

Exercise-based functional recovery from severe upper extremity arterial disease due to bilateral subclavian artery obstruction in a person with giant cell arteritis

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ABSTRACT

We report the case of a 71-year-old woman diagnosed with giant cell arteritis with bilateral subclavian and axillary obstruction and severe arm claudication that occurred 3 months earlier and was non-regressed after corticosteroids. Before possible revascularization, the patient was initiated to a personalized home-based graded exercise program including walking, hand-bike pedaling, and muscle strength training. During the 9 months of treatment, the patient progressively improved radial pressure values (10 to 85 mmHg), hand temperature values by infrared-thermography (+2.1 °C), arm endurance, and forearm muscle oxygenation by near-infrared spectroscopy. Home-based graded exercise proved to be a noninvasive option for upper limb claudication. (*J Vasc Surg Cases Innov Tech* 2023;9:101179.)

Keywords: Claudication; Exercise; Near-infrared spectroscopy; Rehabilitation; Thermography; Upper extremity arterial disease

Upper extremity arterial disease, even less frequently than that in the lower limbs, is responsible for a disabling condition that worsens the patient's quality of life.^{1,2} A revascularization approach in symptomatic patients is recommended (IIa level, C class)² in the absence of established rehabilitation and/or exercise treatment. In this clinical case, we report the effects on arm claudication of low-intensity graded exercise derived from an original program for lower limb claudication.³⁻⁵

CASE REPORT

A 71-year-old female subject with a history of dyslipidemia and non-hemodynamically significant carotid stenosis was referred to the emergency department complaining of high fatigability in both arm muscles during daily activities in September 2021. The symptoms, present since June and progressively worsening, were associated with occasional paleness of both hands and headache. At admission, radial pulses were not detectable in the absence of pain at rest. The therapy included antiplatelets (100 mg aspirin) and low-dose statins. The ultrasound examination detected monophasic indirect flow at the brachial arteries,

and the subsequent computed tomography (CT) scan confirmed stenotic lesions to the proximal subclavian arteries, complete occlusion of the distal subclavian arteries, and subsequent occlusion of the axillary arteries (Fig 1). The diagnosis of giant cell arteritis was based on clinical signs, presence of elevated inflammatory markers (erythrocyte sedimentation rate: 64 mm/hr; C-reactive protein: 4.7 mg/dL) and inflammatory response at the subclavian arteries evidenced by 18F-deoxyglucose positron emission tomography/CT.

During the hospital stay, the patient was initially treated with high-dose corticosteroids and, in the face of a low response, with anti-interleukin-6 antibodies (Tocilizumab) administration for 1 month. This therapy improved headache symptoms without significant benefits on arm claudication. By mutual agreement, given the lesion extension and the arteries involved (Fig 1), revascularization was considered the second option. The patient, discharged with medical therapy (steroids, calcium



Fig 1. Three-dimensional reconstruction of arterial tree showing the narrowing of both subclavian arteries with significant focal stenosis (yellow arrows) and their occlusion in the distal segment, both axillary arteries occluded.

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Table I. Structure of the training program

	Weeks	Walking	Hand biking	Shoulder abduction and elbow flexion
Phase 1	1-3	1:1 walk:rest ratio per 8 times (twice/day) Speed: 60 to 66 steps/min	–	–
Phase 2	4-32	1:1 walk:rest ratio per per 8 times (twice/day) Speed: 66 to 100 steps/min	1:1 bike:rest ratio per 6 times (twice/day) Speed: 30 to 60 rpm	–
Phase 3	33-40	–	–	5 reps × 4 series Load: 1 kg

Table II. Outcome measures over time

Date	Phase 1		Phase 2			
	Dec 1, 2021	Dec 24, 2021	Feb 7, 2022	Mar 28, 2022	May 25, 2022	July 28, 2022
Radial pressure (right), mmHg	10	45	50	85	80	85
Radial pressure (left), mmHg	45	55	50	75	70	85
Brachial ankle index, right	0.06	0.29	0.33	0.50	0.48	0.52
Brachial ankle index, left	0.26	0.35	0.33	0.44	0.42	0.52
Hand temperature (°C), right	29.3	30.6	30.9	31.5	31.1	31.4
Hand temperature (°C), left	30.2	30.7	30.8	31.5	31.4	31.9
6-minute hand bike repetitions	289	421	418	436	417	441
Rate of perceived exertion at the end (0-10)	6	3	4	2	2	1
Oxygenation area during endurance hand bike test (OxyHb _{AUC}) (a.u.), right	–3120	–873	1083	76	104	837
Oxygenation area during endurance hand bike test (OxyHb _{AUC}) (a.u.), left	–674	1047	1387	539	83	422

OxyHb_{AUC}: Area under the curve of oxygenated hemoglobin.

antagonists, and angiotensin-converting enzyme inhibitors), was referred to the Vascular Rehabilitation Program at the Hospital of Ferrara in December.

At entry, the patient complained of early and pronounced fatigability of both upper limbs, especially at the right arm, during activities of daily living (cooking, drying hair, light gardening, etc).

Being the first case of arm claudication referred to the program, methods and protocols already in use in our lab for lower limb claudication were applied. The outcome measurements, performed with the patients at rest in a temperature-controlled environment, included the following:

- Segmental pressure values at the bilateral radial arteries were measured using a Doppler ultrasound transducer (Dopplex SD2, Huntleigh Healthcare, Cardiff, UK) and a blood pressure cuff. The value obtained was divided by the highest tibial artery pressure as a reference value;
- Hand temperature, as assessed at the dorsum of both hands in correspondence with the proximal phalange of the third finger by infrared thermal camera (FlirOne PRO, Italy);
- A 6-minute upper limb pedaling test was used to determine the maximal number of rotations performed with a pedal hand bike with display and counter (GIMA, Italy).

Changes in muscle oxygenation at the upper arms measured with near-infrared spectroscopy were also recorded by a continuous wave system (Oxymon MKIII, Artinis, The Netherlands) with optodes placed on the bilateral forearm, 3 cm distal from the cubital fossa. Finally, the area under the curve of oxygenated hemoglobin (OxyHb_{AUC}) was calculated.^{6,7}

Exercise program. The patient was addressed to composite progressive exercise including different activities aimed at inducing both hemodynamic and functional adaptations.

The first phase (weeks 1-3) was exclusively based on short interval in-home walking exercises^{3,8} at the prescribed speed. The speed, maintained by a metronome application for smartphones, was initially low (60 steps/min or less than 1 mile/hour) and increased weekly by 3 ± 1 steps/min.^{3,5}

The second phase (weeks 4-32) included the progressive walking program plus low-intensity interval arm pedaling training on a hand bike. The speed from 30 revolutions per minute (rpm) was increased by 5 rpm every 2 weeks.

The third phase (weeks 33-40) was aimed at the recovery of strength of deconditioned muscles (bilateral brachial biceps

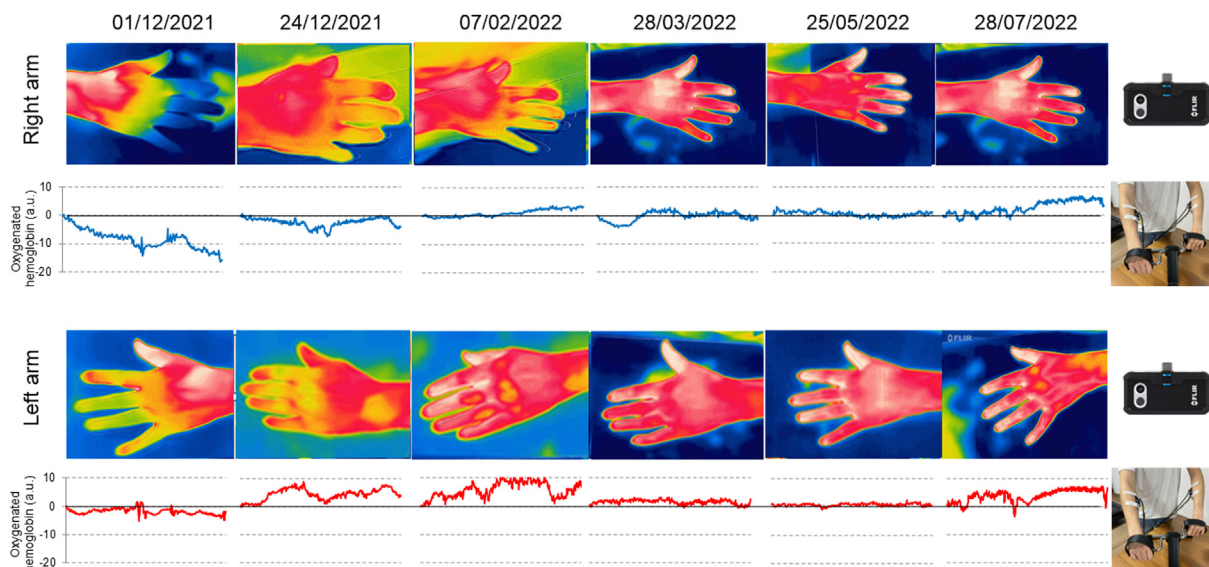


Fig 2. Over-time variations of the thermographic images of the hand and of the oxygenated hemoglobin trace collected by near-infrared spectroscopy in both forearms during the 6-minute hand pedaling test.

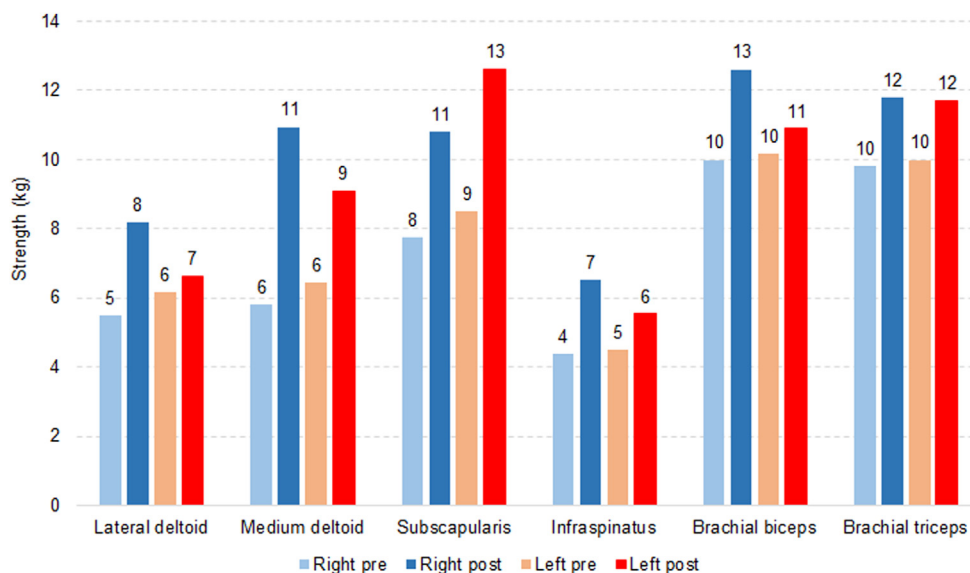


Fig 3. Maximal strength of the different muscles before and after the third phase of the program.

and triceps, deltoid, and shoulder rotator muscles). After baseline strength assessment (Microfet, Hoggan Scientific, Salt Lake City, USA), a home program was delivered to the patient based on shoulder abduction and elbow flexion exercise with a 1-kg external load.

A training diary was provided to record the exercise execution and any symptoms.

During the 9-month rehabilitation period, a total of six follow-up visits were performed to update the program. A maintenance program was delivered at discharge. A graphical representation of the training program and of the assessment periods is reported in [Table 1](#).

The patient provided written informed consent to anonymously publish the data.

RESULTS

No changes in drug therapy occurred during the observation period. The patient executed 100% of the prescribed training sessions safely and in the absence of symptoms. The patient progressively reported greater exercise capacity in performing daily activities, with delayed onset of arm fatigue.

Arterial pressures and hand temperature. The radial arterial pressure values progressively improved in both arms (right: from 10 to 85 mmHg, left: from 45 to 85 mmHg), as did the radial-tibial pressure values (right: from 0.06 to 0.52; left: from 0.26 to 0.52). The hand temperature also gradually increased over time (right:

from 29.3 °C to 31.4 °C; left: from 30.2 °C to 31.9 °C) (Table II).

Arm endurance and strength. The total number of repetitions performed in the 6-minute hand biking test significantly increased from 289 total, with one resting pause, to 441 without interruptions. Likewise, the near-infrared spectroscopy-assessed OxyHb_{AUC} values at the forearm, which were negative at baseline (right: -3120; left: -674), were normalized from the third visit onward (Table II, Fig 2).

The strength of the muscle districts tested improved from 20% to 60% (Fig 3).

DISCUSSION

A composite progressive exercise program was associated with hemodynamic improvements and satisfactory functional recovery, with greater exercise capacity and reported autonomy in everyday activities involving the upper arms.

The noticeable and decisive outcome was the hemodynamic recovery measured after the first 3 weeks of training, exclusively based on low-intensity walking exercises. These changes, in the absence of definite evidence but in agreement with our previous observations in patients with peripheral artery disease,^{9,10} may represent shear stress-induced vascular adaptations with changes in vessel tone.^{11,12} Increased nitric oxide production was reported after exercise training, particularly with the involvement of large muscle masses.^{11,12} Low-intensity exercise was also associated with improved endothelial function,¹²⁻¹⁴ lower inflammation and oxidative stress,^{12,14,15} and reduced sympathetic activation of the arteriolar tone.¹⁶ On the basis of these possible expectations and of our previous experiences with patients with peripheral artery disease,^{9,17} the exercise program was designed. Later phases of the program also involving the arm muscles allowed for specific vascular and muscle adaptations.

The limitations include the lack of CT-angiography measurement at discharge, the absence of a quality-of-life questionnaire, and the blinding of outcome assessors, even though the same two skilled operators performed all the measurements.

CONCLUSION

Low-intensity graded training involving walking and arm exercises successfully improved hemodynamics and exercise capacity in a patient affected by symptomatic upper extremity artery disease.

The importance of the case reported is inherent in the possible exploitation of methods and technologies to design targeted exercise therapy programs, supportive or alternative to revascularization, to improve patient function and quality of life in vascular diseases.

REFERENCES

- Greenfield LJ, Rajagopalan S, Olin JW. Upper extremity arterial disease. *Cardiol Clin* 2002;20:623-31.
- Aboyans V, Ricco J-B, Bartelink M-LEL, Björck M, Brodmann M, Cohnert T, et al. 2017 ESC Guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal. *Eur Heart J* 2018;39:763-816.
- Manfredini F, Malagoni AM, Mascoli F, Mandini S, Taddia MC, Basaglia N, et al. Training rather than walking - the test in-train out program for home-based rehabilitation in peripheral arteriopathy. *Circ J* 2008;72:946-52.
- Manfredini F, Conconi F, Malagoni AM, Manfredini R, Basaglia N, Mascoli F, et al. Training guided by pain threshold speed. Effects of a home-based program on claudication. *Int Angiol* 2004;23:379-87.
- Malagoni AM, Vagnoni E, Felisatti M, Mandini S, Heidari M, Mascoli F, et al. Evaluation of patient compliance, quality of life impact and cost-effectiveness of a "Test in-train out" exercise-based rehabilitation program for patients with intermittent claudication. *Circ J* 2011;75:2128-34.
- Manfredini F, Malagoni AM, Felisatti M, Mandini S, Mascoli F, Manfredini R, et al. A Dynamic Objective Evaluation of peripheral arterial disease by near-infrared spectroscopy. *Eur J Vasc Endovasc Surg* 2009;38:441-8.
- Manfredini F, Lamberti N, Rossi T, Mascoli F, Basaglia N, Zamboni P. A Toe flexion NIRS assisted test for Rapid assessment of Foot Perfusion in peripheral arterial disease: Feasibility, Validity, and Diagnostic Accuracy. *Eur J Vasc Endovasc Surg* 2017;54:187-94.
- Manfredini F, Mallamaci F, D'Arrigo G, Baggetta R, Bolignano D, Torino C, et al. Exercise in patients on dialysis: a multicenter, randomized clinical trial. *J Am Soc Nephrol* 2017;28:1259-68.
- Manfredini F, Traina L, Gasbarro V, Straudi S, Caruso L, Fabbian F, et al. Structured pain-free exercise progressively improves ankle-brachial index and walking ability in patients with claudication and compressible arteries: an observational study. *Intern Emerg Med* 2022;17:439-49.
- Manfredini F, Lamberti N, Guerzoni F, Napoli N, Gasbarro V, Zamboni P, et al. Rehabilitative exercise reduced the impact of peripheral artery disease on vascular outcomes in Elderly patients with claudication: a three-year Single Center retrospective study. *J Clin Med* 2019;8:210.
- Andrade-Lima A, Silva Junior N, Chehuen M, Miyasato R, Souza RWA, Leicht AS, et al. Walking training improves systemic and Local Pathophysiological Processes in intermittent claudication. *Eur J Vasc Endovasc Surg* 2021;61:954-63.
- Green DJ, Hopman MTE, Padilla J, Laughlin MH, Thijssen DHJ. Vascular adaptation to exercise in humans: role of hemodynamic stimuli. *Physiol Rev* 2017;97:495-528.
- Battault S, Singh F, Gayraud S, Zoll J, Reboul C, Meyer G. Endothelial function does not improve with high-intensity continuous exercise training in SHR: implications of eNOS uncoupling. *Hypertens Res* 2016;39:70-8.
- Goto C, Higashi Y, Kimura M, Noma K, Hara K, Nakagawa K, et al. Effect of different intensities of exercise on endothelium-dependent vasodilation in humans: role of endothelium-dependent nitric oxide and oxidative stress. *Circulation* 2003;108:530-5.
- Kinlay S, Creager MA, Fukumoto M, Hikita H, Fang JC, Selwyn AP, et al. Endothelium-derived nitric oxide regulates arterial elasticity in human arteries in vivo. *Hypertens (Dallas, Tex 1979)* 2001;38:1049-53.
- Brenner IKM, Brown CA, Hains SJM, Tranmer J, Zelt DT, Brown PM. Low-intensity exercise training Increases Heart rate Variability in patients with peripheral artery disease. *Biol Res Nurs* 2020;22:24-33.
- Lamberti N, López-Soto PJ, Guerzoni F, Napoli N, Gasbarro V, Zamboni P, et al. Changes in exercise capacity and risk of all-cause mortality in patients with peripheral artery disease: a 10-year retrospective cohort study. *Intern Emerg Med* 2020;15:289-98.