High Intensity Aerobic Exercise Enhances Function in Parkinson’s disease

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Course Objectives
At the end of the presentation, the participants will:

• Describe the potential mechanism underlying high intensity aerobic exercise in individuals with PD.
• Discuss the motor and non-motor outcomes following a forced exercise paradigm in individuals with PD.
• Discuss the clinical translation of a forced exercise paradigm to a rehabilitation program for individuals with PD.
• Discuss the application of forced-exercise in the management of other diseases and conditions including obesity and stroke
• Understand the value of using objective measures of cognitive and motor function to compliment clinical measures of motor and non-motor function.

Introduction

• The primary cause of PD is loss of dopamine projections to the basal ganglia.
  – Degeneration of dopamine containing neurons in the substantia nigra pars compacta (SNc).

Disclosures

JLA has authored intellectual property associated with the forced exercise bike and iPad modules

Course Outline

I. Current medical management of patients with PD
II. Rationale for the use of forced-exercise in animal models of PD
III. Description of forced-exercise intervention for patients with PD
IV. The global motor and non-motor impact of forced-exercise in patients with PD – results from our clinical trials
V. Forced exercise in other neurological and non-neurological populations
VI. Question and Answer

Role of basal ganglia in motor control

[Diagram of basal ganglia and motor control]
Therapeutic Window

- Therapeutic window narrows with advancing disease
- Difficult to produce symptom relief without side effects
- Surgical therapies are available for late stage PD

Adapted from Sage and Mark, Neurology 1992

Therapies

- Pharmacological
  - L-DOPA
  - DA agonists
  - MAO inhibitor
  - Glutamate antagonists

- Surgical
  - Pallidotomy
  - Deep Brain Stimulation
  - STN
  - GPi

- Physical, occupational, speech therapies
- Needed: Neuroprotection
  - A neuroprotective therapy is the single most important unmet medical need in Parkinson's disease (Olanow et al., 2008)

Rehabilitation Models of PD

- High amplitude, high velocity movements
- Strategies to reduce freezing, improve spatiotemporal aspects of gait (step length, cadence, velocity, etc.)
  - Auditory cuing/metronome/music: external rhythm compensates for defective internal rhythm of the basal ganglia
  - Visual cuing: motor planning deficit, no longer an “automatic,” rhythmic task that is processed through the basal ganglia

Adapted from Wu, 2005, 2013

What can animal models tell us about forced exercise and neuroplasticity in PD?

Adapted from Jay, 2005

Forced exercise and neuroprotection in rodent models of PD

Adapted from Jay, 2005
Effects of Forced-Exercise in Animal Models of PD

- Increased release of dopamine
- Decreased synaptic clearance of dopamine
- Increase in dopamine D2 receptor
- Increase in neurotrophic factors (BDNF, GDNF, IGF-1)
  - Greater intensity (forced-exercise) results in higher levels of neurotrophic factors and more extensive the anatomical regions involved

- FE is neuroprotective and improves motor function.

From the Cornfields to a Clinical Trial to Clinical Practice

Pie or Pedaling???

What is forced-exercise for PD patients?

- Voluntary efforts of the patient are augmented
  - Exercise rate increased
  - Consistent pedaling rate at high RPMs
  - Consistent pedaling pattern
- Aerobic
  - 65-80% target HR zone
- Participant is not passive

Proposed Forced-Exercise Mechanisms of Action
Closing the gap between animal and human studies

Rationale for Forced-Exercise

- Decreased activation in cortical areas
- Impaired sensory-motor integration
  - Degraded quantity and quality of sensory info.
- Exercise rate is important (animal studies)
- Augment, not replace, voluntary efforts (robotic studies)
  - Increase quantity and quality of afferent info.

Hypothesis: Forced, not voluntary, exercise will result in global motor improvements in PD patients.

Forced vs. Voluntary Exercise

Forced Exercise (FE)
- Three sessions/wk for 8 weeks
- 5-10 min warm up, 40 min main set, 5-10 min cool down
- 60-80% target HR
- FE group pedaled 30% faster compared to the VE group

Voluntary Exercise (VE)
- Three sessions/wk for 8 weeks
- 5-10 min warm up, 40 min main set, 5-10 min cool down
- 60-80% target HR

Aerobic exercise improves fitness, only FE improves clinical ratings

High intensity exercise improves UE motor function
Motor, CNS improvements appear to be related to cycling intensity

- Colors represent change in functional connectivity from baseline to EOT that is related to cadence.
- Greater increase in connectivity between thalamus and motor cortex in those who cycled faster.

High Intensity Exercise Induces CNS Changes Measured with fMRI

Study design
10 PD patients
Three conditions:
1. No meds
2. Meds
3. No meds + FE
   - 40 min of FE (80-90 RPMs)

Cyclical Lower-extremity Exercise (CYCLE) Trial

Study Overview

Participant screening

Inclusion Criteria
- Clinical diagnosis of idiopathic PD
- Age between 30-75 years
- Hoehn & Yahr stage II-III when on-medication
- Not currently engaged in formal PD-specific exercise intervention or clinical study

Exclusion Criteria
- Existing cardiopulmonary disease or stroke
- Dementia
- Other medical or musculoskeletal contraindications to exercise
Cardiopulmonary Stress Test (CPX)

- Upright stationary bike
- Increasing workload by 25W every two minutes until 100W, then increase by 50W until termination
- Continuous 12-lead EKG to monitor for cardiac abnormalities
- Gas analysis to determine peak VO2
- 99% of stress tests were normal

CYCLE Trial Demographics

<table>
<thead>
<tr>
<th>Factor</th>
<th>FE (N = 40)</th>
<th>VE (N = 39)</th>
<th>Control (N = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>23 (57)</td>
<td>21 (54)</td>
<td>14 (70)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63 ± 8</td>
<td>61 ± 9</td>
<td>65 ± 6</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>4 (1.4)</td>
<td>3 (1.6)</td>
<td>3 (1.4)</td>
</tr>
<tr>
<td>Levodopa dosage (mg)</td>
<td>475 [300, 600]</td>
<td>500 [305, 600]</td>
<td>490 [145, 562]</td>
</tr>
<tr>
<td>Years of education</td>
<td>16 ± 3</td>
<td>16 ± 3</td>
<td>17 ± 2</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>38 (95)</td>
<td>38 (97)</td>
<td>19 (95)</td>
</tr>
<tr>
<td>Black</td>
<td>1 (2)</td>
<td>1 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Hispanic ethnicity</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>UPDRS (on medication)</td>
<td>34 ± 9</td>
<td>35 ± 11</td>
<td>35 ± 9</td>
</tr>
<tr>
<td>UPDRS (off medication)</td>
<td>38 ± 10</td>
<td>40 ± 10</td>
<td>35 ± 12</td>
</tr>
</tbody>
</table>

* FE = forced exercise; VE = voluntary exercise.

Summary statistics presented as mean ± standard deviation (normally distributed characteristics), median [first quartile, third quartile] (characteristics with skewed data), or N (%) (categorical data).

Groups were not significantly different from each other (p > 0.25)

Disease Progression

- High intensity exercise delays disease progression

**Example of HR training data from one exercise session and time spent in target HR range**
- Both FE and VE exercised 3x/wk for 8 weeks; 60-80% of HRR
High intensity exercise delays disease progression

Does MDS-UPDRS III change from baseline (off medication) to EOT?

• Do the slopes differ by exercise group?

• Is there a significant difference between groups on mean MD-UPDRS III at EOT?

Mean (95% CI) MDS-UPDRS III by exercise group over time.

Medication and high intensity exercise have similar effects on disease progression

Does MD-UPDRS III change from baseline (on medication) to EOT?

Does MDS-UPDRS III change from baseline (on medication) to baseline (off medication)?

Do the slopes differ by exercise group?

Is there a significant difference between groups on mean MD-UPDRS III at EOT?

Mean (95% CI) MDS-UPDRS III by exercise group over time.

Overall Results

Gross Motor Outcomes
Individuals with PD display deficits in gait and turning performance which increases fall risk. 70% of PD subjects will develop gait and postural impairments. • 35-90% of these patients will experience at least one fall/year • Despite such high fall rates clinicians do not currently have an effective and reliable method for characterizing fall risk. iTUG provides a quantitative assessment of balance and gait during common daily tasks to accurately determine level of function.

Mobility-Timed Up & Go Test: iTUG

High intensity exercise improves overall mobility

Outcome Measures from iTUG
• Time to complete task: Total Trial Time (sec)

Gait:
– Normalized Jerk Score (NJS) of linear acceleration in AP, ML, V (m): higher values indicate increased dynamic movement and increased mobility

\[
\text{Gait NJS} = \frac{1}{N} \sum_{i=1}^{N} \left( \frac{a_i - \text{mean}(a)}{\text{std}(a)} \right)^2
\]

Turning:
– Root mean square (RMS) of linear acceleration in AP, ML, and V (m): higher values indicate increased acceleration amplitude

\[
\text{RMS} = \sqrt{\frac{1}{N} \sum_{i=1}^{N} a_i^2}
\]

High intensity exercise improves gait dynamics
High intensity exercise improves turning acceleration

![Graph showing improvement in turning acceleration](image)

- **Significant difference from Baseline Off**
- **Significant difference from Baseline On**

Exercise Improves Walking Gait

Subject BG_026
VE group
Right side affected
Single-Task condition

Cognitive Outcomes

High intensity exercise improves information processing & motor performance

High intensity exercise improves complex information processing

![Graph showing improvement in cognitive outcomes](image)

- **Significant difference from Baseline Off**
- **Significant difference from Baseline On**
High intensity exercise improves complex information processing & motor performance

Computerized Trail Making Test (TMT)

High intensity exercise improves visual scanning and motor performance on TMT

High intensity exercise improves motor performance on TMT
High intensity exercise improves visual scanning/cognitive performance on TMT

Cardiovascular Outcomes

Aerobic exercise increases CV fitness

Maximal and submaximal VO₂ increase for FE and VE
Submaximal VO₂ decreased over time in the control group

Average Cadence During Exercise and Stress Test

<table>
<thead>
<tr>
<th>Exercise characteristics</th>
<th>Forced exercise</th>
<th>Voluntary exercise</th>
<th>Control (no exercise)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average cadence during exercise</td>
<td>79 ± 10</td>
<td>75 ± 15</td>
<td></td>
</tr>
<tr>
<td>Pre stress test average cadence</td>
<td>64 ± 14</td>
<td>62 ± 13</td>
<td>63 ± 13</td>
</tr>
<tr>
<td>Post stress test average cadence</td>
<td>70 ± 16</td>
<td>66 ± 13</td>
<td>62 ± 15</td>
</tr>
</tbody>
</table>

Relationship Between Cadence and Peak VO₂

At 60 rpms and greater, there is a linear relationship between peak VO₂ and rpms
As rpms increase, peak VO₂ increases

Quality of Life
High intensity exercise may improve depression symptomology

<table>
<thead>
<tr>
<th>Variable</th>
<th>Exercise (n=72)</th>
<th>Control (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent change pre to post:</td>
<td>-8% (improvement)</td>
<td>15% (worsening)</td>
</tr>
<tr>
<td>Number of participants depressed at baseline:</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Participants who improved depression categories:</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Participants who worsened depression categories:</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Participants with improved SRD*:</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Participants with worsened SRD:</td>
<td>9</td>
<td>3</td>
</tr>
</tbody>
</table>

*SRD: Smallest Real Difference detectable in daily living

Can FE be used to enhance Recovery of Function after Stroke?

Applying high intensity exercise to individuals with stroke

Prime the CNS via AE

Intensive Motor Practice

Hypothesis: Aerobic exercise will influence motor recovery and non-motor function in individuals with stroke

Anticipated Outcome:
Those in the FE group will have a greater recovery of motor and non-motor function than VE and RTP alone

Proposed Mechanism of FE after Stroke

Study Aims

• To determine the differential effects of forced and voluntary exercise on motor function, non-motor function, and cardiovascular fitness in individuals with chronic stroke
Study Overview

- Screening & Consent
- Baseline Sitting Stress Test
- Baseline Testing
- 3x/wk for 8 wks
- FE + RTP
- VE + RTP
- RTP Only
- End of Treatment (EOT) Testing
- EOT Biking Stress Test
- EOT + 4 weeks

Repetitive Task Practice (RTP)

- Focus on maximizing reps
  - Typically between 75-100+ reps of 1 task
- Type of practice
  - Blocked, whole part
  - Patient goal setting with reps or time
- Standing vs. Sitting
- Minimize rest time
- Incorporate ROM into functional activity
- Grading of activities

Three Time-Matched Intervention Groups

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Intensity</th>
<th>Intervention</th>
<th>Intensity</th>
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</thead>
<tbody>
<tr>
<td>FE + RTP</td>
<td></td>
<td>VE + RTP</td>
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<tr>
<td>RTP only</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>45 min</th>
<th>45 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>FE + RTP</td>
<td>60-80% HRR</td>
<td>1% HRR</td>
</tr>
<tr>
<td>VE + RTP</td>
<td>60-80% HRR</td>
<td>1% HRR</td>
</tr>
<tr>
<td>RTP only</td>
<td>1% HRR</td>
<td>1% HRR</td>
</tr>
</tbody>
</table>

Training Example

RTP videos

Motor Outcomes
High intensity exercise improves gross motor function

Non-Motor Outcomes

Forced Aerobic Exercise Preceding Task Practice Improves Motor Recovery Poststroke
Susan M. Linder, Jenison R. Rosenkrantz, Tanztu De, Jay L. Alberts
The American Journal of Occupational Therapy
March/April 2002, Volume 56, Number 2

Depression scores declined over time across groups

Quality of life items improved over time across groups

Quality of life cognitive composite score improves over time only among FE

Cardiovascular Outcomes
High intensity exercise improves cardiovascular fitness

Clinical Implementation

What other equipment can be used for FE?

Eliminating barriers to cycling intervention

• Keeping feet on pedals
  —PD: Rigidity, dystonia, dyskinesia
  —Stroke: Hyper/hypotonic, altered sensation and proprioception
  —Clip in biking shoe
  —Theraband for pedals, hip abduction
  —Warm up time

• Baseline deconditioning
  —10 min increments with seated rest breaks if needed

Clinical Translation

Summary

• High intensity exercise is feasible in individuals with PD and stroke
• May be altering disease progression in PD
  —Motor and non motor improvements
• Neuroplasticity vs. compensation
• Clinical implementations: aerobic exercise as HEP vs. in conjunction with disease-specific intervention
First, I bike…

…then, I fish.”

References


Acknowledgements

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- The stroke studies were supported by a grant from the NIH R03HDO73566 and American Heart Association 15MCPRP25700312. ClinicalTrials.gov registration numbers NCT02076776, NCT02494518.

- The References section lists multiple entries, but the full list is not provided in the visible part of the image.

- The image includes a Cleveland Clinic logo and text indicating references and acknowledgments.

Is Exercise Medicine?

Yes

No
References