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Exercise training in patients with ventricular assist devices: a review of the evidence and practical advice. A position paper from the Committee on Exercise Physiology and Training and the Committee of Advanced Heart Failure of the Heart Failure Association of the European Society of Cardiology

Stamatis Adamopoulos[1], UgoCorrà[2], Ioannis D. Laoutaris[1], Massimo Pistono[2], Pier Giuseppe Agostoni[3], Andrew J.S. Coats[4], Maria G. Crespo Leiro[5], Justien Cornelis[6], Constantinos H.Davos[7], Gerasimos Filippatos[8], Lars H. Lund[9], Tiny Jaarsma[10], Frank Ruschitzka[11], Petar M. Seferovic[12], Jean-Paul Schmid[13], Maurizio Volterrani[4], and Massimo F. Piepoli[14]

[1] Heart Failure and Heart Transplantation Unit, Onassis Cardiac Surgery Center, Athens, Greece; [2] Cardiology Department, Istituti Clinici Scientifici Maugeri, Centro Medico di Riabilitazione di Veruno, Novara, Italy; [3] Centro Cardiologico Monzino, IRCCS, Milan, Italy; Department of Clinical Sciences and Community Health, Cardiovascular Section, University of Milan, Milan, Italy; [4] Department of Cardiology, IRCCS San Raffaele Pisana, Rome, Italy; [5] Heart Failure and Transplant Unit, Complexo Hospitalario Universitario A Coruña (CHUAC), INIBIC, CIBERCV, UDC, La Coruña, Spain; [6] Faculty of Medicine and Health Sciences, Translational Pathophysiological Research, University of Antwerp, Antwerp, Belgium; [7] Cardiovascular Research Laboratory, Biomedical Research Foundation, Academy of Athens, Athens, Greece; [8] Heart Failure Unit, Attikon University Hospital, Athens, Greece; [9] Department of Medicine, Karolinska Institutet and Heart and Vascular Theme, Karolinska University Hospital, Stockholm, Sweden; [10] Department of Nursing, University of Linköping, Linköping, Sweden; [11] Department of Cardiology, University Heart Center, Zürich, Switzerland; [12] University of Belgrade School of Medicine, Belgrade, Serbia; [13] Chefarzt Kardiologie, Klinik Barmelweid AG, Barmelweid, Switzerland; and [14] Heart Failure Unit, Cardiac Department, Guglielmo da Saliceto Hospital, Piacenza, Italy

Abstract

Exercise training (ET) and secondary prevention measures in cardiovascular disease aim to stimulate early physical activity and to facilitate recovery and improve health behaviours. ET has also been proposed for heart failure patients with a ventricular assist device (VAD), to help recovery in the patient's functional capacity. However, the existing evidence in support of ET in these patients remains limited.

After a review of current knowledge on the causes of the persistence of limitation in exercise capacity in VAD recipients, and concerning the benefit of ET in VAD patients, the Heart Failure Association of the European Society of Cardiology has developed the present document to provide practical advice on implementing ET. This includes appropriate screening to avoid complications and then starting with early mobilisation, ET prescription is individualised to meet the patient's needs. Finally, gaps in our knowledge are discussed.

Keywords

Exercise training; Left ventricular assist device; Mechanical circulatory support; Chronic heart failure

Introduction

Around 5–25% of heart failure (HF) patients reach an end-stage condition, despite the use of optimal medical therapy.[1,2] At this stage three options are currently indicated: ventricular assist device (VAD) implantation, heart transplantation (HT), or palliative care.[3,4] In the modern setting of an increasing HF population and because of the scarcity of heart donors, the VAD option is emerging as a strategy for bridge to HT or as a destination therapy (DT) for those ineligible for HT[3]: a small number of VAD patients may have sufficient recovery of myocardial function (bridge to recovery) to allow device to be explanted.[4] Although functional capacity usually improves compared to the pre-implantation status, VAD recipients still experience an impaired exercise capacity.[5,6]

Exercise training (ET) is highly recommended in HF because of its beneficial effects on functional capacity and prognosis.[3,7-10] More recently, it has been proposed also in VAD recipients.[11,12] This latter strategy, however, has not been uniformly implemented, as shown by the European Exercise Training Survey,[13] a fact that has been attributed to lack of knowledge, low prioritization, variability in official recommendations, heterogeneity of the surgical intervention (simple or shared device implantation, combined valve surgery, linked with ventricular ablation), indication (INTERMACS ranking), or simply because the patients were considered too severely frail (such as very elderly HF patients).

Based on the current consistent, but still limited evidence supporting the safety and the benefit of early mobilisation (EM) and ET in the VAD population, the Heart Failure Association (HFA) of the European Society of Cardiology has developed this document with the aim of promoting the implementation of exercise in VAD recipients in clinical practice. First, the current knowledge on the origin of limitations in exercise capacity and the available evidence concerning the benefit of ET in VAD recipients are reviewed, thereafter advice on the optimal modalities to implement ET in clinical practice are presented and, finally, the gaps in knowledge are discussed.

Exercise capacity in ventricular assist device recipients

The transition from rest to exercise induces cardiovascular adjustments to allow adequate tissue perfusion as well as increased peripheral oxygen extraction. The normal physiologic response to exercise is characterised by increased heart rate (HR) and cardiac contraction force at a given left ventricular (LV) pressure, leading to higher cardiac output (CO), through activation of the sympathetic nervous system. During maximal exercise, CO normally increases four- to six-fold, shifting the Frank–Starling curve to the left and upward, associated with peripheral vasodilatation.[14] Although age, sex, fitness, inherited factors and the presence of congenital cardiovascular abnormalities may have some influence, the ability to augment CO in response to the higher metabolic demand is one of the key factors regulating the cardiovascular response to exercise.[14]

This situation is markedly different in individuals with heart disease, when coexistent demographic factors seem to be less critical.[14] Usually, HF patients are limited in their exercise capacity by maladaptive changes in the cardiovascular, musculoskeletal, and respiratory systems.[15,16] In particular in response to stress, advanced HF patients are unable to augment CO adequately due to impaired myocardial contractility, with consequent multi-organ under-perfusion, hypoxia and muscular inefficiency.[17] Exercise limitation and deconditioning favour a feedback negative loop.3

Cardiopulmonary exercise testing (CPET) is considered the gold standard tool in assessing the physiologic response to exercise,[3,18] and in identifying individuals in need of advanced therapies (e.g. HT or VAD implantation).[18] However, pre-implantation VAD patients may be too ill to perform CPET[4,5] and thus comparisons of peak oxygen consumption (VO_2) values post-implantation are mostly lacking[19,20] or show conflicting results.[21-23] In fact, there is evidence that, over longer implant periods (i.e. 2 years), recipients can show an enhanced exercise performance,[24,25] either in terms of CPET parameters or 6 min walking test (6MWT) distances.[6,19,25-28] In contrast, some patients may still exhibit significant impairment in exercise capacity[6] due to a variety of causes:

- Device characteristics (e.g. inability to increase CO during exercise due to the absence of ramp function, unloading speed, the presence of the operating console and the drive line).
- Cardiac abnormalities (e.g. native LV contribution, right ventricular dysfunction, chronotropic incompetence).
- Co-morbidities (e.g. impaired pulmonary function, skeletal myopathy, endothelial dysfunction, anaemia).
- Patient's characteristics (i.e. age, gender, disease aetiology and duration of disease, length of hospitalisation, physical deconditioning, and frailty).

Left ventricular unloading is important during VAD support,[5] and as a result, device speed is adjusted accordingly. The pump flow is determined by the pump motor activity, the rotational speed, and the VAD characteristics;[29] however, only approximate estimation of CO is possible because of the unknown volume of orthograde blood flow across the aortic valve, which is affected by residual LV myocardial function and pre- and afterload conditions. Rotational speed affects flow and exercise tolerance as well,[30,31] and speed increase affects exercise capacity and peak VO_2.[32,33]

After VAD implantation, the contribution of native ventricular contractility is complex: at rest, the VAD provides most of the CO, whereas, during exercise, a variable contribution of the native heart to CO has been described depending on right and left ventricular contractile reserve interplay.[6,27,30] The role of HR seems to be less important, because it does not affect LVAD flows,[34] although chronotropic incompetence, at least during the early phase of the post-implant period, has been witnessed.[35] Right ventricular (RV) dysfunction may significantly limit maximal CO during exercise,[33,36,37] but tricuspid annular plane systolic excursion, a known marker of RV function, and RV diastolic dimension did not correlate with symptom-limited exercise capacity.[34] Possibly, RV longitudinal strain, a less load-dependent index of RV function, might represent a much more pathophysiologically relevant contributor to exercise capacity in a VAD patient, from the right side of the heart.

Finally the contribution of pulmonary function and peripheral factors remain unclear,[35-37] but a key role of the peripheral circulation has been proposed. There is evidence that the improvement in leg blood flow accounts for most, if not all, of the increase in CO observed post-implantation of a continuous-flow VAD.[35] Also an increased venous return associated with reduced peripheral resistance and increased cardiac contractility has been advocated.[36]

Exercise training may enhance the benefit on peripheral haemodynamic factors induced by VAD implantation.

In conclusion, exercise adaptation of the VAD recipient is complex to understand: most studies have been focused on one limiting factor rather describing the integrated exercise response, therefore a complete description of exercise adjustment has not yet fully been worked out. There is recent evidence of the multiple effects of VAD during exercise, such as improvements in central (CO) and peripheral haemodynamics (muscle blood flow and oxygenation) but with a detrimental effect on pulmonary function (lung diffusion deterioration with increased obstructive apnoea, likely due to an increase of intra-thoracic fluids).[38]

Review of the evidence in favour of exercise testing in ventricular assist device patients

Limited but promising data are available concerning the safety and efficacy of EM (7–10 days post-implant) and ET in VAD recipients (*Table* 1).[39-48] In 2011, Laoutaris *et al.*[42] provided the first evidence of the feasibility and efficacy of ET in patients with either left ventricular (LVAD) or biventricular (BiVAD) assist devices participating in a 10-week exercise program, 6.3 ± 4 months post-implantation. ET improved functional capacity (peak VO_2, 6MWT), exertional ventilatory response (VE/VCO_2 slope), and quality of life (QoL). Subsequently, Adamopoulos *et al.*[43] extended these findings, showing that long-term ET also decreased N-terminal pro B-type natriuretic peptide (NT-proBNP) and triggered myocardial growth factors involved in evolution signalling pathways, in both LVAD and BiVAD patients. A multi-model long-term (18 months) ET intervention increased the percentage of predicted peak VO_2 in LVAD recipients,[44] while a shorter (8-week) ET, started early after implantation and on a small population (14 patients), provided no benefit with respect to the control group.[45] In a retrospective analysis, Karapolat *et al.*[46] observed that an 8-week ET programme improved peak VO_2, pulmonary function and QoL similarly in LVAD recipients, HF or HT patients. Kerrigan *et al.*[47] in a 2:1 randomisation trial comparing usual care vs. ET (which included 18 aerobic exercise sessions at 60–80% of HR reserve), showed that ET improved exercise capacity (peak VO_2 by 10%, treadmill time by 3.1 min, 6MWT distance by 52.3 m), QoL (Kansas City Cardiomyopathy Questionnaire score by 14.4 points), and leg strength (17%). More recently, Marko *et al.*[48] confirmed the improvement in peak VO_2 and muscle strength in patients with LVAD after ET.

Table 1. Main studies on exercise training in cardiac rehabilitation of patients with ventricular assist devices

Study	Type of recipients, and distribution in intervention and control groups	Time of enrolment after device implantation	Type of intervention	Main results	Other findings
Laoutaris[42] 2011, randomized	LVAD/BiVAD recipients E = 10, C = 5 patients	6.3 ± 4 months	E: Home-based, aerobic training, for 3–5 times/week. Supervised high-intensity IMT for 3 times/week. Duration: 10 weeks C: Advice for walking	Peak VO_2: +2.5 mL/kg/min VO_2 at AT: +2.9 mL/kg/min VE/VCO_2 slope: –4.1 6MWT: +65 m	Improvement in QoL and inspiratory muscle function
Kugler[44] 2012, non-randomized	LVAD recipients E = 34,C = 36 patients	6 weeks	E: Home aerobic training, dietary counselling and psychosocial support. Duration: 18 months C: No standard suggestion (only recommendation for healthy diet/routine exercise)	Peak predicted VO_2: +7%	Improvement in QoL
Hayes[45] 2012, randomized	LVAD recipients E = 7, C = 7 patients	Able to mobilise for 70 m	E: Supervised aerobic training, 3 times/week. Strength exercise. Duration: 8 weeks C: Advice for walking	Peak VO_2: +2.96 mL/kg/min 6MWT: +51 m	Similar improvements in peak VO_2, 6MWT, QoL in both E and C
Karapolat[46] 2013, retrospective and randomized	LVAD recipients E = 11 patients compared to HF = 46 and to HT = 40 patients	2.8 ± 2.13 months	E: Supervised flexibility, aerobic, strengthening, and relaxation exercises for 3 times/week. Duration: 8 weeks	Peak VO_2: +0.45 mL/kg/min	Improvement in QoL and depression scale
Adamopoulos[43] 2013, non-randomized	LVAD/BiVAD recipients E = 11, C = 11 patients	3 months	Training up to HT E: Home-based aerobic training for 3-5 times/week. Supervised high-intensity IMT for 3 times/week. Duration: 10 weeks C: Advice for walking	Peak VO_2: +4 mL/kg/min	Improvement in NT-proBNP, T3, p-Akt/t-Akt p-JNK/t-JNK
Kerrigan[47] 2014, randomized	LVAD recipients E = 16, C = 7 patients	Not available	E: Supervised aerobic exercise, for 3 times/week. Intensity = 60% of heart rate reserve. Duration: 6 weeks	Time at treadmill: +3.1 min Peak VO_2: +1.7 mL/kg/min VE/VCO_2 slope: –1, 6MWT: +52 m	Improvement in QoL and leg strength
Marko[48] 2015, retrospective and non-randomized	LVAD recipients E = 41 patients	After 48 ± 34 days	E: Supervised aerobic training/strengthening/ walking/gymnastics Duration: 32 ± 6 days	Peak VO_2: +3.13 mL/kg/min VE/VCO_2 slope: –4.2	Improvement in peak VO_2 and muscle strength

6MWT, 6-minute walking test; AI, after intervention; AT, aerobic threshold; BiVAD, biventricular assist device; C, control group; E, exercise group; HF, heart failure; HT, heart transplantation; IMT, inspiratory muscle training; LVAD, left ventricular assist device; NT-proBNP, N-terminal pro B-type natriuretic peptide; QoL, quality of life; VE/VCO_2 slope, ventilation vs. carbon dioxide response to exercise; VO_2, oxygen consumption

In conclusion, although the small study populations limit the evidence regarding the role of ET in VAD recipients, all data support the feasibility, safety, and potential for benefit.[40]

How to implement exercise

Based on the available data, the HFA Committees hereby presents practical advice on the modality of exercise implementation in VAD patients. However the reader should bear in mind that the following are only general recommendations: the implementation in clinical practice is conditioned by local expertise, individual recipient factor (e.g. timing of referral, type of intervention delivered, multidisciplinary approach), characteristics of the VAD recipients (e.g. combined vs. single surgical interventions, indications for implantation, underlying clinical condition, co-morbidities), and available national recommendations and facilities.

Preliminary step – clinical assessment and health professionals' education

Medical professionals may be hesitant to start mobilisation because of the presence of the device in a still debilitated patient, and specific skills and expertise are required. Thus, health care providers should be familiar not only with exercise physiology and the different exercise modalities but also with device functioning,[44] in order to face promptly all potential complications. *Tables* 2-6 provide information on what health care providers/exercise therapists should know before, during and after EM and ET.

Table 2. Instruction to reduce the risk of adverse events when exercising ventricular assist device patients

1. Individualised assessment and prescription.
2. Pre-screening with risk stratification.
3. Prolonged graduated warm-up and cool-down.
4. Low-to-moderate intensity exercise training.
5. Avoiding breath holding and Valsalva manoeuvre.
6. Avoiding any trauma, as ventricular assist device recipients are anticoagulated and (some, not all) treated with antiplatelet drugs.
7. Adaptation for co-morbidities.
8. Monitoring and supervision.
9. Keeping the feet moving during active recovery, if appropriate.
10. Observation of patients for 15 min post-cessation of exercise.

Table 3. Preliminary evaluation and precautions during early mobilisation in ventricular assist device recipients

1. Assessment

   a. Recent and past medical history, and level of exercise capacity previous to disease state.
   b. Mental status and cognitive ability.
   c. Vital signs and risk of cardiovascular instability (haemodynamic, arrhythmic, clinical).
   d. Clinical assessment (persistence of VAD-related and HF symptoms, even medications have been prescribed).
   e. Medications, i.e. need for continuous or intermittent infusions (inotropic drugs), ventilator settings or oxygen requirements.
   f. Screen range of motion, coordination, balance, strength, endurance, functional capacity (bed mobility, transfers, gait, daily living activities).
   g. Baseline haemochromocytometric, ionic and renal functional assessment. We suggest to start exercise when haemoglobin < 9 g/dL, sodium < 130 mEq/L, potassium < 3.8 mEq/L and/or creatininemia <1.9 mg/dL.

2. Follow sternotomy (6 weeks post-surgery screening of wound) and skin integrity.
3. Patients should always wear a driveline stabilization belt during exercise.
4. The patient should have his/her travel bag nearby at all times. It should include a back-up controller, battery clips and spare batteries.
5. Make early mobilization and exercise sessions comfortable. Organize an appropriate place to put monitor, console-controller and batteries (visible for patient and health care professionals). Discuss this topic with everybody implicated in the exercise programme.
6. The VAD equipment location should not impede emergency procedures.

Table 4. How to set up an early mobilisation programme in ventricular assist device recipients

Consider

1. Positioning.
2. Bed mobility activities.
3. Sitting on edge of bed, in association with exercises.
4. Transfers from bed to stretcher-chair, chair or commode.
5. Gait, with pre-gait activities: weight shifting, stepping in place and sideways. Gait training is allowed with rolling walker.
6. Breathlessness management and recovery strategies.
7. Attempt to achieve a target of 11 to 14 out of 20 of the Rate of Perceived Exertion scale.
8. Patient's native heart rate should not exceed 120 b.p.m. during exercise, unless under physician's supervision: heart rate is not always detectable during early mobilisation/exercise, and its monitoring depends on device.

Promote

- Low-to-moderate intensity dynamic large muscle group work (e.g. walking, stationary cycling), or involving upper body muscles.
- 'Walk & talk' approach is suggested.

Limit

- Knee lifts.
- Resistance training (low weight/high repetitions) and with seated exercise (reduced venous return).

Avoid

- Excessive muscle fatigue.
- Abrupt postural changes and stooped activities.
- Rowing machine.
- Initially, biking due to increased risk of infection near ventricular assist device percutaneous line exit site.

Table 5. Criteria for exercise contraindications in ventricular assist device recipients

1. Symptoms and signs compatible with exercise intolerance including light headedness, severe intolerable dyspnoea, chest pain or discomfort, tachycardia and exaggerated blood pressure response.
2. Symptomatic hypotension (fainting, dizziness, or diaphoresis, as extreme fatigue or claudication and new onset of neurological changes).
3. Supine resting heart rate > 100 b.p.m.
4. Oxygen saturation < 90% (caveat: oxymetry readings might be difficult to obtain due to low pulsatility).
5. VAD complications during or after exercise sessions:
    a. Alarm activation curves, numbers and alarms should be displayed on the VAD monitor: trends are useful to track pump function and patient perfusion. Significant drop in LVAD flow, or suction alarm are criteria for interrupting the session.
    b. Complex and frequent ventricular arrhythmia on exertion (caveat: may be asymptomatic).
    c. Infection, mainly at the driveline site (infection control procedures should be followed at all times, e.g. cleaning of equipment, hand washing, disposal of sharps).
    d. Evidence of bleeding as VAD recipients are anticoagulated or treated with antiplatelet drugs (not all): these drugs are essential for device working, but they can also enhance exercise-related bleedings and haematomas.
    e. Thrombus (usually evidenced by an increase in the number of watts/energy necessary for device working).
6. Request of VAD recipient to stop.
7. Increase > 1.8 kg in body mass over the previous 1 to 3 days.
8. Implantable cardioverter-defibrillator intervention (anti-tachycardia pacing and shocks).

Table 6. Summary of clinical parameters to be considered when exercising in ventricular assist device patients

Clinical stability	EM	Functional capacity	ET
• Unchanged VAD parameters • Appropriately tackled VAD-related and not-related complications	• Duration of EM according to patient's condition, VAD parameters, co-morbidities and complications • According to institutional administrative legacy, but maximal duration of 6 weeks is suggested	• Preliminary assessment by CPET or 6MWT	• Duration of ET according to patient's condition, VAD parameters, co-morbidities and complications • According to institutional administrative legacy • Setting: in- or outpatient approach
Clinical stability, i.e. • Stable diuresis • Stable weight • No ECG changes • No complex and/or sustained ventricular arrhythmias • No new sustained supraventricular arrhythmias • No changes in mean blood pressure (*< 60 mmHg or > 100 mmHg*)	• Meanwhile management of acute care factors including surgical wound, skin integrity maintenance, pulmonary hygiene, a range of motion, cardiovascular, and muscle strength maintenance should be addressed with the goal of free ambulation. • The cannulas, drivelines and the VAD external equipment must be secured to prevent damage during mobility and attention should be directed to abrupt posture changes and body balance issues that may result from carrying a bag, and might lead to disconnection of VAD.	• CPET: progressive ramp protocol is recommended, starting with a warm-up 0 W phase, following a ramp protocol of 1 min steps of 10 W/min), aiming subjective exhaustion or appearance of criteria for interruption. • 6MWT: should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom travelled. The walking course must be 30 m in length. The turnaround points should be marked and a starting line, which marks the beginning and end of each 60 m lap, should be marked on the floor. Only standardized phrases for encouragement must be used during the test.	• Light exercise intensities are recommended, with monitoring of exercise sessions. • If peak VO_2 > 14 mL/kg/min, or > 300 m are ambulated at 6MWT, a more intensive exercise session might be prescribed.
and no device failure • No flow < 3 L/min • No suction events • No device alarms			
and concomitant disease addressed • No thrombosis-haemorrhage • No infection • No right ventricular failure • No lung, liver and kidney failure • No neurological problems			

LVAD, left ventricular assist device; VAD, ventricular assist device.

A full patient medical history and clinical and functional evaluations are prerequisites along with HR monitoring for the detection and treatment of arrhythmias. Vital signs, self-reported symptom scores, and VAD function should be monitored, in particular including the mean arterial pressure in patients on non-pulsatile VAD support because hypertension would affect the VAD capacity to pump blood forward; hypotension and VAD blood flow alterations might be related to under-filling of the left ventricle secondary to high pump speed, RV failure, arrhythmias, etc. The VAD team should be consulted if the mean arterial pressure is below 70 mmHg or higher than 90 mmHg, especially when accompanied by VAD alarm activation. It is also important that the patient is well informed, reassured and feels safe and secure.

An exercise physiologist or physical therapist should be responsible for securing the cannulas, drivelines and the VAD external equipment, to prevent damage during mobility.[49,50] Once the recipient is confident with transfers from bed, and shows the ability to carry and to manage the VAD, batteries, and controller,[49] EM can start. The external controller and batteries of recent generations of VADs are highly portable and do not significantly interfere with exercise activities, however, some attention should be directed to avoid abrupt postural changes and body balance issues that may result from carrying a bag, weighing from 2 to 2.5 kg. Complications such as disconnection from the VAD external power supply have been described.[51,52] *Table* 2 provides instruction to reduce the risk of adverse events when exercising VAD patients, while *Table* 3 lists the preliminary evaluation and precautions during EM.

Early mobilisation

In every patient, as well as in VAD recipients, EM is defined as initiating physical exercise within the early illness phase, i.e. the first step for initiation of exercise therapy, and it constitutes the basic standard modality for ET implementation during the post-acute phase (*Table* 4). This preliminary phase is important but not standardised,[53,54] as it is conditioned by the patient's status, facilities and timing of referral. According to the patient's needs, EM should be adapted, and every day treatment changes should be considered: supervision from family members and/or nursing staff is warmly requested, to monitor VAD and clinical parameters.

This phase is important to rule out contraindications to exercise[49] (*Table* 5) and should start only when troublesome accounts after VAD implantation are mostly over.[51,52]

Early mobilisation prevents the complications of muscle deconditioning and cachexia and, through a broad range of activities, facilitates independence.[54] EM favours ambulation and includes functional strengthening, muscle endurance and aerobic training, as for all other HF patients.[55-58] Changes in gait are possible as a result of premature fatigue, appearance of new symptoms or unexpected VAD/clinical parameters changes. Possible falls and some complications such as disconnection from the VAD external power supply, due to the fact that the driveline has a relatively short distance from the skin to the controller, have been described.[51] The duration of EM is individualised according to progresses and facilities.[19,51]

As regards the timing to start, limited available data suggest the safety of a 6-week interval after implantation,[59,60] but in our expert opinion EM should be considered as soon as the patient's haemodynamic and clinical status is stable (including surgical wound, skin integrity maintenance, and pulmonary hygiene), and VAD functioning and troubleshooting have been correctly directed.[49,51,59] An algorithm for EM for VAD-supported patients and the transition to ET is here proposed, based on expert opinion and patient's aptitudes/clinical state (*Figure* 1).

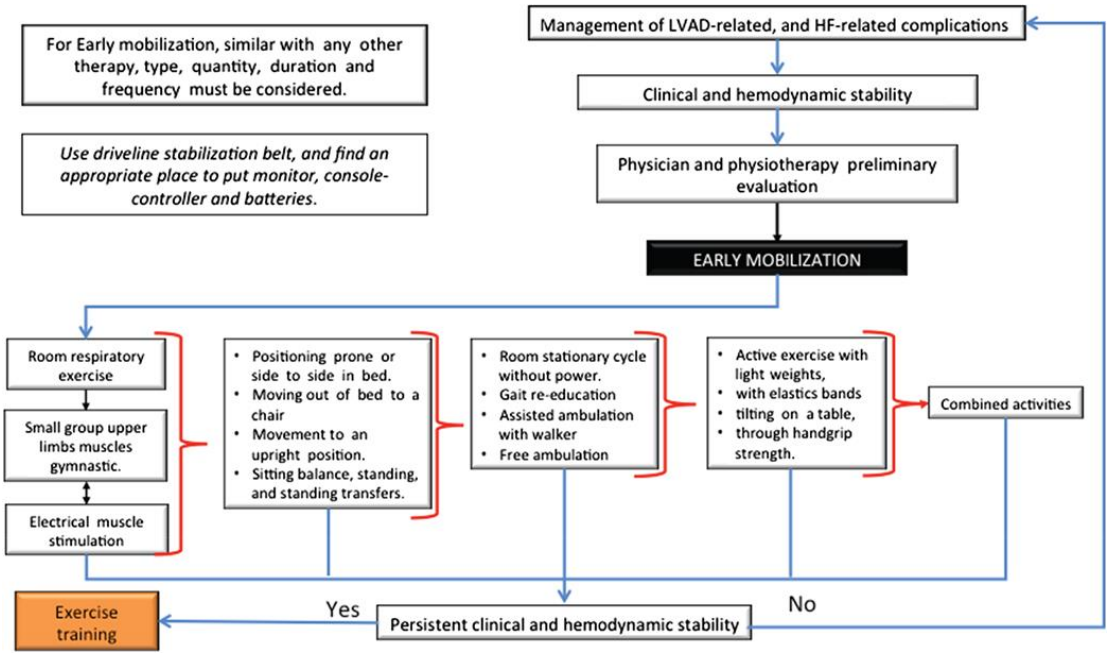

Figure 1. Ventricular assist device recipients and early mobilisation. HF, heart failure; LVAD, left ventricular assist device.

Exercise training

No guidelines describing the specific ET setting, modality and duration for VAD-supported patients are available, but, as described in *Table* 1, only limited evidence of implementation of light exercise intensities is available. A proper evaluation of symptoms and clinical signs, and functional capacity may help in identifying the most appropriate settings. Although it is reasonable to assume that longer ET interventions could improve physical fitness and QoL, the length and the long-term adherence to these interventions has not yet been described. Monitoring of exercise sessions is, however, crucial, at least initially, including supervision of the patient, clinical adaptation, and VAD functioning.[49,59]

To optimise exercise workload prescription, a symptom-limited CPET (or 6MWT) is advisable according to administrative constraints and local availability,[60,61] in order to aim at a peak workload below the pre-determined ventilatory anaerobic threshold. If the patient demonstrates a peak VO_2 >14 mL/kg/min or 6MWT distance >300 m, a more intensive exercise test can be considered. *Figure* 2 provides an algorithm for ET in VAD patients.

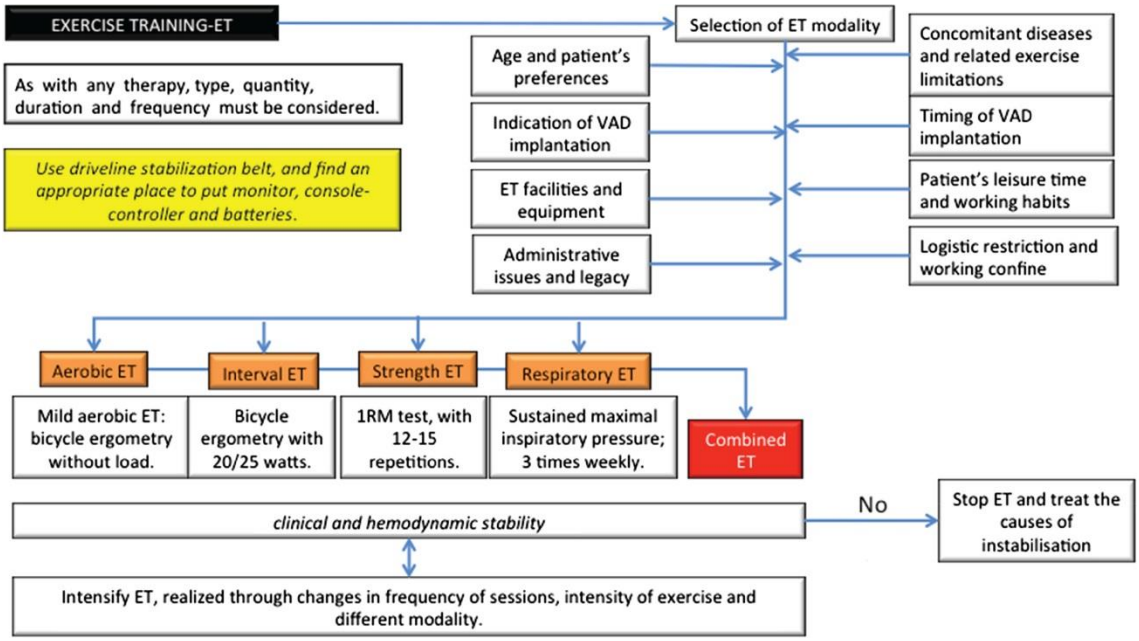

Figure 2. Ventricular assist device (VAD) recipients and exercise training. ET, exercise training.

Additionally, caution is recommended to avoid excessive sweating and dehydration, as well as rapid changes of posture from supine to upright positions, which could reduce venous return and negatively impact VAD function[40,49,51,59]: patients should be urged to drink regularly.

Each single ET session starts with a warm up phase and is followed by cool down phase and includes conditioning and endurance exercises: some exercise activities exert torsion on the driveline and, therefore, must be avoided.

In summary, based on the available experience in both HF[8,9] and VAD patients,[18,20-24] both dynamic and resistance exercise are indicated: treadmill (increase ramp, not speed), static bike, hamstring curls in standing position, leg press, bicep curls, core stability, respiratory muscle training, or arm ergometry. Contraindicated forms of exercise include running, rowing machine, cross trainer, abdominals exercises, bilateral arms above the head with weights or abduction with weights or swimming.

When to stop exercise

The exercise programme should be stopped if:

1. New symptoms or signs are elicited (i.e. fainting, headache, shortness of breath, chest pain or thoracic pressure, fever, supraventricular or ventricular arrhythmias).
2. VAD alarms or related problems occur.
3. Unexpected changes are detected in VAD parameters, i.e. flow, speed and watt operation.

Thus, monitoring of new signs and symptoms and VAD activity (alarms and related problems) during EM and ET sessions are needed (*Table* 5). Of note, arrhythmias may appear during EM and ET: ventricular arrhythmias are frequent in VAD supported patients,[62] due to a variety of causes.[63,64] Sometimes, ventricular arrhythmias persist over time: arrhythmias do not seem to be a major concern in recipients, since they provide mostly only modest haemodynamic deterioration, but they should be

carefully evaluated for, if sustained, they might cause device dysfunction, through a detrimental effect on the right ventricle, and they might also promote VAD-related symptoms. Before the prescription of specific anti-arrhythmic drugs, some features should be considered: optimization of pharmacological therapy (fluid infusion and/or reduction of daily dose of diuretics), device setting change (if appropriate), and postural changes during exercise sessions (i.e. different sitting position during bicycle ergometer). Of note, initially ET should be discontinued. When arrhythmias have been controlled at rest, exercise can be resumed, albeit at lower frequency and intensity, and all exercise activities should be strictly supervised and ECG monitored. This is a cautionary attitude, not yet supported by scientific evidence. During exercise, atrial fibrillation might occur: atrial fibrillation may worsen symptoms and lead to deterioration of the patient's clinical status, because of loss of atrioventricular synchrony and impaired ventricular filling; thus, electrical cardioversion should be considered.[62,63]

Different factors should be considered when planning an exercise programme in VAD recipients,[40,49,51,58,59,65] as summarised in *Table* 6.

Gaps in knowledge

1. The majority of studies so far have included mainly aerobic ET, and data focusing on different components of exercise physiology in VAD recipients are scarce. Thus, the potential benefits of long-term alternative ET programmes, such as resistance training, balance training and electrical muscle stimulation, should be still investigated. Prolonged periods of ET are needed to observe significant effects in myocardial bioenergetics. This effect might be associated with ventricular unloading and better organ perfusion provided by the VAD.
2. The vast majority of studies included only LVAD recipients, which highlights the need to investigate the benefit of ET in BiVAD patients.
3. Studies comparing exercise capacity pre- and post-VAD implantation are lacking and might add understanding on the role of ET in these patients.
4. Based on individual response and adaptation, EM usually starts early, a few days after the intervention, while ET is considered to continue indefinitely. However, the optimal timing and duration of each single ET session are not yet known.
5. At the beginning, ECG and clinical monitoring are vital: for how long VAD recipients should be monitored is as yet unknown. Intuitively, more complicated VAD recipients need more prolonged supervision.
6. The most effective way to make a patient confident and feeling safe, and the role of the caregiver have rarely been addressed. The potential beneficial contribution of patient education or of a dedicated website needs to be investigated.[66,67]
7. The important role of CPET in the exact prescription of ET is advocated: unfortunately, CPET is poorly implemented, and the interpretation is unclear in VAD patients. Where evidence is scant, anecdotal actions predominate, and therefore, for cautionary reasons, low intensity of aerobic training is here recommended.[51,66,67]
8. Arterial blood pressure is frequently indeterminable during ET or EM sessions; this is a limiting factor in monitoring EM and ET in VAD recipients. If detectable, measurement of blood pressure before and after exercise is useful, as an excessive rise in blood pressure may induce adverse events, including cerebral haemorrhage, stroke and pump thrombosis. Unfortunately, the blood pressure warning level is not known yet; new symptoms due to exertional maladaptations and alert device-related problems (i.e. excessive work) should be considered as alarming signs.
9. Ideally, ET may increase the possibility for a VAD implantation episode to lead a bridge-to-recovery situation, favouring the possibility of weaning, throughout the occurrence of metabolic changes in the failing myocardium and anabolic effects, together with the positive role an adjuvant pharmacotherapy.[68-70] The activation of thyroid hormone signalling has been suggested to act as a biological driver for the up-regulation of physiological growth signalling pathways as indicated by the training-induced activation of the pro-survival signalling Akt and inactivation of the anti-hypertrophic JNK in cardiomyocytes, leading to physiological growth even in the failing

myocardium. Anabolic pharmacotherapy (such as β_2-adrenergic receptor agonist clenbuterol) has been used to facilitate myocardial recovery.

10. VAD unloading therapy and ET might work together for the improvement of exercise capacity. Vignati *et al.*[32] showed that LVAD *per se* might improve exertional profile in recipients, independently of any ET approach. Only a randomised, non-exercising control group would be able to differentiate the improvements due to ET from those of device implantation.
11. The factors involved in determining exercise capacity in the post-VAD patient need to be investigated in more detail: it would be an advantage to identify the most important determinants in an individual patient and focusing therapeutic strategies on them. For instance, the approach to the sarcopenic patient may differ from that to the patient whose main limitation is RV dysfunction.
12. When ET should be started after implantation? Although ET should be commenced as soon as possible, warning and cautionary criteria are still to be established, and, up-to-now, personal experience guides the timing of ET in VAD recipients.
13. Target HR of ET sessions need to be defined, with an individualised approach being recommended.

Conclusions

Despite LV unloading, impairments persist in VAD patients, with functional capacity frequently below 50% of predicted peak VO_2. ET may provide additional benefit. Despite some encouraging small trials, clinical evidence remains limited. Actions should be taken to expand our understanding fn the potential role of ET therapy in VAD recipients to promote its wider implementation in clinical practice.

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