CHAPTER XX.PERIPHERAL ARTERIAL DISEASE

INTRODUCTION

Peripheral arterial disease (PAD) or peripheral vascular disease commonly refers to the process of atherosclerosis in the arteries of the lower extremities. This atherosclerotic process causes the arteries to become narrow, hardened, and lead to obstruction or total occlusion of arterial blood flow (1). PAD can be both symptomatic and asymptomatic with approximately three asymptomatic patients for every one symptomatic patient (2). PAD is a common condition and estimates in 2015 demonstrated that the global prevalence was approximately 237 million (3). Total disease prevalence is approximately 3% of those aged under 50, rising to around 20% in those over 70 years of age (3). The manifestation and development of PAD is complex and multifactorial. There are a number of 'modifiable' (e.g. smoking, hypertension etc.) and 'non-modifiable' (age, ethnicity, sex etc.) risk factors that contribute to risk of disease and disease progression (4). The most 'classic' symptomatic manifestation of PAD is intermittent claudication (IC), which is classically characterised by a cramp-like pain, ache or burning sensation in the buttock, thigh or calf region during physical activity and relieved by rest (5). Generally, the site of pain can provide an indication of the site of disease (i.e. location of stenosis) (5). The pain is caused by an exercise-induced ischemia, whereby there is an imbalance between oxygen demand and supply at the muscle level (6). IC is often associated with significant reductions in walking capabilities, quality of life and physical activity levels.

DIAGNOSIS OF PAD

The diagnosis of PAD is established via patient history and general, clinical and lower limb examination. It can be confirmed by Doppler assessment of the ankle brachial pressure index (ABPI or ABI). The ABPI is defined as the ratio of systolic blood pressure measured in the arm (brachial artery) to that in the ankle. The ABPI has good sensitivity and specificity and can provide information regarding disease severity (7). In addition to Doppler assessment there are a number of imaging modalities that can provide anatomical localisation of disease. Duplex ultrasound assessment is widely regarded as the 'gold-standard' imaging modality (8). Other imaging modalities include magnetic resonance angiography or computerised tomographic angiography, often used prior to surgical intervention rather than for diagnostic purposes. The combination of examination, diagnostic testing and exercise testing can be used to classify patients. Two classification systems are currently utilised; Fontaine and Rutherford (2).

Table One: Fontaine and Rutherford classifications for peripheral arterial disease (9).

Fontaine		**Rutherford**		
Stage	**Clinical**	**Grade**	**Category**	**Clinical**
I	Asymptomatic	0	0	Asymptomatic
IIA	Mild claudication	I	1	Mild claudication
IIB	Moderate – severe claudication	I	2	Moderate claudication

		I	3	Severe claudication
III	Ischemic rest pain	II	4	Ischemic rest pain
IV	Ulceration or gangrene	III	5	Minor tissue loss
		III	6	Major tissue loss

ANKLE BRACHIAL PRESSURE INDEX

To accurately measure ABPI, patients should be in the supine position and rest for a period of 5 to 10 minutes (7). An appropriately sized blood pressure cuff should then be used for both sites (the arm and the ankle) to measure systolic blood pressure. The recommended width of the cuff should be at least 40% of the limb circumference (10). A small amount of electro-conductive ultrasound gel should be placed at the measurement sites; namely the brachial, the posterior tibial and dorsalis pedis artery. Anatomically, the posterior tibial artery can be palpated behind the medial malleolus and the dorsalis pedis can be palpated between the first and second metatarsal bones. A hand held 8 – 10 MHz Doppler ultrasound probe is placed at each site to detect any audible pulsatile blood flow. The blood pressure cuff should then be inflated above the pressure level where the audible signal is no longer detected and then slowly released until the signal returns. The pressure at which the signal returns should be recorded. This process is repeated at each site and in both lower limbs. The ABPI is then calculated by taking the highest systolic pressure in the lower limb (either posterior tibial or dorsalis pedis) and dividing it by the highest systolic pressure in the arms. A normal reading should be equal to or slightly higher than the systolic pressure in the arm, equating to a ratio of around 1.0. It should be noted that in some patients a pulse may not be detectable at both sites. In such cases, a single measure of either the posterior tibial or dorsalis pedis artery is acceptable. Some patients with long-standing diabetes or other disorders may have vascular calcification. This may cause falsely elevated systolic pressures due to the artery being non-compressible. Non-compressible values are defined as an ABPI >1.4 or systolic ankle pressure (>250mmHg). In this situation, a toe-brachial pressure index is required to provide an accurate measurement. To measure toe pressure a small cuff can be used on the first or second toe (2). An ABPI value less than 0.4 in the presence of other signs and symptoms can be associated with critical limb ischemia.

Table Two: Interpretation of the ankle brachial pressure index (7, 11).

ABPI	Interpretation
>1.4	Falsely elevated due to tibial artery calcification. Measure toe-pressures of evaluate tibial artery flow using duplex ultrasound
1.0 – 1.4	Normal
0.91 – 0.99	Borderline. Need to obtain exercise treadmill testing if exercise-induced calf pain is present
<0.9	Abnormal. Peripheral arterial disease
0.7 – 0.9	Mild arterial occlusive disease
0.4 – 0.7	Moderate arterial occlusive disease. “Typical ABPI range in claudicants”
<0.4	Severe arterial ischemia. Critical limb ischemia when associated with systolic toe pressure <30 mmHg, rest pain or non-healing ulcers.

EXERCISE TESTING IN PATIENTS WITH PERIPHERAL ARTERIAL DISEASE

Whilst ABPI is an important diagnostic test, in some cases patients with PAD may have a normal ABPI at rest. Furthermore, ABPI is a poor predictor of walking performance in patients with symptomatic disease. Therefore, the assessment of resting ABPI alone is inadequate for assessing the impact of disease on a patient's functional impairment. For this reason, exercise testing should be used for further diagnosis. Outcome measures for patients with PAD typically comprise of pain-free walking distance (PFWD) and/or time (defined as the walking distance or time when patients report the first experience of pain, aching or burning in calves or buttocks) and maximum walking distance (MWD) and/or time (defined as the walking distance or time which patient's cannot continue due to maximal pain). Patients may also report a 'claudication pain score' during exercise testing ranging from 1 = no pain, up to 5 = severe pain (or a 0 to 4 scale in some clinical practices).

TREADMILL WALKING TESTS FOR PATIENTS WITH PERIPHERAL ARTERIAL DISEASE

Walking capacity is considered an important clinical outcome in PAD and treadmill tests can be used to assess the impact of the disease on functional impairment and the efficacy of clinical therapeutic interventions in this population. There are two different treadmill protocols that are often used in PAD: constant-load (single-stage) and graded exercise testing.

Constant-load treadmill tests are performed at a single work rate with a variation of 2 to 4 km/h and 10 to 12% for speed and grade, respectively. Graded protocols are performed at the same speed but with a variation on treadmill grade at predetermined intervals, (e.g. speed at 3.2 km/h with increase in grade by 2% every 2-3 min). The two most commonly used include the Hiatt (3.2 km/h and 3.5% increase in grade every 3 min) (12) and the Gardner/Skinner protocol (3.2 km/h and 2% increase in grade every 2 min)(13).

Conducting the Exercise Test

Treadmill walking exercise test must be performed under standardized and reproducible conditions. Patients should be asked to refrain from any exercise, avoid smoking cigarettes and drinking alcohol at least 24 hours before the test. It is also important to make sure that patients are familiarized with the treadmill before conducting a formal test for analysis to reduce the learning effect. During the test patients must be instructed to walk until maximal levels of pain. If patients terminate for other reasons, this should be recorded as this would not be a true reflection of MWD. It is also good practice to cover the stop watch and / or face of the treadmill so that patients cannot see the duration of exercise.

As patients with PAD often have additional comorbidities and systemic atherosclerosis, electrocardiogram and blood pressure monitoring during maximal treadmill exercise tests is recommended to enhance patient safety and help to detect possible coexisting cardiovascular diseases.

Constant-load vs graded treadmill exercise testing

Constant-load protocols are easier to perform as a programmable treadmill is not required. However, they present low reliability with coefficients of variation of 30% to 45% for PFWD and MWD, respectively (14). This is typically due to the heterogeneity of clinical characteristics of PAD patients, with some unable to walk 50 meters whereas others have minimal physical activities restrictions (able to walk more > 1 km with low levels of pain). Moreover, constant-load protocols that employ low speed (e.g. 2.0 km/h) and without grade commonly result in a longer period for PFWD, whereas protocols with a high grade from 10 to 12% may be quite extreme for patients with mild so severe PAD, leading to inability to complete the test. Finally, constant-load protocols are more affected by a placebo effect

(multiple exercise tests in the placebo group) with an increase in walking distance ranging from 25% to 100% for the MWD over a 2-week period (14).

In contrast, graded treadmill tests present higher reliability compared to continuous protocols with a coefficient of variation for PFWD in 15% to 25% and 12% to 13% for MWD. Graded treadmill tests progressively increase the workload by 2% every 2-3 minutes. In addition, the graded treadmill test is less affected by a placebo effect with response change to 9% to 12% at 3 months and 13% to 23% at 6 months of follow-up (15). Thus, despite both treadmill exercise protocols being considered useful, the graded test better reflects the mechanism of the walking impairment in PAD, presenting greatest reliability, and allows testing in a wide range of PAD severity.

ALTERNATIVE WALKING ASSESSMENTS

Although treadmill-based exercise tests can establish maximum walking capacity, it is a relatively artificial measure of walking for patients with PAD and therefore, may not fully evaluate or establish the functional capacity limitations due to IC. Evidence has shown there is a poor correlation between treadmill outcomes and self-reported walking distance and free-living activity (measured through pedometer, activity monitoring or global positioning system (GPS). There is also a significant learning effect with treadmill use, especially when the intervention involves solely treadmill walking (16). A more realistic measure of ambulatory function, and limitation, can be made through the use of alternative walking measures such as the six-minute walk test (6MWT), and GPS devices. Research has shown that such field tests correlate better to outdoor walking as well as health-related quality of life (HRQOL) measures than treadmill-based protocols (16, 17)

Six-minute Walk Test (6MWT)

As described in XX chapter, the 6MWT is a well-validated and low-cost test that is utilised across a range of different clinical populations. The PAD-specific outcome measures of PFWD and MWD can be easily incorporated into the 6MWT. An excellent test retest reliability has been shown in patients with PAD, with a correlation coefficient of 0.90 ($p<0.001$) and a coefficient of variation of 8.9% with testing performed one to two weeks apart (18). The 6MWT is also sensitive to declines in walking ability over time, which is associated with PAD. Change in 6MWT can be used to predict mortality and mobility loss in patients with PAD, and clinically meaningful changes in the 6MWT have been defined. (McDermott et al., 2014) add Gardner here

As with all 6MWTs, the protocol needs to be strictly followed e.g. standardised walking course and consistency of encouragement provided during the test (please see Chapter XX for further details).

Global Positioning System (GPS) Recorders

Where the 6MWT provides a reflective measure of outdoor walking capacity, a measure of “real-life” outdoor walking has been made available through the use of GPS recorders. Patients are given a GPS recorder and instructed to walk on a predefined course nearby to the research laboratory or clinic, or at a location close to their home. The walking course should be flat, with minimal barriers that would cause the individual to stop or pause for any other reason that PAD-related symptoms (e.g. road crossings). Therefore, athletics tracks and local parks are good options for walking courses. The duration of the walk should be between 40-60 minutes, with the aim of getting at least 30 minutes of consistent data recorded. Walking at a habitual pace should be encouraged and continue until limited by maximal walking pain, rather than initial experienced pain. Individuals should be advised to resume walking either when the pain has subsided completely, or when they feel able to

walk again (depending on the specific outcome measures of the study or intervention). The GPS device should have a function (i.e. button press) that allows the individual to record the point of initial onset of claudication and the maximal pain so that PFWD and MWD can be measured, respectively. In addition to PFWD and MWD, GPS devices allow for the following outcome measure to be recorded: total walking distance achieved, maximal walking distance between two bouts of walking, average walking speed during test, average duration of stops between two bouts of walking (19).

Research has shown that GPS recorders have a good coefficient of variance for accuracy and reliability when compared to known distances walked (20). There are a range of GPS recorders available and they tend to be lightweight and can be easily worn (on waistband, wrist-worn or in a backpack) during outdoor walking therefore not impeding or hindering the individual. Evidence has also been provided to support the use of smartphone applications that utilise GPS to assess outdoor walking performance (17).

CARDIOPULMONARY EXERCISE TESTING

As discussed XX chapter of this book, cardiopulmonary exercise testing (CPET) provides an integrated assessment and quantification of the cardiorespiratory system at rest and under submaximal and maximal exercise. In patients with PAD, treadmill CPET protocols (both constant and graded) have been used with the aim to verify the impairment of walking capacity and metabolic demand until MWD. Studies have demonstrated that anaerobic threshold and VO_2 peak are significantly reduced (50% lower compared to non-PAD patients) (21) and these are closely related to walking performance (22). In addition the oxygen economy of a patient's performance at a given workload has also been demonstrated to be impaired and related to exercise intolerance in PAD (23).

The primary CPET modality is treadmill testing. However, this may be inappropriate for patients with PAD, as the central symptom is pain when walking (peripheral and not central fatigue). For patients with PAD, cycling should be considered as an alternative method, given that minimises the impact of body mass, altered gate on exercise performance and represents a relatively low load placed on the calf muscles during exercise. Previous studies demonstrated that cycle ergometry incurred a similar cardiovascular and metabolic response compared to treadmill walking (24). It also allows for better quality electrocardiogram traces and easiest access for the measurement of blood pressure, both of which would aid in the detection of coexisting cardiac conditions (25). Furthermore a cycling protocol may be able to establish a maximum value without inducing leg symptoms.

In addition to a lower-body cycling protocol, arm-cranking may also be useful for patients with PAD especially for those with extreme walking disabilities. The greatest advantage of arm ergometer is that patients can perform the test without IC symptoms (except for patients with upper limb atherosclerosis) which makes it possible to verify the contribution of central cardiorespiratory on submaximal and maximal efforts. Although in healthy individuals, VO_2 peak for arm-cranking is typically lower compared to leg-cranking (around 70%), in PAD the values are similar (21). In addition, the metabolic responses (anaerobic threshold and VO_2 peak) to arm-cranking are similar compared to control subjects without PAD (21), demonstrating that arm-cranking can be a useful alternative to standard CPET on treadmill tests in PAD patients. The test should be performed in a specific arm ergometer or modified from an existing stationary cycle ergometer by replacing the pedals with handles and mounting the unit on a table at shoulder height. The protocol can start with a 2-minute warm-up against no resistance followed by work rate increments of 7 to 10 watts every 2 to 3 minutes, at a cranking rate of 50 to 60 revolutions per minute until maximal fatigue (10.1042/CS20080688; 10.1177/1358863X08101858.

PERIPHERAL BLOOD FLOW AND SKELETAL MUSCLE OXYGENATION

In addition to ABPI, near-infrared light spectroscopy (NIRS) can be used to noninvasively explore lower limb hemodynamics (26). NIRS measures the saturation of haemoglobin by oxygen from the differential absorption by oxymyoglobin and deoxyhemoglobin of monochromatic light spectrum emitted by laser beams at characteristic wavelengths. In PAD patients, a sensor is attached to the skin on the medial portion of gastrocnemius muscle in the leg with the lowest ABPI to monitor the oxygen muscle saturation in real-time at rest, during and after exercise test.

Previous studies have shown that PAD patients present a sudden fall in muscle oxygen saturation at the beginning of the exercise and present lower values compared to age-matched controls during walking on treadmill 6MWT (27). Additionally, muscle oxygen saturation parameters are strongly associated with objective and subjective measurement of walking capacity (28) (29) and it is sensitive to identify changes in peripheral circulation and skeletal muscle oxygenation after different exercise interventions in PAD (30, 31).

In addition to NIRS, transcutaneous oxygen pressure (TcpO2) can be used to measure local oxygen pressure in patients with PAD (not muscle blood fow). The technique uses the light from a green LED which excites the sensor spots in the matrix layer of the skin to emit fluorescence and, if the sensor spot encounters an oxygen molecule, the excess energy is transferred in a non-radiative way, quenching the fluorescence signal (32). The degree of quenching correlates to the partial pressure of oxygen in the matrix, which is in dynamic equilibrium with oxygen in the sample.

TcpO2 can be measured at proximal and distal areas related to arterial lesion. For this, probes are positioned in upper limbs (chest probe as reference) and in one or more areas of lower limbs (buttocks, thigh and calves). To analyse the local hemodynamic impairment, TcpO2 is measured at rest and during a constant treadmill test (2.0 or 3.2 km at 10% grade). At exercise, the drop of oxygen pressure is calculated (the absolute change in TcPO2 from rest at each of the limb probes minus changes from rest values from the chest reference probe). For the interpretation, previous studies showed that a drop of 15 mmHg is the optimal cut-off point to discriminate normal from abnormal hemodynamic in both the buttock and calf level (32, 33). TcpO2 has not been validated for use in a graded treadmill test.

SUMMARY

Supervised exercise rehabilitation is considered the ‘first-line’ treatment strategy for patients with PAD. Evidence has demonstrated that exercise can improve walking capacity, quality of life, functional capacity and cardiovascular function. There are a multitude of physiological adaptations resulting from exercise rehabilitation including improved blood perfusion, improved muscle metabolism and improved walking efficiency. With appropriate training, the exercise testing methodologies outlined in this chapter can be used to monitor changes in walking capacity, cardiopulmonary function or lower limb haemodynamics following an exercise, lifestyle or surgical intervention.

REFERENCES

1. Ouriel K. Peripheral arterial disease. Lancet. 2001;358(9289):1257-64.
2. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg. 2007;45 Suppl S:S5-67.
3. Song P, Rudan D, Zhu Y, Fowkes FJI, Rahimi K, Fowkes FGR, et al. Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: an updated systematic review and analysis. Lancet Glob Health. 2019;7(8):e1020-e30.

4. Shammas NW. Epidemiology, classification, and modifiable risk factors of peripheral arterial disease. Vasc Health Risk Manag. 2007;3(2):229-34.
5. Morley RL, Sharma A, Horsch AD, Hinchliffe RJ. Peripheral artery disease. BMJ. 2018;360:j5842.
6. Meru AV, Mittra S, Thyagarajan B, Chugh A. Intermittent claudication: an overview. Atherosclerosis. 2006;187(2):221-37.
7. Aboyans V, Criqui MH, Abraham P, Allison MA, Creager MA, Diehm C, et al. Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association. Circulation. 2012;126(24):2890-909.
8. Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, et al. Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA guideline recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127(13):1425-43.
9. Hardman RL, Jazaeri O, Yi J, Smith M, Gupta R. Overview of classification systems in peripheral artery disease. Semin Intervent Radiol. 2014;31(4):378-88.
10. Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, et al. Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. Circulation. 2005;111(5):697-716.
11. Ko SH, Bandyk DF. Interpretation and significance of ankle-brachial systolic pressure index. Semin Vasc Surg. 2013;26(2-3):86-94.
12. Hiatt WR, Nawaz D, Regensteiner JG, Hossack KF. The Evaluation of Exercise Performance in Patients with Peripheral Vascular Disease. 1988;8(12):525-32.
13. Gardner AW, Skinner JS, Cantwell BW, Smith LK. Progressive vs single-stage treadmill tests for evaluation of claudication. Medicine and science in sports and exercise. 1991;23(4):402-8.
14. Hiatt WR, Rogers RK, Brass EP. The treadmill is a better functional test than the 6-minute walk test in therapeutic trials of patients with peripheral artery disease. Circulation. 2014;130(1):69-78.
15. Brass EP, Anthony R, Cobb FR, Koda I, Jiao J, Hiatt WR. The novel phosphodiesterase inhibitor NM-702 improves claudication-limited exercise performance in patients with peripheral arterial disease. Journal of the American College of Cardiology. 2006;48(12):2539-45.
16. McDermott MM, Guralnik JM, Criqui MH, Liu K, Kibbe MR, Ferrucci L. Six-minute walk is a better outcome measure than treadmill walking tests in therapeutic trials of patients with peripheral artery disease. Circulation. 2014;130(1):61-8.
17. Nordanstig J, Taft C, Hensäter M, Perlander A, Osterberg K, Jivegård L. Improved quality of life after 1 year with an invasive versus a noninvasive treatment strategy in claudicants: one-year results of the Invasive Revascularization or Not in Intermittent Claudication (IRONIC) Trial. Circulation. 2014;130(12):939-47.
18. 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, 7 e1.
19. Gernigon M, Le Faucheur A, Fradin D, Noury-Desvaux B, Landron C, Mahe G, et al. Global positioning system use in the community to evaluate improvements in walking after revascularization: a prospective multicenter study with 6-month follow-up in patients with peripheral arterial disease. Medicine. 2015;94(18):e838.
20. Abraham P, Noury-Desvaux B, Gernigon M, Mahé G, Sauvaget T, Leftheriotis G, et al. The inter- and intra-unit variability of a low-cost GPS data logger/receiver to study human outdoor walking in view of health and clinical studies. PLoS One. 2012;7(2):e31338.

21. Bauer TA, Brass EP, Nehler M, Barstow TJ, Hiatt WR. Pulmonary VO2 dynamics during treadmill and arm exercise in peripheral arterial disease. Journal of applied physiology (Bethesda, Md : 1985). 2004;97(2):627-34.
22. Womack CJ, Hyman BA, Gardner AW. Prediction of Peak Oxygen Consumption in Patients with Intermittent Claudication. 1998;49(8):591-8.
23. Bauer TA, Regensteiner JG, Brass EP, Hiatt WR. Oxygen uptake kinetics during exercise are slowed in patients with peripheral arterial disease. Journal of applied physiology (Bethesda, Md : 1985). 1999;87(2):809-16.
24. Tuner SL, Easton C, Wilson J, Byrne DS, Rogers P, Kilduff LP, et al. Cardiopulmonary responses to treadmill and cycle ergometry exercise in patients with peripheral vascular disease. J Vasc Surg. 2008;47(1):123-30.
25. Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. Circulation. 2013;128(8):873-934.
26. Hamaoka T, McCully K, Quaresima V, Yamamoto K, Chance B. Near-infrared spectroscopy/imaging for monitoring muscle oxygenation and oxidative metabolism in healthy and diseased humans. 2007;12 %J Journal of Biomedical Optics(6):062105.
27. Andrade-Lima A, Cucato GG, Domingues WJR, Germano-Soares AH, Cavalcante BR, Correia MA, et al. Calf Muscle Oxygen Saturation during 6-Minute Walk Test and Its Relationship with Walking Impairment in Symptomatic Peripheral Artery Disease. Ann Vasc Surg. 2018;52:147-52.
28. Gardner AW, Montgomery PS, Wang M, Shen B. Association between calf muscle oxygen saturation with ambulatory function and quality of life in symptomatic patients with peripheral artery disease. J Vasc Surg. 2020;72(2):632-42.
29. Gardner AW, Parker DE, Webb N, Montgomery PS, Scott KJ, Blevins SM. Calf muscle hemoglobin oxygen saturation characteristics and exercise performance in patients with intermittent claudication. J Vasc Surg. 2008;48(3):644-9.
30. Monteiro DP, Ribeiro-Samora GA, Britto RR, Pereira DAG. Effects of modified aerobic training on muscle metabolism in individuals with peripheral arterial disease: a randomized clinical trial. Scientific Reports. 2019;9(1):15966.
31. Tew G, Nawaz S, Zwierska I, Saxton JM. Limb-specific and cross-transfer effects of arm-crank exercise training in patients with symptomatic peripheral arterial disease. Clinical science (London, England : 1979). 2009;117(12):405-13.
32. Abraham P, Gu Y, Guo L, Kroeger K, Ouedraogo N, Wennberg P, et al. Clinical application of transcutaneous oxygen pressure measurements during exercise. Atherosclerosis. 2018;276:117-23.
33. Abraham P, Ramondou P, Hersant J, Sempore WY, Feuilloy M, Henni S. Investigation of arterial claudication with transcutaneous oxygen pres. Trends in cardiovascular medicine. 2020.