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GM and SD conducted data collection. EG provided technical expertise and assistance. JB, HJP, and SRH performed data analysis. SRH and HJP wrote and edited the manuscript. AJAM conceptualized the study and edited the manuscript.

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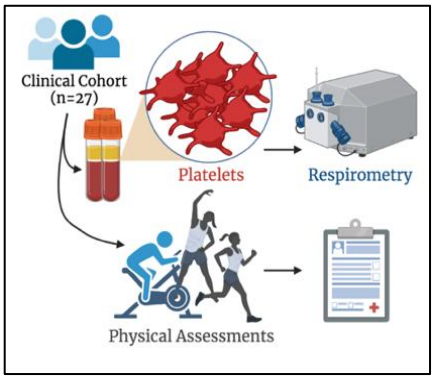
Platelet bioenergetics are associated with resting metabolic rate and exercise capacity in older adult women

Stephanie R Heimler[1*], Howard J Phang[1*], Jaclyn Bergstrom[1], Gargi Mahapatra[2], Stephen Dozier[1], Erich Gnaiger[3], Anthony J A Molina[1**]

[1] Division of Geriatrics, Gerontology, and Palliative Care; Department of Medicine, University of California San Diego School of Medicine, La Jolla, CA, USA.
[2] Section on Gerontology and Geriatrics, Sticht Center for Healthy Aging and Alzheimer's Prevention, Department of Internal Medicine, Wake Forest Baptist Medical Center, Winston-Salem, NC, USA.
[3] Oroboros Instruments, Innsbruck, Austria.

* Co-first authors
** Corresponding author: ajmolina@health.ucsd.edu

Summary



This study investigates relationships between platelet mitochondrial bioenergetics and resting metabolic rate (RMR), body composition, and exercise fitness in older adult women. We report positive correlations between peak respiratory exchange ratio (RER) and RMR with five measures of platelet respiration, supporting the premise that blood cells can be utilized to report on mitochondrial function associated with physical health and fitness. Identifying mechanisms associated with physical performance among older adults supports the development of reliable biomarkers of healthy aging and can advance the development of efficacious interventions.

Keywords – platelets; resting metabolic rate (RMR); cardiopulmonary exercise testing (CPET); OXPHOS capacity *P*; electron transfer capacity *E*; inverted regression analysis

1. Introduction

1.1. Age-related bioenergetic decline and physical function

Mitochondrial dysfunction is a biological hallmark of aging implicated in multiple age-related diseases and disorders, including physical function decline and sarcopenia (López-Otín et al 2013; Lenaz et al 2000; Gonzalez-Freire et al 2018). Age-related skeletal muscle bioenergetic decline is marked by decreased mitochondrial density, ATP production, electron transfer system (ETS) capacity, and tricarboxylic acid cycle enzyme activity (Short et al 2005; Marzetti et al 2013). This decline in skeletal muscle bioenergetics is associated with decreased cardiopulmonary fitness, exercise fitness, and functional capacity (Coen et al 2013, Choi et al 2016; Tyrrell et al 2015).

1.2. Resting metabolic rate

Although physical activity comprises 15-30 % of daily energy expenditure, the major contributor to total energy expenditure is resting metabolic rate (RMR), which accounts for roughly 60 % of the body's total energy demands and is determined by the body's most metabolically active tissues (Ravussin, Bogardus 1989, Wang 2010). Although RMR has been extensively examined in relation with age, sex, body composition, and physical activity, few studies have examined the relationship between mitochondrial function and RMR (Larsen et al 2011; McMurray et al 2014). However, RMR was recently found to be associated with in vivo skeletal muscle oxidative capacity, suggesting a strong link between mitochondrial function and RMR (Edwards et al 2013; Zampino et al 2020).

1.3. Blood-based bioenergetics and study goals

The study presented here examines the relationship of platelet bioenergetics with resting metabolic rate and exercise capacity in community-dwelling, older adult women. Respirometric profiling of blood cells has emerged as a robust and innovative approach for assessing mitochondrial function in a minimally invasive manner (Molina 2017). There is mounting evidence that blood-based bioenergetic profiling can be utilized to report on systemic bioenergetic capacity and is related to mitochondrial function measured in other tissues (Nguyen et al 2019; Mahapatra et al 2018; Sjövall et al 2014). Our group has shown that blood cell respirometry correlates with skeletal and cardiac muscle respirometry (Tyrrell et al 2016). In particular, platelet mitochondrial function has been reported to be correlated with skeletal muscle mitochondrial function and exhibit bioenergetic changes associated with age in humans (Braganza et al 2019). Additional work has shown that alterations in platelet bioenergetics is related to sickle cell and Alzheimer's disease (Cardenes 2014; Wilkins 2017) making platelet respirometry a valuable biomarker for mitochondrial dysfunction. Together, these data suggest that systemic bioenergetic measurements can be utilized to elucidate mitochondrial mechanisms underlying physical performance and disease. The goal of this study is to uncover whether platelet respirometry correlates with RMR, body composition, and

measures of exercise fitness in older adult women. While women have a longer life expectancy than men, they exhibit higher rates of frailty later in life. Moreover, men continue to exhibit higher physical performance, even later in life (Hägg and Jylhävä 2021).

2. Materials and methods

2.1. Participants

Twenty-seven healthy older adult women (mean age = 70.2 years) were included in this study. Screening tests, including electrocardiogram, exercise echocardiogram, and spirometry, indicated that all participants were free from chronic medical illness, current health complaints, abnormal physical examination, and heart disease. Participants who regularly undertook vigorous exercise were excluded from this study. The protocol for this study was approved by the Wake Forest School of Medicine institutional review board, and all participants provided written, informed consent.

2.2. Clinical measures

RMR was measured using indirect calorimetry (MGC Diagnostics) for each participant after an overnight fast as previously described (Nicklas et al 2019).

Exercise fitness was measured by cardiopulmonary exercise testing (CPET), an integrative assessment of exercise responses involving the pulmonary, cardiovascular, hematopoietic, neuropsychological, and skeletal muscle systems (Balady et al 2010, Albouaini et al 2007). Ventilatory and gas exchange responses were measured on a breath-by-breath basis (MGC Diagnostics, St. Paul, MN) using a treadmill ramp protocol to exhaustion as previously described (Nicklas et al 2019). We measured peak V_{O2}, peak V_{CO2}, and peak respiratory exchange ratio (RER), which is the ratio of carbon dioxide output to oxygen uptake (V_{CO2}/V_{O2}).

Several body composition measurements, including BMI, lean mass, and fat mass were recorded. Lean mass and fat mass values were recorded using total body dual-energy x-ray absorptiometry (DXA) on the Prodigy Scanner (General Electric, Madison, WI) as previously described (Nicklas et al 2019).

2.3. Platelet isolation

Acid citrate dextrose (ACD) tubes (Vacutainer; Becton Dickinson, Franklin Lakes, NJ) were used to collect venous blood from overnight-fasted participants. Samples were processed immediately to isolate platelets using previously described methods (Chacko 2014). Briefly, whole blood was centrifuged (500 *g*, 15 min, room temperature). Platelet-rich plasma was removed and centrifuged (1500 *g*, 10 min) to isolate platelets, washed in PBS with 1μM prostaglandin E1 (PGE1; Cayman Chemical, Ann Arbor, MI), centrifuged (1500 *g*, 7 min), and resuspended in MiR05 (Oroboros Instruments, Innsbruck, Austria) before high resolution respirometry. Cells were counted using the Coulter AC.Tdiff2 machine (Beckman Coulter, USA).

2.4. High-resolution respirometry

Platelet mitochondrial function was assessed by high-resolution respirometry using the Oxygraph-2k (Oroboros Instruments, Innsbruck, Austria) at 37 °C in MiR05, which provided a detailed analysis of respiratory pathway control and coupling control (Gnaiger 2020). The platelet concentration was $2 \cdot 10^8$ cells per 2 mL chamber. Our protocol is depicted in Figure 1 and was comprised of the following injections (abbreviation; final concentration): catalase (Ctl; 280 U/mL), ADP (D; 1 mM), magnesium (Mg; 0.6 mM), digitonin (Dig; 40 µg/mL), octanoylcarnitine (Oct; 0.5 mM), malate (M; 0.1 mM and 2 mM), cytochrome *c* (c; 0.01 mM), pyruvate (P; 5 mM), glutamate (G; 10 mM), succinate (S; 10 mM), and glycerophosphate (Gp; 10 mM). After, we titrated the uncoupler FCCP in 1 µM steps until maximal respiration is reached (2-5 µM). Finally, we added rotenone (Rot; 1 µM) and antimycin-A (Ama; 2.5 µM) to stop mitochondrial respiration (residual oxygen consumption, ROX). Although catalase was added to MiR05 as a precaution, reoxygenation was not needed in this protocol. It is also important to note that we used octanoylcarnitine to induce fatty acid oxidation (F_P; described below) because of its ability to bypass the rate-limiting step CPT1-mediated transfer, though other fuels such as palmitoylcarnitine or octanoate may also be used.

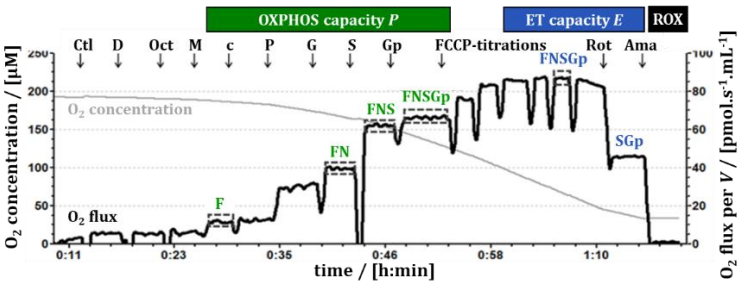


Figure 1. Representative trace of high-resolution respirometry of platelets.

2.5. Statistical analysis

We determined Pearson correlation coefficients *r* and partial correlations between respirometry measures and CPET, body composition, and calorimetry measures, including adjustments for age, BMI, and fat %. Regression lines were calculated according to inverted regression analysis (Gnaiger 2021).

3. Results

3.1. Participant characteristics and platelet respiration

This study included 27 healthy older adult women (mean age 70.2 ± 1.1 years). Platelet OXPHOS capacities *P* [amol·s^{-1}·x^{-1}] were measured for fatty acid oxidation (F_P; 0.194 ± 0.017), F- & NADH(CI)-linked *P* (FN_P; 0.248 ± 0.020), FN- & succinate-linked *P* (FNS_P; 0.376 ± 0.030), FNS- & glycerophosphate-linked *P* ($FNSGp_P$; 0.450 ± 0.036) and the corresponding ET-capacity *E* ($FNSGp_E$; 0.766 ± 0.066; Table 1). These respiratory states have previously been

Table 1. Participant characteristics (*N*=27)

		Mean (SE)
Demographics		
age [years]		70.2 (1.1)
Platelet respirometry		
F_P	[amol·s^{-1}·x^{-1}]	0.194 (0.017)
FN_P	[amol·s^{-1}·x^{-1}]	0.248 (0.020)
FNS_P	[amol·s^{-1}·x^{-1}]	0.376 (0.030)
$FNSGp_P$	[amol·s^{-1}·x^{-1}]	0.450 (0.036)
$FNSGp_E$	[amol·s^{-1}·x^{-1}]	0.766 (0.066)
Indirect calorimetry		
RMR (kcal/day)		1289.4 (31.8)
Cardiopulmonary exercise tests		
peak V_{O2}	[mL·kg^{-1}·min^{-1}]	24.9 (1.0)
peak V_{CO2}	[mL·kg^{-1}·min^{-1}]	27.4 (1.3)
peak RER		1.10 (0.02)
Body composition		
BMI		26.6 (0.7)
body total fat mass	[kg]	29.2 (1.4)
body total lean mass	[kg]	39.8 (9.4)
body total fat percent	[%]	40.6 (1.1)
trunk-only fat percent	[%]	38.5 (1.3)

described as FAO, FAO+Complex I, FAO+Complex I+Complex II, Maximal Uncoupled Respiration, and Max ETS (Mahapatra 2018), respectively. Residual oxygen consumption was not subtracted from these values. We compared these measures of platelet respirometry to RMR, body composition measures (BMI, fat mass, and lean mass), and CPET measures (peak V_{O_2}, peak V_{CO_2}, and peak RER).

Table 2. Correlations of platelet respirometry with RMR, fitness, and body comp.

	Platelet respiration				
	F_P	FN_P	FNS_P	$FNSGp_P$	$FNSGp_E$
Calorimetry					
resting metabolic rate (RMR)	**.409***	**.537****	**.455***	**.436***	**.472***
Cardiopulmonary exercise tests					
peak V_{O_2}	.076	.146	.208	.243	.249
peak V_{CO_2}	.205	.268	.325	.351	.368
peak RER	**.445***	**.475***	**.483***	**.480***	**.517****
Body composition					
BMI	-.147	-.069	-.170	-.223	-.175
body total fat mass	-.057	-.005	-.113	-.167	-.110
body total lean mass	.097	.272	.130	.078	.178
body total fat percent	-.171	-.200	-.278	-.310	-.298
trunk-only fat percent	-.155	-.185	-.242	-.274	-.239

Pearson coefficients of correlation *r* values. *$p \leq 0.05$; **$p \leq 0.01$.

Table 3. Adjusted correlations of platelet respirometry with RMR and peak RER

	Platelet respiration				
	F_P	FN_P	FNS_P	$FNSGp_P$	$FNSGp_E$
RMR					
unadjusted	.409*	.537**	.455*	.436*	.472*
adjusted age	.426*	.541**	.452*	.429*	.456*
adjusted BMI	.513**	.599**	.554**	.554**	.546**
adjusted body total fat percent	.431*	.556**	.482*	.464*	.488*
Peak RER					
unadjusted	.445*	.475*	.483*	.480*	.517**
adjusted age	.473*	.478*	.470*	.460*	.481*
adjusted BMI	.443*	.470*	.478*	.475*	.509**
adjusted body total fat percent	.432*	.455*	.463*	.459*	.496*

Pearson coefficients of correlation *r* values. *$p \leq 0.05$; **$p \leq 0.01$

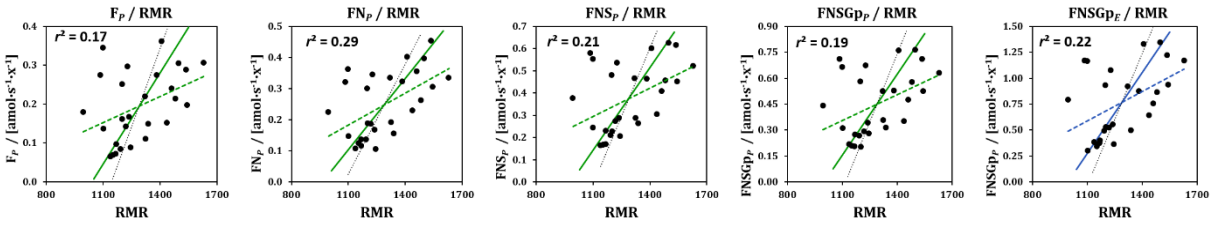


Figure 2. Correlations of platelet bioenergetics and RMR. *Y*/*X* regression lines (dashed; lowest slope using ordinary least squares), ordinate projection of *X*/*Y* abscissal regression lines (dotted), and mean regression lines (full). Coefficients of determination r^2 are independent of axis inversion. See Gnaiger (2021).

3.2. Relationships between platelet bioenergetics and resting metabolic rate

We identified positive correlations between RMR and five measures of platelet respiration (Table 2; Figure 2). Controlling for age, BMI, and percent body fat, indicate that these covariates had little influence on the relationship between RMR and platelet respiration (Table 3).

3.3. Relationships between platelet bioenergetics and measures of exercise fitness

We also identified positive correlations between peak RER and five measures of platelet respiration (Table 2; Figure 3) using Pearson correlation analyses. Peak V_{O2} and peak V_{CO2} were not correlated with measures of platelet respiration. Controlling for age, BMI, and percent body fat, indicate that these covariates had little influence on the relationship between peak RER and platelet respiration (Table 3).

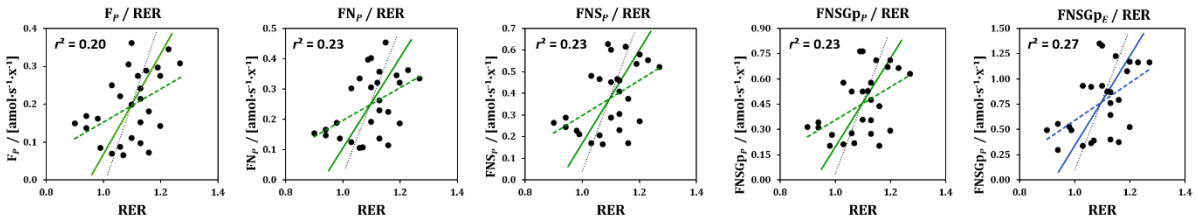


Figure 3. Correlations of platelet bioenergetics and peak RER. Regression lines are calculated as in Figure 2.

3.4. Relationships between platelet bioenergetics and measures of body composition

Relationships between fat % and FNS_P (r=-0.278), maximum OXPHOS capacity ($FNSGp_P$; r=-0.31), and maximum ET capacity ($FNSGp_E$; r=-0.298) are reported in Table 2. Similar relationships were found between trunk fat % and FNS_P (r=-0.242), $FNSGp_P$ (r=-0.274) and $FNSGp_E$ (r=-0.239). While these correlations are trending, all have p-values greater than 0.05.

4. Discussion

This study examines platelet mitochondrial function in healthy older adult women. We found that peak RER and RMR are both positively correlated to all measures of platelet bioenergetic function examined, independent of body composition. We focused on platelets in this study as previous studies have indicated that platelet bioenergetic capacity is correlated to the bioenergetic capacity of peripheral tissues and is associated with physical function. In particular, prior work has indicated that maximal and ATP-linked respirometry, specifically in older adults, is correlated with muscle maximal respiration that differs based on age (Braganza et al 2019). Studies suggest that investigating platelet bioenergetic capacity may serve as a supplement and/or surrogate for measurements derived from muscle biopsies. This also provides evidence that platelets from an older adult population are a good indicator of muscle bioenergetics and could also be indicative of differences in measurements of physical function and health.

Age-related mitochondrial decline and its relationship to physical function has predominantly been studied in skeletal muscle due to the strong association between

sarcopenia and physical function decline. Here, we build on prior literature by focusing on blood-based bioenergetics and the ability of blood cells to report on physical health. Our data are in line with reports that skeletal muscle bioenergetics are associated with RMR (Choi et al 2016; Tyrrell et al 2015). We also found a strong relationship between platelet bioenergetics and peak RER, which has not been previously reported (Knuiman et al 2021). Together, these new findings contribute to our understanding of how blood-based bioenergetic profiling relates to physical fitness and exercise physiology.

RER is the ratio of carbon dioxide output to oxygen uptake (V_{CO2}/V_{O2}). At higher exercise intensity, increased lactate buildup associated with anaerobic metabolism contributes to a disproportionate increase in V_{CO2} that brings RER to values >1 (Balady et al 2010; Milani 2006). Thus, peak RER can be used as a reliable, quantitative measure of maximal exercise effort. Our findings indicate that platelet maximum ET capacity ($FNSGp_E$) most strongly correlates to maximal exercise effort. Additional measures of platelet respirometry, such as fatty acid oxidation as well as individual complex function, also correlate positively to maximal exercise effort.

Interestingly, we did not observe an association between platelet bioenergetics and peak V_{O2}, which has been previously found to be related to skeletal muscle bioenergetics (Knuiman et al 2021; Coen et al 2013; Distefano et al 2017; Gonzalez-Freire 2018). While this finding has been previously reported in skeletal muscle, but not blood, it should be noted that the women enrolled in this study were all healthy older adults with similarly high levels of fitness. The small range and sample size suggest that we may not have been adequately powered to observe this relationship. Future studies should be designed to determine if platelet bioenergetics are associated with RMR and exercise capacity in both men and women, over a larger age range to assess differences across lifespan. Further, other circulating cell types (monocytes, lymphocytes, etc.) were not evaluated in this study, but similar relationships may exist.

Overall, these findings suggest that energy expenditure (both during rest and physical activity) are related to systemic mitochondrial function. These data can be used as a foundation to study how potential interventions, such as diet and exercise, may lead to improvements in both mitochondrial function as well as resting metabolic rate and other measures of physical fitness. Blood-based bioenergetic profiling, a minimally-invasive technique, can be used to track improvements and changes in exercise fitness in clinical studies.

5. Conclusions

In this study, we report positive correlations across five measures of platelet respirometry with both peak RER and RMR, thus contributing to a growing body of evidence indicating that our minimally-invasive evaluation of mitochondrial function relates to physical health. Blood-based bioenergetic profiling may serve as a reliable biomarker of mitochondrial health among older adults and may be utilized to test efficacy and identify targets of interventions designed to promote the health and well-being of older adults.

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