Medical Hypotheses 171 (2023) 111022

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

What are the physiologic effects of Resistance Exercise behind breast cancer-related lymphedema prevention?

Cristina Roldán-Jiménez [a,b,*]

[a] Department of Physiotherapy, Faculty of Health Sciences, Málaga University, Andalucia Tech, Spain
[b] Institute of Biomedical Research in in Málaga (IBIMA), Malaga, Spain

ARTICLE INFO

Keywords:
Breast cancer
Exercise
Lymphedema
Rehabilitation
Resistance exercise

ABSTRACT

Research in the last decades' haven driven a paradigm shift in the approach to physical activity and exercise prescription in breast cancer survivors. Clinical guidelines have moved from bedrest dogma and avoiding strenuous activity in the upper limb to recommending resistance exercise (RE). In recent years, scientific evidence has shown that RE in the upper extremities can even have a preventive effect on breast cancer-related lymphedema (BCRL). This knowledge was achieved thanks to systematic reviews with *meta*-analyses analyzing variables related to RE programs on lymphatic response and volumetry. However, other variables related, such as inflammation or acute responses, have been less addressed. The hypothesis presented in this paper is that there are both acute and chronic inflammatory and lymphatic response to exercise, systemic effects such as arm volume and body composition changes and unknown physiologic mechanics which contribute to BCRL prevention.

An approach to physiologic effects of resistance exercise on breast cancer-related lymphedema

Background to hypothesis

A few decades ago, breast cancer (BC) patients were advised to avoid physical activity and keep at rest. However, it was not until 1989 that the first randomized controlled trial (RCT) reporting the benefits of supervised exercise on body composition in BC patients was published [1]. Since then, research has presented exercise as a supportive care strategy, contradicting prior bedrest dogma. So much so that in 2001, another RCT showed that supervised exercise improved physical function and reduced body weight in women with stages I and II BC [2]. Almost simultaneously, in 1998, the first dragon boating team for breast cancer survivors (BCS) was developed to study the safety of strenuous activity evolving the upper limb in the recovery of BC [3]. This publication stood up for using the affected arm, given the myth that using the affected arm will increase the chance of breast cancer-related lymphedema (BCRL) developing or will exacerbate it [4–6]. In 2010, the American College of Sports Medicine (ACSM) recommended resistance exercises (RE) in cancer survivors, including BC patients [7]. The growing interest in lifting weights in BCRL has lead to several systematic reviews [8–11] to guarantee the safety of RE, including upper limbs in this population. Finally, recent ACSM guidelines (2019) indicated that supervised and progressive RE prevents BCRL [12].Fig. 1

Despite knowing the safety, efficacy, and need for upper limb RE in this population, little is known about its physiological effects on BCRL. On the one hand, systematic reviews have studied changes in variables related to lymphatic response, such as bioimpedance spectroscopy (BIS), X-ray absorptiometry (DXA), as perometry or water displacement [8–11] after an RE completion. That is to say; they are focused on the chronic lymphatic response and the chronic effect on arm volume. On the other hand, RCT included in systematic reviews compare an RE intervention with control (usual care or no intervention), so there is less information on the effects of RE depending on its intensity.

Hypothesis. The hypothesis presented in this paper is that there are both acute and chronic inflammatory and lymphatic response to exercise, systemic effects such as arm volume and body composition changes and unknown physiologic mechanics which contribute to BCRL

Abbreviations: ACSM, American College of Sports Medicine; BC, Breast cancer; BCS, Breast cancer survivors; BCRL, Breast cancer-related lymphedema; BIS, Bioimpedance spectroscopy; DXA, X-ray absorptiometry; IGF, Insulin-like growth factor (IGF); RE, Resistance Exercise.

* Address: Physical Therapy Department, Faculty of Health Sciences, Málaga University, Andalucía Tech, Arquitecto Francisco Peñalosa Avenue, 3. Postal Code 29071, Málaga, Spain.
E-mail address: cristina.roldan@uma.es.

https://doi.org/10.1016/j.mehy.2023.111022
Received 8 July 2022; Received in revised form 19 September 2022; Accepted 3 February 2023
Available online 8 February 2023
0306-9877/

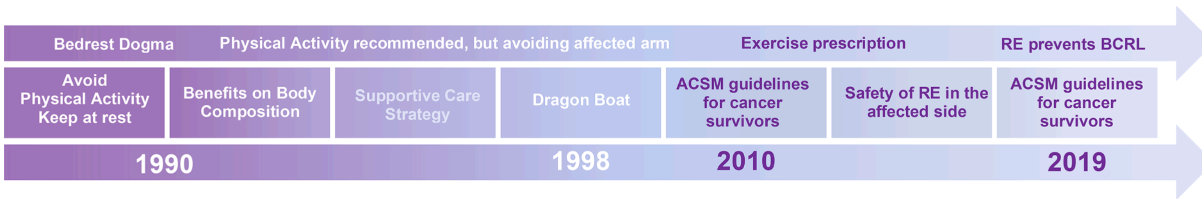

Fig. 1. Overview of exercise recommendations in BC population in the last decades.

prevention. In this manuscript, results of the current literature are presented, and current findings are discussed with theoretical knowledge about how RE can influence lymphedema.

Acute and chronic responses of resistance exercise

Inflammatory response: Blood sample

The anti-inflammatory effect of exercise is of great interest on BCS due to its effects on recurrence and survival [13,14]. Therefore, the vast majority of research focuses on the chronic and systemic anti-inflammatory effect of exercise in this population. In the following lines, both the chronic and acute effect of RE modality is presented.

Chronic inflammatory effect

None of the studies that have looked at the chronic effect of RE in the inflammatory response has explicitly focused on women with BCRL. Some systematic reviews have included other exercise modalities [14] or diet interventions [13]. A systematic review that focused on the chronic effects of RE, including blood biomarkers, did not report any result in this outcome [15]. A RCT with a partial crossover design comparing immediate (at baseline) and delayed (at six months) RE intervention found a significant decrease in insulin-like growth factor (IGF) II (-6.23 versus 28.28 ng/mL, P = 0.02) in favour of the immediate intervention group. However, no significant differences were seen in other biomarkers analyzed, such as IGF-I or IGF-binding proteins [16]. The program comprised 9 common exercises using resistance machines and free weights, including chest, back, shoulders and arms muscles. Patients started with no weight or 0.5 lb wrist weights for the upper body and progressed as symptoms allowed to avoid the onset or worsening of lymphedema symptoms. However, only 14 out of 85 participants had a BCRL diagnosis [16].

Acute inflammatory response

Cormie et al. studied the acute inflammatory response of RE at different intensity loads in 21 BCS who had established lymphedema. Venous blood samples were collected 24 h following the exercise sessions. Findings showed that moderate (10–12 RM) and high-load (6–8 RM) SE did not induce a greater level of muscle damage or inflammation compared with low-load (15–20 RM) SE in terms of creatine kinase and inflammatory biomarkers such as interleukin-6, tumour necrosis factor α, and C-reactive protein [17].

Lymphatic response: Extracellular fluid

BIS was used to assess lymphatic response to obtain a Dex L-Score. This score allows measuring changes in units, although the criteria to establish lymphedema diagnoses varies among studies, as there is no gold standard for assessment [18,19]. While some studies established a threshold of 3.0 L-Dex units on change scores as clinically relevant [20], other studies reporting normative data provide an L-Dex scores range that may fluctuate between 9 and 11 units [21].

Lymphatic response: Extracellular fluid

Studies reporting acute lymphatic response to resistance exercise have not found differences between different weight loads. Bloomquist et al. studied the acute lymphatic response to low-load compared with heavy-load resistance exercise in 21 BCS at risk of BCRL development receiving adjuvant taxane-based chemotherapy. Findings showed that acute changes in the extracellular fluid were similar irrespective of whether the load was performed 24 and 72 h post-exercise sessions—individual responses to resistance exercise sessions varied, with no apparent group trend observed [20]. The study of Cormie et al. [17] also analyzed the acute lymphatic response to SE under three load conditions: low (15–20 RM), moderate (10–12 RM) and high (6–8 RM). No significant increases were observed at any time point during the 3 exercise conditions 24 h post-intervention [17]. When comparing high (6–8 RM) and low (15–20 RM) load SE in women with mild to severe BCRL, neither changes between both groups were found in L-Dex score immediately post-exercise, 24 h post-exercise, and 72 h post-exercise [22].

Chronic lymphatic response

Bloomquist et al. studied the lymphatic response after 12 weeks of intervention and including a 39-week follow-up. A high-intensity intervention including endurance (85–95 % maximal heart rate) and SE (till 80–90 % of 1-RM) was compared to an individualized, home-based walking program supported by a pedometer and on one consultation in inactive breast cancer survivors [23]. L-Dex measures were included after commencement of the study, with data from 40 subjects approximately on each group. As a result, both groups showed a similar response in extracellular fluid, while the high-intensity group significantly improved upper-extremity strength [23]. The study of Comie et al. included 62 women with clinical diagnoses of BCRL who were allocated to 3 groups: control, high load (75–85 % of 1RM) and low load (55–65 % of 1RM), targeting major upper body muscle groups. As a result, there was no difference between groups in L-Dex measures after three months of intervention [24].

Arm volume

Arm volume is the outcome most frequently studied and included by several of the studies included in this review, measured by DXA or arm circumferences (cm). Regarding DXA, two studies analyzing acute lymphatic response did not find significant differences immediately post-exercise, 24 h post-exercise, and 72 h post-exercise [22], and after three months [24] of high or load RE intervention in women with BCRL. Bloomquist et al. also reported no changes in DXA measures when comparing low and high load SE. Individual responses to RE sessions varied, with no apparent group trend observed [20]. The study from Bloomquist et al. comparing high-intensity intervention with individualized, home-based walking programs reported a reduction in arm volume favorable to a high-intensity intervention (including endurance and RE) [23]. When measuring arm circumferences, the study from Cormie et al. comparing three load intensities (low, moderate and high) did not report increases observed in interlimb circumference difference at any time point during the 3 exercise conditions [17]. However, a recent systematic review reports that the effects of RE on arm volume are unknown due to heterogeneous assessment techniques in the current literature [9].

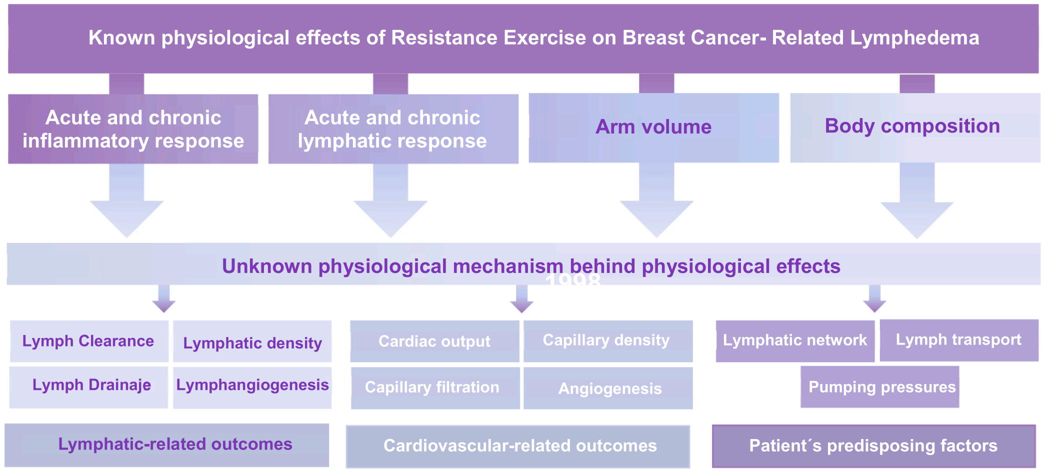

Fig. 2. Physiological effects of RE on BCRL.

Body composition

Research analyzing the effects of exercise in body composition aims to target weight control, as obesity increases the risk of recurrence and death in BCS [25]. A systematic review analyzing the chronic effect of RE in BCS [15] reported that only 1 out of 10 studies included found a significant change in body composition regarding an increase in lean body mass and decrease in body fat [16]. Therefore, the authors could not confirm that RE would induce a relevant reduction in body fat in BCS [15]. However, less is known about body composition changes located in the affected upper extremity. Bot et al. [26] reported changes in muscle thickness measured with a sonographer in 32 patients diagnosed with BCRL compared to a group that only received decongestive physiotherapy. The 8-week program consisted of six analytics upper-limbs resistance exercises performed with a 0.5 kg dumbbell. As a result, the intervention group significantly increased muscle thickness and significantly decreased the thickness of subcutaneous tissue in the forearm of the affected limb [26]. It should be noteworthy that, despite promising results, this study employed a pre-established weight for all participants (a 0.5 kg dumbbell) and analytical exercise, while current guidelines recommend SE comprising great muscle groups at 60–70 % of 1-RM to prevent BCRL [12]. Therefore, although the loads and intensity prescription of RE in BCS to obtain changes in body composition such as an increase in muscle mass remains to be elucidated, the study of Bot et al. [26] showed that even non-tailored loads and possibly well below the minimum intensities recommend for the prevention of BCRL appear to be sufficient to produce a reversal of body composition on the affected side. However, this is the only study to date that has studied the located effect of RE in the body composition of the affected side, and none have measured it at higher intensities. Nevertheless, Bo's findings show that previous studies focused on measuring volume fall short if they do not look at body composition.

Unknown physiological mechanism

Several physiological mechanisms would explain the possible beneficial effect of RE on the lymphatic system. However, these mechanisms are hypothesized since many of them are only known theoretically or have only been tested in healthy subjects, and very few studies have been carried out in patients with BCRL. These are summarized in the Fig. 2 and presented below.

Lymph formation and transport are given by both extrinsic (passive) and intrinsic (active) mechanisms to produce propulsive and centripetal movement of lymph, as the lymphatic system lacks an organ like the heart in the cardiovascular system to act like a pump [27,28]. Among extrinsic mechanisms, active movements of extremities and an increase of the pulse of nearby arteries during RE would benefit lymph transport. In addition, lymph clearance could be improved by a higher capillary density as a consequence of exercise adaptation, as seen in isometric and dynamic contraction in the lower limbs in healthy trained men [29,30]. Higher rates of lymph clearance could also be achieved by lymphangiogenesis and angiogenesis. However, the development of new lymphatic or vascular vessels and lymphatic density has only been studied as the chronic effect in endurance exercise [31,32]. In BCS, lymphoscintigraphy studies have shown that both extrinsic and intrinsic mechanisms are reinforced during exercise, facilitating increasing the propulsion of lymph through the lymphatic vessels. For example, two minutes of exercise [33] and 60 min of an ergometry-based arm cranking protocol [34] accelerates lymph drainage. However, any of these studies included a RE protocol. As systemic effects, it is known that exercise increases arterial blood pressure and cardiac output, which may facilitate capillary filtration [27,28].

Current knowledge and future directions

As outlined before, these local and systemic mechanisms are mainly theorized after few studies in healthy subjects, and those in BCS population included protocols of endurance exercise or a single bouts of exercise. Therefore, physiological findings may not be extrapolated to RE in patients with BCRL. In addition, many factors related to the lymphatic system in these patients have yet to be determined. On the one hand, several studies show that women who develop BCRL may have lymphatic-related predisposing factors [35], such as higher pumping pressures and lymph transport before cancer treatment [36]. On the other hand, local compensatory changes in the affected side may appear after lymphedema develops. For example, mastectomized women with BCRL have shown an enhanced cutaneous lymphatic network compared to those without BCRL [37]. For all these reasons, each patient's response is individualized, and the interventions should also be tailored [12].

Although the literature supports the safety of RE in these patients, and there are even prescription doses for the prevention of BCRL, studies with lymphoscintigraphy are very scarce to understand the short- and long-term effects of RE in this population. While inflammation-related biomarkers, lymphatic response, volume, and body composition are measurable outcomes in BCS, they contained a relatively small sample size, and physiological effects remain unknown. Future studies should include a broader sample and variables related to lymphatic response at current recommended RE intensities for BC patients suffering from BCRL.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. Funding for open access charge: Universidad de Málaga / CBUA.

Consent statement/Ethical approval

Not required.

Data statement

Not applicable.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Winningham ML, MacVicar MG, Bondoc M, Anderson JI, Minton JP. Effect of aerobic exercise on body weight and composition in patients with breast cancer on adjuvant chemotherapy. Oncol Nurs Forum 1989;16:683–9.
[2] Segal R, Evans W, Johnson D, Smith J, Colletta S, Gayton J, et al. Structured exercise improves physical functioning in women with stages I and II breast cancer: results of a randomized controlled trial. J Clin Oncol 2001;19:657–65. https://doi.org/10.1200/JCO.2001.19.3.657.
[3] McKenzie DC. Abreast in a boat–a race against breast cancer. CMAJ Can Med Assoc J J Assoc Medicale Can 1998;159:376–8.
[4] LeVasseur N, Stober C, Ibrahim M, Gertler S, Hilton J, Robinson A, et al. Perceptions of vascular access for intravenous systemic therapy and risk factors for lymphedema in early-stage breast cancer-a patient survey. Curr Oncol Tor Ont 2018;25:e305–10. https://doi.org/10.3747/co.25.3911.
[5] Kent H. Breast-cancer survivors begin to challenge exercise taboos. CMAJ Can Med Assoc J 1996;155:969–71.
[6] Harris SR, Niesen-Vertommen SL. Challenging the myth of exercise-induced lymphedema following breast cancer: a series of case reports. J Surg Oncol 2000; 74:95–8; discussion 98-99. 10.1002/1096-9098(200006)74:2<95::AID-JSO3>3.0.CO;2-Q.
[7] Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvão DA, Pinto BM, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc 2010;42:1409–26. https://doi.org/10.1249/MSS.0b013e3181e0c112.
[8] Paramanandam VS, Roberts D. Weight training is not harmful for women with breast cancer-related lymphoedema: a systematic review. J Physiother 2014;60: 136–43. https://doi.org/10.1016/j.jphys.2014.07.001.
[9] Hasenoehrl T, Keilani M, Palma S, Crevenna R. Resistance exercise and breast cancer related lymphedema - a systematic review update. Disabil Rehabil 2020;42: 26–35. https://doi.org/10.1080/09638288.2018.1514663.
[10] Keilani M, Hasenoehrl T, Neubauer M, Crevenna R. Resistance exercise and secondary lymphedema in breast cancer survivors-a systematic review. Support Care Cancer Off J Multinatl Assoc Support Care Cancer 2016;24:1907–16. https://doi.org/10.1007/s00520-015-3068-z.
[11] Cheema BS, Kilbreath SL, Fahey PP, Delaney GP, Atlantis E. Safety and efficacy of progressive resistance training in breast cancer: a systematic review and meta-analysis. Breast Cancer Res Treat 2014;148:249–68. https://doi.org/10.1007/s10549-014-3162-9.
[12] Campbell KL, Winters-Stone KM, Wiskemann J, May AM, Schwartz AL, Courneya KS, et al. Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable. Med Sci Sports Exerc 2019;51: 2375–90. https://doi.org/10.1249/MSS.0000000000002116.
[13] Bruinsma TJ, Dyer A-M, Rogers CJ, Schmitz KH, Sturgeon KM. Effects of Diet and Exercise-Induced Weight Loss on Biomarkers of Inflammation in Breast Cancer Survivors: A Systematic Review and Meta-analysis. Cancer Epidemiol Prev Biomark 2021;30:1048–62. https://doi.org/10.1158/1055-9965.EPI-20-1029.
[14] Kim TH, Chang JS, Kong ID. Effects of Exercise Training on Physical Fitness and Biomarker Levels in Breast Cancer Survivors. J Lifestyle Med 2017;7:55–62. 10.15280/jlm.2017.7.2.55.
[15] dos Santos WDN, Gentil P, de Moraes RF, Ferreira Júnior JB, Campos MH, de Lira CAB, et al. Chronic Effects of Resistance Training in Breast Cancer Survivors. Biomed Res Int 2017; 2017.. https://doi.org/10.1155/2017/8367803.
[16] Schmitz KH, Ahmed RL, Hannan PJ, Yee D. Safety and efficacy of weight training in recent breast cancer survivors to alter body composition, insulin, and insulin-like growth factor axis proteins. Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol 2005;14:1672–80. https://doi.org/10.1158/1055-9965.EPI-04-0736.
[17] Cormie P, Singh B, Hayes S, Peake JM, Galvão DA, Taaffe DR, et al. Acute Inflammatory Response to Low-, Moderate-, and High-Load Resistance Exercise in Women With Breast Cancer-Related Lymphedema. Integr Cancer Ther 2016;15: 308–17. https://doi.org/10.1177/1534735415617283.
[18] Hayes S, Janda M, Cornish B, Battistutta D, Newman B. Lymphedema secondary to breast cancer: how choice of measure influences diagnosis, prevalence, and identifiable risk factors. Lymphology 2008;41:18–28.
[19] Czerniec SA, Ward LC, Refshauge KM, Beith J, Lee MJ, York S, et al. Assessment of breast cancer-related arm lymphedema–comparison of physical measurement methods and self-report. Cancer Invest 2010;28:54–62. https://doi.org/10.3109/07357900902918494.
[20] Bloomquist K, Oturai P, Steele ML, Adamsen L, Møller T, Christensen KB, et al. Heavy-Load Lifting: Acute Response in Breast Cancer Survivors at Risk for Lymphedema. Med Sci Sports Exerc 2018;50:187–95. 10.1249/MSS.0000000000001443.
[21] Identifying diagnostic criteria for upper- and lower-limb lymphoedema n.d.
[22] Cormie P, Galvão DA, Spry N, Newton RU. Neither heavy nor light load resistance exercise acutely exacerbates lymphedema in breast cancer survivor. Integr Cancer Ther 2013;12:423–32. https://doi.org/10.1177/1534735413477194.
[23] Bloomquist K, Adamsen L, Hayes SC, Lillelund C, Andersen C, Christensen KB, et al. Heavy-load resistance exercise during chemotherapy in physically inactive breast cancer survivors at risk for lymphedema: a randomized trial. Acta Oncol Stockh Swed 2019;58:1667–75. https://doi.org/10.1080/0284186X.2019.1643916.
[24] Cormie P, Pumpa K, Galvão DA, Turner E, Spry N, Saunders C, et al. Is it safe and efficacious for women with lymphedema secondary to breast cancer to lift heavy weights during exercise: a randomised controlled trial. J Cancer Surviv Res Pract 2013;7:413–24. https://doi.org/10.1007/s11764-013-0284-8.
[25] Ballard-Barbash R, Hunsberger S, Alciati MH, Blair SN, Goodwin PJ, McTiernan A, et al. Physical activity, weight control, and breast cancer risk and survival: clinical trial rationale and design considerations. J Natl Cancer Inst 2009;101:630–43. https://doi.org/10.1093/jnci/djp068.
[26] Bok S-K, Jeon Y, Hwang P. Ultrasonographic Evaluation of the Effects of Progressive Resistive Exercise in Breast Cancer-Related Lymphedema. Lymphat Res Biol 2016;14:18–24. https://doi.org/10.1089/lrb.2015.0021.
[27] Scallan JP, Zawieja SD, Castorena-Gonzalez JA, Davis MJ. Lymphatic pumping: mechanics, mechanisms and malfunction. J Physiol 2016;594:5749–68. https://doi.org/10.1113/JP272088.
[28] Breslin JW, Yang Y, Scallan JP, Sweat RS, Adderley SP, Murfee WL. Lymphatic Vessel Network Structure and Physiology. Compr Physiol 2018;9:207–99. https://doi.org/10.1002/cphy.c180015.
[29] Tesch PA, Wright JE. Recovery from short term intense exercise: its relation to capillary supply and blood lactate concentration. Eur J Appl Physiol 1983;52: 98–103. https://doi.org/10.1007/BF00429033.
[30] Havas E, Parviainen T, Vuorela J, Toivanen J, Nikula T, Vihko V. Lymph flow dynamics in exercising human skeletal muscle as detected by scintography. J Physiol 1997;504:233–9.
[31] Gehlert S, Theis C, Weber S, Schiffer T, Hellmich M, Platen P, et al. Exercise-induced decline in the density of LYVE-1-positive lymphatic vessels in human skeletal muscle. Lymphat Res Biol 2010;8:165–73. https://doi.org/10.1089/lrb.2009.0035.
[32] Jensen L, Bangsbo J, Hellsten Y. Effect of high intensity training on capillarization and presence of angiogenic factors in human skeletal muscle. J Physiol 2004;557: 571–82. https://doi.org/10.1113/jphysiol.2003.057711.
[33] Tartaglione G, Pagan M, Morese R, Cappellini GA, Zappalà AR, Sebastiani C, et al. Intradermal lymphoscintigraphy at rest and after exercise: a new technique for the functional assessment of the lymphatic system in patients with lymphoedema. Nucl Med Commun 2010;31:547–51. https://doi.org/10.1097/MNM.0b013e328338277d.
[34] Lane KN, Dolan LB, Worsley D, McKenzie DC. Upper extremity lymphatic function at rest and during exercise in breast cancer survivors with and without lymphedema compared with healthy controls. J Appl Physiol Bethesda Md 1985; 2007(103):917–25. https://doi.org/10.1152/japplphysiol.00777.2007.
[35] Stanton AWB, Modi S, Mellor RH, Levick JR, Mortimer PS. Recent advances in breast cancer-related lymphedema of the arm: lymphatic pump failure and predisposing factors. Lymphat Res Biol 2009;7:29–45. https://doi.org/10.1089/lrb.2008.1026.
[36] Cintolesi V, Stanton AWB, Bains SK, Cousins E, Peters AM, Purushotham AD, et al. Constitutively Enhanced Lymphatic Pumping in the Upper Limbs of Women Who Later Develop Breast Cancer-Related Lymphedema. Lymphat Res Biol 2016;14: 50–61. https://doi.org/10.1089/lrb.2016.0005.
[37] Mellor RH, Stanton AW, Azarbod P, Sherman MD, Levick JR, Mortimer PS. Enhanced cutaneous lymphatic network in the forearms of women with postmastectomy oedema. J Vasc Res 2000;37:501–12. https://doi.org/10.1159/000054083.