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PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA MOTRICIDADE

OS EFEITOS DA MANIPULAÇÃO DO SISTEMA PROPRIOCEPTIVO NA LOCOMOÇÃO DE PESSOAS COM DOENÇA DE PARKINSON COM E SEM CONGELAMENTO DA MARCHA: DESENVOLVIMENTO, OTIMIZAÇÃO E APLICABILIDADE DE UM SISTEMA DE VIBRAÇÃO MUSCULAR.

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Tese apresentada ao Instituto de Biociências do Câmpus de Rio Claro, Universidade Estadual Paulista, como parte dos requisitos para obtenção do título de Doutor em Ciências da Motricidade.

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MARCELO PINTO PEREIRA

Os efeitos da manipulação do sistema proprioceptivo na locomoção de pessoas com doença de Parkinson com e sem congelamento da marcha: desenvolvimento, otimização e aplicabilidade de um sistema de vibração muscular.

Tese apresentada ao Instituto de Biociências do Campus de Rio Claro, Universidade Estadual Paulista Júlio de Mesquita Filho, como parte dos requisitos para obtenção do título de Doutor em Ciências da Motricidade (Biodinâmica da Motricidade Humana).

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Dedico esse trabalho à todas as
pessoas que lutam diariamente contra
a doença de Parkinson.

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“Todo o meu saber consiste em saber que nada sei”.

(Sócrates)

RESUMO

Os déficits no processamento de informações proprioceptivas e as dificuldades em integrar diferentes planos motores são apontados como os principais responsáveis pelo pior desempenho na execução de tarefas locomotoras, em pessoas com doença de Parkinson (DP). Esse déficit proprioceptivo também desempenha um importante papel na ocorrência dos episódios de congelamento da marcha (*freezing of gait:* FOG). Assim, o principal objetivo dessa Tese de Doutorado foi verificar os efeitos da manipulação do sistema proprioceptivo, por meio de um sistema de vibração muscular, sobre o desempenho das tarefas locomotoras e sobre a severidade dos episódios de FOG em pessoas com doença de Parkinson. Entretanto, devido à uma série de dificuldades, foi necessário o desenvolvimento e otimização de um sistema manufaturado de vibração que pudesse atender nossas necessidades. Para isso, também tivemos como objetivo: descrever o desenvolvimento de um sistema manufaturado de aplicação de vibração muscular e sua reprodutibilidade; e otimizar os parâmetros de aplicação de vibração muscular, com intuito de promover, em adultos jovens, a melhora no desempenho das tarefas de levantar e andar e iniciar o andar. Verificou-se que o sistema de vibração manufaturado desenvolvido aqui (chamado de RCVibro System) é altamente reprodutível e promove resultados semelhantes aos observados na literatura. Verificou-se também que a melhor forma de aplicar a vibração muscular, para atender nossos objetivos, é na região proximal dos ventres dos músculos e em paralelo às fibras musculares. Como resultados, observamos que para melhora do desempenho da tarefa de iniciar o andar, a vibração deve ser aplicada somente antes do início do movimento, e que a vibração muscular não promove alterações no padrão locomotor de adultos jovens durante a tarefa de levantar e andar. Por outro lado, pessoas com DP são prejudicados pelo uso dessa técnica durante a execução da tarefa de levantar e andar, possivelmente por uma sobrecarga no sistema proprioceptivo. Para a tarefa de iniciar o andar, verificamos uma melhora do seu desempenho em pessoas com DP e com FOG, sendo observada uma redução do tempo total despendido para execução da tarefa. Efeitos posturais suscitados pela manipulação do sistema proprioceptivo são apontados como responsáveis por esses resultados. A manipulação do sistema proprioceptivo também promoveu um alívio da severidade dos episódios de FOG, quando foi aplicada antes do disparo desse fenômeno. Entretanto, a vibração muscular falha em prevenir

episódios de FOG, levando à uma maior severidade desse fenômeno se aplicada antes do seu disparo. Os resultados sugerem que a manipulação do sistema proprioceptivo tem um efeito benéfico apenas para facilitar o início do movimento em pessoas com DP e com FOG, sendo deletério quando aplicada durante a execução do movimento. Todos esses resultados destacam o papel dos déficits proprioceptivos como fator determinante para o pior desempenho de pessoas com DP durante tarefas locomotoras e principalmente, para a ocorrência de episódios de FOG. Finalmente, destacamos o potencial clínico de aplicação do sistema RCVibro System para facilitar o iniciar o andar de pessoas com DP e para reduzir a severidade dos episódios de FOG nessa população.

Palavras chave: Doença de Parkinson. Congelamento da marcha. Propriocepção. Vibração muscular. Locomoção.

ABSTRACT

Proprioceptive processing deficits and difficulties in integrating different motor plans are pointed as the main mechanisms underlying the worse performance of people with Parkinson's disease during the execution of locomotor tasks (PD). This proprioceptive deficit also plays an important role in the occurrence of freezing of gait (FOG). Thus, the main objective of this Doctoral Thesis was to determine the effects of proprioceptive system manipulation, by means of a muscle vibration system, on the performance of locomotor tasks in people with Parkinson's disease, and on the severity FOG episodes. However, due to a number of difficulties, it was necessary to develop and optimize a homemade vibration system that could fulfill our requirements. To this, we also aimed: to describe the development of a homemade vibratory system and its reliability; to optimize the parameters of muscle vibration to promote an improvement in the performance of sit-to walk and gait initiation in healthy young adults. It had been shown that the homemade vibratory system developed here (named RCVibro System) is highly reliable and elicits similar results to those reported in the literature. The best way to apply muscle vibration is in parallel to muscle fibers and on the proximal region of muscle bellies. As a result, we observed an improvement of gait initiation performance when the vibration is applied only before the movement onset. Additionally, we observed no vibratory effects on the sit-to-walk performance in healthy young adults. On the other hand, the sit-to-walk performance of people with PD are disturbed by muscle vibration, possibly by an overstimulation of the proprioceptive system. We also found an improvement of gait initiation performance of people with PD and FOG when muscle vibration is applied before the movement onset. Postural effects elicited by the proprioceptive system manipulation are suggested to be the mechanism underlying these results. Manipulation of the proprioceptive system also promoted an alleviation of FOG episodes severity, when vibration was applied before FOG onset. However, muscle vibration fails to prevent FOG, leading to worse severity of this phenomenon when it was applied prior to FOG onset. These results suggest that the manipulation of the proprioceptive system has a beneficial effect only to facilitate the movement onset in people with PD and FOG. On the other hand, results suggest that muscle vibration has a deleterious effect when it is applied during movement execution. All these results, taken together, highlight the role of proprioceptive deficits as a main mechanism underlying the motor deficits shown by people with PD during locomotor

tasks execution, and especially as a mechanism underlying FOG. Finally, we highlight the clinical potential of RCVibro System to facilitate gait initiation in people with PD and to reduce the severity of FOG episodes in this population.

Key words: Parkinson's disease. Freezing of gait. Proprioception. Muscle vibration. Locomotion.

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- AC: corrente de voltagem alternada (*alternate current*).
- A-P: antero-posterior.
- APA: ajuste postural antecipatório (*Anticipatory postural adjustment).*
- Be: condição de vibração aplicada somente antes da execução do movimento.
- CoM: centro-de-massa (*Center-of-mass*).
- CoP: centro-de-pressão (*Center-of-pressure*).
- CV: Coeficiente de variação (*coefficient of variation*).
- DC: corrente de voltagem direta (*direct current*).
- DP: doença de Parkinson.
- Du: condição de vibração durante a execução do movimento.
- FI: índice de fluidez (*fluidity index*).
- FOG: congelamento da marcha (*Freezing of gait*).
- FOG+: pessoas com doença de Parkinson e congelamento da marcha.
- GI: iniciar o andar (*Gait initiation*).
- GRF: força de reação do solo (*Ground reaction force*).
- HC: idosos do grupo controle, sem comprometimentos neurológicos (*Healthy Control*).
- ICC: coeficiente de correlação intra-classe (*Intraclass Correlation Coefficient*).
- IRED: luz infravermelha (*infrared*).
- LA: condição em que a vibração muscular foi aplicada no membro inferior menos afetado pela doença (*least affected lower limb*).
- LM: fase de locomoção na tarefa de iniciar o andar (*Locomotor phase*).
- MA: condição em que a vibração muscular foi aplicada no membro inferior mais afetado pela doença (*most affected lower limb*).
- M-L: medio-lateral.
- MoCA*: Montreal Cognitive Assessment.*
- MV: velocidade média (*mean velocity*).
- NB: núcleos da base.
- NFOG: grupo de pessoas com doença de Parkinson sem congelamento da marcha.
- NonVib: condição sem vibração (*No vibration*).

- OFF: Condição experimental sem o uso da vibração muscular.
- ON: Condição experimental com o uso da vibração muscular.
- PA: fase de ajuste postural na tarefa de iniciar o andar (*Postural Adjustment phase*).
- PC: computador pessoal (*personal computer*).
- PD: doença de Parkinson *(Parkinson's disease*) / grupo de pessoas com doença de Parkinson.
- PSD: densidade de poder espectral (*power spectral density*).
- PVC: *non-toxic polyvinyl chloride*.
- SD: desvio-padrão (*standard deviation*).
- SO: músculo sóleo (*soleus muscle*).
- t_0: instante de início da tarefa.
- TA: tibial anterior (*tibialis anterior*).
- UPDRS-III: subescala motora da *Unified Parkinson's Disease Rating Scale.*
- USB: *universal serial bus.*
- Vib: condição experimental com uso da vibração muscular.
- WT: fase de transição do peso na tarefa de iniciar o andar (*Weight transfer phase*).

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1. INTRODUÇÃO

Nessa primeira sessão dessa Tese de Doutorado será apresentada uma breve revisão de literatura abordando os temas discutidos nas demais sessões, bem como as perguntas de pesquisa que norteiam a realização desse trabalho. A Introdução foi dividida em três grandes tópicos apresentados na sequência

1.1. Doença de Parkinson

1.1.1. Epidemiologia e Fisiopatologia da doença de Parkinson.

A doença de Parkinson (DP) é a segunda doença neurodegenerativa mais incidente em indivíduos acima dos 60 anos de idade (OLANOW; STERN; SETHI, 2009), tendo sido relatada uma prevalência de 3,3% na população brasileira em pessoas com mais de 64 anos de (BARBOSA et al., 2006). A DP é caracterizada pelos seguintes sinais e sintomas: tremor de repouso, bradicinesia (lentidão na velocidade do movimento), rigidez, déficits no equilíbrio, comprometimentos da marcha (como redução do comprimento passo – hipocinesia), dificuldades de iniciar o movimento (acinesia) e em casos mais avançados da doença, o congelamento da marcha (*freezing of gait* – FOG) (DELVAL; TARD; DEFEBVRE, 2014; HEREMANS; NIEUWBOER; VERCRUYSSE, 2013; PEREIRA; PELICIONI; GOBBI, 2013; VITORIO et al., 2011). Além desses sintomas motores, os pacientes com DP também apresentam uma série de sintomas não motores como depressão, ansiedade, distúrbios do sono, desequilíbrio do sistema entérico, entre outros (PEREIRA; BATISTELA; SIMIELI, 2014). Apesar de os sintomas não motores terem um grande impacto na qualidade de vida de pessoas com DP (PEREIRA; BATISTELA; SIMIELI, 2014), a presente Tese de Doutorado tem como foco de investigação a locomoção dessas pessoas, sobretudo daquelas que apresentam FOG. Esses déficits locomotores, além de serem responsáveis pela queda de qualidade de vida desses indivíduos, levam a uma maior dependência física e também os predispõem a uma maior ocorrência de quedas (VITÓRIO; LIRANI-SILVA; PELICIONI, 2013) – cerca de 68% dos pacientes com DP caem pelo menos uma vez ao ano, sendo essa a segunda causa de hospitalização nessa população (TEMLETT; THOMPSON, 2006).

A principal característica fisiopatológica responsável pelos sintomas da DP é a degeneração das células dopaminérgicas da substância negra, parte compacta (OLANOW; STERN; SETHI, 2009). Essa estrutura é componente dos núcleos da base, localizados no mesencéfalo, os quais mantém íntimo contato com os centros locomotores e sensoriais do tronco cerebral, bem como com as mais diversas áreas corticais (DELONG; WICHMANN, 2009). Entretanto, a DP não caracteriza-se apenas pela degeneração isolada dos neurônios da substância negra parte compacta. Alguns estudos têm evidenciado que, em pessoas com DP, outras estruturas também apresentam certo nível de disfunção, como por exemplo o córtex (BRAAK et al., 2004). Ainda, outros núcleos de processamento também são afetados, como o de Meynert (TAGLIAVINI et al., 1984), o cerebelo (LEWIS et al., 2011), o núcleo subtalâmico e o globo pálido (HELMICH et al., 2011).

1.1.2. Déficits proprioceptivos na doença de Parkinson

Ainda não há total clareza na literatura sobre qual a principal estrutura responsável pelo processamento de informações proprioceptivas, entretanto alguns estudos têm indicado que o núcleo subtalâmico e o globo pálido têm um papel fundamental no processamento dessas informações (KONCZAK et al., 2009), respondendo com efeito, em condições normais, ao movimento passivo - o que indica seu papel no processamento cinestésico (RODRIGUEZ-OROZ et al., 2001). Portanto, alguns estudos têm apontado que, em consequência da degeneração dos neurônios do núcleo subtalâmico e do globo pálido, pessoas com DP apresentam déficits cinestésicos que indivíduos saudáveis (ZIA; CODY; O'BOYLE, 2000).

Esses déficits, em pessoas com DP, têm sido observados pelo maior limiar de detecção do movimento passivo (KONCZAK et al., 2007), menor capacidade de reproduzir tanto a amplitude como a velocidade de um membro quando esse é movimentado passivamente (DEMIRCI et al., 1997) e pela dificuldade em reproduzir níveis-alvo de força (KHUDADOS; CODY; O'BOYLE, 1999; TAN; ALMEIDA; RAHIMI, 2011). Ainda, esses déficits proprioceptivos têm sido apontados como responsáveis pela instabilidade postural nesses indivíduos (KONCZAK et al., 2009), logo que piores níveis de coordenação postural são observados em pessoas com DP apenas em condições de maior dependência do sistema proprioceptivo (JACOBS; HORAK, 2006). Reforçando a hipótese de que a instabilidade postural é decorrente de déficits

cinestésicos, ambos os sintomas são resistentes ao tratamento medicamentoso (KONCZAK et al., 2009), indicando que outros sistemas, além do dopaminérgico, sejam responsáveis pelo maior desequilíbrio apresentado por essas pessoas. Apesar de não poder ser descartada, a participação do sistema vestibular parece ser pouco afetada pela DP (PASTOR; DAY; MARSDEN, 1993), reforçando a ideia de que déficits no sistema somatosensorial têm uma importante participação na instabilidade postural desses indivíduos (KONCZAK et al., 2009). Os déficits proprioceptivos em pessoas com DP são também responsáveis pelo pior desempenho locomotor dessas pessoas em algumas tarefas de transição, como o iniciar o andar (JACOBS; HORAK, 2006) e o levantar e andar (BUCKLEY; PITSIKOULIS; HASS, 2008). Ainda, esses déficits também são apontados como principais responsáveis por fenômenos locomotores anormais, como os episódios de FOG (EHGOETZ MARTENS; PIERUCCINI-FARIA; ALMEIDA, 2013b), sejam esses os que ocorrem durante ou ao iniciar o andar.

1.2. Déficits locomotores na doença de Parkinson

1.2.1. Doença de Parkinson e a tarefa de levantar e andar

A tarefa de levantar e andar, definida como a transferência do corpo à frente durante o levantar, antes que seja adotada a postura ereta, com intuito de executar o primeiro passo (MAGNAN; MCFADYEN; ST-VINCENT, 1996), tem grande validade ecológica, logo que são raras as ocasiões em que um indivíduo se levanta, sem iniciar o passo (ABERG; FRYKBERG; HALVORSEN, 2010). Apesar dessa tarefa já ter sido amplamente investigada em indivíduos jovens, em idosos saudáveis e em idosos com histórico de quedas, o número de estudos que a investigou em pessoas com DP é bastante restrito (BUCKLEY; PITSIKOULIS; HASS, 2008). Segundo Kerr et al. (2013), a avaliação detalhada dessa tarefa pode trazer novos *insights* sobre as diferenças no comportamento motor de indivíduos saudáveis e com diferentes níveis de instabilidade postural (KERR et al., 2013).

Espera-se que indivíduos saudáveis possam ser capazes de realizar o levantar e andar de forma contínua e fluídica, sem ou com mínima separação entre os dois componentes da tarefa: o componente postural (ficar em pé a partir de uma postura sentada) e o componente locomotor (iniciar a marcha) (KERR et al., 2013). Alguns estudos têm evidenciado um pior desempenho nessa tarefa em indivíduos idosos com

risco de quedas (ABERG; FRYKBERG; HALVORSEN, 2010; CHEN; CHOU, 2013; KERR et al., 2013) e com DP (BUCKLEY; PITSIKOULIS; HASS, 2008). Em especial neste último grupo, foi argumentado que a incapacidade desses indivíduos de integrar dois programas motores (BENECKE et al., 1987) possa também privá-los de realizar essa tarefa de forma mais fluídica (BUCKLEY; PITSIKOULIS; HASS, 2008). Segundo Buckley et al. (2008), pessoas com DP não são capazes de aproveitar a geração de momentum anterior do centro de massa (CoM) gerado no momento de perda de contato com assento, iniciando o primeiro passo com menor força potencial na direção anterior (BUCKLEY; PITSIKOULIS; HASS, 2008). Assim, sugere-se que promover um deslocamento involuntário do corpo à frente no momento de levantar da cadeira poderia ajudar pacientes com DP a integrar os componentes motores da tarefa de levantar e andar.

Entretanto, a adoção de um padrão mais conservador de movimento em pessoas com instabilidade postural (inclusive em pessoas com DP) também tem sido citada como responsável pela menor fluidez de movimento na execução do levantar e andar (BUCKLEY et al., 2009; BUCKLEY; PITSIKOULIS; HASS, 2008). Ao adotar esse padrão de movimento, os indivíduos primeiro atingem a postura em pé e só então iniciam a marcha – dando-lhes maior estabilidade para iniciar o primeiro passo (BUCKLEY et al., 2009). Portanto, espera-se que melhores níveis de estabilidade possam produzir melhores desempenhos na realização dessa tarefa de transição, também em indivíduos com DP (BUCKLEY; PITSIKOULIS; HASS, 2008).

1.2.2. Doença de Parkinson e os episódios de congelamento durante a marcha

Uma linha de pensamento tem argumentado que déficits sensório-perceptuais, especialmente distúrbios no sistema proprioceptivo, também são responsáveis pela ocorrência de episódios de FOG (ALMEIDA; LEBOLD, 2010; EHGOETZ MARTENS; ELLARD; ALMEIDA, 2014; EHGOETZ MARTENS; PIERUCCINI-FARIA; ALMEIDA, 2013b; TAN; ALMEIDA; RAHIMI, 2011). Os episódios de FOG são mais observados em tarefas locomotoras, apesar de serem também encontrados nos membros superiores (NIEUWBOER et al., 2009b). Dois subtipos de FOG são normalmente relatados: os que ocorrem durante o andar e aqueles que ocorrem ao iniciar o andar a partir da postura ereta (NIEUWBOER; GILADI, 2013). De modo geral, episódios de FOG são definidos como "*uma breve e episódica ausência ou redução da progressão*

do pé à frente, apesar da intenção de andar" (NUTT et al., 2011). Esse fenômeno afeta um grande número de pacientes em estágios mais avançados da DP (MORRIS; IANSEK; GALNA, 2008). Têm-se argumentado que os episódios de FOG são uma expressão mais severa da DP e que, invariavelmente, todos os pacientes acabarão por experimentar esse fenômeno em algum momento (NIEUWBOER; GILADI, 2013). De acordo com a teoria levantada por uma série de estudos (ALMEIDA; LEBOLD, 2010; EHGOETZ MARTENS; ELLARD; ALMEIDA, 2014; EHGOETZ MARTENS; PIERUCCINI-FARIA; ALMEIDA, 2013b; TAN; ALMEIDA; RAHIMI, 2011), pessoas com DP que apresentam episódios de FOG (FOG+) têm um déficit na geração de dicas internas (TAN; ALMEIDA; RAHIMI, 2011), levando à redução na geração do ritmo motor (HAUSDORFF et al., 2003) e, em consequência da diminuição desse ritmo, o passo se torna tão comprometido que blocos motores são suscitados (CHEE et al., 2009). Essa teoria é sustentada pelos resultados do estudo de Ehgoetz Martens et al. (2013), que manipulou a informação sensorial em FOG+ durante a marcha, observando maior ocorrência de episódios de FOG quando os indivíduos dependiam exclusivamente do sistema proprioceptivo para a realização da tarefa (EHGOETZ MARTENS; PIERUCCINI-FARIA; ALMEIDA, 2013a). Os resultados do estudo de Tan et al. (2011), em que o sistema proprioceptivo foi manipulado durante a tarefa de reprodução de níveis de força, reforça o papel dos comprometimentos proprioceptivos como mecanismo importante na ocorrência de episódios de FOG (TAN; ALMEIDA; RAHIMI, 2011): ao perturbar o sistema proprioceptivo durante uma tarefa de reprodução de força de extensão do joelho, os indivíduos do grupo que apresentavam FOG tiveram um pior desempenho que seus pares saudáveis (TAN; ALMEIDA; RAHIMI, 2011). Já Khudados et al. (1999) demonstraram evidências que, quando a manipulação do sistema proprioceptivo foi aplicada de maneira a facilitar a tarefa de reprodução de força de tornozelo, houve menores níveis de erro em pessoas com DP (KHUDADOS; CODY; O'BOYLE, 1999). Portanto, em linha com essa teoria, a manipulação do sistema proprioceptivo de forma a facilitar a realização de uma tarefa motora, poderia resultar em melhora do desempenho de tarefas locomotoras em FOG+. Dando um passo adiante, sugerimos que a estimulação do sistema proprioceptivo poderia também evitar ou aliviar a severidade de episódios de FOG.

A busca de estratégias que reduzam a ocorrência/severidade dos episódios de FOG é de grande importância para a prática clínica e para o dia-a-dia dessas pessoas, logo que a eficácia do tratamento medicamentoso sobre a severidade desse

fenômeno ainda permanece em discussão (NIEUWBOER; GILADI, 2013). Diversas estratégias já foram desenvolvidas para promover o alívio da severidade dos episódios de FOG ou para promover o melhor desempenho locomotor em FOG+. Esses estudos evidenciaram efeitos positivos de dicas externas, como visuais, auditivas e táteis sobre esse fenômeno (BURLEIGH-JACOBS et al., 1997; LEE et al., 2012; VERCRUYSSE et al., 2012). Entretanto, o efeito da manipulação proprioceptiva com esse mesmo fim ainda carece de maiores esclarecimentos. Entre os poucos trabalhos que manipularam diretamente o sistema proprioceptivo, destaca-se o estudo de Winfree et al. (2013). Esse estudo encontrou melhoras na marcha de FOG+ após uma semana de treinamento, duas vezes por dia, de estimulação proprioceptiva aplicada na sola dos pés (WINFREE et al., 2013). Nessa mesma linha de resultados, outros estudos também encontraram melhora no desempenho de iniciar a marcha em FOG+ com a estimulação do sistema somatosensorial (BURLEIGH-JACOBS et al., 1997). Por fim, concordando com esses achados, Jacobs et al. (2006) encontraram piores resultados na execução de passos compensatórios em FOG+ quando esses dependiam em maior grau de informações proprioceptivas, sugerindo que essas pessoas têm um déficit na integração proprioceptiva-motora (JACOBS; HORAK, 2006). Portanto, os resultados desses estudos, considerados em conjunto, sugerem que a estimulação do sistema somatosensorial, e sobretudo do sistema proprioceptivo, poderia resultar em melhores desempenhos nos dois principais subtipos de FOG: aqueles disparados durante o andar e também naqueles episódios que ocorrem ao iniciar o andar. Entretanto, os efeitos *online* da manipulação do sistema proprioceptivo sobre a ocorrência e severidade dos episódios de FOG durante o andar e sobre o desempenho do iniciar a marcha em FOG+ permanecem pouco explorados. Outra teoria mais recente tem sugerido que a dissociação de diferentes vias neurais também é responsável pela ocorrência de episódios de FOG durante a marcha; em que o mecanismo subjacente aos episódios de FOG está na dissociação entre as vias frontoestriatais (SHINE et al., 2013c; SHINE et al., 2013d; VERCRUYSSE et al., 2014). De acordo com a teoria de dissociação frontoestriatal (SHINE et al., 2013d), FOG+ apresentam uma reserva neural insuficiente (já alocada para superar a falta de automaticidade de movimentos sequenciais – HEREMANS et al., 2013) e qualquer informação adicional conflitante levaria a um *crosstalk* entre diferentes circuitos (SHINE et al., 2013d; SHINE; NAISMITH; LEWIS, 2011). Como consequência, há um disparo anormal de informações eferentes do globo pálido,

inibindo centros motores do tronco cerebral, como o núcleo pedúnculo-pontino, que é considerado um importante centro de controle da marcha (SHINE et al., 2013d; SHINE; NAISMITH; LEWIS, 2011). A dissociação entre as vias frontoestriatais explica a inabilidade de FOG+ em alternar entre demandas atencionais concorrentes (SHINE et al., 2013e). Esse prejuízo em alternar entre demandas atencionais pode explicar o efeito deletério de tarefas duplas na ocorrência de episódios de FOG (SPILDOOREN et al., 2010) e, também, pode explicar os efeitos positivos de dicas externas no desempenho motor de FOG+ (NIEUWBOER et al., 2009a): dicas externas podem direcionar a atenção, auxiliando essas pessoas a focarem na execução do plano motor desejado (HEREMANS et al., 2013).

1.2.3. Doença de Parkinson e os episódios de congelamento durante o iniciar o andar

Os episódios de FOG durante o iniciar o andar são definidos como *"um atraso ou uma completa incapacidade de iniciar o passo"* (JACOBS et al., 2009). O iniciar o andar, em pessoas com DP, caracteriza-se por ser hipocinético (reduzido comprimento do primeiro passo) e bradicinético (menor velocidade do passo) em comparação aos seus pares saudáveis (DELVAL; TARD; DEFEBVRE, 2014; HALLIDAY et al., 1998; HASS et al., 2005). O desempenho desse primeiro passo durante o iniciar o andar está intimamente ligado ao comportamento de ajustes posturais prévios à iniciação desse passo (BRENIERE; CUONG DO; BOUISSET, 1987; HALLIDAY et al., 1998). Esses ajustes são chamados de ajustes posturais antecipatórios (APA) e no iniciar o andar são bastante característicos para a liberação do pé de balanço do chão, onde se observa um deslocamento anterior do CoM na direção do pé de apoio e um deslocamento do centro-de-pressão (CoP) na direção do pé de balanço - posterior e lateral (BRENIERE; CUONG DO; BOUISSET, 1987) O comportamento da fase de APA em pacientes com DP é também bradicinético e hipocinético, o que justifica o pior desempenho no iniciar o andar nessa população (DELVAL; TARD; DEFEBVRE, 2014; DIBBLE et al., 2004; HALLIDAY et al., 1998). Entretanto, o comportamento durante a fase de APA de FOG+ e de pessoas com DP que não apresentam FOG (NFOG) não é marcadamente diferente (DELVAL et al., 2014). Portanto, como o desempenho do primeiro passo no iniciar a marcha está intimamente ligado à execução da fase de APA (BRENIERE; CUONG DO; BOUISSET,

1987), foi necessária a criação de um novo modelo de disfunção do sistema locomotor para explicar a ocorrência de blocos motores durante o iniciar o andar em FOG+.

Segundo esse novo modelo, a maior dificuldade em distribuir o peso corporal durante a execução do passo em FOG+ tem papel definitivo na ocorrência de episódios de FOG durante o iniciar o andar (BURLEIGH-JACOBS et al., 1997; NANTEL; DE SOLAGES; BRONTE-STEWART, 2011; VERVOORT et al., 2013). Nantel et al. (2011) encontraram uma menor e menos eficiente transferência médio-lateral do peso entre os membros durante uma tarefa de marchar no lugar, sendo essa incapacidade altamente relacionada com a ocorrência de FOG (NANTEL; DE SOLAGES; BRONTE-STEWART, 2011). Da mesma forma, um pior controle voluntário do CoM, principalmente no sentido ântero-posterior foi encontrado em FOG+ (VERVOORT et al., 2013). Essa menor capacidade de controle do CoM justifica porque episódios de FOG são mais frequentes durante a marcha que no iniciar o andar (SCHAAFSMA et al., 2003): no primeiro caso, o CoM se desloca à frente dos pés, diferentemente do que ocorre durante o iniciar o andar (JACOBS et al., 2009). Assim, de acordo com essa teoria que preconiza que déficits na distribuição de peso contribuem para a ocorrência de FOG (BURLEIGH-JACOBS et al., 1997; NANTEL; DE SOLAGES; BRONTE-STEWART, 2011; VERVOORT et al., 2013), sugere-se que o uso de mecanismos que possam facilitar os ajustes posturais necessários para se iniciar a marcha poderiam melhorar o desempenho dessa tarefa em pessoas com FOG. De fato, alguns trabalhos já evidenciaram que a manipulação da distribuição de peso durante a fase de APA pode facilitar o iniciar o andar em pessoas com DP (CREATH et al., 2013; MILLE et al., 2009; ROGERS et al., 2011). Entretanto, essa manipulação ainda está restrita aos ambientes de pesquisa, tendo sido realizada apenas no sentido médio-lateral por meio de plataformas móveis ou dispositivos não portáteis (CREATH et al., 2013; MILLE et al., 2009). Portanto, existe a necessidade de desenvolver e de testar a eficácia de um sistema que seja portátil e que possa facilitar os ajustes posturais no sentido ântero-posterior em pessoas com FOG, facilitando assim, a execução do iniciar o andar dessas pessoas.

Entretanto, os achados de Jacobs et al. (2009) sugerem que a dificuldade apresentada por pacientes com FOG em iniciar o andar não é fruto dos déficits na realização de APAs em si, mas sim da dificuldade de integrar planos motores originados em vias neurais diferentes: os ajustes posturais e a execução do passo *per si* (JACOBS; HORAK, 2006). Segundo um modelo proposto por Massion et al. (1992),

o processamento dos APAs se dão ao nível dos NB e da área motora suplementar, enquanto o processamento de tarefas volitivas se dá em regiões como a área pré-motora dorsolateral e o córtex motor primário (MASSION, 1992). Esses circuitos são então integrados nos centros posturais e locomotores do tronco cerebral (TAKAKUSAKI et al., 2003). Jacobs et al. (2009) sugeriram que déficits na integração entre esses circuitos cerebrais poderia levar as pessoas com DP a falhar também na integração entre os ajustes posturais e a execução do passo (JACOBS et al., 2009).

1.3. Uso da vibração muscular como alternativa de intervenção em pessoas com doença de Parkinson

As tarefas de levantar e andar e de iniciar o andar são realizadas frequentemente durante o dia-a-dia (ABERG, FRYKBERG & HALVORSEN, 2010) e portanto, o sucesso na execução dessas tarefas pode ter um alto impacto na qualidade de vida de pessoas com DP. Como já discutido anteriormente, a ocorrência de episódios de FOG também podem afetar consideravelmente a independência e a qualidade de vida dessas pessoas (PEREZ-LLORET et al., 2014). Portanto, estratégias de intervenção, além da medicamentosa, devem promover uma melhora na execução da tarefa de iniciar o andar e de levantar e andar e também reduzir a severidade e/ou ocorrência dos episódios de FOG.

Considerando os déficits motores responsáveis pelo pior desempenho de pessoas com DP na execução da tarefa de iniciar o andar, essas estratégias de intervenção devem promover ajustes posturais no sentido ântero-posterior (RUGET et al., 2010) e facilitar a execução/integração de planos motores automáticos (RUGET et al., 2010). Já estratégias que busquem o aumento do desempenho da tarefa de levantar e andar nessa população, devem, além de atender os dois objetivos anteriores, promover uma manipulação do sistema proprioceptivo, logo que esse tem um papel bastante importante durante a execução dessa tarefa (BUCKLEY et al., 2009). Por fim, com intuito de diminuir a ocorrência/severidade dos episódios de FOG, essas estratégias alternativas de intervenção devem promover, além de um estímulo proprioceptivo, uma manipulação de recursos atencionais, logo que ambos mantêm uma íntima relação com a ocorrência desse fenômeno (HEREMANS et al., 2013; TAN et al., 2011).

Uma ferramenta que engloba todas essas características é a vibração muscular que, além de estimular o sistema proprioceptivo (BURKE et al., 1976b; ROLL; VEDEL, 1982), promove a ativação involuntária dos músculos estimulados (GURFINKEL et al., 1998) e suscita ajustes posturais consideráveis (CAPICIKOVA et al., 2006; COURTINE et al., 2007a; THOMPSON; BELANGER; FUNG, 2007). Todas essas características podem ter efeitos positivos sobre a locomoção de pessoas com DP, principalmente nas que apresentam FOG, como veremos mais adiante.

1.3.1. Fisiologia da vibração muscular

A vibração muscular é normalmente aplicada utilizando-se de pequenos dispositivos cilíndricos, contendo um motor no qual é afixada, no seu eixo, uma carga excêntrica (UIMONEN et al., 1996). Os efeitos dessa técnica em humanos foram demonstrados inicialmente em meados da década de 1970 e têm sido expandidos até os dias atuais (BURKE et al., 1976a; BURKE et al., 1976b; DUCLOS, N. C. et al., 2014), revelando que essa ainda é uma temática importante. Grande parte do interesse sobre os efeitos da vibração muscular se baseia em achados positivos dessa técnica na locomoção de pessoas com sequelas pós-acidente vascular encefálico (KAWAHIRA et al., 2004), com lesões medulares parciais (COTEY et al., 2009) e também em pessoas com DP (DE NUNZIO et al., 2010; GHOSEIRI et al., 2009; HAN et al., 2014).

O principal efeito fisiológico da vibração muscular é a excitação das fibras sensoriais dos fusos neuromusculares (BURKE et al., 1976a; RIBOT-CISCAR; ROSSI-DURAND; ROLL, 1998). Os fusos neuromusculares são mecanoreceptores posicionados em paralelo com as fibras musculares extrafusais e respondem ao alongamento muscular (MEYER-LOHMANN; RIEBOLD; ROBRECHT, 1974). Apesar de haver certa excitação também das fibras sensoriais secundárias (BURKE et al., 1976a), são as primárias (fibras Ia) as que respondem de forma mais importante aos estímulos mecânicos promovidos pela vibração (ROLL; VEDEL, 1982). Como as fibras sensoriais do fuso neuromusuclar têm um papel cinestésico fundamental, sendo determinante para a percepção da posição dos membros no espaço (ROLL; VEDEL, 1982), assume-se que o uso da vibração muscular promove uma excitação do sistema proprioceptivo (BURKE et al., 1976a; RIBOT-CISCAR; ROSSI-DURAND; ROLL, 1998). Em acordo com essa afirmação, alguns estudos demonstraram evidências de

que a vibração muscular quando aplicada de maneira relevante à tarefa, ou seja, com intuito de facilitar sua execução, é capaz de diminuir o erro de reprodução de níveis de força, inclusive em pessoas com DP (KHUDADOS; CODY; O'BOYLE, 1999).

1.3.2. Efeitos globais da vibração muscular e sua aplicabilidade na doença de Parkinson

Como sugerido anteriormente, déficits no processamento proprioceptivo têm um papel importante no pior desempenho na execução das tarefas de levantar e andar e de iniciar o andar em pessoas com DP e também estão intimamente relacionados com os episódios de FOG. Portanto, sugerimos que a vibração muscular poderia ser utilizada para estimular esse sistema e, assim, promover melhoras na execução desses padrões locomotores nessas pessoas, ou mesmo promover um alívio na ocorrência e/ou severidade dos episódios de FOG.

De Nunzio et al. (2008) demonstraram evidências de que a vibração muscular promoveu, em pessoas com DP, oscilações posturais rítmicas em sincronia com a frequência de pulsos de vibração, indicando que essa técnica pode ser utilizada para promover ajustes posturais durante a postura em pé (DE NUNZIO et al., 2008). De fato, os efeitos posturais da vibração muscular já foram amplamente investigados (CAPICIKOVA et al., 2006; COURTINE et al., 2007a; POLONYOVA; HLAVACKA, 2001; RUGET et al., 2010; THOMPSON; BELANGER; FUNG, 2007; VALKOVIC; KRAFCZYK; BOTZEL, 2006; WIERZBICKA; GILHODES; ROLL, 1998). A vibração, quando aplicada nos músculos do membro inferior, promove um deslocamento do corpo em direção ao músculo estimulado (CAPICIKOVA et al., 2006; COURTINE et al., 2007a; POLONYOVA; HLAVACKA, 2001). Esse efeito é resultado da sensação ilusória de alongamento do músculo que recebe a vibração (COURTINE et al., 2007a). Ou seja, a sensação ilusória de alongamento dá uma impressão ao indivíduo de que seu corpo está se deslocando na direção contrária ao músculo que está sendo estimulado e, para readquirir o equilíbrio, o indivíduo se desloca, equivocamente, na direção da estimulação (CAPICIKOVA et al., 2006). Após a interrupção da vibração, observa-se um efeito bastante interessante: os indivíduos retornam a posição do corpo além da posição original (CAPICIKOVA et al., 2006; DUCLOS, N. C. et al., 2014; THOMPSON; BELANGER; FUNG, 2007). Por exemplo, quando o músculo

gastrocnêmio é estimulado pela vibração durante a postura ereta, o CoP desloca-se posteriormente (CAPICIKOVA et al., 2006; COURTINE et al., 2007a). Entretanto, após o estímulo ser encerrado, o posicionamento do CoP desloca-se mais à frente que sua posição original (CAPICIKOVA et al., 2006; DUCLOS, N. C. et al., 2014; THOMPSON; BELANGER; FUNG, 2007).

Assim, como o uso de perturbações posturais facilitam a execução de tarefas transacionais em pessoas com DP e com FOG (CREATH et al., 2013; MILLE et al., 2009; ROGERS et al., 2011), sugere-se que a vibração muscular pode trazer grande benefício para essas pessoas: além de estimular o sistema proprioceptivo (BURKE et al., 1976b; ROLL; VEDEL, 1982), a vibração muscular também promove perturbações posturais (CAPICIKOVA et al., 2006; COURTINE et al., 2007a; POLONYOVA; HLAVACKA, 2001; WIERZBICKA; GILHODES; ROLL, 1998). Essa ferramenta tem, ainda, a vantagem de ser portátil e, portanto, pode ser utilizada pelos indivíduos a qualquer momento.

Estendendo os efeitos da vibração muscular, o estudo de Gurfinkel et al. (1998), replicado recentemente para postura em pé (DUCLOS, C. et al., 2014), demonstrou que, ao se aplicar a vibração em diversos músculos do membro inferior, quando este está suspenso, pode-se disparar involuntariamente padrões de movimento semelhantes ao do andar (GURFINKEL et al., 1998). Da mesma forma, o estudo de Ivanenko et al. (2000) demonstrou que ao se aplicar a vibração em músculos do membro inferior durante passos no lugar, observa-se um aumento da velocidade de deslocamento do corpo à frente (IVANENKO; GRASSO; LACQUANITI, 2000). Esses achados sugerem que a vibração muscular é capaz de ativar os geradores centrais de padrão localizados na medula espinhal, facilitando a execução de passos (DUCLOS, C. et al., 2014; GURFINKEL et al., 1998; IVANENKO; GRASSO; LACQUANITI, 2000). De fato, foi sugerido que a ativação desses centros é o principal mecanismo responsável pelos efeitos benéficos da vibração na marcha de pessoas com DP (DE NUNZIO et al., 2010). Assim, como pessoas com DP e especialmente os FOG+ apresentam dificuldades de integrar diferentes planos motores (JACOBS; HORAK, 2006), sugerimos que a vibração muscular aplicada durante a execução de uma tarefa essencialmente postural (como o levantar ou a fase de APA no iniciar o andar), pode, por meio do estímulo dos geradores centrais de padrão, auxiliar essas pessoas a iniciarem o andar mais rapidamente, facilitando a integração dos planos motores posturais e locomotores.

Por fim, como discutido anteriormente, a vibração muscular pode auxiliar a locomoção de pessoas com DP e que experimentam FOG ao funcionar como uma dica externa, auxiliando essas pessoas a mudarem o foco de atenção para a tarefa a ser realizada. Portanto, considerando todos esses achados, sugere-se que a manipulação do sistema proprioceptivo, por meio da vibração muscular, possa trazer, para pessoas com DP e sobretudo para aqueles que apresentam episódios de FOG, benefícios na execução de tarefas locomotoras de transição, como o levantar e andar e o iniciar o andar. Ainda, sugere-se que essa manipulação do sistema proprioceptivo possa, também, trazer alivio na severidade de episódios de FOG disparados durante o andar.

1.3.3. Dificuldades na aplicação da vibração muscular

Devido à inexistência de parâmetros de vibração pré-estabelecidos, uma série de dificuldades devem ser superadas antes de sugerirmos a aplicação da vibração muscular como alternativa terapêutica em pessoas com DP, principalmente por se tratar de uma população frágil e que necessita de cuidados especiais. Entre essas dificuldades, destaca-se a inexistência de dispositivos vibratórios comerciais desenvolvidos para fins de pesquisa e reabilitação e, portanto, faz-se necessária a criação de um sistema manufaturado de vibração, bem como, estabelecer padrões ótimos de aplicação desse sistema.

Os poucos trabalhos científicos que discriminam os dispositivos vibratórios utilizados (COURTINE et al., 2007a; LIN; HSU; WANG, 2012; TAN; ALMEIDA; RAHIMI, 2011) fornecem pouco ou nenhum detalhamento técnico para a reprodução desses sistemas. Ainda, os poucos estudos que o fazem (WINFREE et al., 2013), falham em descrever a reprodutibilidade desses sistemas, o que é particularmente importante, sobretudo quando é necessária a manipulação dos parâmetros de vibração (amplitude e/ou frequência). Assim, para atingir os objetivos dessa Tese de Doutorado, foi necessário desenvolver um sistema manufaturado de vibração muscular, que permitisse aplicar esse estímulo enquanto os indivíduos possam se mover livremente e, também, determinar os padrões ótimos de aplicação de vibração. Não só foi necessário desenvolver esse equipamento, mas também testá-lo quanto a sua reprodutibilidade e seus efeitos. Só então, após desenvolver e otimizar esse

equipamento, além de determinar os padrões ótimos de aplicação da vibração, pudemos utiliza-lo para atender nossos objetivos.

Entre os parâmetros que deveriam ser definidos antes da aplicação dessa técnica em pessoas com DP, destaca-se a frequência de vibração a ser utilizada. Sabe-se que maiores amplitudes de vibração promovem maiores efeitos fisiológicos (UIMONEN et al., 1996) e esse parece ser um tema já livre de discussão. Entretanto, o efeito da manipulação das frequências de vibração ainda permanece em aberto. Estudos clássicos de microneurografia evidenciaram que as fibras sensoriais primárias respondem na ordem de 1:1 a frequências de vibração entre 20 e 80Hz (ROLL; VEDEL, 1982). Entretanto, quando frequências mais altas são utilizadas, as fibras Ia são disparadas em frequências sub-harmônicas em relação à frequência de vibração, chegando a serem disparadas na ordem de 1:2 – por exemplo, ao se estimular os músculos flexores do punho com uma frequência de vibração de 200Hz foram observados maiores disparos das fibras Ia na frequência de 100Hz (MARTIN; PARK, 1997). Essa queda nas frequências de disparo das fibras Ia com maiores frequências de vibração são consequência da saturação de vias centrais ou mesmo por uma condição viscoelástica dos músculos estimulados (MARTIN; PARK, 1997; ROLL; VEDEL, 1982): como a vibração de músculos em repouso desencadeia uma contração involuntária, chamada de reflexo tônico de vibração, os músculos se tornam mais rígidos e, portanto, impedem a transmissão das ondas de vibração para fibras mais distantes do ponto de aplicação (MARTIN; PARK, 1997).

Esses estudos de microneurografia são bastante claros em apontar que frequências de vibração em torno de 70-80Hz são ótimas para o disparo das fibras primárias. Porém, ao comparar os efeitos de diferentes frequências de vibração sobre a postura ereta, Polonyova et al. (2001) encontraram maiores respostas em maiores frequências de vibração: 100Hz (POLONYOVA; HLAVACKA, 2001). Portanto, ainda parece haver certa discussão quanto à resposta postural às diferentes frequências de vibração. Assim, como as tarefas de levantar e andar e de iniciar o andar têm um grande componente postural (BRENIERE; CUONG DO; BOUISSET, 1987; MAGNAN; MCFADYEN; ST-VINCENT, 1996), investigar o efeito da manipulação da frequência de vibração sobre o desempenho dessas tarefas se faz de suma importância, para que a vibração possa resultar em maiores efeitos.

Essa investigação também deve se estender para o momento correto de aplicar a vibração com o intuito de melhorar o desempenho das tarefas de levantar e andar e

de iniciar o andar. Os efeitos da vibração sobre os fusos neuromusculares são bastante imediatos: os fusos iniciam seu disparo apenas 82ms após o início do estímulo vibratório, sendo esse comportamento também observado quando o estímulo é interrompido (CALVIN-FIGUIERE et al., 1999; RIBOT-CISCAR; ROSSI-DURAND; ROLL, 1998; VALKOVIC; KRAFCZYK; BOTZEL, 2006). Essa resposta imediata à vibração também é observada quando consideramos os efeitos posturais suscitados pela mesma (CAPICIKOVA et al., 2006): são iniciados tão logo a vibração é acionada e cessados imediatamente após a sua interrupção (CAPICIKOVA et al., 2006). Assim, quando se tem por objetivo disparar efeitos posturais com a vibração, deve-se aplica-la durante a realização da tarefa. Entretanto, alguns estudos também demonstraram evidências de que os efeitos vibratórios são minimizados ou totalmente ignorados durante a realização de movimentos voluntários mais vigorosos, possivelmente por uma supressão desse estímulo por comandos de níveis mais superiores (COURTINE et al., 2007a). Assim, aplicar a vibração muscular, por exemplo, durante a realização da tarefa de levantar e andar, poderia ser de pouca utilidade, logo que considerável nível de contração muscular é necessário para a realização dessa tarefa (DEHAIL et al., 2007). Entretanto, se a vibração muscular for aplicada antes do início da tarefa, seus efeitos podem não mais estarem presentes durante sua execução. A mesma dicotomia se aplica para a tarefa de iniciar o andar. Portanto, como o número de trabalhos que manipularam o sistema proprioceptivo durante essas tarefas é bastante escasso, faz-se necessária uma maior investigação sobre o melhor momento de aplicar a vibração muscular para aumento do seu desempenho.

Devido ao seu posicionamento em paralelo com as fibras musculares extrafusais, quando a vibração é aplicada no tendão, até 86,5% dos fusos neuromusculares apresentam algum nível de resposta (RIBOT-CISCAR; ROSSI-DURAND; ROLL, 1998). Entretanto, Eklund (1972) demonstrou que a aplicação da vibração no ventre muscular promove maior efeito que quando aplicada sobre o tendão (EKLUND, 1972). Esse último trabalho afirmou que a localização dos fusos neuromusculares (posicionados no próprio ventre muscular) seja o principal fator envolvido nesse resultado (UIMONEN et al., 1996). Sabe-se também que a sensibilidade dos fusos neuromusculares ao alongamento varia de acordo com a sua localização (MEYER-LOHMANN; RIEBOLD; ROBRECHT, 1974): fusos posicionados em regiões mais centrais e proximais do ventre muscular respondem mais facilmente ao alongamento (MEYER-LOHMANN; RIEBOLD; ROBRECHT, 1974). Como a

resposta dos fusos à vibração muscular pode ser considerada uma variante do reflexo de estiramento (BURKE et al., 1976b), pergunta-se se a posição dos fusos também é determinante para sua resposta à vibração muscular. Outros estudos também demonstraram evidências de que os fusos neuromusculares respondem apenas aos estímulos realizados ao seu redor (MEYER-LOHMANN; RIEBOLD; ROBRECHT, 1974) e, ainda, que quanto maior é a estimulação sensorial, maior tende a ser a sensação de movimento ilusório disparado pela vibração (RIBOT-CISCAR; HOSPOD; AIMONETTI, 2013). Assim, questiona-se, também, se a aplicação da vibração em regiões mais proximais ou distais do ventre e se a utilização de mais de um dispositivo vibratório no mesmo músculo, resultaria em maiores efeitos posturais.

Outra questão ainda pouco discutida é quanto à influência do posicionamento dos dispositivos vibratórios em relação às fibras musculares na resposta motora. O número de trabalhos que detalham esse posicionamento é bastante pequeno e há uma heterogeneidade entre eles. Alguns trabalhos descrevem o posicionamento em paralelo com as fibras musculares (BOVE; COURTINE; SCHIEPPATI, 2002; COURTINE et al., 2007a; VERSCHUEREN et al., 2002), enquanto outros descrevem um posicionamento em perpendicular (MARTIN; PARK, 1997; RIBOT-CISCAR; ROSSI-DURAND; ROLL, 1998; ROLL; VEDEL, 1982). Para nosso conhecimento, a influência desse posicionamento ainda foi pouco explorada. Em um primeiro momento, juntamente com a influência da posição de aplicação da vibração, a manipulação do posicionamento dos dispositivos vibratórios em relação às fibras musculares, parece ser de pouca importância, já que esses tópicos são pouco explorados pela literatura. Entretanto, a investigação dessas questões é de grande importância para a prática clínica, pois podem aumentar ainda mais os efeitos positivos da vibração muscular observados em pessoas com algum déficit motor (COTEY et al., 2009; DE NUNZIO et al., 2010; GHOSEIRI et al., 2009a; HAN et al., 2014; KAWAHIRA et al., 2004).

1.4. Perguntas de Pesquisa

Considerando todos os aspectos levantados nas Seções 1.1-1.3, algumas questões foram levantadas, como:

- A vibração muscular pode aumentar o desempenho das tarefas de levantar e andar e de iniciar o andar em indivíduos com DP, especialmente nos que apresentam episódios de congelamento da macha?
- A manipulação do sistema proprioceptivo, por meio da vibração muscular, pode resultar em um alívio na severidade dos episódios de congelamento da marcha em pessoas com DP?

Entretanto, ao considerarmos a inexistência de dispositivos comerciais ou de padrões-ouro de aplicação dessa técnica, faz-se necessário, responder outras questões, antes de sugerir sua aplicação em uma população frágil, como em pessoas com DP:

- É possível desenvolver um sistema manufaturado de vibração muscular que seja reprodutível e que reproduza os mesmos efeitos observados pela literatura?
- Qual o melhor posicionamento dos dispositivos vibratórios em relação às fibras e ao ventre muscular para suscitar efeitos posturais?
- Qual é a influência da manipulação tanto da frequência, quanto do momento de aplicação da vibração muscular para promover um aumento do desempenho na execução da tarefa de levantar e andar e de iniciar o andar?

Considerando todas as questões até aqui levantadas, delineamos essa Tese de Doutorado em três grandes Seções (3 a 5), onde discutimos respectivamente: (i) o desenvolvimento de um sistema portátil de vibração muscular; (ii) a otimização desse sistema e avaliação dos parâmetros de vibração a serem utilizados com intuito de facilitar a realização das tarefas de levantar e andar e de iniciar o andar; (iii) a aplicabilidade desse sistema de vibração com intuito de, durante tarefas locomotoras, manipular o sistema proprioceptivo de pessoas com DP, e em especial as que apresentam FOG. A discussão sobre esses temas é feita na forma de artigos científicos, sendo apresentados um total de oito artigos, a serem submetidos/publicados separadamente. Por fim, é apresentada uma seção de Considerações Finais onde são discutidos brevemente, os achados de cada um dos artigos científicos apresentados e sua relevância clínica.

2. OBJETIVOS E HIPÓTESES

Objetivos Gerais:

- Descrever o desenvolvimento de um sistema manufaturado de aplicação de vibração muscular;
- Determinar quais os melhores parâmetros de aplicação de vibração muscular, com intuito de promover um aumento no desempenho das tarefas de levantar e andar e iniciar o andar;
- Investigar os efeitos da manipulação do sistema proprioceptivo, por meio da vibração muscular, em tarefas locomotoras de pessoas com doença de Parkinson com e sem congelamento da marcha.

Objetivos Específicos:

- Descrever os detalhes técnicos, os efeitos e a reprodutibilidade de um sistema manufaturado de aplicação de vibração muscular;
- Determinar o melhor posicionamento dos dispositivos vibratórios, em relação às fibras musculares, e qual a melhor região do ventre muscular deve ser estimulada com o objetivo de suscitar efeitos posturais;
- Investigar o efeito da manipulação do momento e da frequência de vibração muscular com objetivo de melhorar o desempenho da tarefa de iniciar e andar e de levantar e andar em indivíduos jovens saudáveis;
- Avaliar o efeito da manipulação do sistema proprioceptivo, promovida por meio da vibração muscular, no desempenho da tarefa de levantar e andar e de iniciar o andar em indivíduos com doença de Parkinson com congelamento da marcha;
- Examinar os efeitos da manipulação proprioceptiva, promovida por meio da vibração muscular, sobre a severidade de episódios de congelamento da marcha em pacientes com doença de Parkinson.

Hipóteses:

- O sistema de vibração muscular desenvolvido nessa Tese de Doutorado será reprodutível e os seus efeitos serão semelhantes aos reportados pela literatura recente;

- Espera-se que o melhor posicionamento dos dispositivos vibratórios com intuito de suscitar efeitos posturais seja na região proximal do ventre muscular e em paralelo com as fibras musculares;
- A manipulação da frequência de vibração muscular não deve promover alterações no desempenho das tarefas de levantar e andar e de iniciar o andar em indivíduos jovens;
- A vibração muscular deve promover um aumento no desempenho da tarefa de iniciar e andar em indivíduos jovens, em idosos sem comprometimento neurológico e com doença de Parkinson quando aplicada apenas antes do início de execução da tarefa. Por outro lado, espera-se que a vibração muscular aumente o desempenho da tarefa de levantar e andar em todas as populações apenas quando aplicada durante a execução da tarefa.
- Espera-se que a vibração muscular promova um alívio da severidade dos episódios de FOG em indivíduos com doença de Parkinson.

3. DESENVOLVIMENTO DO RCVIBRO SYSTEM.

3.1. Apresentação

Nessa terceira Seção, apresentamos um artigo científico na forma de '*Technical Notes'* com os detalhamentos técnicos de um sistema de aplicação de vibração muscular (denominado RCVibro System). Como já mencionado anteriormente na Seção 1 (Introdução e Justificativa), não existem, no mercado, dispositivos desenvolvidos com fins de pesquisa e/ou reabilitação que contemplassem as nossas necessidades: ser um sistema portátil (para livre movimentação dos indivíduos), permitir a manipulação da frequência e do momento de aplicação da vibração e, principalmente, ser confiável quanto a sua reprodutibilidade. Dessa forma, fez-se necessário o desenvolvimento de um sistema manufaturado que pudesse contemplar todas essas exigências. Esse artigo científico também descreve, além dos detalhamentos técnicos, a reprodutibilidade do RCVibro System. Por fim, com intuito de checarmos se o RCVibro System é capaz de reproduzir os efeitos posturais da vibração muscular já relatados pela literatura, avaliamos seus efeitos na postura ereta de indivíduos jovens.

Como principais achados, encontramos excelentes níveis de reprodutibilidade, quando o sistema é testado no mesmo dia e em dias distintos. Também, demonstramos que o sistema é capaz de replicar os resultados de estudos anteriores, apresentando seu potencial para ser usado nos demais estudos dessa Tese de Doutorado. O artigo científico é apresentado na sequência.

3.2. RCVibro System: full description of a custom-made vibratory system and its reliability.

Marcelo P. Pereira, Paulo H. S. Pelicioni, Lilian T. B. Gobbi

3.2.1. Introduction

Muscle vibration has been used to investigate how the proprioceptive system is affected by pathological processes (RABIN et al., 2010; TAN; ALMEIDA; RAHIMI, 2011) and/or with the intention to improve the gait performance of people with motor disabilities (CELLETTI; CAMEROTA, 2011; LIN; HSU; WANG, 2012). The main vibratory effect is the excitation of sensory intramuscular Ia type fibers (RIBOT-CISCAR; ROSSI-DURAND; ROLL, 1998) leading to an illusory stretching sensation. As a result, an involuntary counteract segment/body displacement is observed (COURTINE et al., 2007a). In this way, during upright standing, it is observed an involuntary center-of-pressure (CoP) shift towards the receptor-bearing muscle (e.g., when the tibialis anterior is stimulated, a forward CoP displacement is perceived (POLONYOVA; HLAVACKA, 2001)). The use of muscle vibration is a non-invasive technique and can be performed at relatively low cost. Therefore, muscle vibration has been used as an interesting instrument to manipulate the proprioceptive system.

Although the suggestions that muscle vibration could be used as a novel strategy to improve movement (CELLETTI; CAMEROTA, 2011; FIELD-FOTE; NESS; IONNO, 2012; LEE; CHO; LEE, 2013), this technique is not well-spread in clinical day-life, possibly due to the lack of commercial equipment with high-standard quality. Those equipment that are commercially available were not designed for research/clinical proposes. Therefore, it is suggested that those equipment are not reliable when precision features, such as the vibration frequency and amplitude, are considered. Indeed, pilot studies investigating four different commercially available vibratory systems demonstrated an extremely low reliability of vibration frequency between test-retest experiments (ICC (Intraclass Correlation Coefficient) < 0.51: data not published).

The majority of published studies investigating vibratory effects on balance/movement control used custom devices (COURTINE et al., 2007a; LIN; HSU; WANG, 2012; TAN; ALMEIDA; RAHIMI, 2011). However, most of them fail to properly describe the technical features of these custom devices, not allowing the data to be

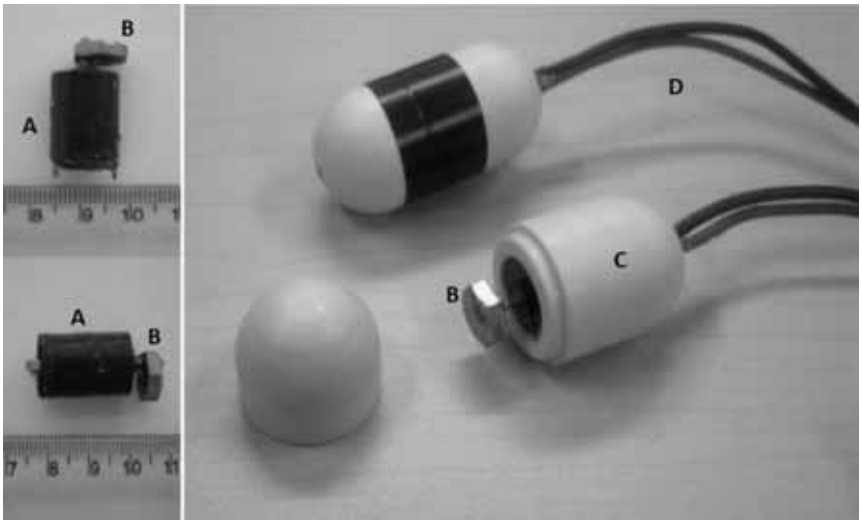
replicated. Another important issue with the use of custom devices is that the system reliability is rarely reported. Hence, the aim of this study is to describe the technical details of a custom-made local vibratory system (named RCVibro System) and its reliability. In addition, another aim is to check if RCVibro System can replicate postural effects already observed by previous studies (CAPICIKOVA et al., 2006; COURTINE et al., 2007a; POLONYOVA; HLAVACKA, 2001). We expect that the RCVibro System will be a highly reliable system, replicating observations of previous studies (CELLETTI; CAMEROTA, 2011; RIBOT-CISCAR; ROSSI-DURAND; ROLL, 1998; SHROUT; FLEISS, 1979). In time, we expect a CoP shift towards the receptor-bearing muscle during upright standing.

3.2.2. Methods

Vibratory devices

The vibratory devices (Figure 3.2.1) were constructed using steel DC micro motors (model 1319 006SR - Faulhaber® - Switzerland) with a maximal nominal tension of 6V, maximal no-load speed of 13100rpm and weighting 12g each. A small eccentric load (weighting around 0.5g, measuring 1cm of diameter) was attached to each micro motor axis. The rotational velocity of the eccentric mass, and therefore the vibration frequency, is linearly determined by the amount of electrical potential difference given to each micro motor (details in the Results section). Hence, electrical wires were fixed to each motor using ordinary soldering. The sets (motor plus eccentric masses) were embedded in a custom cylindrical enclosure made of non-toxic polyvinyl chloride (PVC), measuring 4.5cm x 2cm x 2cm, weighting 12g. In total, each vibratory device weighted around 27g-31g. The designed configuration of each device allowed vibration only in 2-D directions (x and z).

Figure 3.2.1. Vibratory devices.

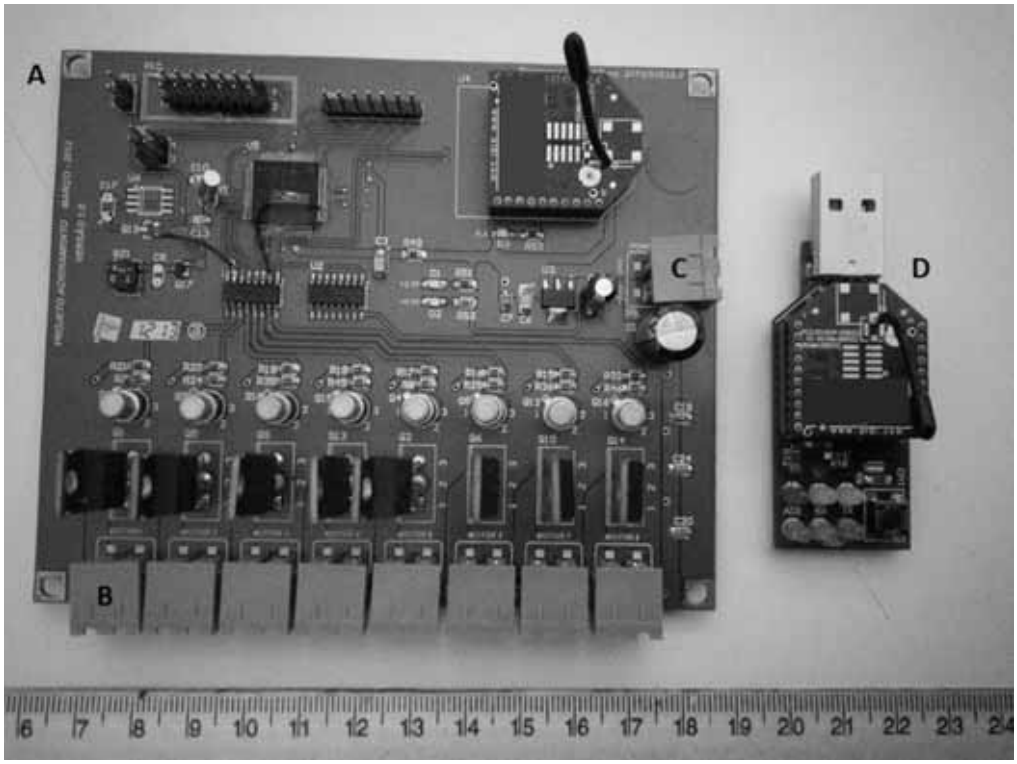


A: Micro motor; B: Eccentric mass; C: PVC cylindrical enclosure; D: Power wires.

Logical control board

In the RCVIbro System, each vibratory device is controlled by a custom electronic board (Figure 3.2.2) measuring 12x12cm and controlled by a Zigbee network protocol (radio transmission). The Zigbee controller module may be connect to any regular PC, via USB (Figure 3.2.2). The custom-made board (powered by an ordinary 5V AC adapter) can control up to eight different vibratory devices and allows, through an ordinary hyperterminal software, the manipulation of both vibration onset moment and frequency. This manipulation can be done for all vibratory devices simultaneously or individually. The vibration frequency of each device is manipulated by the command “at+x=y” in the hyperterminal software, whereas “x” is the target channel and “y” is the percentage of the maximal given electric potential difference (100% is equal to 5V). The board can be fixed on a belt or in a backpack, which allows the participant to move freely while the vibration parameters can be controlled via radio.

Figure 3.2.2. Logical control system.



A: Control board; B: Vibratory devices power output; C: Control board power input; D: USB Zigbee controller module.

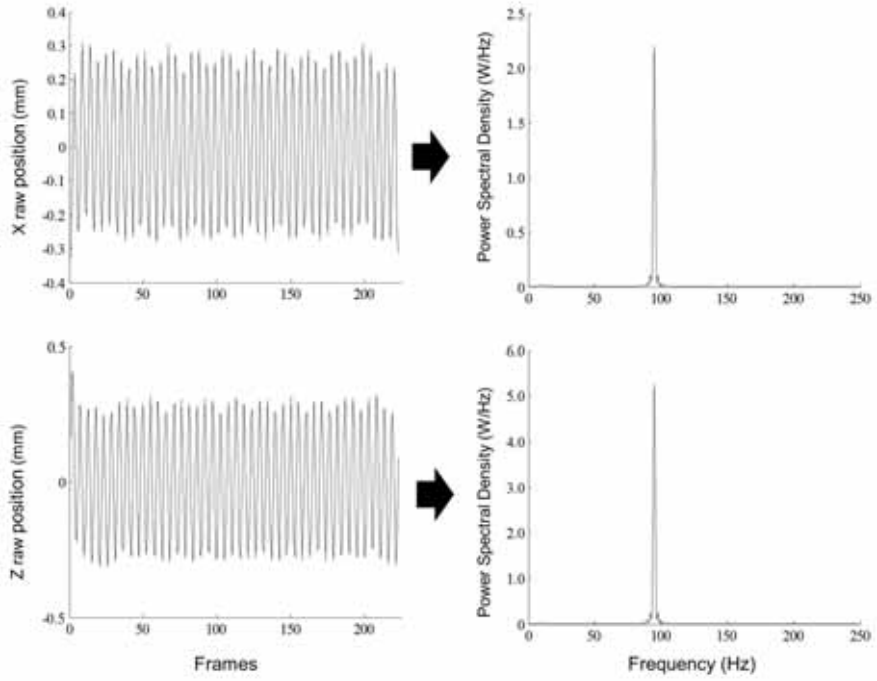
RCVibro System calibration and reliability

Since the motor axis rotational velocity is dependent on the given electric potential difference, it was necessary, for each vibratory device (six were separately tested), to achieve a percentage of electric potential difference/vibration frequency curve. To that, a three-dimensional optoelectronic movement analysis system was used (OPTOPTRAK Certus – NDI®). This system has an accuracy of 0.1mm and a resolution of 0.01mm. Therefore, we are confident that the OPTOPTRAK system is sensitive enough to detect the vibratory movement. Since higher frequencies than 218Hz were not expected (maximal no-load speed of 13100rpm) and in order to respect the Nyquist theorem, a sample acquisition rate of 500Hz was used. In each device, an infrared emissor (IRED) was fixed using adhesive tape. No emissors movement was observed during the assessments. The vibratory devices were fixed in a vertical position, allowing a free A-P and M-L movement.

The electric potential difference for each vibratory device was increased in series of 7% of total, resulting in an eleven points series (14-84%; lower percentages were excluded, since, in some, it did not promote any device movement; higher percentages were not used to avoid any mechanical damage to the vibratory devices). A 5 seconds

vibration period was assessed for each electric potential difference. The position of each marker was offline filtered using a low-pass 4th order Butterworth filter with a 10Hz cut-off frequency. Since vibration frequencies lower than 62Hz were not expected (14% of maximal non-load speed: 3742rpm) the use of 10Hz as a high-pass cut-off frequency guaranteed that no real-data would be missed. The 5 seconds periods was then split into six 0.5-second periods, with 0.5-second overlap (the first and last second of data collection were excluded): 1-1.5s, 1.5-2.0s…3.0-3.5s, 3.5-4.0s. For each period, the power spectrum of the position of each marker was determined using the power spectral density (PSD) analysis through specific-designed MatLab (MathWorks®) codes. The power spectrum had a resolution of 0.66Hz. Afterwards, we determined the peak power frequency for each 0.5-second time series, for each electric potential difference percentage for both A-P and M-L directions (Figure 3.2.3). This procedure allowed us to determine: (i) the percentage of electric potential difference/vibration frequency curve for each device; (ii) the vibration variability within the 5s data-sampling period (through the coefficient of variation ([standard deviation*100]/mean)).

Figure 3.2.3. X and Z raw position of a single marker during one 0.5-second period and the power spectral density plot of both directions. Peak power frequency: 95.07 Hz for both directions.



In order to assess the system test-retest reliability in the same day, these procedures were repeated three times, named: Test, Re-Test 1 and Re-Test 2 (2 hours apart from each order). Additionally, in order to assess the test-retest reliability between different days, a fourth test (named Re-Test D2) was repeated 24 hours after Test. For the reliability procedures, we considered the mean vibration frequency between the six 0.5-second periods. For each device, to assess the reliability across the within days assessments, we used $ICC_{(3,3)}$ procedures between Test, Re-Test 1 and Re-Test 2; to assess the system reliability between days, we used the $ICC_{(3,2)}$ procedures between Test and Re-Test D2 (BILNEY; MORRIS; WEBSTER, 2003; SHROUT; FLEISS, 1979).

RCVibro System functioning test

In order to assess the proper functioning of the entire custom-made system and to assure that the same effects observed in previous studies (CAPICIKOVA et al., 2006; COURTINE et al., 2007a; POLONYOVA; HLAVACKA, 2001) could be replicated by the RCVibro System, we assessed the CoP behavior during upright standing. To that, we assessed the CoP behavior of fifteen (7 males, 8 females; mean age of 26.29±6.46 years; 167.71±7.89cm of height; and 68.86±8.76kg of weight) healthy young adults while standing with eyes closed in two conditions: with and without vibration on the tibialis anterior muscle. The local Ethics Committee Board approved all procedures used in this study[1] and all participants signed an informed consent. During all trials, participants were asked to maintain an upright posture with eyes closed (to enhance the vibratory effect (CAPICIKOVA et al., 2006)) for 40 seconds, standing on a force plate (AMTI®). The stepping position was standardized for each participant and kept consistent across all trials. The position of the CoP in relation to the force plate zero offset was assessed using the Balance Clinic software (AMTI®) with a sample rate of 200Hz. Three trials were performed. A resting period of 30 seconds was respected between trials. For all conditions, the vibratory devices (position detailed below) were switched on at the 10th second of data collection and a 30 seconds vibration period was used to raise postural effects. To investigate the effect of vibration on the CoP behavior we assessed the CoP A-P position, CoP area and CoP mean velocity at two moments: at the close-to-last five seconds without vibration

[1] Anexo 1.

(4-9th seconds of data collection) and at the close-to-last five seconds of vibration, (34-39th seconds of data collection). The decision to exclude the very last second of each condition was adopted to avoid noisy data (switching conditions or data collection termination). The CoP area was determined using the 95% confidence ellipse (MOGHADAM et al., 2011).

Vibration was applied bilaterally on the tibialis anterior muscle belly. This muscle was chosen, since previous studies had already demonstrated that this muscle is sensitive to local vibration (COURTINE et al., 2007a; IVANENKO; GRASSO; LACQUANITI, 2000; POLONYOVA; HLAVACKA, 2001). The devices were distant approximately 4.5cm proximal to the center of the muscle belly. To locate the center of the muscle belly, participants seated on a chair and the center of the muscle was considered as the 1/3 of the distance between the head of the fibula and the tip of the medial malleolus. The center of the vibratory devices were positioned directly on the target spots. Extra care was taken to ensure that both vibratory devices were exclusively on the tibialis anterior muscle. For fixation, we used ordinary elastic bands. A 100Hz frequency was used to determine the vibration effects on the CoP dependent variables, since this frequency was already shown to induce postural adaptations (POLONYOVA; HLAVACKA, 2001).

The Statistica 7.0 (StatSoft®) software for Windows was used for statistical procedures and significant results were considered when $P < .05$. Munro's classification for reliability coefficients was used to describe the degree of reliability: 0.26-0.49 reflects low correlation; 0.5-0.69 reflects moderate correlation; 0.7-0.89 reflects high correlation; 0.9-1.00 indicates very high correlation (MUNRO; VISINTAINER; PAGE, 1986). The difference between the two periods in the CoP behavior was assessed using Student t-test for dependent variables.

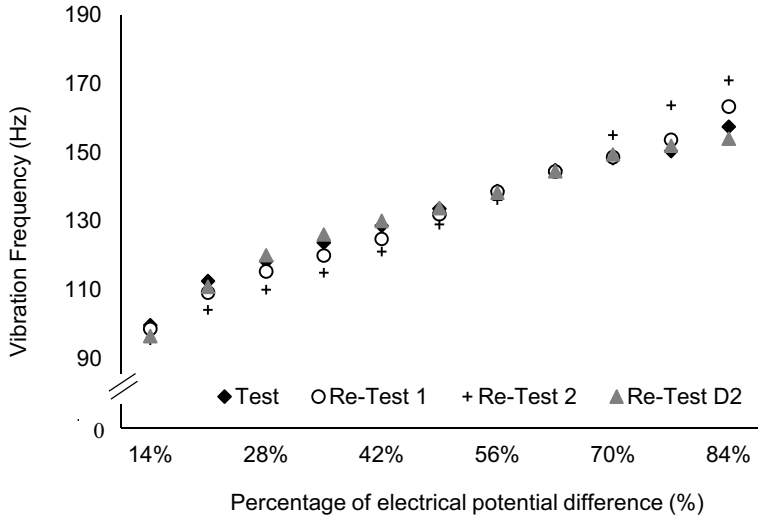
3.2.3. Results

RCVibro System calibration and reliability

Figure 3.2.4 shows the percentage of electrical potential difference/vibration frequency curves achieved for one vibratory device on Test, Re-Test 1, Re-Test 2 and Re-Test D2. The curves show a linear increase of vibration frequency with higher percentages of electrical potential differences. A similar pattern was observed for all

other devices. The vibration amplitude ranged between 0.7 and 1.2mm for different devices. Since the devices were custom-made we did not expected that the same vibration amplitude would be found across all devices

Figure 3.2.4. Percentage of electrical potential difference/vibration frequency curves achieved for one vibratory device on each test session.



Bold diamonds: Test; Open circles: Re-Test 1; Crosses: Re-Test 2; Gray triangles: Re-Test D2. The same pattern was observed for other devices.

Table 3.2.1 presents the variability and the ICC results for each vibratory device in both A-P and M-L directions. It can be noticed an extremely low variability in the vibration frequency within the five seconds testing period (coefficient of variation lower than 2.03%). A single vibratory device demonstrated a high level of agreement within the same day of assessment (device #3 – $ICC_{(3,3)}$ = 0.87). In addition, two devices showed a moderate-to-high level of agreement between two days of assessment (device #3: $ICC_{(3,2)}$=0.68 and device #5: $ICC_{(3,2)}$=0.79). All other devices showed a very high level of agreement between the vibration frequencies achieved within the same day ($ICC_{(3,3)}$ > 0.957) and between different days ($ICC_{(3,2)}$ > 0.959).

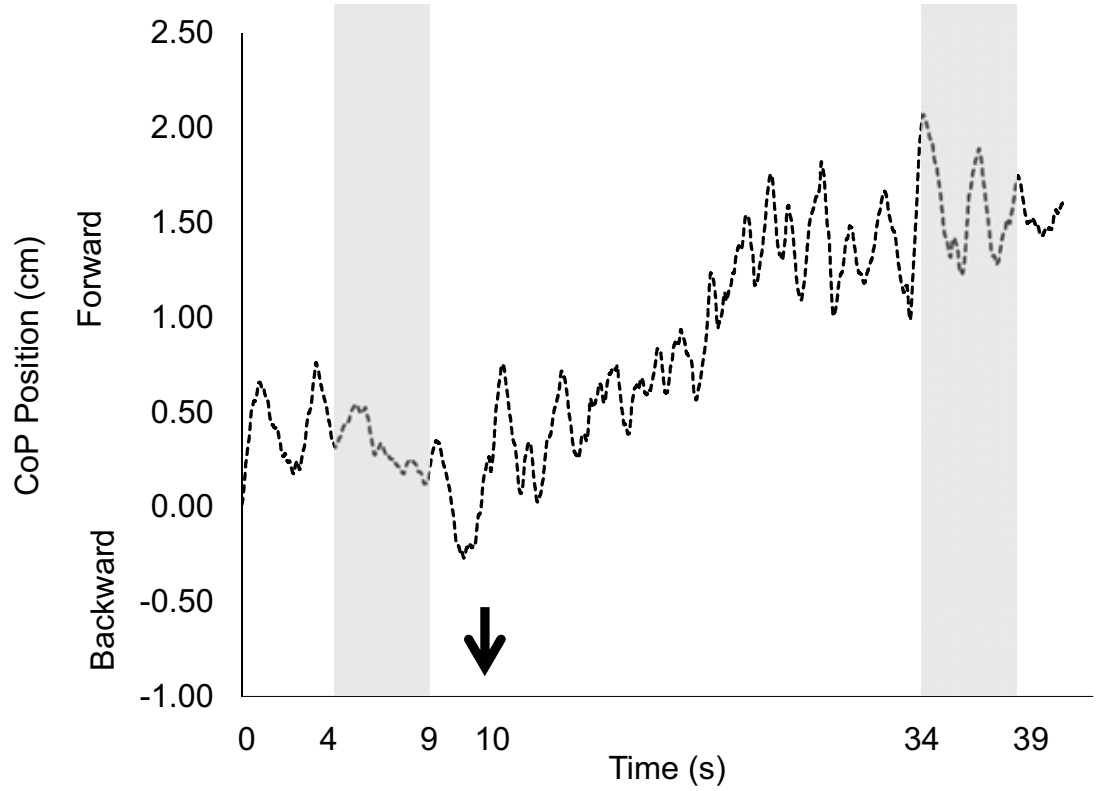
Table 3.2.1: Coefficient of variation (CV) and ICC results for each vibratory device in both X and Z directions.

Device	CV Test (%)	CV Re-Test1 (%)	CV Re-Test2 (%)	$ICC_{(3,3)}$	F value	P value	CV Re-Test D2 (%)	$ICC_{(3,2)}$	F value	P value
#1										
X	0.57	0.50	0.55	.977	45.30	<0.001	0.41	.959	24.65	<0.001
Z	0.56	0.49	0.57	.977	45.30	<0.001	0.41	.959	24.67	<0.001
#2										
X	0.35	0.39	0.40	.985	69.87	<0.001	0.40	.982	56.34	<0.001
Z	0.37	0.39	0.40	.985	69.91	<0.001	0.40	.996	318.2	<0.001
#3										
X	2.03	0.95	0.56	.871	7.75	<0.001	0.56	.668	3.01	0.004
Z	2.03	0.95	0.57	.870	7.74	<0.001	0.57	.667	3.01	0.004
#4										
X	0.80	0.96	0.95	.995	216.4	<0.001	1.01	.974	39.02	<0.001
Z	0.81	0.95	0.96	.995	217.8	<0.001	1.01	.974	39.28	<0.001
#5										
X	0.74	0.77	0.64	.957	23.53	<0.001	0.78	.798	4.97	0.009
Z	0.74	0.77	0.63	.957	23.50	<0.001	0.78	.799	4.97	0.009
#6										
X	0.30	0.38	0.37	.995	211.3	<0.001	0.38	.981	53.85	<0.001
Z	0.30	0.38	0.37	.995	213.6	<0.001	0.38	.981	54.12	<0.001

RCVibro System functioning test

The CoP position behavior of one participant during one trial is shown in Figure 3.2.5. It can be seen that after bilaterally vibration onset on tibialis anterior, a forward CoP displacement was observed. The Student t test results confirmed this observation, demonstrating a mean of 1.10cm forward CoP displacement with vibration (OFF: -0.77±0.62cm and ON: 0.32±0.67cm; $t_{(1,12)}$=3.34, p=0.004). Additionally, vibration increased the CoP mean velocity (OFF: 1.21±0.30cm/s and ON: 1.46±0.46cm/s; $t_{(1,12)}$=2.27, p=0.042). No influence of vibration was observed for CoP area (OFF: 1.20±0.91cm^2 and ON: 1.41±1.04cm^2; $t_{(1,12)}$=1.16; p=0.26).

Figure 3.2.5. The raw center-of-pressure (CoP) response to tibialis anterior vibration, in one subject.



Bold arrow: vibration onset. Gray bars: data acquisition periods.

3.2.4. Discussion

The aim of this study was to describe the technical details of a custom device designed to apply muscle vibration (named RCVibro System) and its reliability. In addition, we aimed to check the ability of the RCVibro System to replicate the observations of previous studies. It was shown that the RCVibro System is a highly reliable system and can replicate previous observations, demonstrating its potential for clinical and research applications.

Muscle vibration is a promising instrument to improve movement in people with motor disabilities (CELLETTI; CAMEROTA, 2011; LIN; HSU; WANG, 2012) and can also be used to investigate pathological mechanisms, as in Parkinson's disease (RABIN et al., 2010). However, most studies that had used local vibration, failed to fully describe their systems' technical details or reliability. Only few studies have described the vibratory devices' characteristics (COURTINE et al., 2007a; LIN; HSU; WANG, 2012; TAN; ALMEIDA; RAHIMI, 2011) and most of them, have not described the

control unit. Indeed the number of studies that fully described the design and functioning of the control unit is close to none. Mostly important, the number of papers that demonstrated the reliability of the systems is also close to inexistent. In this way, the RCVibro System is one of the first systems to be technically full described and shown to be highly reliable. The reliability of vibratory systems is a major concern, since the use of different vibration frequencies can leads to diverse motor effects (POLONYOVA; HLAVACKA, 2001). Therefore, a reliable system guarantees that the same frequency is being applied for all participants across all trials and conditions.

We demonstrated that the RCVibro System is a high reliable system, showing a very high level of agreement within the same day of assessment (ICC>0.957), with the exception of one device that showed a moderate level of correlation (device #3: ICC=0.870). In the same way, all devices, with exception of device #3 (ICC=0.667) demonstrated moderate-to-very high level of agreement (ICC>0.798). The reason for the low level of agreement for device #3 can be linked to the higher variability within the 5-seconds of assessment in Test (2.03%). It is important to remember here that Test was used to assess the reliability of the device within and same day and between different days. Therefore, we ran a new series of $ICC_{(3,2)}$ tests for device #3 considering both Re-Test 1 and Re-Test 2 (for reliability within the same day) and also Re-Test 1 and Re-Test D2 (for reliability between different days). As result, very high correlation levels were found (within the same day: ICC=0.928, F=13.89 and p<0.0001; between days: ICC=0.957, F=23.50 and p<0.0001). The reason why the device #3 showed a higher variability in Test is unknown. However, this issue seems to be solved in the following assessments.

Another important feature of the RCVibro System is its wireless control configuration. This feature allows the manipulation of both vibration frequency and onset moment while the user moves freely. This is an important issue, mainly in experimental designs where the target subject should not be aware when the devices will be switched on.

Previous studies already demonstrated a forward CoP displacement (COURTINE et al., 2007a; IVANENKO; GRASSO; LACQUANITI, 2000; POLONYOVA; HLAVACKA, 2001) when local vibration is applied on the tibialis anterior. Additionally, Capicikova et al (2006) found an increase of CoP velocity (~50%) when calf muscles were stimulated by local vibration, beside no statistical significance was reach (CAPICIKOVA et al., 2006). Therefore, we can argue that RCVibro System

induces the same postural effects already reported by the literature, since we also found an increase in CoP velocity and a forward CoP displacement. However, two points should be further discussed.

No significant results were found for CoP area. This could be due to the short period used to analyze the CoP behavior (5 seconds). A small CoP area increase was observed (~0.21 cm^2, 17% of increase), but no statistical significance was found. Since a high variability was also observed for this variable (coefficients of variation ~75%), we suggest that analyzing longer periods could highlight the vibration influence on CoP area. This is a study limitation and future researches should assess longer periods to analyze the CoP behavior.

Additionally, in comparison to previous studies analyzing the influence of local vibration on the tibialis anterior, we found a shorter CoP A-P displacement: Courtine et al. (2007) found a ~4cm forward CoP displacement (COURTINE et al., 2007a), similar to those reported by Ivanenko et al. (2000) (~4.9 cm) (IVANENKO; GRASSO; LACQUANITI, 2000). Clearly, our results indicate a much slighter CoP forward displacement (1.10 cm). This could be due to the vibration frequency we used to raise the postural effects. In the studies of Courtine et al. (2007) and Ivanenko et al. (2000) a 80Hz vibration frequency was used (COURTINE et al., 2007a; IVANENKO; GRASSO; LACQUANITI, 2000). In another way, in our study, we used a vibration frequency of 100Hz. Physiological studies already demonstrated that vibration frequencies higher than 100-120 Hz could induce muscle spindles to fire in subharmonic frequencies (ROLL; VEDEL, 1982), reducing the effectiveness of local vibration (BURKE et al., 1976a). This could be the reason for the lower vibration effects observed here. However, in the study of Polonyova et al. (2001) greater body displacements were found when the tibialis anterior was stimulated by higher vibration frequencies (100 Hz *vs* 80 Hz) (POLONYOVA; HLAVACKA, 2001). Hence, the reasons for the slighter influence of tibialis anterior vibration on CoP displacement found by this study is not completely understood and the influence of different vibration frequencies in postural adjustments should be further investigated by future researches.

3.2.5. Conclusion

In conclusion, this paper fully described a custom-made vibratory system, named RCVibro System. Additionally, we showed that the RCVibro System is highly reliable. The full description of a vibratory system, as demonstrated in this paper, is important to base future researchers and clinicians whom aim to use this technique as an alternative rehabilitation strategy in motor impaired people. This study also demonstrated that the RCVibro System replicated previous researches observations, demonstrating its potential for clinical and research applications.

4. DEFINIÇÃO DOS PARÂMETROS DE APLICAÇÃO DE VIBRAÇÃO MUSCULAR.

4.1. Apresentação

Em seguida ao desenvolvimento do sistema RCVibro System, foi necessário investigar algumas lacunas encontradas na literatura antes de sugerir a aplicação desse sistema em indivíduos com DP. Sabe-se que a vibração muscular quando aplicada na postura ereta pode promover significativas perturbações posturais, podendo provocar desequilíbrios e até mesmo quedas (EKLUND, 1972; QUONIAM et al., 1995; UIMONEN et al., 1996). Assim, para garantir a segurança dos indivíduos e para não expor uma população tão frágil quanto pessoas com DP a esse tipo de risco, decidiu-se realizar os estudos seguintes apenas em indivíduos jovens saudáveis. Pode-se argumentar que os efeitos encontrados em uma população jovem podem não ser replicáveis em outras populações. Entretanto, nesse momento, não buscamos determinar um padrão 'base' do efeito da vibração sobre o comportamento motor de indivíduos saudáveis. Buscamos, apenas, definir os melhores parâmetros de aplicação dessa técnica para suscitar efeitos motores durante a execução das tarefas de levantar e andar e de iniciar o andar.

Essa investigação prévia foi necessária devido a uma série de questões ainda pouco estudadas e que podem trazer impacto direto sobre as respostas motoras investigadas na Seção 5. A primeira dessas questões foi: qual a melhor disposição, em relação às fibras musculares, os dispositivos vibratórios devem ser posicionados para suscitar respostas posturais? A princípio, essa parece ser uma pergunta pouco aplicável para as tarefas-alvo dessa Seção: o levantar e andar e o iniciar o andar. Entretanto, sabe-se que o comportamento postural nessas tarefas define diretamente o desempenho das mesmas (BRENIERE; CUONG DO; BOUISSET, 1987; BUCKLEY et al., 2009; HALLIDAY et al., 1998; KERR et al., 2013). Portanto, potencializar os efeitos posturais, com o uso da vibração muscular, pode ter influência direta sobre o desempenho das tarefas de levantar e andar e de iniciar o andar.

Em seguida, tendo-se definido que o posicionamento em paralelo com as fibras musculares é o melhor para provocar perturbações posturais, foi necessário responder outras duas questões: estimular mais de um local do mesmo ventre muscular pode promover maiores perturbações posturais? Qual região do ventre muscular deve ser estimulada para se obter resultados mais importantes? Como

resultado, determinou-se que a aplicação da vibração muscular em apenas um local, sendo esse na região proximal do músculo, promove os mesmos ou melhores resultados que as demais condições. Portanto, sugere-se a aplicação da vibração na região proximal do ventre muscular, quando essa tem o intuito de promover perturbações posturais.

Assim, a partir das informações obtidas nesses dois estudos (Seções 4.2 e 4.3), pudemos definir a maneira que os dispositivos vibratórios devem ser posicionados para se obter melhores respostas posturais nos estudos seguintes (Seções 4.4 e 4.5). Entretanto, devido ao baixo número de estudos que tenham investigado o efeito da vibração muscular em tarefas de transição, como o iniciar o andar, desconhecíamos qual o melhor momento de aplicação da vibração: antes ou durante a execução da tarefa. Ainda, como discutido na Seção Introdução, o efeito da manipulação da frequência de vibração durante tarefas que envolvem componentes posturais ainda permanece em aberto. Portanto, nesse momento, avaliamos o efeito da manipulação do momento e da frequência de vibração sobre o desempenho da tarefa de iniciar o andar em indivíduos jovens. Como principal resultado, encontramos um efeito significativo do momento de vibração, sendo que sua aplicação imediatamente antes do início da tarefa promove melhora no desempenho da tarefa. Entretanto, a manipulação da frequência de vibração não teve um papel determinante nesse ínterim.

Em seguida, tendo como informação o resultado do estudo anterior, buscamos identificar qual o melhor momento de aplicação da vibração muscular para promover melhora no desempenho da tarefa de levantar e andar em indivíduos jovens. Inesperadamente, não encontramos nenhum efeito da manipulação do sistema proprioceptivo sobre o desempenho da tarefa de levantar e andar nesses indivíduos.

Cada estudo é apresentado, a seguir, na forma de artigos científicos, sendo os dois primeiros no formato de *'Brief reports'* e os seguintes como Artigos Completos.

4.2. The muscle region stimulated by vibration determines the center-of-pressure behavior in upright standing

Marcelo P. Pereira, Paulo, H. S. Pelicioni, Lilian T. B. Gobbi

4.2.1. Introduction

Muscle vibration has being used to manipulate the proprioceptive system (COURTINE et al., 2007a; IVANENKO IU; TALIS; KAZENNIKOV, 1999; LIN; HSU; WANG, 2012) through the activation of muscle spindle Ia fibres (RIBOT-CISCAR; ROSSI-DURAND; ROLL, 1998). It was already demonstrated that vibration is effective when it is applied on both muscle tendons and bellies (BOVE; NARDONE; SCHIEPPATI, 2003; DE NUNZIO et al., 2008). However, it was suggested that, during upright standing, when vibration is applied on muscles bellies rather than on muscle tendons it could elicit stronger postural effects (EKLUND, 1972; UIMONEN et al., 1996). This last suggestion was based on the logical fact that muscle spindles are located in the muscle bellies and not in tendons (UIMONEN et al., 1996). Additionally, previous studies have shown that muscle spindles respond only to stimulus applied around it (MEYER-LOHMANN; RIEBOLD; ROBRECHT, 1974).

Two major responses are observed during muscle vibration: an illusory stretching sensation and, an involuntary activation of the muscle vibrated (mainly through monosynaptic alpha motorneurons activation) (BURKE et al., 1976b; MARTIN; PARK, 1997; RIBOT-CISCAR; ROSSI-DURAND; ROLL, 1998). In this way, during upright posture, it was already extensively demonstrated that vibration on the lower leg shifts the center-of-pressure (CoP) towards the muscle vibrated due to an illusory body-displacement sensation (CAPICIKOVA et al., 2006; COURTINE et al., 2007a; IVANENKO; GRASSO; LACQUANITI, 2000). As it can be seeing, the major muscle vibration effects can be considered a variant of the classical stretch reflex response (BURKE et al., 1976a). Previous research showed that muscle spindles located in different sites of the same muscle do not respond equally to stretch (MEYER-LOHMANN; RIEBOLD; ROBRECHT, 1974). In this way, we raised the question if the same could be observed for muscle vibration. For our understanding, this has never been tested. Moreover, some could argue that, in contrary to tendon vibration (UIMONEN et al., 1996), the effects of vibration on the muscle belly could be restricted

to surrounding area, since muscles spindles located far from the application site could not be excited (UIMONEN et al., 1996). Thus, in line with this theory, applying more than one vibratory device on the same muscle could trigger a higher number of sensory endings, increasing the responsiveness of the muscle vibrated.

However, we believe that this investigation should not be restricted to micrographic investigation, since the results from this sort of analysis cannot be projected to clinical day-life. In this way, in order to optimize the effects of muscle vibration on postural responses, the aims of this study were: (i) to determine the effects of applying a single vibratory device positioned in different locations (proximal and distal) on postural response during upright standing; (ii) to determine the effects of applying two vibratory devices, on the same muscle, on the postural response during upright standing. We used the effects of lower leg muscle vibration on upright standing to investigate these questions, since these effects were already extensively discussed in previous studies (CAPICIKOVA et al., 2006; COURTINE et al., 2007a; POLONYOVA; HLAVACKA, 2001).

4.2.2. Methods

Fifteen healthy young participants (7 males, 8 females; mean age of 26.29±6.46 years; 167.71±7.89cm of height; and 68.86±8.76kg of weight) responded voluntarily to personal invitation. No participants had done exhausting exercises 24 hours before the assessment session and any of them had any orthopedic and/or neurological condition that could influence the results of this study. All procedures used for assessments were approved by the local Ethical Board[1]. Based on the results of a pilot study (n=5), power analyzes revealed that, in order to reach a power of 0.9, as significant at the 5% level, a sample size of seven participants would be required. Therefore, to ensure a high power effect, we two-folded the number of participants.

A custom-made system (RCVibro System) was used to apply vibration bilaterally on the tibialis anterior (TA) muscle. Four cylindrical vibration devices (measuring 4.5cm x 2cm x 2cm; containing a constant-velocity DC motor device (Faulhaber®) bearing an eccentric mass) were positioned bilaterally on the belly of TA in two different locations: a proximal positioning (Proximal: distant approximately 4.5cm

[1] Anexo 1

proximal to the center of the muscle belly) and a distal positioning (Distal: distant approximately 4.5cm distal to the center of the muscle belly). In addition, a third configuration was used, wherein both devices worked at same time (Both). To find the center of the muscle belly, patients were seated on a chair and the center of the muscle was considered as the 1/3 of the distance between the tip of the fibula and the tip of the medial malleolus. The center of the vibratory devices were positioned directly on the target spots. Extra care was taken to ensure that both vibratory devices were exclusively on the tibialis anterior muscle. For fixation, we used ordinary elastic bands. The vibration parameters used were 120Hz and 1.2mm of amplitude. The decision to use higher vibration frequencies than 80Hz (shown to be optimal to fire sensory muscle spindles' fibers) was based on the study of Polonyova and Lavaca (2001). In this last study, greater postural effects were elicited by higher frequencies (100Hz - POLONYOVA; HLAVACKA, 2001).

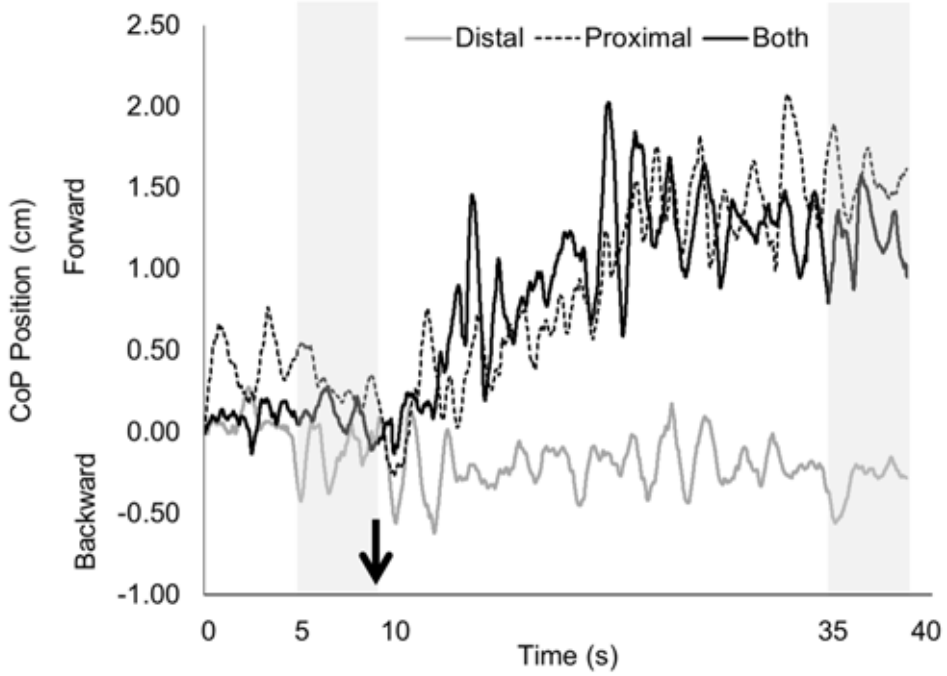
During all trials, participants were asked to maintain an upright posture for 40 seconds, standing on a force plate (AMTI®), while blindfolded (to enhance the vibratory effect (CAPICIKOVA et al., 2006)). The position of the center of pressure (CoP) was assessed using the Balance Clinic software (AMTI®) with a sample rate of 200Hz. Three trials of each condition (Proximal, Distal and Both) were performed. The conditions were fully randomized. The vibratory devices were kept in place for all conditions: e.g. during the Distal condition, the proximal devices were not removed, and vice-versa – this procedure ensured the consistency of vibratory units' positioning and cutaneous sensation. A resting period of 30 seconds was respected between trials. For all conditions, vibratory devices were switched on at the 10th second of data collection and a 30 seconds vibration period was used to raise postural effects. The decision to use 30s of vibration was based on the study of Capicikova et al. (2006) that showed greater postural effects with longer vibration periods. To compare the effects of each condition on the CoP behavior, we assessed the CoP mean antero-posterior position, CoP area and CoP mean velocity (MV) at two moments: at the last five seconds without vibration (5-10th seconds of data collection) and at the last five seconds of vibration (35-40th seconds of data collection). Next, for all variables, the difference between the two periods was assessed: ΔPosition, ΔArea and ΔMV. All procedures were performed using specific MatLab (MathWorks®) algorithms. Data were averaged across trials and participants.

For statistical procedures, we used the Statistica 7.0 software (StatSoft®) for windows. After normal distribution tests (Shapiro-wilk test - $p>0.18$), all dependent variables were analyzed by one-way ANOVA tests for repeated measures, considering the Condition as main factor (Proximal vs. Distal vs. Both). Whenever necessary, a Tukey post-hoc test was used for univariate comparisons. A $p<0.05$ was considered as statistically significant.

4.2.3. Results

Figure 4.2.1 shows the CoP behavior of one participant during a single trial of all assessed conditions. It can be clearly seen the different CoP behavior in Distal when compared to Proximal and Both: after the vibration onset (bold arrow) in Both and Proximal the CoP moves forward, while in Distal, this behavior is not observed. In contrast to Both and Proximal, it seems that, for this particular participant, in Distal, the CoP slightly moves backwards after vibration onset. Another feature that can be observed in Figure 4.2.1 is the persevering forward CoP maintenance in Both and Proximal during all vibration period.

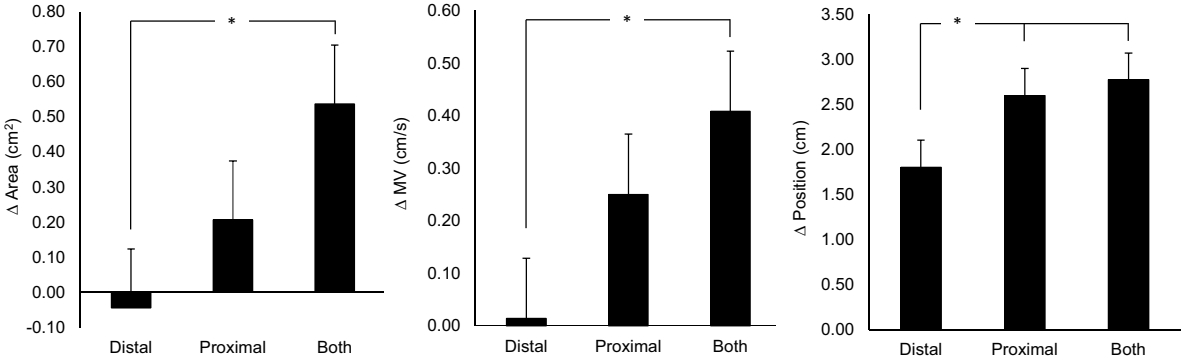
Figure 4.2.1. The raw antero-posterior CoP responses to tibialis anterior vibration, in one subject.



Bold line: Both; Dashed line: Proximal; Gray line: Distal. Bold arrow: vibration onset. Gray bars: data acquisition periods.

Figure 4.2.2 shows the mean results across all participants for all dependent variables. The effect of Condition was statistically significant for ΔArea ($F_{(2,14)}$=3.31; p=0.05; η^2=0.19), ΔMV ($F_{(2,14)}$=4.75; p=0.01; η^2=0.25) and ΔPosition ($F_{(2,14)}$=7.98; p=0.001; η^2=0.36). The univariate comparisons showed a greater ΔArea and ΔMV in Both than in Distal (p=0.04 and p=0.01). In the same way, a higher ΔPosition was found for Both and Proximal in comparison to Distal (p=0.004 and p=0.006). No differences were found between Distal and Proximal for ΔArea and ΔMV (p=0.51 and 0.17). Finally, no differences were found between Proximal and Both for ΔArea (p=0.32), ΔMV (p=0.44) and ΔPosition (p=0.98).

Figure 4.2.2. Mean and Standard Error of ΔArea (Left panel), ΔMV (middle panel) and ΔPosition (right panel) assessed in the all conditions.



*p<0.05

4.2.4. Discussion

The aim of this study was to check the effects of manipulating the application site of vibratory devices in CoP behavior during upright standing. To that, we stimulated the vibrated muscles proximally, distally and at both sites at the same time. The results show that stimulating the vibrated muscle in a proximal approach elicits stronger effects than in a distal positioning. In addition, the stimulation of more than one site at the same time does not have any advantage in comparison to stimulating only a proximal site.

The results observed on Figure 4.2.2 are similar to those reported on previous research (BOVE; NARDONE; SCHIEPPATI, 2003; CAPICIKOVA et al., 2006; UIMONEN et al., 1996). A positive delta value for all variables means a higher CoP area, higher CoP mean velocity and a forward CoP displacement with vibration. This

increase in the CoP sway area with vibration is due to the participants' strategy to recover balance (CAPICIKOVA et al., 2006). Since vibration disrupts the proprioceptive inflow to the central nervous system (VERSCHUEREN et al., 2002), a higher unbalance is expected with the use of muscle vibration (CAPICIKOVA et al., 2006; UIMONEN et al., 1996); as consequence, the increased CoP area found in this study was expected. However, only in Proximal and Both, a positive delta was found, suggesting that in Distal, the effect of vibration, if existent, is insignificant.

In the same way, beside there is no statistically difference between Proximal and Distal for CoP mean velocity, the Distal delta is close to zero, showing a very low effect of vibration on its velocity. In addition, ∆MV in Distal is only 5.85% and 3.59% of ∆MV in Proximal and Both, respectively. These results reinforce the inefficient effect of applying muscle vibration on the distal muscle belly to induce any postural effects.

Finally, as mentioned before, a positive ∆Position represents a forward CoP displacement. Beside the delta value in Distal being also positive, it is clearly shorter than in Proximal and Both. The CoP displacement during upright standing is the result of an illusory stretching sensation, due to Ia sensory fibers excitation in the muscle spindles (BOVE; NARDONE; SCHIEPPATI, 2003; BURKE et al., 1976a; RIBOT-CISCAR; ROSSI-DURAND; ROLL, 1998). Because of this illusory sensation, the subject contracts the vibrated muscle in order to recover balance, since he has the sensation to be moving towards the opposite direction (COURTINE; DE NUNZIO; et al., 2007). Therefore, a forward CoP displacement was expected.

Taken together, the results observed in Figure 4.2.2 suggest that muscle spindles sensitivity to vibration seems to be related to their location in the muscles' bellies. The stronger results in the Proximal positioning are in agreement with previous findings (MEYER-LOHMANN; RIEBOLD; ROBRECHT, 1974). In their study, Meyer-Lohmann et al. (1974) found a local-dependent responsiveness to stretching in feline muscle spindles, showing that those located in the muscle periphery are less sensitive to stretching than those located in the middle part of the muscle (IVANENKO; GRASSO; LACQUANITI, 2000). Additionally, they found a higher sensitivity to stretching in muscle spindles located in the proximal region of the extensor digiterum longus muscle (MEYER-LOHMANN; RIEBOLD; ROBRECHT, 1974). Since the vibration effects can be considered as a variant of the segmental stretch reflex (BURKE et al., 1976a), it is not surprising that the same location sensitivity to muscle stretch is also found for muscle vibration.

The second aim of this study was to investigate if the usage of more than one vibratory device, at the same time and on the same muscle, could enhance vibratory postural effects. As it can be seen in Figure 4.2.2, Both is only different from Distal. This result seems to be more related to the low vibratory responsiveness of muscle spindles located in the distal areas of the muscle belly than to stronger effects with the use of two vibratory devices. If indeed, the use of more than one vibratory device could really enhance the vibratory effects, we would also expect differences between Proximal and Both. Even with slight differences in ΔArea and ΔMV between Both and Proximal (Figure 4.2.2), the statistical procedures failed to show any significant differences. In agreement, the main postural effect entailed by vibration (the forward CoP displacement) is essentially the same in Both and Proximal. All these results, taken together, indicate that using a single vibratory device, positioned proximally on the muscle belly, induces the same postural effects of using more than one vibratory unit. Therefore, we suggested the usage of a single unit, reducing unnecessary expenses.

The present study failed to monitor EMG activity of surrounding muscles to ensure that vibration was not spread. However, as mentioned before, extra care was taken to ensure that all vibratory devices were positioned exclusively on the tibialis anterior. This is a study limitation and future studies should focus on overcoming this issue.

4.2.5. Conclusion

This study showed that applying vibration on the proximal region of muscles' bellies, rather than distally, induces stronger postural effects during upright standing. In agreement, this study showed that using a single vibratory device positioned proximally on the tibialis anterior muscle belly induces the same postural effects than using multiple devices on the vibrated muscle at the same time. In this way, it is suggested, in future studies, the use of a single vibratory device positioned proximally to induce any postural effects.

4.3. Human postural response to lower leg muscle vibration in different positions relative to muscle fibers

Marcelo P. Pereira, Paulo H. S. Pelicioni, Quincy J. Almeida, Lilian T. B. Gobbi

4.3.1. Introduction

During upright standing, muscle vibration on lower limbs results in an involuntary center-of-pressure (CoP) displacement towards the vibrated muscle (CAPICIKOVA et al., 2006; DE NUNZIO et al., 2008) (e.g.: when muscle vibration is applied on gastrocnemius, a backward COP displacement is observed (CAPICIKOVA et al., 2006)). This involuntary CoP displacement is a consequence of muscle spindles Ia fibers excitation, resulting in an illusory stretching sensation (ROLL; VEDEL, 1982). In addition, a higher body sway area and velocity is also expected with the use of muscle vibration on the lower limbs (CAPICIKOVA et al., 2006). These latter responses are the consequence of movements issued by the participant in order to recover balance (CAPICIKOVA et al., 2006; COURTINE et al., 2007a).

Muscle vibration effects are task-dependent (COURTINE et al., 2007a) and depend on vibration frequency (POLONYOVA; HLAVACKA, 2001) and amplitude (UIMONEN et al., 1996). However, for our best understanding, the influence of vibration devices positioning in relation to muscle fibers has never been investigated. In instance, at least in cylindrical devices (as used by the majority of studies), we believe that positioning the vibratory devices parallel to muscle fibers could reduce spread effects to non-target muscles. In addition, positioning the vibratory parallel to muscle fibers could increase the device/muscle interface area. Hence, it is believed that changing the vibration devices' position in relation to muscle fibers direction would elicits different responses. Thus, the aim of this study was to investigate the effects of vibratory devices position in relation to muscle fibers on the CoP behavior in upright standing.

4.3.2. Methods

Seven healthy young participants (3 males; mean age: 25.43±6.00; height: 173±25cm; weight: 75.74±17.55kg) participated in this study. All participants had no

orthopedic and/or neurological condition that could influence the results of this study. All procedures were approved by the local Ethical Board[1] and are in accordance to the Declaration of Helsinki (2000).

A custom-made system (RCVibro System) was used to apply vibration bilaterally on the soleus muscle (SO). Two cylindrical vibratory devices (measuring 4.5cm x 2cm x 2cm; containing a constant-velocity DC motor device bearing an eccentric mass) were positioned on the belly of SO in two different positions (Figure 4.3.1A): a Normal position (the motors axis positioned perpendicularly to muscle fibers) and a Parallel position (motors axis positioned parallel to muscle fibers). For fixation, we used ordinary elastic bands. The vibration parameters used were 100Hz and 1.2mm of amplitude (BURKE et al., 1976a; VERREL et al., 2011). The decision to use higher vibration frequencies was based on the study of Polonyova and Hlavacka (2001), where greater postural effects were elicited by higher frequencies (100Hz).

Participants were asked to maintain an upright posture for 40 seconds with eyes closed, standing on a mat containing pressure-sensing pads (Zeno®). The COP position was assessed with a sample rate of 100Hz using the PKMAS software (ProtoKinetics®). Three trials of three conditions were performed: without vibration (NonVib), Normal and Parallel. For all participants, the first condition assessed was NonVib followed by the other two (randomly distributed across subjects). A resting period of 30s was respected between trials and 2min between conditions. For the NonVib condition, vibratory devices were not switched on during the entire trial. For the other two conditions, they were switched on at the 10th second of data collection. The CoP area (Area) and its mean velocity (MV) were assessed during the last five seconds of each trial (35-40th seconds) using specific MatLab (MathWorks®) algorithms. Also, the antero-posterior (A-P) position of the CoP at the last 5 seconds prior vibration and at the last 5 seconds of data collection were assessed: 5-10th and 35-40th seconds; thereafter, we compared the CoP position at these both moments: ΔPosition. Positive ΔPosition values represent a forward CoP displacement.

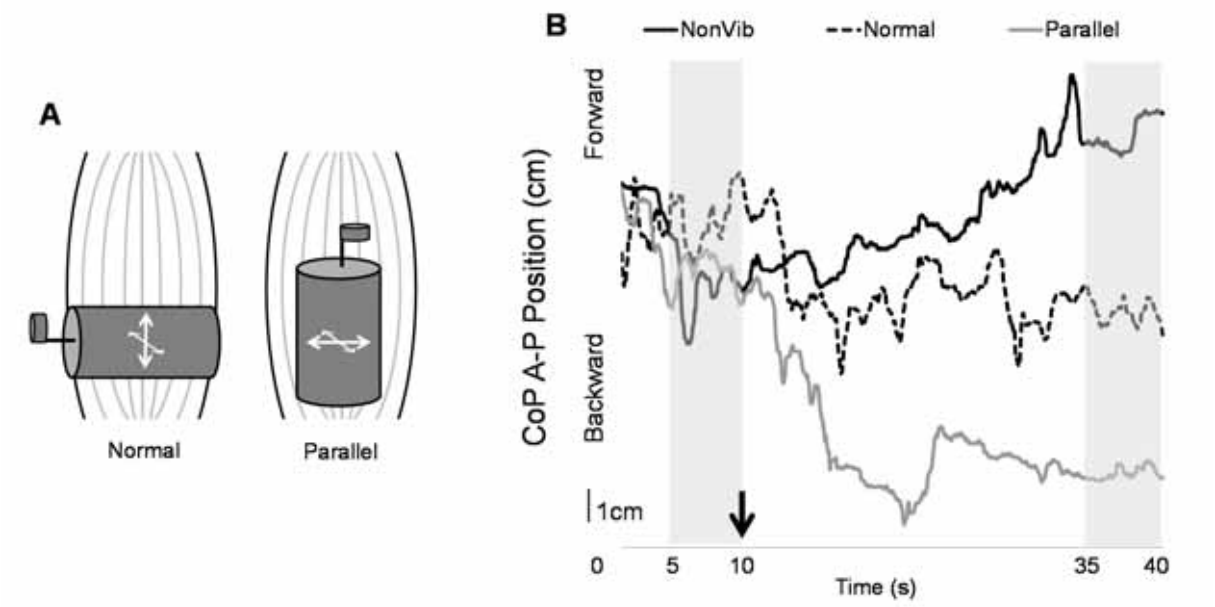
For statistical procedures, the Statistica 7.0 software (StaSoft®) was used. One-way ANOVA tests with repeated measures were used, considering the condition (NoVib *vs* Parallel *vs* Normal) as main factor. Tukey post-hoc tests were used for univariate comparisons. A $p<0.05$ was considered as statistically significant.

[1] Anexo 2

4.3.3. Results

Figure 4.3.1B shows a representative CoP A-P position of one participant during the assessed conditions (one participant, one trial of each condition).

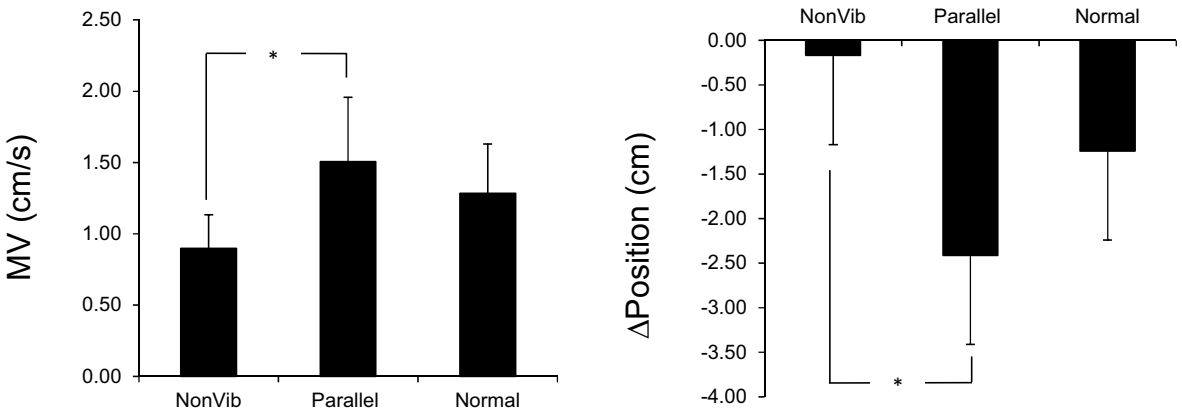
Figure 4.3.1. A: schematic representation of vibratory devices in comparison to muscle fibers; B: representative CoP position during the three assessed conditions for one participant.



A: white arrows: Vibratory devices movement directions; B: Bold full line: NonVib; Dashed Bold line: Normal; Gray line: Parallel. The bold arrow indicates the vibration onset. Light gray areas represent periods where the CoP position was assessed.

A backward CoP displacement can be seen in Figure 4.3.1B in both Normal and Parallel. In addition, according to Figure 4.3.1B, the backward displacement was more evident for Parallel. Indeed a condition effect was found (Figure 4.3.2) for both MV ($F_{(2,6)}$=7.99 and p=0.006) and ΔPosition ($F_{(2,6)}$=7.72 and p=0.006). For both variables post-hoc tests showed that Parallel was different from NonVib (p<0.01). In another way, Normal was not different from both NonVib (p>0.06) and Parallel (p>0.14). For Area, no condition effect was found ($F_{(2,6)}$=1.96 and p=0.18), being NonVib (0.90±0.37cm^2) similar to Normal (2.23±2.24cm^2) and Parallel (1.12±0.61cm^2).

Figure 4.3.2. Mean and Standard Error of CoP velocity and ΔPosition for all conditions.



* p<0.01.

4.3.4. Discussion

The aim of this study was to evaluate the effects of vibratory devices' position in relation to muscle fibers on the CoP behavior during upright standing. The results of this study show that positioning the vibratory device in parallel to muscle fibers elicits greater effects (higher CoP velocity and Δposition) than in a normal position.

As expected, the vibration of soleus muscle resulted in a backward CoP displacement (CAPICIKOVA et al., 2006; DE NUNZIO et al., 2008). In addition, vibration also increased the mean CoP velocity (Figure 4.3.2). According to Figure 4.3.2, even the NonVib condition elicited a slight increase of CoP area and mean velocity. Since the NonVib trials were performed before the other two conditions, any residual vibratory effects cannot explain this result. It must be remembered that during NonVib, despite the vibratory devices were not switched on, they were being pressed against the soleous muscle by the elastic bands. Therefore, the simple vibratory devices' pressure against the muscle could had fired the muscle sensory endings. However, it is evident that greater effects were elicited by vibration.

Beside the significant CoP velocity increase in Parallel (~40%), the statistical procedures failed to find any difference in Area. We believe that CoP Area increase failed to reach statistical significance due to the high variability observed during both vibration conditions. This could be due to minor period used for analysis: 5 seconds. We decided to analyze only the final 5 seconds of each period to be sure that vibration effects would be greater. According to Capacikova et al. (2006), the vibration effects

magnitude is linear to the time stimulation is applied on the muscle (CAPICIKOVA et al., 2006). Therefore, if we had included the initial seconds after vibration onset on the analysis, the vibratory effects could be masked. In addition, the low number of participants could also explain the lack of significance in CoP area. These two issues are pointed as study limitations and should be overcome in future studies. However, even with a short number of participants a high effect size and power was observed for both VM (η^2=0.57; observed power = 0.89) and ΔPosition (η^2=0.56; observed power = 0.87).

The results successfully demonstrated stronger postural effects elicited by vibration in upright standing when the vibratory devices are positioned parallel to muscle fibers. Considering the small width of the receptor-bearing muscle, positioning the vibratory devices in Parallel could had increased device/muscle interface area, increasing the number of sensory endings fired by vibration. Also, this position could had created a lower spread effect to non-target muscles, as reported by others (TAN; ALMEIDA; RAHIMI, 2011).

4.3.5. Conclusion

We conclude that positioning the vibratory devices in a Parallel position to muscle fibers direction elicits stronger postural effects during upright standing than in a Normal position.

4.4. Muscle vibration improves gait initiation performance in healthy young adults

Marcelo P. Pereira, Paulo H. S. Pelicioni, Lilian T. B. Gobbi

4.4.1. Introduction

Voluntary movements, such as gait initiation, are accompanied by postural adjustments performed prior to movement execution (RUGET et al., 2008). These adjustments are called anticipatory postural adjustments (APAs) (BRENIERE; CUONG DO; BOUISSET, 1987). To unload the stepping limb and to allow movement progression, a forward and towards the stance limb center of mass (CoM) displacement is expected (RUGET et al., 2010). This CoM displacement is elicited by a center of pressure (CoP) shift, towards the swing limb and backwards (ROBERT et al., 2004). In this way, the antero-posterior CoP displacement during APAs is as much important to define gait initiation performance as the medio-lateral displacement (HASS et al., 2008).

The setting of APAs are highly based on sensory information (MOUCHNINO; BLOUIN, 2013; RUGET et al., 2010). However, previous studies have shown that APA is robust to proprioceptive manipulation (RUGET et al., 2010; RUGET et al., 2008). In line with this view, Ruget et al. (2008) found no influence of proprioceptive manipulation in APA parameters, suggesting that other sensory information could mask the proprioceptive weight in the APA setting (RUGET et al., 2008). Moving one-step ahead, Ruget et al. (2010) demonstrated an effect of proprioception manipulation in the APA parameters only when all other sensory information was absent (RUGET et al., 2010). These previous studies suggested that other sensory information, as cutaneous, are used in a higher scale to set APAs than proprioceptive information (RUGET et al., 2010; RUGET et al., 2008). In agreement, Mouchnino et al. (2013), using a platform translation paradigm, demonstrated that APA scaling is highly based on the cutaneous system information (MOUCHNINO; BLOUIN, 2013). In common, all these studies (MOUCHNINO; BLOUIN, 2013; RUGET et al., 2010; RUGET et al., 2008) directly manipulated the APA medio-lateral component, leaving behind a lack of information about the proprioceptive system role in the sagittal APA setting.

We believe that manipulating the proprioceptive system to induce antero-posterior body shift, as it has been done in the medio-lateral plane (MOUCHNINO;

BLOUIN, 2013; RUGET et al., 2010; RUGET et al., 2008), would directly influence the APA setting. We believe in that, because previous studies have shown that as larger is the backward CoP displacement, longer and faster is the first step (BRENIERE; CUONG DO; BOUISSET, 1987; HALLIDAY et al., 1998). An instrument that had been used to manipulate the proprioceptive system and to induce postural adjustments is the muscle vibration (COURTINE et al., 2007a; RUGET et al., 2010; RUGET et al., 2008). Since muscle vibration bilaterally applied on the lower limbs during upright standing shifts the CoP in the antero-posterior direction (CAPICIKOVA et al., 2006; COURTINE et al., 2007a; POLONYOVA; HLAVACKA, 2001), it is suggested that some APA adaptations could be elicited by this technique. Two major CoP behaviors are found in those conditions: (i) a CoP displacement towards the vibrated muscles, e.g. when vibration is applied on the tibialis anterior, a forward CoP displacement is observed (CAPICIKOVA et al., 2006; COURTINE et al., 2007a; HASS et al., 2012; POLONYOVA; HLAVACKA, 2001); (ii) it is also observed a CoP over recovery in relation to its initial position after vibration interruption (CAPICIKOVA et al., 2006; DUCLOS, N. C. et al., 2014; THOMPSON; BELANGER; FUNG, 2007).

Therefore, since during gait initiation a backward CoP shift is expected at APA phase (BRENIERE; CUONG DO; BOUISSET, 1987; HALLIDAY et al., 1998; HASS et al., 2008), we suppose that muscle vibration applied bilaterally on the tibialis anterior during the movement execution would act in a non-relevant way to the task, since in this case, a forward CoP shift would be elicited by vibration (COURTINE et al., 2007a; POLONYOVA; HLAVACKA, 2001). As a result, we believe, in a worsening gait initiation performance in this last scenario. In a complete different way, if vibration could be turned-off immediately before APA onset, an over backwards CoP shift would be elicited (CAPICIKOVA et al., 2006) – assisting the APA execution. Thus, in order to investigate this theory and the role of proprioception manipulation on the APA sagittal set, we applied vibration to induce an antero-posterior CoP displacement in two ways: (i) a non-relevant way to the task: during the gait initiation execution; (ii) a relevant way: only before gait initiation onset, assisting the APA performance). As hypothesis, a worse gait initiation performance is expected in the first scenario. Additionally, it is also expected an improvement in the gait initiation performance when vibration is applied only before the task execution. As alternative hypothesis, if proprioception is not important to set APA (MOUCHNINO; BLOUIN, 2013; RUGET et al., 2010; RUGET et

al., 2008), even in the sagittal plane, gait initiation and APA will not be influenced by vibration in any way.

Additionally, previous studies have shown that muscle vibration effects are task-, amplitude-, timing- and frequency-dependent (CAPICIKOVA et al., 2006; COURTINE et al., 2007a; POLONYOVA; HLAVACKA, 2001; UIMONEN et al., 1996). Polonyova et al. (2001) found greater postural effects during upright standing when the gastrocnemius was stimulated by higher vibration frequencies: 100Hz (POLONYOVA; HLAVACKA, 2001). This was an unexpected result, since physiological assessments showed poorer vibratory effects with the use of vibration frequencies higher than 80Hz (ROLL; VEDEL, 1982), due to subharmonic motor unit synchronization mechanisms (BURKE et al., 1976a; ROLL; VEDEL, 1982). In this way, since this seems to be an unsolved issue, we also aimed to investigate whether the application of different vibration frequencies would influence APA and gait initiation performance. Based on the results of Polonyova et al. (2001), we believe that higher vibration frequencies will influence gait initiation in a greater extent.

4.4.2. Methods

Participants

Fourteen healthy young participants (7 males; mean age: 21.40±4.26 years; height: 164.61±10.08cm; mass: 66.17±10.04kg) participated in the study. Participants gave written informed consent approved by the institution Human Ethical Committee[1]. All subjects were self-reported right-foot preference. Exclusion criteria included any neurological, orthopedic, vestibular or not corrected visual disturbances. Subjects were asked to not perform any physical activity 24 hours before the assessment.

Vibratory devices

A custom-made vibration system was used (named RCVibro System). This system is composed by up to eight vibrating devices and a movable electronic board that receives information from regular personal computers via radio. The RCVibro System interface allows the control of both vibration onset Moment and vibration Frequency. Three pairs of cylindrical vibratory devices (measuring 4.5cm x 2cm x 2cm;

[1] Anexo 2

containing constant-velocity DC motors (Faulhaber®) bearing eccentric masses) were positioned bilaterally in the muscles' bellies proximal region of Trapezius superior, Tibialis anterior and Rectus Femoris, in parallel to muscle fibers. For fixation, ordinary elastic bands were used. These muscles were chosen because their stimulation elicits a forward CoP displacement (COURTINE et al., 2007b; GURFINKEL et al., 1998). All devices' vibration amplitude was 0.8mm.

Task and Procedures

Subjects were asked to walk a 4 meters pathway looking ahead, initiating the movement from an upright posture with arms on body side. The participants were asked to always start the task with their preferred lower limb and to walk at their self-selected pace. Each participant executed three trials in three different experimental conditions: a baseline condition - without vibration (NonVib); vibration applied during (Du) the movement; and vibration applied only immediately Before (Be) movement onset. In addition, two different vibration frequencies were tested: 80Hz (80) and 120Hz (120). Therefore, each participant executed a total of 15 trials in five experimental conditions: NonVib, 80Du, 120Du, 80Be and 120Be. For all participants, NonVib was the first condition to be tested. The other conditions were randomly distributed in blocks. A rest period of 30 seconds between trials and 3 minutes between conditions was given.

For all conditions, the vibration stimulus was continuously applied for 30 seconds, since greater postural effects are elicited after this period (CAPICIKOVA et al., 2006). For the Du conditions, participants started the movement after a verbal command given at the 28th second of vibration. For the Be conditions, participants were asked to execute the movement immediately after the devices were switched-off: at the 30th second of vibration. This procedure ensured that all participants were exposed to the same period of vibration: 30 seconds. During the NonVib conditions, the vibratory units were also kept in contact with the skin and fixed with elastic bands, but no vibration was applied.

Data Acquisition

Four camcorders (sampling rate of 60Hz) were used to capture the position of four passive markers attached to the following anatomic landmarks: bilaterally on the 3rd metatarsal bones and heels. Markers were digitized automatically on Digital Video

for Windows (DVIDEOW) software (FIGUEROA; LEITE; BARROS, 2003). As kinematic dependent variables, we assessed the first step time (from heel off until heel strike), length, width and velocity, duration of the Postural Adjustment phase (PA: from beginning of the movement – first change on the ground reaction force (GRF – manually detected) – until swing limb heel-off) and duration of the entire task (PA + step time).

To assess kinetic data, two force plates (AMTI®) were positioned one aside other allowing the subjects to step with one foot on each force plate. Initial position of the feet was self-selected and was kept consistent. Kinetic data was assessed with a sampling rate of 100Hz. As kinetic dependent variables, we assessed the maximal vertical and horizontal ground reaction force (GRF - normalized to participants' body weight) for the swing and stance limb. We also assessed the GRF of each limb during quiet standing (1 second before the movement onset). The CoP behavior (duration, A-P and M-L displacement and mean velocity) was also assessed in three different phases (HASS et al., 2012; HASS et al., 2008): Anticipatory Postural Adjustment phase (APA: from the first change in the vertical GRF until the most posterior and lateral position of the CoP towards the swing limb); the Weight Transfer phase (WT – from the end of the previous phase until the peak medial and posterior CoP position towards the stance limb); the Locomotor phase (LP – from the end of the previous phase until stance limb toe-off). All data analysis were assessed using specific MatLab (MathWork®) codes.

Statistical Analysis

Two rows of analysis were used. In the first row, we analyzed vibration parameters effects on each variable by means of two-way Analysis of Variance (2x2 ANOVAs): considering Moment (Be x Du) and Frequency (80 and 120) as within-subjects factors. In this way, during this row of analysis, we excluded the NonVib condition. During the second row, we ran a new series of one-way ANOVAs, including the NonVib condition. For that, we considered only the factor that reached significance in the first row, combining the other factor into one. For example, if for step length we found only a Moment effect during the first row, in the second row, the conditions used for the one-way ANOVA were NonVib, Du and Be (the conditions 80 and 120 were averaged into Moment). Wherever necessary, we used the Tukey post-hoc test to investigate any univariate comparisons.

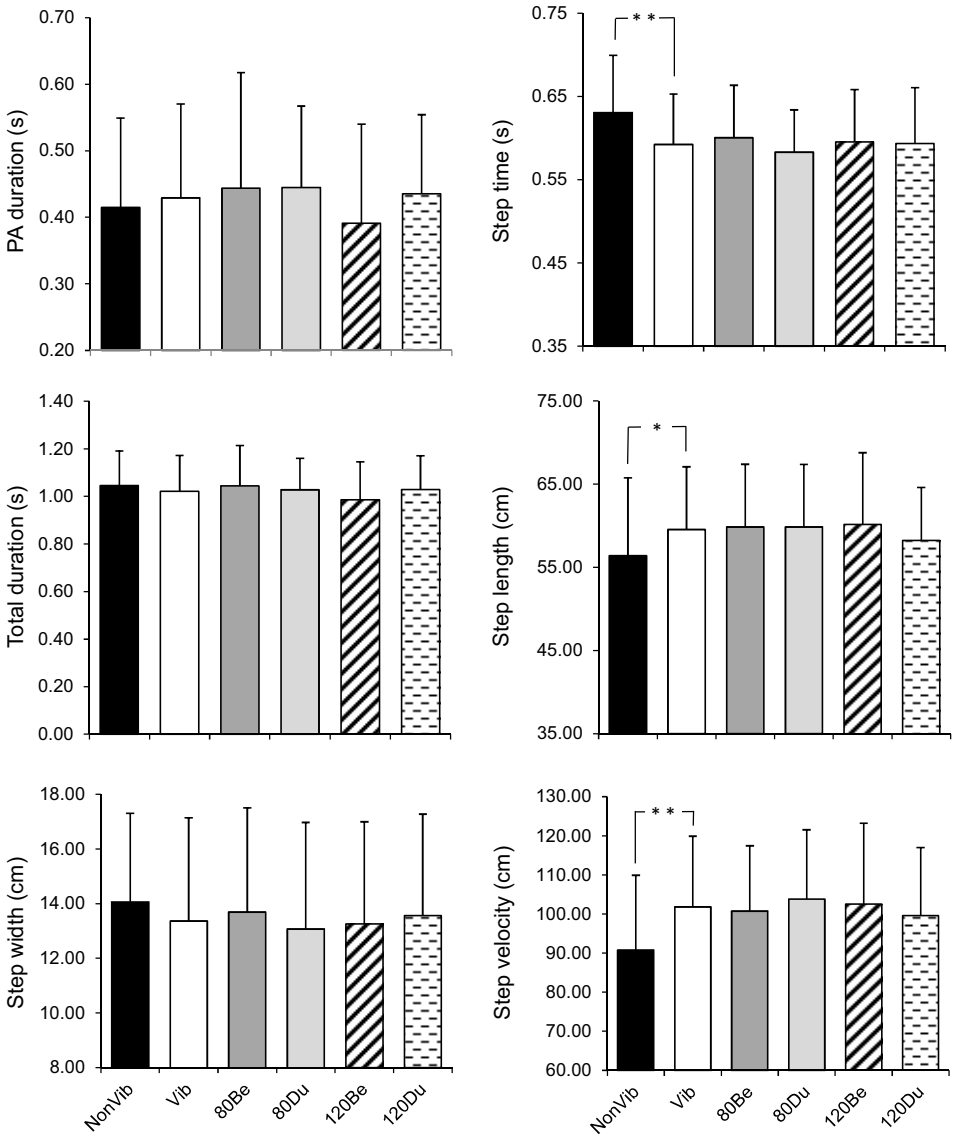
In all cases, where no significance was found in the first row of analysis, we used a Student T test for dependent variables considering the conditions NonVib and Vib (where all conditions were averaged). This procedure was used to guarantee that the lack of significant effects of a condition would not mask positive effects of other conditions. The Statistica 7.0 software was used for all statistical procedures.

4.4.3. Results

Kinematic variables

No main effects of both Frequency and Moment were observed during the first row of analysis for all kinematic variables (for all variables: Frequency: $p>0.18$; Moment: $p>0.12$). During the second row of analysis, we found a decrease in step time, an increase in step length and an increase in step velocity with the use of muscle vibration (Comparison between NonVib and Vib - Figure 4.4.1).

Figure 4.4.1. Mean and standard deviation of kinematic variables in all conditions.



Comparisons were made only between NonVib and Vib - the other conditions are shown for overall comparisons.
PA: Postural Adjustment phase.
*p<0.1; **p<0.001.

Kinetics

The only kinetic variable that showed influence of Moment was the swing limb vertical GRF during standing (F=5.39; p=0.02) without any effect of Frequency (p=0.15). In this case, after the one-way ANOVA (F=3.68; p=0.03) considering the conditions NonVib, Be and Du, the univariate analysis showed that Be (48.02±2.88%BW) was higher (p=0.02) than NonVib (46.00±4.12%BW). Du (47.00±3.58%BW) was not different from other conditions (p>0.16). No other variable was influenced by either Frequency (p>0.22) or Moment (p>0.12). Table 4.4.1 summarizes the comparisons between NonVib and Vib conditions for the kinetic

variables. At the end of these analysis, we can affirm that vibration decreased the body weight on the stance limb (independently of vibration conditions) and reduced the GRF on swing limb (only during the Be condition, independently of vibration frequency).

Table 4.4.1. Mean and ±standard deviation values of Ground Reaction Forces (GRF); Student-t test and p values are shown.

	NonVib	Vib	t	p
Maximal Vertical GRF (%BW)				
Swing Limb	64.05 ±7.56	65.11 ±8.34	-0.64	0.52
Stance Limb	113.55 ±7.43	114.30 ±5.89	-0.61	0.54
Maximal Horizontal GRF (%BW)				
Swing Limb	1.14 ±0.89	0.88 ±1.26	1.11	0.27
Stance Limb	0.84 ±0.29	0.89 ±0.41	-0.59	0.55
Vertical Standing GRF (%BW)				
Stance Limb	**56.00 ±4.24**	**53.26 ±4.59**	**3.01**	**<0.01**

Only those variables that did not show any Moment or Frequency effects in the first row of analyzes are shown;
%BW: % of body weight.
Significant effects are bolded.

CoP Behavior

The Moment and Frequency effects in the CoP dependent variables are summarized on Table 4.4.2. As it can be seen, we found a Moment effect for APA duration and for CoP M-L velocity during LM phase. We also found a Moment and Frequency effect for APA A-P velocity.

Table 4.4.2. ANOVAs F and p values for Moment and Frequency effects on CoP dependent variables.

	df	Frequency		Moment	
		F	p	F	p
APA phase					
Duration (s)	1, 32	0.05	0.82	**14.86**	**<0.01**
Velocity (cm/s)	1, 32				
Medio-Lateral		1.71	0.20	1.56	0.35
Antero-Posterior		**5.05**	**0.03**	**16.66**	**<0.01**
WT phase					
Duration (s)	1, 32	0.46	0.50	0.03	0.86
Velocity (cm/s)	1, 32				
Medio-Lateral		0.49	0.49	3.46	0.07
Antero-Posterior		0.02	0.88	0.02	0.88
LM phase					
Duration (s)	1, 32	0.86	0.36	3.56	0.07
Velocity (cm/s)	1, 32				
Medio-Lateral		2.90	0.10	**4.23**	**0.05**
Antero-Posterior		0.04	0.84	0.10	0.76

APA: Antecipatory Postural Adjustment; WT: Weight Transfer phase; LM: Locomotor phase. df: degrees of freedom.
Significant effects are bolded.

For the APA duration, the one-way ANOVA, considering NonVib, Be and Du, showed a significant result (F=3.36, p=0.04), where Be (0.33±0.12s) was shorter than both Du (0.38±0.11s; p=0.033) and NonVib (0.36±0.14s; p=0.042). For CoP M-L velocity during Locomotor phase the one-way ANOVA did not reach significance (F=0.84, p=0.43).

The only variable that showed significance for both Moment and Frequency was the A-P velocity during APA phase (Table 4.4.3). In that case, we ran a one-way ANOVA considering all experimental conditions and a statistical significance was found (F=6.12, p=0.001). The univariate comparisons showed that CoP velocity in the 120Be (20.72±9.45cm/s) was higher than almost all other conditions: NonVib: 10.99±5.09cm/s (p=0.003); 80Du: 10.03±5.00cm/s (p=0.003); 120Du: 9.46±4.79cm/s

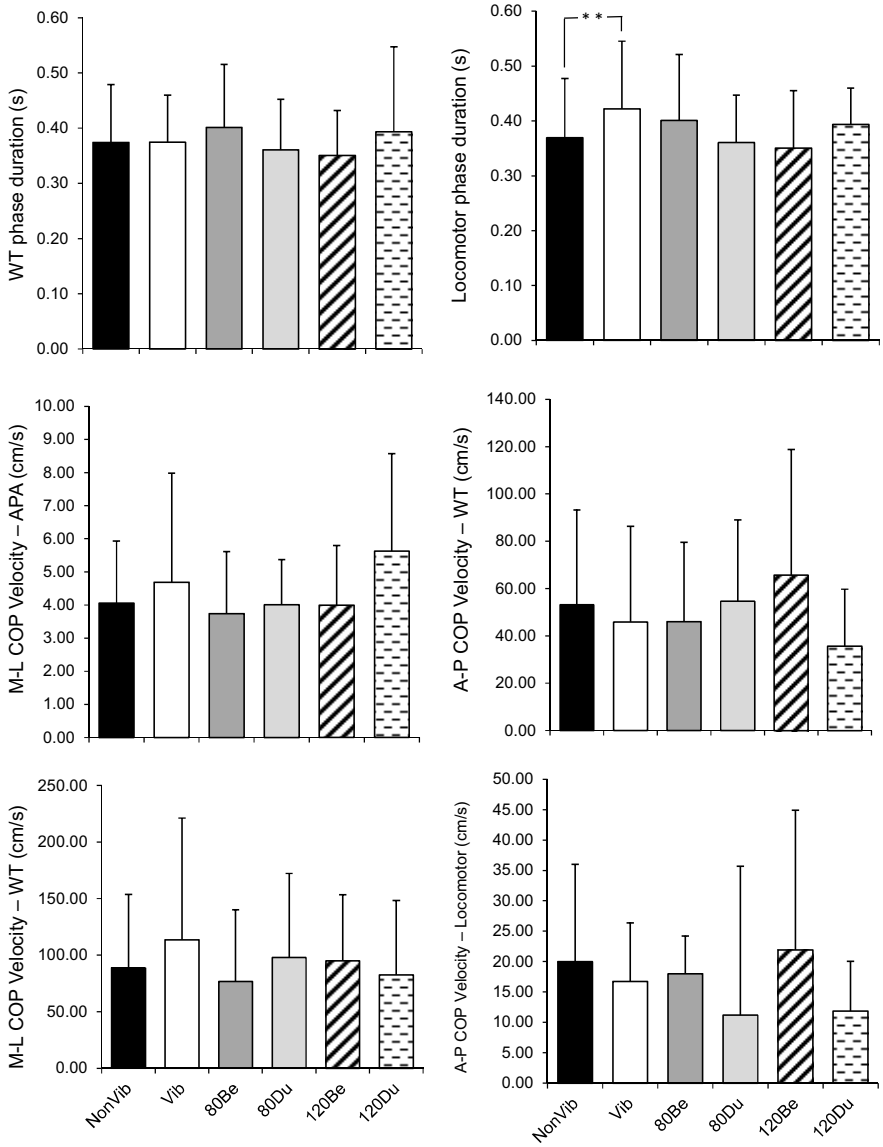
(p=0.004). However 120Be was not different from 80Be (11.51±5.91cm/s; p>0.18). All other comparisons were not different between each other (p>0.20).

The Student T test comparing NonVib and Vib conditions for other variables (Figure 4.4.2) showed that vibration increased the LM duration.

In resume, vibration reduces the duration of APA and increases its A-P velocity (especially in the 120Be and 80Be conditions). Vibration also increased the LM duration, no matters the parameters that had being used.

No interactions between factors were found for any variables (p>0.10).

Figure 4.4.2. Mean and standard deviation of kinetic variables in all conditions.



Comparisons were made only between NonVib and Vib - the other conditions are shown for overall comparisons.
APA: Anticipatory Postural Adjustment phase; WT: Weight Transfer phase; LM: Locomotor phase. **p<0.001.

4.4.4. Discussion

The main aim of this study was to investigate the effects of manipulating the proprioceptive system on the performance of gait initiation in healthy young adults. Additionally, another aim of this study was to investigate the effects of different vibration frequencies on the performance of this task. As main result, we found an improvement of gait initiation performance with muscle vibration, mainly when it was applied immediately before the task execution. Three mechanisms are pointed as major causes of this improvement: postural post-vibratory effects, attentional mechanisms or a combination of both. Finally, we found that the vibration frequency does not play an important role in this scenario.

To properly execute gait initiation, a backward CoP displacement towards the swing limb is expected (DESSERY et al., 2011; HENRIKSSON; HENRIKSSON; BERGENIUS, 2011). As greater is the velocity and as shorter is the duration of this displacement, higher is the first step length and velocity (BRENIERE; CUONG DO; BOUISSET, 1987; HALLIDAY et al., 1998). Since we observed a shorter APA phase and a faster A-P CoP velocity when vibration was applied only immediately before gait initiation onset, we suggest that post-vibratory effects benefited the participants, leading to an increase of both step length and velocity (BRENIERE; CUONG DO; BOUISSET, 1987; HALLIDAY et al., 1998). The GRF results support this hypothesis – we found a greater GRF in the swing limb with the use of muscle vibration before movement initiation, suggesting that participants were already prepared to perform a faster CoP backwards displacement. However, if the improvement of gait initiation performance was related only to post-vibratory effects (CAPICIKOVA et al., 2006; DUCLOS, N. C. et al., 2014; THOMPSON; BELANGER; FUNG, 2007; WIERZBICKA; GILHODES; ROLL, 1998), we would also have found a Moment effect in the first step spatiotemporal parameters. Since we did not find this result, the vibration benefits to gait initiation performance cannot be restricted to post-vibratory effects.

Tard et al. (2013) demonstrated that stimulus-driven attention can modify the motor behavior of APAs. In addition, a previous study demonstrated that sensory stimulus might change the step preparation and execution (BURLEIGH-JACOBS et al., 1997). Therefore, we suggest that muscle vibration applied during the movement execution shifted the participants' attentional mechanisms to the task performance. This might have improved the first step spatiotemporal parameters without changing

the APA behavior. However, if attentional shifting was the only mechanism underlying our results, we should not find any Moment effects, since in both Be and Du, vibration was being applied equally. Taken together, our results suggest that both mechanisms (postural post-vibratory effects and attentional mechanisms) play some role in the improvement of gait initiation performance when muscle vibration is applied in healthy young adults.

In this way, differently than previous studies, that did not find important effects of muscle vibration when it was applied to induce postural adaptations in the frontal plane (RUGET et al., 2010; RUGET et al., 2008), we found an improvement of gait initiation performance when muscle vibration was applied to induce sagittal plane adaptations. These results suggest that proprioception is used in a higher instance to set APA in the A-P rather than in the M-L plane.

Another aim of this study was to investigate the effects of manipulating the vibration frequency on the gait initiation performance. As main result, we found that different vibration frequencies do not influence gait initiation motor behavior. This was not expected since previous studies showed a linear increase in postural responses with higher vibration frequencies (POLONYOVA; HLAVACKA, 2001). One possible explanation for this lack of significant results is that the vibration frequency range used in this study (80-120Hz) is not high enough to induce postural adaptations. However, Polonyova et al. (2001) showed that an increase of just 20Hz is enough to change the body shift magnitude during upright standing (POLONYOVA; HLAVACKA, 2001). For our best understanding, this is the first study to investigate the effects of different vibration frequencies on transitional tasks performance, as gait initiation. We suggested that during the movement execution, the sensory vibratory effects were suppressed by superior volitional commands (COURTINE et al., 2007a). Voss et al. (2006) findings support this hypothesis – the authors found that pre-programed movement setting interrupts the somatosensory influx to the central neural system. Therefore, if sensory manipulation was neglected by the participants, increasing vibration frequency would not lead to different motor adaptations. This model explains why higher vibration frequencies induces postural effects on upright standing (POLONYOVA; HLAVACKA, 2001), but not during gait initiation.

Finally, since vibration reduced APA duration, some could argue that a reduction of the WT and LM would also expected with muscle vibration. However, a shorter WT and LM were not expected. In the Be condition, since vibration effects are

cessed as soon as the vibration is interrupted (BURKE et al., 1976a) and considering that the participants took another ~0.37 second to perform APA, the vibration effects would already have disappeared at the WT onset. In another way, in the Du condition, as we suggested before, vibration effects would have been suppressed by the volitional movement execution (COURTINE et al., 2007a).

4.4.5. Conclusion

At the end of this study, we can affirm that muscle vibration applied immediately before the task onset, improves the gait initiation performance in young healthy adults, reducing the first step time and increasing its both length and velocity. We suggest that a combination of postural and attentional mechanisms underlies our results. In addition, this study shows that proprioceptive system plays some role in the A-P APA setting. Manipulating vibration frequency does not lead to any motor adaptation.

4.5. Does proprioceptive system stimulation improve sit-to-walk performance in healthy young adults?

Marcelo P. Pereira, Paulo H. S. Pelicioni, Juliana Lahr, Lilian T. B. Gobbi

4.5.1. Introduction

Muscle vibration elicits an activation of muscle spindles Ia sensory endings (BURKE et al., 1976b; HAGBARTH et al., 1976; MARTIN; PARK, 1997). This sensory firing results in an illusory stretching sensation of the receptor-bearing muscle (MARTIN; PARK, 1997). As a result, an involuntary muscle contraction of the receptor-bearing muscle is observed via the monosynaptic spinal reflex (BURKE et al., 1976b; MARTIN; PARK, 1997). Local vibration has been used like this to manipulate the proprioceptive system (RABIN et al., 2010; TAN; ALMEIDA; RAHIMI, 2011) in two different ways: to facilitate movement execution or to disturb the proprioceptive system (COURTINE et al., 2007a; DE NUNZIO et al., 2010; RUGET et al., 2010). During upright standing, lower limb muscle vibration elicits a center-of-pressure (CoP) displacement towards the receptor-bearing muscle (CAPICIKOVA et al., 2006). On the other hand, when trunk muscles are stimulated, CoP displacement towards the opposite side is noticed (COURTINE et al., 2007a). For instance, when the tibialis anterior, rectus femoris and upper trapezius are stimulated, the CoP shifts forward (COURTINE et al., 2007a). Therefore, stimulation of the proprioceptive system through muscle vibration applied to these muscles could improve motor patterns that require forward movement, such as gait initiation and the sit-to-walk movement.

The sit-to-walk movement is a sequential task in which a person performs a continuous transition from sitting to walking (KOUTA; SHINKODA; KANEMURA, 2006). The success of this task relies on the generation of a forward momentum (CHEN; CHOU, 2013; KOUTA; SHINKODA, 2007). Thereafter, when sufficient forward momentum is generated, the center of mass (CoM) shifts forward, eliciting the first step (CHEN; CHOU, 2013). Previous research observed a poorer sit-to-walk performance in fragile populations, as in older people or in people with Parkinson's disease (BUCKLEY; PITSIKOULIS; HASS, 2008; KOUTA; SHINKODA, 2007; KOUTA; SHINKODA; SHIMIZU, 2007). This poorer performance was related to an impaired proprioceptive system (BUCKLEY; PITSIKOULIS; HASS, 2008). As a

consequence of an impaired proprioceptive system, a more cautious strategy is adopted by these fragile populations (KOUTA; SHINKODA, 2007). Therefore, it is suggested that increasing the proprioceptive information inflow to the central nervous system could improve the sit-to-walk performance of these people. In the same way, the forward movement elicited by vibration applied to the tibialis anterior, rectus femoris, and upper trapezius could enhance the forward momentum generated to perform the sit-to-walk movement.

However, to the best of our knowledge, the effect of proprioceptive system manipulation on the sit-to-walk performance has never been tested. Thus, before we could suggest that it be used on frail individuals, we needed to establish its effects on healthy young adults. One issue that needs to be resolved is the best moment to apply this specific sensory manipulation to enhance sit-to-walk performance: before or during the movement execution. Previous physiological studies showed that the effects of vibration on sensory endings are interrupted as soon as the stimulus is ceased (BURKE et al., 1976b; MARTIN; PARK, 1997). This observation suggests that in order to elicit any effects, a vibration stimulus should be applied during movement. On the other hand, previous studies also demonstrated that vibration-induced effects continues to be observed after the end of stimulation during gait (COURTINE; POZZO; SCHIEPPATI, 2001). In addition, another study showed that during transitional movements, such as gait initiation, greater postural effects are elicited when vibration is applied before movement execution (RUGET et al., 2008). Therefore, it is clear that there is no consensus about this topic.

Therefore, the aims of this study were: (i) to evaluate the effects of proprioceptive manipulation through muscle vibration on the performance of the sit-to-walk task and (ii) to determine whether applying vibration during or before the sit-to-walk task could elicit different performance effects. As hypotheses, we believe that (i) muscle vibration will improve sit-to-walk performance and (ii) the effects induced by vibration will be greater when the vibration is applied during movement execution.

4.5.2. Subjects and Methods

Fifteen healthy young adults (7 males; mean age, 21.40±4.26 years; height, 164.61±10.08 cm; body-mass, 66.17±10.04 kg) participated in this study. The

institution's Human Ethics Committee approved all procedures[1]. All participants reported that they were right-footed and signed an informed consent form before participation in the study. Exclusion criteria included any neurological, orthopedic, vestibular or uncorrected visual disturbances that could interfere with the procedures. Participants were personally invited to participate, and none refused or were excluded. The participants were asked to not perform any physical activity 24 hours before the assessment.

A custom-made system was used (named the RCVibro System). This system was composed of up to eight vibrating devices and a movable electronic board capable of receiving information from regular personal computers via radio waves emitted by a USB interface device. Three pairs of cylindrical vibratory devices (measuring 4.5 cm x 2 cm x 2 cm; containing constant-velocity DC motors (Faulhaber®) bearing eccentric masses) were positioned bilaterally on the bellies of the upper trapezius, tibialis anterior, and rectus femoris. For fixation, elastic bands were used. These muscles were chosen because stimulation of them elicits a forward CoP displacement (COURTINE et al., 2007a). The used vibration frequency and amplitude were the same for all devices: 120 Hz and 0.8 mm.

Prior to movement initiation, participants were seated on an armless 45cm-high stool with their arms crossed over their chest and looking ahead. They positioned their feet as they wanted and kept the position consistent during all trials. After the examiner finished explaining the instructions, the participants were instructed to stand up from the stool and initiate gait at their own speed in a fluid and smooth way. They were instructed to not split the movement into two phases: they should initiate gait before reaching the full standing position. Participants performed three trials under three different experimental conditions: a baseline condition, without vibration (NonVib); with vibration applied during (Du) movement; and with vibration applied before (Be) movement. For all participants, the first condition tested was always NonVib, and it was always followed by the other two (randomly distributed). Rest periods of 30 seconds between trials and 3 minutes between conditions were given.

For all conditions, the vibration stimulus was continuously applied for 30 seconds. For the Du trials, participants started the movement after a verbal command given at the 28th second of vibration. For the Be trials, the participants were asked to

[1] Anexo 1

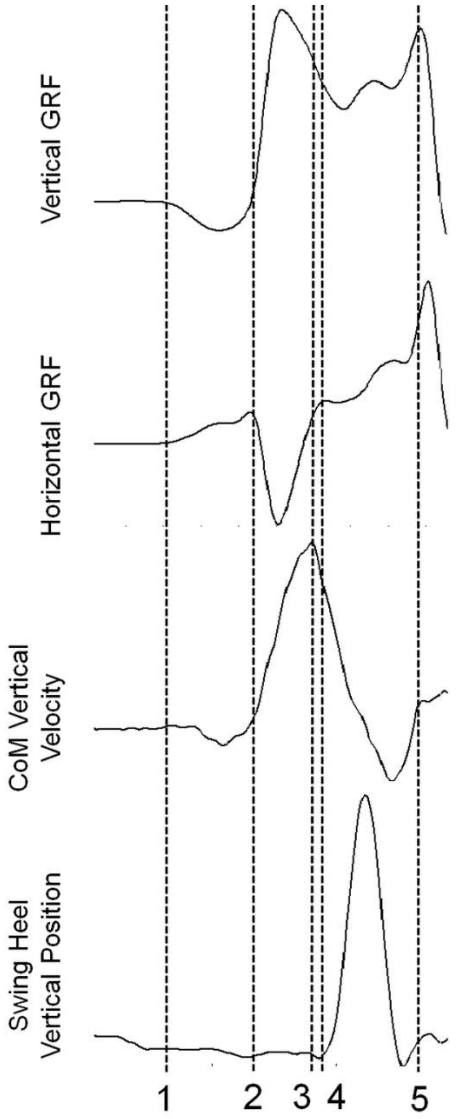
perform the movement immediately after the devices were switched-off, that is, at the 30th second of vibration. This procedure ensured that all participants performed the movement after the same amount of time: 30 seconds. During the NonVib trials, the vibratory units were kept in place, but not switched on.

Four camcorders (sampling rate of 60 Hz) were used to capture the positions of 22 passive markers attached to the following anatomic landmarks: bilaterally on the 3rd metatarsal bones, heels, lateral malleolus, femoral condyles, great trochanters, anterior superior iliac spine, hip joint projection, superior face of the acromion, lateral condyle of the humerus and temporal regions. Additionally, one marker was attached to the top of the head, and another was attached to sacral region (between second and third sacral vertebras). To assess kinetic data, two force plates (50x50 cm - AMTI®) were positioned side by side, allowing the subjects to step with one foot on each force plate. Kinetic data were obtained with a sampling rate of 200 Hz using the NetForce (AMTI®) software.

In order to assess kinematic variables, the passive markers position were digitized automatically by the Digital Video for Windows (DVIDEOW) software (FIGUEROA; LEITE; BARROS, 2003). The trajectories of all markers were filtered offline (low-pass 4^{th} order Butterworth filter with cut-off frequency of 8 Hz). To determine the center-of-mass (CoM) behavior, thirteen rigid segments were determined using classical anthropometric tables. The CoM position was assessed through the sum of these thirteen rigid segments (HAHN; CHOU, 2004). After offline filtering (low-pass 4^{th} order Butterworth filter with cut-off frequency of 9 Hz), kinetic data were used to determine specific task events.

The sit-to-walk task was subdivided in four phases (Figure 4.5.1), according to previous published papers (BUCKLEY et al., 2009; KERR et al., 2007): (i) flexion phase: from the movement initiation (first detectable event in the total vertical ground reaction force) until seat-off (identified as the first peak in the total horizontal ground reaction force); (ii) extension phase: from the end of the previous phase until the CoM peak vertical velocity; (iii) transition phase: from the end of the extension phase until the swing limb heel off; and (iv) execution phase: determined from the swing limb heel off until heel strike for the same limb. Figure 4.5.1 shows the kinematic and kinetic traces of a single trial of one participant under the NonVib condition. Data were processed using specific MatLab (MathWorks®) algorithms.

Figure 4.5.1. Kinematic and kinetic data traces used to define each task phase.



1: movement onset; 2: seat-off; 3: standing position; 4: swing heel-off; 5: swing heel-strike. GRF: ground reaction force; CoM: Center of mass.

The following kinematic dependent variables were determined: first step time, length, width, velocity, and total duration (time between movement onset and swing limb heel strike). In addition, the CoM horizontal, latero-lateral and vertical displacements and velocities were determined for each movement phase.

The Statistica 7.0 software was used for all statistical procedures. Seeking to determine whether experimental conditions (NonVib *vs* Du *vs* Be) could influence dependent variables, a series of one-way ANOVAs with repeated measures was used. Whenever necessary, for univariate comparisons, Tukey post hoc tests were used. P values were considered as statistically significant when <0.05.

4.5.3. Results

Table 4.5.1 shows a complete absence of vibration effects on the durations of the sit-to-walk phases. The only phase that presented a tendency for statistical significance was the flexion phase. All other variables showed no statistical significance (p>0.57).

Table 4.5.1: Mean duration (± standard deviation) of sit-to-walk phases.

	Be	Du	NonVib	P-value
Phases Duration (s)				
Flexion	0.56 (0.09)	0.64 (0.07)	0.62 (0.06)	0.06
Extension	0.37 (0.11)	0.34 (0.07)	0.36 (0.09)	0.80
Transition	0.10 (0.05)	0.11 (0.07)	0.12 (0.14)	0.93
Execution	0.56 (0.07	0.59 (0.07)	0.59 (0.08)	0.57
Total Duration (s)	2.42 (0.25	2.51 (0.24)	2.50 (0.25)	0.67

Be: vibration applied before the movement; Du: vibration applied during the movement; NonVib: no vibration.

Hence, according to Table 4.5.1, local vibration was ineffective in modifying the duration of any of the task phases. Confirming this result, Table 4.5.2 shows that vibration was not able to modify CoM displacement (p>0.44) or velocity (p>0.66) in any direction during any of the task phases and main events. These results show no movement-pattern modification with the use of local vibration as applied in this study.

In agreement with the above results, the spatiotemporal parameters of the first step were not modified by vibration. This was the case for step duration (Be, 0.56±0.07s; Du, 0.59±0.07s; NonVib, 0.59±0.08s; p=0.56), step length (Be, 67.10±6.24cm; Du, 66.21±6.24cm; NonVib, 64.00±5.20cm; p=0.24), step width (Be, 20.12±5.34cm; Du, 19.85±7.12cm; NonVib, 21.32±8.02cm; p=0.32) and step velocity (Be, 121.77±15.06cm/s; Du, 114.42±13.33cm/s; NonVib, 111.04±11.18cm/s; p=0.25).

Table 4.5.2: Mean displacement and velocity (standard deviation) of the center-of-mass in three directions for all sit-to-walk phases and events.

	Vertical				Horizontal				Latero-lateral			
	Be	Du	NonVib	P	Be	Du	NonVib	P	Be	Du	NonVib	P
Displacement (cm)												
Flexion	-0.95 (1.96)	-1.97 (0.88)	-1.08 (2.91)	0.45	18.45 (5.47)	19.89 (4.22)	18.19 (4.07)	0.59	-2.38 (2.01)	-2.06 (2.42)	-2.36 (2.60)	0.79
Extension	16.24 (3.74)	15.87 (1.96)	14.68 (3.48)	0.44	16.24 (4.85)	15.45 (2.28)	18.11 (3.55)	0.20	-1.84 (1.49)	-1.88 (1.15)	-1.89 (1.55)	0.99
Transition	-6.94 (2.38)	-7.11 (3.20)	-7.29 (5.94)	0.98	-3.30 (1.32)	-3.10 (1.47)	-2.88 (2.24)	0.88	0.78 (0.83)	0.90 (0.86)	0.93 (0.64)	0.83
Execution	6.52 (3.34)	7.21 (2.99)	7.99 (4.90)	0.67	32.53 (3.52)	33.11 (5.24)	32.99 (5.89)	0.95	32.53 (3.52)	33.11 (5.24)	32.99 (5.89)	0.83
Velocity (cm/s)												
Seat-off	7.51 (14.71)	3.88 (8.37)	1.89 (17.65)	0.66	65.31 (13.70)	67.62 (10.20)	70.22 (9.48)	0.68	0.39 (1.36)	0.31 (0.77)	0.16 (0.60)	0.86
Standing	78.41 (10.46)	77.36 (8.44)	79.50 (1.76)	0.98	32.74 (7.88)	33.44 (9.96)	33.98 (9.61)	0.85	-5.86 (4.39)	-5.89 (4.64)	-5.28 (3.17)	0.94
Heel off	66.47 (12.06)	66.35 (14.12)	68.62 (17.38)	0.93	33.50 (8.06)	32.85 (9.90)	32.95 (10.18)	0.98	9.61 (7.30)	11.01 (6.61)	10.54 (6.19)	0.89
Heel strike	0.56 (6.03)	2.89 (9.68)	1.64 (6.72)	0.81	95.05 (12.17)	92.87 (18.84)	93.13 (13.76)	0.93	-2.30 (3.34)	-2.70 (2.64)	-2.05 (4.10)	0.89

Be: vibration applied before the movement; Du: vibration applied during the movement. NonVib: no vibration. Positive values refers to upward, forward and towards the swing-limb.

4.5.4. Discussion

The aim of this study was to investigate if muscle vibration could influence sit-to-walk performance in healthy young adults. In addition, we aimed to investigate whether the timing of vibration application (before or during movement) could influence the sit-to-walk motor behavior and performance. The results clearly show that, at least in healthy young adults, local vibration does not change the motor behavior and performance of the sit-to-walk task. Thus, we suggest that the proprioceptive system does not play an important role in the CoM scaling movement during the sit-to-walk movement.

The lack of vibration effects under the Be condition was not surprising, since previous studies have shown that muscle vibration effects are lost as soon as the vibration is interrupted (BURKE et al., 1976b; CAPICIKOVA et al., 2006; WIERZBICKA; GILHODES; ROLL, 1998). In line with this hypothesis, a previous study did not find significant effects on the gait performance when participants walked after neck muscles vibration (BOVE et al., 2001).

On the other hand, the lack of positive results under the Du condition is opposite to our initial hypothesis. The presence of preprogramed motor patterns could have masked the vibration effects (COURTINE et al., 2007a). This hypothesis is based on the notion that healthy young adults do not rely on proprioception information to scale transitional movements (MOUCHNINO; BLOUIN, 2013; RUGET et al., 2010).

The sit-to-walk movement is a transitional task in which potential energy transfer to kinetic energy is needed in order to allow the first step (BUCKLEY et al., 2009; BUCKLEY; PITSIKOULIS; HASS, 2008). Previous research suggested that lower limbs vibration could disturb transfer between gravitational potential energy and kinetic energy (DE NUNZIO et al., 2010). However, our participants were not disturbed by vibration, suggesting that the proprioceptive information inflow provided by vibration was ignored. This result suggests that during transitional tasks, such as the sit-to-walk movement, proprioception does not have a great importance in scaling the movement execution. This hypothesis is in line with the findings of a previous study (MOUCHNINO; BLOUIN, 2013; RUGET et al., 2008) that demonstrated a lack of proprioception information usage during gait initiation. In agreement with this, Ruget et al. (2010) showed that proprioceptive information is only used to scale gait initiation in heathy young adults when all other sensory information was absent.

Taken together, all these results suggest that, at least in healthy young adults, preprogrammed motor patterns are not modified by proprioceptive system manipulation. In agreement with this idea, previous results have shown few if any vibration effects in healthy young people when walking on normal ground (COURTINE et al., 2001; DE NUNZIO et al., 2008; IVANENKO; GRASSO; LACQUANITI, 2000). Otherwise, when vibration is applied to the lower limbs of patients with impairments in the execution of preprogrammed motor patterns, such as Parkinson's disease patients (HAUSDORFF, 2009), vibration improves walking performance (DE NUNZIO et al., 2010; GHOSEIRI et al., 2009a). Thus, our results reinforce the hypothesis that proprioception information is neglected during the execution of preprogrammed motor patterns (MOUCHNINO; BLOUIN, 2013; RUGET et al., 2010; RUGET et al., 2008). To confirm this hypothesis, we suggest that future studies should assess the effects of local vibration on people showing impairments in the pre-programmed motor patterns execution, such as Parkinson's disease patients.

We cannot explain by our results the true reason why vibration did not elicit any response in the sit-to-walk performance in healthy young adults. However, our results, reinforce the hypothesis that in healthy young adults, sensory information other than proprioception is more important in scaling transitional movements (MOUCHNINO; BLOUIN, 2013; RUGET et al., 2010; RUGET et al., 2008). The present study has some limitations, such as the small number of participants assessed. However, the kinematic data are clear in showing a complete absence of vibration effects in the sit-to-walk execution performance in healthy young adults.

The results of this study show that healthy young adults do not benefit from muscle vibration when performing the sit-to-walk task. This lack of motor adaptation to vibration occurs regardless of when vibration is applied: before or during the movement. The reasons for this lack of significant effects is not clear, but the lack of significant effects suggests that healthy young adults neglect proprioceptive information when executing preprogrammed motor patterns.

5. EFEITOS DA MANIPULAÇÃO DO SISTEMA PROPRIOCEPTIVO SOBRE O DESEMPENHO LOCOMOTOR DE PESSOAS COM DOENÇA DE PARKINSON COM E SEM CONGELAMENTO DA MARCHA.

5.1. Apresentação

Como apresentado na Seção 1 dessa Tese de Doutorado, sugerimos que a manipulação do sistema proprioceptivo, por meio da vibração muscular, pode trazer benefícios na execução de tarefas locomotoras em pessoas com doença de Parkinson, com e sem congelamento da marcha. Ainda, sugerimos que o uso dessa técnica pode, também, promover alívio da severidade dos episódios de FOG nessa população.

Assim, com intuito de testarmos essas hipóteses e estando embasados nos resultados encontrados nas Seções 3 e 4, desenvolvemos essa quinta Seção que julgamos ser a principal dessa Tese de Doutorado. Nessa Seção apresentamos, na sequência, três estudos na forma de artigos científicos completos, que avaliaram: (i) o efeito da manipulação do sistema proprioceptivo no desempenho da tarefa de levantar e andar em pacientes com DP e idosos saudáveis; (ii) o efeito dessa manipulação no desempenho da tarefa de iniciar o andar em pessoas com DP (com e sem FOG) e em idosos saudáveis; (iii) o efeito da vibração muscular, como ferramenta de estimulação do sistema proprioceptivo, na severidade de episódios de FOG em pessoas com DP.

Como objetivo inicial, buscávamos avaliar a aplicabilidade da vibração muscular na melhora do desempenho da tarefa de levantar e andar também em pessoas que apresentavam FOG. Entretanto, esses indivíduos foram incapazes de realizar essa tarefa: de um total de 15 indivíduos, apenas dois foram capazes de realizar a tarefa de levantar e andar. Assim, limitamos essa investigação apenas às pessoas que não apresentavam FOG.

Ainda, por questões óbvias não testamos os efeitos da vibração na severidade dos episódios de FOG em pacientes que não apresentavam esse fenômeno. Pode-se argumentar que, diferentemente do procedimento realizado para as tarefas de iniciar o andar e de levantar e andar, não foram realizados estudos prévios para definição dos melhores parâmetros de vibração, quando o intuito é aplica-la para reduzir a severidade de episódios de FOG. Entretanto, o efeito do momento de aplicação da

vibração (antes ou depois do disparo dos episódios de FOG) foi investigado no próprio estudo em questão. Ademais, não quisemos expor esses indivíduos a uma nova série de testes por um principal motivo: como poderá ser observado no último estudo dessa quinta Seção (página 120), episódios de FOG são raramente disparados em ambientes de pesquisa. Portanto, julgamos não ser prudente expor as poucas pessoas que exibiram episódios de FOG a uma nova série de testes onde suscitaríamos um fenômeno tão debilitante como esse. Por fim, pode-se questionar o por que nesse último estudo não realizamos a estimulação de diversos músculos ao mesmo tempo, como nos demais. Essa decisão foi tomada considerando duas questões. Primeiramente, diferente dos demais estudos, não buscávamos induzir efeitos posturais com o uso da vibração muscular e, portanto, evitamos amplificar os efeitos vibratórios com a estimulação de mais de um músculo simultaneamente. Em segundo lugar, baseando-se nos resultados do primeiro artigo dessa quinta Seção, buscamos evitar uma superestimulação do sistema proprioceptivo, o que poderia causar um conflito sensorial (TAN; ALMEIDA; RAHIMI, 2011), aumentando ainda mais a severidade dos episódios de FOG.

Como principais resultados dessa Seção destacam-se: (i) piora do desempenho na tarefa de levantar e andar em pacientes com DP frente ao uso da vibração muscular; (ii) melhora, com o uso da vibração muscular, no desempenho do iniciar o andar em ambos os grupos de pessoas com DP (com e sem FOG); (iii) significativa melhora na severidade dos episódios de FOG com o uso da vibração muscular quando essa é aplicada no membro menos afetado pela doença.

Todos esses resultados, considerados em conjunto, evidenciam o papel dos comprometimentos proprioceptivos como um importante mecanismo responsável pelo pior desempenho locomotor de pessoas com DP, sobretudo na ocorrência de episódios de FOG. Os três estudos são apresentados na sequência.

5.2. The effects of muscle vibration on the sit-to-walk performance highlight the proprioceptive deficits in people with Parkinson's disease

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5.2.1. Introduction

Sit-to-walk movement can be defined as a '*sequential, postural-locomotor task whereby the individual transitions from sitting through standing to walking*' (BUCKLEY; PITSIKOULIS; HASS, 2008). This task is highly used during day-life (KOUTA; SHINKODA; KANEMURA, 2006) and therefore, deficits in the sit-to-walk execution might severely impact people's independency and quality of life. Sit-to-walk execution demands a proper postural and locomotor control and, therefore, this task is considered more challenging than sit-to-stand or gait initiation (BUCKLEY; PITSIKOULIS; HASS, 2008). Sufficient number of papers have identified motor dissimilarities in the sit-to-walk execution between young adults and elderly and between fallers and non-fallers (ABERG; FRYKBERG; HALVORSEN, 2010; BUCKLEY et al., 2009; KOUTA; SHINKODA, 2007; KOUTA; SHINKODA; KANEMURA, 2006). These studies have revealed, in people with postural instability, an inability to merge the two motor components of sit-to-walk, whereas motor impaired people show a longer transition phase (BUCKLEY et al., 2009; BUCKLEY; PITSIKOULIS; HASS, 2008; KERR et al., 2013; MALOUIN et al., 2003). This less fluid movement indicates a stability-first motor strategy rather than a mobility-first (BUCKLEY; PITSIKOULIS; HASS, 2008). This is clearly observed by the center-of-mass (CoM) behavior: both elderly fallers and non-fallers, at the time they lost contact with the seat, they show higher upward and lower forward CoM velocities than young people (CHEN; CHOU, 2013). Taken together, these results indicate that motor-impaired people, in order to retain stability (CHEN; CHOU, 2013), are still standing up than moving forward (ABERG; FRYKBERG; HALVORSEN, 2010; BUCKLEY; PITSIKOULIS; HASS, 2008) at the time they should be generating sufficient CoM forward momentum to perform the first step (MAGNAN; MCFADYEN; ST-VINCENT, 1996). Because of this more conservative strategy, motor-impaired people perform a shorter and slower first step during the sit-to-walk movement (BUCKLEY; PITSIKOULIS; HASS, 2008; CHEN; CHOU, 2013).

Parkinson's disease (PD) is a neurodegenerative disease distinguished by bradykinesia (swollenness of movement) and hypokinesia (reduction in the movement amplitude). People with PD present a degeneration in the dopaminergic cells located in the *substantia nigra pars compacta*, that is part of the basal ganglia (OBESO; LANCIEGO, 2011; OLANOW; STERN; SETHI, 2009). Because of this degeneration, a malfunction of neural networks involving basal ganglia leads to a series of motor impairments (RINALDI; PEREIRA; BATISTELA, 2013; RODRIGUEZ-OROZ et al., 2009). One malfunctioning neural network in PD is that responsible to code and implement sequential tasks (GOERENDT et al., 2003). In addition, people with PD have an inability to merge discrete tasks (BENECKE et al., 1987). These motor impairments result in a worse sit-to-walk performance in people with PD (BUCKLEY; PITSIKOULIS; HASS, 2008). The few studies investigating the sit-to-walk movement performance in people with PD patients (BUCKLEY; PITSIKOULIS; HASS, 2008) reported motor behavior impairments very similar to those observed in elderly fallers (ABERG; FRYKBERG; HALVORSEN, 2010; CHEN; CHOU, 2013): a shorter and slower first step, a longer time to execute the entire task and an inability to merge the postural and locomotor components of the sit-to-walk movement (BUCKLEY; PITSIKOULIS; HASS, 2008). Therefore, postural instability, another important feature of PD (BLOEM et al., 1996), can also play a major role in the worse performance of sit-to-walk movement in people with PD (BUCKLEY; PITSIKOULIS; HASS, 2008).

The postural stability deficits in PD is reflected on both orientation and stabilization components of postural control (VAUGOYEAU; HAKAM; AZULAY, 2011). The main mechanism underlying postural instability in people with PD patients is still inconclusive (VAUGOYEAU; HAKAM; AZULAY, 2011). However, sensory deficits, especially in the proprioceptive system, have been pointed as the major cause of unbalance in people with PD (KONCZAK et al., 2009; VAUGOYEAU; HAKAM; AZULAY, 2011). The study of Pastor et al. (1993) was one of the first to suggest that an inability to properly use proprioceptive feedback contributes to postural control impairments in PD (PASTOR; DAY; MARSDEN, 1993). In line with this idea, the manipulation of the proprioceptive system could improve the performance of motor tasks that are influenced by stability deficits, such as sit-to-walk.

A spread instrument used to enhance the amount of proprioceptive inflow to the central nervous system is muscle vibration (BURKE et al., 1976b; ROLL; VEDEL, 1982) . Vibratory stimulus on both muscles belly and tendons stimulates the muscle

spindles' primary sensory fibers (BURKE et al., 1976b; ROLL; VEDEL, 1982), leading to peripheral and central effects (PAOLONI et al., 2010; RIBOT-CISCAR; ROSSI-DURAND; ROLL, 1998). Between the motor effects elicited by vibration, involuntary postural response is the most discussed by the literature (CAPICIKOVA et al., 2006; POLONYOVA; HLAVACKA, 2001; UIMONEN et al., 1996): during upright stance, when lower limbs and trunk muscles are stimulated, an involuntary body displacement towards the vibrated muscle is noticed (e.g. tibialis anterior stimulation elicits a forward body displacement (COURTINE et al., 2007b; IVANENKO; GRASSO; LACQUANITI, 2000; POLONYOVA; HLAVACKA, 2001)). Therefore, muscle vibration could assist people with PD to perform the sit-to-walk movement by two mechanisms: (i) since PD have difficulties to merge different motor programs (BENECKE et al., 1987), the postural vibratory effect could promote a forward body displacement during the postural component of the sit-to-walk, assisting the participants to generate a stronger forward CoM momentum; (ii) the enhance of proprioceptive information inflow into the central nervous system elicited by vibration (BURKE et al., 1976b; ROLL; VEDEL, 1982) could improve the sit-to-walk movement performance by alleviating the kinesthetic impairments in PD that are linked to postural instability (KONCZAK et al., 2009).

Previous studies have already shown positive effects of muscle vibration on the performance of motor tasks in PD (DE NUNZIO et al., 2010; GHOSEIRI et al., 2009b; PEREIRA; ALMEIDA; GOBBI, 2014; WINFREE et al., 2013). However, the number of papers that have investigated the vibration effects on the performance of sit-to-walk movement is not sizable, mainly in PD. Pereira et al. (2015) found out that in young adults, vibratory stimulus applied on lower limbs and torso muscles is not effective to improve sit-to-walk movement performance. The reasons for this lack of vibratory effects were attributed to the inexistence of motor/sensory impairments in young adults: participants simply ignored the stimulus (PEREIRA et al., 2015). This theory is reinforced by the results reported by de Nunzio et al. (2010): positive vibratory effects were found only in people with PD, but not in their healthy pairs (DE NUNZIO et al., 2010). In this way, we believe that similar to the results reported by de Nunzio et al. (2010), people with PD could be benefited by muscle vibration when executing the sit-to-walk movement. However, for our best understanding this topic had not been deeply examined yet.

The aim of this study was to investigate the proprioceptive system manipulation effects, on the sit-to-walk movement performance in both healthy elderly and people with PD. We used muscle vibration to manipulate the proprioceptive system. Additionally, since there is only little information about the motor performance of PD patients during the sit-to-walk execution, we also aimed to further investigate the CoM behavior during this task in both healthy elderly and people with PD. As hypothesis, we believe in a lower forward CoM momentum generation, in a less fluid movement and in a more hypokinetic and bradykinetic movement pattern in PD than in healthy elderly. It is also believed that muscle vibration will alleviate these deficits in PD.

5.2.2. Methods

Thirty-one participants were assigned into two groups: a group of people with PD (n=18) and a group of healthy elderly people (HC; n=13). The groups were matched by age, height and body-mass (Table 5.2.1). To be included, the PD group should have a previous clinical diagnosis of idiopathic PD and participants should not have important co-morbid conditions that could influence the study (e.g. history of stroke, visual impairments, hearing loss, peripheral neuropathies, diabetes and dementia). All participants gave written consent prior the participation in the study and all procedures were approved by the Local Ethical Committee[1].

Table 5.2.1: Means and standard deviations of anthropometrics and clinical variables.

	PD (n=18)	**HC (n=13)**	**P**
Age (years)	65.93 ± 9.55	66.14 ± 6.51	0.84
Height (cm)	152.40 ± 12.2	152 ± 5.12	0.27
Body-weight (kg)	76.20 ± 11.33	82.55 ± 11.79	0.27
MoCA (points)	26.57 ± 2.03	27.71 ± 1.59	0.21
UPDRS-III (points)	26.73 ± 12.73	-	-

PD: group of people with Parkinson's disease; HC: healthy control group; MoCA: Montreal Cognitive Assessment; UPDRS-III: Unified Parkinson's disease rating scale.

[1] Anexo 2

Based on pilot-studies results (n=3 in each group; interaction effect size of 0.25), a power analysis using the GPower computer program (FAUL et al., 2007) indicated that a total sample of 12 people (6 in each group) would be needed to reach 90% power using an 2 x 2 (group and vibration conditions) Analysis of Variance (ANOVA) with alpha set at .05. Therefore, the number of people assessed here can be considered satisfactory. The variable used for the sample size calculation was the fluidity index (described forward).

Procedures

All assessments were performed during the "on-phase" of the medication (~1.5h after the antiparkinsonian medication intake). All participants' cognitive screening was assessed through the Montreal Cognitive Assessment (MoCA) scale[1] and, afterwards, people with PD were assessed by a movement disorder specialist. The motor subscale of the Unified Parkinson's disease Rating Scale (UPDRS-III)[2] was used to assess the disease motor impairments in the PD group. No exclusions due to dementia were reported.

For the data collection, participants initiated the task seated in an armless 40cm-high stool with arms resting on thighs and looking ahead. They positioned their feet as they wanted and kept the position consistent during all trials. Participants were instructed to stand-up from the stool in a fluid and smooth way and start walking at their self-selected speed. Participants were free to choose the lower limb (right or left) used to take the first step. Each participant executed three trials of two experimental conditions: with (ON) and without (OFF) muscle vibration. The conditions were fully randomized across trials. A resting period of 30 seconds between trials was given. Some practical trials were performed before data collection to ensure that all participants were comfortable and they have properly learned how to execute the sit-to-walk movement.

During ON trials, the vibratory stimulation was continuously applied for 30 seconds (PEREIRA et al., 2015) and participants were asked to execute the movement after the investigator command: 'Get ready and go' - given at the 28th of vibration. During OFF trials, participants also waited 28 seconds to initiate the movement. The

[1] Anexo 4
[2] Anexo 5

same verbal command was given in the OFF conditions and the vibratory units were kept in contact with the skin, but no vibration was applied.

Vibratory devices

The RCVibro System (PEREIRA et al., 2015) was used in this study. Three pairs of cylindrical vibratory devices (measuring 4.5cm x 2cm x 2cm; containing constant-velocity DC motors (Faulhaber®) bearing eccentric masses) were positioned in parallel to muscle fibers in the proximal region of the following muscles' bellies: Trapezius superior, Tibialis anterior and Rectus femoris. For fixation, ordinary elastic bands were used. These muscles were chosen because stimulation of them elicits a forward CoP displacement (COURTINE et al., 2007b; IVANENKO; GRASSO; LACQUANITI, 2000; POLONYOVA; HLAVACKA, 2001). The used vibration frequency and amplitude were the same for all devices: 80Hz and 1.2mm.

Data Acquisition and processing

Five OPTOTRAK (Northern Digital, NDI®) cameras calibrated with a sample frequency of 100Hz were used to capture the position of eighteen infrared markers positioned on well-described body-marks (ESPY; YANG; PAI, 2010; HAHN; CHOU, 2004): bilaterally on the lateral face of heels, fifth metatarsal joints, lateral malleolus, lateral tibial condyle, hip joint projection, lateral acromion, lateral humeral condyle, wrists and temporal regions. The markers positions were filtered offline using a low-pass 4^{th} order Butterworth filter with a 8Hz cut-off frequency and were used to assess the center-of-gravity of ten rigid segments, based on anthropometric tables (WINTER, 2009). Afterwards, the body CoM was determined as the sum of all rigid segments (MERELLO; FANTACONE; BALEJ, 2010).

Kinematic data was used to determine four biomechanical events in pseudo automatic procedures: (i) t_0: the instant participants initiated the task, determined when the angle between the trunk and the horizontal plane exceeded the mean plus 2 SD (standard deviation) of this angle, calculated during a 200ms resting period (DEHAIL et al., 2007); (ii) Seat-off: the instant participants lost contact with the chair. This moment was determined as the moment when the swing-limb knee angle felt behind the mean minus 2 SD of this angle calculated during same resting period mentioned before (DEHAIL et al., 2007). (iii) Standing: the instant when participants achieved the peak vertical CoM velocity (BUCKLEY; PITSIKOULIS; HASS, 2008; PEREIRA et al.,

2015); (iv) Heel-off: determined when the vertical position of the swing heel exceeded the mean plus 2 SD of its position calculated during the resting period. The kinematic data was inspected during the data analysis and if any error was detected, the biomechanical events were visually determined. The 200ms resting period was also visually determined as the period, prior t_0, with the lower data variability.

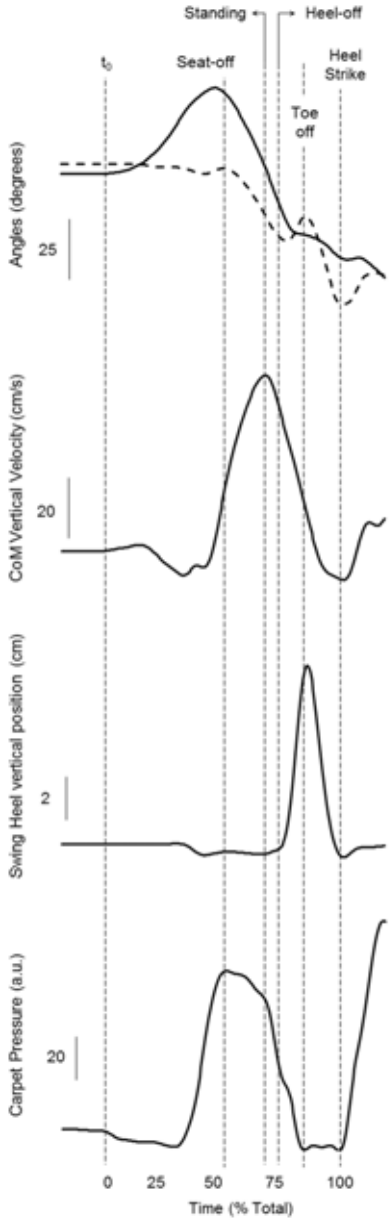
A pressure-sensing system (PKMAS System - ProtoKinetics®), calibrated with a sample acquisition rate of 100Hz and electronic synchronized with the OPTOTRAK cameras was used. This system captures and analyzes the data from a pressure-sensing carpet (Zeno - ProtoKinetics®) that contains 1.061cm^2 sensors and is sensitive to 16 pressure levels. The sensor-pressure data was used to determine toe-off and heel-strike: the instants when the pressure under the swing-limb was equal or higher than zero, respectively. Therefore, with both systems synchronized (kinematic and pressure-sensing), it was possible to split the entire task into four phases: Flexion phase (from t_0 until Seat-off), Extension phase (from the end of the last phase until Standing), Transition phase (from Standing until gait initiation: Heel-off) and Step phase (from Heel-off until Heel-strike). Note that the Transition phase could be either negative (meaning that the participant started the task previously than the total vertical position was achieved) or positive (meaning that participants achieved the vertical position prior to gait initiation). Figure 5.2.1 shows the raw biomechanical data from one PD participant, executing one trial in the OFF condition.

As dependent variables, we determined the Total Duration of the task (time between t_0 and Heel-Strike), phases durations (as a percentage of the Total Duration), the first step spatiotemporal parameters (step length, width, duration and velocity), the antero-posterior (A-P) and medio-lateral (M-L) CoM momentum at each biomechanical event (calculated as the body-weight multiplied by CoM velocity in the related direction) and the vertical CoM momentum at Standing. Additionally, we determined the Fluidity Index as a marker of movement fluency (KERR et al., 2013; MALOUIN et al., 2003). The Fluidity Index (FI) was determined as the maximal percentage drop in the CoM forward momentum (KERR et al., 2013; MALOUIN et al., 2003). Larger FI (close to 100%) indicates a greater movement fluidity, meaning a complete merge between tasks: standing and gait initiation. Finally, in order to determine if muscle vibration elicited any postural effects, we determined the CoM A-P position (in relation to the swing-limb malleolus A-P position) at the first two biomechanical events (t_0 and Seat-off). Positive values indicate a forward heel position in relation to CoM.

Statistical Analysis

All statistical procedures were conducted using the Statistica 10.0 software (StaSoft®) for windows. To assess the effects of both Group (PD x HC) and Condition (OFF x ON), a series of two-way ANOVAs with repeated measures for Condition was used. The Tukey post-hoc test was used to assess univariate differences, whenever an interaction between factors was detected. A $p<0.05$ value was considered as statistically significant for all analysis.

Figure 5.2.1: Biomechanical recordings of a PD participant executing one trial without the use of local vibration (OFF).



In the upper panel, full line: trunk angle; dotted line: swing knee angle. t_0: task initiation; A-P: anteroposterior; CoM: Center-of-mass;

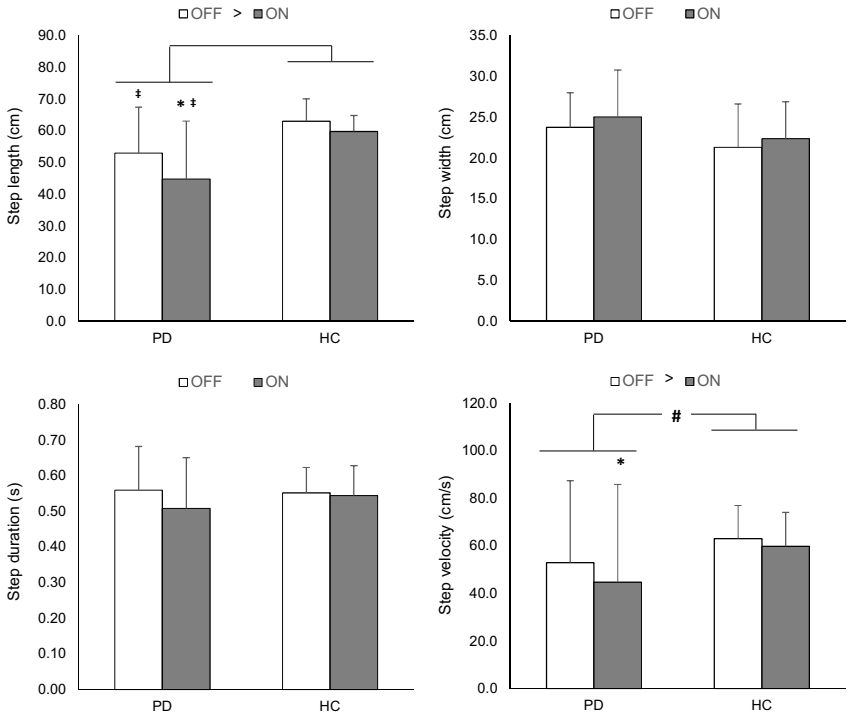
5.2.3. Results

First step and task execution

The first step spatiotemporal characteristics are showed on Figure 5.2.2. An interaction between factors was observed for both variables ($F_{(1,29)}$=5.94 and p=0.021; $F_{(1,29)}$=7.04 and p=0.012), indicating an vibration effect only in PD: vibration led to a shorter and slower first step (p<0.001 for both variables); no differences were observed in HC for both variables (p>0.52). In addition, PD also demonstrated a shorter step length than HC in both OFF (p=0.006) and ON (p=0.025). A main effect of Group was observed for step length ($F_{(1,29)}$=6.15 and p=0.019) and step velocity ($F_{(1,29)}$=4.06 and p=0.05), showing a longer and faster step for HC. Additionally, both step length and velocity showed a main effect of Condition ($F_{(1,29)}$=20.49 and p<0.001; $F_{(1,29)}$=10.95 and p=0.002), indicating a worse performance with vibration. However, No Group ($F_{(1,29)}$<1.50 and p>0.23), Condition ($F_{(1,29)}$<3.36 and p>0.10) or interaction between factors ($F_{(1,29)}$<1.39 and p>0.24) were observed for step width and duration.

Table 5.2.2 shows that the Total Duration was longer in ON than in OFF. This result seems to be highly influenced by the PD group, since they increased in 8.7% the time expended to perform the task, whereas HC showed only a 3.9% increase. Vibration effects were not observed until the end of the two initial phases in both groups (no Condition effect was found for Flexion and Extension phases). In a different way, vibration negatively influenced the Transition phase duration only in PD (Table 5.2.2). Finally, Table 5.2.2 also shows that PD group took a longer time to execute the Transition phase than HC.

Figure 5.2.2. Means and standard deviations of the first step spatiotemporal characteristics in both Groups and Conditions.



PD: group of people with Parkinson's disease; HC: healthy control group; Conditions; OFF: no vibration; ON: vibration. Horizontal bars denote Group effects; *p<0.05 within the same Group; ‡p<0.05 within the same Condition; #marginal effect: p=0.05.

Table 5.2.2. Means and standard deviations of Total task and phases durations in both Groups and Conditions. F and p values for each factor are shown.

	PD		HC		Group		Condition		Interaction	
Duration	OFF	ON	OFF	ON	$F_{(1,29)}$	p	$F_{(1,29)}$	P	$F_{(1,29)}$	p
Total (s)	1.72 ±0.52	1.87 ±0.66	1.51 ±0.15	1.57 ±0.10	2.72	0.10	**5.33**	**0.028**	1.22	0.27
Flexion (%)	28.10 ±10.77	29.82 ±13.57	28.54 ±7.90	28.00 ±8.97	0.04	0.82	0.16	0.69	0.64	0.42
Extension (%)	33.61 ±8.97	34.62 ±6.43	35.74 ±10.57	38.59 ±7.57	1.13	0.29	1.18	0.28	0.24	0.62
Transition (%)	7.14 ‡ ±5.30	10.64* ‡ ±6.74	5.26 ±3.55	3.19 ±2.20	**10.52**	**0.002**	0.54	0.46	**6.55**	**0.01**

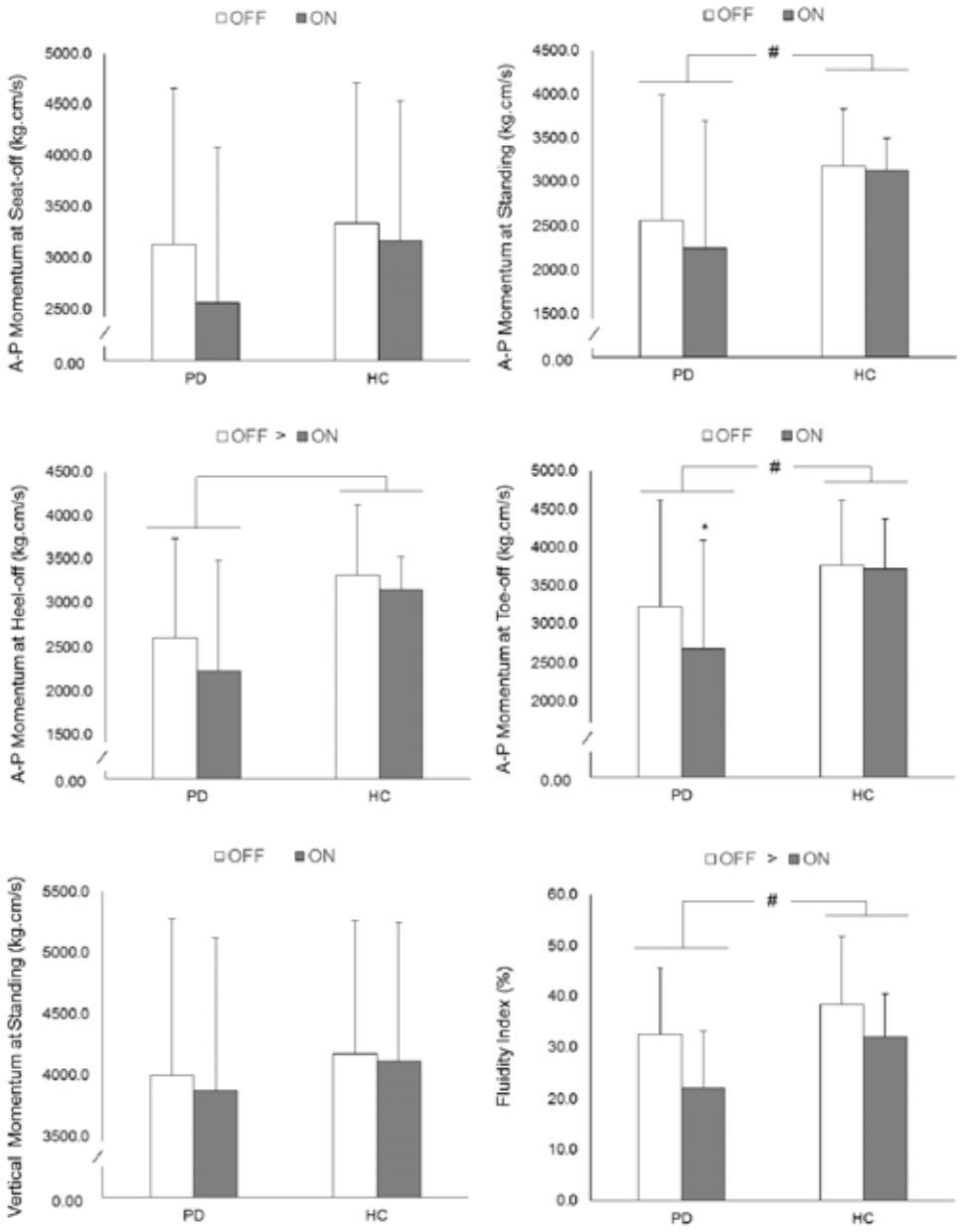
PD: group of people with Parkinson's disease; HC: healthy control group; OFF: no vibration; ON: vibration. *p<0.05 in comparison to OFF. ‡p<0.05 in comparison to HC.

Center-of- mass behavior

Figure 5.2.3 shows the CoM momentum generation and FI results. An interaction between factors was found for CoM A-P momentum generation at Toe-off ($F_{(1,29)}$=4.85 and p=0.035): the univariate comparisons showed that only in PD, ON was lower than OFF (p=0.003). No difference was found for HC (p=0.98). Marginal or main Group effects were found for the CoM A-P momentum at Standing ($F_{(1,29)}$=3.35 and p=0.07), Heel-off ($F_{(1,29)}$=5.67 and p=0.023) and Toe-off ($F_{(1,29)}$=3.64 and p=0.06). In all cases, PD presented a lower CoM A-P momentum than HC. No Group effects were observed for the CoM A-P momentum at Seat-off ($F_{(1,29)}$=0.31 and p=0.57) and for CoM Vertical momentum at Standing ($F_{(1,29)}$=0.44 and p=0.50). As expected, PD also demonstrated a strong tendency to show a lower FI than HC ($F_{(1,29)}$=3.77 and p=0.06). Vibration negatively impacted the CoM A-P momentum generation at Heel-off ($F_{(1,29)}$=5.02 and p=0.032). In this case, PD showed a decrease of 14.51%, whereas HC showed only a 5.06% detriment in the CoM A-P momentum generation at Heel-off. Fluidity index was also affected by vibration in both groups ($F_{(1,29)}$=29.29 and p<0.0001). No Condition effects ($F_{(1,29)}$<3.08 and p>0.09) and Interaction between factors ($F_{(1,29)}$<1.88 and p>0.18) were observed for CoM A-P momentum generation at Seat-off and Standing, as well as for CoM Vertical momentum at Standing.

The CoM M-L momentum analysis showed no effect of all factors at Seat-off (PD: 144.81±155.17kg.cm/s and 103.85±90.30kg.cm/s in OFF and ON respectively; HC: 128.88±91.26kg.cm/s and 114.66±132.14kg.cm/s; $F_{(1,29)}$<0.98 and p>0.32), at Standing (PD: 642.80±436.98kg.cm/s and 571.48±391.74kg.cm/s; HC: 762.02±488.60kg.cm/s and 733.89±450.14kg.cm/s; $F_{(1,29)}$<0.73 and p>0.39), at Heel-off (PD: 720±519.02kg.cm/s and 784.20±427.00kg.cm/s; HC: 740.66±497.86kg.cm/s and 687.78±436.38kg.cm/s; $F_{(1,29)}$<1.14 and p>0.29) and at Toe-off (PD: 586.83±402.51kg.cm/s and 568.36±446.97kg.cm/s; HC: 589.82±417.70kg.cm/s and 536.78±382.37kg.cm/s; $F_{(1,29)}$<0.52 and p>0.47).

Figure 5.2.3: Means and standard deviations of the Center-of-mass (CoM) momentum generation in the antero-posterior (A-P) and Vertical directions, and Fluidity Index in both Groups and Conditions.



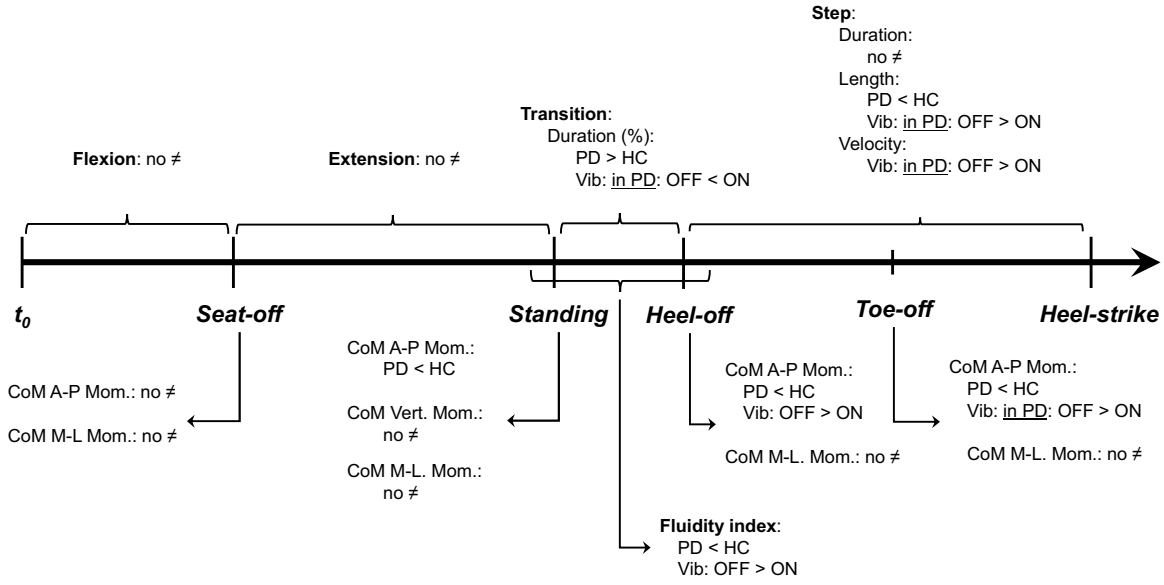
PD: group of people with Parkinson's disease; HC: healthy control group. OFF: no vibration; ON: vibration. Horizontal bars denote Group effects; *p<0.05 within the same Group; ‡p<0.05 within the same Condition; #marginal effect: p<0.07.

In the same way as the CoM M-L momentum, the CoM position at t_0 (PD: 25.29±5.70cm in OFF and 24.63±5.36cm in ON; HC: 25.60±5.86cm and 25.69±5.52cm) and at Seat-off (PD: 24.84±6.14cm in ON and 24.40±5.71cm in OFF; HC: 26.07±6.27cm and 25.88±5.85cm) were not influenced by Group ($F_{(1,29)}$<0.66 and p>0.42) and Vibration ($F_{(1,29)}$<1.77 and p>0.19), showing that no postural effects were

elicited by vibration. No interactions between factors were observed ($F_{(1,29)}$<0.65 and p>0.20).

Figure 5.2.4 shows a timeline of events where all results are summarized.

Figure 5.2.4: Time-line of events showing all observed results. In the upper panel, phases durations' results are summarized. In the bottom panel, results at biomechanical events are shown.



t_0: first detectable biomechanical event; PD: group of Parkinson's disease patients; HC: healthy control group; Vib: vibration; OFF: without vibration; ON: with vibration; CoM: center-of-mass; A-P: anterio-posterior; Vert: vertical. M-L: medio-lateral.

5.2.4. Discussion

The main aim of this study was to investigate the effects of proprioceptive system manipulation on sit-to-walk movement performance in people with PD and in their healthy pairs. In line with the literature, PD patients performed worse than HC. However, opposite to our hypotheses, we found a markedly negative effect of vibration on sit-to-walk movement performance, mainly in PD. These results, as we might see, reinforce the proprioceptive deficits as the main mechanism underlying the worse performance in people with PD during the execution of transitional motor plans, such as sit-to-walk.

Similar to previous studies (BUCKLEY; PITSIKOULIS; HASS, 2008) our results clearly show a worse sit-to-walk performance in PD than in HC. PD patients performed a shorter and slower step with a greater separation between the two motor programs

that compose sit-to-walk movement: sit-to-stand and gait initiation. Buckley et. al (2008) argued that PD have a worse performance than HC in sit-to-walk movement execution due to an inability to merge different discrete tasks and also due to adoption of a stability-first motor strategy. According to Buckley et al. (2009), the A-P CoM momentum generated prior or at Seat-off regulates the individuals' ability to use the inverted pendulum mechanism (BRENIERE; CUONG DO; BOUISSET, 1987), thereby resulting in a better merge of seat-to-stand and gait initiation (BUCKLEY et al., 2009). Therefore, since no Group differences were found in the A-P CoM momentum at both t_0 and Seat-off, we suggest that rather than a difficult to merge discrete tasks (BENECKE et al., 1987), the separation between postural and locomotor components observed during sit-to-walk execution in PD is due to unbalance (ABERG; FRYKBERG; HALVORSEN, 2010). An interesting result reinforce this theory: the differences between groups only became evident during more destabilizing events, like close to- or after gait initiation. PD showed a worse performance in all assessed variables after Standing (Figure 5.2.4), showing that group differences appeared only after participants attained full upright posture and prepared themselves to initiate gait. Some could argue that if PD patients were in a more unstable condition than HC, we would see an increase in their base of support (KREBS et al., 2002) or a reduction in the M-L CoM momentum generation. However, Aberg et al. (2010) have already showed that motor-impaired people present a robust M-L CoM behavior during sit-to-walk execution (ABERG; FRYKBERG; HALVORSEN, 2010). Nevertheless, this robust M-L CoM strategy seems to be unsuccessful (ABERG; FRYKBERG; HALVORSEN, 2010), since the PD group demonstrated others signs of instability, as a lower step velocity and less fluid movement (BUCKLEY; PITSIKOULIS; HASS, 2008; CHEN; CHOU, 2013; KERR et al., 2013).

The instability in people with PD is related to proprioceptive impairments (KONCZAK et al., 2009; VAUGOYEAU; HAKAM; AZULAY, 2011). Therefore, we hypothesized that enhancing the amount of proprioceptive information into the central nervous system could reduce the kinesthetic deficits in PD, leading to a better performance in sit-to-walk movement execution. Positive effect of vibration in PD reported by others reinforced our hypotheses (DE NUNZIO et al., 2010; GHOSEIRI et al., 2009b; WINFREE et al., 2013). However, what we found was a detriment effect of vibration, especially in the PD group. The results suggest that in face of vibration, PD participants assumed an even more stabilization-first motor strategy: they reduced the

CoM A-P momentum generation, executed the movement with less fluidity and executed a shorter and slower step. All these adjustments are signs of a more conservative motor strategy (BUCKLEY; PITSIKOULIS; HASS, 2008; CHEN; CHOU, 2013; KERR et al., 2013). Therefore, we suggest that rather than improving the proprioceptive coding, vibration disrupted even more this system.

A series of studies have suggested that the main brain structures responsible to process the proprioceptive information are the subthalamic nucleus (STN) and the globus pallidus internal (GPi) (RODRIGUEZ-OROZ et al., 2001). Rodriguez-Oroz et al. (2001) demonstrated during neurosurgery that 1/3 of the neuros in the STN responded to passive movements. In addition, it was observed, in monkeys, that the vast majority neurons in the GPi responded selectively to single-joint passive movements (BORAUD et al., 2000), showing the high relevance of these structures in the kinesthesia processing. However, when these monkeys were made parkinsonian through 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine treatment, a larger number of cells responded to passive movements (BORAUD et al., 2000). Additionally, these cells started to respond to movement in distal joints (BORAUD et al., 2000). The interpretation of these results were that PD leads to an enlargement in the sensory-receptive fields in the basal ganglia, altering the signal/noise ratio (KONCZAK et al., 2009): according to this hypothesis, PD patients present higher levels of noisy information, increasing the sensory thresholds and reducing kinesthesia (MASCHKE et al., 2003). This theory is in line with the findings of Maschke et al. (2005), that showed a better discriminative capacity after deep brain stimulation (DBS) in the STN. According to the authors, the DBS reduced the noise signal processed in the STN, reducing the somatosensory threshold (MASCHKE et al., 2005) .

Considering our findings and the literature about the mechanism underlying the proprioceptive deficits in PD, we suggest that the use of vibration increased the neural noise, leading to an even worse motor performance in PD. However, previous studies demonstrated a beneficial effect of vibration on walking performance of people with PD (DE NUNZIO et al., 2010; GHOSEIRI et al., 2009b; WINFREE et al., 2013). In this way, we raised the question of why, rather than improving the proprioceptive processing, vibration, as used in this study, led to a worse motor performance. Two major differences between our study and those that found positive effects of vibration in the gait performance of PD people were found (DE NUNZIO et al., 2010; GHOSEIRI et al., 2009b; WINFREE et al., 2013): (i) we applied vibration continuously during the

motor task execution, since Ivanenko et al. (2000) observed greater vibration effects when muscle vibration is applied during the entire gait cycle rather than exclusively at stance or swing phases (IVANENKO; GRASSO; LACQUANITI, 2000). On the other hand, Winfree et al. (2009) and de Nunzio et. al (2010) applied alternate rhythmic vibration stimulus in synchrony (WINFREE et al., 2013) or not (DE NUNZIO et al., 2010) with the step time. (ii) in our study, more than one muscle was stimulated at the same time, seeking for greater postural effects. Differently, in the study of Goshieri et al. (2009) and de Nunzio et al. (2010) vibration-stimulus was applied to a single muscle at a time. These findings let us to believe that we overstimulated the proprioceptive system in PD (both in time and in number of stimulation spots), creating a too noisy situation, thereby compromising patients' stability. This theory is in line with the study of Ribot-Ciscar et al. (2013); the authors showed that some noise elicited by vibration can enhance the participants' kinesthetic ability (RIBOT-CISCAR; HOSPOD; AIMONETTI, 2013). However, when the noise magnitude was increased, the ability to properly detect passive movements was compromised, suggesting that there is an 'optimal level' of vibratory-noise to enhance kinesthesia (RIBOT-CISCAR; HOSPOD; AIMONETTI, 2013). This might be particularly true to PD patients, since they already show an altered signal/noise ratio in the somatosensory system (KONCZAK et al., 2009). The existence of this 'optimal noise level' in PD should be addressed by future studies.

Some could argue that since vibration elicits postural effects, a movement trajectory error could had be raised by vibration (CALVIN-FIGUIERE et al., 1999). However, we did not find any effect in the CoM position at t_0 and Seat-off, showing that no postural effect was elicited here. This reinforces even more a proprioceptive disruption as the main mechanism underlying these worsening vibratory effects found in people with PD.

The use of muscle vibration also deteriorated the movement fluidity of the healthy control group, what could not be attributed to the neuropathologies observed in PD. However, the participants that attended our invitation to participate in the study cannot be considered high-functioning elderly. The HC performed, at baseline, a first step velocity around 60cm/s, lower than the 80cm/s cut-off limit for poor mobility (LAURETANI et al., 2003) and also lower to the 74cm/s in people with PD reported by Buckley et al. (2008). In the same way, at baseline, the HC showed a fluidity index around 40% (meaning a 60% drop in the A-P CoM momentum), values even lower

than the 53% (drop of 47%) reported in elderly at risk of falling (KERR et al., 2013). Participants did not report any falls in the past year before their participation in the study. However, our data is clear to show that they had some motor impairments. Therefore, we suggest that proprioception on these participants could also be compromised in some way, justifying the negative effect of vibration in their movement fluidity (Figure 5.2.3). This reduction in the movement fluidity means a lower ability to retain the initial A-P CoM momentum generation (KERR et al., 2013), what can explain the extra time expended by the HC group to perform the task. However, even with some motor impairments at base line, the HC were able to overcome the loss of movement fluidity and correct the motor plan after Heel-off, showing similar step velocity and amplitude in ON and OFF. Even showing some instability at baseline, the vibration effects were much discreet in HC: they showed only a 5.06% reduction in the FI in comparison to the 14.51% observed in PD. In the same way, vibration increased only 3.9% in the time HC expended to execute the task (Total Duration – Table 5.2.2), a much more discreet increase than the 8.7% observed in PD. Our group have already showed no vibration effects (applied in the same way as in this study) in the sit-to-walk performance of healthy young adults (PEREIRA et al., 2015). Taken the findings of Pereira et al. (2015) together with the results of this study, it seems that as greater is the motor control deficits presented by the individual, more deleterious is the vibration effect in sit-to-walk execution performance. However, a study comparing people with multiple levels of motor impairments should be conducted to prove this theory.

5.2.5. Conclusion

At the end of this study, we can conclude that muscle vibration applied in the way as described here, failed to improve the sit-to-walk performance in people with PD. Actually, the use of local vibration, as applied here, has a serious deleterious effect in this task execution performance. However, our results highlight the involvement of proprioceptive deficits in people with PD as the main mechanism underlying the worse motor performance showed by this population during the execution of transitional movements, such as sit-to-walk.

5.3. The effects of muscle vibration on gait initiation performance of Parkinson's disease patients with and without freezing of gait.

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5.3.1. Introduction

Gait initiation (GI) is accompanied by postural adjustments named Anticipatory Postural Adjustments (APA) (BRENIERE; CUONG DO; BOUISSET, 1987; RUGET et al., 2008). APA allows the swing-limb release and the body forward progression (RUGET et al., 2010). APA during gait initiation is characterized by a stereotypical pattern: the body Center-of-mass (CoM) shifts forward accompanied by a backward Center-of-Pressure (CoP) displacement (BRENIERE; CUONG DO; BOUISSET, 1987). This initial GI phase, before swing limb foot-off, can be considered an intentional and controlled forward fall – since CoM moves ahead the base of support (DELVAL; TARD; DEFEBVRE, 2014). Both scaling and timing of APA is closely linked to GI performance (BRENIERE; CUONG DO; BOUISSET, 1987; HALLIDAY et al., 1998): as longer and faster is APA, larger and faster is the first step (BRENIERE; CUONG DO; BOUISSET, 1987; HALLIDAY et al., 1998).

GI is impaired in Parkinson's disease (PD) (DELVAL; TARD; DEFEBVRE, 2014; HALLIDAY et al., 1998; HASS et al., 2005), where it is noted typical signs of bradykinesia and hypokinesia/akinesia (DELVAL; TARD; DEFEBVRE, 2014): PD patients expend more time to execute APA (HALLIDAY et al., 1998), exhibit a shorter CoP displacement (DIBBLE et al., 2004), and a slower and shorter step (DELVAL et al., 2014). In advanced PD, akinesia becomes even worse (HAWKES; DEL TREDICI; BRAAK, 2010), often leading to complete 'motor blocks' known as freezing of gait (FOG). FOG is one of the most disabling mobility problems in PD and it is defined as "*brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk*" (NUTT et al., 2011). FOG can be triggered during ongoing walking or at volitional movement initiation, such as GI (DELVAL; TARD; DEFEBVRE, 2014; HEREMANS; NIEUWBOER; VERCRUYSSE, 2013). Up to 80% of late-stages PD patients experience FOG episodes (MORRIS; IANSEK; GALNA, 2008). Additionally, FOG is closely linked to a higher number of falls (BLOEM et al., 2004) and a worse quality of life (PEREZ-LLORET et al., 2014).

As for FOG episodes, external cueing, such as auditory cues, improves GI performance in people who experience FOG (FOG+) (DELVAL et al., 2014; DIBBLE et al., 2004). These findings suggest that GI impairments in FOG+ are linked to an internal cueing deficit (DELVAL et al., 2014). In agreement with this model, a line of thought has argued that sensory processing deficits, especially impairments in the proprioceptive system, may play a major role in the occurrence of FOG (ALMEIDA; LEBOLD, 2010; EHGOETZ MARTENS; ELLARD; ALMEIDA, 2014; EHGOETZ MARTENS; PIERUCCINI-FARIA; ALMEIDA, 2013b). According to this theory, FOG+ have an internal cueing deficit (TAN; ALMEIDA; RAHIMI, 2011), leading to a reduction in internal rhythm generation (HAUSDORFF et al., 2003). In line with this idea, it is suggested that the manipulation of proprioceptive system and the enhance of proprioceptive information into the central nervous system could improve GI performance in FOG+.

On the other hand, Vervoort et al. (2013) demonstrated that FOG+ and people with PD who do not experience FOG (NFOG) respond equally to a sensory integration test, arguing that FOG+ do not experience sensory impairments(VERVOORT et al., 2013). Vervoort et al. (2013) also revealed a deficit in body-weight shifting, especially in the antero-posteior (A-P) direction. In line with this last finding, Deval et al. (2014) reported multiple and inadequate APAs in FOG+ during GI. The involvement of postural deficits as the mechanism underlying the bradykinetic pattern of gait initiation in FOG+ (BURLEIGH-JACOBS et al., 1997; HEREMANS; NIEUWBOER; VERCRUYSSE, 2013; VERVOORT et al., 2013) is reinforced by results of other studies showing that postural disturbance can have a beneficial effect in the GI execution (BURLEIGH-JACOBS et al., 1997; CREATH et al., 2013; MILLE et al., 2009; ROGERS et al., 2011). However, to elicit the postural responses these past studies used strategies that cannot be transferred to clinical day-life: they manipulated postural alignment using stepping surface disturbance (BURLEIGH-JACOBS et al., 1997; CREATH et al., 2013; ROGERS et al., 2011) or a robot-assistance training paradigm (MILLE et al., 2009). In both case, it is not possible to trigger the desired postural effects whenever individuals desire.

A portable instrument that induces simultaneously (i) postural responses (CAPICIKOVA et al., 2006; COURTINE et al., 2007a; THOMPSON; BELANGER; FUNG, 2007), and (ii) a stimulation of proprioceptive system (BURKE et al., 1976b; BURKE et al., 1996; ROLL; VEDEL, 1982) is muscle vibration. Muscle vibration

induces excitation of muscle spindles' primary sensory fibers (BURKE et al., 1976b), increasing the amount of proprioceptive information inflow into the central nervous system (BURKE et al., 1976a; RIBOT-CISCAR; ROSSI-DURAND; ROLL, 1998). Additionally, in response to primary sensory fibers stimulation, the individual experiences an illusory stretching of the vibrated muscle (ROLL; VEDEL, 1982) and during upright stance, in order to recovery balance, an involuntary postural response is observed (CAPICIKOVA et al., 2006; COURTINE et al., 2007a; THOMPSON; BELANGER; FUNG, 2007). In instance, when lower limbs muscles are stimulated, there is a body involuntary movement towards the muscle being stimulated: e.g., if tibialis anterior are exposed to muscle vibration, a forward body displacement is induced (COURTINE et al., 2007a; THOMPSON; BELANGER; FUNG, 2007). Our group already found positive effects of muscle vibration in gait initiation performance of healthy young adults (data not published[1]), when muscle vibration is applied in a relevant-way to the task (immediately before GI execution).

However, the effects of local vibration in FOG+ have not been deeply investigated. Winfree et al. (2013) found gait improvements in FOG+ after a twice-daily one-week training period of vibration applied to the feet in synchrony to the gait cycle. In a more recent study, our group found a reduction in FOG severity (e.g. FOG duration) in face of vibration applied online during a walking paradigm; these benefits were linked to sensory stimulation (PEREIRA; ALMEIDA; GOBBI, 2014). Taken together, these results suggest that GI performance in FOG+ could be benefited by muscle vibration by two mechanisms: (i) vibration could enhance the proprioceptive information to the central nervous system, alleviating sensory deficits; (ii) vibration could induce A-P postural responses, reducing body-weight shifting deficits.

Therefore, the aim of this study is to investigate the effects of proprioceptive system manipulation, by using muscle vibration, in GI performance of healthy elderly, FOG+ and NFOG. As hypothesis, we believe that muscle vibration will improve the GI performance in a higher extent in FOG+ than in NFOG and healthy elderly.

[1] Verificar resultados da Seção 4.4 - páginas 62-74.

5.3.2. Methods

Participants

Thirty people with PD and fifteen elderly without any neurological impairments (healthy control: HC) were invited to participate in this study. Twenty people with PD (11 FOG+ and 9 NFOG) and eleven HC accepted the invitation. To be included, the PD group should have a previous clinical diagnosis of idiopathic PD and for the FOG+, the presence of FOG was confirmed through the UPDRS-II[1] and visually observed during the individual's assessment by a movement disorder specialist (EHGOETZ MARTENS; PIERUCCINI-FARIA; ALMEIDA, 2013b). In addition, as exclusion criteria, patients could not have important co-morbid conditions that could influence the study (e.g. history of stroke, visual impairments, hearing loss, peripheral neuropathies, diabetes and dementia). From the twenty people with PD who responded to the invitation, one was excluded due to dementia and one due to severe motor impairments. Therefore, a total of 9 FOG+ and 9 NFOG were assessed. All participants gave written consent prior the participation in the study and all procedures were approved by the Local Ethical Committee[2].

Based on pilot-studies results (n=5 in each group; effect size of 0.51), a power analysis using the GPower computer program (FAUL et al., 2007) indicated that a total sample of 18 people (6 in each group) would be needed to reach 90% of power using an Analysis of Variance (ANOVA) test for two repeated measures and three groups with alpha set at .05. The variable used for sample size calculation was step length.

Procedures

Since the main aim of the study was to investigate the effects of an instrument that could be used during daily life, all assessments were undertaken during the "on-phase" of the medication (~1.5h after the medication intake). A movement disorder specialist assessed the motor impairments of NFOG and FOG+ using the motor subscale of the Unified Parkinson's disease Rating Scale (UPDRS-III[3]). Afterwards, all participants' cognitive screening was assessed through the Montreal Cognitive

[1] Anexo 6
[2] Anexo 2
[3] Anexo 5

Assessment (MoCA[1]). After the clinical and cognitive assessment, participants were asked to walk 5 meters on an electronic walkway (Zeno Walkway – ProtoKinetics®). Participants initiated the movement standing on the electronic walkway with arms along the body and were instructed to walk looking ahead and at their self-selected speed. No constrains about the initiating leg was given. Each participant executed three trials of two experimental conditions: without vibration (OFF) and with vibration applied only immediately before movement initiation (ON). The conditions were fully randomized across trials. A resting period of 30 seconds between trials was given. Whenever necessary, further resting periods were given according to participants' request. Some practical trials were executed before testing to ensure that participants were comfortable and they have learned how to properly execute the task.

For execution of ON trials, the vibration stimulus was continuously applied for 30 seconds (CAPICIKOVA et al., 2006) and participants were asked to execute the movement immediately after the devices were switched-off: at the 30th second of vibration. To ensure that participants would initiate the task immediately after vibration interruption, a verbal command ('Get ready and go') was given at the 28th of vibration. To perform OFF trials, participants stood still for 30 seconds and initiated the movement after the same verbal command; during OFF, vibratory units were also in contact with the skin, but no vibration was applied.

Vibratory devices

The RCVibro System (PEREIRA et al., 2015) was used in this study. Three pairs of cylindrical vibratory devices (measuring 4.5cm x 2cm x 2cm; containing constant-velocity DC motors (Faulhaber®) bearing eccentric masses) were positioned in parallel to muscle fibers in the proximal region of the following muscles' bellies: Trapezius superior, Tibialis anterior and Rectus femoris. For fixation, ordinary elastic bands were used. These muscles were chosen because stimulation of them elicits a forward CoP displacement (COURTINE et al., 2007b; IVANENKO; GRASSO; LACQUANITI, 2000; POLONYOVA; HLAVACKA, 2001). The used vibration frequency and amplitude were the same for all devices: 80Hz and 1.2mm.

[1] Anexo 4

Data Acquisition and processing

Five OPTOTRAK (Northern Digital, NDI®) cameras calibrated with a sample acquisition rate of 100Hz were used to capture the position of eighteen infrared markers positioned on well-described body-marks (ESPY; YANG; PAI, 2010; HAHN; CHOU, 2004): bilaterally on the lateral face of heels, fifth metatarsal joints, lateral malleolus, lateral tibial condyle, hip joint projection, lateral acromion, lateral humeral condyle, wrists and temporal region. The markers positions were offline filtered using a low-pass 4^{th} order Butterworth filter with a 8Hz cut-off frequency and were used to assess the center-of-gravity of ten rigid segments (WINTER, 2009), based on anthropometric tables (WINTER, 2009). Afterwards, the body CoM was determined as the sum of all rigid segments (MERELLO; FANTACONE; BALEJ, 2010).

CoM velocity and acceleration were used to determine the first biomechanical event, considered as the instant participants initiated the task (named t_0): an increase of CoM velocity and acceleration (VINTI; COUILLANDRE; THOUMIE, 2010) higher than 3 times the standard deviation of a resting period. CoM instant velocity was also assessed at three biomechanical events: at heel-off, toe-off and at heel-strike. In order to investigate if any postural adaptations were elicited by vibration, we determined the CoM A-P position (in relation to the malleolus of the swing limb) at t_0. Additionally, markers positioned on the heels allowed us to assess the first step length and velocity.

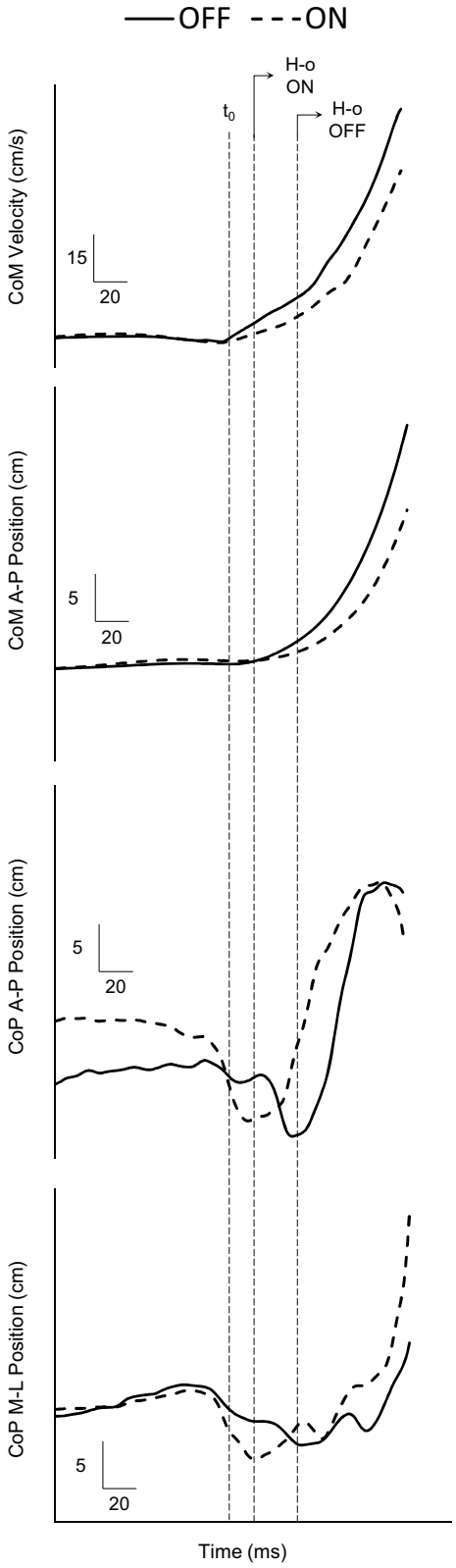
The PKMAS System software (ProtoKinetics®), calibrated with a sample acquisition rate of 100Hz and electronic synchronized with the OPTOTRAK system, was used. This software captures and analyzes the data from a pressure-sensing carpet (Zeno - ProtoKinetics®) that contains 1.061cm^2 sensors and is sensitive to 16 pressure levels. The sensor-pressure data was used to determine toe-off and heel-strike: the instants when the pressure under the swing-limb was equal or higher than zero, respectively. Additionally, this system creates a CoP projection that allowed us to determine the end of the APA phase: the instant when the CoP reaches the most posterior and lateral position (HALLIDAY et al., 1998; HASS et al., 2005). To assess this instant, the CoP projection position was offline filtered using a low-pass 4th Butterworth filter with a 10Hz cut-off frequency. The end of the APA phase coincides with the heel-off instant (DELVAL et al., 2005; HALLIDAY et al., 1998). Therefore, with both systems integrated it was possible to additionally determine: APA duration (period between t_0 and heel-off), Total duration (period between t_0 and heel-strike), step duration (period between heel-off and heel-strike) and the A-P CoM velocity at heel-off

(or step initiation). Since the CoP measures acquired by the PKMAS System have not been validated yet, we decided to use the CoP projection only to define biomechanical events and not to assess CoP measures, as displacement and velocities. Figure 5.3.1 displays the major biomechanical tracings assessed during one trial of one FOG+ participant during OFF and ON conditions.

Statistical Analysis

All statistical procedures were conducted using the Statistica® 10.0 software for windows. To assess the effects of Group (FOG+ x NFOG x HC) and Condition (OFF x ON) a series of two-way ANOVAs (3 x 2) with repeated measures for Condition was used. The Tukey post-hoc test was used to assess univariate differences, whenever an interaction between factors was found. A $p<0.05$ value was considered as statistically significant.

Figure 5.3.1. Biomechanical recordings during one trial without (OFF) and with (ON) the use of local vibration in a FOG+ participant.



T_0: task initiation; A-P: antero-posterior; M-L: medio-lateral; CoM: Center-of-mass; CoP: Center-of-pressure. H-o OFF: heel-off instant during OFF condition; H-o ON: Heel-off instant during ON condition.

5.3.3. Results

Anthropometric and clinical variables results are shown in Table 5.3.1. No differences between groups were noticed.

Table 5.3.1. Means and standard deviations of anthropometrics and clinical variables.

	FOG+ (n=9)	NFOG (n=9)	HC (n=13)	P
Age (years)	73.77 ± 7.82	70.44 ± 11.06	69.63 ± 3.80	0.48
Height (cm)	169.23 ± 14.05	166.65 ± 12.80	174.31 ± 16.31	0.49
Body-weight (kg)	82.63 ± 13.05	80.50 ± 20.13	80.40 ± 12.90	0.94
MoCA (points)	25.00 ± 4.27	26.33 ± 1.93	27.45 ± 2.06	0.19
UPDRS-III (points)	38.50 ± 10.45	32.77 ± 7.43	-	0.19

FOG+: PD group with FOG; NFOG: PD group without FOG; HC: healthy control group; MoCA: Montreal Cognitive Assessment; UPDRS-III: Unified Parkinson's disease rating scale.

Interactions and Effects of Vibration

An interaction between factors ($F_{(2,26)}$=4.64, p=0.01) indicated that only FOG+ reduced step length when performing the task in the ON condition in comparison to OFF (p=0.001) (NFOG: p=0.19; HC: p=0.98). An interaction between factors ($F_{(2,26)}$=8.63, p=0.001) was also found for step duration, indicating that only NFOG took a longer time to execute the step in ON (p=0.01) (FOG+: p=0.26; HC: p=0.99). These results initially indicate a negative effect of vibration. However, a main effect of vibration indicated that vibration reduced APA duration ($F_{(2,26)}$=6.40, p=0.017) and the time that all participants took to execute the entire task (Total Duration: $F_{(2,26)}$=8.25, p=0.007). Vibration also reduced the step length ($F_{(2,26)}$=21.19, p<0.0001) and step velocity ($F_{(2,26)}$=14.12, p<0.001); additionally, a main of vibration in CoM forward displacement at t_0 ($F_{(2,26)}$=16.12, p<0.001), indicates that vibration elicited significant postural effects in all groups. Means and standard errors values are displayed on Figure 5.3.1.

Table 5.3.2 shows an interaction between factors indicated that only FOG (p=0.023) and NFOG (p<0.0001) reduced the A-P CoM displacement during step. HC showed a trend to A-P CoM displacement reduction in step, however, no statistical

significance was reached (p=0.070). Additionally an interaction between factors was found for A-P CoM velocity at heel-strike, indicating that only NFOG (p<0.0001) was influenced by vibration, whereas FOG+ (p=0.250) and HC (p=0.250) were not. A main effect of Condition indicated that vibration reduced CoM A-P displacement during APA and step. Vibration also reduced the A-P CoM velocities at heel-off, toe-off and heel-strike in all groups. However, it can be clearly seen that greater reductions were found for FOG+ and NFOG at heel-off (24.57% and 30.14%) than in HC (19.02%).

Effects of Group

Kinematic analysis indicated a main effect of Group for step length, step duration, step velocity and also for Total duration ($F_{(2,26)}$=17.75 and p<0.001; $F_{(2,26)}$=6.88 and p=0.003; $F_{(2,26)}$=3.25 and p=0.05; $F_{(2,26)}$=15.75 and p<0.001; and $F_{(2,26)}$=6.40 and p=0.005 respectively). For these variables, as expected, FOG+ presented a shorter step length and a slower step velocity than both NFOG (p=0.003; p=0.040) and HC (p<0.001, p<0.001). NFOG also showed a slower step than HC (p=0.020). A longer step (p=0.040) and a shorter task time (Total Duration: p=0.026) was found in HC than in NFOG. Total duration in NFOG was also longer than in FOG+ (p=0.006). Unexpectedly, no main effect of Group was found for APA duration ($F_{(2,26)}$=0.15 and p=0.85), indicating that all groups expended the same time to perform APA. No effect of Group was found for CoM A-P position at t_0, indicating that all groups executed the task starting at the same posture ($F_{(2,26)}$=1.24 and p=0.30). Means and standard deviations values are shown in Figure 5.3.1.

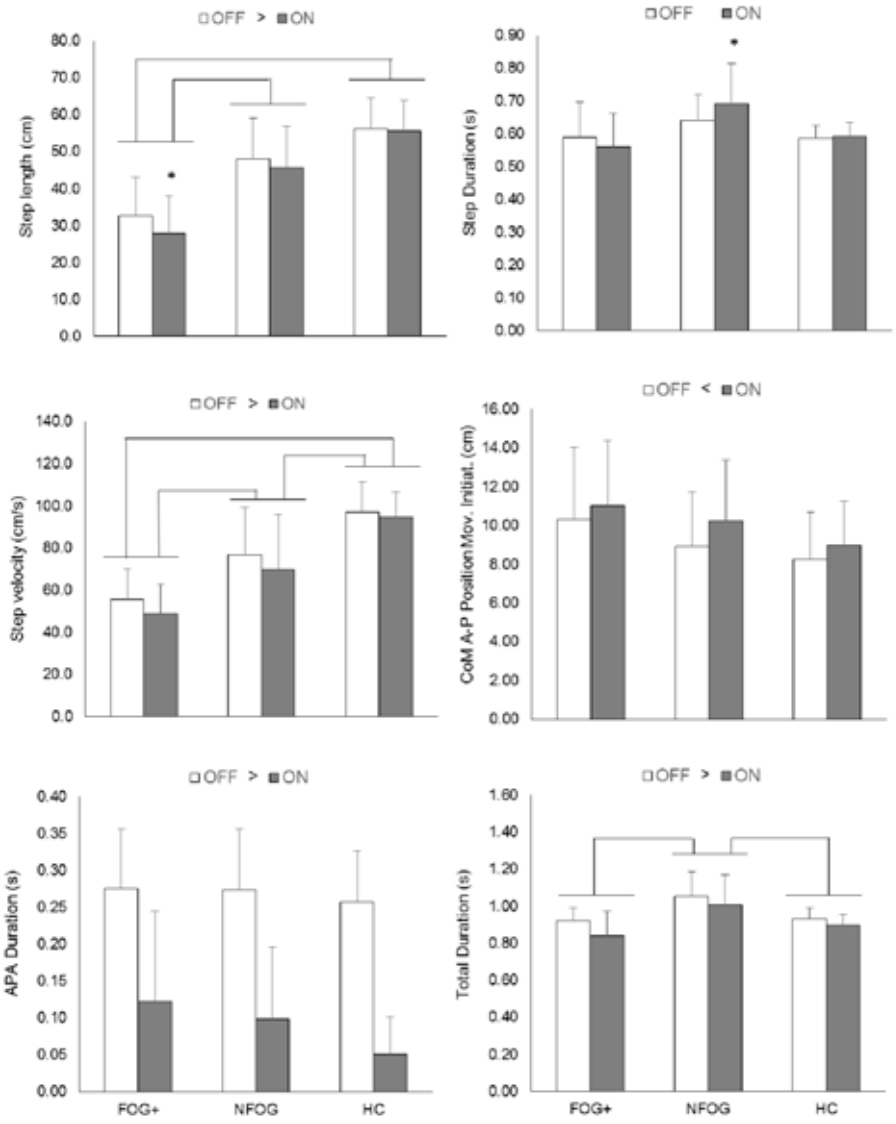
CoM variables' results indicated a main effect of Group for A-P CoM displacement during APA and step (Table 5.3.2). In addition, the same effect was observed for CoM A-P velocity at heel-off, toe-off and heel-strike. The univariate analysis demonstrated, as expected, a higher CoM displacement for HC in comparison to FOG+ (p=0.033) during APA. No difference was found between other groups (p>0.10). During step, FOG+ presented a shorter CoM displacement in comparison to both NFOG (p=0.002) and HC (p=0.0001). In the same way, A-P CoM velocities were higher in HC than in FOG+ at all biomechanical events (p<0.0001-p=0.03). NFOG was not different from other two groups (p>0.14).

Table 5.3.2. Means and standard deviations values of the Center-of-mass antero-posterior displacement and velocities at specific biomechanical events for all groups.

	FOG+		NFOG		HC		Group		Vib		Interaction	
	OFF	ON	OFF	ON	OFF	ON	F	p	F	p	F	P
A-P Disp. (cm)												
APA	1.25 ±0.78	0.92 ±0.87	2.48 ±1.41	1.41 ±1.14	2.40 ±0.54	1.84 ±0.40	**3.93**	**0.032**	**46.50**	**<0.001**	3.87	0.094
Step	13.88 ±4.99	11.44* ±4.83	22.56# ±4.98	17.75#* ±3.73	25.04# ±4.23	23.16# ±3.76	**17.86**	**<0.001**	**57.99**	**<0.001**	**5.01**	**0.014**
A-P Velocities (cm/s)												
Heel-off	7.57 ±3.69	5.71 ±3.60	12.24 ±5.28	8.55 ±6.23	14.61 ±3.29	11.83 ±2.12	**6.55**	**0.005**	**60.22**	**<0.001**	2.03	0.152
Toe-off	16.31 ±5.19	13.73 ±5.79	22.18 ±6.56	16.60 ±6.90	25.84 ±5.25	21.63 ±3.52	**6.68**	**0.005**	**44.92**	**<0.001**	1.87	0.174
Heel-strike	46.70 ±15.97	41.03 ±14.54	72.12# ±20.33	57.10* ±14.09	82.20# ±11.63	77.06# ±9.60	**16.23**	**<0.001**	**37.26**	**<0.001**	**5.06**	**0.014**

A-P: Antero-posterior; Disp.: Displacement; FOG+: PD with Freezing of gait; NFOG: PD without Freezing of gait; HC: healthy control; OFF: without vibration; ON: after vibration; Vib: Vibration factor;
F: ANOVA values; *p<0.05 vibration effect within the same group; #p<0.05 in comparison to FOG+ within the same condition.

Figure 5.3.2. Mean and standard error values of kinematic variables assessed during OFF (without vibration) and ON (after vibration) for all groups.



5.3.4. Discussion

The aim of this study was to investigate the effects of proprioceptive manipulation on the performance of GI in people with PD who experience and do not experience FOG. As main result, we found a reduction in time expended to perform the task, mainly in the APA phase. The postural effects of vibration seems to be the underlying mechanism of these positive results. This study also observed interesting findings about how each group deals with the postural perturbation elicited by vibration.

Effects of group

The main effects of Group observed in this study are in line with previous studies (BURLEIGH-JACOBS et al., 1997; DELVAL et al., 2014; DIBBLE et al., 2004; HALLIDAY et al., 1998; HASS et al., 2005), with the exception of APA duration. It is known that FOG+ have difficulties in shifting the body-weight in the A-P direction, resulting in longer and weaker APAs (BURLEIGH-JACOBS et al., 1997; DELVAL et al., 2014; DELVAL; TARD; DEFEBVRE, 2014; VERVOORT et al., 2013). However, our data showed that people with PD expended the same amount of time than HC to execute the APA phase (Figure 5.3.2). The main reason for this lack of Group effect in the APA duration is not fully understood by now. We suggest that both PD groups could had used some CoP displacement strategies to alleviate the bradykinetic APA pattern usually observed in this population (DELVAL et al., 2014). They could had performed a shorter CoP displacement than HC, what invariably reduced the time to execute APA. This strategy could also had been responsible to the similar Total Time in all groups. However, since we did not assess any CoP variables, due to the equipment limitation, future studies should explore this issue deeply. The shorter A-P CoM displacement during APA found in FOG+ (Table 5.3.2) supports this theory. It seems that FOG+ performed a weaker APA (DELVAL et al., 2014) reducing the CoM displacement during this phase, what allowed them to expend less time to execute APA.

Since the first step length and velocity are closely related to APA scaling (BRENIERE; CUONG DO; BOUISSET, 1987; HALLIDAY et al., 1998), the short step length showed by FOG+ possibly is due to their short CoM displacement during APA (Table 5.3.2). In line with this finding, the short step length in FOG+ cannot be explained by worse motor impairment, usually observed in FOG+ patients (HEREMANS; NIEUWBOER; VERCRUYSSE, 2013), since we did not find any differences between groups in the UPRDS-III score (Table 5.3.1).

Taken together, the results of our study reinforce previous findings (DELVAL et al., 2014), that revealed a weaker APA and a hypokinetic first step in FOG+. A disruption between the first step preparation and execution has been suggested as the main cause of this impairment (BURLEIGH-JACOBS et al., 1997; HEREMANS; NIEUWBOER; VERCRUYSSE, 2013; JACOBS et al., 2009; MORRIS; IANSEK; GALNA, 2008). According to previous studies (MASSION, 1992), the neural circuit responsible to generate APA includes the supplementary motor area (SMA) and the basal ganglia (MASSION, 1992). A different circuit, including the dorsolateral premotor

cortex and the primary motor cortex, is responsible to generate goal-directed movements (e.g., the first step) (MASSION, 1992). Recent brain imaging studies have shown a disruption between different brain circuitries in FOG+ (SHINE et al., 2013a; SHINE et al., 2013b; SHINE et al., 2013c; VERCRUYSSE et al., 2014). As a consequence, FOG+ presents an impaired integration of these circuitries in the pedunculopontine nucleus, which is deemed to be important in gait control (SHINE et al., 2013d; SHINE; NAISMITH; LEWIS, 2011). Therefore, the postural-gait integration impairment shown by FOG+ (BURLEIGH-JACOBS et al., 1997; HEREMANS; NIEUWBOER; VERCRUYSSE, 2013; JACOBS et al., 2009; MORRIS; IANSEK; GALNA, 2008) is pointed as the main cause of the hypokinetic behavior in this group, as observed in our study. Some vibration effects also highlight this model, as we might see.

Effects of Vibration

In order to release the swing limb and to initiate gait, a CoP backward shift and a CoM forward displacement are expected during APA (BRENIERE; CUONG DO; BOUISSET, 1987). Since the use of muscle vibration on the stimulated muscles in our study promoted a CoM forward displacement in all groups (a higher A-P CoM position at t_0 - see Figure 5.3.2), we suggest that the postural disturbance elicited by vibration assisted participants to release the swing limb faster in ON than in OFF. In this way, participants did not have to move voluntarily the CoM forward as much in ON as in OFF (Table 5.3.2) to release the swing limb. Because of the reduced need to move the CoM forward to release the swing limb, a reduction in APA time was observed for all groups in ON, thereby reducing Total Time (Figure 5.3.2).

The reduction in the step velocity with the use of vibration can be justified by the slighter APA CoM displacement in ON (Table 5.3.2). Since the first step velocity is closely related to APA scaling (BRENIERE; CUONG DO; BOUISSET, 1987; HALLIDAY et al., 1998), a weaker APA could had not allowed participants to use the inverted pendulum mechanism (DALTON et al., 2011) as much in ON as in OFF, thereby reducing the first step velocity. This decrease in the step velocity during ON also justify decreased A-P CoM velocities with vibration (Table 5.3.2). At first sight, a reduction in the first step velocity and a decrease in the CoM A-P velocities denotes a detriment effect of vibration. However, since bradykinesia is the main feature of GI in PD (HALLIDAY et al., 1998; HASS et al., 2005) and a difficulty to initiate gait with

association with multiple APAs in FOG+ (BURLEIGH-JACOBS et al., 1997; DELVAL et al., 2014; DIBBLE et al., 2004; JACOBS et al., 2009), we aimed to reduce the time participants expend to perform task. This goal has been met, mainly by a reduction of APA time. However, both PD groups showed some first step performance detriment in face of vibration.

The postural perturbation elicited by vibration promoted a step length reduction in FOG+ and a step time decrease in NFOG. On the other hand, HC did not show any difference in the step spatiotemporal parameters with vibration (Figure 5.3.2). Previous studies have shown that PD patients have difficulties to plan and execute motor patterns, needing to reprocess each step individually (VITORIO et al., 2014). In this way, we suggest that differently than HC, PD patients did not had the ability to process ahead the new motor pattern elicited by the vibratory postural perturbation and needed to online perform some adaptations (VITORIO et al., 2014). This theory explains the increase of step duration with a concomitant maintenance of step length in NFOG in face of vibration: they needed more time to plan the first step and this longer period in the swing phase allowed them to perform a similar first step length than in OFF. On the other hand, since FOG+ shows an even worse motor plan ability than NFOG (PIERUCCINI-FARIA; JONES; ALMEIDA, 2014), due to their loss of motor automaticity and attentional impairments (HAUSDORFF et al., 2003; RICCIARDI et al., 2014), they choose to perform a safer motor plan in ON, reducing the first step length. In a completely different scenario, HC could properly reprogram the new motor pattern elicited by vibration and no step spatiotemporal parameter had been compromised. These results also highlight the theory that PD have an impaired ability to merge postural and pre-programmed locomotion motor plans (BURLEIGH-JACOBS et al., 1997; JACOBS et al., 2009): the benefits elicited by vibration during APA phase were not reflected in the first step in both FOG+ and NFOG. Some could argue that rather than beneficiating the first step, vibration elicited a compensatory step, what could justify the shorter step length in FOG+. However, this was not observed for any participant. Future researches should focus on the ongoing gait to verify if the postural perturbations elicited here could had compromised the following steps.

Taken all our findings together, it seems that the vibratory postural effects rather than enhance of sensory information were the main mechanism underlying our results. It has being suggested that FOG+ have an impaired sensory integration (ALMEIDA; LEBOLD, 2010; EHGOETZ MARTENS; PIERUCCINI-FARIA; ALMEIDA, 2013b;

PEREIRA; ALMEIDA; GOBBI, 2014; TAN; ALMEIDA; RAHIMI, 2011), that could compromise the performance of pre-program motor patterns (HAUSDORFF et al., 2003), such as gait initiation. Therefore, if the enhance of internal cueing was the major mechanism responsible for the benefits observed here, we would observe benefits exclusively in the PD groups, especially in FOG+. However, this was not the case: all benefits observed in FOG+ were also noticed in all other groups, including HC. Investigating the specific mechanism underlying possible vibration effects on the performance of GI in PD was not the main aim of this study. Instead, we were interested to investigate if the proprioceptive system manipulation could be used an interesting alternative strategy to improve the bradykinetic GI behavior of PD patients, especially those with FOG. We observed positive results, showing that all groups were benefited by the postural perturbation elicited by vibration. However, FOG+ compromised the first step length to achieve a reduction in task execution time, while NFOG compromised the first step duration.

5.3.5. Conclusion

At the end of this study, we could verify that postural perturbations elicited by vibration, reduces the APA phase duration in PD patients with and without FOG in the same way as in HC. As the consequence of this shorter APA duration, all participants reduced the time needed to execute the task. However, PD patients without FOG compromised the step duration to counterbalance this postural perturbation, while those who experience FOG compromised the step length. In either way, muscle vibration, as applied in our study, is able to reduce the bradykinetic GI behavior usually observed in PD.

5.4. Muscle vibration alleviates the severity of freezing of gait in people with Parkinson's disease: evidences of sensory deficits as an underlying mechanism.

Marcelo P. Pereira, Lilian T. B. Gobbi, Quincy J. Almeida

5.4.1. Introduction

Freezing of gait (FOG) is one of the most debilitating symptoms in Parkinson's disease (PD) (MOORE; PERETZ; GILADI, 2007) and it is defined as *'brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk'* (NUTT et al., 2011). The mechanisms underlying FOG are not fully understood (HEREMANS; NIEUWBOER; VERCRUYSSE, 2013), however, sensory-perceptual (in special proprioceptive) deficits seem to play an important role in this phenomenon occurrence (ALMEIDA; LEBOLD, 2010; EHGOETZ MARTENS; ELLARD; ALMEIDA, 2014; EHGOETZ MARTENS; PIERUCCINI-FARIA; ALMEIDA, 2013b; TAN; ALMEIDA; RAHIMI, 2011). Ehgoetz Martens et al. (2013) found a higher number of FOG episodes when PD patients relied exclusively on proprioception to walk through a doorway. However, when any visual feedback was given, the number of FOG episodes decreased drastically (EHGOETZ MARTENS; PIERUCCINI-FARIA; ALMEIDA, 2013b). This previous study reinforced the theory raised by others that sensory-deficits profoundly influence FOG episodes (ALMEIDA; LEBOLD, 2010; MARTENS; ALMEIDA, 2012; TAN; ALMEIDA; RAHIMI, 2011). In agreement, Tan et al. (2011) showed that patients that experience FOG (FOG+) have a poorer performance in a force-matching task, especially when proprioceptive feedback was artificially disturbed (TAN; ALMEIDA; RAHIMI, 2011). An internally generated cueing deficit was suggested to be responsible to higher force-match errors in FOG+ in this last study (TAN; ALMEIDA; RAHIMI, 2011). Therefore, since locomotion also relies on internally generated cueing information, the authors suggested that FOG episodes could be the result of an impaired sensory processing deficit, especially in the proprioceptive system (TAN; ALMEIDA; RAHIMI, 2011)

Therefore, we believe that enhancing proprioceptive feedback to the central nervous system could improve sensory processing, reducing the severity of FOG episodes. To elicit an increase of proprioceptive feedback, previous studies have used

muscle vibration on lower limbs and/or torso muscles (COURTINE et al., 2007a; RUGET et al., 2010; VAUGOYEAU; HAKAM; AZULAY, 2011). The physiological effects of muscle vibration were already extensively described, but briefly, vibration elicits a stimulation of muscle spindles Ia sensory fibers (BURKE et al., 1976b; RIBOT-CISCAR; ROSSI-DURAND; ROLL, 1998), leading to a contraction of antagonistic muscles (CALVIN-FIGUIERE et al., 1999; ROLL; VEDEL, 1982). Previous studies already demonstrated a beneficial effect of muscle vibration on walking velocity of PD patients (DE NUNZIO et al., 2010; GHOSEIRI et al., 2009; HAN et al., 2014). In addition, a case-study paper observed an improvement of gait pattern in FOG+ after a twice-daily one-week training period of vibration applied on the feet (WINFREE et al., 2013). Finally, previous research have already shown positive effects of other sensory stimulation in FOG, as visual and auditory cueing (ARIAS; CUDEIRO, 2010; BURLEIGH-JACOBS et al., 1997; LEE et al., 2012; LIM et al., 2005; NIEUWBOER et al., 2007; ROCHESTER et al., 2009). All these findings, taken together, suggest that vibration could be used as an interesting strategy to alleviate FOG. However, for our best understanding, the direct effects of stimulating the proprioceptive feedback on the severity of FOG episodes, has never been tested. In this way, the main aim of this study was to investigate the effects of muscle vibration applied on lower limbs on FOG episodes severity (e.g.: FOG episodes duration). As hyphotesis we believe that vibration applied on both lower limbs will reduce the severity of FOG episodes.

5.4.2. Methods

Participants

Eighteen PD patients that experience FOG were recruited to participate in the study. To be included, patients should have a previous clinical diagnosis of idiopathic PD. The presence of FOG was confirmed through the UPDRS-II[14] and visually observed during the individual's assessment by a movement disorder specialist (EHGOETZ MARTENS; PIERUCCINI-FARIA; ALMEIDA, 2013b). In addition, as inclusion criteria, patients should not have important co-morbid conditions that could influence the study (e.g. history of stroke, visual impairments, hearing loss, peripheral

[14] Anexo 6

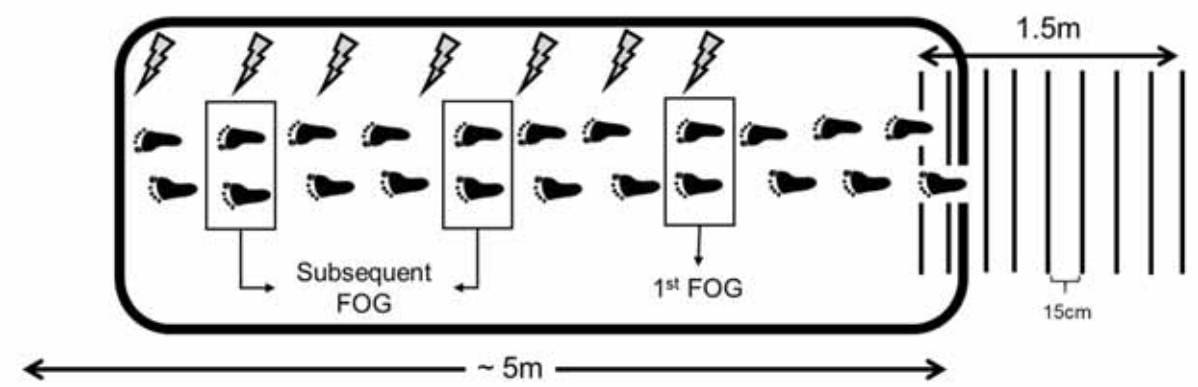
neuropathies, diabetes and dementia). The Montreal Cognitive Assessment (MoCA)[15] screened the participants' cognition status. From the eighteen patients invited to participate, three were excluded due to dementia and/or severe motor impairments. Therefore, a total of 16 FOG+ were assessed (fourteen males; UPDRS-III: 25.73±3.10 points, age: 70.71±7.77 years; MoCA: 25.73±3.10 points). All participants gave written consent prior the participation in the study and all procedures were approved by the Local Ethical Committee[16].

Experimental setup

Since the main aim of this study was to investigate the effects of an instrument that could be used during daily life, all assessments were undertaken during the "on-phase" of the medication (~1.5h after the medication intake). In order to investigate the effects of local vibration in FOG severity, it was necessary to elicit FOG episodes. To that, we used an adaptation of the sequence effect paradigm described by others (CHEE et al., 2009): all participants were asked to walk 5m on an electronic walkway (Zeno Walkway – ProtoKinetics®) at their self selected pace using a 15cm step length (corresponding to 29.42±12.86% of their regular step length). A total of ten strip lines were positioned on the floor, perpendicularly to the walkway, to be used as visual cues of the required step length. Participants were asked to step on each line with one foot and after the last line, to keep the same step length until the end of the pressure-sensing mat. To avoid any possible effect, two lines were positioned after the mat border (already on the sensing area) – Figure 5.4.1. Participants were also instructed to walk 2.5m beyond the end of the mat, to avoid any step velocity reduction close to the end of the mat.

[15] Anexo 4
[16] Anexo 2

Figure 5.4.1. Experimental set-up.



Note that vibration was not switched on before the first FOG onset. Vibration was kept on until the end of the trial (see Methods for details).

Vibration was applied on the Achilles tendon by custom-made vibratory devices (constructed using steel DC micro motors bearing eccentric masses; devices measures: 4.5cm x 2cm x 2cm, 27-3g) positioned in parallel to muscle fibers were fixed by ordinary elastic bands. An electronic board (transported as a belt and controlled via Wi-Fi) was used to control vibratory devices. This system allowed the participants to walk freely on the experimental environment. The used vibration parameters were 100Hz and 1.2mm of amplitude.

Data analysis

Three conditions were compared to assess the effectiveness of vibration to reduce FOG severity (duration of FOG episode): (i) without vibration (OFF), (ii) vibration on the least affected lower limb (LA), and (iii) vibration on the most affected lower limb (MA). Scores of the Unified Parkinson's Disease Rating Scale subsection III (UPRDS-III[17]) were considered to determine the least and most affected lower limbs. During LA and MA conditions, vibration was switched on manually by the experimenter on the first detectable FOG episode onset and kept on until the end of the trial. Therefore, it was possible to assess two different vibration effects on FOG severity: (i) an acute vibration effect - duration of the first FOG episode; and (ii) a "preventive" vibration effect: duration of subsequent FOG episodes (excluding the first one), wherein the vibration was already switched on before the FOG onset (Figure 5.4.1).

[17] Anexo 5

Each participant performed four trials of each condition, independently of number of trials with FOG episodes. Therefore, each participant performed a total of twelve trials.

FOG episodes were considered as events lasting longer than one second wherein the participants were unable to continue the ongoing walking. Since the experimental set-up demanded an online decision of when a FOG episode was triggered, an off-line confirmation was necessary. To that, the projection of center-of-mass velocity (assessed by the PKMAS software – ProtoKinetics®) was considered. Only those episodes wherein the center-of-mass projection velocity felt until zero (meaning a complete gait stop) were considered for further analysis. This complete walking stop should had last at least one second to be included in the analysis. These procedures ensured that shuffling episodes were not considered. After these procedures, eight false FOG episodes were excluded after offline inspection. As outcome measure describing the FOG severity, FOG episodes duration were considered: period between the heel-strike before the FOG occurrence and the subsequent heel-strike. The heel-strike instants were assessed using the PKMAS software (ProtoKinetics®). In the LA and MA conditions, the used lower limb to take the next step after FOG cessation was also assessed.

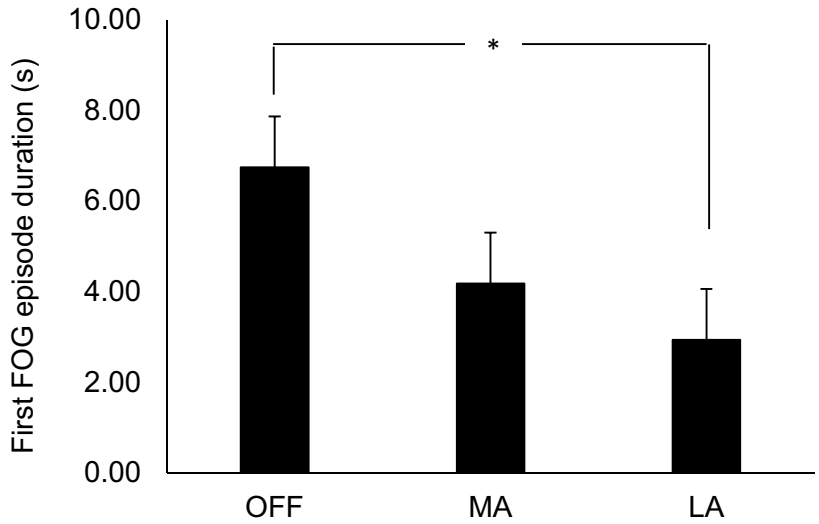
Considering the difficulty to elicit FOG episodes in a research environment (HEREMANS; NIEUWBOER; VERCRUYSSE, 2013; NIEUWBOER; GILADI, 2013), the number of trials wherein FOG episodes were elicited was not the same across all participants (e.g. FOG episodes were elicited in a single trial for one participant, whereas another individual manifested FOG episodes in three trials). Therefore, we averaged the duration of FOG episodes across conditions and across participants. To assess the acute and preventive effect of vibration on the FOG episodes severity, two series of repeated measure ANOVAs were used, considering the condition as main factor. In the first series, we considered only duration of the first FOG episode. In the second series, all the subsequent FOG episodes (excluding the first one) were took into account. In this last case, for OFF we also excluded the first FOG episode duration. Whenever necessary, a Tukey post-hoc test was used to assess further differences between conditions. In addition, we used a Chi-square test do investigate if the vibrated limb influences the leg used to take the next step after FOG cessation. All statistical procedures were conducted using the Statistica® 10.0 software for windows. A $p<0.05$ value was considered as statistically significant.

5.4.3. Results

From the total of sixteen participants who were assessed, only eight experienced FOG episodes. However, two of them did not experience FOG in all conditions and therefore, were not considered for further analysis. Therefore, data of only six participants were considered (six males; UPDRS-III: 44.33±14.51 points, age: 76.40±9.07 years; MoCA: 26.33±3.50 points). A total of 102 FOG episodes were detected: 29 as the first FOG episode and 73 as subsequent episodes.

A main effect of condition was observed for the first FOG episode duration (Figure 5.4.2 - $F_{(2,5)}$=4.36, p=0.04, η^2=0.466), whereas the post-hoc test showed that only in LA muscle vibration reduces the FOG severity (p=0.038) when compared to OFF. On the other hand, MA was not different from both OFF (p=0.174) and LA (p=0.623).

Figure 5.4.2. Mean and standard error of the first FOG episode duration in all conditions.

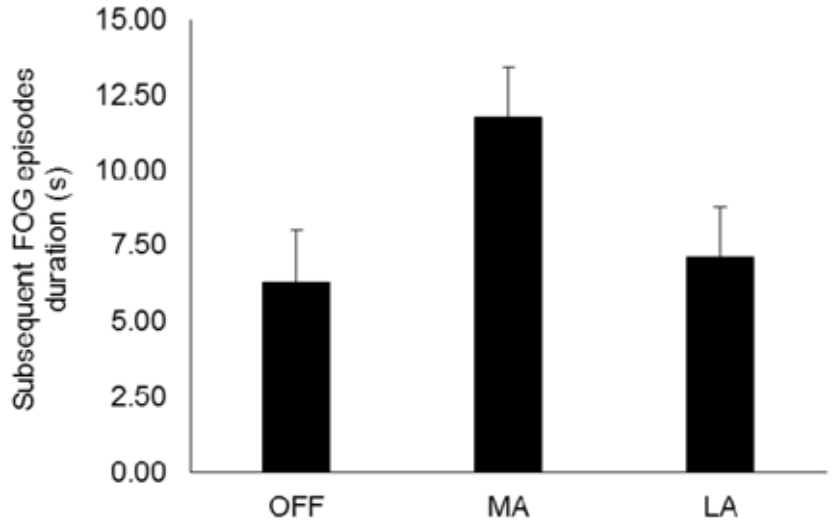


OFF: no vibration; MA: vibration on the most affected limb; LA: on the least affected limb. *p<0.05.

For the subsequent FOG episodes duration (Figure 5.4.3), the repeated-measure ANOVA found only a marginal effect ($F_{(2,5)}$=3.71, p=0.062, η^2=0.426). However, since a moderate-to-high effect size was observed, we decided to run the Tukey post-hoc test. What we found was also a marginal effect, showing that vibration

fails as a preventive strategy, since the FOG duration while walking with vibration is close to be longer in MA than in OFF (p=0.071) and is not different in LA in comparison to OFF (p=0.930). There was no difference between MA and LA (p=0.127)

Figure 5.4.3. Mean and standard error of the subsequent FOG episode duration during the three assessed conditions.



OFF: no vibration; MA: vibration on the most affected limb; LA: on the least affected limb.

From the 102 FOG episodes, 55 were observed in LA or MA conditions. From this, 54.55% in LA and 45.45% in MA. In 38.18% of the trials the participants used the same limb that were being stimulated to take the next step and in 61.82% of the trials, they used the contralateral limb to the next step after FOG (X^2=4.026; p=0.044). This result shows that participants used the contralateral limb that was being stimulated to reinitiate gait.

5.4.4. Discussion

The main aim of this study was to investigate the effects of proprioceptive system stimulation, through muscle vibration, in the severity of FOG episodes in people with PD. As main results, we found no positive effects of muscle vibration when it was applied before FOG onset. This result shows that this instrument may not be used as a preventive strategy. Actually, our results suggest FOG severity becomes even worse when muscle vibration is applied before FOG episodes onset. On the other hand, our results clearly show that FOG severity is alleviated by proprioceptive stimulation when

it was applied after FOG onset. Our results also highlight sensory deficits in PD as the mechanism underlying FOG, despite this was not our main goal.

Previous studies have suggested that muscle vibration applied on both torso or lower limbs improves gait performance in people with PD (DE NUNZIO et al., 2010; GHOSEIRI et al., 2009b; HAN et al., 2014). In this way, we hypothesized that those people who experience FOG could also be benefited by muscle vibration. However, our intention was not only to investigate if vibration could improve FOG+ gait performance. Rather, our main aim was to investigate if muscle vibration could alleviate FOG episodes severity. Confirming initial hypothesis, our results show that vibration applied after the FOG episodes onset alleviates these 'motor blocks' severity. Some mechanisms are pointed out as being responsible to this positive vibration effect: (i) a cue-related effect, (ii) issues related to cognitive/attentional resources, and (iii) an enhanced proprioceptive processing.

Others already demonstrated beneficial effects of cutaneous, visual and auditory cueing on FOG (ARIAS; CUDEIRO, 2010; BURLEIGH-JACOBS et al., 1997; LEE et al., 2012). These previous studies suggested that cues could help patients in maintaining the gait automaticity (ARIAS; CUDEIRO, 2010; HEREMANS; NIEUWBOER; VERCRUYSSE, 2013) and therefore, avoided the accumulation of motor deficits responsible to fire FOG episodes (CHEE et al., 2009). In this way, some could argue that in our study, participants could have used vibration as an auditory or step-synchronized cue. In that case, if vibration was used as an external cue, we would had observed few subsequent FOG episodes, since vibration would diminish walking rhythm generation deficits, responsible to fire FOG episodes (CHEE et al., 2009). However, we observed a high number of subsequent FOG episodes (n=42): a total of 76.36% of FOG episodes wherein vibration was used. In agreement, if vibration was used as an auditory or step-synchronized cue, we would also perceive a positive vibration effect after stimulating the most affected lower limb, what was not noticed (Figure 5.4.1).

This last argument could also be used to disclose any cognitive/attentional mechanism underlying the positive effects of vibration. Previous research have showed that FOG episodes could be the consequence of reduced central processing resources to deal with conflicting information (SHINE et al., 2013c; SHINE et al., 2013d; VERCRUYSSE et al., 2014). According to this theory, vibration could have shifted patients' attention to the lower limb stimulated by vibration and helped them to

focus on what do next: to take the next step (HEREMANS et al., 2013). However, if this was the main mechanism underlying our results, we would expect positive effects also when the most affected lower limb was stimulated. Since peripheral somatosensory processing is not impaired in people with PD (RABIN et al., 2010), we suggest that proprioceptive stimulation would also trigger attentional mechanisms when the most affected limb was stimulated. Finally, if attentional mechanism underlined our results, it was expected that, after FOG cessation, the stimulated lower limb would take the majority of the first step. However, in 61.82% of the trials the participants used the contralateral lower reinitiate gait.

Therefore, an enhanced proprioceptive information processing is pointed as the main mechanism underlying our results. According to Tan et al. (2011), FOG+ have a deficit in internal cueing (TAN; ALMEIDA; RAHIMI, 2011), reducing the internal rhythm generation (HAUSDORFF et al., 2003). In agreement with this statements, Ehgoetz Martens et al. (2013) found a higher number of FOG episodes when patients relied only on proprioception. Finally, also agreeing with this theory, Tan et al. (2011) found a worsening in a force-match task performance in FOG+ when proprioception was disturbed. Therefore, since muscle vibration stimulates the proprioceptive system (BURKE et al., 1976b; ROLL; VEDEL, 1982), it is believed that this manipulation played a major role in reducing the FOG severity episodes, when it was applied after FOG onset.

Recently, a brain imaging study showed that during upper limb motor blocks, people with PD that experience FOG show a higher motor cortex activation in comparison to non-FOG patients (VERCRUYSSE et al., 2014). This study also suggested that this increased cortical activation level during the motor block was the consequence of a late response to restore movement (VERCRUYSSE et al., 2014). Moreover, Rosnkranz and Rothwell (2003) showed that local vibration induces a selective and focused motorcortical activation of the vibrated area. Therefore, we suggest that vibration, when switched on after FOG onset, worked as flashlight pointing to specific brain regions that should be activated, fastening the motor breakdown. On the other hand, the study of Vercruysse et al. (2014) also showed a reduced activation level in dorsolateral prefrontal cortex, dorsal premotor cortex and in motor cortex before the motor block onset. It was suggested that this reduced activation level before the motor blocks was the response of a hyperinhibited signal from the subcortical structures trying to inhibit nonselective action programs (VERCRUYSSE et al., 2014).

This theory may explain why vibration did not lead to positive effects when it was applied before FOG onset. Since local vibration leads to higher activation levels in the motor cortex (ROSENKRANZ; ROTHWELL, 2003), when it was applied before FOG onset, it may have increased the number of nonselective action programs, requiring an even higher inhibitory subcortical level. As consequence, FOG+ may have experienced an even later activation of the motor cortex, thereby worsening subsequent FOG episodes severity. These theories remain speculative and should be further investigated in the future.

However, the positive effect of vibration only on the least affect lower limb supports the involvement of superior centers in the mechanisms underlying our results. Since PD is an asymmetrical disease (OLANOW; STERN; SETHI, 2009), it is suggested that the most impaired basal ganglia was not able to properly process the proprioceptive stimulation driven by vibration. On the other hand, when the least affected lower limb was stimulated, a slighter more preserved basal ganglia could had being able to properly process the enhanced information, thereby reducing FOG episodes severity.

Taken together, our results highlight the involvement of a sensory processing deficit in FOG. However, the main aim of this study was to investigate whether muscle vibration could be used as an alternative rehabilitation strategy to alleviate FOG severity. Our results clearly show that vibration applied after the FOG onset can reduce its duration. Some study limitations are obvious, as the low number of patients that presented FOG episodes (n=6). However, we found moderate-to-high vibration effect size (η^2=0.466) showing that type II error is not responsible for our results. In addition, the manual vibration triggering method by the examiner could have influenced the time patients remained frozen, biasing the results. However, since FOG duration was higher in OFF, an automatic vibration triggering after FOG onset would have reduced even more the FOG duration in LA and MA conditions.

5.4.5. Conclusion

As conclusion, we can state that vibration FOG episodes severity is reduced by muscle vibration applied on the gastrocnemius tendon after FOG onset. On the other hand, when vibration is applied before FOG occurrence, it does not lead to positive effects. An enhanced proprioceptive feedback is pointed to be responsible for these

results, highlighting the involvement of sensory deficits in the mechanisms underlying FOG.

6. CONSIDERAÇÕES FINAIS

As principais hipóteses dessa Tese de Doutorado eram de que a estimulação do sistema proprioceptivo, por meio da vibração muscular, poderia aumentar o desempenho de tarefa locomotoras de pessoas com doença de Parkinson. Entretanto, para se obter melhores resultados, foi necessário o desenvolvimento e otimização de um sistema manufaturado de vibração muscular, que mostrou ser altamente reprodutível. Após determinar os parâmetros ótimos de aplicação da vibração muscular (posicionamento dos dispositivos em paralelo com as fibras e na região proximal dos ventres musculares, calibrados com uma frequência de 80Hz e aplicados em momentos específicos para cada tarefa: antes ou durante o início do movimento) pudemos confirmar parte das hipóteses levantadas incialmente: a manipulação do sistema proprioceptivo promove uma melhora do padrão bradicinético do iniciar o andar em pacientes com DP, com e sem FOG. Além disso, o uso da vibração muscular propicia alívio na severidade dos episódios de FOG quando disparados durante o andar. Entretanto, ao contrário da nossa hipótese inicial, essa manipulação do sistema proprioceptivo causa piora no desempenho da tarefa de levantar e andar apenas em pessoas com DP e não em idosos sem comprometimento neurológico.

Os mecanismos posturais suscitados pela vibração muscular são apontados como os principais mecanismos responsáveis pela melhora no desempenho da tarefa de iniciar o andar, tanto em adultos jovens saudáveis, como em pessoas com DP. Esses efeitos posturais puderam ser observados por meio da avaliação do CoP no caso dos jovens adultos e do CoM nas pessoas com DP. Como esperávamos, o uso da vibração muscular, aplicada nos músculos estimulados aqui, promoveu um deslocamento anterior do corpo, devido à sensação ilusória de alongamento promovida pela vibração muscular. Em consequência desse deslocamento involuntário do corpo, houve redução da duração da fase de APA e consequente redução do tempo total de execução da tarefa em todos os grupos avaliados.

Já durante o andar, como apresentado na Seção 5.4, apesar de mecanismos atencionais não poderem ser totalmente descartáveis, o estímulo do sistema proprioceptivo *per si* é apontado como o mecanismo fundamental na melhora da severidade dos episódios de FOG com o uso da vibração muscular. Esse estudo também demonstrou que a aplicação da vibração não é eficaz em prevenir episódios de FOG, levando ao aumento da sua severidade quando utilizada antes dos disparos

desse fenômeno. Assim, os resultados desse estudo destacam o papel do sistema proprioceptivo como mecanismo importante no desenvolvimento dos episódios de FOG.

Os resultados encontrados na Seção 5.2 também reforçam o papel do comprometimento proprioceptivo como mecanismo importante no baixo desempenho de tarefas locomotoras de transição, em pessoas com DP. Demonstramos evidências de que a superestimulação do sistema proprioceptivo, durante a tarefa de levantar e andar, fez com indivíduos com DP assumissem um padrão motor menos fluídico. Como sugerimos, a vibração muscular pode ter causado um aumento do ruído neural já pré-existente em pessoas com DP, resultado da perda de especificidade dos neurônios sensoriais dos núcleos da base. Essa teoria explica também porque a severidade dos episódios de FOG durante a marcha tende a piorar quando essa manipulação é realizada antes de seu disparo: sugerimos que a vibração muscular sobrecarrega o processamento de informações proprioceptivas em um sistema já debilitado, levando à piora na severidade dos episódios de FOG.

Portanto, demonstramos evidências de que a manipulação do sistema proprioceptivo pode trazer resultados positivos, bem como prejudicar a locomoção de pessoas com DP, especialmente nos que apresentam FOG. Os resultados dessa Tese evidenciam que o momento de aplicação dessa manipulação é um fator determinante para o desempenho da tarefa motora sendo executada. Assim, pudemos observar que a vibração muscular, em pessoas com DP, é eficaz para facilitar a inicialização da locomoção, mas não para sua manutenção: os efeitos positivos da vibração muscular foram observados apenas quando os indivíduos deveriam iniciar o andar ou retomar a marcha após o disparo dos episódios de FOG; entretanto, quando a estimulação foi aplicada enquanto os indivíduos executavam o movimento (durante o levantar e andar e antes do disparo dos episódios de FOG na marcha), os efeitos da vibração foram negativos. Todos esses resultados, considerados em conjunto, reforçam o importante papel que os déficits do sistema proprioceptivo desempenham na locomoção de pessoas com DP.

Para que o RCVibro System seja ainda mais otimizado para ser aplicado nessa população, sugerimos que algumas questões sejam respondidas por futuros estudos: (i) a estimulação vibratória de apenas um músculo promove melhores resultados que a estimulação de diversos músculos ao mesmo tempo? (ii) é possível desenvolver um mecanismo que possibilite, ao próprio sujeito, acionar o momento de aplicação da

vibração? (iii) os efeitos positivos da vibração muscular podem ser mantidos após longos períodos de utilização, sem que haja acomodação do sistema sensorial?

Finalmente, não podemos deixar de destacar, considerando todos os nossos achados, o potencial de aplicação clínica do RCVibro System. Esse sistema demonstrou ser eficaz em auxiliar a locomoção de pessoas com DP, sendo relativamente baixo o seu custo de fabricação. Por ser um sistema não invasivo, pode ser aplicado por quaisquer profissionais da área de saúde que tenham recebido suficiente treinamento. Ainda, mesmo que não se utilizando do RCVibro System, apresentamos o potencial clínico da manipulação do sistema proprioceptivo para melhora da locomoção em pessoas com doença de Parkinson.

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ANEXOS

ANEXO 1 – Aprovação do Comitê de Ética em Pesquisa no Brasil

unesp

UNIVERSIDADE ESTADUAL PAULISTA
"JÚLIO DE MESQUITA FILHO"
Câmpus de Rio Claro

Protocolo nº: 3563
Data Registro CEP: 24-05-2010

Rio Claro, 22 de outubro de 2010.

Ofício CEP 083/2010

Prezado Senhor,

Aprovo "ad *referendum*" do Comitê de Ética em Pesquisa do Instituto de Biociências, UNESP, Campus de Rio Claro (CEP-IB-UNESP), o projeto de pesquisa intitulado *"Efeito da manipulação proprioceptiva em indivíduos jovens, idosos e portadores da Doença de Parkinson"*, sob sua responsabilidade –orientadora: Profa. Dra. Lilian Teresa Bucken Gobbi.

Atenciosamente,

Profa. Dra. **Maria Izabel Souza Camargo**
Coordenadora

Ilmo. Sr.
MARCELO PINTO PEREIRA
Rua 8-B, 1171
13506-739 Rio Claro SP

Instituto de Biociências – Seção Técnica Acadêmica
Avenida 24-A nº 1515 - CEP 13506-900 – Rio Claro - S.P. – Brasil - tel 19 3526-4105 - fax 19 3534-0009 - http://www.rc.unesp.br

ANEXO 2 – Aprovação do Comitê de Ética em Pesquisa no Canadá

Marcelo Pereira

De: REB@wlu.ca
Enviado em: September 19, 2013 9:08 AM
Para: Mr. Marcelo Pereira (Principal Investigator)
Cc: Quincy Almeida (Co-Investigator); REB@wlu.ca
Assunto: REB approval notification3757

September 19, 2013

Dear Marcelo,

REB # 3757
Project, "The effects of proprioceptive system manipulation on the performance of motor tasks in people with Parkinson's disease and freezing of gait."
Expiry Date: April 30, 2014

The Research Ethics Board of Wilfrid Laurier University has reviewed the above proposal and determined that the proposal is ethically sound. If the research plan and methods should change in a way that may bring into question the project's adherence to acceptable ethical norms, please submit a "Request for Ethics Clearance of a Revision or Modification" form for approval before the changes are put into place. This form can also be used to extend protocols past their expiry date, except in cases where the project is more than four years old. Those projects require a new REB application.

Please note that you are responsible for obtaining any further approvals that might be required to complete your project.

If any participants in your research project have a negative experience (either physical, psychological or emotional) you are required to submit an "Adverse Events Form" to the Research Office within 24 hours of the event.

According to the Tri-Council Policy Statement, you must complete the "Annual/Final Progress Report on Human Research Projects" form annually and upon completion of your project. All forms, policies and procedures are available via the REB website: http://www.wlu.ca/research/reb.

All the best for the successful completion of your project.

Yours sincerely,

Robert Basso, PhD
Chair, University Research Ethics Board
Wilfrid Laurier University

/pb

ANEXO 3 – Aceite de publicação da revista Journal of Physical Therapy Science

Marcelo Pinto Pereira

De: onbehalfof+jpts+ipec-pub.co.jp@manuscriptcentral.com em nome de jpts@ipec-pub.co.jp
Enviado em: Thursday, December 11, 2014 12:45 AM
Para: mppereir@yahoo.com.br
Assunto: The Journal of Physical Therapy Science - Decision on Manuscript ID JPTS-2014-654.R2

11-Dec-2014

Dear Mr. Pereira:

It is a pleasure to accept your manuscript entitled "Does the proprioceptive system stimulation improve the sit-to-walk performance in healthy young adults?" in its current form for publication in the The Journal of Physical Therapy Science.

Thank you for your fine contribution. On behalf of the Editors of the The Journal of Physical Therapy Science, we look forward to your continued contributions to the Journal.

Sincerely,
The Journal of Physical Therapy Science Editorial Office jpts@ipec-pub.co.jp

[Editor's Comments]
Associate Editor
Comments to the Author:
(There are no comments.)

[Reviewer(s)' Comments]

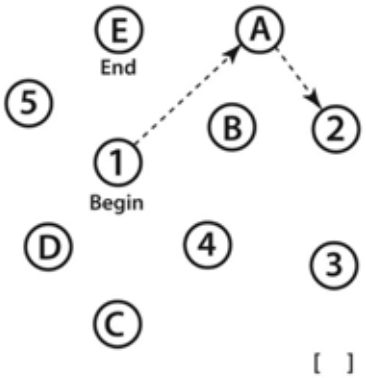
ANEXO 4 – *Montreal Cognitive Assessment* (MoCA) – versão em inglês e português

NAME :

MONTREAL COGNITIVE ASSESSMENT (MOCA) Education : Date of birth :

Version 7.1 Original Version Sex : DATE :

VISUOSPATIAL / EXECUTIVE



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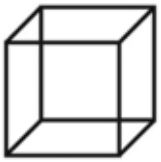


[ ] [ ]

Draw CLOCK (Ten past eleven) (3 points)

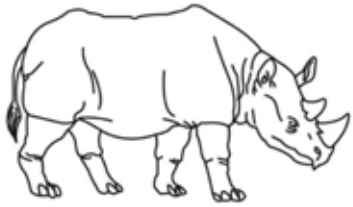
[ ] Contour [ ] Numbers [ ] Hands

POINTS

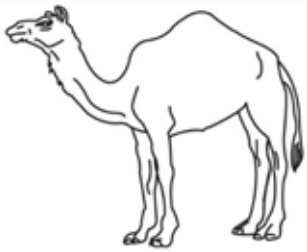
__/5

NAMING

[ ]



[ ]



[ ]

__/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

__/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)

__/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

__/2

DELAYED RECALL

	Has to recall words **WITH NO CUE**	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

www.mocatest.org

Normal ≥ 26 / 30

TOTAL __/30

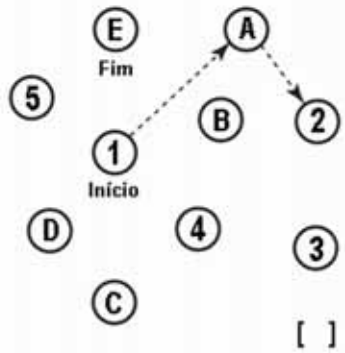
Add 1 point if ≤ 12 yr edu

Administered by: _____

MONTREAL COGNITIVE ASSESSMENT (MOCA)
Versão Experimental Brasileira

Nome:_____ Data de nascimento: __/__/__
Escolaridade:_____ Data de avaliação: __/__/__
Sexo:_____ Idade:____

VISUOESPACIAL / EXECUTIVA — Pontos



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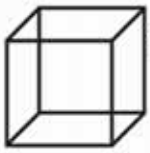


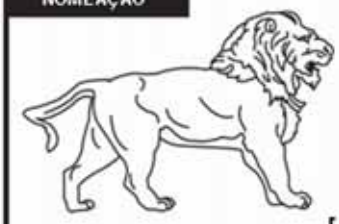
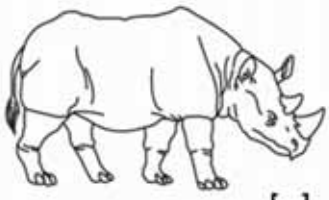
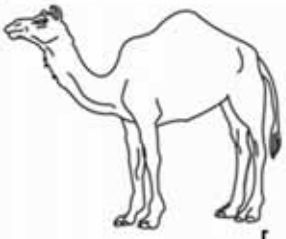
[ ] [ ]

Desenhar um RELÓGIO (onze horas e dez minutos) (3 pontos)

[ ] Contorno [ ] Números [ ] Ponteiros

__/5

NOMEAÇÃO

[ ] [ ] [ ]

__/3

MEMÓRIA — Leia a lista de palavras, O sujeito deve repeti-la, faça duas tentativas. Evocar após 5 minutos.

	Rosto	Veludo	Igreja	Margarida	Vermelho
1ª tentativa					
2ª tentativa					

Sem Pontuação

ATENÇÃO — Leia a seqüência de números (1 número por segundo)

O sujeito deve repetir a seqüência em ordem direta [ ] 2 1 8 5 4
O sujeito deve repetir a seqüência em ordem indireta [ ] 7 4 2

__/2

Leia a série de letras. O sujeito deve bater com a mão (na mesa) cada vez que ouvir a letra "A". Não se atribuem pontos se ≥ 2 erros.

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Subtração de 7 começando pelo 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 ou 5 subtrações corretas: 3 pontos; 2 ou 3 corretas 2 pontos; 1 correta 1 ponto; 0 correta 0 ponto

__/3

LINGUAGEM — Repetir: Eu somente sei que é João quem será ajudado hoje. [ ]

O gato sempre se esconde embaixo do Sofá quando o cachorro está na sala. [ ]

__/2

Fluência verbal: dizer o maior número possível de palavras que comecem pela letra F (1 minuto). [ ]_____ (N ≥ 11 palavras)

__/1

ABSTRAÇÃO — Semelhança p. ex. entre banana e laranja = fruta [ ] trem - bicicleta [ ] relógio - régua

__/2

EVOCAÇÃO TARDIA

Deve recordar as palavras SEM PISTAS	Rosto	Veludo	Igreja	Margarida	Vermelho	Pontuação apenas para evocação SEM PISTAS
	[ ]	[ ]	[ ]	[ ]	[ ]	

__/5

OPCIONAL

Pista de categoria					
Pista de múltipla escolha					

ORIENTAÇÃO — [ ] Dia do mês [ ] Mês [ ] Ano [ ] Dia da semana [ ] Lugar [ ] Cidade

__/6

Versão experimental Brasileira: *Ana Luisa Rosas Sarmento Paulo Henrique Ferreira Bertolucci - José Roberto Wajman*
(UNIFESP-SP 2007)

TOTAL __/30
Adicionar 1 pt se ≤ 12 anos de escolaridade

ANEXO 5 – *Unified Parkinson's disease Rating Scale* III – Exame motor. Em inglês e português.

Versão em inglês:

18. Speech
0 = Normal.
1 = Slight loss of expression, diction and/or volume.
2 = Monotone, slurred but understandable; moderately impaired.
3 = Marked impairment, difficult to understand.
4 = Unintelligible.

19. Facial Expression
0 = Normal.
1 = Minimal hypomimia, could be normal "Poker Face".
2 = Slight but definitely abnormal diminution of facial expression
3 = Moderate hypomimia; lips parted some of the time.
4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.

20. Tremor at rest (head, upper and lower extremities)
0 = Absent.
1 = Slight and infrequently present.
2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.
3 = Moderate in amplitude and present most of the time.
4 = Marked in amplitude and present most of the time.

21. Action or Postural Tremor of hands
0 = Absent.
1 = Slight; present with action.
2 = Moderate in amplitude, present with action.
3 = Moderate in amplitude with posture holding as well as action.
4 = Marked in amplitude; interferes with feeding.

22. Rigidity (Judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored.)
0 = Absent.
1 = Slight or detectable only when activated by mirror or other movements.
2 = Mild to moderate.
3 = Marked, but full range of motion easily achieved.
4 = Severe, range of motion achieved with difficulty.

23. Finger Taps (Patient taps thumb with index finger in rapid succession.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

24. Hand Movements (Patient opens and closes hands in rapid succesion.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

25. Rapid Alternating Movements of Hands (Pronation-supination movements of hands, vertically and horizontally, with as large an amplitude as possible, both hands simultaneously.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

26. Leg Agility (Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude should be at least
3 inches.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

27. Arising from Chair (Patient attempts to rise from a straightbacked chair, with arms folded across chest.)
0 = Normal.
1 = Slow; or may need more than one attempt.
2 = Pushes self up from arms of seat.
3 = Tends to fall back and may have to try more than one time, but can get up without help.
4 = Unable to arise without help.

28. Posture
0 = Normal erect.
1 = Not quite erect, slightly stooped posture; could be normal for older person.
2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.
3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.
4 = Marked flexion with extreme abnormality of posture.

29. Gait
0 = Normal.
1 = Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion.
2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.
3 = Severe disturbance of gait, requiring assistance.
4 = Cannot walk at all, even with assistance.

30. Postural Stability (Response to sudden, strong posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared.)
0 = Normal.
1 = Retropulsion, but recovers unaided.
2 = Absence of postural response; would fall if not caught by examiner.
3 = Very unstable, tends to lose balance spontaneously.
4 = Unable to stand without assistance.

31. Body Bradykinesia and Hypokinesia (Combining slowness, hesitancy, decreased armswing, small amplitude, and poverty of movement in general.)
0 = None.
1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.
2 = Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.
3 = Moderate slowness, poverty or small amplitude of movement.
4 = Marked slowness, poverty or small amplitude of movement.

Versão em português:

18. fala
0 = normal.
1 = perda discreta da expressão, volume ou dicção.
2 = comprometimento moderado. Arrastado, monótono mas compreensível.
3 = comprometimento grave, difícil de ser entendido.
4 = incompreensível.

19. expressão facial
0 = normal.
1 = hipomimia mínima.
2 = diminuição pequena, mas anormal, da expressão facial.
3 = hipomimia moderada, lábios caídos/afastados por algm tempo.
4 = fácies em máscara ou fixa, com pedra grave ou total da expressão facial. Lábios afastados ¼ de polegada ou mais.

20. tremor de repouso
0 = ausente.
1 = presente mas infrequente ou leve.
2 = persistente mas de pouca amplitude, ou moderado em amplitude mas presente de maneira intermitente.
3 = moderado em amplitude mas presente a maior parte do tempo.
4 = com grande amplitude e presente a maior parte do tempo.

21. tremor postural ou de ação nas mãos
0 = ausente
1 = leve, presente com a ação.
2 = moderado em amplitude, presente com a ação.
3 = moderado em amplitude tanto na ação quanto mantendo a postura.
4 = grande amplitude, interferindo com a alimentação.

22. rigidez (movimento passivo das grandes articulações, com paciente sentado e relaxado, ignorar roda denteada)
0 = ausente
1 = pequena ou detectável somente quando ativado por movimentos em espelho de outros.
2 = leve e moderado.
3 = marcante, mas pode realizar o movimento completo da articulação.
4 = grave e o movimento completo da articulação só ocorre com grande dificuldade.

23. bater dedos continuamente – polegar no indicador em seqüências rápidas com a maior amplitude possível, uma mão de cada vez.
0 = normal
1 = leve lentidão e/ou redução da amplitude.
2 = comprometimento moderado. Fadiga precoce e bem clara. Pode apresentar parada ocasional durante o movimento.
3 = comprometimento grave. Hesitação freqüente para iniciar o movimento ou paradas durante o movimento que está realizando.
4 = realiza o teste com grande dificuldade, quase não conseguindo.

24. movimentos das mãos (abrir e fechar as mãos em movimentos rápidos e sucessivos e com a maior amplitude possível, uma mão de cada vez).
0 = normal
1 = leve lentidão e/ou redução da amplitude.
2 = comprometimento moderado. Fadiga precoce e bem clara. Pode apresentar parada ocasional durante o movimento.
3 = comprometimento grave. Hesitação freqüente para iniciar o movimento ou paradas durante o movimento que está realizando.
4 = realiza o teste com grande dificuldade, quase não conseguindo.

25. movimentos rápidos alternados das mãos (pronação e supinação das mãos, horizontal ou verticalmente, com a maior amplitude possível, as duas mãos simultaneamente).
0 = normal
1 = leve lentidão e/ou redução da amplitude.
2 = comprometimento moderado. Fadiga precoce e bem clara. Pode apresentar parada ocasional durante o movimento.
3 = comprometimento grave. Hesitação freqüente para iniciar o movimento ou paradas durante o movimento que está realizando.
4 = realiza o teste com grande dificuldade, quase não conseguindo.

26. agilidade da perna (bater o calcanhar no chão em sucessões rápidas, levantando toda a perna, a amplitude do movimento deve ser de cerca de 3 polegadas/ ±7,5 cm).
0 = normal
1 = leve lentidão e/ou redução da amplitude.
2 = comprometimento moderado. Fadiga precoce e bem clara. Pode apresentar parada ocasional durante o movimento.
3 = comprometimento grave. Hesitação freqüente para iniciar o movimento ou paradas durante o movimento que está realizando.
4 = realiza o teste com grande dificuldade, quase não conseguindo.

27. levantar da cadeira (de espaldo reto, madeira ou ferro, com braços cruzados em frente ao peito).
0 = normal
1 = lento ou pode precisar de mais de uma tentativa
2 = levanta-se apoiando nos braços da cadeira.
3 = tende a cair para trás, pode tentar se levantar mais de uma vez, mas consegue levantar
4 = incapaz de levantar-se sem ajuda.

28. postura
0 = normal em posição ereta.
1 = não bem ereto, levemente curvado para frente, pode ser normal para pessoas mais velhas.
2 = moderadamente curvado para frente, definitivamente anormal, pode inclinar-se um pouco para os lados.
3 = acentuadamente curvado para frente com cifose, inclinação moderada para um dos lados.
4 = bem fletido com anormalidade acentuada da postura.

29. marcha
0 = normal
1 = anda lentamente, pode arrastar os pés com pequenas passadas, mas não há festinação ou propulsão.
2 = anda com dificuldade, mas precisa de pouca ajuda ou nenhuma, pode apresentar alguma festinação, passos curtos, ou propulsão.
3 = comprometimento grave da marcha, necessitando de ajuda.
4 = não consegue andar sozinho, mesmo com ajuda.

30. estabilidade postural (respostas ao deslocamento súbito para trás, puxando os ombros, com paciente ereto, de olhos abertos, pés separados, informado a respeito do teste)
0 = normal
1 = retropulsão, mas se recupera sem ajuda.
2 = ausência de respostas posturais, cairia se não fosse auxiliado pelo examinador.
3 = muito instável, perde o equilíbrio espontaneamente.
4 = incapaz de ficar ereto sem ajuda.

31. bradicinesia e hipocinesia corporal (combinação de hesitação, diminuição do balançar dos braços, pobreza e pequena amplitude de movimentos em geral)
0 = nenhum.
1 = lentidão mínima. Podia ser normal em algumas pessoas. Possível redução na amplitude.
2 = movimento definitivamente anormal. Pobreza de movimento e um certo grau de lentidão.
3 = lentidão moderada. Pobreza de movimento ou com pequena amplitude.
4 = lentidão acentuada. Pobreza de movimento ou com pequena amplitude.

ANEXO 6 – *Unified Parkinson's disease Rating Scale* II – Atividades da vida diária. Em inglês e português.

Versão em inglês:

5. Speech
0 = Normal.
1 = Mildly affected. No difficulty being understood.
2 = Moderately affected. Sometimes asked to repeat statements.
3 = Severely affected. Frequently asked to repeat statements.
4 = Unintelligible most of the time.

6. Salivation
0 = Normal.
1 = Slight but definite excess of saliva in mouth; may have nighttime drooling.
2 = Moderately excessive saliva; may have minimal drooling.
3 = Marked excess of saliva with some drooling.
4 = Marked drooling, requires constant tissue or handkerchief.

7. Swallowing
0 = Normal.
1 = Rare choking.
2 = Occasional choking.
3 = Requires soft food.
4 = Requires NG tube or gastrotomy feeding.

8. Handwriting
0 = Normal.
1 = Slightly slow or small.
2 = Moderately slow or small; all words are legible.
3 = Severely affected; not all words are legible.
4 = The majority of words are not legible.

9. Cutting food and handling utensils
0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can cut most foods, although clumsy and slow; some help needed.
3 = Food must be cut by someone, but can still feed slowly.
4 = Needs to be fed.

10. Dressing
0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Occasional assistance with buttoning, getting arms in sleeves.
3 = Considerable help required, but can do some things alone.
4 = Helpless.

11. Hygiene
0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Needs help to shower or bathe; or very slow in hygienic care.
3 = Requires assistance for washing, brushing teeth, combing hair, going to bathroom.
4 = Foley catheter or other mechanical aids.

12. Turning in bed and adjusting bed clothes
0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can turn alone or adjust sheets, but with great difficulty.
3 = Can initiate, but not turn or adjust sheets alone.
4 = Helpless.

13. Falling (unrelated to freezing)
0 = None.
1 = Rare falling.
2 = Occasionally falls, less than once per day.
3 = Falls an average of once daily.
4 = Falls more than once daily.

14. Freezing when walking
0 = None.
1 = Rare freezing when walking; may have starthesitation.
2 = Occasional freezing when walking.
3 = Frequent freezing. Occasionally falls from freezing.
4 = Frequent falls from freezing.

15. Walking
0 = Normal.
1 = Mild difficulty. May not swing arms or may tend to drag leg.
2 = Moderate difficulty, but requires little or no assistance.
3 = Severe disturbance of walking, requiring assistance.
4 = Cannot walk at all, even with assistance.

16. Tremor (Symptomatic complaint of tremor in any part of body.)
0 = Absent.
1 = Slight and infrequently present.
2 = Moderate; bothersome to patient.
3 = Severe; interferes with many activities.
4 = Marked; interferes with most activities.

17. Sensory complaints related to parkinsonism
0 = None.
1 = Occasionally has numbness, tingling, or mild aching.
2 = Frequently has numbness, tingling, or aching; not distressing.
3 = Frequent painful sensations.
4 = Excruciating pain.

Versão em português:

5. fala
0 = normal
1 = comprometimento superficial. Nenhuma dificuldade em ser entendido.
2 = comprometimento moderado. Solicitado a repetir frases, às vezes.
3 = comprometimento grave. Solicitado frequentemente a repetir frases.
4 = retraído, perda completa da motivação.

6. salivação
0 = normal
1 = excesso mínimo de saliva, mas perceptível. Pode babar à noite.
2 = excesso moderado de saliva. Pode apresentar alguma baba (drooling).
3 = excesso acentuado de saliva. Baba frequentemente.
4 = baba continuamente. Precisa de lenço constantemente.

7. deglutição
0 = normal
1 = engasgos raros
2 = engasgos ocasionais
3 = deglute apenas alimentos moles.
4 = necessita de sonda nasogástrica ou gastrostomia.

8. escrita
0 = normal
1 = um pouco lenta ou pequena.
2 = menor e mais lenta, mas as palavras são legíveis.
3 = gravemente comprometida. Nem todas as palavras são comprometidas.
4 = a maioria das palavras não são legíveis.

9. cortar ou manipular alimentos
0 = normal
1 = lento e desajeitado, mas não precisa de ajuda.
2 = capaz de cortar os alimentos, embora desajeitado e lento. Pode precisar de ajuda.
3 = alimento cortado por outros, ainda pode alimentar-se, embora lentamente.
4 = precisa ser alimentado por outros.

10. vestir
0 = normal.
1 = lento mas não precisa de ajuda.
2 = necessita de ajuda para abotoar e colocar os braços em mangas de camisa.
3 = necessita de bastante ajuda, mas consegue fazer algumas coisas sozinho.
4 = não consegue vestir-se (nenhuma peça) sem ajuda.

11. higiene
0 = normal.
1 = lento mas não precisa de ajuda.
2 = precisa de ajuda no chuveiro ou banheira, ou muito lento nos cuidados de higiene.
3 = necessita de assistência para se lavar, escovar os dentes, pentear-se, ir ao banheiro.
4 = sonda vesical ou outra ajuda mecânica.

12. girar no leito e colocar roupas
0 = normal.
1 = lento e desajeitado mas não precisa de ajuda.
2 = pode girar sozinho na cama ou colocar os lençóis, mas com grande dificuldade.
3 = pode iniciar, mas não consegue rolar na cama ou colocar lençóis.
4 = não consegue fazer nada.

13. quedas (não relacionadas ao freezing)
0 = nenhuma
1 = quedas raras.
2 = cai ocasionalmente, menos de uma vez por dia.
3 = cai, em média, uma vez por dia.
4 = cai mais de uma vez por dia.

14. Freezing enquanto anda
0 = nenhum
1 = raro freezing quando anda, pode ter hesitação no início da marcha.
2 = freezing ocasional, enquanto anda.
3 = freezing frequente, pode cair devido ao freezing.
4 = quedas frequentes devido ao freezing.

15. marcha
0 = normal.
1 = pequena dificuldade. Pode não balançar os braços ou tende a arrastar as pernas.
2 = dificuldade moderada, mas necessita de pouca ajuda ou nenhuma.
3 = dificuldade grave na marcha, necessita de assistência.
4 = não consegue andar, mesmo com ajuda.

16. tremor
0 = ausente.
1 = presente, mas infrequente.
2 = moderado, mas incomoda o paciente.
3 = grave, interfere com muitas atividades.
4 = marcante, interfere na maioria das atividades.

17. queixas sensitivas relacionadas ao parkisonismo
0 = nenhuma.
1 = dormência e formigamento ocasional, alguma dor.
2 = dormência, formigamento e dor frequente, mas suportável.
3 = sensações dolorosas frequentes.
4 = dor insuportável.