Comparison of $\dot{V}O_2$-Kinetic Parameters for the Management of Heart Failure

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Objective: The aim of this study was to analyze whether $\dot{V}O_2$-kinetics during cardiopulmonary exercise testing (CPET) is a useful marker for the diagnosis of heart failure (HF) and to determine which $\dot{V}O_2$-kinetic parameter distinguishes healthy participants and patients with HF.

Methods: A total of 526 healthy participants and 79 patients with HF between 20 and 90 years of age performed a CPET. The CPET was preceded by a 3-min low-intensity warm-up and followed by a 3-min recovery bout. $\dot{V}O_2$-kinetics was calculated from the rest to exercise transition of the warm-up bout (on-kinetics), from the exercise to recovery transition following ramp test termination (off-kinetics) and from the initial delay of $\dot{V}O_2$ during the warm-up to ramp test transition (ramp-kinetics).

Results: $\dot{V}O_2$ off-kinetics showed the highest z-score differences between healthy participants and patients with HF. Furthermore, off-kinetics was strongly associated with $\dot{V}O_2$\textsubscript{peak}. In contrast, ramp-kinetics and on-kinetics showed only minimal z-score differences between healthy participants and patients with HF. The best on- and off-kinetic parameters significantly improved a model to predict the disease severity. However, there was no relevant additional value of $\dot{V}O_2$-kinetics when $\dot{V}O_2$\textsubscript{peak} was part of the model.

Conclusion: $\dot{V}O_2$ off-kinetics appears to be superior for distinguishing patients with HF and healthy participants compared with $\dot{V}O_2$ on-kinetics and ramp-kinetics. If $\dot{V}O_2$\textsubscript{peak} cannot be determined, $\dot{V}O_2$ off-kinetics provides an acceptable substitute. However, the additional value beyond that of $\dot{V}O_2$\textsubscript{peak} cannot be provided by $\dot{V}O_2$-kinetics.

Keywords: $\dot{V}O_2$\textsubscript{max}, $\dot{V}O_2$-kinetics, CRF, risk stratification, heart failure

INTRODUCTION

The incidence and prevalence of heart failure (HF) are high and continue to increase in the developed world with aging of the population. Concomitant deaths and healthcare costs related to this syndrome are increasing (Virani et al., 2020). Accurate diagnostic and risk assessment methods for HF are essential to guide clinical decisions for therapeutic strategies with the ultimate...
The COmPLETE-Study is a cross-sectional single-center study and consists of two parts, namely, COmPLETE-Health and COmPLETE-Heart. COmPLETE-Health included healthy men and women without any known exercise-limiting diseases between 20 and 90 years of age equally distributed across age decades and sex. COmPLETE-Heart included cardiac patients with stable HF with NYHA functional classes I–III, with symptoms and signs stable for at least 1 month. Diagnosis of HF was confirmed by clinical history, physical examination, assessment of natriuretic peptide (NT-proBNP), and echocardiographically documented structural heart disease or diastolic dysfunction according to the European Society of Cardiology guidelines (Ponikowski et al., 2016). Details on recruitment procedures and complete inclusion and exclusion criteria can be found in the study protocol (Wagner et al., 2019).

Setting
The study was carried out at the Department of Sport, Exercise, and Health at the University of Basel, Switzerland, and was funded by the Swiss National Science Foundation (grant no. 182815). The study complies with the Declaration of Helsinki and was approved by the Ethics Committee of Northwestern and Central Switzerland (EKNZ 2017-01451). Written informed consent was obtained from all participants before the start of the study.

Acquisition of Participant Characteristics
Resting systolic and diastolic blood pressures were measured with the participant in the supine position using a non-invasive vascular screening system (VaSera VS-1500N; Fukuda Denshi, Tokyo, Japan). Physicians assessed medical history and medications by the questionnaire onsite. Based on clinical data, structured questions, and self-reported exercise tolerance, each patient with HF was assigned to an NYHA functional class by a physician who was blinded to both CPET results and laboratory data. Blood samples were drawn via venipuncture by trained medical staff in fasting state (at least 3 h). Samples were immediately centrifuged, the plasma aliquots were frozen at a temperature of −80°C, and all samples were analyzed together after completion of the study.

Cardiopulmonary Exercise Testing
An exercise test to maximal voluntary exertion using an electromagnetically braked cycle ergometer (Ergoselect 200; Ergoline, Bitz, Germany) was performed according to one of the following five ramp protocols: (i) a 3-min warm-up either unloaded, a load of 10 or 20 W for protocols 1–3, or a load of 50 W for protocols 4 and 5 followed by (ii) a ramp protocol with a linear workload increases of 7, 10, 15, 20, or 30 W/min for protocols 1–5, respectively, followed by (iii) a 3-min recovery phase at the same workload as the warm-up. The protocol was chosen to achieve a duration of approximately 10 min.

Gas exchange and ventilatory variables were analyzed breath-by-breath continuously using an electromagnetically braked cycle ergometer (MetaMax 3B; Cortex Biophysik GmbH, Leipzig, Germany). Each test was preceded by a resting period of 3 min to reach steady-state conditions. In the absence of clinical symptoms or electrocardiographic abnormalities, all tests were continued until maximal exertion. Before and during the test, the participants were verbally encouraged to reach maximal exhaustion. Before each test, the equipment was calibrated in standard fashion.
with reference gas and known volume. \( \dot{V}O_2 \text{peak} \) was defined as the highest 30 s average value during the CPET. The slope of ventilation vs. carbon dioxide consumption (\( \dot{V}E/\dot{V}CO_2 \) slope) was calculated from 1 min after beginning of the ramp test up to the respiratory compensation point. As recommended earlier (Gargiulo et al., 2014; Salvioni et al., 2020), we also calculated \( \dot{V}O_2 \text{peak} \) and \( \dot{V}E/\dot{V}CO_2 \) slope expressed as percentage of the predicted values. For this purpose, we used our recently published data (Wagner et al., 2021), which are mainly based on the healthy cohort of the present study.

\( \dot{V}O_2 \)-Kinetic Assessment

Figure 1 displays the different methods used to determine \( \dot{V}O_2 \)-kinetics. Initially, \( \dot{V}O_2 \) was filtered by removing all outliers that differed more than three standard deviations from the local mean (moving average of six breaths). The filtered \( \dot{V}O_2 \) values were then linearly interpolated to provide second-by-second values, as previously recommended (Benson et al., 2017). \( \dot{V}O_2 \) on-kinetics was assessed from the rest to exercise transition of the 3-min constant load warm-up period. In accordance with earlier studies, we calculated the time constant of \( \dot{V}O_2 \) on-kinetics by two different approaches:

1. (1) \( \tau \) \( \dot{V}O_2 \) on-kinetics. A mono-exponential function was fit (see Appendix for the exact equation) from the beginning to the end of the warm-up period using non-linear least-squares method regression analyses (Hummel et al., 2016) (see Eq. 1 in Appendix).

2. (2) \( \tau \) \( \dot{V}O_2 \) on-kinetics by \( \dot{V}O_2 \)-deficit. This was determined by the oxygen deficit and the steady-state increase of \( \dot{V}O_2 \) above the resting value (Sietsema et al., 1994; Schalcher et al., 2003) (see Eq. 2 in Appendix).

\( \dot{V}O_2 \) off-kinetics was assessed from the active recovery period that directly followed the incremental phase of the CPET. This was done using three different approaches:

1. (1) \( \tau \) \( \dot{V}O_2 \) off-kinetics. Determined by the time constant of a mono-exponential function that was fitted from the beginning to the end of the recovery period using non-linear least-squares method regression analyses (de Groote et al., 1996; Pavia et al., 1999; Hummel et al., 2016) (see Eq. 3 in Appendix).

2. (2) Slope linear \( \dot{V}O_2 \) off-kinetics. Determined by the slope of a linear function that was fitted into the \( \dot{V}O_2 \)-time relationship of the first minute of recovery using linear least-squares method regression analyses (Nanas et al., 2001) (see Eq. 4 in Appendix).

3. (3) \% rel \( \dot{V}O_2 \) reduction 60 s and 120 s post-test. Determined by the decrease in \( \dot{V}O_2 \) from the end of the incremental phase up to the first (\% rel \( \dot{V}O_2 \) reduction 60 s post-test) and second minute (\% rel \( \dot{V}O_2 \) reduction 120 s post-test) expressed as percentages of \( \dot{V}O_2 \text{peak} \) (Fortin et al., 2015).

Ramp test kinetics were assessed from the initial delay of \( \dot{V}O_2 \) at the beginning of the incremental exercise phase (mean response time; MRT), as previously described (Meyer et al., 1998; Niemeyer et al., 2020). For this purpose, the intersection between a horizontal line crossing the \( \dot{V}O_2 \) of the final 30 s of the warm-up phase (\( \dot{V}O_2 \) warm-up) and a straight line, which was fitted into the linear \( \dot{V}O_2 \)-work rate response of the incremental phase was calculated (see Eq. 5 in Appendix).

Statistical Analysis

We investigated potential differences in \( \dot{V}O_2 \)-kinetics variables between healthy participants and patients with HF using linear regression models, which were adjusted for age and sex. In detail, residual diagnostics were used to see whether the model assumptions were satisfied, and some kinetic parameters were subsequently log-transformed.

To investigate the associations between \( \dot{V}O_2 \)-kinetic parameters and \( \dot{V}O_2 \text{peak} \), linear regression analyses with \( \dot{V}O_2 \text{peak} \) as the dependent variable and age, sex, and the kinetic variables as independent variables were calculated. Separate models for each kinetic parameter were built. Therefore, we modeled age using restricted cubic splines (natural splines) with four knots included along with an interaction by sex to control for potential non-linear age progression (Harrell, 2015). For some models, the residuals exhibited heteroscedasticity, and we present robust \( p \)-values and confidence intervals for those models (HC3) (Long and Ervin, 2000).

Descriptive statistics were used to compare the \( \dot{V}O_2 \)-kinetic variables between NYHA classes I, II, and III and the healthy participants. To achieve comparability, we first created a matched dataset where we matched two healthy participants to every patient with HF according to age and sex (2:1 matching). We used the R package “MatchIt” for these calculations (version 3.0.2) (Ho et al., 2011).

The age- and sex-specific quantile curves were calculated using healthy participants only and applying generalized additive models for location, scale, and shape (GAMLSS, R package version 5.1-6) (Stasinopoulos et al., 2017). The age trajectories were modeled using penalized B-splines (P-splines). We adopted the Bayesian information criterion to select the conditional distribution that offered the best compromise between model complexity and goodness-of-fit. The models were inspected using diagnostic residual plots such as worm plots (van Buuren and Fredriks, 2001) and Q–Q plots. The \( z \)-scores of the patients with HF were calculated based on the established reference curves using the healthy participants.

Proportional odds ordinal logistic regressions were used to analyze whether the kinetic parameters with the largest mean difference in the \( z \)-scores added additional predictive information for disease severity (NYHA class). We used the unitless adequacy index to quantify the predictive information contained in \( \dot{V}O_2 \text{peak} \), age, and sex compared to the full set of predictors including the kinetic parameters (Harrell, 2015). An adequacy index near one indicates that \( \dot{V}O_2 \text{peak} \), age, and sex contain nearly all predictive information already, and that the kinetic parameters add little predictive information. We used likelihood ratio tests to assess whether the kinetic parameters improved the model fit. R version 3.6.1 or later (R Foundation for Statistical Computing, Vienna, Austria) was used for all analyses, and \( p \)-values \( \leq 0.05 \) were considered statistically significant. All tests were two sided.
RESULTS

Participant Characteristics
A total of 526 healthy participants and 79 patients with HF (NYHA functional classes I–III) were included in the study. All patients with HF were in stable condition; their etiologies were cardiomyopathy ($n = 8$), coronary artery disease ($n = 60$), pulmonary hypertension ($n = 1$), valvular regurgitation ($n = 8$), and valvular stenosis ($n = 2$). Thirty-five patients with HF had a preserved ejection fraction ($\geq 50\%$), 15 patients with HF had mid-range ejection fraction ($40–49\%$), and 23 patients with HF had a reduced ejection fraction ($<40\%$) while the data of six patients
with HF were missing. Participant characteristics are presented in Table 1.

**VO₂-Kinetics in Health and Heart Failure**

Group differences between healthy participants and patients with HF irrespective of their NYHA class are reported in Table 2. Six out of eight VO₂-kinetic parameters showed evidence for a difference between the groups (p ≤ 0.007). The number of participants involved in the analysis of the respective kinetic parameter indicates the susceptibility to minor measurement difficulties during the CPET and the number of outliers due to the determination method which were excluded.

Figure 2 presents violin plots of all analyzed kinetic parameters for NYHA class I, II, and III and the age- and sex-matched healthy reference group. In addition to the kinetic parameters, violin plots were presented for CPET markers known to have high predictive value (Wagner et al., 2018) including VO₂peak, OUES, and VE/VCO₂ slope for comparison.

### Table 1 | Descriptive characteristics of the study population separated into healthy participants and patients with heart failure by NYHA functional classes.

| Participants, no. (%) | Healthy | Healthy controls* | NYHA I | NYHA II | NYHA III |
|------------------------|---------|-------------------|--------|---------|---------|
| N                      | 526     | 158               | 37     | 28      | 14      |
| Sex (m/f)              | 275/251 | 129/29            | 35/2   | 20/8    | 9/5     |
| Age (yr)               | 526     | 54 ± 19.6         | 158    | 65.9 ± 13.7 | 37     | 65.4 ± 13 | 28     | 64 ± 14.3 | 14     | 72.9 ± 10.7 |
| Height (cm)            | 526     | 171.8 ± 9.2       | 158    | 173.9 ± 9  | 37     | 174.8 ± 6.6 | 28     | 172.1 ± 8.3 | 14     | 168.4 ± 9.1 |
| BMI (kg/m²)            | 526     | 23.7 ± 2.7        | 158    | 24.7 ± 2.8  | 37     | 28.1 ± 4.0  | 28     | 28.3 ± 4.0  | 14     | 27.7 ± 6.6  |
| NTproBNP (pg/mL)       | 518     | 121.4 ± 9.2       | 157    | 122.6 ± 11.8 | 28     | 84.5 ± 16.4 | 14     | 184 ± 13.4  | 14     | 146 ± 10.7  |
| LDL cholesterol (mg/dL)| 518     | 5.2 ± 0.4         | 157    | 6.5 ± 0.7   | 37     | 7.0 ± 0.6   | 28     | 6.8 ± 1.5   | 14     | 6.3 ± 0.7   |
| Height (cm)            | 526     | 54 ± 19.6         | 158    | 65.9 ± 13.7 | 37     | 65.4 ± 13 | 28     | 64 ± 14.3 | 14     | 72.9 ± 10.7 |
| Body mass (kg)         | 526     | 171.8 ± 9.2       | 158    | 173.9 ± 9  | 37     | 174.8 ± 6.6 | 28     | 172.1 ± 8.3 | 14     | 168.4 ± 9.1 |
| BMI (kg/m²)            | 526     | 23.7 ± 2.7        | 158    | 24.7 ± 2.8  | 37     | 28.1 ± 4.0  | 28     | 28.3 ± 4.0  | 14     | 27.7 ± 6.6  |
| Resting systolic BP (mmHg)| 526   | 125.4 ± 13.9      | 158    | 131.6 ± 12.8 | 37     | 128 ± 13.7 | 28     | 127.8 ± 21.9 | 14     | 130 ± 15.1  |
| Resting diastolic BP (mmHg)| 526  | 77.4 ± 9.0        | 158    | 81.4 ± 7.8  | 37     | 79.4 ± 12.2 | 28     | 77.7 ± 14.4 | 14     | 75.9 ± 8.4  |
| Left ventricular ejection fraction (%) | 526 | n.a.             | 158    | n.a.       | 37     | 46.4 ± 11.5 | 28     | 46.3 ± 11.0 | 12     | 44.6 ± 15.4 |
| Etiology, ischemic, (%) | 526     | n.a.             | 158    | n.a.       | 37     | 28 (76)    | 28     | 21 (75)    | 14     | 11 (79)     |

Data are presented as mean ± standard deviation if not stated otherwise. BMI, body mass index; BP, blood pressure; HR, heart rate; Pmax, maximal power; VO₂max, maximal oxygen uptake; VE, volume of expiration; VCO₂, carbon dioxide output; RERmax, maximal respiratory exchange ratio; HRmax, maximal heart rate; BLmax, maximal blood lactate.

* Two participants from the healthy cohort were matched to every patient with heart failure according to age and sex (2:1 matching).
TABLE 2 | Group differences between healthy participants and patients with heart failure, Z-scores and the association with VO$_2$peak for all kinetic parameters.

| Parameter                                      | N$^1$ | Mean difference (95%-CI) | P-value | Healthy | HF | Mean difference healthy-HF (95% CI) | Coefficient estimate (95% CI) | Partial R$^2$ | P-value |
|------------------------------------------------|-------|--------------------------|---------|---------|----|-------------------------------------|-------------------------------|----------------|---------|
| τ VO$_2$ on-kinetics (s)                       | 529   | 0.16 (0.04; 0.28)        | 0.007   | 0.00    | −0.48 (−0.79; −0.16)                | −0.01 (−0.01; −0.002)         | 0.04           | 0.005   |
| τ VO$_2$ on-kinetics by VO$_2$-deficit (s)     | 541   | 0.07 (−0.00; 0.15)       | 0.055   | 0.00    | −0.43 (−0.78; −0.09)                | −0.01 (−0.01; −0.003)         | 0.04           | 0.000   |
| MRT ramp kinetics (s)                         | 514   | 0.00 (−0.13; 0.12)       | 0.963   | 0.01    | 0.02 (0.02; 0.30)                   | −0.0003 (−0.01; 0.0005)       | 0.00           | 0.899   |
| τ VO$_2$ off-kinetics (s)                      | 558   | 0.17 (0.06; 0.27)        | 0.001   | 0.00    | −0.74 (−1.04; −0.43)                | −0.011 (−0.015; −0.008)       | 0.09           | < 0.001 |
| Slope linear VO$_2$ off-kinetics (ml/min/s)   | 567   | 4.96 (3.63; 6.30)        | 0.000   | −0.01   | −0.88 (−1.15; −0.62)                | −0.48 (−0.51; −0.41)          | 0.39           | < 0.001 |
| % rel VO$_2$ reduction 60 s post-test (%)      | 582   | −5.76 (−7.94; −3.59)     | 0.000   | 0.00    | −0.89 (0.59; 1.18)                  | 0.37 (0.28; 0.46)             | 0.16           | < 0.001 |
| % rel VO$_2$ reduction 120 s post-test (%)     | 579   | −3.54 (−5.84; −1.23)     | 0.003   | 0.00    | −0.64 (0.29; 0.98)                  | 0.34 (0.25; 0.44)             | 0.12           | < 0.001 |

HF, heart failure; τ, tau; MRT, mean response time; VO$_2$, oxygen uptake; rel, relative.

$^1$Adjusted for age and sex.

$^1$Including data of healthy participants and patients with heart failure.

The Z-scores (Table 2) show that τ VO$_2$ on-kinetics was the best VO$_2$ on-kinetic parameter to discriminate between healthy participants and patients with HF. Slope linear VO$_2$ off-kinetics (ml/min/s) and % rel VO$_2$ reduction 60 s post-test performed best among the VO$_2$ off-kinetic parameters. These three parameters were therefore considered superior to the others, and further analyses were limited to these parameters.

Quantile curves for τ VO$_2$ on-kinetics, slope linear VO$_2$ off-kinetics (ml/min/s), and % rel VO$_2$ reduction 60 s post-test are presented in Figure 3. The quantile curves based on the healthy participants tend toward pathological numbers with increasing age. For the parameter τ VO$_2$ on-kinetics, 60% of the patients with HF were located above the 50th percentile. For the slope linear VO$_2$ off-kinetics (ml/min/s), 85% of the patients with HF were...
located below the 50th percentile, and for rel \( \dot{V}O_2 \) reduction 60 s post-test, 78% were located above the 50th percentile.

**Association of \( \dot{V}O_2 \)-Kinetics and \( \dot{V}O_2 \)peak**

There was strong evidence for associations between \( \dot{V}O_2 \)peak (ml/kg/min) and all \( \dot{V}O_2 \) on- and off-kinetics parameter except for MRT ramp kinetics in which there was no evidence for such an association observed (Table 2, last three columns). The direction of the association can be described as follows: the faster the \( \dot{V}O_2 \)-kinetic response (depending on the parameter, a positive or negative association) the higher the \( \dot{V}O_2 \)peak values are observed. By far, the largest adjusted \( R^2 \) was observed for the slope linear \( \dot{V}O_2 \) off-kinetics (ml/min/s).

**Predicting Disease Severity (New York Heart Association-Classification) Using Kinetic Parameters**

Table 3 shows the results of several models for NYHA class prediction by kinetic parameters. All kinetic parameters improved the model when the base model contained sex and age. As indicated by the Chi\(^2\), slope linear \( \dot{V}O_2 \) off-kinetics (ml/min/s) improved the model from the three kinetic parameters most but not to the extent that \( \dot{V}O_2 \)peak did.

**Additional Value of Kinetics to Predict Disease Severity**

There was little evidence that any of the three kinetic parameters improved the models already containing sex, age, and \( \dot{V}O_2 \)peak. The adequacy index comparing the base models containing age, sex, and \( \dot{V}O_2 \)peak to a model additionally containing the kinetic parameters was between 0.98 and 0.99. This means that the base models without the \( \dot{V}O_2 \) kinetic parameters contain nearly all the predictive information already.

**DISCUSSION**

To our knowledge, the current study is the first to provide detailed \( \dot{V}O_2 \) kinetic results in large cohorts of healthy

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**FIGURE 3** | Quantile curves for \( \dot{V}O_2 \) on-kinetics, slope linear \( \dot{V}O_2 \) off-kinetics (ml/min/s), and % rel \( \dot{V}O_2 \) reduction 60 s post-test for males and females, separately. The quantile curves are based on the healthy participants only (light blue data points). Values of the patients with heart failure are presented in orange. \( \dot{V}O_2 \), oxygen uptake.
Differences Between Healthy Participants and Patients With Heart Failure

This study provides evidence that \( \dot{V}O_2 \)-kinetic parameters differ between healthy participants and a group of mild to moderate functionally impaired patients with HF for all kinetic calculation methods with the exception of \( \tau \) \( \dot{V}O_2 \)-on-kinetics by \( \dot{V}O_2 \)-deficit and MRT of the ramp kinetics. The observed differences are in line with previous findings showing that patients with HF had significantly slower \( \dot{V}O_2 \)-kinetics compared to healthy volunteers (Sietsema et al., 1994; Meyer et al., 1998; Pavia et al., 1999; Hummel et al., 2016). The slowing of \( \dot{V}O_2 \)-kinetics in HF is closely related to impaired ventricular-pulmonary vascular function (Kemps et al., 2009; Chatterjee et al., 2013) and/or impaired peripheral oxygen utilization (Weiss et al., 2017).

Mean differences in \( z \)-scores (Table 2) clearly indicate that \( \dot{V}O_2 \) off-kinetics, irrespective of the calculation method, discriminate better between healthy participants and patients with HF compared to \( \dot{V}O_2 \) on-kinetics.

These results are in line with previous research showing that off-kinetics can be determined with greater fidelity (Kemps et al., 2009) and higher reproducibility (Kemps et al., 2007) than on-kinetics in patients with HF. Further, irrespective of the methodological difficulties with on-kinetics, off-kinetics may discriminate patients with HF better from their healthy counterparts as has been observed in a previous study (Sietsema et al., 1994).

The comparison between the off-kinetics parameters (different calculation approaches) revealed a higher potential to distinguish healthy participants and patients with HF for \% rel \( \dot{V}O_2 \) reduction 60 s post-test and slope linear \( \dot{V}O_2 \) off-kinetics compared to \% rel \( \dot{V}O_2 \) reduction 120 s post-test and \( \tau \) \( \dot{V}O_2 \) off-kinetics. Interestingly, both superior off-kinetics parameters were determined from the first minute of the recovery period only, while the other parameters were calculated from the first 2 min (\% rel \( \dot{V}O_2 \) reduction 120 s post-test) or the entire recovery duration (\( \tau \) \( \dot{V}O_2 \) off-kinetics). This indicates that the very early phase of the off transition better distinguished between healthy participants and patients with HF.

Association With \( \dot{V}O_2_{peak} \)

Strong significant associations between \( \dot{V}O_2_{peak} \) and off-kinetics were observed. Slope linear \( \dot{V}O_2 \) off-kinetics explained 39% of the variation in \( \dot{V}O_2_{peak} \) among healthy participants and patients with HF. In contrast, \( \dot{V}O_2 \) on-kinetics showed significant but only weak associations with \( \dot{V}O_2_{peak} \), the on-kinetics parameter \( \tau \) \( \dot{V}O_2 \) (s) explained only 4% of the variation in \( \dot{V}O_2_{peak} \). The stronger association of the off-kinetics compared to the on-kinetics can likely be explained by the methodological considerations of the on-kinetics described above.

A recent study showed that the level of exhaustion had no impact on \( \dot{V}O_2 \) off-kinetics (Ichikawa et al., 2020). That the determination of \( \dot{V}O_2 \)-kinetics, unlike \( \dot{V}O_2_{peak} \), does not require the subject to perform the test to maximal voluntary exertion is a large advantage. Many patients lack the motivation to perform a maximal exercise test, are not familiarized with severe exercise, or may have a contraindication to maximal exertion (Green and Askew, 2018). In contrast, the successful determination of \( \dot{V}O_2_{peak} \) requires either a \( \dot{V}O_2 \)-plateau or a confirmation of a secondary exhaustion criteria (Wagner et al., 2020). Considering the large existing evidence base for the valuable information \( \dot{V}O_2 \)-kinetics provides coupled with the present results, \( \dot{V}O_2 \) off-kinetics can be suggested as potential substitute for \( \dot{V}O_2_{peak} \).

Predicting Disease Severity

The ability of a model to predict health status and disease severity of the patients with HF improved significantly when the \( \dot{V}O_2 \) on-kinetic parameter (\( \tau \) \( \dot{V}O_2 \) on-kinetics) and the \( \dot{V}O_2 \) off-kinetic parameter (\% rel \( \dot{V}O_2 \) reduction 60 s post-test) were added. However, only \( \dot{V}O_2 \) off-kinetics added substantial information to the model. Thus, \( \dot{V}O_2 \) off-kinetics could be a tool to discriminate not only between healthy participants and those with mild functional impairment (NYHA class I) but

### Table 3: Predicting Disease Severity (NYHA Functional Class) Using \( \dot{V}O_2 \) Kinetic Parameters

| Base model | Additional variable | Adequacy of base model | Likelihood ratio test |
|------------|---------------------|------------------------|----------------------|
| Sex, age   | \( \tau \) \( \dot{V}O_2 \) on-kinetics (s) | 0.88 | \( \chi^2 \) (1) = 7.87, \( p = 0.005 \) |
| Sex, age   | \% rel \( \dot{V}O_2 \) reduction 60 s post-test | 0.54 | \( \chi^2 \) (1) = 53.81, \( p < 0.001 \) |
| Sex, age   | Slope linear \( \dot{V}O_2 \) off-kinetics (ml/min/s) | 0.51 | \( \chi^2 \) (1) = 56.15, \( p < 0.001 \) |
| Sex, age   | \( \dot{V}O_{2peak} \) slope linear \( \dot{V}O_2 \) on-kinetics (ml/min/s) | 0.27 | \( \chi^2 \) (1) = 176.82, \( p < 0.001 \) |
| \( \dot{V}O_{2peak} \), sex, age | \( \tau \) \( \dot{V}O_2 \) on-kinetics (s) | 0.98 | \( \chi^2 \) (1) = 5.36, \( p = 0.02 \) |
| \( \dot{V}O_{2peak} \), sex, age | \% rel \( \dot{V}O_2 \) reduction 60 s post-test | 0.99 | \( \chi^2 \) (1) = 0.54, \( p = 0.46 \) |
| \( \dot{V}O_{2peak} \), sex, age | Slope linear \( \dot{V}O_2 \) on-kinetics (ml/min/s) | 0.99 | \( \chi^2 \) (1) = 0.46, \( p = 0.50 \) |

NYHA class, New York Heart Association-Classification; \( \dot{V}O_2 \), oxygen uptake; \( \tau \), tau; rel, relative.
also between NYHA classes as visualized by Figure 2. Our results are in line with previous studies showing the potential of VO$_2$-kinetics for risk stratification (Schalcher et al., 2003; Fortin et al., 2015) but are in contrast to others who did not demonstrate better predictive value by the addition of VO$_2$ off-kinetics (de Groote et al., 1996; Pavia et al., 1999; Hummel et al., 2016).

Since we could already show the association with VO$_2$-peak—considered the gold standard criteria for risk stratification—another established parameter, NYHA functional class, was used to stratify risk in patients with HF. Based on the different underlining physiological aspects represented by VO$_2$-peak and VO$_2$-kinetics (Sietsema et al., 1994; Chatterjee et al., 2013), some additional predictive value of VO$_2$-kinetics could be expected. However, our results showed minimal evidence of additional value of VO$_2$ on- or off-kinetics. Two reasons likely explain these results: (i) VO$_2$-peak is already a very strong risk predictor in patients with HF and the association of VO$_2$-peak and NYHA class is already known to be high and (ii) VO$_2$-kinetics are likely to provide the same predictive information as VO$_2$-peak, which is underscored by the association between VO$_2$ off-kinetics and VO$_2$-peak in this study. Therefore, even though we observed that VO$_2$-kinetics has predictive value, it does not appear to have value beyond VO$_2$-peak.

Practical Applications

Our results indicate that the method of quantifying VO$_2$-kinetics is critical to its clinical application. They suggest that the determination of VO$_2$ on-kinetics from rest to a light constant load phase is not optimal; rather, the results favor the analysis of off-kinetics when using a ramp protocol. The calculation of rel VO$_2$ reduction 60 s post-test (%) or slope linear VO$_2$ off-kinetics (ml/min/s) is recommended to distinguish between healthy individuals and patients with HF. Since VO$_2$ off-kinetics is not affected by the level of exhaustion (Ichikawa et al., 2020), these parameters might be used as a substitute for VO$_2$-peak when maximal exhaustion is not reached or when VO$_2$-peak cannot be interpreted.

Using some basic spreadsheet calculation tools, the calculation of rel VO$_2$ reduction 60 s post-test (%) and slope linear VO$_2$ off-kinetics (ml/min/s) are quite simple (see Appendix). To facilitate the routine application of VO$_2$ off-kinetics in the clinical setting, we recommend that the incorporation of these parameters in CPET application software.

LIMITATIONS

Our study has limitations. The study was cross-sectional, and therefore no hard endpoints such as mortality or hospitalization were available. Furthermore, our HF cohort is predominantly represented by male ischemic patients with mildly reduced left ventricular ejection fraction and comparatively preserved exercise capacity as suggested by their mean values of VO$_2$ peak. This may not fully reflect the real-world HF population, which partly limits the transferability of our findings. To further improve the reliability and validity of the VO$_2$ on- and off-kinetics determination, a warm-up and a cool-down phase of 5 min instead of 3 min could be applied.

CONCLUSION

Differences in VO$_2$-kinetics between healthy participants and patients with HF are observed and are highly dependent on how they are calculated. VO$_2$ off-kinetics appears to be superior for distinguishing patients with HF and healthy participants compared with VO$_2$ on-kinetics and ramp-kinetics. If VO$_2$-peak cannot be determined, VO$_2$ off-kinetics provides an acceptable substitute. However, additional value beyond that of VO$_2$-peak cannot be provided by VO$_2$-kinetics.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Northwestern and Central Switzerland (EKNZ 2017-01451). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JW, MN, JM, RK, DI, and AS-T: conception and design of the research and analysis and interpretation of the data. JW and RK: acquisition of data. DI: statistical analysis. AS-T and RK: obtaining funding and supervising the work. JW and MN: drafting the manuscript. DI, JM, OP, AS-T, and RK: critical revision of the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

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**APPENDIX**

**\( \dot{\text{VO}}_2 \)-Kinetic Calculation**

\( \dot{\text{VO}}_2 \) on-kinetics:

\[ \dot{\text{VO}}_2 = \dot{\text{VO}}_{2\text{rest}} + \Delta \dot{\text{VO}}_{2\text{SS}} \cdot \left( 1 - \exp^{-\frac{t}{\tau}} \right) \]  

(1)

where \( \dot{\text{VO}}_{2\text{rest}} \) was defined as the mean of the final 60 s of the resting period preceding the warm-up. \( \Delta \dot{\text{VO}}_{2\text{SS}} \) was the steady-state increase of \( \dot{\text{VO}}_2 \) above \( \dot{\text{VO}}_{2\text{rest}} \) and \( \tau \) the time constant of the overall response. \( \tau \) thereby includes the cardio-dynamic and the primary component of \( \dot{\text{VO}}_2 \) on-transient kinetics and is equivalent to that what previously has been also called mean response time (MRT) of square wave exercise.

\[ \tau = \frac{\dot{\text{VO}}_2 \text{ deficit}}{\Delta \dot{\text{VO}}_{2\text{SS}}} \]  

(2)

where \( \Delta \dot{\text{VO}}_{2\text{SS}} \) was previously calculated from the mean \( \dot{\text{VO}}_2 \) of the final 30 s of the warm-up period. The \( \dot{\text{VO}}_2 \)-deficit was calculated from the difference between the consumed \( \dot{\text{VO}}_2 \) and the \( \dot{\text{VO}}_2 \)-demand, which was calculated by multiplying \( \Delta \dot{\text{VO}}_{2\text{SS}} \) with the duration of the warm-up period (for further details see: Schalcher et al., 2003).

\( \dot{\text{VO}}_2 \) off-kinetics:

\[ \dot{\text{VO}}_2 = \dot{\text{VO}}_{2\text{rec}} + \Delta \dot{\text{VO}}_{2\text{SS}} \cdot \left( \exp^{-\frac{t}{\tau}} \right) \]  

(3)

where \( \dot{\text{VO}}_{2\text{rec}} \) was defined as the asymptotic value of the recovery response. \( \Delta \dot{\text{VO}}_{2\text{SS}} \) was the steady-state decrease of \( \dot{\text{VO}}_2 \) above \( \dot{\text{VO}}_{2\text{rec}} \) and \( \tau \) the time constant of the overall response.

\[ \dot{\text{VO}}_2 = a \ t + b \]  

(4)

where \( a \) represents the slope and \( b \) the intercept of the linear \( \dot{\text{VO}}_2 \)-time relationship.

**Mean Response Time Ramp Test**

\[ MRT \text{ ramp test} = \frac{\dot{\text{VO}}_{2\text{warm-up}} - b}{a \ S} - \frac{P_{\text{warm-up}}}{S} \]  

(5)

where \( \dot{\text{VO}}_{2\text{warm-up}} \) and \( P_{\text{warm-up}} \) are defined as the \( \dot{\text{VO}}_2 \) and the work rate of the warm-up phase preceding the incremental phase. \( a \) and \( b \) represent the slope and the intercept of the \( \dot{\text{VO}}_2 \)-work rate relationship of the incremental phase. \( S \) is defined as the ramp slope. The \( \dot{\text{VO}}_2 \) work rate slope was previously calculated using linear least-squares method regression analyses. To avoid any effects of a non-linear \( \dot{\text{VO}}_2 \) response due to the initial lag of \( \dot{\text{VO}}_2 \) or a potential plateau, the first minute and the last 2 min were excluded for the calculation.