Reply to McCarthy et al.

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Response to Letter to the Editor

We thank McCarthy and colleagues (1) for their interest in our recent publication on the effects of exogenous ketone supplementation (EKS) during hypoxic exercise (2), (2) and agree that further scrutinizing the observed inter-individual responses could yield additional insights. Ketone bodies are weak acidic molecules that induce blood acidosis, subsequently stimulating ventilation ($\dot{V}_E$). This may in turn increase blood and tissue oxygenation in hypoxic conditions, but also accentuates CO_2 exhalation and bicarbonate (HCO_3^-) depletion (3). This drop in [HCO_3^-] is believed to primarily underlie the ergolytic effects that are frequently observed with EKS during high-intensity exercise (4). Remarkably, we did not observe such ergolytic effect during a 15-min time trial performed after 3h at a simulated altitude of 3,000 m (5), leading to the hypothesis that an increased blood and/or muscle oxygenation with EKS counteract performance declines (1). As such, individuals experiencing a greater increase in oxygenation upon EKS may be less prone to performance declines.

In line with the suggestions of McCarthy (1), we thus performed additional correlation analyses on our data. Each parameter is presented as the difference between the value obtained during the EKS versus control session for n = 13. All data was checked for normality (Shapiro-Wilk test, $p > 0.05$), with a probability level of $p < 0.05$ for significant Pearson's (normally distributed) or Spearman's (skewed) coefficients (r) between two parameters.

First, we investigated whether physiological variability upon reaching peak power output (PPO) was associated with changes in PPO. As shown in Figure 1, significant correlations were observed between ΔPPO and $\Delta\dot{V}_E$, r = 0.629, p = 0.021), Δ[HCO_3^-] (r = -0.724, p = 0.005), and the partial O_2 pressure corresponding to a blood saturation (SpO_2) of 50% (Δp50, r = 0.645, p = 0.017). However, these correlations are most likely caused by differences in exercise duration (*e.g.,* higher PPO and thus longer exercise duration results in higher $\dot{V}_E$) rather than reflecting distinct physiological responses to EKS.

A more correct interpretation emerges when linking individuals' PPO to the differences in physiological parameters obtained at the end of the 10-minute warm-up at 1.5 $W.kg^{-1}$ (Figure 2). This revealed non-significant, moderate correlations between ΔPPO and ΔSpO_2 (r = -0.481, p = 0.096), ΔpH (r = -0.505, p = 0.079), and [HCO_3^-] (r = -0.457, p = 0.116). These negative correlations are counterintuitive, as elevated SpO_2, pH, and [HCO_3^-] are all expected to exert an ergogenic, rather than ergolytic, effect. This raises the question of why individuals who perform better with EKS paradoxically present with lower SpO_2, lower pH, and lower [HCO_3^-] following the standardized warm-up. A first plausible mechanism is that an acidosis-induced right-shift of the oxyhemoglobin dissociation curve facilitates oxygen delivery to the working muscle. Nonetheless, p50 and muscle tissue oxygenation index (mTOI) were not correlated with PPO, rendering this explanation unlikely. Alternatively, an earlier study reported that an accentuated reduction in pH with EKS was accompanied by a substantially lower β-hydroxybutyrate (βHB) oxidation (6). Thus, a greater fall in pH may favor glucose over ketone utilization, thereby enhancing high-intensity exercise performance, particularly under hypoxic conditions marked by higher reliance on glycolytic energy production (7) combined with the higher oxygen-efficiency of glucose (8). Although the contribution of βHB oxidation to energy expenditure during exercise is limited (<5%) in normoxic conditions (6), early evidence in rat brain slices found increased βHB oxidation in hypoxia (9), suggesting that this response may gain relevance under hypoxic conditions. Moreover, the effects of EKS highly depend on exercise intensity. As such, any actual correlations may have gone unnoticed by the unfortunate timing of our data sampling, given that the data collected during the warm-up phase may not reflect high-intensity physiological

responses, while the data collected during peak effort are confounded by differences in exercise duration. Finally, we acknowledge the possibility that more indirect and complicated mechanisms may be in play, including effects on central fatigue and/or mitochondrial efficiency.

In summary, while EKS clearly induces physiological effects both at rest and during exercise, the lack of clear correlations implies that the inter-individual variability in exercise responses results predominantly from methodological noise rather than distinct physiological responses. Nonetheless, the presence of moderate correlations, albeit not statistically significant, warrants further investigation on larger sample sizes. All relevant data were made available, and we encourage the interested reader to explore any hypotheses arising from this work.

Additional information

Data availability: All anonymized data are available on Figshare (doi: 10.6084/m9.figshare.30146047).

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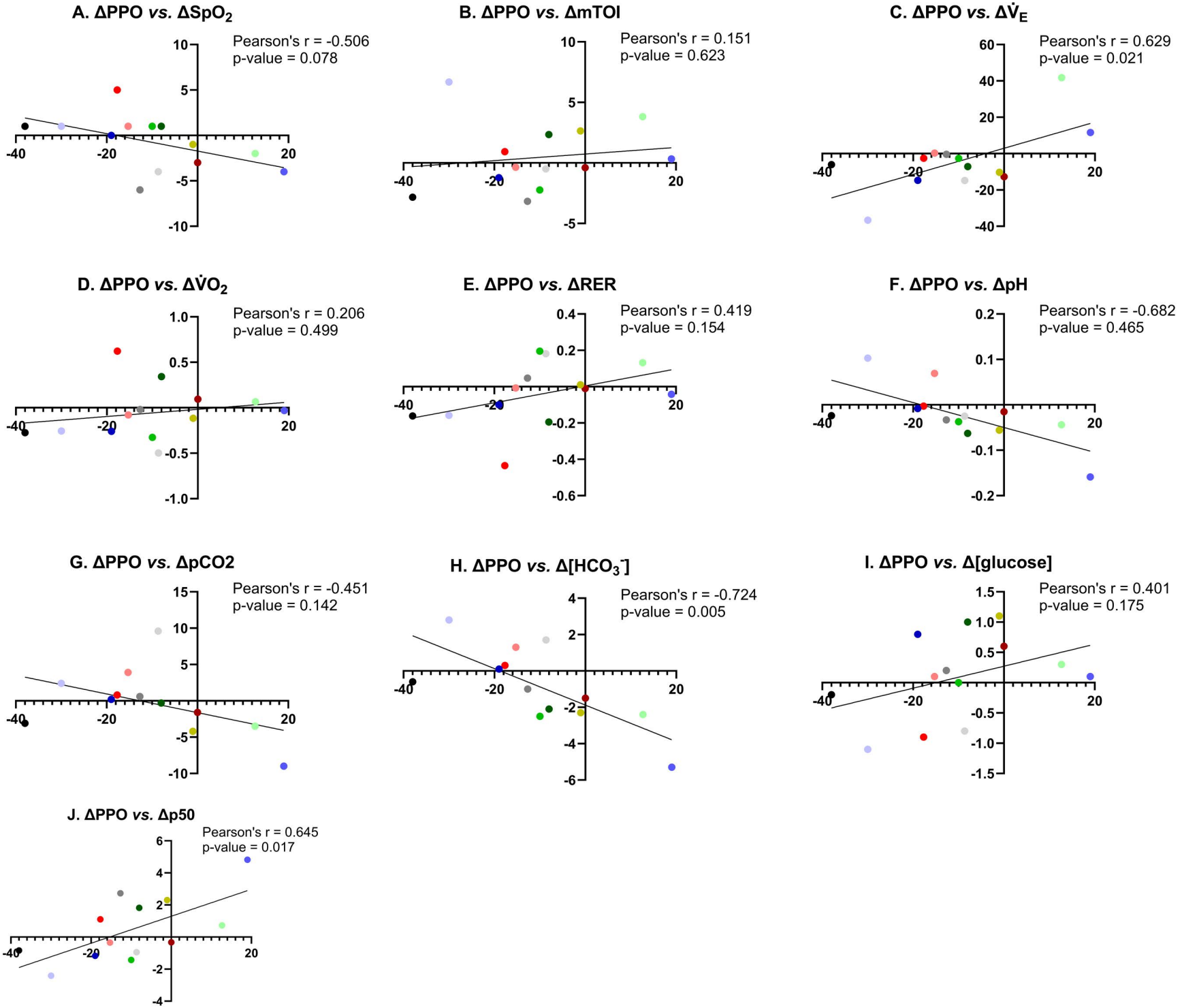
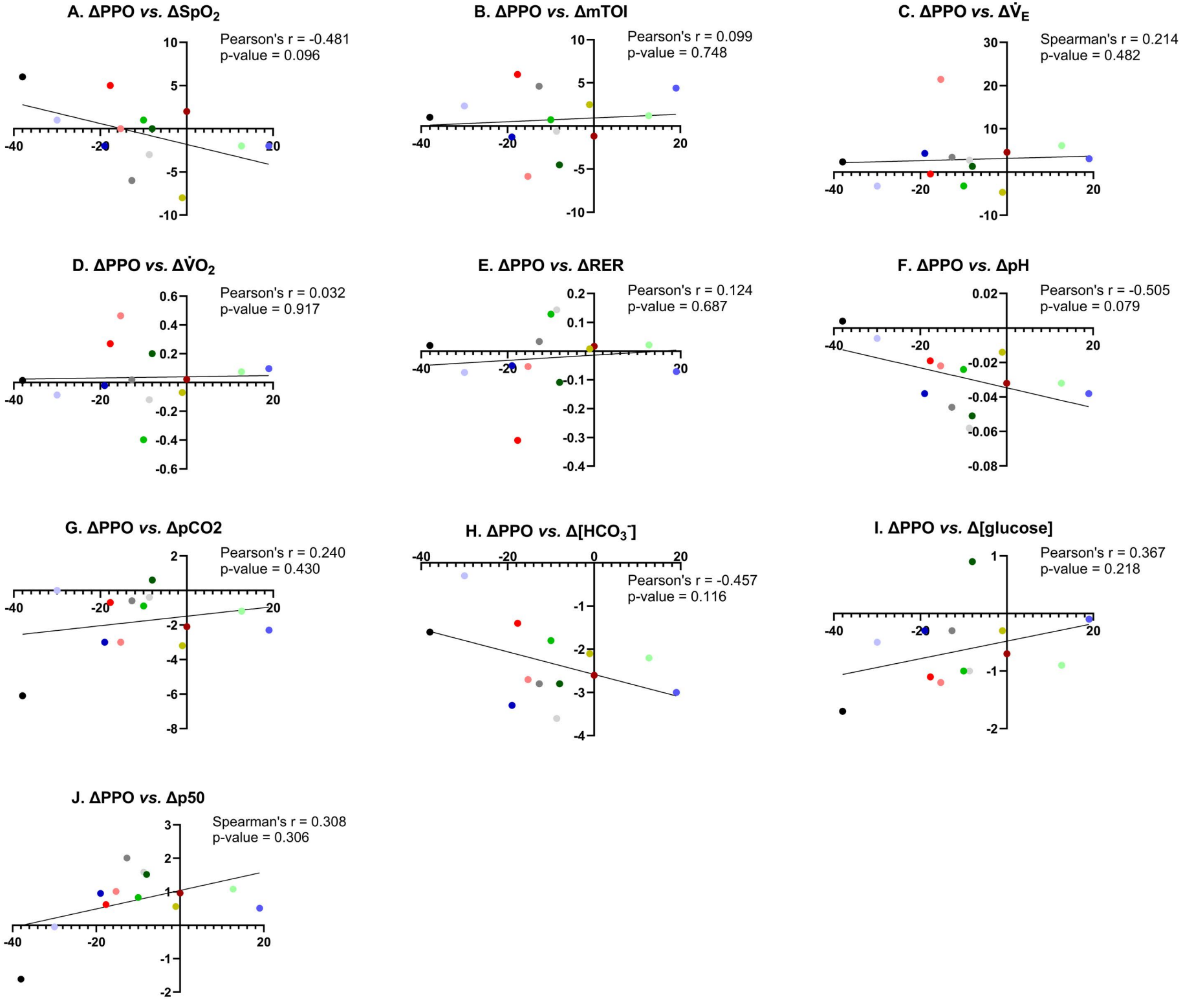
Figure 1: Correlation between peak power output (PPO) and physiological data collected when individuals reached their PPO. Correlations are shown between the difference in PPO (x-axis) and the difference in (y-axis) A) blood oxygen saturation (SpO_2), B) muscle tissue oxygenation index (mTOI), C) minute ventilation ($\dot{V}_E$), D) oxygen consumption rate ($\dot{V}O_2$), E) respiratory exchange ratio (RER), F) capillary blood hydrogen potential (pH), G) partial pressure of carbon dioxide (pCO_2), H) bicarbonate concentrations ($[HCO_3^-]$), I) glucose concentrations, and J) the partial pressure of oxygen (pO_2) corresponding to an SpO_2 of 50% (p50), all collected when participants reached their PPO. During a normobaric hypoxic protocol at a simulated altitude of 4,000 m, involving intermittent ketone ester (KE) or placebo (CON) ingestion, participants completed a graded maximal exercise test after 1.5 h. Data are presented as the difference between both sessions (ΔKE-CON), with positive Δvalues reflecting higher values in the KE *vs*. CON session. Each individual is assigned the same color in all panels. For methodological details, please see (2).

Figure 2: Correlation between peak power output (PPO) and physiological data collected at the end of the standardized warm-up phase. Correlations are shown between the difference in PPO (x-axis) and the difference in (y-axis) A) blood oxygen saturation (SpO_2), B) muscle tissue oxygenation index (mTOI), C) minute ventilation ($\dot{V}_E$), D) oxygen consumption rate ($\dot{V}O_2$), E) respiratory exchange ratio (RER), F) capillary blood hydrogen potential (pH), G) partial pressure of carbon dioxide (pCO_2), H) bicarbonate concentrations ($[HCO_3^-]$), and I) glucose concentrations, and J) the partial pressure of oxygen (pO_2) corresponding to an SpO_2 of 50% (p50), all collected at the end of the standardized warm-up phase. During a normobaric hypoxic protocol at a simulated altitude of 4,000 m, involving intermittent ketone ester (KE) or placebo (CON) ingestion, participants completed a graded maximal exercise test after 1.5 h. Data are presented as the difference between both sessions (ΔKE-CON), with positive Δvalues reflecting higher values in the KE *vs*. CON session. Each individual is assigned the same color in all panels. For methodological details, please see (2).


A. ΔPPO vs. ΔSpO2
Pearson's r = -0.506
p-value = 0.078
B. ΔPPO vs. ΔmTOI
Pearson's r = 0.151
p-value = 0.623
C. ΔPPO vs. ΔV̇E
Pearson's r = 0.629
p-value = 0.021
D. ΔPPO vs. ΔV̇O2
Pearson's r = 0.206
p-value = 0.499
E. ΔPPO vs. ΔRER
Pearson's r = 0.419
p-value = 0.154
F. ΔPPO vs. ΔpH
Pearson's r = -0.682
p-value = 0.465
G. ΔPPO vs. ΔpCO2
Pearson's r = -0.451
p-value = 0.142
H. ΔPPO vs. Δ[HCO3-]
Pearson's r = -0.724
p-value = 0.005
I. ΔPPO vs. Δ[glucose]
Pearson's r = 0.401
p-value = 0.175
J. ΔPPO vs. Δp50
Pearson's r = 0.645
p-value = 0.017


A. ΔPPO vs. ΔSpO2
Pearson's r = -0.481
p-value = 0.096
B. ΔPPO vs. ΔmTOI
Pearson's r = 0.099
p-value = 0.748
C. ΔPPO vs. ΔV̇E
Spearman's r = 0.214
p-value = 0.482
D. ΔPPO vs. ΔV̇O2
Pearson's r = 0.032
p-value = 0.917
E. ΔPPO vs. ΔRER
Pearson's r = 0.124
p-value = 0.687
F. ΔPPO vs. ΔpH
Pearson's r = -0.505
p-value = 0.079
G. ΔPPO vs. ΔpCO2
Pearson's r = 0.240
p-value = 0.430
H. ΔPPO vs. Δ[HCO3-]
Pearson's r = -0.457
p-value = 0.116
I. ΔPPO vs. Δ[glucose]
Pearson's r = 0.367
p-value = 0.218
J. ΔPPO vs. Δp50
Spearman's r = 0.308
p-value = 0.306