

Supplementary Material

Chronotropic Incompetence During Exercise Testing as a Marker of Autonomic Dysfunction in Individuals with Early Parkinson's Disease

SUPPLEMENTARY RESULTS

Alternative Definitions of Chronotropic Incompetence

Failure to achieve 80% APMHR

Six patients (5.8% of the sample not on chronotropic medication) failed to achieve 80% of APMHR during CPET (PD_{chron_{80%}}). There was a difference in self-reported lightheadedness based on the MDS-UPDRS Part 1.12 score ($F[2,125] = 10.689, p < 0.001$), with PD_{chron_{80%}} having increased lightheadedness compared to those with normal maximal HR responses (PD_{non-chron_{80%}}, 1.2 ± 1.2 and 0.3 ± 0.5 , respectively, $p < 0.001_{\text{adj}}$). There was also a difference in the orthostatic systolic blood pressure response ($F[2, 122] = 5.128, p = 0.007$), with PD_{chron_{80%}} experiencing a greater drop in systolic blood pressure upon standing than PD_{non-chron_{80%}} (-21.3 ± 24.5 and -3.2 ± 12.5 mmHg, respectively, $p = 0.005_{\text{adj}}$) (Supplementary Table 2). Deviation from APMHR and systolic orthostatic response was positively correlated for PD_{non-chron_{80%}} ($r = 0.209, p = 0.043$), but not in PD_{chron_{80%}} ($r = 0.728, p = 0.101$). There was a reduction in $\text{VO}_{2\text{peak}}$ of 4.5 mL/kg/min in the PD_{chron_{80%}} group compared to the PD_{non-chron_{80%}} group. These results were not statistically significant, which is probably due to the reduced size of the PD_{chron_{80%}} group. CPET characteristics according to this definition of chronotropic incompetence are shown in Supplementary Table 3.

Wilkoff method

The chronotropic index was calculated (i.e., Wilkoff method applied) for patients who failed to achieve 85% of APMHR and reached an RER < 1.05 , and for whom submaximal exercise testing data were available. From our initial PD_{chron_{80%}} group ($n=13$), 4 participants had an RER ≥ 1.05 ; therefore, the Wilkoff method was not applied. Submaximal exercise data during CPET were unavailable for 1 of the 9 remaining participants. The chronotropic index was calculated for the remaining 8 patients with an RER < 1.05 , and for whom submaximal exercise testing data were available. Of these 8 patients, 6 had a chronotropic index ≤ 0.80 , which is the definition of

chronotropic incompetence. In total, we had 4 participants with an RER ≥ 1.05 , 6 participants with a chronotropic index ≤ 0.80 , and 1 participant that achieved 74.0% of APMHR, but on whom we were unable to apply the Wilkoff method. These make up the 11 patients (10.7% of the sample not on chronotropic medications) in the chronotropic incompetence according to the Wilkoff method (PDchronowilk), as outlined above. Two participants did not meet these more stringent criteria for chronotropic incompetence.

There was a difference in self-reported lightheadedness based on the MDS-UPDRS Part 1.12 score ($F[2,125] = 3.316, p = 0.040$), as PDnon-chronowilk showed increased lightheadedness compared to PDchronomed (0.3 ± 0.5 and 0.2 ± 0.4 , respectively, $p = 0.037_{\text{adj}}$). There was also a difference in the orthostatic systolic blood pressure response ($F[2, 122] = 4.201, p = 0.017$), with PDchronowilk experiencing a greater drop in systolic blood pressure upon standing than PDnon-chronowilk (-15.5 ± 20.6 and -2.9 ± 12.4 mmHg, respectively, $p = 0.014_{\text{adj}}$) (Supplementary Table 4).

There was a difference in resting HR among the 3 groups ($F[2,125] = 9.069, p < 0.001$). *Post hoc* testing showed that the mean resting HR in the PDnon-chronowilk group (74.8 ± 10.3 bpm) was higher than those in the PDchronowilk group (63.7 ± 11.2 bpm, $p = 0.004_{\text{adj}}$) and PDchronomed group (67.2 ± 11.3 bpm, $p = 0.005_{\text{adj}}$). There was a reduction in $\text{VO}_{2\text{peak}}$ of 3.5 mL/kg/min in the PDchronowilk group compared to the PDnon-chronowilk group. These results were not statistically significant, which is probably due to the reduced size of the PDchronowilk group. CPET characteristics according to this definition of chronotropic incompetence are shown in Supplementary Table 5.

Supplementary Table 1. Medication with a negative chronotropic effect in SPARX individuals

Presence or Absence of Chronotropic Incompetence	Participant ID#	Chronotropic Medication Information
Presence of Chronotropic Incompetence (Maximal HR < 85% APMHR)	C006	Propranolol
	C010	Atenolol
	C015	Propranolol
	C063	Atenolol
	C068	Metoprolol
	C073	Metoprolol
	C075	Propranolol
	C076	Atenolol
	C084	Metoprolol, Diltiazem
	D027	Propranolol
	P019	Metoprolol
	Absence of Chronotropic Incompetence (Maximal HR ≥ 85% APMHR)	C002
C008		Metoprolol
C023		Propranolol
C027		Metoprolol
C032		Metoprolol
C041		Metoprolol
C044		Propranolol
C048		Propranolol
C083		Metoprolol
D008		Digoxin
D012		Propranolol
D015		Propofenone
D032		Nebivolol
D035		Timolol

Supplementary Table 2. Clinical assessment of autonomic function, orthostatic vital signs, and heart rate response during CPET of SPARX individuals (80% APMHR criteria for chronotropic incompetence)

	Group 1 PDnon- chron_{80%}	Group 2 PDchron_{80%}	Group 3 PDchronomed	Overall
N	97	6	25	128
MDS-UPDRS, mean (SD), median (IQR)				
Part 1.10 Score (Urinary Dysfunction)	0.5 (0.7), 0 (0, 1)	0.2 (0.4) 0 (0, 0.25)	0.6 (0.7) 0 (0, 1)	0.5 (0.7) 0 (0, 1)
Part 1.11 Score (Constipation)	0.4 (0.7) 0 (0, 1)	0.8 (0.4) 1 (0.75, 1)	0.3 (0.6) 0 (0, 0.50)	0.4 (0.7) 0 (0, 1)
Part 1.12 Score (Lightheadedness on Standing)	0.3 (0.5) 0 (0, 0)	1.2 (1.2) 1 (0, 2.25)	0.2 (0.4) 0 (0, 0)	0.3 (0.5) 0 (0, 0)
Part 1.13 Score (Fatigue)	0.6 (0.6) 1 (0, 1)	0.5 (0.5) 0.5 (0, 1)	0.7 (0.7) 1 (0, 1)	0.6 (0.6) 1 (0, 1)
Lying SBP, mmHg ^a	127.5 (15.5)	130.3 (18.3)	130.0 (15.7)	128.2 (15.6)
Lying DBP, mmHg ^a	78.4 (10.4)	76.0 (9.2)	77.0 (8.8)	78.0 (10.0)
Lying HR, bpm ^b	72.1 (9.9)	62.3 (5.8)	66.1 (10.2)	70.4 (10.2)
Seated SBP, mmHg ^c	124.3 (15.8)	118.3 (17.6)	125.4 (18.4)	124.2 (16.4)
Seated DBP, mmHg ^c	77.2 (10.5)	72.3 (11.0)	76.6 (11.8)	76.9 (10.7)
Seated HR, bpm ^c	76.6 (14.6)	67.5 (7.6)	67.8 (10.6)	74.4 (14.1)
Standing SBP, mmHg ^c	125.2 (15.7)	109.0 (18.1)	124.8 (15.7)	124.4 (16.0)
Standing DBP, mmHg ^c	78.6 (10.5)	68.7 (10.0)	76.7 (12.3)	77.8 (11.0)
Standing HR, bpm ^d	83.4 (15.1)	73.3 (7.5)	71.6 (11.8)	80.5 (15.0)
Δ SBP (Standing-Lying), mmHg ^e	-3.2 (12.5)	-21.3 (24.5)	-5.2 (13.8)	-4.5 (13.9)
Δ DBP (Standing-Lying), mmHg ^e	-0.1 (5.8)	-7.3 (9.2)	-0.2 (8.6)	-0.4 (6.7)
Δ HR (Standing-Lying), bpm ^f	10.3 (8.5)	11.0 (5.5)	5.8 (6.9)	9.4 (8.2)
Deviation from APMHR (Maximal HR-APMHR)	-3.7 (12.5)	-36.8 (7.4)	-17.8 (18.8)	-8.0 (16.1)
Δ HR / Δ SBP (Standing- Lying) ^g	-0.30 (4.15)	-0.92 (0.70)	-0.74 (2.80)	-0.41 (3.81)

^aLying BP data included $n=126$; ^bLying HR data included $n=119$; ^cSeated BP, Seated HR, and Standing BP data included $n=127$; ^dStanding HR data included $n=126$; ^eΔ SBP and Δ DBP data included $n=125$; ^fΔ HR data included $n=117$; ^gΔHR/ΔSBP data included $n=105$.

MDS-UPDRS, Movement Disorders Society Unified Parkinson's Disease Rating Scale; SBP, systolic blood pressure; mmHg, millimeters of mercury; DBP, diastolic blood pressure; APMHR, age-predicted maximal heart rate. Data are mean (SD). For MDS-UPDRS 1.12, $p<0.001$ for PDnon-chron_{80%} vs. PDchron_{80%} and $p<0.001$ for PDchron_{80%} vs. PDchronomed; For lying HR, $p=0.026$ for PDnon-chron_{80%} vs. PDchronomed; For seated HR, $p=0.016$ for PDnon-chron_{80%} vs. PDchronomed; For standing HR, $p<0.001$ for PDnon-chron_{80%} vs. PDchronomed; For ΔSBP, $p=0.005$ for PDnon-chron_{80%} vs. PDchron_{80%}, and $p=0.029$ for PDchron_{80%} vs. PDchronomed; For ΔDBP, $p=0.030$ for PDnon-chron_{80%} vs. PDchron_{80%}; For deviation from APMHR, $p<0.001$ for PDnon-chron_{80%} vs. PDchron_{80%}, $p<0.001$ for PDnon-chron_{80%} vs. PDchronomed, and $p=0.008$ for PDchron_{80%} vs. PDchronomed.

Supplementary Table 3. Cardiopulmonary exercise testing characteristics in SPARX individuals (80% APMHR criteria for chronotropic incompetence)

	Group 1 PDnon- chrono_{80%}	Group 2 PDchrono_{80%}	Group 3 PDchronomed	Overall
N	97	6	25	128
Resting Heart Rate, bpm	74.1 (10.9)	65.0 (5.7)	67.2 (11.3)	72.3 (11.2)
Peak Treadmill Speed, mph	2.9 (0.6)	2.8 (0.3)	3.1 (0.7)	3.0 (0.6)
Peak Treadmill Grade, %	11.0 (3.5)	7.7 (2.9)	10.7 (3.2)	10.8 (3.5)
Exercise Duration, min	12.3 (3.2)	9.2 (3.3)	11.9 (3.0)	12.0 (3.2)
Maximal HR, bpm	153.3 (15.4)	113.8 (9.2)	137.4 (22.1)	148.3 (19.3)
VO _{2peak} , mL/kg/min ^a	24.0 (5.8)	19.5 (4.0)	23.8 (6.7)	23.8 (6.0)
Peak RER	1.06 (0.07)	1.00 (0.02)	1.06 (0.06)	1.06 (0.07)
RPE (<i>n</i> with maximal effort, %) ^b	52 (53.6)	2 (33.3)	11 (44.0)	65 (50.8)

^aVO_{2peak} data included *n*=127 as 1 data point was determined to be an outlier; ^bMaximal effort defined by an RPE ≥ 18/20, or an RPE > 8/10.

bpm, beats per minute; HR, heart rate; mph, miles per hour; min, minutes; mL/kg/min, milliliters of oxygen per kilogram of body weight per minute; RER, respiratory exchange ratio. Data are mean (SD). For resting HR, *p*=0.015 for PDnon-chrono_{80%} vs. PDchronomed; For maximal HR, *p*<0.001 for PDnon-chrono_{80%} vs. PDchrono_{80%}, *p*<0.001 for PDnon-chrono_{80%} vs. PDchronomed, and *p*=0.007 for PDchrono_{80%} vs. PDchronomed.

Supplementary Table 4. Clinical assessment of autonomic function, orthostatic vital signs, and heart rate response during CPET of SPARX individuals (Wilkoff method for chronotropic incompetence)

	Group 1 PDnon- chronowilk	Group 2 PDchronowilk	Group 3 PDchronomed	Overall
N	92	11	25	128
MDS-UPDRS, mean (SD), median (IQR)				
Part 1.10 Score (Urinary Dysfunction)	0.6 (0.7) 0 (0, 1)	0.2 (0.4) 0 (0, 0)	0.6 (0.7) 0 (0, 1)	0.5 (0.7) 0 (0, 1)
Part 1.11 Score (Constipation)	0.4 (0.7) 0 (0, 1)	0.6 (0.5) 1 (0, 1)	0.3 (0.6) 0 (0, 0.50)	0.4 (0.7) 0 (0, 1)
Part 1.12 Score (Lightheadedness on Standing)	0.3 (0.5) 0 (0, 0.75)	0.6 (1.0) 0 (0, 1)	0.2 (0.4) 0 (0, 0)	0.3 (0.5) 0 (0, 0)
Part 1.13 Score (Fatigue)	0.7 (0.6) 1 (0, 1)	0.4 (0.5) 0 (0, 1)	0.7 (0.7) 1 (0, 1)	0.6 (0.6) 1 (0, 1)
Lying SBP, mmHg ^a	127.5 (15.2)	129.3 (19.1)	130.0 (15.7)	128.2 (15.6)
Lying DBP, mmHg ^a	78.4 (10.2)	76.9 (10.8)	77.0 (8.8)	78.0 (10.0)
Lying HR, bpm ^b	72.8 (9.6)	60.5 (5.6)	66.1 (10.2)	70.4 (10.2)
Seated SBP, mmHg ^c	124.7 (15.6)	117.8 (17.4)	125.4 (18.4)	124.2 (16.4)
Seated DBP, mmHg ^c	77.3 (10.4)	73.8 (11.5)	76.6 (11.8)	76.9 (10.7)
Seated HR, bpm ^c	77.4 (14.3)	65.0 (10.9)	67.8 (10.6)	74.4 (14.1)
Standing SBP, mmHg ^c	125.5 (15.6)	113.8 (18.2)	124.8 (15.7)	124.4 (16.0)
Standing DBP, mmHg ^c	78.6 (10.4)	73.3 (11.9)	76.7 (12.3)	77.8 (11.0)
Standing HR, bpm ^d	84.0 (14.9)	71.7 (10.3)	71.6 (11.8)	80.5 (15.0)
Δ SBP (Standing-Lying), mmHg ^e	-2.9 (12.4)	-15.5 (20.6)	-5.2 (13.8)	-4.5 (13.9)
Δ DBP (Standing-Lying), mmHg ^e	-0.1 (5.6)	-3.6 (9.7)	-0.2 (8.6)	-0.4 (6.7)
Δ HR (Standing-Lying), bpm ^f	10.5 (8.6)	9.3 (5.4)	5.8 (6.9)	9.4 (8.2)
Deviation from APMHR (Maximal HR-APMHR)	-2.5 (11.6)	-31.8 (7.9)	-17.8 (18.8)	-8.0 (16.1)
Δ HR / Δ SBP (Standing-Lying) ^g	-0.34 (4.22)	-0.30 (1.29)	-0.74 (2.80)	-0.41 (3.81)

^aLying BP data included $n=126$; ^bLying HR data included $n=119$; ^cSeated BP, Seated HR, and Standing BP data included $n=127$; ^dStanding HR data included $n=126$; ^eΔ SBP and Δ DBP data included $n=125$; ^fΔ HR data included $n=117$; ^gΔHR/ΔSBP data included $n=105$.

MDS-UPDRS, Movement Disorders Society Unified Parkinson's Disease Rating Scale; SBP, systolic blood pressure; mmHg, millimeters of mercury; DBP, diastolic blood pressure; APMHR, age-predicted maximal heart rate. Data are mean (SD). For MDS-UPDRS 1.12, $p=0.037$ for PDchronowilk vs.

PDchronomed; For lying HR, $p<0.001$ for PDnon-chronowilk vs. PDchronowilk, and $p=0.008$ for PDnon-chronowilk vs. PDchronomed; For seated HR, $p=0.014$ for PDnon-chronowilk vs. PDchronowilk, and $p=0.006$ for PDnon-chronowilk vs. PDchronomed; For standing HR, $p=0.029$ for PDnon-chronowilk vs. PDchronowilk, and $p<0.001$ for PDnon-chronowilk vs. PDchronomed; For ΔSBP, $p=0.014$ for PDnon-chronowilk vs. PDchronowilk; For ΔHR, $p=0.043$ for PDnon-chronowilk vs. PDchronomed; For deviation from APMHR, $p<0.001$ for PDnon-chronowilk vs. PDchronowilk, $p<0.001$ for PDnon-chronowilk vs. PDchronomed, and $p=0.011$ for PDchronowilk vs. PDchronomed.

Supplementary Table 5. Cardiopulmonary exercise testing characteristics in SPARX individuals (Wilkoff method for chronotropic incompetence)

	Group 1 PDnon- chronowilk	Group 2 PDchronowilk	Group 3 PDchronomed	Overall
N	92	11	25	128
Resting Heart Rate, bpm	74.8 (10.3)	63.7 (11.2)	67.2 (11.3)	72.3 (11.2)
Peak Treadmill Speed, mph	2.9 (0.6)	2.9 (0.6)	3.1 (0.7)	3.0 (0.6)
Peak Treadmill Grade, %	11.0 (3.6)	8.4 (2.7)	10.7 (3.2)	10.8 (3.5)
Exercise Duration, min	12.4 (3.2)	9.9 (2.9)	11.9 (3.0)	12.0 (3.2)
Maximal HR, bpm	154.6 (14.6)	121.1 (12.4)	137.4 (22.1)	148.3 (19.3)
VO _{2peak} , mL/kg/min ^a	24.1 (5.9)	20.6 (4.4)	23.8 (6.7)	23.8 (6.0)
Peak RER	1.06 (0.08)	1.04 (0.06)	1.06 (0.06)	1.06 (0.07)
RPE (<i>n</i> with maximal effort, %) ^b	52 (56.5)	2 (18.2)	11 (44.0)	65 (50.8)

^aVO_{2peak} data included *n*=127 as 1 data point was determined to be an outlier; ^bMaximal effort defined by an RPE ≥ 18/20, or an RPE > 8/10.

bpm, beats per minute; HR, heart rate; mph, miles per hour; min, minutes; mL/kg/min, milliliters of oxygen per kilogram of body weight per minute; RER, respiratory exchange ratio. Data are mean (SD). For resting HR, *p*=0.004 for PDnon-chronowilk vs. PDchronowilk and *p*=0.005 for PDnon-chronowilk vs. PDchronomed; For maximal HR, *p*<0.001 for PDnon-chronowilk vs. PDchronowilk, *p*<0.001 for PDnon-chronowilk vs. PDchronomed, and *p*=0.019 for PDchronowilk vs. PDchronomed.

Supplementary Figure 1. The Wilkoff method applies the chronotropic index (i.e., the ratio of the HR reserve to the metabolic reserve during submaximal exercise) to CPETs with an RER <1.05. A chronotropic index ≤ 0.80 is indicative of chronotropic incompetence. The Wilkoff method resulted in 11 patients being identified as having chronotropic incompetence in this study. These participants are represented by the shaded boxes.

