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Original research

Correlation properties of heart rate variability for exercise prescription during prolonged running at constant speeds: A randomized cross-over trial

Running title: HRV for prolonged exercise prescription

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None.

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Data are available from the corresponding author on reasonable request.

Authors' contributions:
OH and TG designed the research. LH and OH conducted the experiments and data processing. TG and OH conducted data analysis and interpretation. TG drafted the raw manuscript. All authors provided critical comments on the manuscript, read, and approved the final version of the manuscript.

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Abstract

The study explores the validity of the non-linear index alpha 1 of detrended fluctuation analysis (DFAa1) of heart rate (HR) variability for exercise prescription in prolonged constant load running bouts of different intensities.

21 trained endurance athletes (9w, 12m) performed a ramp test for ventilatory (vVT1, vVT2) and DFAa1 based (vDFAa1-1 at 0.75, vDFAa1-2 at 0.5) running speed detection, as well as two 20-min running bouts at vDFAa1-1 and vDFAa1-2 (20-vDFAa1-1, 20-vDFAa1-2), in which HR, oxygen consumption (VO_2), respiratory frequency (RF), DFAa1, and blood lactate concentration (BLC) were assessed.

20-vDFAa1-2 could not be finished by all participants (finisher group (FG), n=15 vs. exhaustion group (EG), n=6). Despite similar mean external loads of vDFAa1-1 and vDFAa1-2 compared to vVT1 and vVT2, considerable differences were present for 20-vDFAa1-2 in EG. 20-vDFAa1-1 and 20-DFAa1-2 yielded significant differences in FG for HR (76.2±5.7 vs. 86.4±5.9%HR_{MAX}), VO_2 (62.1±5.0 vs. 77.5±8.6%VO_{2PEAK}), RF (40.6±11.3 vs. 46.1±9.8bpm), DFA-a1 (0.86±0.23 vs. 0.60±0.15) and BLC (1.41±0.45 vs. 3.34±2.24mmol/l). In FG, during 20-vDFAa1-1 HR and RF increased significantly, VO_2 and DFAa1 were stable, while during 20-vDFAa1-2 HR and RF showed a large, significant increase, while VO_2 increased moderately, and DFA-a1 tended to decrease.

DFAa1 based exercise prescription from incremental testing could be useful for most participants in prolonged running bouts, at least in the moderate to heavy intensity domain. In addition, an individually different increased risk of overloading may occur in the heavy to severe exercise domains and should be further elucidated in the light of durability and decoupling assessment.

Highlights:

- DFAa1 based exercise prescription from incremental testing shows potential for prolonged constant load exercise, at least in the moderate to heavy intensity domains for most trained runners.
- Caution is advised for the heavy to severe exercise domains as individual overload may occur.
- The relationship of DFAa1 and vDFAa1 seems to be highly individual as well as perspectives for durability and decoupling assessment and should be further elucidated during longer exercise bouts.

Keywords: HRV, DFAa1, Intensity distribution, Endurance sports, Decoupling

Introduction

Analyses of the non-linear characteristics of heart rate (HR) variability (HRV) show that the short-term scaling exponent alpha1 of detrended fluctuation analysis (DFAa1) may be a sensitive marker for assessing global organismic demands during acute endurance exercise (Gronwald & Hoos, 2020; Gronwald et al., 2020). DFAa1 was shown to provide a wide dynamic range encompassing the moderate, heavy and severe exercise intensity domains (3-zone-model) during exercise compared to linear metrics of HRV (Rogers & Gronwald, 2022). In general, the exponent quantifies the fractal scale and correlation properties of HR time series in cardiac beat-to-beat intervals and represents a rather qualitative marker of autonomic nervous system (ANS) regulation, which means that under resting conditions DFAa1 values around 1.0 mirror the homeodynamic behavior of control systems to dynamically self-organize in between order (persistence) and disorder (Kauffman, 1995; Goldberger et al., 2002; de Godoy et al., 2016). During exercise DFAa1 shows strongly correlated patterns (values well above 1.0) at low-intensity exercise in the moderate domain, transitions to fractal patterns (value at around and below 1.0) at moderate to heavy exercise intensities, and drops to uncorrelated and anticorrelated patterns at the highest intensities with values around and below 0.5, which indicates a loss of fractal dynamics and a change towards random and/or anti-correlated behavior (Hautala et al., 2003). Easily accessible HRV data acquisition with chest belt sensors allows for laboratory and in-field use, and also opens up opportunities to provide real-time feedback on exercise intensity (Gronwald et al., 2021a; Rogers & Gronwald, 2022). Given these properties, and based on signal-theory background applying this metric may be used as a biomarker for exercise intensity domain delineation. It could be shown, that discrete numerical values of this biomarker may demarcate the transition from moderate to heavy intensity exercise around the aerobic threshold (DFAa1 of 0.75) and from heavy to severe intensities around the anaerobic threshold (DFAa1 of 0.5), respectively, corresponding to traditional threshold markers based on different organismic subsystem measures like blood lactate concentration (BLC) or gas exchange data, taking into account the potential limitations and deviations on an individual level (Rogers et al., 2021a,b; Mateo-March et al., 2022, van Hooren et al., 2023b, Schaffarczyk et al., 2023). Further, DFAa1 has been shown to be useful as a marker of acute fatigue in terms of a systemic perturbation (Rogers et al., 2021c; Schaffarczyk et al., 2022; van Hooren et al., 2023a,b) or as a measure of fatigue resistance in studies with prolonged exercise (Gronwald et al., 2018, 2019, 2021b). Therefore, expanding these findings to future approaches of real-time monitoring of prolonged exercise seems to be promising, as the DFAa1 marker might bear the potential to mirror decoupling mechanisms as alterations of external-to-internal-load relationships or “durability” aspects of endurance performance, that were recently described as “the time of onset and magnitude of deterioration in physiological-profiling characteristics over time during prolonged exercise” (Maunder et al., 2021; Smyth et al., 2022). Jones (2023) introduced this construct as physiological resilience and independent determinant of endurance exercise. However, validation data of DFAa1 during prescribed prolonged exercise bouts are still scarce and the true significance for exercise prescription remains to be fully elucidated. In addition, exercise prescription based on a percentage of maximum HR, oxygen consumption or various approaches of fixed BLC and individual gas exchange utilization most often lead to an inaccurate representation of the relationship between external and internal load during prolonged exercise (Mann et al., 2013; Jamnick et al., 2020; Brownstein et al., 2022; Fleckenstein et al., 2023). Therefore, the aim of the present pilot study was to evaluate the ability of DFAa1 to prescribe and monitor exercise intensity during continuous running bouts at the transition of moderate to heavy, and heavy to severe exercise domains.

Methods and Materials

Participants

21 trained (McKay et al., 2022) endurance athletes (9w, 12m; age: 25.9±3.6years, height: 178.4±9.9cm, body weight: 70.8±8.7kg, body fat: 12.2±4.4%, maximum heart rate - HR_{MAX}: 198.4±7.9bpm, maximum oxygen consumption - VO_{2PEAK}: 59.0±8.3 ml/kg/min) voluntarily participated in this study. All subjects were informed about risks and benefits of the procedures and signed an informed-consent form. The ethics committee of the XXX (reference no.: XXX) approved all tests performed in the study. The study was also carried out in accordance with the principles set forth in the most recent revision of the Declaration of Helsinki.

Study design

All participants visited the laboratory on three separate days. On the first day they were informed about risks and benefits of the study and were accustomed to treadmill, face mask and blood lactate concentration measurement procedures. Body fat percentage (BF%) was measured using bio-impedance analysis (InnerScanV, Amsterdam, Netherlands). Afterwards participants completed an incremental running test on a treadmill (Woodway DESMO Pro XL, Woodway Europe, Weil am Rhein) with an increment of 1km/h per minute starting at 7km/h for women and 8km/h for men until volitional exhaustion. Prior to the test, athletes completed a 10-min warm-up on the treadmill at the initial test speed. The running speeds (v) at the first and second ventilatory threshold (vVT1, vVT2) and at DFAa1 of 0.75 and 0.5 (vDFAa1-1, vDFAa1-2) were determined during the running test. Afterwards, two 20-min continuous running bouts at vDFAa1-1 and vDFAa1-2 (20-vDFAa1-1, 20-vDFAa1-2) were conducted in randomized and counterbalanced order within one week. Prior to 20-vDFAa1-1 and 20-vDFAa1-2 all participants warmed-up on the treadmill at a speed corresponding to 80% of their vDFAa1-1 speed (see Figure 1). All tests were conducted at similar times of the day with at least a 72 hours' time-lag to the next or previous test or intense exercise session. Other influencing factors such as sleep, food intake and personal preparation for the test were standardized as far as possible.

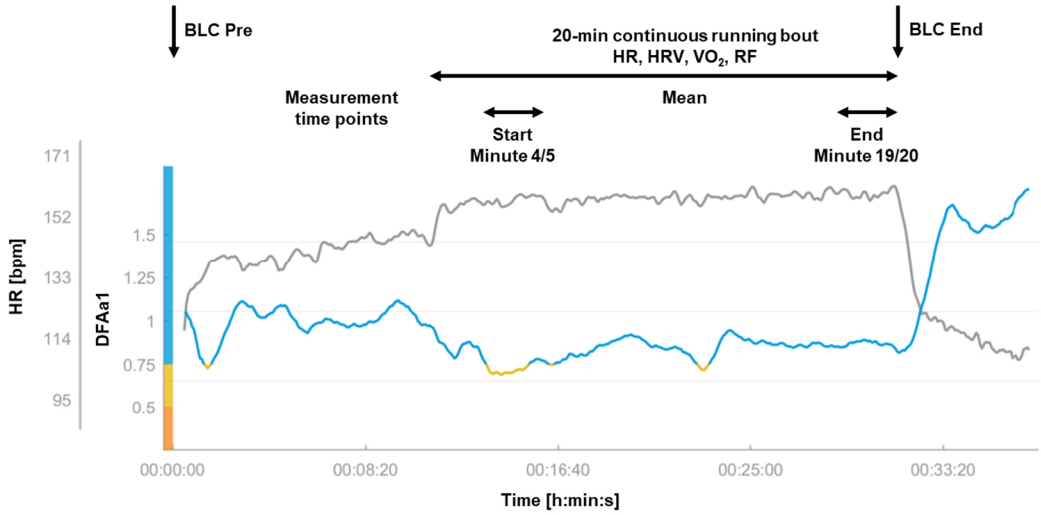

Figure 1: Schematic view of heart rate (HR, grey) and DFAa1 (blue) of one 20-min continuous running bout at vDFAa1-1; warm-up and recovery data included (Kubios HRV Scientific, 2023). Data of HR, HR variability (HRV), oxygen consumption (VO_2), and respiratory frequency (RF) were continuously recorded, blood lactate concentration (BLC) before (Pre) and at the end (End) of the running bouts.

Data measurement

On all three laboratory days HR and HRV were continuously measured during a 5-min resting period and during all test conditions using Polar V800 and H10 HR devices (Polar Electro Oy, Kempele, Finland). BLC was collected from the ear lobe before and at the end of the continuous running bouts using an enzymatic-amperometric method (Biosen C-line, EKF-Diagnostics, Eppendorf, Germany). Further, oxygen consumption (VO_2 in ml/kg/min) and respiratory frequency (RF in breaths per minute, bpm) were continuously measured during all three exercise sessions using a portable breath-by-breath metabolic cart (Metamax 3B, Cortex Biophysik GmbH, Leipzig, Germany).

HRV analysis and threshold determination

To analyze RR-intervals (in ms) and HR (in beats per minute, bpm) data were exported from Polar Flow webservice (Polar Electro Oy, Kempele, Finland) and processed in Kubios HRV Scientific (Biosignal Analysis and Medical Imaging Group, Department of Physics, University of Kuopio, Kuopio, Finland). Preprocessing settings were set to the default values, including the RR detrending method, which was kept at "smoothness priors" (Lambda = 500). The RR-interval series were then corrected using the Kubios HRV "automatic correction" method. To calculate DFAa1, the root mean square (RMS) fluctuations of the integrated and detrended RR-intervals were analyzed in observation windows of different sizes and then further processed as the slope between the RMS-fluctuation data in relation to the different window sizes on a log-log scale (Peng et al., 1995). Window size was set to $4 \leq n \leq 16$ beats in the software preferences. Data were also scanned visually for artefacts by an expert with experience in HRV-data analysis and removed manually if necessary. Data sets with >5% artefacts were excluded from HRV analysis. The time varying DFAa1 kinetic was then calculated over a 120s window width with grid intervals of 10s. HRV thresholds were determined based on fixed values of DFAa1. Linear regression was performed on the subset of data consisting of the rapid, near straight-line drop from DFAa1 values close to 1.0 to approximately 0.5, or below if the values continued in a non-deviating fashion. The running speeds where DFAa1 reached either 0.75 (vDFAa1-1) and 0.5 (vDFAa1-2) were calculated based on the regression equation from that linear section (Rogers et al., 2020, 2021), or based on established multiphasic dose-response modeling (Di Veroli et al., 2015), if its goodness-of-fit exceeded the one of standard linear regression.

Ventilatory threshold determination

To determine VT1 the V-slope method was used (Beaver et al., 1986). In case of inconclusive VCO_2 and VO_2 curves, additionally an increase in end tidal O_2 pressure vs. time and a rise in the O_2 equivalent without a simultaneous increase in CO_2 equivalent was used as criteria for VT1. VT2 was defined as the point of an over proportional rise in minute volume (VE) vs. VCO_2. Additional criteria were a decrease in end expiratory CO_2 pressure vs. time and an increase in the CO_2 equivalent vs. time (Meyer et al., 2005). VT1 and VT2 were both determined independently by two researchers.

Efficiency factor

For the analysis of internal-to-external-load relationship and a possible decoupling mechanism an efficiency factor (EF) was defined. This internal-to-external workload ratio was calculated for the start and end of the continuous running bouts using the ratio of internal load indicators (HR, VO_2, RF, DFAa1) and running pace (in km/h). For the participants which exhausted before the end of 20-vDFAa1-2, minutes 4/5 vs. the last two minutes of exercise were used. The difference of the EF from the start and end was calculated and divided by the EF

from the start multiplied by 100 to get a percentage of alteration (%). Thus, a value of 10% indicates that internal-to-external ratio was 10% greater at the end segment compared to that observed in the start segment (Maunder et al., 2021; Smyth et al., 2022).

Statistical Analyses

Statistics were conducted using SPSS 27.0 (IBM, Chicago, USA), and Microsoft Excel (Microsoft Corp, Redmond, USA). Prior to all tests, normality of distribution was tested using Shapiro-Wilk testing. To analyze the effects of the exercise bouts on dependent variables, a two-way analysis of variance with repeated measures (ANOVA; intensity x time) was applied and both the main effects and the interaction (intensity × time) were reported. In addition, post-hoc testing and comparison of different approaches of external load assessment at estimated exercise intensity thresholds, as well as mean differences between 20-vDFAa1-1 and 20-vDFAa1-2 were conducted via paired t-tests. Additionally, partial η^2 was used to denote the effect sizes of main effects and Cohen's d for the effect size of t-test results (difference between mean values divided by the pooled standard deviation). In addition to mean values for the complete continuous running bouts, the values at start and end at minutes 4/5 vs. 19/20 were used for comparisons (see Figure 1). Statistical tests were deemed to be significant at $p \leq 0.05$. All results are reported as means ± standard deviation (SD).

Results

External loads of vDFAa1-1 (10.6±1.9km/h) and vDFAa1-2 (13.1±2.4km/h) for all participants were comparable to vVT1 (10.8±1.7km/h, p=0.418, d=0.13) and vVT2 (13.2±1.9km/h, p=0.661, d=0.08), but considerable differences between both methods were present for 20-vDFAa1-2 in EG (see also descriptive analysis and differentiation for FG and EG in Table 1). 20-vDFAa1-1 was successfully performed by all participants. However, 20-vDFAa1-2 was completed by only 15 participants (Finisher group, FG), while six participants had to stop ahead of time at 11:47±03:13min:s due to exhaustion (Exhaustion group, EG), as indicated by BLC mean values of 9.98±2.41mmol/l (see Table 1). Due to artefact rates >5% in RR-interval raw data two participants had to be excluded from the analysis of 20-vDFAa1-2 (for DFA a1) in the FG.

Table 1: Comparison of vDFAa1-1, vDFAa1-2, vVT1, vVT2, and blood lactate concentration (BLC) before (Pre) and at the end (End) of both running bouts for all participants, the Finisher (FG) and the Exhaustion group (EG).

	All [n=21]	**FG [n=15]**	**EG [n=6]**
vDFAa1-1 [km/h]	10.6±1.9	10.0±1.5	12.0±2.5
vVT1 [km/h]	10.8±1.7	10.6±1.8	11.5±1.4
vDFAa1-2 [km/h]	13.1±2.4	12.3±1.9	15.2±2.4
vVT2 [km/h]	13.2±1.9	13.1±2.0	13.6±1.5
BLC Pre 20-vDFAa1-1 [mmol/l]	0.95±0.29	0.92±0.27	1.01±0.37
BLC End 20-vDFAa1-1 [mmol/l]	1.56±0.59	1.41±0.45	1.94±0.78
BLC Pre 20-vDFAa1-2 [mmol/l]	1.08±0.22	1.09±0.24	1.07±0.15
BLC End 20-vDFAa1-2 [mmol/l]	5.24±3.79	3.34±2.24	9.98±2.41

FG: Group of 15 participants who finished both prolonged exercise tests; EG: Group of 6 participants which did not finish 20-vDFAa1-2.

ANOVA results indicate a significant main effect for intensity in comparison of 20-vDFAa1-1 and 20-DFAa1-2 for all analyzed parameters in FG. In addition, a significant main effect of time could be determined in HR, VO_2, and RF, but not for DFAa1. An effect of interaction

(intensity × time) could only be found for HR (Intensity: $F = 43.3$, $p < 0.001$, $\eta^2 = 0.756$; Time: $F = 139.9$, $p < 0.001$, $\eta^2 = 0.909$; Interaction: $F = 18.2$, $p = 0.001$, $\eta^2 = 0.565$) and VO_2 (Intensity: $F = 34.6$, $p < 0.001$, $\eta^2 = 0.712$; Time: $F = 25.7$, $p < 0.001$, $\eta^2 = 0.647$; Interaction: $F = 15.3$, $p = 0.002$, $\eta^2 = 0.522$), but not for RF (Intensity: $F = 21.9$, $p < 0.001$, $\eta^2 = 0.610$; Time: $F = 17.5$, $p = 0.001$, $\eta^2 = 0.556$; Interaction: $F = 4.3$, $p = 0.056$, $\eta^2 = 0.236$) and DFAa1 (Intensity: $F = 12.3$, $p = 0.004$, $\eta^2 = 0.505$; Time: $F = 1.1$, $p = 0.320$, $\eta^2 = 0.082$; Interaction: $F = 0.4$, $p = 0.526$, $\eta^2 = 0.034$), respectively.

20-vDFAa1-1 and 20-DFAa1-2 yielded substantial mean differences in FG for HR (150.4±10.6 vs. 170.3±9.8bpm, $p<0.001$, $d=1.95$; 76.2±5.7 vs. 86.4±5.9%HR_{MAX}, $p<0.001$, $d=1.75$), VO_2 (36.7±5.2 vs. 46.0±8.7ml/kg/min, $p<0.001$, $d=1.28$; 62.1±5.0 vs. 77.5±8.6%VO_{2PEAK}, $p<0.001$, $d=2.22$), RF (40.6±11.3 vs. 46.1±9.8bpm, $p<0.001$, $d=0.52$), DFA-a1 (0.86±0.23 vs. 0.60±0.15, $p=0.004$, $d=-1.32$) and BLC at the end of the running bouts (1.41±0.45 vs. 3.34±2.24mmol/l; $p<0.001$, $d=1.19$, see Figures 2-5, and descriptive analysis and differentiation data for EG in Table 1 and 2).

In comparison of start and end of 20-vDFAa1-1 in FG HR and RF increased moderately from 148.4±11.0 to 153.9±11.0bpm ($p<0.001$, $d=0.50$) and 38.7±10.7 to 41.3±11.8bpm ($p=0.023$, $d=0.22$), while VO_2 and DFAa1 remained rather stable with values of 36.6±5.0 vs. 37.1±5.6ml/kg/min ($p=0.108$, $d=0.09$), and 0.86±0.28 vs. 0.84±0.19 ($p=0.666$, $d=-0.10$), respectively (see Table 3). Regarding the alteration of the calculated EF, all parameters showed small changes for FG (HR: 3.7%, VO_2: 1.3%, RF: 6.0%, DFAa1: -2.5%). In addition, EG showed also small alterations of EF <10% for 20-vDFAa1-1 (HF: 4.8%, VO_2: 1.4%, RF: 7.8%, DFAa1: -8.3%).

During the 20-vDFAa1-2 running bout of FG HR und RF rose substantially from 166.6±9.9 to 175.7±10.5bpm ($p<0.001$, $d=0.88$), and 42.0±11.2 vs. 48.4±9.5bpm ($p=0.002$, $d=0.61$); while VO_2 increased moderately with 44.2±7.7 vs. 46.8±9.0ml/kg/min ($p<0.001$, $d=0.31$), and DFA-a1 remained rather stable with 0.65±0.21 vs. 0.57±0.17 ($p=0.262$, $d=-0.41$) (see Table 3). The calculated EF showed small changes for HR and VO_2 (HR: 5.4%, VO_2: 5.6%), while RF and DFAa1 showed more substantial alterations above 10% (RF: 15.6%, DFAa1: -12.8%). In addition, in EG small to moderate alterations of EF indices during 20-vDFAa1-2 were present for HR (2.9%) and VO_2 (6.7%), while changes in RF (20.1%) and DFAa1 (-35.9%) were substantially more pronounced.

Table 2: Summary of all physiological mean data from 20-vDFAa1-1 and 20-vDFAa1-2 for the Finisher (FG) and the Exhaustion group (EG).

	FG [n=15]			**EG [n=6]**	
	20-vDFA1-1	**20-vDFA1-2**	**Statistics**	**20-vDFA1-1**	**20-vDFA1-2**
HR [bpm] (%HR_{MAX})	150.4±10.6 (76.2±5.7)	170.3±9.8 (86.4±5.9)	$p<0.001$, $d=1.95$	165.1±10.5 (82.3±5.3)	189.3±5.5 (94.3±2.1)
VO_2 [ml/kg/min] (%VO_{2PEAK})	36.7±5.2 (62.1±5.0)	46.0±8.7 (77.5±8.6)	$p<0.001$, $d=1.28$	41.5±7.2 (71.7±10.7)	53.9±7.3 (92.9±2.2)

RF [bpm]	40.6±11.3	46.1±9.8	p<0.001, d=0.52	40.6±6.8	51.1±3.4
DFAa1	0.86±0.23	0.60±0.15	p=0.004, d=-1.32	0.76±0.27	0.48±0.17

FG: Group of 15 participants who finished both prolonged exercise tests; EG: Group of 6 participants who did not finish 20-vDFAa1-2.

Table 3: Summary of all physiological data from the start and end of 20-vDFAa1-1 and 20-vDFAa1-2 for the Finisher (FG) and the Exhaustion group (EG).

	20-vDFA1-1			**20-vDFA1-2**		
	Start	**End**	**Statistics**	**Start**	**End**	**Statistics**
FG [n=15]						
HR [bpm] (%HR_{MAX})	148.4±11.0 (75.2±6.0)	153.9±11.0 (78.0±5.8)	p<0.001, d=0.50	166.6±9.9 (84.5±6.1)	175.7±10.5 (89.1±6.2)	p<0.001, d=0.88
VO_2 [ml/kg/min] (%VO_{2PEAK})	36.6±5.0 (61.9±5.1)	37.1±5.6 (62.7±5.7)	p=0.108, d=0.09	44.2±7.7 (74.5±7.3)	46.8±9.0 (78.9±9.2)	p<0.001, d=0.31
RF [bpm]	38.7±10.7	41.3±11.8	p=0.023, d=0.22	42.0±11.2	48.4±9.5	p=0.002, d=0.61
DFAa1	0.86±0.28	0.84±0.19	p=0.666, d=-0.10	0.65±0.21	0.57±0.17	p=0.262, d=-0.41
EG [n=6]						
HR [bpm] (%HR_{MAX})	161.8±10.1 (80.7±4.7)	169.7±11.2 (84.6±5.9)	-	188.5±4.7 (94.0±2.7)	194.3±5.9 (96.8±2.5)	-
VO_2 [ml/kg/min] (%VO_{2PEAK})	41.2±6.4 (71.1±8.4)	41.8±7.4 (72.3±12.3)	-	51.9±6.8 (89.4±2.4)	55.5±8.3 (95.4±2.0)	-
RF [bpm]	38.8±7.6	42.0±7.3	-	46.3±5.4	55.7±3.2	-
DFAa1	0.81±0.36	0.62±0.26	-	0.55±0.25	0.34±0.13	-

FG: Group of 15 participants who finished both prolonged exercise tests; EG: Group of 6 participants who did not finish 20-vDFAa1-2.

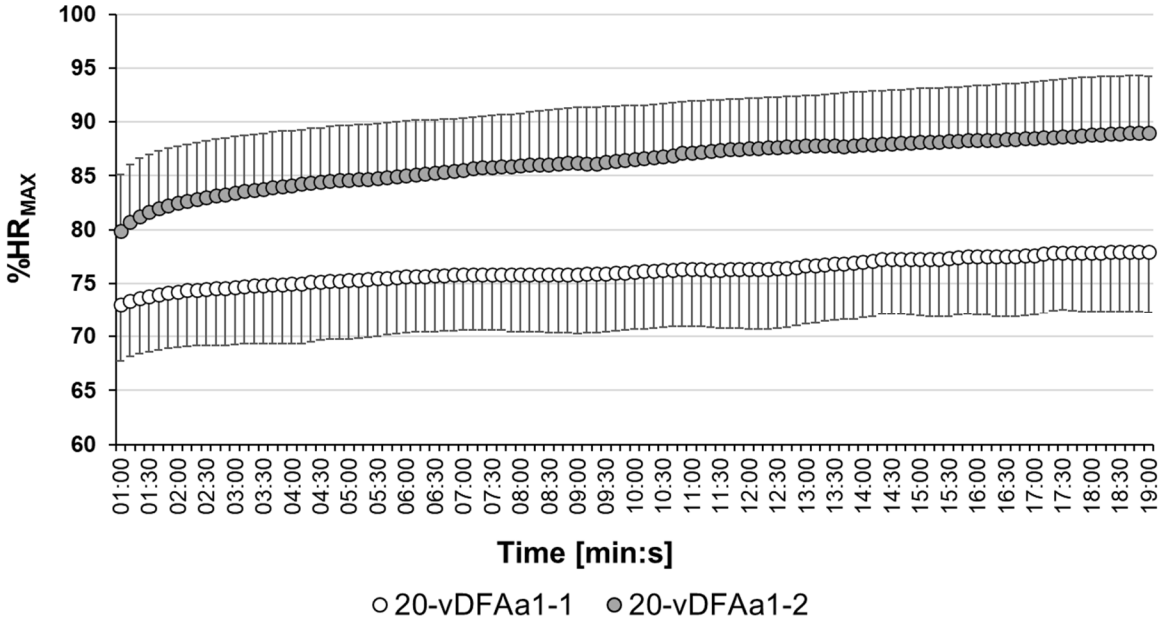

Figure 2: Comparison of heart rate (%HR_{MAX}, mean and SD) kinetics during 20-vDFAa1-1 and 20-vDFAa1-2 of the Finisher group.

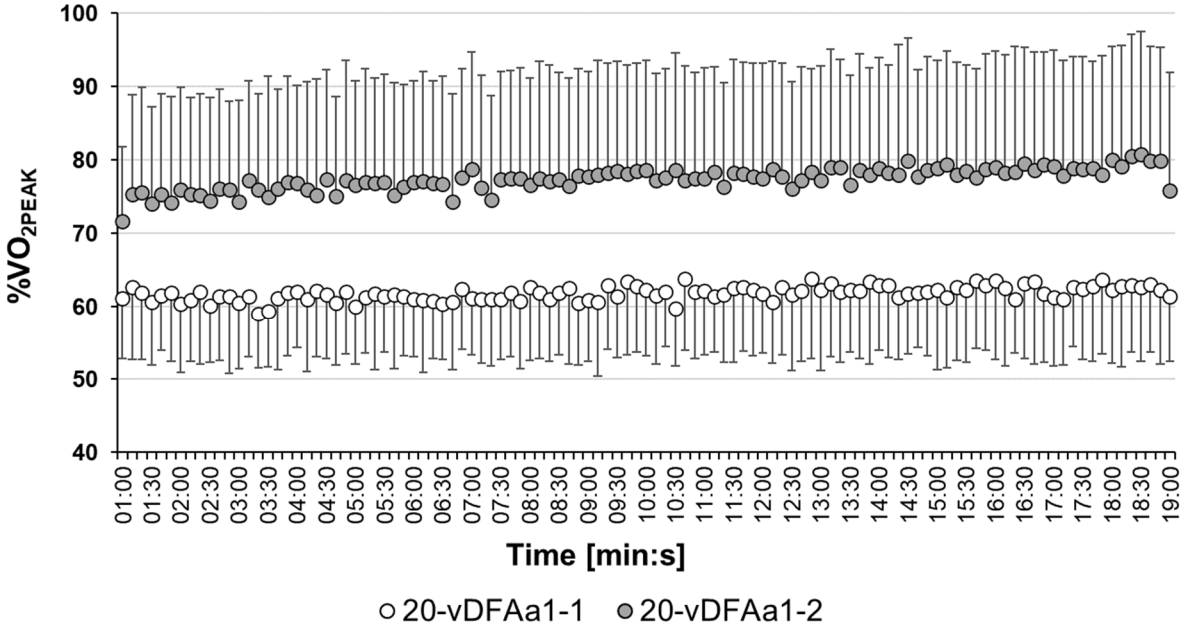

Figure 3: Comparison of oxygen consumption (%VO_{2PEAK}, mean and SD) kinetics during 20-vDFAa1-1 and 20-vDFAa1-2 of the Finisher group.

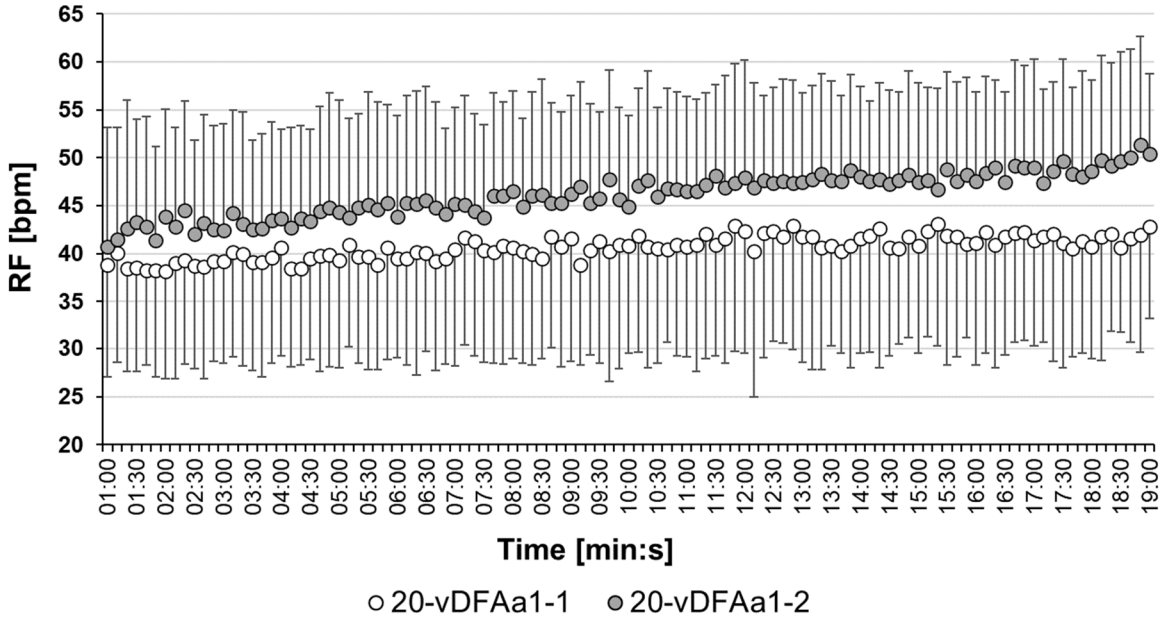

Figure 4: Comparison of respiratory frequency (RF, mean and SD) kinetics during 20-vDFAa1-1 and 20-vDFAa1-2 of the Finisher group.

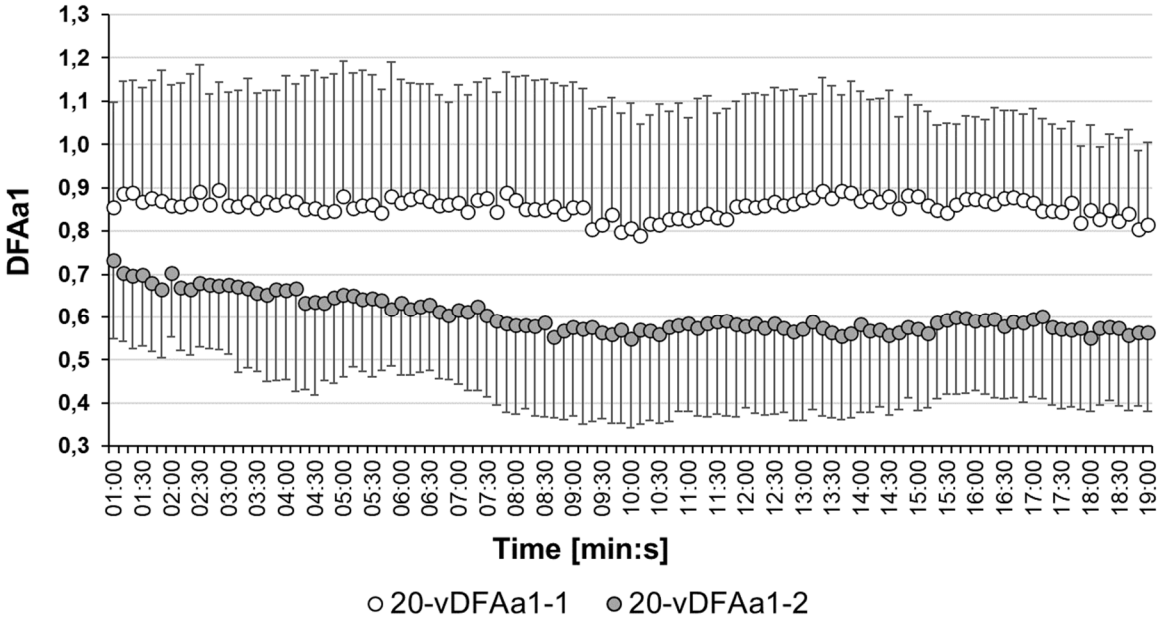

Figure 5: Comparison of DFAa1 (mean and SD) kinetics during 20-vDFAa1-1 and 20-vDFAa1-2 of the Finisher group.

Discussion

The aim of this pilot study was to evaluate the ability of DFAa1 to prescribe and monitor exercise intensity during continuous running at the boundaries of moderate to heavy, and heavy to severe exercise intensities, respectively. Even though it was not the primary goal to directly compare different approaches of exercise intensity domain demarcation (see e.g., Galán-Rioja et al., 2020; Kaufmann et al., 2023), our data indicate that external loads of vDFAa1-1 and vDFAa1-2 were comparable to vVT1 for all participants and to vVT2 for most of the participants (FG), respectively. In addition, the overall comparison of mean values from 20-

vDFAa1-1 and 20-vDFAa1-2 yielded a clear distinction between the two exercise intensities in all physiological parameters and indicate a reasonable demarcation of a 3-zone-model of intensity distribution for moderate, heavy and severe exercise domains (Jamnick et al., 2020; Haugen et al., 2022). Therefore, as already suggested based on signal-theory and findings from prior studies using incremental exercise tests (Gronwald & Hoos, 2020; Gronwald et al., 2020; Rogers & Gronwald, 2022; Sempere-Ruiz et al., 2024), exercise prescription using running speeds at DFAa1 values of 0.75 and 0.5 (vDFAa1-1, vDFAa1-2) separate reasonable intensity domains for prolonged constant exercise bouts for most participants. In our approach these different domains do not directly rely on metabolic markers, but rather are based on the complex changes in autonomic modulation due to parasympathetic withdrawal, sympathetic activation, altered non-neural factors, and the potential loss of interaction between the two branches of the ANS with increased exercise intensity (Persson, 1996; White & Raven, 2014). However, substantial inter-individual fluctuations in internal load occur for both prolonged running bouts that are related to general problems of exercise prescription for prolonged exercise when intensity zone markers are derived from incremental exercise tests (Iannetta et al., 2019a; Zuccarelli et al., 2018; Jamnick et al., 2020). Further, our data also support the notion that the magnitude and practical relevance of these inter-individual differences depend on the addressed intensity domain, as substantial and practically relevant differences were mainly found in vDFAa1-2, and these differences lead to premature exhaustion in the high intensity running bout for more than 25% of the participants (EG, n=6).

Prolonged constant load exercise prescription from incremental testing

Prolonged constant load exercises derived from external load prescriptions of incremental tests bears the general problem that the physiological response may vary considerably between individuals both at the beginning and throughout the constant load exercise (e.g., Iannetta et al., 2019a; Jamnick et al., 2020). This could be seen in all our metabolic and cardiorespiratory markers including DFAa1, which was used for prescription of vDFAa1-1 (DFAa1 = 0.75) and vDFAa1-2 (DFAa1 = 0.5). In addition, recent findings even indicate an unclear assignment of an intensity domain during constant load exercise of prolonged duration when using the highly individual acute responses of $\%HR_{MAX}$ as a benchmark (Iannetta et al., 2019a). In that regard, for prolonged exercise prescription it must be considered that laboratory testing with incremental design (step, ramp) needs to account for specific response kinetics of the corresponding physiological markers, and the magnitude of the inter-individual variability depends on the interaction of the used biomarker, its response kinetics, and the incremental exercise protocol (Zuccarelli et al, 2018; Iannetta et al., 2019b). External load prescription assumes that physiological responses are rather static (Jamnick et al., 2020; Maunder et al., 2021) and neglect the influence of internal and external factors leading to heterogeneity in exercise tolerance and physiological responses over time (e.g., personal or environmental factors, Gronwald et a., 2020; Meyler et al., 2023). The large variation of internal load responses in our data seem to be also present when prescriptions based on fixed submaximal threshold approaches (e.g., BLC) or individual submaximal threshold approaches are made (e.g., GET) (Fleckenstein et al., 2023; Brownstein et al., 2022). In addition, pre-exhaustion due to incremental testing may also lead to an altered internal-to-external-load relationship at an intensity domain transition compared to the beginning of prolonged exercise (with or without standardized warm-up procedures), revealing the need to address exercise duration as an important independent prescription factor (Hofmann & Tschakert, 2017; Tschakert et al., 2022). This also applies for other external load indicators like movement frequency (e.g., cadence in cycling exercise; Beneke & Leithäuser, 2017; Gronwald et al., 2018). In this regard, recent findings from DFA of HRV during running show that repeated incremental running

tests shift the agreement between gas exchange thresholds and DFAa1-derived boundaries for intensity demarcation, leading to the assumption of fatigue-related inter- and intra-individual physiological perturbations depicted in DFAa1 kinetics (van Hooren et al., 2023a,b). Therefore, it seems reasonable to address these issues using an internal-load-based approach of exercise prescription for prolonged constant load exercise to consider the individual and daily responses to a prescribed external load accounting for personal and environmental influences on the most prominent underlying trend in HR data, the cardiovascular drift (Ekelund, 1967). Recently, a HR-based exercise intensity control approach using a HR clamp that kept HR constant over time by adjusting speed/power (Zuccarelli et al., 2018; Li et al., 2023) showed substantial differences for standard HRV metrics during exercise when compared to constant load exercise with corresponding HR drifts (Hernando et al., 2018; Hunt & Saengsuwan, 2018; Brockmann & Hunt, 2023). In this context, however, further questions need to be clarified about suitability of different subsystem parameters of internal load and a "best" and feasible real-time monitoring approach for the control of exercise intensity (e.g., HR drift and the potential underestimation of rating of perceived exertion (RPE); Cartón-Llorente et al., 2022). Here, a dimensionless, global, and systemic internal load indicator like DFAa1 (in addition to RPE as an easily accessible subjective marker) could provide the potential for further investigation in prolonged exercise regimes (Gronwald et al., 2021a; Rogers & Gronwald, 2022). However, it seems mandatory to evaluate mid- and long-term training outcomes when controlling exercise intensity based on internal load markers, as this may lead to significant and inter-individual varying reduction in exercise and training stimuli (Zuccarelli et al., 2018).

Intensity domain dependency for prolonged exercise prescription

Besides the already discussed general problems of exercise prescription for prolonged constant load exercise from incremental testing our data also points towards an intensity specific aspect of these issues, that needs to be further addressed. On the one hand, our data shows that the intensity prescription for 20-vDFAa1-1 elicits a BLC below 2 mmol/l, and magnitudes of $\%HR_{MAX}$ and $\%VO_{2PEAK}$ for FG and EG (Tables 1-3) that clearly mirror medium to upper levels of a moderate intensity domain in established 3-zone-models (Jamnick et al., 2020; Haugen et al., 2022). Besides the mean values the inter-individual differences in $\%HR_{MAX}$ and $\%VO_{2PEAK}$ are in line with the magnitudes shown in a recent study based on BLC-derived LT prescription (Fleckenstein et al., 2023). In addition, when considering recently proposed ratios for the assessment of internal-to-external-load relationship and decoupling mechanism (Maunder et al. 2021; Smyth et al., 2022) in terms of EF of HR, VO_2, RF, and DFAa1 in relation to running speed, a comparison of start and end of the running bouts lead to rather small alterations of EF <10% in all parameters in both FG and EG. These values of a small HR drift without a slow component in VO_2 support the notion of a DFAa1-derived separation of moderate and heavy intensity domain.

On the other hand, for 20-vDFAa1-2 derived from DFAa1 values of 0.5 during incremental testing, BLC-values of approx. 3.5 mmol/l, as well as $\%HR_{MAX}$ and $\%VO_{2PEAK}$ in FG (n=15) can be matched within the lower to medium range of the heavy intensity domain, while the corresponding values for EG (n=6) that couldn't sustain the 20-min exercise duration clearly exceed the boundary towards the severe intensity domain (Jamnick et al., 2020; Haugen et al., 2022), respectively. Further, 20-vDFAa1-2 lead to substantial alterations of EF with a magnitude of >10% for RF and DFAa1 in FG, and >20% for EG, which shows the potential of these two internal load parameters regarding further decoupling analysis of internal-to-external relationship. In this context, RF was recently mentioned as a promising internal load marker in

exercise physiology and offers new possibilities for wearable analyses in research and practical settings (Nicolo et al., 2017; Nicolo & Sacchetti, 2023).

The probable overestimation of running velocity in the subsample of EG is further in line with previous studies that already discussed potential overestimations for a relevant number of participants using the present approach of non-linear HRV analysis to delineate the heavy from the severe intensity domain (Rogers et al., 2020, 2021; Mateo-March et. al., 2022). One factor might be that (linear) HRV metrics are both intensity and time dependent and may reach their near minimum values with low signal-to-noise ratio rapidly (Brockmann & Hunt, 2023). However, to what extent this is true for non-linear measures like DFAa1 needs to be further elucidated in e.g., HR clamp exercise. Further, as stated before (Gronwald & Hoos, 2020; Rogers & Gronwald, 2022; Kaufman et al., 2023), despite the need for comparison with established intensity domain threshold concepts, it should be kept in mind that the present approach is based on the theoretical framework of a self-organized dynamic regulation of the central autonomic network (CAN, Benarroch, 1993) that is reflected in the correlation properties of HR dynamics. Therefore, it is rather complimentary to and does not necessarily coincide with classical metabolic threshold concepts based on metabolic and/or respiratory biomarkers. As mentioned above, the definition of intensity domain boundaries might involve different approaches based on performance indicators of external load (e.g., critical speed or power, CS, CP), subsystem indicators of internal load like BLC (e.g., lactate threshold, maximal lactate steady state), and/or gas exchange data (e.g., gas exchange threshold, GET), that interact with their corresponding different testing protocols. This may produce inconsistent results leading to substantially different delineations of the boundaries in a 3-zone-model of intensity zones, and is reflected in the still ongoing debate about gold standard approaches to delineate moderate from heavy, and especially heavy from severe intensity domains (Chicharro et al., 1997; Hopker et al., 2011; Pallarés et al., 2016; Jamnick et al., 2018; Iannetta et al., 2019a; Galán-Rioja et al., 2020; Poole et al., 2021). Therefore, misleading comparisons between protocols as well as undesired training outcomes in athletes attempting to emulate a proposed method are also present when other approaches are used, and this seems to be most problematic for the boundary of heavy to severe exercise intensity (Jamnick et al., 2018; Iannetta et al., 2019a; Galán-Rioja et al., 2020; Poole et al., 2021).

Taken together based on the present results and the available data of previous studies using DFAa1 as an complementary exercise prescriptor (Rogers et al., 2021a,b; Mateo-March et al., 2022, van Hooren et al., 2023b, Schaffarczyk et al., 2023), it must be noted that for some individuals the present approach does not lead to an adequate specification of exercise intensity at the boundary of the heavy to severe exercise domain. Therefore, further investigations should be dedicated to the considerable differences of DFAa1-derived threshold determination for 20-vDFAa1-2 in EG, leading to overestimation of running velocity in this subsample. Here, for example the influence of individuality in time and intensity dependent changes in the scaling behavior of DFA (Molkkari et al., 2020; Kanniainen et al., 2023) as well as model fitting and model type (e.g., linear, polynomial, sigmoidal) of DFAa1-derived threshold determination could be subject to further investigations. In prior studies, we observed inappropriate suppression of correlation properties of HR time series in some individuals losing dynamic range of DFAa1 despite good ECG waveform and little artefact (van Hooren et al., 2023b). In addition, future studies should enlighten the relevance of standardization of methodological aspects (e.g., quality of data acquisition, pre-processing, artifact correction methods depending

on the type/mode of exercise and/or laboratory vs. field conditions) on DFAa1 derived exercise prescription and evaluate more thoroughly the significance of primary internal (e.g., breathing) and external influencing factors (e.g., environmental conditions).

Limitations

The prolonged exercise bouts were too short to provide evidence whether our approach of DFAa1 derived exercise prescription may be useful for typical duration of running training (e.g., 30-60min), as these longer durations may even complicate potential "decoupling mechanisms". However, our data as well as findings from prior studies at least indicated that the magnitude of duration-related influences and the potential for fatigue resistance assessment during prolonged exercise regimes could be further evaluated using a DFAa1 approach (Gronwald et al., 2018, 2019, 2021b). Longer exercise bouts are also needed to increase sensitivity for the evaluated EF. In addition, since external load was maintained constant for the prolonged exercise bouts the analysis of internal-to-external-load relationship and decoupling mechanism would be more appropriate to use within the application in field conditions and/or self-paced scenarios. Whether other theoretically appealing approaches using ratios of individually designed external to internal load markers like e.g., maximal or submaximal external load markers like CP or CS in combination with DFAa1 and/or %HR recovery or $\%HR_{MAX}$ might be helpful also remains an open question.

Conclusion

For most participants DFAa1 shows great potential as a dimensionless and systemic index for internal load-based exercise prescription with a clear demarcation perspective for a 3-zone training intensity distribution model. However, for some individuals the present approach does not lead to an adequate separation of exercise intensities, especially not for the heavy to severe exercise domains. Therefore, further investigations are recommended to account for inter-individual differences and to better understand the relationship of DFAa1 and vDFAa1, and its relevance for the time evolution of fatigue during prolonged constant load exercise. In this regard the potential for internal load-based real-time monitoring and intra-individual internal-to-external load analysis as a regular biological calibration procedure accounting for personal and environmental factors might be strengthened by further exercise specific methodological refinements of DFA. In addition, future studies should elucidate possible decoupling mechanisms of DFAa1 and other internal load measures in relation to external load (and other influencing factors, e.g., exercise mode, environmental conditions, pre-exhaustion) during even longer exercise bouts that correspond to typical exercise durations of real-world running training (>30min).

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