mellitus. Additionally, these findings for reduced systemic and peripheral PWV in the present study may be clinically relevant. Although most re-search regarding clinical relevance for PWV focuses on aortic stiffness (8, 15, 86) and clinical relevance of PWV specific to the lower limb is not well understood, epidemiological data has reported that increases in baPWV by a mere 1.0 m/s are associated with a 12% increase in cardiovascular event risk (80). The observed reductions in the present study for baPWV in both LBET and HWET groups by ~0.7 m/s reveal that both training modalities may be clinically relevant for reducing risks of cardiovascular diseases and further disease manifestation in this population.

Furthermore, legPWV was reduced by ~1.0 m/s in the LBET group and ~1.2 m/s in the HWET group. Although there may have been a systemic vascular response to the exercise therapies, as indicated by baPWV in both groups, the results of legPWV may suggest that the lower limb adaptation may be more sensitive to the heated-water exercise therapy. These reductions in PWV following heated-water exercise therapy can be impacted by a variety of factors, such as improvements in endothelial function and improved micro- vascular function.

Table 4. *Participant Fontaine staging, comorbidities, and medications in the LBET (n = 25) and HWET (n = 28) groups*

|  |  | LBET (*n* = 25) | HWET (*n* = 28) |
|---|---|---|---|
| Fontaine staging |  |  |  |
|  | Fontaine stage II | 18 | 20 |
|  | Fontaine stage III | 7 | 8 |
| Comorbidity or condition other than PAD |  |  |  |
|  | Diabetes mellitus | 8 | 11 |
|  | Hypertension | 25 | 28 |
|  | Dyslipidemia | 18 | 15 |
|  | Arthritis | 19 | 22 |
|  | Cardiac/other vascular diseases | 9 | 8 |
| Medications |  |  |  |
|  | Angiotensin-converting enzyme inhibitors | 13 | 16 |
|  | Angiotensin II receptor blockers | 8 | 6 |
|  | Diabetic medication/insulin therapy | 8 | 11 |
|  | β-Blockers | 7 | 6 |
|  | Calcium channel blockers | 3 | 3 |
|  | Diuretics | 7 | 5 |
|  | Nonsteroidal anti-inflammatory medication | 17 | 19 |

HWET, heated-water exercise therapy; LBET, land-based exercise therapy; PAD, peripheral artery disease.
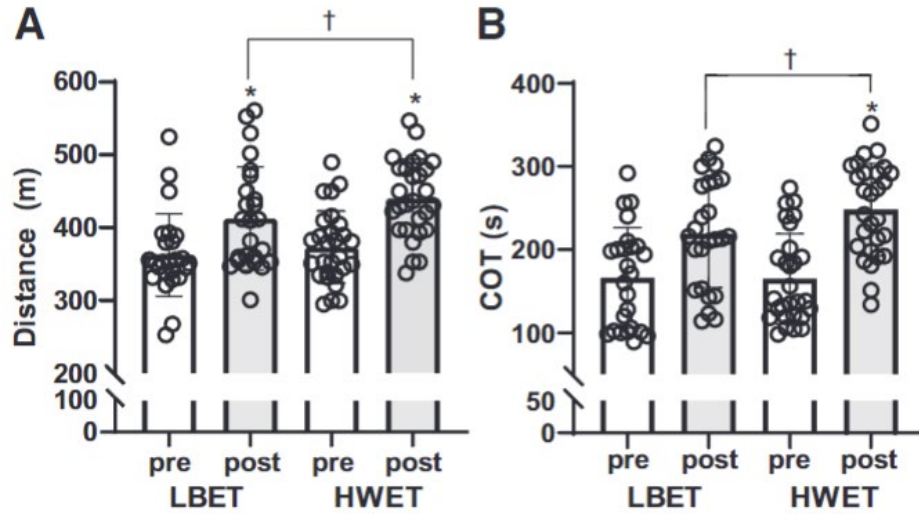
Fig. 3. Changes in 6-min walking distance and claudication onset time (COT) before and after 12 wk of land-based exercise therapy (LBET; $n = 25$) or heated-water exercise therapy (HWET; $n = 28$), as determined by the 2 X 2 repeated-measures analysis of variance (ANOVA) and Tukey's post hoc test. A: 6-min walking distance significantly increased in LBET and HWET after 12 wk, and post-HWET 6-min walking distance was significantly greater than post-LBET 6-min walking distance B: COT significantly increased in LBET and HWET after 12 wk, and post-HWET COT was significantly greater than post-LBET COT. Values are means ± SD. *$P < 0.05$, different from pre; †$P < 0.05$, different from LBET.
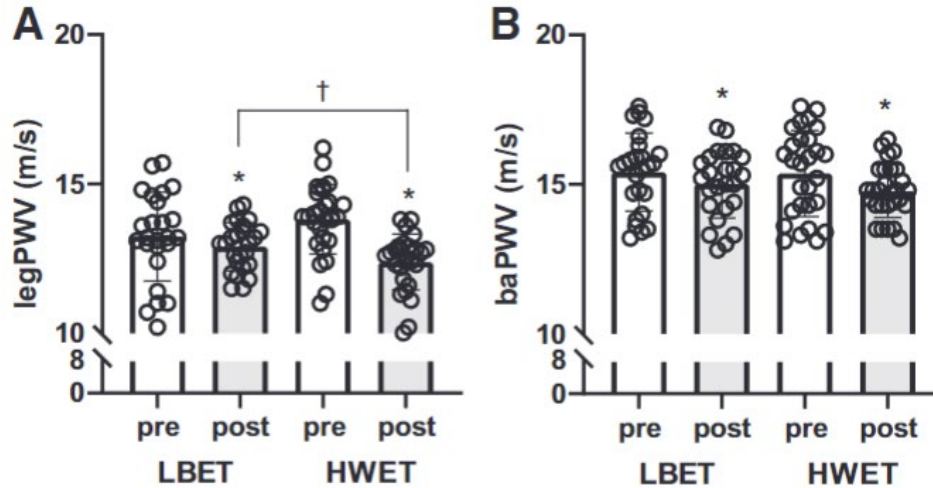
Fig. 4. Changes in femoral-to-ankle pulse wave velocity (legPWV) and brachial-to-ankle pulse wave velocity (baPWV) before and after 12 wk of land-based exercise therapy (LBET; $n$ = 25) or heated-water exercise therapy (HWET; $n$ = 28), as determined by the 2 X 2 repeated-measures analysis of variance (ANOVA) and Tukey's post hoc test. $A$: legPWV significantly decreased in LBET and HWET after 12 wk, and post-HWET legPWV was significantly lower than post-LBET legPWV $B$: baPWV significantly decreased in LBET and HWET after 12 wk, and post-HWET baPWV was significantly lower than post-LBET (post) baPWV. Values are means ± SD. *$P$ < 0.05, different from pre; †$P$ < 0.05, different from LBET. COT, claudication onset time.

Endothelial function has been reported to play a role in arterial wall smooth muscle tone and may influence arterial elasticity (55), and endothelial function has been shown to improve following heated-water exercise therapy protocols. Measurements of brachial artery flow-mediated dilation (FMD) and popliteal artery FMD, both nitric oxide (NO)-dependent measures of endothelial function (79), improved following 12 wk of heated water-immersion cycling and 3 mo of heated water rehabilitative exercise training (59, 68). Notably, the investigation by Quarto et al. (59) resulted in greater improvements in FMD in the heated water rehabilitative exercise training group (3 times/wk for 12 wk) compared with the treadmill training group in patients with PAD. In particular, shear stress has been reported to stimulate endothelial nitric oxide synthase (eNOS) phosphorylation (13), and popliteal artery shear stress has been shown to significantly increase during lower-limb heated water immersion in patients with PAD while favorably improving claudication symptoms (72). Therefore, in the present study, the HWET group may have experienced greater shear stress and NO-dependent response, both of which may have played a role in the greater reduction in PWV in the HWET group. Increased endothelium-derived NO specifically is a major factor in determining arterial elasticity and, therefore, may play a role in reduced PWV (43), and changes in NO bioavailability have been reported as a potential mechanism for reductions in PWV in previous studies (28, 45, 67), although the increase in NO bioactivity is often considered a short-term vascular adaptation in response to exercise training (33). Reductions in arterial stiffness may also be impacted in the long term to a greater degree by shear stress-dependent structural changes that induce vascular remodeling, such as increases in elastin and/or decrease in collagen fibers, increases in lumen diameter of conduit arteries, and increases in capillarization in response to

exercise training (33, 73). Addition- ally, a previous study reported that arterial shear stress has been shown to significantly increase in the lower limb during warm water immersion in patients with PAD (72). Therefore, the heated-water immersion component for the HWET group may have induced greater arterial structural change compared with the LBET group, which may have induced synergistic effects on PWV in conjunction with the exercise adaptation HWET group.

Another potential mechanism for the reduction in arterial stiffness may be due to improvements in microvascular function. Recent evidence reported microvascular dysfunction in patients with PAD (7), and microvascular dysfunction is associated with elevated arterial stiffness, which is thought to damage smaller vessels and contribute to increased peripheral vascular resistance that impairs blood flow in the skeletal muscle (61). Therefore, improvements in microvascular function may subsequently contribute to decreases in arterial stiff- ness. Treadmill exercise for 12 wk has been shown to be beneficial for improving microvascular function in older adults(39); however, results have been different for disease populations. Suntraluck et al. (68) demonstrated that 12 wk of heated water cycling exercise significantly improves microvascular function in patients with type 2 diabetes mellitus, whereas land-based cycling did not show these improvements. These authors suggested that a decrease in sympathetic vasoconstrictor activity during the heated water immersion therapy may have played a role in this microvascular improvement (68). Improvements in microvascular function in response to HWET may have also contributed to the greater decrease in arterial stiffness compared with LBET in the present study, although this mechanism warrants further investigation.

Increased BP has been reported as an important predictor for the risk cardiovascular event occurrence in patients with PAD (65), and nearly half of those diagnosed with PAD also have hypertension (21). Regarding the effects of HWET on BP, our findings showed reductions in systolic BP (Δ-8 mmHg) and diastolic BP (Δ-4 mmHg) that were greater in magnitude than the reductions seen in the LBET group. According to the latest American Heart Association guidelines, this decline in systolic

BP dropped the BP values of our participants from stage 1 to the elevated BP category (84). Data from a previous report by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure shows that in hypertensives, a reduction of 2 mmHg in resting systolic BP is associated with a decline in mortality from events such as stroke and myocardial infarction by 6% and 4%, respectively (19). Hence, the decrease of ~8 mmHg in resting systolic BP in the current study boasts important clinical implications in our hypertensive PAD patients, as it may translate into a reduction in cardiovascular mortality (19).

The greater reduction seen in HWET compared with LBET may be partially due to the significant reduction in body fat seen in the HWET group. Adipose tissue functions as an endocrine organ that is responsible for synthesizing and releasing autocrine and paracrine compounds to regulate vascular tone (22), and excessive accumulation of adipose tissue can result in overproduction of inflammatory adipokines and vasoconstriction (90). Overproduction of these inflammatory adipokines is thought to contribute to endothelial cell dysfunction, inflammation, and oxidative stress, and these factors are thought to significantly contribute to hypertension development (90). Additionally, an attenuation of the reninangioten-sin-aldosterone system may have played a role in the reduction in BP in the present study. Cruz et al. (23) showed that heated-water exercise therapy decreases plasma renin and aldosterone levels in subjects with resistant hypertension, and both decreased renin and aldosterone levels affect BP through reductions in extracellular fluid and systemic vascular resistance. However, the mechanisms of body fat, renin, and aldosterone reductions underlying the significant reduction in BP warrant further study.

*Walking distance and exercise tolerance.* For patients with PAD undergoing therapeutic interventions, it has been reported that the 6-min walk test is a better outcome parameter than treadmill tests (51). Walking distance was significantly improved in both groups, and the improvement in the HWET group was significantly greater than the LBET group improvement. Our finding is well-aligned with previous 12-wk HWET interventions, which showed significant increases in walking distance in both male and female subjects with PAD (3, 56). In fact, our finding is clinically relevant. The minimally clinically relevant difference (MCID) is a quantity that is representative of the

smallest threshold change that can be considered beneficial for patients (41). Gardner et al. (31) revealed the MCID for 6-min walk, stating that increases in 10, 25, and 40 m during the 6-min walk were identified as small, moderate, and large meaningful change, respectively. The LBET group demonstrated an increase of 40 ± 10 m following the 12 wk of treadmill training, which is considered to be a large meaningful clinical change. However, the HWET group showed an even greater change of 60 ± 39 m, which exceeds the minimum value for the large meaningful change. An increase in walking distance by ~60 m in particular has been reported to be clinically meaningful for improvements in quality of life and physical function in older adults (57). Therefore, the HWET intervention may be beneficial to a greater extent for improving quality of life and physical function in this population.

One of the major barriers for exercise participation and reduced physical activity in patients with PAD is the walking- induced pain called intermittent claudication (1). Therefore, improving the time to walking-induced leg pain may be particularly relevant for patients to continue exercise therapy for treating their symptoms. For exercise-training therapies, it has been recommended that the intensity of exercise is the most important factor that determines improvements in walking tolerance (32), and repeated walking to the onset of pain is frequently recommended for patients with PAD to improve their walking tolerance (35). In the present study, the improvements in COT in the LBET group and to a greater extent in the HWET group may be particularly beneficial. The COT was extended in both groups (LBET, Δ50 s; HWET, Δ85 s) following their respective exercise therapy. Therefore, both groups may have a greater capacity to exercise to their COT, with the HWET having an additional ~35 s to their pain-free walking time. Interestingly, HWET group reported relatively lower-rated perceived exertion (RPE), a quantification of exercise intensity, during exercise compared with LBET. This lower RPE may be partially due to several factors, including both the cardiovascular response and psychological perception of exercise intensity due to water immersion. Water immersion induces a decrease in peripheral vascular resistance and in- crease in cardiac output, which implies an increased peripheral vasodilatory response and peripheral blood flow (5, 12, 14), which may be evidence that supports a greater distribution of blood flow to the skeletal muscle. It has been shown

that blood lactate clearance rate increased when individuals were immersed in 30°C water following submaximal exercise, which may imply that blood flow in the skeletal muscle increases during 30°C water immersion (53). However, during exercise, core temperature and skin temperature may rise and cutaneous vasodilation may prevail to dissipate body heat. A previous study examined the impacts of acute land treadmill exercise (25°C air temperature) versus water-immersion treadmill exercise (25°C, 30°C, and 35°C water temperature), and these authors revealed that the 30°C water condition exhibited no significant differences in core or mean skin temperature com- pared with the land treadmill condition (62). Therefore, the temperature used in the present study (30 –31°C) likely did not induce a significant increase in core or skin temperature, which may not require a significant amount of cutaneous blood flow but may preferentially distribute blood flow to the working skeletal muscle. However, blood flow to the muscle and cutaneous perfusion were not assessed in this study and warrant further investigation.

Additionally, the buoyancy effect may have reduced perceived fatigue by mitigating gravitational forces acting on the musculoskeletal system (85), which may partially be a reason for the relatively lower RPE reported by the HWET group. The upward force exerted by the water helps support the body immersed in it, which may have played a role in reducing joint impact and strain during exercise (85), thereby reducing additional pain and/or discomfort experienced. This may have allowed for these participants to feel more comfortable and be able to exercise longer and at a greater intensity before they felt pain.

*Muscular strength.* In addition to improvements in walking distance and exercise tolerance, we also found significant improvements in leg strength in both exercise groups. Muscular strength is important for performing many activities of daily living, and strength is also strongly associated with protection against arterial stiffness, hypertension manifestation, and other cardiovascular disease conditions (48, 66, 87). In particular, leg strength has been shown to be associated with increases in functional performance and increased ABI in patients with PAD (50). Although significant improvements in leg strength were seen in both LBET and HWET groups, the HWET group showed leg strength that was significantly greater than LBET after 12 wk. This

may be partially explained by the water resistance component of the HWET program (24, 56, 76). Additionally, the increased resistance with water locomotion may lead to increased caloric expenditure compared with treadmill walking, which may account for the decrease in body fat percentage in the present study (81).

*Physical function.* Physical function is crucial factor for performance of daily living activities, and exercise therapy has been shown to be beneficial for improving physical function in older adults (20). Previous studies examining 3– 6 mo of treadmill training for patients with PAD reported significantly improved physical function measures (49, 75). We also previously reported that physical function scores were significantly improved following a 12-wk aquatic walking training program for patients with PAD (56). In the present study, we confirmed that both the HWET and LBET group improved physical function scores (HWET: Δ9.0 ± 3.0%, LBET: 6 ± 4.0%) following 12 wk of exercise therapy. However, the improvements were similar between the HWET and LBET group. Therefore, improved physical function may potentially allow patients with PAD to have improved physical performance and also to continue their physical activity for a longer period of time with less leg pain.

*Potential bias, strengths, and limitations.* The present study poses several strengths and limitations in addition to potential experimental bias. To avoid experimental bias in our exercise therapy protocols, our group performed the experiments in a double-blinded manner. *1*) We did not inform the trainers conducting the HWET and LBET exercise sessions of the study of the experimental hypotheses, *2*) the researchers per- forming the experimental measures before and after the 12-wk therapy program periods were blinded to the randomization of participants, and *3*) study participants were informed that the researchers were testing the effects of the specific exercise intervention that they were assigned (i.e., treadmill walking or heated-water walking), but the participants were not aware of the study hypotheses or previous pilot data.

The present study also had several limitations. First, the participant pool was limited to mild to moderate PAD (no tissue loss/gangrene, no stage IV PAD, no previous revascularization procedures), females, and nonsmokers. Therefore, the results of the present study may not be generalized to patients with severe PAD, males, or current

smokers. Further research is warranted to elucidate the effects of these exercise therapies on sex differences (74), disease condition, and PAD with other comorbidities. Second, the cardiovascular responses during the exercise therapy sessions were not directly investigated. Specifically, the blood flow redistribution to cutaneous, subcutaneous, and skeletal muscle regions during the exercise therapies was not examined, and future work warrants the examination of blood flow redistribution to skeletal muscle and skin using Doppler flowmetry and ultrasound. Third, the mechanism(s) that underlies the improvements in arterial stiffness was not directly investigated. Future work should focus on elucidating these potential mechanisms for improved vascular function, including changes in vasoactive substances, endothelial function, and/or assessment of structural changes within the vasculature (i.e., arterial diameter, formation of collateral vessels). Last, medications were not withheld throughout the exercise therapy interventions for either group. This may have limited the effectiveness of these exercise programs on the measures examined in the present study.

This study also poses several strengths to the design and perspectives for clinical application. A recent systematic re- view regarding supervised exercise program participation for claudicating patients reported that ~75% of patients completed their exercise programs (37), which may indicate that both the HWET and LBET adherence levels, ~88% and ~81% respectively, may be indicated as above average for participation and adherence. Although both groups demonstrated above average adherence, it has previously been shown that an adherence rate of ~84% is deemed as relatively high adherence in a similar PAD population participating in an exercise program of 12 wk duration (56). Therefore, it may be justifiable that the HWET group had a relatively higher adherence rate when compared with the LBET group.

*Conclusion and clinical implications.* The present study reveals that although both modes of exercise therapy, land- based exercise therapy and heated-water exercise therapy, are beneficial for patients with PAD, heated water-based therapy may be beneficial to a greater extent in comparison. HWET improved several measures to a greater extent when compared with LBET, including reductions in arterial stiffness, BP, and resting HR while improving walking distance, COT, and muscular strength. These

results support that HWET may be a beneficial exercise modality for the treating and preventing of further disease manifestation in patients with PAD.

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