Heart Rate and $\dot{V}O_2$ Concordance in Continuous-Flow Left Ventricular Assist Devices

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ABSTRACT

KERRIGAN, D. J., C. T. WILLIAMS, C. A. BRAWNER, J. K. EHRMAN, M. A. SAVAL, E. L. PETERSON, D. E. LANFEAR, C. TITA, M. VELEZ, Y. SELEKTOR, and S. J. KETEYIAN. Heart Rate and $\dot{V}O_2$ Concordance in Continuous-Flow Left Ventricular Assist Devices. *Med. Sci. Sports Exerc.*, Vol. 48, No. 3, pp. 363–367, 2016. The American College of Sports Medicine currently recommends the HR reserve (HRR) method to guide exercise in individuals who have heart failure with reduced ejection fraction. This recommendation is based on the known association between %HRR and percentage of $\dot{V}O_2$ reserve (%$\dot{V}O_2$R) in this population. However, to our knowledge, no studies exist regarding this relation in individuals with a left ventricular assist device (LVAD). **Purpose**: This article aimed to describe the relation between $\dot{V}O_2$ and surrogate markers of exercise intensity among patients with LVAD. **Methods**: Patients with continuous-flow LVAD (n = 24, seven females) completed a symptom-limited graded exercise test on a treadmill. HR and $\dot{V}O_2$ were measured continuously and averaged every 20 s. Regression equations were determined using a generalized estimating equation to predict %$\dot{V}O_2$R from %HRR, Borg RPE, and LVAD flow, overall and stratified by presence of pacing. **Results**: Although the association between %HRR and %$\dot{V}O_2$R was good (R^2 = 0.75), the slope and y-intercept for %HRR versus %$\dot{V}O_2$R was different from the line of identity (P = 0.002). However, when paced subjects were excluded (n = 8) from the analysis, there was no significant difference between the slope and y-intercept (= 0.036 + 0.937 × %HRR; SEE, 2%; P = 0.052). RPE showed a strong association with %$\dot{V}O_2$R (R^2 = 0.84), whereas LVAD flow showed a weak (albeit statistically significant) association (R^2 = 0.05). Both had slopes and y-intercepts that were different from the line of identity (P < 0.05). **Conclusions**: In patients with LVAD who are not paced during exercise, the use of %HRR is a good predictor of %$\dot{V}O_2$R. However, for patients in this population who are also paced during exercise, RPE is a suitable surrogate measure of exercise intensity. **Key Words:** LEFT VENTRICULAR ASSIST DEVICE, HEART RATE RESERVE, $\dot{V}O_2$ RESERVE, EXERCISE PRESCRIPTION, PACEMAKER

Because of the limited availability of donors for heart transplant, the use of implantable left ventricular assist devices (LVAD) has proliferated as a therapeutic option for patients with end-stage heart failure (7). To date, more than 10,000 continuous-flow devices have been implanted, with 1- and 2-yr survival rates at 80% and 70%, respectively (7). As the length of time that patients remain on these devices has extended, adjunctive therapies are needed to optimize quality of life and functional capacity. Exercise training is a class 1A recommendation for patients with chronic, stable heart failure due to reduced ejection fraction (HFrEF), with demonstrated improvements in functional capacity, quality of life, and clinical outcomes (11,15). However, at present, the American College of Sports Medicine does not provide clear recommendations for exercise intensity for patients with LVAD.

We have previously shown that among patients with HFrEF without an LVAD, the percentage of HR reserve (%HRR) accurately estimates percent oxygen uptake reserve (%$\dot{V}O_2$R) (2). Recent guidelines recommend training at an exercise intensity of 40%–80% of HRR to improve cardiorespiratory fitness for healthy adults and most individuals with chronic health conditions, including HFrEF (1).

However, an HR-based method may not be appropriate when prescribing exercise intensity in patients with an LVAD. Similar to patients with heart transplant, those with a continuous-flow LVAD undergo therapy that functions largely independent of sympathovagal-mediated HR modulation. In the case of transplant, this is due to decentralized autonomic influence. However, patients with an LVAD do have intact efferent sympathovagal postganglionic nerve fibers that may still lead to appropriate HR responses for a given metabolic demand. This article describes the relation between %$\dot{V}O_2$R and %HRR in a cohort of patients with

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TABLE 1. Patient demographic and clinical characteristics.

Characteristics	All Subjects (n = 24)
Male/female (n)	17/7
Age (yr)	55 ± 13
Body mass (kg)	176 ± 34
Body mass index (kg·m^{-2})	27 ± 5
Etiology of heart failure (ischemic/nonischemic, n)	7/17
Ejection fraction (%)	21 ± 8
Medications (n (%))	
Beta-adrenergic blocking agent	18 (75)
Angiotensin-converting enzyme inhibitor	13 (54)
Diuretics	18 (75)
Angiotensin receptor blocker	2 (8)
Digoxin	1 (4)
Warfarin	23 (96)
Device type (n (%))	
Heart Mate II (Thoratec Corporation)	18 (75)
HeartWare (HeartWare International, Inc.)	6 (25)

Data are presented as mean ± SD.

continuous-flow LVAD. In addition, because the exercise training of patients in cardiac rehabilitation is often in the absence of a recent exercise stress test, we sought to examine the relation between %$\dot{V}O_2R$ and the commonly used Borg RPE. Furthermore, in most patients with an LVAD, device-specific measures such as power (i.e., watts) and flow rate (L·min^{-1}) can be taken during exercise and may also provide additional metrics of exercise intensity. Therefore, we also examined the relation between %$\dot{V}O_2R$ and flow rate measured from the LVAD.

METHODS

Subjects. Eligible and consented patients (n = 24) who underwent an LVAD implantation at Henry Ford Hospital (mean duration from implant, 78 ± 34 d) and performed a symptom-limited cardiopulmonary exercise test (CPX) as part of cardiac rehabilitation in patients with LVAD (Rehab-VAD) trial (NCT01584895). The complete methods and design for the Rehab-VAD trial have been described previously (6). Eligibility criteria included the following: an implanted continuous-flow LVAD within the previous 6 months, free of orthopedic limitations to exercise, not currently participating in a regular exercise program, and free of any contraindications to exercise. Patients currently in sinus rhythm or with a rate responsive pacemaker were both included. This study was approved by the Henry Ford Health System institutional review board, and all subjects signed informed consent.

Data collection and exercise testing protocol. Demographic and clinical characteristic information (age, height, race, sex, medical/surgical history, medications) were gathered before CPX testing from the patient or the patient's electronic medical record. Patients were instructed to take all medications as prescribed at least 2 h before testing, including those on beta-blockade therapy (75% of subjects). Body mass was computed using an upright beam arm scale, with the LVAD controller attached to the patient and connected to a power base unit in lieu of the batteries.

Before testing, resting HR and resting $\dot{V}O_2$ were measured during the last 2 min of upright seated rest (5 min). Expired air was sampled breath by breath and analyzed using a Medgraphics (Minneapolis, MN) metabolic cart. After seated rest, the CPX test was performed using the modified Naughton treadmill protocol (i.e., 1-MET increase every 2-min stage). During the test, patients were encouraged to exercise until a sign or symptom-limited maximum. Throughout exercise testing, HR was transferred, via an electronic interface, from the 12-lead ECG monitoring system (Q3000; Quinton Instruments, Seattle, WA) to the metabolic cart. Gas exchange and HR data were reported in 20-s interval averages. $\dot{V}O_{2peak}$ (mL·kg^{-1}·min^{-1}) and HR_{peak} were defined as the highest values for a given 20-s interval average measured during the last 1 min of exercise or the first 20 s of recovery. Both the RPE and LVAD flow rate (L·min^{-1}) were taken during the last 10–15 s of each stage and at peak. For RPE, subjects would point at a number on the 6–20 Borg scale, whereas the LVAD flow rate was recorded directly from the device at the given period. Finally, mean blood pressure before, during, and after exercise was obtained from the brachial artery using a handheld Doppler (LifeDop 150; Summit Doppler Systems, Inc., Golden, CO).

Data analysis and statistics. Gas exchange data were forwarded to the Henry Ford CPX Core Laboratory, where an independent reviewer analyzed the data. Testing was conducted in accordance with the American College of Cardiology's and The American Heart Association's guidelines. Percentages of peak HRR and $\dot{V}O_2R$ were calculated for each 20-s interval. %HRR was calculated using the Karvonen method (%HRR = [exercise HR − resting HR]/[HR_{peak} – resting HR]). %$\dot{V}O_2R$ was also calculated using the Karvonen method (%$\dot{V}$O2R = [exercise $\dot{V}O_2$ − resting $\dot{V}O_2$]/[$\dot{V}O_{2peak}$ − resting $\dot{V}O_2$]). Each of these calculations was performed twice. One calculation based on a resting $\dot{V}O_2$ that represented the measured $\dot{V}O_2$ averaged across 2 min of

TABLE 2. Results of the linear regression analysis between %$\dot{V}O_2R$ and selected methods of exercise intensity.

Independent Variable[a]	Group	Intercept	P Value[b]	Slope	P Value[c]	R^2	P Value[d]
%HRR	All	0.10 ± 0.04	**0.008**	0.89 ± 0.04	**0.002**	0.75	0.001
%HRR	Not paced	0.04 ± 0.03	0.296	0.94 ± 0.03	0.052	0.80	0.001
%HRR	Paced	0.19 ± 0.06	**0.002**	0.82 ± 0.07	**0.017**	0.74	0.001
%RPE-R	all	0.31 ± 0.03	**0.001**	0.87 ± 0.06	**0.042**	0.84	0.001
%RPE-R	paced	0.27 ± 0.08	**0.001**	0.92 ± 0.12	0.490	0.97	0.001
%VFlowR	all	0.63 ± 0.01	**0.001**	0.18 ± 0.08	**0.001**	0.05	0.018

[a] %$\dot{V}O_2R$ is the dependent variable.
[b] Tests if y-intercept = 0.
[c] Tests if slope = 1.
[d] Tests if R^2 = 0.

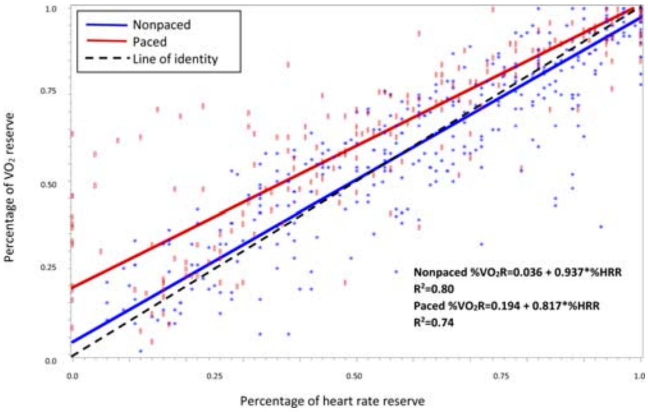

FIGURE 1—Regression lines for %$\dot{V}O_2$R vs %HRR in paced (*red*) and nonpaced (*blue*) subjects.

seated rest and the second based on an estimated resting $\dot{V}O_2$ of 3.5 mL·kg^{-1}·min^{-1}. To better compare with %$\dot{V}O_2$R, both RPE and LVAD flow were scaled similarly. Therefore, a percentage of RPE reserve (%RPE-R) of 50% would be equal to 12 on the Borg scale for an individual who had a peak RPE of 18 (i.e., %RPE-R = [12 − 6]/[18 − 6] × 100).

A generalized estimating equation was used to average the slopes and *y*-intercepts for all subjects and then stratified on the basis of the presence of a paced rhythm during exercise, and the LVAD device type (i.e., Heartware vs Heartmate II). One-sample *t*-tests (two-tailed) were used to determine whether the mean slope and *y*-intercept differed from the line of identity (slope, 1; *y*-intercept, 0). Alpha level was set at $P \leq 0.05$.

RESULTS

Patient demographic and clinical characteristics are shown in Table 1. Although %HRR was strongly associated with %$\dot{V}O_2$R (Table 2), both the slope and *y*-intercept deviated from the line of identity and *y*-intercept, respectively ($P <$ 0.01). This relation was unaltered when comparing device type (i.e., Heart mate II or Heartware) or when comparing how resting $\dot{V}O_2$ was determined (i.e., the use of individually measured oxygen uptake at rest vs an assumed resting $\dot{V}O_2$ of 3.5 mL·kg^{-1}·min^{-1}). However, when separating individuals between paced versus nonpaced during exercise, we found that nonpaced individuals showed better %HRR/%$\dot{V}O_2$R relation (R^2 = 0.80) and both the slope and *y*-intercept between %$\dot{V}O_2$R and %HRR were not statistically different from the line of identity (Fig. 1). Furthermore, Table 3 shows that when examining the estimated percentage $\dot{V}O_2$R for a given %HRR, nonpaced subjects showed less relative error and were closer to predicted percentages (i.e., 50% of HRR = 50% ± 2% of %$\dot{V}O_2$R for nonpaced compared with 60% ± 3% of $\dot{V}O_2$R for paced). Differences between the two groups were found for body mass index, which was lower in the paced subjects, but no other statistical differences could be found (Table 4).

Similarly to %HRR, %RPR-R showed some variance when compared with the %$\dot{V}O_2$R regression equation (Fig. 2). However, the R^2 between %RPE-R and %$\dot{V}O_2$R was greater than the R^2 between %HRR and %$\dot{V}O_2$R (Table 2). Although the percentage of ventricular assist device flow rate reserve (%VFlowR) was statistically related to %$\dot{V}O_2$R, this relation was found to be very weak (Table 2).

DISCUSSION

We have shown that in the absence of a paced rhythm during exercise, %HRR has a linear relation with %$\dot{V}O_2$R and does not differ from a line of identity (slope, 1; *y*-intercept, 0) in patients who have an LVAD. In addition, when examining the SEE (Table 3), %HRR has a relative error of 2% when estimating %$\dot{V}O_2$R throughout the spectrum of exercise intensities. This supports the notion that despite the presence of an external device contributing to cardiac output, the sympathovagal-modulated HR response to increased metabolic demand remains intact, making HR a good measure of exercise intensity. Because individuals with an LVAD who were artificially paced during exercise showed greater variance from the line of identity, using an HR-based method for exercise intensity may be less accurate. However, it should be pointed out that paced individuals still showed a strong %HRR/%$\dot{V}O_2$R relation (R^2 = 0.74), and the SEE was only slightly greater than that in the nonpaced (Table 3).

Reasons for the increased variance in this subgroup (i.e., paced) are not clear. Out of the eight patients who were paced during exercise, two were in VVI mode, indicating that they did not sense and pace off of atrial depolarizations, but instead, HR was modulated by the pacemaker itself (both patients had devices with accelerometer-based HR modulation). The other six patients had dual-chamber pacemakers that did sense from atrial depolarizations. In addition to having an HR response that is not intrinsically linked to metabolic demand or central command, another potential reason for some of the observed discordance between %HRR and %$\dot{V}O_2$R is that individuals who have heart failure, and are paced, may exhibit more chronotropic incompetence (12). Until more studies are conducted, the use of HRR as a measure of exercise intensity

TABLE 3. Resultant %$\dot{V}O_2$R based on a fixed %HRR.

	%HRR 40%	50%	60%	70%	80%
%$\dot{V}O_2$R (all subjects) 95% CI	45% ± 2% (41%–50%)	54% ± 2% (50%–58%)	63% ± 2% (59%–67%)	72% ± 2% (69%–75%)	81% ± 2% (78%–84%)
%$\dot{V}O_2$R (nonpaced) 95% CI	41% ± 2% (36%–46%)	50% ± 2% (46%–55%)	60% ± 2% (56%–64%)	69% ± 2% (66%–73%)	79% ± 2% (75%–82%)
%$\dot{V}O_2$R (paced) 95% CI	52% ± 4% (45%–60%)	60% ± 3% (54%–67%)	68% ± 3% (63%–74%)	77% ± 2% (72%–81%)	85% ± 2% (80%–89%)

Data are presented as mean ± SEE.

TABLE 4. Comparison of resting and peak exercise hemodynamic measures in patients with an LVAD who were paced during exercise vs those who were not paced.

	Nonpaced (*n* = 16)	Paced (*n* = 8)	*P* Value
Age (yr)	52 ± 13	59 ± 14	0.232
Body mass index ($kg \cdot m^{-2}$)	28 ± 5	24 ± 2	0.014
Resting, seated HR (bpm)	89 ± 12	86 ± 15	0.578
Resting, seated mean blood pressure (mm Hg)	86 ± 13	93 ± 7	0.177
HR_{peak} (bpm)	125 ± 21	115 ± 16	0.247
HRR_{peak} (bpm)	36 ± 18	29 ± 14	0.340
Peak mean blood pressure (mm Hg)	105 ± 16	115 ± 26	0.285
$\dot{V}O_{2peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	13.1 ± 3.9	12.4 ± 2.0	0.618
$\dot{V}O_2R_{peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	9.1 ± 3.6	8.4 ± 2.1	0.621
Peak RER	1.15 ± 0.06	1.24 ± 0.11	0.077

Data are presented as mean ± SD.

may not be appropriate in patients with both an LVAD and rate responsive pacemaker.

Another important finding from this study is the confirmation that RPE is a good surrogate of exercise intensity and can be used in the absence of a recent exercise stress test or in those individuals who are paced (Table 2). Similar to Norman et al. (10) we found a strong correlation between $\%\dot{V}O_2R$ and RPE in all subjects as well as in those who were paced ($r > 0.90$). Unfortunately, although the LVAD flow rate did increase with exercise, this was found to be a poor predictor of exercise intensity and should not be used in place of HR or RPE.

To our knowledge, this is the first report of HR-to-$\dot{V}O_2$ relation in patients with an LVAD. These results are important for clinicians charged with prescribing exercise in these patients and support the utility of the HRR method, as well as RPE, to guide exercise intensity in patients with an LVAD. Exercise training after LVAD implant is important because many of these patients will have persistent functional deficits as a result of their end-stage disease, prolonged bed rest due to lengthy hospital stays, and peripheral abnormalities that are not soon improved despite improved forward flow (9).

Relative to appreciating our observations within the context of prescribing exercise, current guidelines suggest that the training intensity stimulus needed to induce the expected benefits from exercise in patients with HFrEF is between 40% and 80% HRR (1). There are very few exercise training studies in patients with LVAD (5,6,8), and in most of those training studies, exercise intensity was measured through perceived exertion scales and not HR (5,8). Recently, we demonstrated in a randomized controlled trial that patients with continuous-flow LVAD exercising at an average of 60% of HRR showed gains in $\dot{V}O_{2peak}$ and patient-reported health status (6). This previous finding along with our current data demonstrating good concordance between %HRR and $\%\dot{V}O_2R$ supports the use of HR as a measure of exercise intensity.

Although the error of estimate for $\%\dot{V}O_2R$ is distributed evenly throughout the range of %HRR, this relation is associated with some individual variability as indicated by the 95% confidence interval (CI). For example, if estimating 50% of HRR for an individual, actual $\%\dot{V}O_2R$ can vary from 46% to 55% in a nonpaced individual. As mentioned previously, because of the severity and progression of heart failure in this population, chronotropic incompetence may explain some of the observed variability.

A limitation of our study is that it reflects findings derived from one laboratory and it involved a relatively small sample of patients; therefore, it requires duplication by others. That said, our data are novel and we trust that it provides some guidance to clinicians charged with prescribing exercise and overseeing the exercise programs for these patients. Further work is needed relative to confirming our findings and evaluating patient subgroups (e.g., females, older patients, those more fit, and patients with a permanent pacemaker).

As suggested in an article by Cunha et al. (4), another limitation of our study is that resting HR and $\dot{V}O_2$ were measured for 2 min after <10 min of seated rest. Although we found no difference in our main outcome when using an estimated resting $\dot{V}O_2$ (i.e., 3.5 $mL \cdot kg^{-1} \cdot min^{-1}$) versus a measured resting $\dot{V}O_2$, the 5 min of seated rest and 2 min of data collection at the end of rest may have not been sufficient to reflect accurate resting values. However, because a longer rest period would not likely result in a higher resting $\dot{V}O_2$, this would only affect the relation between $\%\dot{V}O_2R$ and %HRR if true resting $\dot{V}O_2$ values in our subjects were significantly lower than 3.5 $mL \cdot kg^{-1} \cdot min^{-1}$.

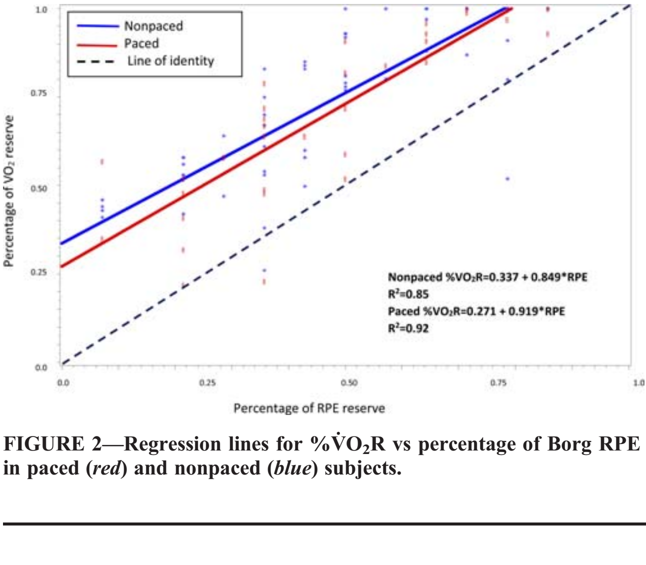

FIGURE 2—Regression lines for $\%\dot{V}O_2R$ vs percentage of Borg RPE in paced (*red*) and nonpaced (*blue*) subjects.

CONCLUSIONS

The rationale for using %HRR to approximate $\%\dot{V}O_2R$ when prescribing exercise or evaluating exercise intensity in apparently healthy people or patients with heart disease or HFrEF is well described (2,3,13,14). We now extend this same tenet to include patients with an implanted continuous-flow LVAD. However, this relation seems less concordant in the presence of a rate responsive pacemaker, suggesting that RPE should be used instead in patients with both an LVAD and a rate responsive pacemaker.

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The authors report that no conflicts of interest associated with the current study have occurred.

The results of this study do not constitute endorsement by the American College of Sports Medicine.

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