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LVAD speed increase during exercise, which patients would benefit the most? A simulation study.

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Simulation of LVAD hemodynamics during exercise

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Abstract

Patients supported with an LVAD have impaired cardiovascular adaptations during exercise, resulting in reduced total cardiac output and exercise intolerance. The aim of this study is to report associations among these impaired cardiovascular parameters and exercise hemodynamics, and to identify in which conditions an LVAD speed increase can provide substantial benefits to exercise.

A cardiorespiratory simulator was used to reproduce the average hemodynamics of LVAD patients at exercise. Then, a sensitivity study was conducted where cardiovascular parameters were changed individually ±20% of their baseline value at exercise (heartrate, left/right ventricular contractility, total peripheral resistance and valve pathologies). Simulations were performed at a baseline LVAD speed of 2700 rpm and repeated at 3500 rpm to evaluate the benefits of a higher LVAD support on hemodynamics.

Total cardiac output (TCO) was mostly impaired by a poor left ventricular contractility or vasodilation at exercise (-0.6 L/min), followed by a poor chronotropic response (-0.3 L/min) and by a poor right ventricular contractility (-0.2 L/min). LVAD speed increase better unloads the left ventricle and improves total cardiac output in all the simulated conditions. The most substantial benefits from LVAD speed increase were observed in case of poor left ventricular contractility (TCO +1.6 l/min) and vascular dysfunction (TCO +1.4 l/min) followed by lower heartrate (TCO +1.3 l/min) and impaired right ventricular contractility (TCO +1.1 l/min).

Despite the presence of the LVAD, exercise hemodynamic is strongly depending on the ability of the cardiovascular system to adapt to exercise. A poor left ventricular inotropic response and a poor vascular function can strongly impair cardiac output at exercise. In these conditions LVAD speed increase can be an effective strategy to augment total cardiac output and unload the left ventricle. These results evidence the need to design a physiological LVAD speed controller, tailored on specific patient's needs.

Introduction

Left ventricular assist devices (LVADs) have become an established therapy to manage end-stage heart failure patients and implantation numbers increased within the last decade (1). Despite patients' hemodynamic normalization at rest and improvements in functional capacity after LVAD implantation, exercise capacity remains substantially lower compared to gender and age predicted values (2).

LVAD patients share typical multiorgan impairments observed in heart failure patients, such as chronotropic incompetence, poor left/right ventricular function, valve diseases, impaired autonomic functions along with others (2). As a result of these impairments, substantial differences are observed both in terms of exercise performance and in the ability to increase total cardiac output (TCO) (2).

Current LVADs work at a constant pump speed and do not embed physiological controllers to adapt the support to body needs at exercise. Therefore, patients mainly rely on their remaining cardiac function to increase TCO by the output through the aortic valve (Q_{AV}) and achieve higher peak VO_2 levels (3,4). Dependencies between low LVAD speed (below baseline value) and reduced exercise capacities were found in previous clinical studies (5,6). However, other studies investigating the effects of an LVAD speed increase under exertion, reported moderate to no improvements in terms of exercise capacity or TCO (7–13). Given the large patients diversity in terms of cardiovascular impairments, the benefits of an increased LVAD speed during exercise are still unclear.

How and to which extent each cardiovascular impairment affects exercise hemodynamics, and in turn how the hemodynamics would be affected by a higher LVAD support at exercise, is difficult to investigate clinically. The cardiovascular system, highly regulated by several physiological controls, the presence of comorbidities and the LVAD itself, define a complex system where cause effects mechanisms are hardly identifiable.

Given these premises, this work offers a systematic analysis of exercise hemodynamics in LVAD patients. Using a computational simulator, cardiovascular parameters were changed individually to obtain different exercise profiles, used to analyse the contribution of LVAD speed increase in accommodating a higher TCO. This simulation study offers an analysis on the underlying physiological mechanisms limiting exercise capacity in LVAD patients and defines exercise profiles that would benefit from an LVAD speed control the most.

Methods

Cardiorespiratory simulator

A computational lumped parameters simulator was used for the study. The simulator was implemented in LabVIEW (National Instruments Austin, TX) and it represents the cardiovascular and respiratory systems with the relative impairment observed in heart failure condition. A general overview of the simulator is reported in Figure 1, more information about its components and its validation are reported in (14,15). The cardiovascular model included a time varying elastance model for the representation of the atria and ventricles, contracting in diastole and systole respectively. Heart valves were represented with a diode and a resistance, in case of regurgitation a backflow resistance was added to the model. The circulation was split into different circulatory regions (ascending and descending aorta, upper body, kidneys, splanchnic circulation, left and right leg, superior and inferior vena cava and pulmonary circulation) each represented by a Windkessel model connected in series or in parallel with the rest of the circulation. The ventilation was represented in terms of flow (tidal volume and frequency) and pleural pressure that in turn affects the intrathoracic pressure in the rib cage. The ventilated air was used to reproduce the gas exchange in the

lungs for the oxygenation and deoxygenation of blood. In the peripheral tissues, the oxygen consumption and production of carbon dioxide was represented locally, according to the metabolic state of the considered circulatory region.

Specific cardiorespiratory control mechanisms permitted to reproduce the evolution of hemodynamics from rest to exercise condition. A model of autonomic control regulated the systemic circulation and induced vasoconstriction during exercise due to sympathetic nerve overstimulation and vagal withdrawal. The autonomic control regulated also the positive inotropic and chronotropic response of the heart during exercise. A model of metabolic control regulated the vasodilation in the peripheral tissues, if hypoxia was detected. Concerning ventilation, a specific control was implemented that regulated tidal volume and ventilation frequency according to the oxygen and carbon dioxide partial pressure sensed in the upper body.

LVAD model

A model of a HVAD pump (Medtronic Inc., Minneapolis, MN, USA) was implemented and connected between the left ventricle (LV) and the aorta. The model included an inflow cannula (diameter 1.9 cm and length 2.5 cm) and outflow graft (diameter 0.9 cm and length 20 cm), each modelled with an inertance and a resistance as reported in (16). For the pump a second order polynomial equation was used to reproduce the pressure-flow characteristics (16), in line with the in-vitro measurements reported in (17).

Simulator verification

In the present work we started from an average hemodynamic condition of LVAD patients at rest. The HVAD was run at a speed of 2700 rpm to obtain a full support with an LVAD flow rate (Q_{LVAD}) of 4.8 L/min. The simulator was left running until a steady condition at rest was reached. Then simulations data were collected and compared to clinical data from the literature (5,7,9,10,18).

For exercise, a bicycle ergometer test of 80 watts was simulated, corresponding to an oxygen uptake of 15.2 ml/min/kg, a typical maximum value reached in LVAD patients (19). Thanks to the implemented control mechanisms, the simulator automatically performed the following adaptations to exercise: increase in TCO and ventilation, vasodilation, increase in heart rate and contractility. The simulator was left run until a steady state of the exercise condition was reached. Then simulations data were collected and compared to clinical data from the literature (5,7,9,10,18).

The exercise simulation of this “average” LVAD patient will be referred to as baseline (BL) hereafter.

Simulation of different exercise profiles

In addition to the BL patient, other exercise profiles were simulated. For the purpose, some cardiovascular parameters were released from the control mechanisms and manually changed one at a time. Heart rate (HR), left/right ventricular contractility (EmaxL/EmaxR) and total peripheral resistance (TPR) were

increased and decreased of 20% compared to BL simulation at exercise. This permitted to mimic LVAD patients with a better/poorer chronotropic, inotropic or peripheral circulatory response to exercise. Additionally, aortic insufficiency (AI) and aortic valve stenosis (AS) sometimes observed in LVAD patients, were also simulated (20,21). A comprehensive overview of the cardiovascular parameters at BL and of their manual changes are reported in Table 1 and in SupplFig1. To investigate the potential benefit with an increased LVAD speed, each exercise profile was analyzed at a baseline LVAD speed of 2700 and at an increased speed of 3500rpm.

Results

BL simulation

The BL profile simulated at rest and at exercise was compared to clinical data taken from the literature (5,7,9,10,18). Results are reported in Table 2 and show that the simulator can replicate the exercise response of LVAD patients in terms of central hemodynamics, TCO and its repartition between the LVAD and the LV. While at rest the LV is in full support and TCO is 4.8 L/min, at exercise TCO increases to 6.8 L/min with the LVAD contribution 5.3 L/min and of the LV 1.5 L/min. For a more detailed validation, additional results are reported in (14,15).

Effects of cardiovascular parameters on Q_{AV}, Q_{LVAD} and TCO

Starting from the BL profile, other exercise responses were simulated by manually changing cardiovascular parameters individually. The results of these simulations are shown in Figure 2 and evidence the following changes in TCO and its repartition between Q_{AV} and Q_{LVAD}:

- HR: the comparison between HR+ and HR- indicated that a better chronotropic response significantly improved TCO (+0.7 L/min) at exercise. This was mostly at the expense of the left ventricle, since a higher HR induced a significant increase in Q_{AV} (+0.5 L/min) and only a minimal increase in Q_{LVAD} (+0.1 L/min).
- EmaxL: the comparison between EmaxL+ and EmaxL- showed that a better left ventricular inotropic response resulted in a higher TCO (+1.3 L/min), mostly accommodated by the LV (+2.5 L/min) that overcomes the LVAD. In fact EmaxL+ resulted in an increased mean aortic pressure (see SupplTab1) and in a consequent decreased Q_{LVAD} (-1.2 L/min). Hence, higher EmaxL levels during exercise are associated with a higher Q_{AV} and with an increase in afterload that ultimately limits Q_{LVAD}.
- EmaxR: the comparison between EmaxR+ and EmaxR- evidenced that a better right ventricular function positively affected TCO (+0.4 L/min) mainly at the expenses of the Q_{LVAD} (+0.4 L/min). The general effects of EmaxR+ on TCO were less substantial compared to those observed for HR+ and EmaxL+.

- TPR: the comparison between TPR+ and TPR- evidenced that a lower TPR resulted in an increased TCO (+1.3 L/min), as the combined contribution of Q_{LVAD} (+0.4 L/min) and Q_{AV} (+0.9 L/min).
- AI: TCO at exercise progressively decreased (6.5, 6.4 and 6.0 L/min) for increasing levels of AI severity (1,2,3). Q_{LVAD} increased (5.6, 5.7 and 6.2 L/min) for higher AI grades, resulting in more regurgitant flow (see SupplTab1). For mild regurgitation (AI1) the systolic Q_{AV} exceeded diastolic regurgitant flow, thus resulting in an overall positive Q_{AV} over the heart cycle of +0.9 L/min. For severe aortic insufficiency (AI 3), regurgitant flow exceeded systolic Q_{AV} resulting in a negative Q_{AV} over the heart cycle of -0.3 L/min.
- AS: the presence of AS (severity 1,2,3) limits Q_{AV} (1.3, 1.2 and 0.9 L/min) with consequent increase in Q_{LVAD} (5.4, 5.5 and 5.6 L/min) . This finally resulted in lower TCOs (6.7, 6.6 and 6.5 L/min) since the limited output through the aortic valve was not fully compensated by the LVAD pump flow.

Hemodynamics during exercise with different LVAD speeds

The simulations of the BL profile and of the other exercise profiles were repeated also with a higher LVAD speed of 3500 rpm. The resulting hemodynamics were compared to the corresponding simulations with baseline LVAD speed of 2700 rpm. The comparative analysis was focused on TCO and LAP_{MAX} and is reported in Figure 3.

For the BL exercise profile, the increase in LVAD speed augmented TCO of +1.0 L/min and reduced LAP_{MAX} by -6.1 mmHg. These changes indicated the possible benefits a BL patient could experience from an LVAD speed modulation under exertion. More pronounced benefits were observed for EmaxL-, TPR+, HR- and AS1,2,3 profiles. Less benefit, below those observed for BL, occurred for the simulations EmaxL+, HR+ and AI.

Discussion

Aim of this work was to investigate the exercise hemodynamics of LVAD patients and the effects of LVAD speed increase. A cardiorespiratory simulator was used to reproduce the hemodynamics of patients in agreement to literature data (BL). Additionally, different exercise profiles were created to investigate how a single cardiovascular impairment can affect exercise hemodynamics.

Q_{AV} and Q_{LVAD} in different exercise profiles

The change of cardiovascular parameters elicited to different Q_{AV} and Q_{LVAD} responses, as reported in Figure 2. A rough classification is provided below:

- Concomitant increase in Q_{AV} and Q_{LVAD}: the exercise profile with a better chronotropic response (HR+), better right ventricular contractility (EmaxR+) and a better vasodilation (TPR-) elicited to both Q_{AV} and Q_{LVAD} increase compared to the BL patient.

- Reduction in Q_{AV} and increase in Q_{LVAD}: AS and AI reduce Q_{AV} and increase Q_{LVAD} compared to BL, in the first case due to the obstruction the blood flow encounters through the aortic valve (AV), in the second case due to the backflow through the AV in diastole.
- Reduction in Q_{LVAD} and increase in Q_{AV}: a better inotropic response of the LV (EmaxL+) positively affects Q_{AV} while limiting Q_{LVAD}. This inverse trend is named "competing mechanism" between the LV and the LVAD and has been discussed previously (3,22). The competing mechanism occurs with AV opening and results in a reduced sensitivity of Q_{LVAD} to preload compared to full-support. A higher Q_{AV} augments systolic aortic pressure and consequently Q_{LVAD} reduces. Exercise is a potent facilitator of the competing mechanism due to the positive inotropic and chronotropic response combined with peripheral vasodilation and an augmented venous return that facilitate the LV to eject.

Evolution of TCO in different exercise profiles

- EmaxL*:* among all the investigated parameters, EmaxL is one of the most important in assuring a higher TCO at exercise. These results are in line with previous clinical studies evidencing the crucial role of the residual LV function in eliciting a higher TCO and exercise capacity (3,4,9). Noor et al (6) observed that patients with a residual LV contractility are able to better accommodate an increase in TCO, resulting in higher exercise capacities. Fresiello et al (8) reported that LVAD power increased less at peak exertion in patients with better exercise capacity, indicating a possible increase in TCO mostly at the expenses of the LV. In addition, Gross et al. (3) reported the importance of the cardiac response during exercise by observing correlations of peak oxygen consumption with HR and AV status, whereas Q_{LVAD} showed no correlation.
- EmaxR: substantial changes in LAP_{MAX} (+5 mmHg) and pulmonary pressure (+5.2 mmHg) compared to BL were observed for EmaxR+. This rather utterly high LAP_{MAX} indicates an insufficient capacity of the LVAD+LV system in balancing the increased right ventricular output, in agreement with (23,24). This ultimately translates into a rather modest increase in TCO (+0.2 L/min). This mild effect could be the reason why different relationships between the resting RV function and exercise capacity were reported in clinical studies (10, 11, 25) with a non clear understanding of the impact of the RV on patient's outcome under exertion.
- TPR: is another important parameter in affecting exercise hemodynamics. Impairments in vasodilation with exercise (TPR+) resulted in a reduced TCO (-0.6 L/min compared to BL). This result is in agreement with the clinical study of Martina et al. (4), in which vascular resistance was reported as the strongest correlated parameter to TCO at exercise. Several clinical observations reported compromised vascular function in patients assisted with a continuous flow LVAD (26–28). The effects of vascular impairment at exercise is difficult to be quantified in clinics, due to the challenges in collecting arterial pressure data in LVAD patients non-invasively.

- HR: a higher HR helps the RV in pumping more blood to the pulmonary circulation, resulting in a higher pulmonary pressure (+4.6 mmHg) and a higher LAP_{MAX} (+3.8 mmHg) compared to HR- (see SupplTab1). The increased HR and LV preload resolved in a higher Q_{AV} (+0.5 L/min) while only a minimal increase in Q_{LVAD} (+0.1 L/min). This rather mild relationship between HR and Q_{LVAD} during exercise is in agreement with previous clinical observations (3,18). Regardless the individual contribution of the LV and the LVAD, simulations evidenced that an increase in HR does translate ultimately in an increase in TCO (+0.7 L/min). This is in line with previous studies demonstrating a strict positive correlation between peak HRs and exercise capacity in LVAD patients (3,6,9,29).

In summary, the parameters mostly sensitive to change TCO during exercise are in order (see Figure 2): EmaxL± (+1.3 L/min), TPR± (-1.3 L/min), HR± (+0.7 L/min) and EmaxR± (+0.4 L/min). Additionally, the presence of AI or AS negatively affect hemodynamics by promoting aortic backflow in the first case and by halting Q_{AV} in the second case.

Effects of LVAD speed increase in different exercise profiles

Sensitivity to LVAD speed increase in different exercise profiles

It was evidenced that LVAD patients at exercise are characterized by lower TCO and a higher LAP_{MAX} compared to healthy subjects (23). It is therefore of clinical interest to evaluate if and for which patients, an increase in LVAD speed could counteract these two phenomena. Hence, in this work benefits with LVAD speed increase were quantified in terms of increase in TCO and decrease in LAP_{MAX} compared to BL.

Results evidenced that for the BL patient an LVAD speed increase at exercise would significantly improve TCO (+1.0 L/min) and decrease LAP_{MAX} (-6.1 mmHg). The improvement in TCO predicted by the simulator is in agreement with Mezzani et al (from 7.1±1.8 to 7.6±1.9 L/min) (11).

Concerning the other simulated exercise profiles, LVAD speed increase evidenced benefits in all conditions but with different magnitudes. The simulations with cardiac or vascular impairments such as EmaxL-, HR-, TPR+ or AS showed higher benefits from an increased LVAD speed during exercise compared to BL and to their less impaired counterparts EmaxL+, HR+, TPR-. These findings are in line with (30) that older patients tended to benefit more from LVAD speed increase during exercise than younger patients. As a matter of fact, the chronic changes of the cardiovascular system in older LVAD patients most likely would result in a poorer EmaxL, higher TPR and lower peak HR.

How much should we increase LVAD speed?

An overview on the effect of LVAD speed increase on peak exercise was reported Laoutaris (31). In two studies a positive increase in peak oxygen consumption was found, 11 studies reported moderate increase

within the range of 7-9%, two studies reported little or no effect on TCO and five studies did not observe significant differences in oxygen consumption at peak exercise. Most of these studies however used only mild to moderate increase in LVAD speed, executed equally on the entire cohort regardless the specific hemodynamic condition of each patient.

In our study, we operated a substantial increase in HVAD speed, higher than what was tested in clinics and even beyond the clinical limit of 3200 rpm. This choice was motivated from the observation that all the exercise profiles simulated evidenced a high LAP_{MAX}. This observation is in agreement with Hayward et al (23) that evidenced a substantial increase pulmonary capillary wedge pressure in LVAD patients performing exercise. As such, there is room to higher LVAD speed increase than what has been tested so far clinically.

Especially EmaxL-, EmaxR+ and HR+ exercise profiles, show high values of LAP_{MAX} due to an unbalance of the LV+LVAD system in accommodating the flow of the RV. In these conditions it would be beneficial to operate even further LVAD speed increases.

In summary, according to the degree of cardiac or peripheral impairment more or less hemodynamic benefit can be expected from the increase in LVAD speed. Furthermore, high chronotropic response or a preserved right heart function may lead to increased preload at exercise indicating a higher tolerance for further LVAD speed upregulation.

Study limitations

This work is a simulation study with clear limitations since the computational simulator is unable to mimic the entire complexity of the human body at rest and during exercise. The pulmonary circulation is rather simple with no hypoxic vasoconstriction mechanisms. (15) The cardiorespiratory simulator reproduces LVAD hemodynamics from scattered clinical data taken from different sources, although results of this study are in line with clinical evidences. The increased LVAD speed (3500 rpm) is out of the range of recommended HVAD pump speeds (2400 to 3200 rpm) (32) and may increase shear stress.

Conclusion

The impact of LVAD speed increase on exercise hemodynamics is subject depending and is not completely understood at present. A cardiovascular simulator was used to explain this inter-subject variability and the different effects that LVAD speed increase can elicit during exercise. Increased LVAD speed resulted in higher total cardiac output and better left ventricular unloading for all the simulated exercise profiles. Hemodynamic improvements were more evident in case of a poorer inotropic response, chronotropic response or peripheral vasodilation. High ventricular preloads at exercise were observed for simulations

with a poor left ventricular contractility or with a better right ventricular function, indicating a left/right hemodynamic unbalance and the possibility to operate even further LVAD speed increase.

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List of abbreviations

AV… aortic valve

AI … aortic Insufficiency

AS … aortic Stenosis

BL … baseline simulation

EmaxL/EmaxR … left/right ventricular contractility

HR … heartrate

LAP_{MAX} … maximum left atrial pressure

LV … left ventricle

LVAD … left ventricular assist device

PAP … pulmonary arterial pressure

Q_{LVAD} … LVAD flow-rate

Q_{AV}… aortic valve flow

TCO … total cardiac output

TPR … total peripheral resistance

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Tables

Table 1: Cardiovascular parameters used to simulate different exercise profiles. Simulations are labelled as: baseline condition (BL), higher/lower left ventricular contractility (EmaxL+/ EmaxL-), higher/lower right ventricular contractility (EmaxR+/ EmaxR-), higher/lower total peripheral resistance (TPR+/ TPR-), aortic regurgitation (AR) and aortic valve stenosis (AS).

Cardiovascular parameter	Cardiovascular Parameter Values (Baseline/-20%/+20%)	Simulation Label
Heart Rate [bpm]	113/90/136	BL/HR-/HR+
Left ventricular contractility [mmHg/cm³]	0.65/0.52/0.78	BL/EmaxL-/EmaxL+
Right ventricular Contractility [mmHg/cm³]	0.46/0.37/0.55	BL/EmaxR-/EmaxR+
Total peripheral resistance [mmHg*s/cm³]	0.47/0.37/0.56	BL/TPR-/TPR+
Aortic insufficiency	None/mild/moderate/severe	BL/AI1/ AI2/ AI3
Aortic stenosis	None/mild/moderate/severe	BL/AS1/ AS2/ AS3

Table 2: Comparison between simulated and literature data (5,7,9,10,19) at rest and at exercise for the baseline patient (BL).

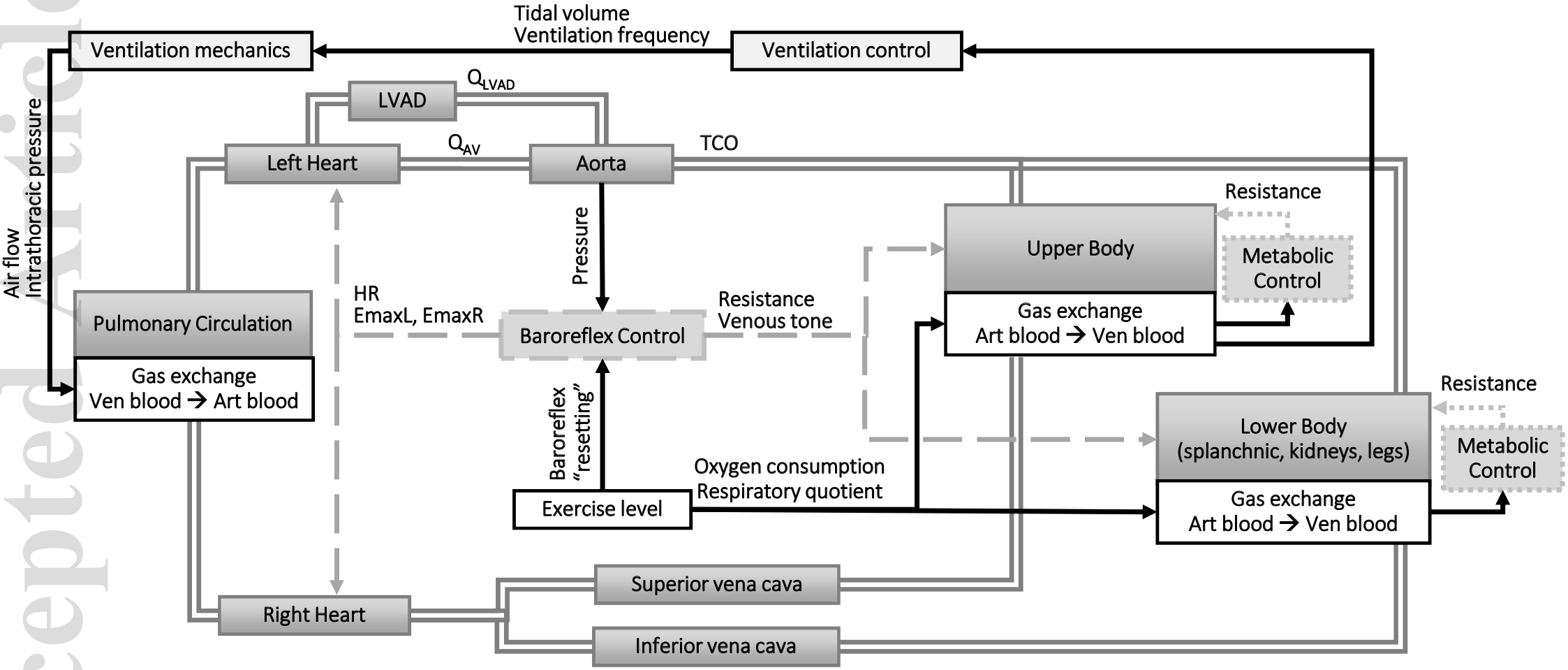
	TCO [L/min]	Q_{LVAD} [L/min]	Q_{AV} [L/min]	HR [bpm]	PAP [mmHg]	LAP_{MAX} [mmHg]	AOP_{MEAN} [mmHg]	RAP [mmHg]
BL Rest - Simulation	4.8	4.8	0.0	75	19.3	13.2	92	8.7
BL Rest - Literature	5.0±0.4	5.3±0.0	0.0±0.0	76±3	21.5±1.2	15.1±2.7	91±9	7.4±1.4
BL Exercise- Simulation	6.8	5.3	1.5	113	34.3	25.6	100	16.5
BL Exercise- Literature	7.3±1.4	6.1±0.1	1.6±1.5	117±15	31.6±1.8	22.3±3.1	98±13	13.0±4.0

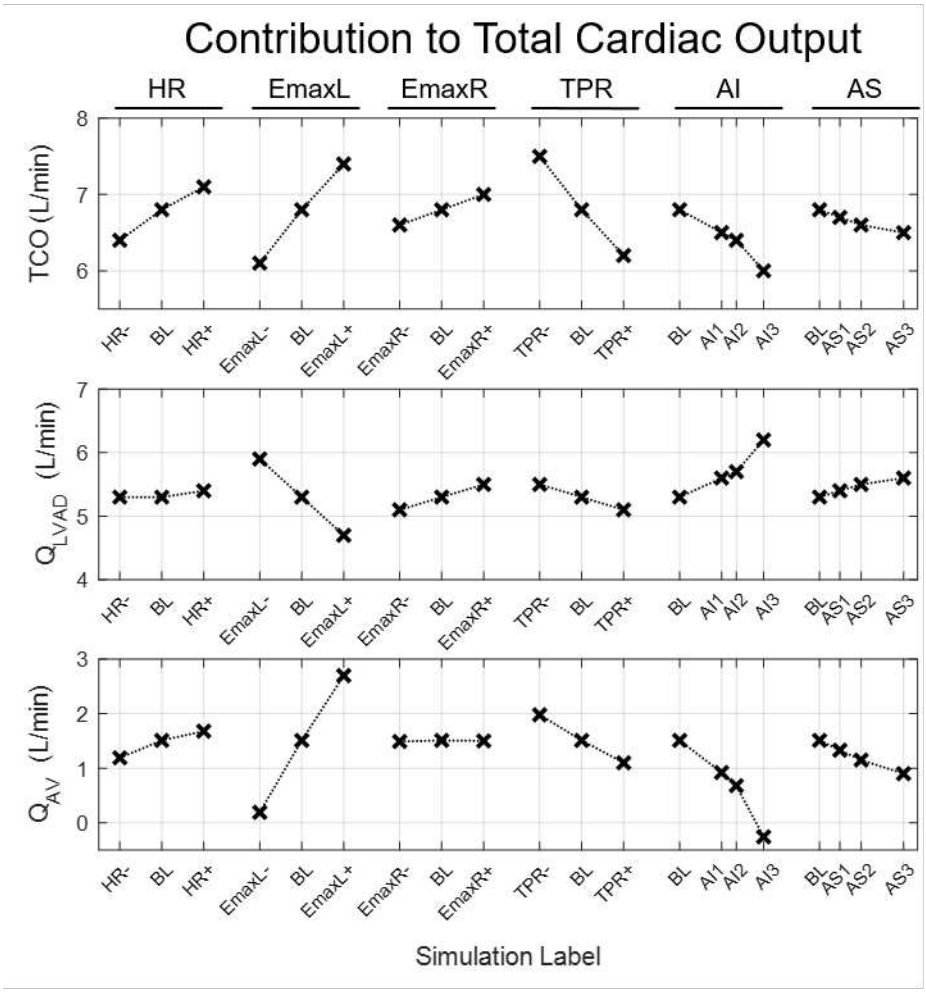
Figure legends

Figure 1: Block diagram of the cardiorespiratory simulator. The cardiovascular model includes left and right hearts, systemic and pulmonary circulations, baroreflex and metabolic peripheral controls. The respiratory model includes ventilation mechanics, gas exchange and ventilation control. The simulator is capable of mimicking the hemodynamic and respiratory response to exercise physiology in heart failure condition. The model also reproduces the effects of an LVAD connected between the left ventricle and the ascending aorta.

Figure 2: Simulation results for total cardiac output (TCO), LVAD flow (Q_{LVAD}) and left ventricular flow (Q_{AV}) at exercise for the baseline patient and for the other exercise profiles.

Figure 3: Hemodynamic benefits due to an increase in LVAD speed during exercise (from 2700 to 3500 rpm). The dashed line indicates the improvements in total cardiac output (TCO) and maximum left atrial pressure (LAP_{max}) observed from the increase in LVAD speed in BL simulation.





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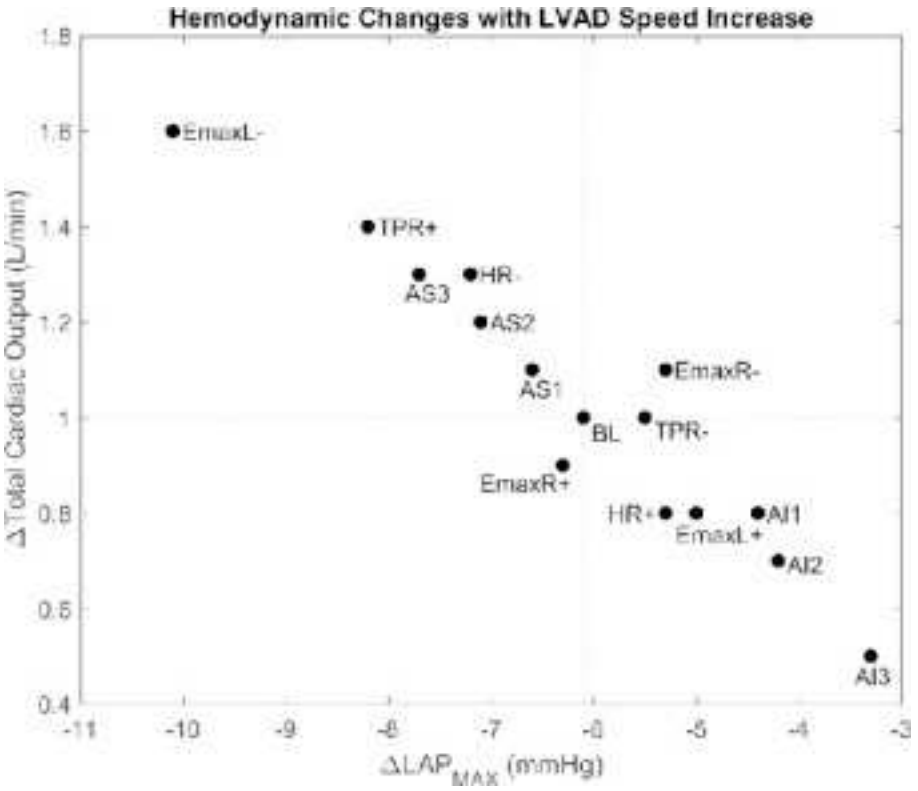

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