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VINÍCIUS ARANTES COELHO

RELAÇÃO ENTRE O BLOQUEIO DA ANGIOTENSINA II, FORÇA MUSCULAR E CAPACIDADE FUNCIONAL DE EXERCÍCIO EM IDOSOS

Londrina
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Dissertação apresentada ao Programa de Pós-Graduação em Ciências da Reabilitação (Programa Associado entre Universidade Estadual de Londrina [UEL] e Universidade Norte do Paraná [UNOPAR]), como requisito parcial à obtenção do título de Mestre em Ciências da Reabilitação.

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Dedico esse trabalho ao meu pai,
Ayrton Ramos Coelho.

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“De cada amor tu herdarás só o cinismo
Quando notares estás à beira do abismo
Abismo que cavaste com os teus pés.”

Cartola – O Mundo é Um Moinho

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RESUMO

O uso de Inibidores da Enzima Conversora de Angiotensina (IECA) previne o declínio na capacidade funcional em pacientes idosos portadores de Insuficiência Cardíaca Congestiva. Estudo transversal em pacientes idosos saudáveis apresentou correlação positiva entre o uso de IECA e massa muscular esquelética nestes pacientes. Embora existam relatos de que o uso de IECA possa prevenir o declínio da força muscular e capacidade de exercício relacionados ao processo de envelhecimento, mais estudos são importantes para confirmar esta hipótese. Este estudo objetivou avaliar se existe relação entre o bloqueio da angiontensina II e a capacidade funcional de exercício e força muscular em idosos fisicamente independentes. Participaram do estudo idosos integrantes do projeto EELO (Estudo sobre Envelhecimento e Longevidade), os quais foram subdivididos em três grupos(segundo a medicação utilizada): Grupo Controle (GC): idosos fisicamente independentes e com capacidade de exercício e força muscular superior a 80% do valor predito (n=235); Grupo IECA: pacientes que utilizavam os IECA há pelo menos seis meses de tratamento (n=140); Grupo BRA: pacientes que utilizavam os Bloqueadores dos Receptores de Angiotensina II (n=32). Foram levantados dados sobre as co-morbidades e consumo de medicamentos através de questionários estruturados. A força muscular foi mensurada através de um dinamômetro de preensão manual e capacidade funcional de exercício foi medida por meio do teste de caminhada de 6 minutos (TC6min), sendo analisadas a distância percorrida e a porcentagem do valor predito. Foi observada maior distância percorrida entre os homens do grupo IECA em relação aos pacientes do grupo controle, segundo análise de variância (p= 0,04). Contudo, os pacientes do grupo BRA foram similares tanto ao grupo controle quanto ao grupo IECA. Dados similares foram observados em relação às mulheres (p=0,04). Além disso, tanto os pacientes do grupo IECA (Média: 99 ± 12 %) quanto os pacientes do grupo BRA (Média: 101 ± 14 %) apresentaram maior porcentagem do valor predito no teste de caminhada em relação ao GC (Média: 96 ± 10 %, p=0,001). Ainda, foi observada maior força muscular entre os homens do grupo IECA em relação aos pacientes do grupo controle, segundo análise de variância (p= 0,01). Contudo, os pacientes do grupo BRA apresentaram força muscular similar tanto ao grupo controle quanto ao grupo IECA. Resultados semelhantes foram observados em relação às mulheres (p=0,03). Além disso, tanto os pacientes do grupo IECA (Média: 105 ± 19 %) quanto os pacientes do grupo BRA (Média: 105 ± 19 %) apresentaram maior porcentagem do valor predito em relação ao GC (Média: 98 ± 18 %, p=0,001). Pode-se concluir que idosos que utilizam Inibidores da Enzima Conversora de Angiotensina ou Bloqueadores do Receptor de Antagonistas do receptor de Angiotensina II apresentam melhor capacidade funcional de exercício e força muscular em relação aos controles. Desta forma, idosos que utilizam esta medicação poderiam apresentar menor declínio de capacidade física relacionada ao processo de envelhecimento.

Palavras-chave: Envelhecimento, Inibidores da Enzima Conversora de Angiotensina, Capacidade de Exercício

COELHO, Vinícius Arantes. **RELATIONSHIP BETWEEN ANGIOTENSIN-II BLOCKAGE, MUSCLE STRENGTH AND FUNCTIONAL EXERCISE CAPACITY IN ELDERLY.** 2012. 54 p. Dissertação (Mestrado em Ciências da Reabilitação). Universidade Norte do Paraná, Londrina, 2011.

ABSTRACT

The use of inhibitors of angiotensin converting enzyme (ACE) inhibitors prevent the decline in functional capacity in elderly patients with congestive heart failure. There are reports that this therapeutic effect is due to the blockade of the renin-angiotensin system, which prevents ventricular remodeling, modulates myocardial oxygen consumption and promotes peripheral vasodilation. Cross-sectional study in healthy elderly patients showed a positive correlation between the use of ACE inhibitors and skeletal muscle mass in these patients. Still, there are reports of an increase in exercise capacity after treatment with perindopril equivalent to a six-month treinamento.There are reports that the use of ACE inhibitors can prevent the decline in muscle strength associated with aging, further studies are hipótese. This is important to confirm this pilot study aimed to evaluate whether a relationship exists between the blockade of angiotensin II and functional exercise capacity and muscle strength in elderly physically independent. The study included elderly members of the project SAL (Study on Aging and Longevity), which were subdivided into three experimental groups according to medication used: control group (CG): physically independent elderly with functional exercise capacity higher than 80% of predicted value (n=235); ACEIG: patients using Angiotensin-Converting-Enzime Inhibitors for at least six months (n=140); ABRG: patients using Angiotensin Blocking Receptor Agents (n=32). Data were collected on co-morbidities and drug use through structured questionnaires. Muscle strength was measured using a handgrip dynamometer, and functional exercise capacity was measured by means of the 6-minute walking test (TC6min), and analyzed the distance traveled and the percentage of predicted value. Greatest distance was observed among men in the ACEIG compared to patients from control group according one way ANOVA (p=0.04). However, patients from ABRG were similar to ACEIG and control groups. Similar data were observed concerning women (p=0.04). Moreover, both patients from ACEIG (Mean: 99 ± 12 %) and ABRG (Mean: 101 ± 14 %) showed higher predicted values in 6-minute walking test (TC6min) when compared to control group (Mean: 96 ± 10 %, p=0.001). Additionally, it was observed higher muscle strength between men from ACEIG when compared to patients from control group, according to one-way ANOVA (p=0.01). However, patients from ABRG were similar to ACEIG and control groups. Similar data were observed concerning women (p=0.03). Moreover, both patients from ACEIG (Mean: 105 ± 19%) and ABRG (Mean: 105 ± 19%) showed higher predicted values in comparison to control group (Mean: 98 ± 18%, p=0.001). It was concluded that elder people using Angiotensin-Converting Enzime Inhibitors or AngiotensinBlocking Receptor Agents have better functional exercise capacity as well as muscle strength when compared to control ones. Thus, seniors who use this medication would present a lower decline of physical capacity related to ageing.

Keyword: Aging, Inhibitors of Angiotensin Converting Enzyme, Exercise Capacity

LISTA DE ILUSTRAÇÕES

LISTA DE ABREVIATURAS E SIGLAS

BRA - Bloqueadores do receptor Angiotensina II

CNS - Conselho Nacional de Saúde

EELO - Estudo sobre Envelhecimento e Longevidade

FC - frequência cardíaca

GIECA - Grupo Inibidores da Enzima Conversora de Angiotensina

GBRA - Grupo Bloqueadores do Receptor de Angiotensina

HAS - Hipertensão arterial sistêmica

IBGE - Instituto Brasileiro de Geografia e Estatística

IECA - Inibidores da Enzima Conversora de Angiotensina

ICC - Insuficiência Cardíaca Congestiva

Kg - Quilogramas

PA - Pressão arterial

SRAA - Sistema Renina Angiotensina Aldosterona

TC6 - Teste de caminhada de 6 minutos

UBS - Unidades básicas de saúde

VO_2max - Captação de oxigênio máxima

SUMÁRIO

1 INTRODUÇÃO

O fenômeno do envelhecimento da população é um tema que tem despertado grande atenção do setor de saúde e do meio acadêmico, representando um dos maiores desafios para a saúde pública em âmbito mundial.

Segundo a Organização Mundial de Saúde, existem no mundo atualmente 650 milhões de idosos (acima de 60 anos) e a projeção para 2025 é que este grupo populacional chegue a dois bilhões de idosos. Destes, aproximadamente 66% vivem em países em desenvolvimento e este percentual poderá atingir 75% em 2025 (1).

O aumento da expectativa de vida está também relacionado a um aumento da morbidade por doenças crônicas não-transmissíveis (2,3). Em um estudo realizado por DUARTE e REGO (4), constatou-se alta prevalência de comorbidades em pacientes idosos, sendo as mais frequentes a hipertensão arterial (HA), Diabetes mellitus, dislipidemia, osteoartrose e incontinência urinária.

Além disso, esse processo pode afetar a funcionalidade do idoso gerando repercussões em seu comportamento e consequentes alterações em seu estilo de vida, tornando o idoso dependente (5,6). Nesse contexto, OKOSHI (2005)(7) relatou que a perda da capacidade funcional de idosos estava relacionada à presença de comorbidades.

Embora vários mecanismos possam estar relacionados a esta perda da função física nesta população, a perda gradativa de massa e força muscular é frequentemente associada com o início e progressão destas comorbidades (8). Contudo, há poucos relatos sobre a eficácia de intervenções farmacológicas capazes de prevenir o declínio da capacidade funcional em pacientes idosos.

Estudo transversal em pacientes idosos saudáveis apresentou correlação positiva entre o uso de Inibidoresa da Enzima Conversora de Angiotensina (IECA) e massa muscular esquelética nestes pacientes (9).

Ainda, Sumukadas et al. (10) relataram um aumento na capacidade de exercício após tratamento com perindopril equivalente a um programa de seis meses de treinamento.

Além dos IECA, os bloqueadores do receptor de angiotensina II (BRA) também modulam o efeito da angiotensina-II, uma vez que bloqueiam o receptor AT1, independentemente da quantidade de Angiotensina II circulante (11).

Embora existam relatos de que o uso de IECA possa prevenir o declínio da força muscular e da capacidade de exercício relacionado ao processo de envelhecimento, mais estudos são importantes para confirmar esta hipótese, especialmente porque muitos estudos avaliaram este efeito somente em pacientes com Insuficiência Cardíaca Congestiva (ICC) e não na população idosa de forma geral. Desta forma, este estudo objetivou avaliar possível associação entre o uso de IECA ou BRA com a capacidade funcional de exercício e a força muscular em idosos.

2 REVISÃO DE LITERATURA – CONTEXTUALIZAÇÃO

2.1 Envelhecimento Populacional

O envelhecimento é normalmente definido como o acúmulo de diversas alterações deletérias em células e tecidos, sendo responsável pelo aumento do risco de doença, quebra da homeostasia e por fim a morte (1).

A busca pela longevidade, querer viver mais e usufruir de seu estado de bem estar e de saúde constitui um dos principais valores cultuados em toda a história da humanidade e se tornou um fenômeno mundial, que vem trazer mudanças nos campos sociais e econômicos (2). Estimativas mundiais mais recentes trazem que o número de pessoas com idade superior aos 60 anos irá dobrar até o ano de 2030 passando de 756 milhões para 1,4 bilhão de pessoas (3).

Os avanços em determinadas áreas como no saneamento básico, medicina e nutrição fizeram com que o processo de envelhecimento fosse cada vez se prolongando aumentando assim a expectativa de vida (3;4). Estudos demográficos mostram o quão rápido e expressivo é o crescimento da população de idosos no mundo (4-6). Isso é resultado da diminuição progressiva das taxas de fecundidade, das taxas de mortalidade e do aumento da expectativa de vida, caracterizando as modificações das pirâmides etárias (6).

Esse processo, que há alguns anos se restringia a países desenvolvidos, hoje ocorre também em países em desenvolvimento, como é o caso do Brasil (7). No último censo, foi observada uma menor população com idade até 25 anos e por outro lado, os demais grupos etários apresentaram um aumento de sua proporção em comparação com a última década, com destaque para os grupos com idade superior a 65 anos, correspondendo a 7,4% da população em 2010 (8).

Com o passar dos anos, ocorrem alterações fisiológicas e essas mudanças podem causar condições patológicas muitas vezes referidas como síndromes ou patologias geriátricas. Além disso, algumas alterações fisiopatológicas as quais muitas vezes não acarretam grandes implicações para

adultos jovens tendem a ser exacerbadas em idosos, principalmente quando em presença de doenças pré-existentes, quando se tem essa adição de duas ou mais podendo isso gerar um estado crítico sobre a saúde do indivíduo, principalmente dos idosos (3).

Considerando o aumento da prevalência da população idosa, são necessários maiores cuidados médicos e de saúde pública, além de saber como direcionar os recursos para superar esse desafio, promovendo uma melhor preservação da saúde do idoso (7). Esse aumento da expectativa de vida está também relacionado a uma maior morbidade por doenças crônicas não-transmissíveis (9;10), tais como hipertensão arterial, *Diabetes mellitus*, dislipidemia, osteoartrose e incontinência urinária (4;11).

2.2 Inibidores da Enzima Conversora de Angiotensina e os Antagonistas do receptor de Angiotensina II na Hipertensão Arterial Sistêmica

A hipertensão arterial sistêmica (HAS) é uma condição clínica multifatorial caracterizada por níveis elevados e sustentados da pressão arterial (PA). Associa-se frequentemente a alterações funcionais e/ou estruturais dos órgãos-alvo (coração, encéfalo, rins e vasos sanguíneos) e a alterações metabólicas, com consequente aumento do risco de eventos cardiovasculares fatais e não-fatais (12).

Segundo a VI Diretriz de Hipertensão Arterial (2010) é considerado normotenso pessoal com PA 130/85mmHg. Porém pessoas com PA igual ou superior a 115/75 mmHg, apresentam um aumento linear e progressivo da mortalidade por doenças cardiovasculares.

Em dois estudos foi considerado hipertenso o indivíduo que apresentava nível pressórico igual a 140/90 mmHg e, a prevalência observada na população idosa foi de 50% e 75% para indivíduos de 60 a 69 anos e com idade maior que 70 anos, respectivamente (13;14).

Em relação ao gênero, a HAS é mais freqüente em homens, com uma prevalência de 35,8%, já as mulheres apresentam uma prevalência de 30% semelhante à média global (15).

O tratamento para HAS pode ser realizado com estratégias de prevenção (12), abordagem não medicamentosa, tais como: estilo alimentar, prática de atividade física regular, redução de estresse, do sal, tabagismo e etilismo (16) e abordagem medicamentosa (17), onde os principais medicamentos utilizados são os Inibidores da Enzima Conversora de Angiotensina (IECA) e os Bloqueadores do receptor de angiotensina II (BRA), ambos atuando no sistema Renina Angiotensina Aldosterona (SRAA).

A cascata do SRAA inicia-se com o angiotensinogênio, que é sintetizado nos hepatócitos. O angiotensinogênio é um substrato da renina que, após ser sintetizado, é secretado na corrente sanguínea (18).

A maior produção de renina liberada para corrente sanguínea é produzida pelo sistema renal, porém não apenas esse sistema produz a renina. De 80 – 90% da renina circulante em nosso corpo é de origem da prorenina, uma forma primária da renina (19). Um aspartilprotease (armazenada nos grânulos das células justaglomerulares nas paredes das arteríolas aferentes renais) após ser liberada para corrente sanguínea, atua na conversão do angiotensinogênio em angiotensina-I (20). Tanto a renina quanto a prorenina, quando liberadas na circulação podem ligar-se a receptores como os encontrados no coração e nas glândulas adrenais sendo alvo de captação extra-renal (21;22). Quando a renina e a prorenina ligam-se em seus receptores teciduais começam a catalisar a conversão do angiotensinogênio em angiotensina I, localmente e ativando vias de sinalização intracelular como a proteína quinase (23).

Após a síntese da angiotensina I, está é clivada em angiotensina II, um potente vasopressor (24). Os receptores transmembrana acoplados à proteina G, são responsáveis por mediar os efeitos da angiotensina II circulante, sendo dois subtipos os principais receptores os AT1 e AT2 (25). Outro mediador importante do SRAA é a aldosterona, responsável pelo balanço eletrolítico e regulação da pressão arterial, sendo esta sintetizada e secretada pelas glândulas supra-renais em sua camada glomerulosa, em resposta a estímulo do receptor AT1 pela ligação da angiotensina-II (26).

2.3 Influência dos IECA no Desempenho Físico

O envelhecimento tem sido claramente associado com o declínio do desempenho físico e declínio da força muscular, levando potencialmente à deficiência na vida adulta.

Até o presente momento, não existem evidências de intervenções farmacológicas definitivas e comprovadas pra uma prevenção do declínio do desempenho físico (27). As únicas exceções, que podemos salientar são os IECA e BRA, onde são associados a benefícios clínicos (por exemplo, redução da morbidade, hospitalizações e mortalidade) em pacientes com doenças cardiovascular e condições metabólicas (28).

Estes efeitos deletérios estão associados a redução da massa muscular relacionada ao envelhecimento ocorre de maneira gradativa, sendo estimada uma perda de 5% a cada década, iniciando após os 40 anos, sendo mais vigorosa após os 65 anos (29). A atrofia muscular decorrente do envelhecimento é provavelmente causada pela redução das fibras do tipo II (30) e também por alterações do tamanho e angulação das fibras musculares (31).

Essa alteração no sistema muscular vem causar alterações, como o declínio no desempenho funcional, restrições da adaptação, diminuição da força muscular e da capacidade de produção de força, devido a essa perda progressiva de tecido muscular com o passar dos anos (32). Essas alterações são denominadas de sarcopenia (33).

A sarcopenia foi inicialmente descrita por Irwin Rosenberg, que propôs o termo, sarcopenia, em 1989, onde “sarco” significa carne e “penia” significa perda. Atualmente, o termo é definido como uma grave alteração na estrutura dos músculos esqueléticos, associada ao envelhecimento humano, uma vez que ocorre a diminuição de força muscular e funcionalidade com o passar dos anos (34).

Sendo essa diminuição da massa muscular mais acentuada após os 40 anos, existe uma maior chance do aparecimento de doenças, já que os

músculos são os principais reservatórios de proteínas e aminoácidos, os quais são utilizados para produção de energia (31).

Além disso, é observado que, nos indivíduos com mais de 70 anos, 25% apresentam sarcopenia e, após os 80 anos, essa proporção aumenta para 40%(35;36). Esta sarcopenia observada em idosos geralmente é decorrente de redução do número de fibras musculares, estando relacionada a uma diminuição da produção de hormônios anabólicos(30;35), como por exemplo, a testosterona, hormônio do crescimento, IGF-1, e um aumento na liberação de agentes catabólicos e interleucina-G (36;37).

Ainda, ocorre depósito de tecido adiposo na musculatura (38) e alterações na síntese de colágeno, acarretando redução na elasticidade dos ligamentos(31). Nesse contexto,(39) relatou que, após os trintas anos, existe uma diminuição da densidade dos músculos da coxa e aumento de gordura intramuscular.

Há relatos de que os IECA atuam sobre a estrutura e a função do sistema músculo-esquelético, causando uma melhora clínica, uma vez que a IECA pode causar alterações nos tipos de fibras musculares, redução do processo inflamatório (21), melhora da comunicação neuromuscular, aumento da angiogênese nas estruturas musculares, inibição da Interleucina-6(39), redução das catecolaminas, atividade do sistema nervoso simpático, aumento a sensibilidade à insulina e a glicose(41) e aumento da eficiência metabólica do tecido (42). Além disso, em um estudo realizado com pacientes com HA ou com ICC, tratados com IECA notou-se uma manutenção do peso entre 0,10 e 0,18 Kg/ano, relacionado a manutenção de massa muscular (35).

Quanto a capacidade de exercício, existem poucos estudos que avaliaram especificamente o efeito dos IECA sobre a capacidade de exercício, e seus resultados ainda são limitados e muitas vezes controversos devido as variáveis pesquisadas(43-47).

Steen (43) demonstrou em ratos obesos com administração crônica de IECA apresentaram melhora na capacidade de exercício em comparação ao grupo controle. Neste estudo, este efeito foi justificado pela melhora na capacidade da insulina em transportar maior quantidade de glicose para o

tecido muscular, aumentando à resistência do músculo à fadiga. Dados similares foram observados por Newman et al (45),o qual descreve que o tratamento com IECA melhora a capacidade de exercício, por desencadear aumento na perfusão dos músculos esqueléticos, efeito relacionado à redução do declínio da função física em idosos.

Em um estudo onde foi avaliado o teste de caminhada de 6 minutos (TC6), observou-se um melhor desempenho em idosos que apresentaram disfunção sistólica do ventrículo esquerdo e faziam uso contínuo do medicamento perindropil em comparação ao placebo. Neste estudo, observou-se um aumento da distância de 37 m (aumento de 13,5%), quando comparado ao grupo controle, indiferente se os pacientes fossem do grupo menos assintomáticos ou mais assintomáticos (48).

Curiosamente, Steen et al. (43) demonstraram em ratos obesos Zucker, que os IECA aumentaram ainda mais a capacidade de exercício comparado com o treinamento físico isolado. Tal resultado parece ser mediado pela melhora na capacidade da insulina em transportar a glicose para o tecido muscular.

Os IECA, quando administrados em pacientes com ICC, apresentam uma melhor capacidade de exercício, que foi relacionada com modificação no tipo de fibra muscular, com aumento no número de fibras do tipo I (49) causando melhora na resistência a fadiga devido a propriedade das fibras.

Entretanto, o uso de IECA não alterou a duração do exercício em pacientes hipertensos e não conseguiram restaurar a função muscular e a capacidade de exercício em ratos diabéticos (50;51).

Neste contexto, seria possível que este grupo de fármacos poderia reduzir o declínio da força e da massa muscular, resultante da sarcopenia em idosos (45;52).

Os IECA além do seu efeito sobre a gênese de angiotensina II, também potencializam a ação da bradicinina, uma vez que a enzima conversora de angiotensina é sua principal via de inativação. A bradicinina pertence ao grupo das cininas, que são polipeptídeos sintetizados no plasma e/ou líquido

intersticial, a partir de proteínas de elevado peso molecular, envolvidos em diversos eventos biológicos, incluindo aumento da permeabilidade vascular, relaxamento da musculatura lisa e vasodilatação. Dessa forma, após tratamento com IECA ocorre aumento nos níveis circulantes de bradicinina, com posterior liberação de prostaglandinas, prostacilcinas e óxido nítrico (NO), causando natriurese, redução da pressão arterial, oferecendo efeito adicional cardioprotetor desempenhado pelos IECA. Ou seja, os efeitos cardiovasculares benéficos produzidos pelos IECA não se devem apenas à redução na síntese de angiotensina II, mas também à potenciação dos efeitos biológicos da bradicinina, devido sua menor degradação endógena (53;54).

Além disso, outra classe de medicamentos que atuam sobre o SRAA são os bloqueadores do receptor de angiotensina (BRA), os quais inativam o receptor AT1(55;56), não interferindo, portanto, com os níveis circulantes de bradicinina.

Embora vários estudos tenham apresentado efeitos benéficos dos IECA sobre o declínio da força muscular e capacidade funcional de exercício, os resultados ainda são controversos e nenhum dos estudos avaliou de forma comparativa os efeitos dos IECA em comparação com os BRA.

ANGIOTENSIN-II BLOCKAGE, MUSCLE STRENGHT AND FUNCTIONAL EXERCISE CAPACITY IN PHYSICALLY INDEPENDENT OLDER ADULTS

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Running Title: Angiotensin-II and Physical Performance

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ABSTRACT

Aims: To evaluate a possible relationship between the blockage of Angiotensin-II and functional exercise capacity and muscle strength in elderly. **Methods**: 235 older adults were recruited for this study. All subjects were physically independent and took part in the EELO project (Study on Aging and Longevity). Data concerning comorbidities and medication's use was assessed through structured questionnaires and the individuals were separated into three groups: control group (CG): elderly with functional exercise capacity higher than 80% of the predicted value (n=235); ACEIG: individuals using Angiotensin-Converting Enzyme Inhibitors (n=140); ABRG: patients using Angiotensin-II Receptor Blockers (n= 32). The functional exercise capacity was evaluated by the 6-minute walking test (6MWT) and muscle strength was measured using a handgrip dynamometer. **Results**: Patients from ACEIG (Mean: 99 ± 12%) and ABRG (Mean: 101 ± 14%) showed higher predicted values in 6MWT when compared to control group (Mean: 96 ± 10%, p=0.001). Additionally, it was observed that patients from ACEIG (Mean: 105 ± 19%) and ABRG (Mean: 105.1 ± 18.73%) showed higher predicted values of muscle strength in comparison to control group (Mean: 98.15 ± 18.77%, p=0.001). **Conclusions**: Older adults using Angiotensin-Converting Enzyme Inhibitors or Angiotensin-II Receptor Blockers have better functional exercise capacity as well as muscle strength when compared to control ones. Thus, elderly who use this medication may show a lower decline of physical performance age-related.

Keyword: Aging, Inhibitors of Angiotensin Converting Enzyme, Exercise Capacity

INTRODUCTION

The aging process is a phenomenon, representing one of the biggest challenges to public health worldwide. According to the World Health Organization (WHO), there are currently 650 million elderly (over 60) nowadays and the projection for 2025 is that this population will reach two billion people. Of these, approximately 66% live in developing countries and this percentage may reach 75% in 2025[1]. This markedly raise in life expectancy is also related to an increased morbidity from chronic diseases [2,3]. Duarte and Rego[4] found that hypertension, *Diabetes mellitus*, dyslipidemia, osteoarthritis and urinary incontinence are the main diseases observed in this population.

Furthermore, the aging process may affect the physical performance of older adults, evoking negative impact on their behavior and consequent changes in lifestyle, making them dependent [5,6]. Several studies have reported that the loss of functional capacity of elder people is usually related to the presence and complexity of comorbidities [7]. Although several mechanisms may be related to this impairment on physical function in this population, the gradual loss of muscle mass and strength is often associated with the onset and establishment of disabilities[8]. The association between genetic variations of the angiotensin converting enzyme (ACE) gene and differences in physical performance phenotypes have been explored during the last years. Since a positive association between the insertion/deletion (I/D) polymorphism of the ACE gene and the exercise performance was described by Montgomery and colleagues [9], various corroborative studies were performed.

According to the literature, individuals with the ACE insertion (I allele) presents a lower ACE plasma levels[10] and an increase in slow-twitch rather than fast-twitch muscle fibers [11,12] which in turn confers a better response to training in both skeletal muscle and cardiovascular system[11,13] and in an advantage in endurance sporting events [14,15].

There are few reports about the effectiveness of pharmacological interventions which can prevent the decline in functional capacity in older adults. However, cross-sectional study in healthy elder individuals showed a positive correlation between the use of Angiotensin-Converting Enzyme Inhibitors (ACEI) and skeletal muscle mass in these hypertensive patients[16].

Moreover, Sumukadas et al.[17] reported that the increase in exercise capacity after perindopril treatment is similar to a six-month training program.

In addition to ACEI, Angiontensin Receptor Blockers (ARB) also modulate the effects of angiotensin II, as they block the AT_1 receptor, regardless of the amount of angiotensin II circulating levels[18].

Although there are some reports that the use of ACE inhibitors can prevent the decline in muscle strength aging-related, further studies are necessary to confirm this hypothesis, especially because many studies have evaluated this effect only in patients with congestive heart failure (CHF) and not in the elder population in general. Thus, this study aimed to evaluate a possible association between the use of ACEI or ARB and functional exercise capacity and muscle strength in physically independent older adults.

MATERIALS AND METHODS

Ethical Procedures and Study Design

All subjects enrolled in this study agreed and signed a written informed consent. The study was approved by the Ethics Committee of the University of Northern Parana (PP070/09).

This cross-sectional study followed the criteria established by Strengthening the Reporting of Observational Studies in Epidemiology – STROBE[19]. The convenience sample consisted of older adults (age over 60, according to recommendations of World Health Organization for developing countries – [20] who participated on an interdisciplinary project (EELO Project - Study on Aging and Longevity). The EELO Project is a thematic project developed at University of Northern Parana (UNOPAR) which aimed to evaluate the socio-demographic factors and indicators of health conditions of older adults in Londrina, a city of Northern Paraná, Brazil. Information can be found at http://www2.unopar.br/sites/eelo/. This study was developed in Londrina as the

elder population of this city represents 12% of the total population, which is similar to what has been described in other developed countries[21,22]. The total sample of the EELO project consisted of 508 individuals, which is representative of the 43610 citizens older than 60 years living in Londrina. Of those, 101 individuals did not match the inclusion criteria and they could not be included in the study. Therefore, the convenience sample of the present study consisted of 407 physically independent elderly according to the classification proposed by the Functional Status Spirduso (levels 3 and 4). This means that older adults are able to perform basic and instrumental activities of daily life. The individuals from level 3 have low exercise capacity and are sedentary, and individuals from level 4 have exercise capacity above average and are considered as physically active[23].

Eligibility Criteria of the Study Population

The studied subjects were separated into three experimental groups (according to the medication used): Control Group (CG): physically independent elderly with exercise capacity and muscle strength exceeding 80% of the predicted value; ACEI Group: patients who used Angiotensin Converting Enzyme Inhibitors (ACEI) for at least six months; ARB Group: patients who are using Angiotensin Receptor Blockers (ARB) for at least six months. Figure 1 shows a flowchart concerning the inclusion/exclusion

Older adults who are using another antihypertensive drugs that may influence the muscle strength or exercise capacity (ex: Calcium Channel Blockers) or individuals performing less than 80% of the predicted value of the tests were excluded from this study.

Data Collection

Comorbitity and medication questionaries

The presence of comorbidities and medication consumption were investigated using structured questionnaires. Additionally, questions concerning height and weight were also included in order to determine the anthropometric characteristics.

Functional Exercise Capacity

The functional exercise capacity was measured using the 6-minute walking test (6MWT). This test was performed in accordance with the guidelines established by the American Thoracic Society [24] and the reference values used were those described by Troosters[25]. Data were expressed as walking distance (in meters) and as the percentage of the predicted value.

Blood pressure, heart rate (HR), respiratory rate, symptoms of dyspnea and fatigue as well as oxygen saturation was measured before, immediately after and 2 minutes later of the recovery of the test. Two tests were performed with, at least, 30 minutes of rest between them.

Muscle Strenght

A dynammometer was used to assess muscle strength which was calibrated according to the methodology described by Vianna[26]. The subject was placed in the standing position and, after adjusting for the size of the hand, the device was held comfortably in line with the forearm, running parallel to the longitudinal axis of the body. The proximal inter-phalangeal joint of the hand was adjusted under the support bar, which was then pressed between fingers and thenar region.

During handgrip, the arm remains still, with only flexion of the interphalangeal and matacarpo-phalangeal joints. Considering standardization, the movement of the elbow or wrist during the act of handling was not allowed. The handgrip strength was measured in both members and the best result was

considered. The values obtained were compared to the reference values described by Mathiowetz [27].

Statistical Analysis

Data were analyzed using the GraphPad Prism 5.0 statistical program (GraphPad Software Inc., San Diego, CA, USA). The normality of data distribution was verified using the Shapiro-Wilk test. Since data were normally distributed, parametric tests were used and descriptive data were expressed as meab and standard deviation. Significance level was set at $p<0.05$ for all tests.

For data analysis, the older adults were separated into three groups, according to the medication used: Control Group (CG); ACEI Group: patients who used Angiotensin Converting Enzyme Inhibitors (ACEI); ARB Group: patients who are using Angiotensin Receptor Blockers (ARB).

One-way ANOVA was used to compare the groups regarding muscle strenght and functional exercise capacity.

RESULTS

No differences concerning gender ($p=0.99$), age ($p=0.46$), height ($p=0.11$), weight ($p=0.06$) and body mass index ($p=0.07$) were observed among the experimental groups. Therefore, it may be assumed that the groups were similar regarding anthropometric data, being these results shown in table 1.

It was observed a higher walking distance performed by men from the ACEIG when compared to CG. However, the individuals from ARBG were similar to individuals from ACEIG and CG, according to one-way ANOVA ($p=0.04$, Table 2). Similar data were observed concerning women ($p=0.04$, Table 3). However, when the percentage of predicted value was considered, it was observed that individuals from both ACEIG and ARBG had better performance than individuals from CG (Table 4).

Regarding muscle strength, it was observed that men from ACEIG had higher values when compared to CG. However, the individuals from ARBG were similar to individuals from ACEIG and CG, according to one-way ANOVA (p=0.04, Table 2). Similar data were observed concerning women (p=0.04, Table 3). However, when the percentage of predicted value was considered, it was observed that individuals from both ACEIG and ARBG had better performance than individuals from CG (Table 4).

DISCUSSION

In this study, we found that elder individuals who use ACEI or ARB have better exercise capacity compared to the elderly who do not use this medication. This result is in agreement with Onder et al.[28] who also observed a better physical performance in individuals using ACEI.

Additionally, it was also observed in this study an increase in muscle strength in older adults patients treated with both ACEI and ARB, agreeing with the study of Di Bari et al.[9] that describes a raise in muscle mass in elder patients treated with ACEI.

Moreover, Sumukadas et al.[10] reported that the increase in exercise capacity after treatment with Perindopril was equivalent to a six-month program of physical training. Vescovo et al.[29] reported significant increases in maximum oxygen uptake (VO_2max) and ventilatory threshold after six months of treatment with losartan. In another longitudinal study of patients with CHF, Corder et al.[30] observed an increase in VO_2max and exercise duration after twelve weeks of treatment with Cilazapril. However, treatment with enalapril in patients with CHF resulted in no significant increase in VO_2max and exercise capacity although it was observed significant increase in the density of skeletal muscle fibers[31].

The exact mechanism by which pharmacological blockade of angiotensin-II influences the physical performance is still unclear. However, several hypotheses could be postulated according to Onder et al.[28].

Initially, it can be assumed that the blockade of angiotensin-II could trigger metabolic and mechanical changes in skeletal muscle. In this context, ACEI increase insulin sensitivity, glycogen stockage and glucose uptake by skeletal muscles, improving muscle metabolic efficiency[32]. In addition, decreased degradation of bradykinin by blocking the angiotensin converting enzyme (ACE) could improve the blood flow to the skeletal muscles through vasodilatation and a raise capillary permeability, thus increasing the uptake of glucose and amino acids also contributing to a higher metabolic efficiency[33,34].

Moreover, ACEI can reduce the inflammatory response produced by angiotensin-II [35], which increases the production of interleukin 6 (IL-6) and alpha tumor necrosis factor (TNFα) in vascular smooth muscle cells[36], being this reduction directly related to the prevention of loss of muscle mass. The ACEI may exhibit this effect since they indirectly potentiate the action of bradykinin which, in turn, releases nitric oxide, a potent suppressant agent of the inflammatory response[37].

From these results, it can be suggested that the beneficial effect observed by treatment with ACEI may be at least partially mediated by bradykinin, since the ACEI limit the degradation of bradykinin, which plays an important role in modulating endotelium relaxing factors[38].

The reduction of bradykinin as a result of ACE inhibition may increase the blood supply to skeletal muscle by causing vasodilation and increased capillary density, favoring the uptake of glucose and amino acids, leading to a higher metabolic efficiency[39,40]. These data may suggest that this beneficial effect on the physical performance is due to ACE inhibition and not only the pharmacological effects of angiotensin II.

As limitations of this study, it is important to analyze whether this effect was dose or time dependent. Moreover, inflammatory biomarker levels (such as IL-6 and TNFα) were not assessed at this study. Furthermore, it should be highlighted that cohort as well as clinical randomized trials should be conducted to confirm this hypothesis.

Considering the beneficial effect of these drug types on physical performance, it can be suggested that these drugs may contribute to a smaller decline in physical capacity related to the aging process.

CONCLUSIONS

It can be concluded that older adults who use Angiotensin Converting Enzyme Inhibitors or Angiotensin Receptor Blockers have a better functional exercise capacity and muscle strength compared to controls. Thus, elderly who use this medication may present a lower decline of functional capacity related to aging process.

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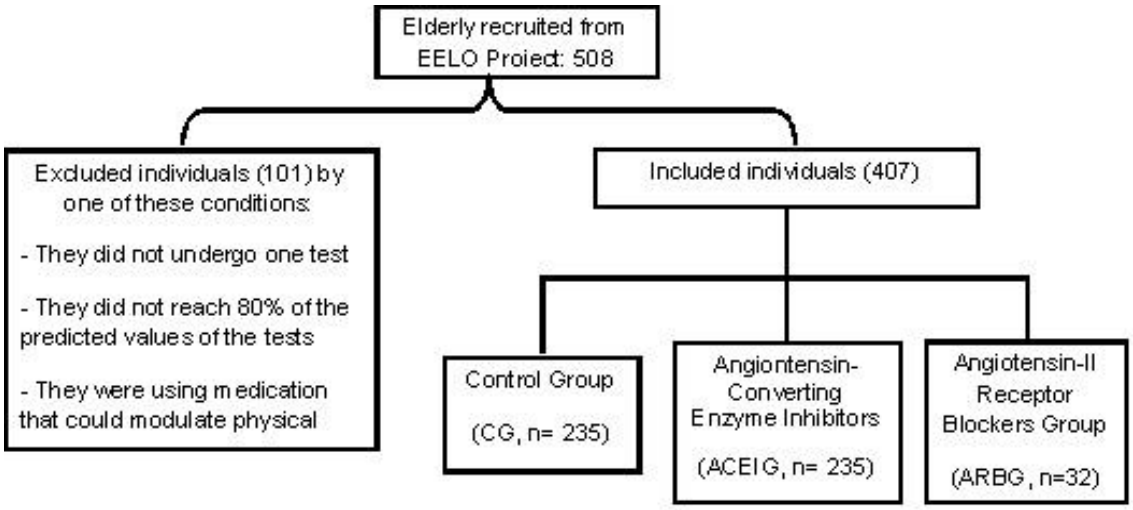

FIGURE 1- Flowchart of the population enrolled at the study after inclusion/exclusion criteria.

TABLE 1 – Distribution of anthropometric data among groups.

Anthropometric Data		**CG** (n=235)	**ACEIG** (n =140)	**ARBG** (n =32)	***p***
Gender	**M**	80 (34%)	48 (34 %)	11 (34%)	0.99
	F	155 (66%)	92 (66%)	21 (66%)	
Age (years)		69 ± 6	69 ± 6	70 ± 6	0.46
Height (cm)		157 ± 9	157 ± 10	154 ± 6	0.11
Weight (Kg)		68 ± 12	71 ± 12	70 ± 12	0.06
BMI		28 ± 4	28 ± 4	29 ± 4	0.07

Male (M), Female (F), Body mass index (BMI), Control group (CG), Angiotensin Converting Enzime Inhibitor Group (ACEIG), Angiotensin-II Receptor Blockers Group (ARBG).
* Values are expressed as mean and standard deviation (Mean ± SD).

TABLE 2 – Walking distance and muscle strenght among men from the Control Group (CG); Angiotensin-Converting Enzyme Inhibitors Group (ACEIG) and Angiotensin Receptor Blockers Group (ARBG).

Variables	**Experimental Groups** (Mean ± SD)			*p*
	CG (n=235)	**ACEIG** (n =140)	**ARBG** (n =32)	
6MWT (m)	500 ± 76	538 ± 73*	517 ± 84	0.04
Muscle Strenght (Kg)	34 ± 6	37 ± 7*	32 ± 6	0.01*

*Statistically different from control group, one-way ANOVA, followed by Bonferrroni's post-test.

TABLE 3 – Walking distance and muscle strenght among women from the Control Group (CG); Angiotensin-Converting Enzyme Inhibitors Group (ACEIG) and Angiotensin Receptor Blockers Group (ARBG).

Variables	**Experimental Groups** (Mean ± SD)			*p*
	CG (n=235)	**ACEIG** (n =140)	**ARBG** (n =32)	
6MWT (m)	504 ± 74	529 ± 82*	525 ± 62	0.04
Muscle Strenght (Kg)	23 ± 4	25 ± 5*	23 ± 5	0.03

* Statistically different from control group, one-way ANOVA, followed by Bonferrroni's post-test.

TABLE 4 - Comparison of the walking distance obtained in six-minute walking test (6MWT) and muscle strength among the experimental groups: Control Group (CG); Angiotensin-Converting Enzyme Inhibitors Group (ACEIG) and Angiotensin Receptor Blockers Group (ARBG).

Variables	**Experimental Groups** (Mean ± SD)			***p***
	CG (n=235)	**ACEIG** (n =140)	**ARBG** (n =32)	
6MWT (% pred.)	96 ± 10	99 ± 12*	101 ± 14	0.001
Muscle Strenght (% pred.)	98 ± 18	105 ± 19*	105± 19	0.001

* Statistically different from control group, one-way ANOVA, followed by Bonferrroni's post-test.

CONCLUSÃO GERAL

Pode-se concluir que idosos que utilizam Inibidores da Enzima Conversora de Angiotensina ou Bloqueadores do Receptor de Angiotensina II apresentam melhor capacidade funcional de exercício e força muscular em relação aos controles. Desta forma, idosos que utilizam esta medicação poderiam apresentar menor declínio de capacidade física relacionada ao processo de envelhecimento.

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ANEXOS

ANEXO A

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All articles submitted to the Journal must comply with these instructions. Failure to do so will result in return of the manuscript and possible delay in publication. Manuscripts should be written so that they are intelligible to the professional reader who is not a specialist in the particular field. Where contributions are judged as acceptable for publication on the basis of scientific content, the Editor or the Publisher reserve the right to modify typescripts to eliminate ambiguity and repetition and improve communication between author and reader. If extensive alternations are required, the manuscript will be returned to the author for revision.

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- Specify any special characters used to represent non-keyboard characters.
- Take care not to use l (ell) for 1 (one), O (capital o) for 0 (zero) or ß (German esszett) for b (Greek beta).

- Use a tab, not spaces, to separate data points in tables.
- If you use a table editor function, ensure that each data point is contained within a unique cell; i.e. do not use carriage returns within cells.
- All pages should be numbered consecutively in the top right-hand corner, beginning with the title page.

- Indent new paragraphs.

- The top, bottom and side margins should be 30 mm.

Each figure should be supplied as a separate file, with the figure number incorporated in the file name. For submission, low-resolution figures saved as .jpg or .bmp files should be uploaded, for ease of transmission during the review process. Upon acceptance of the article, high-resolution figures (at least 300 d.p.i.) saved as .eps or .tif files should be uploaded. Digital images supplied only as low-resolution files cannot be used. Further instructions are available at the submission site.

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Abbreviations. Abbreviations should be used sparingly – only where they ease the reader's task by reducing repetition of long, technical terms. Initially use the word in full, followed by the abbreviation in parentheses. Thereafter use the abbreviation only.

Trade names. Drugs should be referred to by their generic names, rather than brand names.

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Word limit: 3,000 words including abstract but excluding references, tables and figures
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Abstract: 250 words, structured

Figures/tables: Up to 5 in total

Description: Full-length reports of current research in either basic or clinical science

(2) Review Article

Word limit: 5,000 words including abstract but excluding references, tables and figures
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Abstract: 250 words, structured

References: Up to 30

Figures/tables: Up to 5 in total

Description: Full-length reports of current research in either basic or clinical Science

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References: Up to 5

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PARTS OF THE MANUSCRIPT

Manuscripts should be presented in the following order: (i) title page, (ii) abstract and key words, (iii) text, (iv) acknowledgments, (v) disclosure statement, (vi) references, (vii) figure legends, (viii) tables (each table complete with title and footnotes), (ix) figures. Footnotes to the text are not allowed and any such material should be incorporated into the text as parenthetical matter.

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The title page should contain: (i) the title of the paper (ii) the full names of the authors (iii) the addresses of the institutions at which the work was carried out together with (iv) the full postal and email address, plus facsimile and telephone numbers, of the author to whom correspondence about the manuscript should be sent. In keeping with the latest guidelines of the International Committee of Medical Journal Editors, each author's contribution to the paper is to be quantified. The present address of any author, if different from that where the work was carried out, should be supplied in a footnote. The title should be short, informative and contain the major key words. Do not use abbreviations in the title. A short running title (less than 40 characters) should also be provided.

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Articles must have a structured abstract that states in 250 words or fewer the purpose, basic procedures, main findings and principal conclusions of the study. Divide the abstract with the headings: Aim, Methods, Results, Conclusions. The abstract should not contain abbreviations or references. Five key words, for the

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Yamauchi J, Nakayama S, Ishii N. Effects of bodyweight-based exercise training on muscle functions of leg multi-joint movement in elderly individuals. *Geriatr Gerontol Int* 2009. doi: 10.1111/j.1447-0594.2009.00530.x

Book
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These should be placed at the end of the paper, numbered in Roman numerals and referred to in the text. If written by a person other than the author of the main text, the writer's name should be included below the title.

Tables
Tables should be self-contained and complement, but not duplicate, information contained in the text. Number tables consecutively in the text in Arabic numerals. Table should be double –spaced and vertical lines should not be used to separate columns. Column headings should be brief, with units of measurement in parentheses; all abbreviations must be defined in footnotes. Footnote symbols: †, ‡, §, , should be used (in that order) and *, **, *** should be reserved for *P*-values. The table and its legend/footnotes should be understandable without reference to the text.

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sharp, black and white graphs or diagrams, drawn professionally or with a computer graphics package. Lettering must be included and should be sized to be no larger than the journal text.

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ANEXO B – Carta de Aprovação do Comitê de Ética em Pesquisa

UNOPAR

Universidade Norte do Paraná
Comitê de Ética em Pesquisa

PARECER CONSUBSTANCIADO

PROTOCOLO: PP 0070/09
RESPONSÁVEL: *Vanessa Suziane Probst*
CATEGORIA DE PROJETO: *Pesquisa*

O Comitê de Ética em Pesquisa da Unopar analisou e APROVOU quanto ao aspecto ético o projeto **"Estudo Epidemiológico dos fatores sócio-demográficos e indicadores das condições de saúde de idosos do município de Londrina-PR."**
O projeto somente poderá ser iniciado após a apresentação da carta de autorização da Secretaria da Saúde.

O CEP/UNOPAR estabelece:

a) O sujeito da pesquisa tem a liberdade de recusar-se a participar ou de retirar seu consentimento em qualquer fase da pesquisa, sem penalização alguma e sem prejuízo ao seu cuidado (Res. CNS 196/96 – Item IV.1.f) e deve receber uma cópia do Termo de Consentimento Livre e Esclarecido, na íntegra, por ele assinado (Item IV.2.d).

b) O pesquisador deve desenvolver a pesquisa conforme delineada no protocolo aprovado e descontinuar o estudo somente após análise das razões da descontinuidade pelo CEP/UNOPAR (Res. CNS Item III.3.z), aguardando seu parecer, exceto quando perceber risco ou dano não previsto ao sujeito participante ou quando constatar a superioridade de regime oferecido a um dos grupos da pesquisa (Item V.3) que requeiram ação imediata.

c) O CEP/UNOPAR deve ser informado de todos os efeitos adversos ou fatos relevantes que alteram o curso normal do estudo (Res. CNS Item V.4). É papel do pesquisador assegurar medidas imediatas adequadas frente a evento adverso grave ocorrido (mesmo que tenha sido em outro centro) e enviar notificação ao CEP/UNOPAR junto com seu posicionamento.

d) Eventuais modificações ou emendas ao protocolo devem ser apresentadas ao CEP/UNOPAR de forma clara e sucinta, identificando a parte do protocolo a ser modificada e suas justificativas.

e) Semestralmente devem ser encaminhados relatórios parciais e ao término do projeto o relatório final.

Londrina, 28 de abril de 2009.

Prof. Dr. Hélio Hiroshi Suguimoto
Presidente do C.E.P. UNOPAR