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RESEARCH ARTICLE

Wefelnberg et al: Dynamic retinal vessel symmetry

Interocular symmetry in dynamic retinal vessel analysis among healthy adults

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ABSTRACT

Dynamic retinal vessel analysis is a non-invasive approach for assessing retinal microvascular endothelial function, yet the extent to which eye selection, interocular variability, and systemic physiological factors influence dynamic retinal vessel analyzer (DRVA)-derived biomarkers remains insufficiently defined. This prospective methodological study aimed to evaluate the interocular symmetry and absolute and relative reliability of arterial flicker-induced dilation (aFID), venular flicker-induced dilation (vFID), and arteriolar constriction (aCON), and to determine whether these parameters are moderated by eye dominance, peak oxygen uptake (VO_2 peak), or intraocular pressure (IOP) in healthy individuals. Twenty apparently healthy adults completed two laboratory visits. During the first visit, aerobic capacity was assessed by cardiopulmonary exercise testing until volitional exhaustion. During the second visit, IOP, resting blood pressure, eye dominance, and retinal vascular endothelial function were assessed using DRVA in both eyes in randomized order. Interocular differences were examined using paired comparisons, Bland–Altman analysis, reliability statistics, and linear mixed-effects models accounting for bilateral measurements within participants. No significant differences were observed between the left and right eyes for aFID, vFID, or aCON. Bland–Altman analysis showed no systematic interocular bias across DRVA-derived parameters, although the limits of agreement were widest for aFID, indicating greater interocular variability. Relative reliability was highest for vFID, followed by aCON, whereas aFID showed only fair agreement. Similarly, absolute reliability analyses identified vFID as the most stable biomarker, with the lowest coefficient of variation, while aFID demonstrated the greatest variability. Linear mixed-effects models showed no significant moderating effects of eye dominance, VO_2 peak, or IOP on aFID, vFID, or aCON. These findings suggest that retinal vascular endothelial responses measured by DRVA are not systematically influenced by eye dominance or selected systemic physiological factors in healthy young adults. However, given the observed interocular variability, particularly for aFID, assessment of both eyes should be considered in clinical and research settings to improve measurement precision and reproducibility.

Keywords: Microvascular circulation, oxygen kinetics, flow mediated dilation.

INTRODUCTION

Dynamic retinal vessel analyzer (DRVA) is a rather novel, non-invasive imaging technique that assesses the vascular endothelial responses by measuring real-time changes in retinal vessel diameter during flicker-light provocation [1]. It serves as a unique "*window*" into cardiometabolic health, allowing the evaluation of dilation and constriction capacity of the retinal vasculature and detecting early signs of pathohistological remodeling of the microvasculature [1,2,3]. Over the recent years, a growing body of literature has shown that a reduction in flicker-light dilation (FID) is instrumental to an increased cardiometabolic risks, such as hypertension, type 2 diabetes, kidney diseases and obesity [4,5,6]. On the other hand, recent work in clinical populations had shown that aerobic exercise is a strong stimulus of microvascular improvements when measured via DRVA [7,8,9]. For example, our recent work demonstrated that an 8-week HIIT intervention led to an 11% improvement in peak oxygen uptake (VO_2 peak) in a choroidal melanoma patient, which was paralleled by a two-fold increase in both arteriolar and venular dilation in response to FID stimulation [9]. Moreover, the retinal aFID was found to be a sensitive biomarker to detect short-term exercise effectiveness, as Twerenbold et al. [8] found improvements in the microvascular endothelial function assessed following 8-weeks of high-intensity interval training in older hypertensive patients. According to authors of this study, these improvements were superior to those measured in large conduit arteries assessed via gold-standard flow mediated dilation (FMD) technique. Recently, the same group of researchers had shown good- to excellent day-to-day and interobserver relative reliability (e.g., the intraclass correlation coefficient, ICC) of maximum arteriolar (aFID) and venular flicker-light induced dilation (vFID) in twenty-six middle-age men and women [10]. Interestingly, data on measures of absolute reliability, such as coefficient of variation (CV%) and standard error of measurement (SEM) are not yet presented in the literature, so a complete picture of the device measurement resolution (e.g., consistency and reliability) is not given. While DRVA technique is a validated surrogate biomarker for systemic health, some challenges still remain. For example, there is a lack of standardized eye selection protocols, as the current research often relies on the arbitrary selection of a single eye, typically the right, without a standardized physiological justification [3-8]. Moreover, while reference values for FID of the right eye exist [3], there remains a critical gap in comprehensive data analysis regarding the potential moderating effects of systemic

factors, such as VO_2 peak, intraocular pressure (IOP), and biological eye dominance. Thus, one of the aims of this work is to examine (i) the interocular symmetry and its reliability in both absolute and relative terms, and to (ii) analyze how systemic factors like VO_2 peak, IOP and biological eye dominance moderate local vascular beds and their responses to FID stimulus. Our work seeks to determine if the current practice of arbitrary eye selection is scientifically justified or if specific physiological moderators must be considered to ensure the accuracy and reproducibility of DRVA measurements. We hypothesize that the retinal vascular reactivity is not perfectly symmetrical; specifically, the dominant eye will exhibit a distinct microvascular response profile compared to the non-dominant eye, suggesting that eye selection must be standardized based on dominance rather than convenience. To wit, we believe that the individual physiological characteristics, such as aerobic fitness VO_2 peak and resting IOP, will moderate the magnitude of the flicker-induced response, indicating that FID results cannot be interpreted accurately without accounting for these systemic variable, and that the sensitivity to these moderators will differ among vessel types, with venous reactivity (vFID) and arterial constriction (aCON) showing different degrees of variation compared to arterial dilation (aFID).

MATERIALS AND METHODS

This study is a prospective, methodological investigation looking at measurement resolution of the DRVA device, and the potential effects of moderators such as VO_2 peak, IOP and eye dominance. Over the course of the study, data were collected on two separate lab visits. More precisely, following medical clearance, study participants were advised to refine from excessive physical activity, caffeine or alcohol at least 24 h prior to data collection. During the first lab visit, all study participants performed a cardiopulmonary exercise test (CPET) until voluntarily exhaustion, while on the second visit their IOP, resting blood pressure and vascular endothelial function was assessed using the dynamic retina vessel analyzer for both left and right eye, in random order respectively.

Study participants

Study participants were recruited via word of mouth, social media advertisement, and flyers distributed across the University Hospital and Faculty of Medicine. Inclusion criteria required participants to be apparently healthy men and women older than 18 years of age with no history of eye disease, cardiovascular, metabolic, or any chronic

disease, including obesity (BMI >34.9 kg/m²). Exclusion criteria included diabetic retinopathy, peripheral arterial disease, any known neuromuscular injury, current smoking, and the use of oral contraceptives, medications, or dietary supplements (e.g., creatine, whey protein, or nitric oxide boosters). Additionally, individuals with acute orthopedic issues or contraindications to exercise were excluded (11). All study participants who met the inclusion criteria provided medical clearance and written informed consent prior to data collection.

Cardio-pulmonary exercise testing

Data were collected at the University Hospital Cologne, diagnostics laboratory of the Exercise oncology department. More precisely, the aerobic capacity of the study participants was assessed using an Ergoline 900 cycle ergometer (Hamburg, Germany) connected with a metabolic chart (MetaLyzer 3B system, Cortex, Leipzig Germany) in agreement with previously published work [9,11,12]. Following the collection of resting vital signs (heart rate, blood pressure, and SpO_2) the study participants were fitted with a silicone mask (Hans Rudolph, Kansas City, USA) connected to a metabolic chart, and a Polar H10 heart rate monitor (Polar Oy, Finland). A standardized ramp protocol was performed, beginning with a 3-minute rest period followed by an initial workload of 30 W, which increased by 15 W per minute until volitional exhaustion was reached. Task failure was defined as the inability to maintain required-cadence of 70 rpm for more than 10 seconds. Breath-by-breath gas exchange was monitored throughout the test using a calibrated metabolic chart (MetaLyzer 3B system) to determine systemic gas exchange, as well as peak power output (PPO), and heart rate maximal (HR max).

Dynamic retina vessel analyzer

Vascular endothelial function assessment of the retina for both left and the right eye was performed using Dynamic Vessel Analyzer (DRVA, Imedos Health GmbH, Jena, Germany). This technique is widely recognized for causing retinal vessel dilation through the stimulation of an optoelectronic shutter within the retinal camera [1-3]. Prior to DRVA assessment, we measured best-corrected distant visual acuity using an automatic refractometer (ARK-1s, Nidek, Tokyo, Japan), and IOP using rebound tonometry (ic100, Icare, Vanda, Finland). To determine the eye dominance, a simple ring bearing test was applied. This requires that a participant looks at the at the

examiner's nose in a distance of three meters through a circle of roughly five cm diameter, which is created by the subject via overlapping hands with arms outstretched in front. The eye that is visible through the circle is then determined as the dominant eye [13]. The DRVA data collection protocol started with resting blood pressure measurement and the application of tropicamide (1%) to provoke pupil dilation. Then, study participants received instructions to concentrate on a green cross positioned within the camera, and not to move during the measurement. The measurement process began with a baseline recording lasting 50 seconds, next, during the 350 seconds of measurement, three phases of flicker-light lasting 20 seconds each were applied on the participants' eyes in order to provoke vessel dilation by overstimulating the photoreceptors in the retina, at a frequency of 25 Hz. The alterations in the retina diameter, resulting from the applied stimulus were automatically computed using the integrated Retinal Vessel Analyzer software (RVA 4.61; IMEDOS Systems GmbH, Jena, Germany) as a function of diameter change relative to the individual baseline. To quantify maximum dilation, we applied the protocol recently published by Streese et al. [3]. We chose one vene and one artery from each eye's superior or inferior vascular arch depending on criteria of measurability (e.g. density of branches, clearances to adjacent vessels). Subsequently, the following variables were derived from the device: arteriolar (aFID) and venular dilation (vFID) and constriction (aCON) in compliance with the manufacturer's guidelines. A representative trace of the DRVA measurement is given in **Figure 1** for both eyes**.**

Ethical statement

The Institutional Review Board of the Medical Faculty at the University of Cologne approved this study (No. 13-050), conducted within the framework of the Oncological Exercise Therapy (OTT) initiative established at University Hospital Cologne [14]. All procedures followed the Declaration of Helsinki (version from 2013) and Good Clinical Practice guidelines.

Statistical analysis

All data were analyzed using the JAMOVI open access tool (version 2.7.6., www.jamovi.org) and are presented as mean ± SD, while the graphs were created using GraphPad Prism version 11.00 (Graph-Pad Software, La Jolla, CA, USA). The normality of the data distribution was assessed using the Shapiro–Wilk test. A paired Student's t-test was used to assess the inter-ocular symmetry. The relative reliability

of all dependent DRVA-derived variables was calculated using the ICC, two-way random model with 95% confidence interval. Reproducibility was considered as poor with an ICC ≤ 0.20, fair between 0.21 and 0.40, satisfactory between 0.41 and 0.61, good between 0.61 and 0.80, and excellent with an ICC ≥ 0.81 (12). The SEM and the CV (%) were provided as measures of the absolute reliability. Moreover, to detect any potential systemic bias, a Bland–Altman plots were generated. To evaluate the influence of potential moderators on DRVA-derived parameters, a linear mixed-effects models (LMM) were performed using the GAMLj module. This approach was selected to account for the two eyes per participant, thereby controlling for interocular dependency while maximizing statistical power, in a limited sample size (n=20). Separate models were constructed for each dependent DRVA variable: aFID, vFID, and aCON. In each model, the $\dot{V}O_2$ peak and IOP were entered as fixed-effect covariates to determine their respective contributions to the variance in vessel response. To account for the correlated nature of the bilateral measurements, a participant ID was included as a random effect (random intercept). Parameters were estimated using the restricted maximum likelihood (REML) method. The significance of fixed effects was assessed using Satterthwaite's approximation for degrees of freedom. Normality and homoscedasticity of the residuals were verified through visual inspection of Q-Q plots and residual-versus-predicted value plots. Statistical significance was set at $p < 0.05$, using a two-tailed approach.

RESULTS

The study population comprised 20 healthy young men and women, with baseline biometric characteristics summarized in Table 1. Initially, a total of 25 participants met the inclusion criteria and provided written informed consent from a baseline pool of 28 individuals. Of the five participants excluded from the final analysis, two were removed due to elevated brightness sensitivity (e.g., the flicker-light stimulus), and three withdrew from the study without providing a reason. The overall quality of the FID signal (in German *Gültigkeit* - an internal measure provided by the manufacturer was >70% for veins and arteries of both eyes). Data on the vFID response for one participant were lost due to a technical error (right eye). Participants included in the data analysis exhibited normal BMI, resting blood pressure, and IOP, while their peak oxygen uptake was slightly higher compared to relative to age-matched normative values. According to t-test analysis, there were no differences observed for aFID

(p=0.775), vFID (p=0.681), and aCON (0.564) between the left and right eye. Data on the relative reliability analysis for demonstrated good -to- satisfactory relative agreement (ICC readings for vFID: 0.662 and aCON: 0.504, respectively), while aFID exhibited fair reliability (0.377). Similar pattern was observed for absolute measures of reliability (CV% and SEM) where a high inter-individual variability was further evidenced, with aFID showing the highest fluctuation (CV: 46.4%, SEM: 1.66), followed by aCON (CV: 42.8%, SEM: 0.49), while vFID remained the most stable metric with a CV of 28.9% and an SEM of 1.19, Table 2. In Figure 1 a representative trace of the FID response recorded during DRVA assessment of both eyes of a single participant is given. Data presented in Figure 1. were averaged over a 5 second interval. In Figure 2, the Bland–Altman analysis showed that there was no systemic bias within the data for all depended variables (Panels A - C). More precisely, for the aFID parameter, the Bland-Altman analysis revealed a negligible mean bias of 0.190 (95% CI: -1.04 to 1.42), indicating no systematic difference between eyes. However, the 95% limits of agreement (LOA) were wide, ranging from -4.97 to 5.35. The vFID data demonstrated superior interocular agreement compared to arterial responses. The Bland-Altman analysis showed a negligible mean bias of 0.184 (95% CI: -0.835 to 1.20) and narrower 95% LOA (-3.96 to 4.33). Lastly, the aCON data demonstrated the narrowest absolute LOA (-3.21 to 2.73) among all DRVA parameters, with a non-significant mean bias of -0.240 (95% CI: -0.948 to 0.468). The LMM analysis presented on the Forest plot (Figure 3, panels A - C) suggested that the eye dominance did not significantly bias the outcome FID measures (panel A: for aFID p=0.474, vFID=0.094 and for aCON p=0.876). Also, the Forest plot analysis of the systemic moderators revealed the following: IOP and VO_2 peak data also did not influence the FID outcomes (panel B: for aFID p=0.69, vFID=0.652 and for aCON p=0.31 and for panel C: aFID p=0.751, vFID=0.492 and for aCON p=0.344, respectively). In regard to Model diagnostics, reliability was highest for the vFID model (Conditional R^2=0.68, with 95% CI: -1.731 – 0.124), followed by aCON (Conditional R^2=0.52, with 95% CI: -0.758 – 0.649), while the aFID model (Conditional R^2=0.38, with 95% CI: -1.624 – 0.766) was more susceptible to individual variation. Visual inspection of Q-Q plots and Shapiro-Wilk tests confirmed that the residuals for all parameters followed a normal distribution, while the absence of distinct patterns in residual-versus-fitted plots indicated a lack of significant data heterogeneity across all three models.

DISCUSSION

The aim of our study was to evaluate the interocular symmetry and reliability of the retinal vascular reactivity, measured via arterial and venous flicker-induced dilation (aFID, vFID) and arterial contrast (aCON) - and to determine if these biomarkers are influenced by biological and systemic moderators. We hypothesized that retinal vascular reactivity is not perfectly symmetrical; meaning that the dominant eye will exhibit a distinct microvascular response profile compared to the non-dominant eye, thereby affecting the eye selection procedure. Also, we hypothesized that the individual physiological characteristics, such as VO_2 peak and resting IOP, will significantly modulate the magnitude of the flicker-induced response, thereby moderating among different small blood vessels with different degrees of variation. The main findings of the present study are partially in line with our initial study hypothesis, as we observed a satisfactory to good agreement for relative reliability in aCON and vFID, while aFID exhibited fair agreement for the interocular readings. Importantly, the confidence intervals for all three DRVA-derived variables were quite wide and considering relatively small sample size, the ICC readings observed here should be interpreted with caution. This was also mirrored by absolute measures, where vFID remained the most stable metric compared to the high inter-individual variability and fluctuation observed in aCON and aFID (CV > 42 %, Table 2). These findings on the relative and absolute reliability analysis provide the first evidence in the literature on eye-symmetry assed via DRVA device, as previous work was predominantly based on relative day to day reliability or correlation analysis (10). One possible explanation for this variation among FID biomarkers was recently offered by Streese et al. [10], who reported satisfactory-to good relative intra-day and intra-observer variability in FID response of the right eye, and suggested that in percentage-based methods, such as aFID, for example, should be corrected for baseline diameters. This approach was also recommended by other experts in the filed [15], and this is already implemented into the FMD analyses that also measures vascular endothelial function of the large conduit artery's [8]. Still, the observed variations in retinal FID parameters are relevant data for both preclinical and clinical research, since aFID is a sensitive biomarker to track microvasculature adaptation to exercise interventions [7-9], while in clinical research early signs of microvascular disfunction and blood vessel remodeling manifest in the retina vessels long before clinical onset of various cardiometabolic diseases occur [1]. This is especially

important in the filed of microvascular circulation and its integration into clinical medicine [16,17]. However, since this was an observational study, and this filed of research is still growing, we cannot provide a straightforward explanation on the sources of biological variation in primary outcome variables. We can only outline that data presented on FID response here, foremostly aligns with reference values provided by Stredese et al. [3] for this age and fitness level group. What is important and relevant in this line of examination is that Bland-Altman analysis (Figure 2, panels A-C) revealed a small mean bias for all three depended variables, indicating no systematic difference between eyes. More precisely, the mean differences were minimal (Figure 2), and the 95% LOA varied by metric; aCON (-3.21 to 2.73) and vFID (-3.96 to 4.33) demonstrated relatively tight intervals, whereas aFID exhibited substantially wider limits (-4.97 to 5.35). These results suggest that, while the eye selection does not introduce directional bias, venous and contrast-based metrics provide superior interocular precision compared to arterial dilation, meaning that measurements between eyes cannot be assessed interchangeable for clinical decision-making. Previous work in this line of research had focused on arbitrary selection of the right eye [2-5, 7, 8] or the dominant eye Günthner et al. [6]. To best of our knowledge, only one original research on cardiovascular patients had tested both eyes using DRVA device [18], with an aim to show early signs of major adverse cardiovascular events. Here, we aimed to comprehensively evaluate the interocular symmetry and the role of systemic factors on DRVA accuracy in healthy individuals. According to the mixed model analysis, the microvascular FID response remained independent of eye dominance and systemic physiological moderators, indicating that there is no clear evidence of these effects in studied population (Figure 3, panels A-C). The explanation of such findings is that here we tested healthy, normotensive, aerobically fit individuals and found no cofounding effects on FID. What we know from previous research is that changes in microvascular function and aerobic fitness often coincide, due to exercise induced rise in nitric oxide bioavailability. This is why researchers often report of around 25-30% of the shared variance between measures of small and large conduit arteries and systemic O_2 uptake measured via CPET [7, 19]. Therefore, it would be interesting to see if such findings would be also described in sedentary, aging or clinical populations where influence of such confounders is expected [20]. This certainly requires further investigation. Some limitations to our work should be outlined and acknowledged. Sample size is rather small, comprised of

only healthy individuals and these conclusions should not be extended to clinical populations. To better explain our approach, and justify limited sample size in this work, we had examined both eyes, meaning that the overall workload of data collection and analysis was two-fold greater compared to similar studies in this area. For example, the study on normative DRVA data from Stresse et al. [3] for this age group tested 39 participants, meaning that 39 measurements were taken, and 39 data sets were analysed. Here we reported the same amount of workload divided by two eyes, in attempt to compressively evaluate factors that influence DRVA assessments in healthy population.

CONCLUSION

This was the first study to comprehensively evaluate absolute and relative reliability of the DRVA-derived biomarkers, as well as the influence of potential moderators. The vFID biomarker showed the highest absolute and relative reliability, followed by aCON, while aFID was identified as the least consistent and symmetrical parameter. Our second main conclusion is based on the finding that there is no clear evidence that the vascular endothelial response of the retina is moderated by biological eye dominance, or systemic factors in this population. Data from the relative reliability analysis depict that confidence intervals for all three DRVA-derived variables were quite wide (aFID: -0.355 – 0.709; vFID: 0.276 – 0.843; aCON: -0.064 – 0.770) and considering relatively small sample size, the interocular ICC readings observed here should be interpreted with caution. Still, to enhance diagnostic precision and detection of cardiovascular risk factors derived from FID assessment, we recommend assessing both eyes in clinical practice. This will promote data reliability as significant interocular variability observed, especially for the aFID parameter, most commonly used biomarker in exercise intervention studies. Notably, this study represents an initial step toward future methodological research, and its findings should not be generalized to other populations.

Conflicts of interest: Authors declare no conflicts of interest.

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Data availability: The data collected and analyzed in this study are not publicly available due to privacy and ethical constraints. However, they can be obtained from the corresponding author upon a reasonable request.

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TABLES AND FIGURES WITH LEGENDS

Table 1. Biometric characteristics of study participants

	n=20 (55% ♀)	95% CI
Age, years	30 ± 5	28 - 32
Body height, cm	178 ± 9	174 - 182
Body mass, kg	75 ± 12	69 - 79
BMI, $kg \cdot m^{-2}$	23.4 ± 2.4	22.3 - 24.4
Resting MAP, mmHg	84 ± 8	80 - 87
Resting IOP, L eye, mmHg	13.9 ± 3.6	12.3 - 15.4
Resting IOP, R eye, mmHg	13.5 ± 3.8	11.8 - 15.1
VO_2 peak ($mL \cdot min^{-1} \cdot kg^{-1}$)	39.6 ± 6.3	36.8 - 42.4
Peak power output, W	245 ± 55	221 - 270
HR max., bpm	175 ± 8	171 - 178

Data are presented as mean ± SD. **Abbreviations**: BMI, body mass index; bpm, beats per minute; CI, confidence interval; HR max., maximum heart rate; IOP, intraocular pressure; L, left; MAP, mean arterial pressure; R, right; VO_2 peak, peak oxygen uptake.

Table 2. Reliability analysis of parameters from the dynamic retina vessel analyzer

	Right eye	Left eye	T-test	*p* value	*Cohens d*	ICC	95% CI	SEM	CV (%)
aFID	4.11 ± 1.82	3.92 ± 2.31	0.288	0.775	0.09	0.377	(-0.354 – 0.709)	1.66	46.4
vFID[#]	5.27 ± 2.13	5.00 ± 1.99	0.414	0.681	0.13	0.662	(0.276 – 0.843)	1.19	28.9
aCON	-2.62 ± 1.37	-2.38 ± 1.22	0.582	0.564	-0.18	0.504	(-0.064 – 0.770)	0.49	42.8

The symbol # indicates that data for the right eye is missing for *n*= 19; for all other variables, *n*=20. **Abbreviations**: aCON, arteriolar constriction; aFID, arteriolar flicker-induced dilation; CI, confidence interval; CV, coefficient of variation; ICC, intraclass correlation coefficient; SEM, standard error of measurement; vFID, venular flicker-induced dilation.

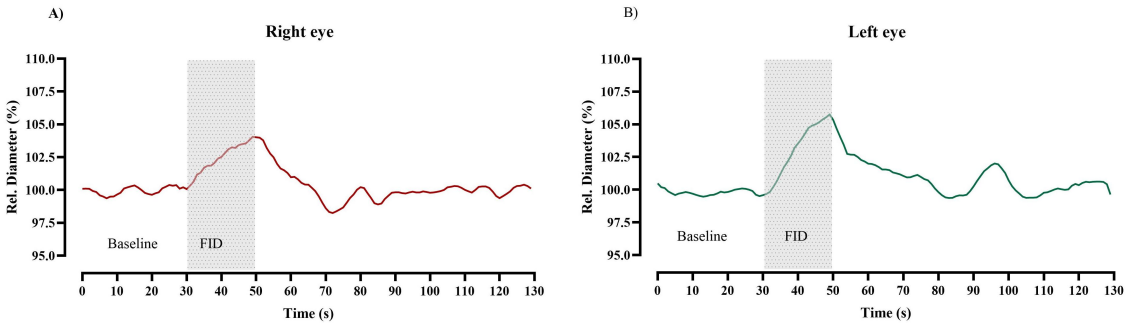

Figure 1. Representative retinal vessel diameter response during DRVA assessment. Representative time-course traces of relative retinal vessel diameter recorded during dynamic retinal vessel analyzer assessment in the right eye **(A)** and left eye **(B)** of a single participant. The shaded area indicates the flicker-light stimulation period used to provoke retinal vessel dilation, following the baseline recording phase. Data are expressed as relative vessel diameter change (%) and were averaged over 5-second intervals. **Abbreviations**: DRVA, dynamic retinal vessel analyzer; FID, flicker-induced dilation.

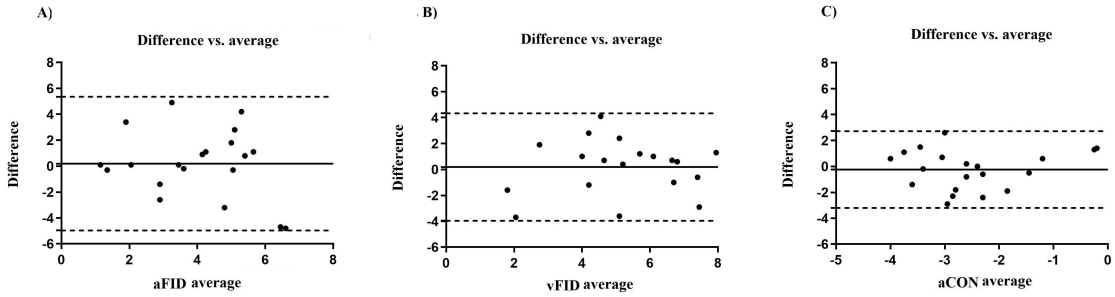

Figure 2. Bland–Altman analysis of interocular agreement for DRVA-derived biomarkers. Bland–Altman plots showing interocular agreement for arteriolar flicker-induced dilation **(A)**, venular flicker-induced dilation **(B)**, and arteriolar constriction **(C)**. The x-axis represents the mean value of both eyes for each parameter, while the y-axis represents the interocular difference between eyes. Each dot represents one participant-level comparison. The solid horizontal line indicates the mean interocular difference, reflecting systematic bias, whereas the dashed lines indicate the upper and lower 95% limits of agreement. **Abbreviations**: aCON, arteriolar constriction; aFID, arteriolar flicker-induced dilation; DRVA, dynamic retinal vessel analyzer; vFID, venular flicker-induced dilation.

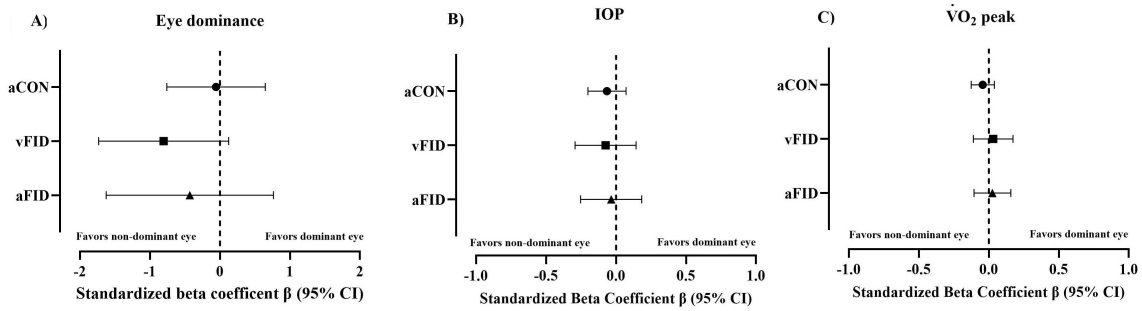

Figure 3. Linear mixed-effects model analysis of biological and systemic moderators of DRVA-derived biomarkers. Forest plots showing the standardized beta coefficients and 95% confidence intervals for the association of eye dominance **(A)**, intraocular pressure **(B)**, and peak oxygen uptake **(C)** with arteriolar flicker-induced dilation, venular flicker-induced dilation, and arteriolar constriction. The vertical dashed line represents the null effect. Estimates crossing the null line indicate no significant moderating effect of the examined variable on DRVA-derived retinal vascular responses. **Abbreviations**: aCON, arteriolar constriction; aFID, arteriolar flicker-induced dilation; CI, confidence interval; DRVA, dynamic retinal vessel analyzer; IOP, intraocular pressure; vFID, venular flicker-induced dilation; $\dot{V}O_2$ peak, peak oxygen uptake.