High Intensity Aerobic Exercise Enhances Function in Parkinson’s disease

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Disclosures

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

ABR has nothing to disclose.

Course Objectives

At the end of the presentation, the participant 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 individuals with PD.
• Discuss the application of forced exercise in the management of stroke.
• Understand the value of using objective measures of cognitive and motor function to compliment clinical measures of motor and non-motor function.

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 Stroke
VI. Question and Answer

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) in putamen

Role of basal ganglia in motor control

[Diagram showing the role of basal ganglia in 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

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)

Who is being referred to therapy services?

- Nijkrae 2008 (Netherlands)
  - Survey of 216 PD patients
  - % of patients utilizing service
    - Physical Therapy: 62.5%
    - Occupational Therapy: 9.5%
    - Speech Therapy: 14.4%
  - 60% reported a fall in the past year → 33% received PT

Rehabilitation Models of PD

- **Compensation vs. Neuroplasticity** — using cerebello-thalmo-cortical circuit to bypass the defective basal ganglia
- 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

What can animal models tell us about forced exercise and neuroplasticity in PD?
**Forced exercise and neuroprotection in rodent models of PD**

**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???”**
- Closing the gap between animal and human studies
Closing the gap between animal and human studies

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

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

Aerobic Exercise Preserves Olfaction Function in Individuals with Parkinson’s Disease
J. B. Rosenfeld, T. E. Jell, and J. L. Albert

Aerobic Exercise Preserves Olfaction 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)

High Intensity Exercise Induces CNS Changes Measured with fMRI

Study enrollment

Cyclical Lower-extremity Exercise (CYCLE) Trial

Cyclical Lower-extremity Exercise (CYCLE) Trial
From Tandem to Automation

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 (ACSM screening criteria)
- 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 participants were cleared to exercise

CYCLE Trial Consort Diagram

CYCLE Trial Demographics
**CYCLE Trial Training Example**

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

**Cardiovascular Outcomes**

Aerobic exercise increases CV fitness

- Maximal and submaximal VO2 increase for FE and VE, not control

**Relationship Between Cadence, Peak VO2**

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

As rpms increase, peak VO2 increases

**Primary Clinical Motor Outcome**

Individuals were able to maintain exercise intensity

<table>
<thead>
<tr>
<th>Exercise characteristics</th>
<th>FE (N = 36)</th>
<th>VE (N = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise Attendance (out of 24 sessions)</td>
<td>97%</td>
<td>92%</td>
</tr>
<tr>
<td>HRR %</td>
<td>66% [60%, 70%]</td>
<td>69% [64%, 79%]</td>
</tr>
<tr>
<td>Average heart rate (bpm)</td>
<td>111 ± 12</td>
<td>114 ± 14</td>
</tr>
<tr>
<td>Average cadence (rpms)</td>
<td>73 ± 10</td>
<td>75 ± 15</td>
</tr>
<tr>
<td>Average power (W)</td>
<td>34 [21, 56]</td>
<td>41 [25, 54]</td>
</tr>
</tbody>
</table>

Summary characteristics are mean ± SD, median [Q1, Q3], or N (%).
MDS-Unified Parkinson’s disease Rating Scale (UPDRS) – Motor

- Rates global motor symptoms of PD
- Based on the 4 cardinal motor symptoms (rigidity, bradykinesia, tremor, gait/posture)
- Subjective 0-4 rating
  - 0 = no symptoms
  - 4 = most severe

High intensity exercise improves motor symptoms

- 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 MDS-UPDRS III at EOT?

Medication and high intensity exercise have similar effects on motor symptoms

- Does MDS-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 MDS-UPDRS III at EOT?
Overall motor symptoms results

Secondary Outcomes – Functional Mobility

Functional mobility analysis

- To characterize exercise prescription on PD-related functional mobility
  - Evaluate exercise modality by comparing the 2 types of aerobic exercise

<table>
<thead>
<tr>
<th>FE (n=30)</th>
<th>VE (n=30)</th>
</tr>
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</table>

Individuals with PD experience mobility dysfunction

- Up to 87% of individuals exhibit gait dysfunction in the early stages of diagnosis
  - 35-90% will experience at least one fall/year
  - In PD, 80% of falls occur in the home when individuals are performing daily activities such as walking, standing, and transferring
  - Turning increases the risk for falls due to postural control impairments with weight shifting, asymmetry of producing different step lengths, and freezing

- The Timed Up and Go (TUG) is a quick and simple mobility assessment

iTUG can discriminate between functional tasks

iTUG Data from IMU Sensor in iPad
Overall mobility improves following aerobic exercise

Overall mobility improves in VE but not FE

Gait Speed Increase in VE, but not FE

Turning velocity is faster in both FE and VE

Improvements in mobility

VE
• Improvements in turning, gait speed

• Improvements are due to increased acceleration and amplitude of movement following exercise → Reduction in bradykinesia

FE
• Improvements in gait speed

Improvements in mobility

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Summary characteristics are mean ± SD, median [Q1, Q3] or N [%].
Secondary Outcomes – Gait Assessment

Biomechanical Gait Analysis

High Intensity Cycling Improves Gait

High intensity exercise elicits increase in arm swing

High intensity exercise elicits increase in gait speed
High intensity exercise normalized gait speed

- Velocity was not significantly different from healthy controls post intervention

Secondary Outcomes - Quality of Life

High intensity exercise normalized stance phase & step length

- Spatiotemporal variables were not significantly different from healthy controls post intervention

Relationship between PD and depression

- 40-50% of individuals with PD will experience depression
- Aerobic exercise is effective in treating depression in those without PD
- Less is known about aerobic exercise, PD, and depression

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

High intensity exercise may improve depression symptomology

<table>
<thead>
<tr>
<th>Percent change pre to post:</th>
<th>Exercise (n=73)</th>
<th>Control (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8% improvement</td>
<td></td>
<td>15% worsening</td>
</tr>
<tr>
<td>Participants with mild-severe depressive symptomology 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>
</tbody>
</table>
Applying high intensity exercise to individuals with stroke

**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

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**Proposed Mechanism of FE after Stroke**

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**Inclusion/Exclusion Criteria**

**Inclusion**
- 18-85 years old
- >6 months post ischemic stroke
- Approval from physician to participate in stress test
- 19-55 on Fugl-Meyer upper extremity motor assessment
- Ability to follow 1-2 step commands

**Exclusion**
- Cardiac or pulmonary contraindication to exercise (cardiomyopathy, PE, afib, MI, etc.)
- Other musculoskeletal contraindications to exercise
- Major psychiatric disorder
- Anti-spasticity injections (botox) within the past 3 months
- Uncontrolled BP

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**Study Overview**

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**Aerobic Exercise + Task Practice promotes recovery in rodent models of stroke**

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**Ploughman 2007**
# Participant Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FE = RTP</th>
<th>VE + RTP</th>
<th>RTP Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>44.8 (11.7)</td>
<td>46.7 (12.1)</td>
<td>61.8 (8.3)</td>
</tr>
<tr>
<td>Gender, M/F</td>
<td>5/5</td>
<td>5/5</td>
<td>5/5</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>White</td>
<td>African-American</td>
<td>Asian</td>
</tr>
<tr>
<td>Left-handed</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Motion score [1]</td>
<td>47 (27)</td>
<td>53 (26)</td>
<td>57 (21)</td>
</tr>
<tr>
<td>Luria</td>
<td>36.9 (20.0)</td>
<td>54.0 (21.4)</td>
<td>55.7 (23.8)</td>
</tr>
</tbody>
</table>

Note: FE = forced exercise; VE = voluntary exercise; RTP = repetitive task practice.

## Three Time-Matched Intervention Groups

<table>
<thead>
<tr>
<th>FE + RTP</th>
<th>VE + RTP</th>
<th>RTP Only</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
<td><strong>Intensity</strong></td>
<td><strong>Intervention</strong></td>
</tr>
<tr>
<td>RTP only</td>
<td>45 min</td>
<td>RTP only</td>
</tr>
<tr>
<td>45 min</td>
<td>RTP only</td>
<td></td>
</tr>
</tbody>
</table>

## Repetitive Task Practice (RTP)

- **Focus on maximizing reps**
  - Selected 3-5 tasks/session
  - 75-100+ reps of each task
- **Type of practice**
  - **ACTIVE**
    - Incorporate ROM into functional activity
  - Blocked, target/goal-oriented, specificity of training
- **Standing vs. Sitting**
- **Minimize rest time**
- **Grading of activities**

## RTP with varying levels of UE function

<table>
<thead>
<tr>
<th>Impairment/Functional Limitation</th>
<th>Task</th>
<th>Grading of Task</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower functioning UE</td>
<td>Decreased shoulder AROM and strength making donning a coat difficult</td>
<td>Using gross motor shoulder flex/abduction to knock down dominos dispersed on tray table</td>
</tr>
<tr>
<td>Higher functioning UE</td>
<td>Impaired intrinsic hand coordination limiting writing legibility</td>
<td>Writing practice on a lined white board</td>
</tr>
<tr>
<td></td>
<td>Decreased shoulder ER resulting in difficulty washing hair</td>
<td>Overhead throwing to target with emphasis on external rotation during “wind-up”</td>
</tr>
</tbody>
</table>

## RTP Videos

## Representative Day of HR Data
Cardiovascular Outcomes

Individuals achieved AHA/ASA recommendations for aerobic exercise

High intensity exercise improves cardiovascular fitness

Motor Outcomes

The RTP group performed 60% more reps

High intensity exercise improves gross motor function
Secondary Outcome – Non-Motor

Depression and Stroke

- Rehabilitation following stroke aims not only to improve physical limitations, but also to restore QOL
- Approximately 1 in 3 survivors of stroke develop post-stroke depression (PSD)
- PSD is associated with increased disability, lower QOL, and higher mortality
- Benefits of aerobic exercise on depression in individuals without stroke

Aerobic exercise improved QOL

Forced exercise improved cognitive composite

Further investigation into aerobic exercise and depression

Quality of Life Outcome Analysis

- A second study with identical aerobic exercise groups was completed
- Additional patients completed the intervention
  - Comparison with a control group who completed stroke education sessions + RTP

FE-RTP  (n=16)
VE-RTP  (n=16)
EDU-RTP  (n=8)
Clinical Implementation

**Recommended Screening for PD**

Screening Tool Utilized: Pre-Participation for Exercise Questionnaire (American College of Sports Medicine)

- 100 patients enrolled
- 94 cleared from initial metabolic stress test
- 5 underwent follow-up testing and obtained clearance
- 1 chose not to follow-up (could not proceed)

Do all patients need a formal stress test after stroke?

- AHA/ASA recommend that individuals with stroke undergo a graded exercise test with EKG.
- “If the physician overseeing the patient’s care determines an exercise test is not indicated or such an assessment in a given facility is not possible, the initiation of an exercise training program, individually tailored to a patient’s physical capabilities, should not be delayed.”
- “In lieu of graded maximal exercise tests, submaximal tests may be considered for stroke survivors.”
  - 6MWT

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 pedaling, hip abduction
  - Warm up time
- Baseline deconditioning
  - 10 min increments with seated rest breaks if needed

Clinical Translation
Physical Therapy “Check-Ups” for PD

- Every 6-12 months
- Pts can perform aerobic exercise as part of a comprehensive HEP
- Referral for H&Y 1-2

Future Directions

- Schenkman 2017 (n=128)
  - High intensity treadmill training (80-85% HRR) in de novo patients
  - Mean change in UPDRS motor score in the high intensity group was 0.3 (95% CI, −1.7 to 2.3) compared with 3.2 (95% CI, 1.4-5.1) in the usual care group over 6 months
  - Moderate exercise group was not different from usual care
  - Nonfutility study → larger sample to determine efficacy

Community Tandem Cycling Program

- N=41 PD, tandem cycled 3x/week for 10 weeks with a healthy partner in a group setting
- Intensity of 60 min sessions: 80-90 rpms, 60-75% of estimated max HR
  - Medical screen was adequate, no stress test
- Improvements in gait (velocity, cadence), balance, and transfers
- 100% retention rate

Pedaling for Parkinson’s Community-based Model

Summary

- High intensity exercise is feasible in individuals with PD and stroke
- May be altering disease progression in PD and heightening recovery in stroke
  - Motor and non motor improvements
  - Changing CNS connectivity in PD
- Neuroplasticity vs. compensation
- Clinical implementations: aerobic exercise in conjunction with disease-specific intervention

Is Exercise Medicine?

Yes No
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References


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Cleveland Clinic

Every life deserves world class care.