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Short Communication

Longitudinal PBMC respirometry reveals preserved electron-transfer capacity but constrained bioenergetic flexibility in Parkinson's disease



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Introduction

In Parkinson's disease (PD), peripheral respiratory changes may reflect reduced electron-transfer (ET) capacity, altered respiratory control, or both [1,2]. Protein-normalized oxygen flux quantifies respiratory activity, whereas internally normalized flux control indices describe its relative allocation across coupling states [3]. We assessed these features longitudinally in peripheral blood mononuclear cells (PBMCs).

Methods

This two-year cohort included 114 participants: PD1 (N = 29), PD2 (N = 28), HC1 (N = 28), and HC2 (N = 29); HC1/HC2 were age- and sex-matched healthy controls corresponding to PD1/PD2. PD groups were assigned at baseline using Hoehn–Yahr staging and motor severity (UPDRS III for H–Y = 2.0), and assignments were retained at follow-up. All PD participants were chronically treated; according to the neurologist, sampling took place in a clinically assessed OFF state, with the morning dose omitted. The exact interval since the previous dose was not recorded. Samples were collected at baseline (Year 0), Year 1, and Year 2. Fresh PBMC respiration was measured in MiR05 using an Oroboros O2k [4]. Routine (R), oligomycin-induced leak (L), and CCCP-stimulated electron-transfer capacity (E) were determined, corrected for antimycin A-insensitive residual oxygen consumption (rox), and normalized to protein.

Methods (indices and analysis)

The *R*-ATP coupling ratio j_{RLE} = (*R*−*L*)/*E* quantifies ATP-linked routine respiration relative to *E*; the *E*−*R* excess ratio j_{E-R} = (*E*−*R*)/*E* quantifies the fraction of ET capacity above routine respiration; the *R*-ATP control efficiency j_{R-L} = (*R*−*L*)/*R* and coupling efficiency j_{E-L} = (*E*−*L*)/*E* describe complementary coupling-control properties. Age- and sex-adjusted mixed-effects models evaluated Group × Year with participant random intercepts and Tukey-adjusted contrasts. Exploratory baseline clustering/PCA used j_{RLE}, j_{R-L}, and j_{E-R} in 113 complete cases; PERMANOVA used 999 permutations [5].

Results and discussion

Protein-normalized *R*, *L*, and *E* showed no consistent between-group differences over three assessments. j_{RLE} was higher in PD1 versus HC1 at Years 0, 1, and 2 (adjusted p = 0.008, 0.006, 0.010) and in PD2 versus HC2 at Years 0 and 1 (p = 0.006, <0.001), but not Year 2 (p = 0.060). j_{E-R} was lower in PD1 versus HC1 at Years 0, 1, and 2 (p = 0.015, 0.013, 0.020) and in PD2 versus HC2 at Years 1 and 2 (p = 0.001, 0.015). j_{R-L} differed for PD1 versus HC1 at Year 0 (p = 0.033) and PD2 versus HC2 at Years 0 and 1 (p < 0.001, 0.033); j_{E-L} differed only for PD2 versus HC2 at Year 0 (p = 0.011).

Exploratory profiles and interpretation: Baseline combined-cohort clustering summarized three descriptive profiles (C1, *N* = 28; C2, *N* = 43; C3, *N* = 42). C1 had relatively higher j_{E-R}/lower j_{RLE} and included predominantly controls (23 HC, 5 PD); C2 (17 HC, 26 PD) and C3 (16 HC, 26 PD) contained more PD participants. PCA/PERMANOVA showed differing group distributions with overlap (p = 0.001). As these indices depend algebraically on *R*/*E* and *L*/*E*, clustering is descriptive rather than evidence of independent biological subtypes. Overall, PD was associated with greater routine engagement of measured ET capacity and a smaller *E*−*R* excess fraction without consistent loss of protein-normalized *E*. This peripheral respiratory phenotype does not demonstrate altered substantia nigra function, mitochondrial oxidative stress, or actual OXPHOS reserve.

Conflicts of interest: EG is Chief Executive Officer of Oroboros Instruments and provided methodological advice and manuscript review. The company had no role in funding, data collection, data ownership, or submission. The other authors declare no competing interests. EG holds the position of Editor-in-Chief for BEC and is blinded from reviewing or making decisions for the manuscript.

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