

Effects of pump speed changes on exercise capacity in patients supported with a left ventricular assist device – an overview

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Abstract: The implantation of left ventricular assist devices (LVAD) has been established as a successful treatment for terminal heart failure (HF) for many years. Patient benefits include significantly improved survival, as well as improved quality of life. However, peak exercise capacity following LVAD implantation remains considerably restricted. This could be due to the predominate use of continuous-flow pumps, which operate at a fixed rotational speed and do not adapt to exercise conditions. Therefore, current research is focused on whether, and to what extent, adaptations in pump speed can influence and improve patient exercise capacity. We performed a systematic PubMed literature search on this topic, and found 11 relevant studies with 161 patients. Exercise time, peak work load, total cardiac output (TCO), peak oxygen consumption (peak VO₂) and, if available, values at the anaerobic threshold (AT) were all taken into consideration. Possible complications were documented. This paper aims to compare the results from these studies in order to discuss the effects of pump speed adaptations on exercise capacity.

Keywords: Heart failure (HF); left ventricular assist device (LVAD); pump speed; exercise capacity; quality of life

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Introduction

As a disease affecting continually increasing patient numbers, heart failure (HF) remains a significant global health problem (1). The implantation of left ventricular assist devices (LVAD) has been successfully performed for treating terminal HF for several years (2-5).

Over the past few decades, a great deal of technical progress has been made in the field of LVAD therapy, leading to a reduction in the complication rate, as well as significant improvement in patient survival (6,7). The devices predominantly used today are continuous-flow pumps, which operate at a fixed rotational speed. The success of treatment with continuous-flow pumps is indisputable, with support durations of over 5 (up to 10) years

now often being achieved (8,9). With treatments of such duration, regaining adequate exercise capacity becomes important. Existing literature however shows that exercise capacity following LVAD implantation remains considerably restricted (10-12). One possible cause could arise from the pump speed which remains unchanged during exercise, leading to resulting pump flow which cannot sufficiently adapt to haemodynamic changes (10). As the underlying disease also limits the output via the aortic valve, the total cardiac output (TCO) cannot be sufficiently increased. Consequentially the prerequisites for good exercise capacity are not met as they are in healthy persons (13).

In order to tackle this problem head on, automatic pump control has been an ongoing research field for several years now. One of the goals of automatic pump

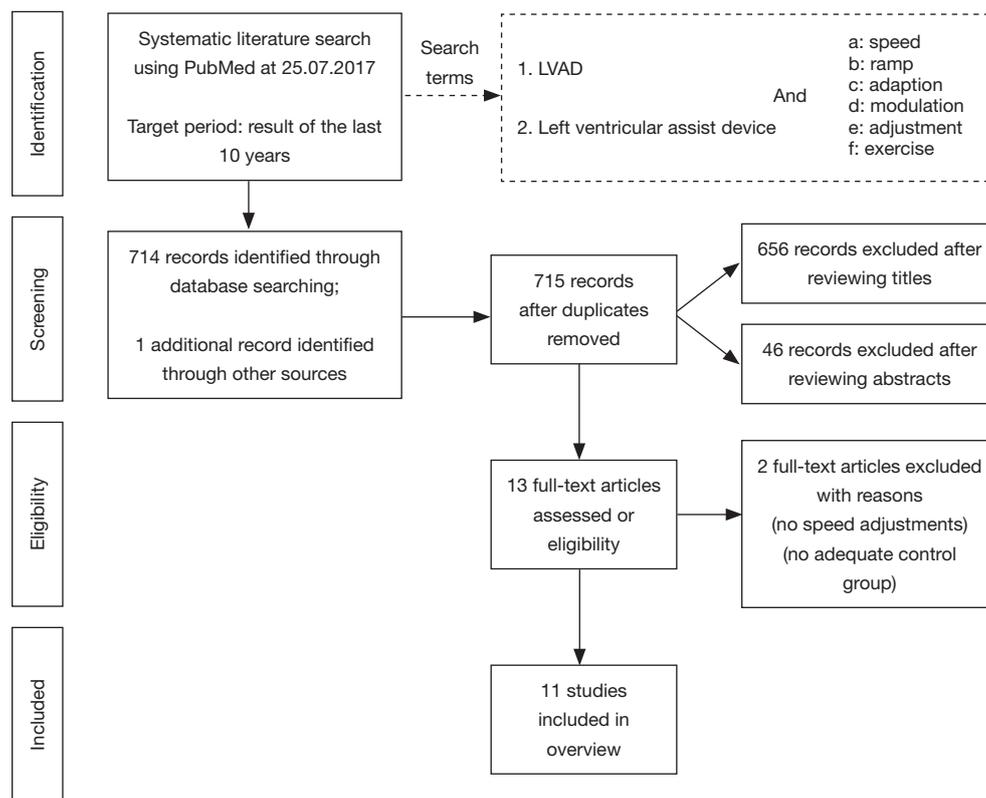


Figure 1 Flow diagram of inclusion criteria and selection procedure of appropriate studies according to PRISMA Guidelines (20). LVAD, left ventricular assist device.

control is to increase TCO during exercise in order to deliver more oxygen for the muscles. To date, many strategies have been developed and evaluated both *in silico* and *in vitro* (14-18). Such algorithms have yet to find their way into routine use and this will probably also remain the case in the coming years. Their introduction is currently hindered, amongst other things, by the non-existence of reliable and robust sensors which could provide information about the filling pressure of the heart in high temporal resolution (17,18).

The current research focus is on whether, and to what extent, automatic pump control can positively influence exercise capacity, which parameters are altered as a result, and what level of improvement can be expected (19). Numerous studies have been published over the past few years in which pump speed has been manually adjusted before or during physical exercise, under medical supervision. The aim of this paper is to compare the results from these studies and to discuss the impact of pump speed adaptations on exercise capacity.

Review strategy

A systematic research of the literature was undertaken in PubMed using defined search criteria (Figure 1). Studies from the last 10 years which investigated the effect of at least two different pump speed settings on exercise capacity were considered. Ultimately, 11 relevant studies with a total of 161 patients could be included (21-31). Table 1 summarizes patient baseline characteristics, device type, time after implantation, as well as the exercise mode and the various pump speed settings. In order to evaluate exercise capacity, we took into consideration exercise time, peak work load, TCO, peak oxygen consumption (peak VO_2) and, where available, values at the anaerobic threshold (AT). Possible complications were documented (Table 2).

Pump types and settings

Setting the LVAD pump speed (at rest) generally involves a compromise between suction prevention, optimal left-ventricular unloading and aortic valve opening. On one

Table 1 Comparison of general parameters of 11 studies evaluating exercise capacity at different pump speed settings in patients with a left ventricular assist device

Author	Year	N	Male (%)	Age (years)	Time after implantation (days)	Device	Exercise mode	Comparison	Changes in rpm
Jakovljevic <i>et al.</i> (21)	2010	12	100	33±13	169±97	HM II	Treadmill, modified Bruce protocol	Reduced speed vs. baseline speed	6,000 vs. 9,300 rpm
Brassard <i>et al.</i> (22)	2011	8	87.5	39±18	329±190	HM II	Semi-supine ergometer cycle, 60 W + 30 W every 2 minutes	Baseline speed vs. incremental increased speed	9,775±311 rpm vs. increasing speed from baseline +400 rpm per stage up to 11,500 rpm at peak exercise
Noor <i>et al.</i> (23)	2012	30	93	35±13	183	HM II	Treadmill, modified Bruce protocol	Reduced speed vs. baseline speed	6,000 vs. 9,000 rpm
Salamonsen <i>et al.</i> (24)	2013	7	89	43±15	NA	VentrAssist	Upright ergometer cycle, 5 or 10 W increase every minute	Reduced speed vs. increased speed	NA
Jung <i>et al.</i> (25)	2014	14	86	55±13	465±483	HM II	Upright ergometer cycle, 25 W + 25 W increase every 2 minutes	Baseline speed vs. incremental increased speed	9,357±238 rpm vs. increasing speed from baseline +400 rpm per stage up to 10,843±835 rpm at peak exercise
Mezzani <i>et al.</i> (27)	2014	22	95	57±9	156±186	HM II, HVAD, INCOR	Upright ergometer cycle, 20 W + 5 to 10 W increase every minute	Baseline speed vs. incremental increased speed	HM II: 9,156±240 rpm; HVAD: 2,628±133 rpm; INCOR: 7,230±277 rpm vs. increasing speed from baseline +1.5% every 10 W up to HM II: 9,622±307 rpm; HVAD: 2,779±123 rpm; INCOR: 8,090±296 rpm at peak exercise
Jung <i>et al.</i> (26)	2015	10	NA	60±4	668±596	HM II	Supine ergometer cycle, constant load at 25 W	Baseline speed vs. increased speed	9,300±241 vs. 10,100 rpm
Hayward <i>et al.</i> (28)	2015	10	80	39±16	274±230	VentrAssist	Upright ergometer cycle, 5–20 W + continuous increase of 10 W every minute	Reduced speed vs. baseline speed vs. increased speed	1,840±62 vs. 2,055±76 vs. 2,285±106 rpm
Fresiello <i>et al.</i> (29)	2016	14	71	57±16	258±171	HM II	Upright ergometer cycle, 10 W + 10 to 20 W increase per minute	Baseline speed vs. incremental increased speed	9,371±328 rpm vs. increasing speed from baseline +200 rpm every minute up to 10,843±567 rpm at peak exercise

Table 1 (continued)

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Author	Year	N	Male (%)	Age (years)	Time after implantation (days)	Device	Exercise mode	Comparison	Changes in rpm
Jung <i>et al.</i> (30)	2017	19	79	58±12	1,017±828	HM II	Upright ergometer cycle, 10 W increase per minute up to 10 W below AT	Baseline speed vs. increased speed	9,326±378 vs. 10,126±378 rpm
Vignati <i>et al.</i> (31)	2017	15	100	61±8	411±441	Jarvik 2000	Upright ergometer cycle, personalized ramp protocol	Reduced speed vs. increased speed	9,133±340 vs. 11,000 rpm

HM II, HeartMate II; NA, not available; rpm, revolutions per minute; AT, anaerobic threshold.

Table 2 Comparison of the results of 11 studies evaluating exercise capacity at different pump speed settings in patients with a left ventricular assist device

Author	Adverse events	Effects of higher rpm on peak exercise			Other remarkable effects of higher rpm
		Exercise time or work load	TCO	VO ₂	
Jakovljevic <i>et al.</i> (21)	None	↑ 18%	↑ 30%	↑ 23%	At peak exercise: CPO ↑ 39%
Brassard <i>et al.</i> (22)	None	↔	↔	NA	At 60 W: TCO ↑ 7%; MCAV ↑ 10%; At peak exercise: MCAV ↑ 8%
Noor <i>et al.</i> (23)	NA	↑ 10 %	NA	↔	At AT: VO ₂ ↔; in general: VE/VCO ₂ ↓ 13%; also, the impact of reduced speed was higher in patients with LVEF <40%
Salamonsen <i>et al.</i> (24)	NA	↑ 16 %	NA	↑ 9 %	At AT: VO ₂ ↑ 23%; At peak exercise: LVAD flow ↑ 35%; in general: BNP ↓ 78%
Jung <i>et al.</i> (25)	None	↔	NA	↑ 9 %	At peak exercise: LVAD flow ↑ 24%; in general: VE/VCO ₂ ↓ 13%
Mezzani <i>et al.</i> (27)	None	NA	↑ 7%	↑ 7 %	At peak exercise: LVAD flow ↑ 9%; in general: the impact of increasing speed was higher in patients with TAPSE >13 mm
Jung <i>et al.</i> (26)	NA	NA	NA	NA	At 25 W: TCO ↑ 17%, RVEDD ↑ 9%; in general: no impact of increasing speed in PCWP and LVEDD
Hayward <i>et al.</i> (28)	NA	↔	NA	↔	At peak exercise: LVAD flow ↑ 40%, NT-proBNP ↓ 21%; of note: impact of increasing speed on peak workload (P=0.08) and 6MWD (P=0.10)
Fresiello <i>et al.</i> (29)	Yes	↔	NA	↔	At peak exercise: LVAD flow ↑ 27%
Jung <i>et al.</i> (30)	None	NA	NA	NA	At 10 W below AT: exercise time ↑ 13%; in general: older patients tended to benefit from increased speed
Vignati <i>et al.</i> (31)	NA	NA	↑ 11%	↑ 8%	At AT: VO ₂ ↑ 11 %; in general: VE/VCO ₂ ↓ 13%

AT, anaerobic threshold; BNP, brain natriuretic peptide; CPO, cardiac power output; LVAD, left ventricular assist device; LVEDD, left ventricular end-diastolic diameter; MCAV, middle cerebral artery mean velocity; NA, not available; NT-proBNP, NT-pro-brain natriuretic peptide; rpm, revolutions per minute; PCWP, pulmonary capillary wedge pressure; RVEDD, right ventricular end-diastolic diameter; TAPSE, tricuspid annular plane systolic excursion; TCO, total cardiac output; VE/VCO₂, relationship between minute ventilation and the rate of carbon dioxide reduction; VO₂, oxygen uptake; 6MWD, six-minute walking distance.

Table 3 Characteristics of the five different left ventricular assist devices used in the included studies

Device	Pump type	Lowest rpm	Highest rpm	Peak pump flow
HM II (34)	Axial rotary pump	6,000	15,000	10 L
HVAD (35)	Centrifugal rotary pump	1,800	4,000	10 L
INCOR (36,37)	Axial rotary pump	5,000	10,000	7 L
Jarvik 2000 (38)	Axial rotary pump	8,000	12,000	8.5 L
VentrAssist (39)	Centrifugal rotary pump	1,800	3,000	NA

HM II, HeartMate II; NA, not available; rpm, revolutions per minute.

hand, sufficient TCO must be generated, but on the other possible complications (e.g., aortic valve fusion or arrhythmias) must be avoided (13,32,33).

The studies included used five different continuous-flow pumps in total. All devices had different rotational speed ranges (Table 3) and displayed individual pump characteristics (40). Shah *et al.* (41) recently reported that adapting the pump speed of the HeartMate II (HM II, Thoratec Corp., Pleasanton, CA, USA) by 400 rpm, for example, has the same effect on TCO (at rest) as adapting the HeartWare ventricular assist device (HVAD) device (HeartWare Inc., Framingham, MA, USA) by 130 rpm. Against this background, the speed adaptations performed in these studies must be evaluated individually. In the studies presented, four different types of pump speed were applied in total: reduced speed, baseline speed, increased speed and incremental increased speed during exercise. The magnitude of the speed adaptations differed in each case (Table 1).

Effects of pump speed adaptations

Safety and complications

A major problem when adapting pump speed is the risk of possible complications. In 5 out of the 11 studies, no short or long-term adverse events could be observed as a consequence of speed adaptations (21,22,25,27,30). Five other studies did not report any complications, but did not explicitly negate them either (23,24,26,28,31). Only Fresiello *et al.* (29) explicitly refer to observed complications: in their study, adverse events occurred in 2 out of 14 patients during incremental increased speed. In one case, non-sustained ventricular tachycardia was observed at maximum work load; in the other case, at the end of the examination the patient had a “hypotensive episode ... due to a shift of the interventricular septum towards the left

ventricle” (29).

Such data taken together suggests that increased speeds can incur risk. Overall, the LVAD speed was increased beyond the baseline level in 119 patients (from nine different studies); the two observed adverse events correspond to a percentage of 1.7 %. However, if we take a look at the maximum pump speed in the study in question (HM II, 10,843 rpm) (29), we see that in two studies with comparable (HM II, 10,843 rpm) (25) or higher (HM II, 11,500 rpm) (22) pump speeds, no complications occurred.

There can be no doubt that increasing LVAD pump speed without any cardiac control parameters (e.g., intracardiac pressure values) remains difficult and risky. Nevertheless, in most cases manual speed adaptations could be performed safely, albeit without the maximum possible pump speeds ever being reached (Tables 1,3). Further investigation is required to test this hypothesis.

Work load, exercise time and six-minute walking distance (6MWD)

The peak work load or peak exercise time was observed in seven different studies: in 3 of them (21,23,24), increases between 10% and 18% could be achieved, in one study (28) a trend was observed ($P=0.08$). In the other three studies, authors (22,25,29) were unable to observe significant improvements. A look at the various pump speed types reveals that effects were only observed when reduced speed was compared with baseline or increased speed. Increases beyond baseline speed were unable to improve peak work load or peak exercise time significantly.

At submaximal level, the study by Hayward *et al.* (28) suggests a trend towards improvement in the 6MWD ($P=0.10$), although here, too, the effect only seems to be between reduced and baseline speed. Jung *et al.* (30), on the other hand, could achieve a 13% improvement in exercise

time by changing from baseline speed to increased speed, with a constant work load just below AT.

TCO

TCO comprises LVAD flow and ejection through the aortic valve (11,13,26). The proportions can differ depending on the myocardial residual function, especially with increasing physical exercise (27,42). A change in pump speed can also shift the proportions (10,27,29). The combined overall quantity of blood which can be circulated through the body is crucial for exercise capacity.

Overall, 4 of the 11 studies measured TCO at peak exercise (21,22,27,31). In three studies, TCO could be significantly increased by means of a higher rotational speed (21,27,31). Comparable with workload and exercise time, the largest improvements could be achieved in conjunction with reduced speed *vs.* baseline speed (30%) (21). In contrast, increases beyond baseline speed achieved only little (7%) (27) or no effect (22).

TCO was observed at a submaximal level in two studies (22,26). Here, little to moderate effect (7% and 17%) could be observed. Notably, the study by Brassard *et al.* (22) was the only one to be conducted on a semi-supine ergometer cycle. Due to the deviating position of the body, the comparability of the TCO values in this study to those achieved on an upright ergometer cycle is difficult to estimate (43).

Oxygen consumption

VO₂ at peak exercise was observed in 8 of the 11 studies. In five studies, VO₂ could be significantly increased by means of a higher rotational speed (21,24,25,27,31). One study revealed a significant trend (28). The effects occurred independently of the initial pump speed (reduced or baseline) and were mostly within a range of 7–9%. In two studies no effects could be shown (23,29).

At a submaximal level VO₂ was observed in three studies. In two of them, a significant increase in VO₂ could be achieved at AT (11% and 23%) (24,31); in one study no effect could be seen (23).

Other effects

Speed adaptation affects not only TCO, but also blood pressure. At baseline speed, blood pressure was significantly

higher at peak exercise compared with reduced speed. In combination with TCO, a 39% increase in the cardiac power index could be observed, and this is seen as a marker for cardiac performance (21).

By increasing the pump speed, Brassard *et al.* (22) observed an 8% improvement in cerebral perfusion at peak exercise (10% at submaximal exercise), compared with baseline speed.

Three further studies (23,25,31) found during cardiopulmonary exercise test (CPET) evidence for a 13% reduction in the relationship between minute ventilation and the rate of carbon dioxide reduction (VE/VCO₂ slope), which is universally recognized as a prognostic mortality index for HF patients (44).

At the hormonal level, increasing pump speed (reduced speed *vs.* increased speed) leads to an observed decrease in brain natriuretic peptide (BNP) (78%) (24) and NT-pro-BNP (NT-proBNP) (21%) (28), an indication of significantly reduced pressure load in the cardiac atria.

Role of the residual myocardial function

The residual myocardial function of both ventricles generally plays an important role. Noor *et al.* (23) were able to prove that at reduced speed patients with a left-ventricular ejection fraction (LVEF) below 40% achieved a significantly poorer VO₂ at peak exercise and a poorer VE/VCO₂ slope during CPET; patients with an LVEF above 40% were able to compensate the reduced pump performance with their residual myocardial function. To date there has been no proven influence of LVEF when speed is increased beyond baseline.

The right-ventricular systolic function is also crucial (10,13). Through an increased pump speed and during physical exercise, venous reflux is considerably increased. There is a danger that the non-supported right ventricle is no longer fully capable of moving along the increased quantity of blood to the left ventricle (27,33). Mezzani *et al.* (27) found out that the only patients to profit from an increase in speed (improved peak VO₂) were those who had a tricuspid annular plane systolic excursion (TAPSE) of >13 mm.

Muthiah *et al.* (45) report that the right ventricle can additionally suffer an overload when the left ventricle is not sufficiently unloaded (despite increased speed) and more blood accumulate. Further investigation is required to corroborate such data.

Clinical implications

The parameters TCO, VO₂ and exercise time/work load are theoretically interdependent: through an increase in TCO, more oxygen can be transported through the circulatory system and ultimately be absorbed by the muscle (provided that oxidative capacity is sufficient). Through this increased supply of oxygen, more energy is made available to the muscle, ultimately leading to an increase in exercise time/work load (46,47).

Corresponding to these considerations, *Table 2* shows that in most cases a study measured similar effects on the mentioned parameters. It was conspicuous that an acute reduction in pump speed below baseline speed led to considerable loss in exercise capacity (21,23,24,28). This particularly affects patients with a poor left-ventricular residual function who are unable to compensate the reduced pump flow (23). These results are in line with those of Camboni *et al.* (48), who found that an open aortic valve strategy leads to impaired exercise capacity and hemodynamics.

To date, increases in pump speed beyond baseline have had only little (25,27) or no (22,29) effect on exercise capacity. Fatigue and dyspnoea scores (28) as well as the rating of perceived exertion (30) remain unchanged. In one study, such increases even led to complications (29).

One possible reason for insufficient improvement in exercise capacity at increased speed is that LVAD patients often have an impaired right-ventricular systolic function (27,33). Some authors also report that pump speeds were probably not increased to a sufficient degree (22,28). A comparison between *Table 1* and *Table 3* shows, at least, that in no study was the rotational speed increased to its maximum level, although it is also true that this could not be expected for safety reasons.

In contrast to peak exercise, it was interesting that the effects of increasing pump speed at submaximal level were positive (22,24,26,30,31). This is very promising and should be pursued further since improved submaximal capacity (AT) is crucial to the mastering of everyday tasks (30) and can lead to improved patient participation.

Conclusions

In conclusion, it remains unclear whether or not pump speed is the crucial determining factor in the bid to increase exercise capacity (29). There are at least indications that physiological pump speed adaptation can contribute to

improved submaximal exercise capacity which is crucial for activities of daily living. An increase in peak exercise, in contrast, seems to be only possible in some patients. However, research attempts at physiological pump speed adaptation are yet to be realized. In future, further studies will be required in order to improve our understanding of the special hemodynamics in LVAD patients under exercise conditions, and to identify those patients who could benefit from automatic pump speed control.

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Footnote

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