UNIVERSIDADE FEDERAL DE CIÊNCIAS DA SAÚDE DE PORTO ALEGRE – UFCSPA
PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA SAÚDE

Candissa Silva da Silva

Impacto do Treinamento Aeróbio em Fatores de Risco Cardiovascular e Qualidade de Vida em Pessoas Vivendo com HIV/AIDS.

Porto Alegre
2018

Candissa Silva da Silva

Impacto do Treinamento Aeróbio em Fatores de Risco Cardiovascular e Qualidade de Vida em Pessoas Vivendo com HIV/AIDS.

Tese submetida ao Programa de Pós-Graduação em Ciências da Saúde da Universidade Federal de Ciências da Saúde de Porto Alegre como requisito para a obtenção do grau de Doutora

Orientador: Dr.Pedro Dal Lago
Coorientador: Dr. Luís Fernando Deresz

Porto Alegre
2018

Catalogação na Publicação

Silva da Silva, Candissa
Impacto do Treinamento Aeróbio em Fatores de Risco Cardiovascular e Qualidade de Vida em Pessoas Vivendo com HIV/AIDS : Treinamento Aeróbio em Pessoas Vivendo com HIV/AIDS / Candissa Silva da Silva. -- 2018.
105 f. : graf., tab. ; 30 cm.

Tese (doutorado) -- Universidade Federal de Ciências da Saúde de Porto Alegre, Programa de Pós-Graduação em Ciências da Saúde, 2018.

Orientador(a): Dr Pedro Dal Lago ; coorientador(a): Dr Luís Fernando Deresz.

1. HIV. 2. TARV. 3. Treinamento Aeróbio. 4. Doença Cardiovascular. 5. Qualidade de Vida. I. Título.

Sistema de Geração de Ficha Catalográfica da UFCSPA com os dados fornecidos pelo(a) autor(a).

Dedicatória

Dedico esta tese a:

Minha mãe Ione e meu esposo Fernando pelo amor incondicional e por serem meus exemplos de força e determinação;

As pessoas vivendo com HIV/AIDS pela confiança e por acreditarem em meu trabalho;

Aos que trilharam esse caminho junto a mim.

Agradecimentos

Esse trabalho é a finalização não só de uma etapa, mas sim de todo um ciclo da minha vida. Uma trajetória se teve início na pré-escola. Hoje, quando olho para trás, percebo que tudo foi como deveria ter sido e que bom ou ruim foram importantes para construir essa trajetória e transformar a pessoa que sou hoje. Sei que ninguém chega até aqui sozinho, por isso meu mais profundo agradecimento a todos que estiveram presentes em meu caminho. Agradeço a **Deus** por ter colocado em minha vida pessoas tão especiais.

À minha mãe, **Ione Silva da Silva**: obrigada por ser desde sempre meu exemplo e referência de mulher, coragem, força e integridade. Obrigada por acreditar nos meus sonhos, fazê-los deles teus e permitir eu ir tão longe. Por estares sempre ao meu lado, pelo amor incondicional, mesmo nos momentos em que minha ausência foi a única presença. Meu amor infinito. Ao meu pai **Jesus Mendonça da Silva** (*in memmoriam*) que certamente de onde estiver sempre esteve ao meu lado.

Ao meu esposo **Fernando Rudem Brasil**, meu grande parceiro e cúmplice de vida. Obrigada por tornar meus dias mais leves, por ser meu porto seguro, além de me contemplar com um amor grandioso. Obrigada por ter me ajudado não apenas como expectador ou com palavras de incentivo, mas de ter feito parte desse trabalho e ter tantas vezes dividido a carga quando ela se tornava pesada demais. És o homem que amo e que admiro infinitamente.

Ao meu orientador Prof **Pedro Dal Lago**, por ter me recebido e acolhido durante todo esse período. Obrigada contribuição científica, confiança, oportunidade de crescimento, confiança, discussões e aprendizado que levarei no meu caminho.

Ao meu co-orientador Prof **Luís Fernando Deresz**, meu grande parceiro de jornada. Apesar da distância, fez-se tão presente, até mesmo nos momentos de ansiedade, sempre acalmando com as palavras de incentivo. Obrigada contribuição fundamental para finalização desse trabalho. Admiro tua humildade e capacidade em difundir e trocar conhecimentos.

Ao meu irmão **Andrei Silva da Silva** que mesmo distante torce por minhas conquitas.

À minha segunda mãe, madrinha **Elaine da Silva Leonardi** e minhas primas-irmãs: **Evelise Leonardi**, **Litiane Leonardi** e **Guilene Leonardi**, por serem minhas grandes incentivadoras de uma vida inteira. Obrigada por todo o amor e carinho.

Às minhas queridas bolsistas de iniciação científica **Giovana Castelli** e **Letícia Mignoni** agradeço por toda a dedicação e empenho a esse trabalho. A responsabilidade de vocês foi um dos fatores que fizeram com que esse trabalho pudesse ser realizado. Agradeço à vontade de aprenderem, por me ensinarem e por compartilharmos tantos momentos.

Ao querido **Gilson Dorneles**, agradeço a grande parceria, troca de conhecimentos e por toda a contribuição no desenvolvimento e finalização desse trabalho.

Ao ambulatório de Infectologia da Santa Casa, em especial à Dra. **Marília Maria Severo**, pelo acolhimento, amizade, carinho e ajuda fundamental na execução desse trabalho.

Às **pessoas que vivem com HIV/AIDS**, especialmente as que participaram desse trabalho, minha profunda gratidão pela confiança e por permitirem que esse trabalho tivesse acontecido. Obrigada por compartilharem suas histórias. Meu respeito e agradecimento por me fazerem crescer tanto como profissional quanto ser humano.

As minhas amigas de faculdade **Lícia Cogo**, **Marília Silva**, **Marília Marques** e **Mayra Weege** pelo incentivo, amizade e carinho independentes da distância e pelo compartilhamento e compreensão das ansiedades.

Ao meu querido ex-professor, mas grande amigo **Jadir Lemos** pela confiança, incentivo e carinho desde o início da graduação.

Aos meus **amigos** pela amizade, carinho e compreensão de tantas ausências.

Ao **Grupo de Estudos em Interação Cardiopulmonar** agradeço às amizades que construi ao longo desse período e que levo para a vida. Especialmente aos colegas do início desse processo: **Douglas Rossato, Jadson Alves, Luís Fernando, Marlus Karsten, Ramiro Barcos, Rodrigo Jaenisch, Vítor Scotta e Tatiana Rondinel.** Obrigada pelo compartilhamento de ensinamentos e discussões tão ricas e engrandecedoras.

À **Universidade Federal de Ciências da Saúde de Porto Alegre** pela oportunidade da realização desse trabalho e de crescimento profissional. A todos os funcionários representados por **Carmem Andrades**, **Edi Pulrolnik**, **Luciani Spencer**, **Maristela Pasin**, **Simone Schulze**, obrigada pela ajuda em todas as etapas dessa jornada.

A todos os **Professores** que marcaram meu caminho nos seguintes lugares por onde passei: **Escola Estadual de Ensino Médio Demétrio Ribeiro** (ensino fundamental), **Colégio Estadual Emílio Zuñeda** (ensino médio), **Universidade Federal de Santa Maria** (graduação) e **Universidade Federal de Ciências da Saúde de Porto Alegre** (pós-graduação) que me ajudaram a construir essa história. A todos meu respeito, carinho e admiração. Obrigada pelos ensinamentos e por me ajudarem a trilhar esse caminho.

À empresa **RTS Rio** em nome do *CEO* **Rogério Ferneda** pelo incentivo, por não me deixar desistir e pela confiança em meu trabalho em todos os momentos. Aos gerentes **Ivo Soeiro** e **Wagner Locatelli** agradeço toda a compreensão, confiança e apoio. Aos demais funcionários representados pelos meus queridos parceiros: **Alessandro Spigolon**, **Anderson Peçanha**, **Daniel Agostini**, **Euclides Neto**, **Rainer Maldonado** e **Rodrigo Volpatto** agradeço o carinho, respeito, incentivo e aprendizado.

Aos meus queridos colegas do **Serviço de Fisioterapia** do **Hospital de Clínicas de Porto Alegre**, especialmente aos amigos **Ane Margarites**, **Camila Zanette**, **Priscilla Paesi**, **Robledo Condessa** e **Rubia Fuentefria** pela amizade, apoio e incentivo.

Aos meus queridos **estagiários** do curso de Fisioterapia da Universidade Federal do Rio Grande do Sul, obrigada por permitirem eu exercer a educação, pela confiança e pela troca de saberes.

Obrigada a todos que acreditaram e acreditam em meu trabalho pelo carinho, incentivo e ajuda para a construção desse caminho. Saibam que por mais revoltos que sejam os mares da vida e nos levem por caminhos diferentes, contem comigo.

“Que os meus ideais sejam tanto mais fortes quanto maiores forem os desafios, mesmo que precise transpor obstáculos aparentemente intransponíveis. Porque metade de mim é feita de sonhos e a outra metade é de lutas”.

Vladimir Vladimirovich Mayakovsky (1893 - 1930)

Resumo

Pessoas vivendo com o vírus da imunodeficiência humana (HIV) e síndrome da imunodeficiência adquirida (AIDS) – PVHA apresentam um elevado risco cardiovascular associado ao processo inflamatório crônico causado pela replicação do HIV e a toxicidade medicamentosa decorrente da terapia antirretroviral combinada (TARV) mesmo em PVHA com carga viral indetectável. O objetivo da presente tese é apresentar os principais fatores de risco cardiovascular e verificar os efeitos do treinamento aeróbio sobre esses fatores. Assim, foram desenvolvidos 3 trabalhos: um estudo quase experimental que avaliou os efeitos do treinamento aeróbio na capacidade funcional, fatores de risco cardiovascular, citocinas inflamatórias, estresse oxidativo e qualidade de vida de PVHA; um estudo piloto que avaliou os efeitos do treinamento aeróbio na variabilidade da frequência cardíaca em PVHA; um estudo transversal com avaliação dos fatores de risco cardiovascular entre homens e mulheres vivendo com HIV.

No estudo 1, intitulado ***"Aerobic training improves functional capacity, cardiovascular risk factors, quality of life and modulates the inflammatory and oxidative stress markers in people living with HIV"***, foram avaliados os efeitos de 24 sessões de treinamento aeróbio de moderada à alta intensidade em 15 PVHA (11 homens) em dados antropométricos, capacidade funcional, função endotelial, perfil lipídico e glicêmico, perfil inflamatório, estresse oxidativo e qualidade de vida. Os resultados indicaram que o treinamento aeróbio melhora a capacidade funcional, perfil lipídico e glicêmico, escorre de qualidade de vida, além de reduzir medidas de dados antropométricos e promover modulação nos marcadores inflamatórios e estresse oxidativo em PVHA. Os resultados mostraram que a prática de exercício aeróbio melhora os fatores de risco para doença cardiovascular e causa impacto na qualidade de vida de PVHA.

O estudo 2, intitulado ***"Aerobic training improve the autonomic function of people living with HIV – A pilot study"*** apresenta os efeitos do treinamento aeróbio nas variáveis do domínio do tempo e da frequência da variabilidade da frequência cardíaca em PVHA. Foram realizadas 24 sessões de treinamento aeróbio em 8 PVHA. Verificou-se aumento das variáveis do domínio do tempo e da frequência e correlações entre variáveis do domínio do tempo com contagem T CD4+ e HDL; além de correlações do domínio da frequência com tempo de

diagnóstico do HIV e tempo de uso de TARV. Esses achados sugerem que o treinamento aeróbio pode impactar no sistema nervoso autônomo em PVHA.

O estudo 3 intitulado: **"*Presence of cardiovascular risk despite control of the disease among men and women with HIV using antiretroviral therapy - a cross-sectional study*"** avaliou os fatores de risco cardiovascular em PVHA verificando a diferença dessas variáveis entre homens (n = 11) e mulheres (n = 5). Foram avaliados dados antropométricos, perfil lipídico e glicêmico, capacidade funcional, função endotelial, marcadores inflamatórios, estresse oxidativo e escorre de Framingham. Os resultados mostram alta presença de disfunção endotelial, fortes correlações entre marcadores inflamatórios e de estresse oxidativo com dados antropométricos, contagem T CD4+ e capacidade funcional, além de apresentar maior risco cardiovascular na próxima década de vida entre mulheres que convivem com o HIV.

Quando associados os resultados dos 3 estudos, verificamos a presença de diversos fatores de risco cardiovascular entre PVHA em uso de TARV e os benefícios do treinamento aeróbio para a modificação desses fatores de risco, além da promoção de qualidade de vida decorrente dos efeitos do exercícios físico executado deforma regular.

Palavras-chave: HIV. TARV. Treinamento aeróbio. Doença cardiovascular. Qualidade de vida.

Abstract

People living with the human immunodeficiency virus (HIV) and Acquired Immunodeficiency Syndrome (AIDS) - PLWH present a high cardiovascular risk associated with the chronic inflammatory process caused by HIV replication and drug toxicity from combination antiretroviral therapy (ARV) even in PLWHA with undetectable viral load. The purpose of this thesis is to present the main cardiovascular risk factors and to verify the effects of aerobic training on these risk factors. Thus, three studies were carried out: a quasi-experimental study that evaluated the effects of aerobic training on functional capacity, cardiovascular risk factors, inflammatory cytokines, oxidative stress and quality of life in PLWH; a pilot study that evaluated the effects of aerobic training on heart rate variability in PLWH; a cross-sectional study evaluating cardiovascular risk factors among men and women living with HIV.

The study 1, entitled ***"Aerobic training improves functional capacity, cardiovascular risk factors, quality of life and modulates the inflammatory and oxidative stress markers in people living with HIV"***, assessed the effects of 24 moderate to high intensity aerobic training sessions in 15 PLWH (11 men) on anthropometric data, functional capacity, endothelial function, lipid and glycemic profile, inflammatory profile, oxidative stress and quality of life were evaluated. The results indicate that aerobic training improves functional capacity, lipid and glycemic profile, quality of life, reduces anthropometric measurements and promotes modulation in inflammatory markers and oxidative stress. The results show that the practice of aerobic exercise improves the risk factors for cardiovascular disease and impact on quality of life in PLWH.

The study 2, entitled ***"Aerobic training improve the autonomic function of people living with HIV – A pilot study"*** presents the effects of aerobic training on time and frequency domains variables of heart rate variability in PLWH. Twenty four aerobic training sessions were performed in 8 PLWH. There was an increase in time and frequency domain variables and correlations between time domain variables with CD4+Tcell and HDL; in addition to frequency domain correlations with HIV diagnosis time and ARV time. These findings suggest that aerobic training may impact the autonomic nervous system on PLWH.

The study 3 entitled: **“*Presence of cardiovascular risk despite control of the disease among men and women with HIV using antiretroviral therapy - a cross-sectional study*”** evaluated the cardiovascular risk factors in PLWHA by verifying the difference of these variables between men (n = 11) and women (n = 5) were evaluated. Anthropometric data, lipid and glycemic profile, functional capacity, endothelial function, inflammatory markers, oxidative stress and Framingham score were evaluated. The results show a high presence of endothelial dysfunction, strong correlations between inflammatory markers and oxidative stress with anthropometric data, CD4+Tcell and functional capacity, as well as a higher cardiovascular risk in the next decade of life among women living with HIV.

When associated with the results of the 3 studies, we verified the presence of several cardiovascular risk factors between PLWH in ARV use and the benefits of aerobic training for the modification of these risk factors, as well as the promotion of quality of life due to physical exercise performed regularly.

Keywords: HIV. ARV. Aerobic training. Cardiovascular disease. Quality of life.

Lista de figuras dos artigos

Artigo 1

Artigo 2

Artigo 3

Lista de tabelas dos artigos

Artigo 1

Artigo 3

Lista de abreviaturas da contextualização

AIDS - *Acquired Immunodeficiency Syndrome* – Síndrome da Imunodeficiência Adquirida.

D:A:D: *Data Collection on Adverse Events of Anti-HIVA Drugs.*

DCV: Doença cardiovascular.

ERO: espécies reativas de oxigênio.

FC: frequência cardíaca.

HAS: hipertensão arterial sistêmica.

HAT-QoI: Quality of Life questionnaire – questionário de qualidade de vida.

HF: *high frequency* – alta frequência.

HIV: *Human Immunodeficiency Virus* – Vírus da Imunodeficiência Humana.

IAM: infarto agudo do miocárdio.

IL-1ra: receptor antagonista da interleucina 1.

IL-6: interleucina 6.

IL-10: interleucina 10.

IL1β: interleucina 1-beta.

LF: *low frequency* – baixa frequência.

MCP-1: *monocyte chemoattractant protein* 1 - monócito quimiotático da proteína-1.

NN: *standart deviation of all NN intervals* - desvio padrão de todos os intervalos NN.

PCR: proteína C reativa.

pNN50: *intervals differing by more than 50 ms* - intervalo sucessivo de RR que diferem mais do que 50 ms dividido pelo número total de intervalos RR.

PVHA: pessoas vivendo com HIV/AIDS.

RHI: *reactive hyperaemia índex* – índice de hiperemia reativa.

RHPAT: *reactive hyperaemia peripheral arterial tonometry* - tonometria arterial periférica por hiperemia reativa

RMSSD: *square of the differences between adjacent RR intervals* - quadrado das diferenças entre as adjacentes dos intervalos RR.

RS: Rio Grande do Sul.

SDNN: *standart deviation of the RR intervals* - desvio padrão de todos os intervalos RR.

sICAM: *soluble intercellular adhesion molecule* - molécula de adesão intercelular solúvel.

SM: síndrome metabólica.

SNA: sistema nervoso autônomo.

sVCAM: *soluble vascular cell adhesion molecule* - molécula de adesão das células vasculares solúveis.

TARV: terapia antirretroviral combinada.

TBARS: *thiobarbituric acid reative susbstance* - substância reativa do ácido tiobarbitúrico.

TNF-α: fator da necrose tumoral.

UNAIDS: Programa Conjunto das Nações Unidas para HIV/AIDS.

VFC: variabilidade da frequência cardíaca.

VO_{2max}: consumo máximo de oxigênio.

Anexos

Sumário

1. Contextualização

A epidemia causada pela síndrome da imunodeficiência adquirida (*acquired immunodeficiency syndrome* – AIDS) ocorreu no início da década de 1980. No ano de 1983 ocorreu o isolamento do agente causador identificado como retrovírus (Barré-Sinoussi *et al.,* 2013). A AIDS é caracterizada como o estágio avançado da contaminação pelo vírus da imunodeficiência humana (*human immunodeficiency virus* – HIV) que pode levar anos após a contaminação com o HIV até se tornar sintomática. A classificação da AIDS ocorre quando existe queda da contagem de linfócitos T CD4+ a valores inferiores a 200 unidades por mm^3 de sangue. Geralmente, essa fase é marcada por elevados valores de carga viral na corrente sanguínea.

Assim, apesar das políticas públicas estarem cada vez mais voltadas para o diagnóstico precoce da infecção pelo HIV, na maioria dos casos, esse é o momento em que o diagnóstico é realizado e se inicia o tratamento medicamentoso com a terapia antirretroviral combinada (TARV). Na ausência de tratamento e/ou realização de forma incorreta, pode ocorrer a evolução para o óbito das pessoas vivendo com HIV/AIDS (PVHA) (Barré-Sinoussi *et al.,* 2013).

O Programa Conjunto das Nações Unidas para HIV/AIDS (UNAIDS) estimou que o HIV foi responsável pela morte de mais de 35 milhões de pessoas desde o início da epidemia. Sendo que no ano de 2016, a estimativa foi de que 36,7 milhões de pessoas viviam no mundo com HIV. Segundo o Boletim Epidemiológico de HIV/AIDS do Brasil, do período compreendido entre (1980 – junho de 2017) foram identificados 882,810 casos de AIDS. Desse total de casos, a região sul concentrou 20,1% dos casos, com uma predominância no sexo masculino (65,3%). Anualmente, há o registro médio de 40 mil novos casos de AIDS nos últimos 5 anos. No entanto, nos últimos 10 anos ocorreu uma queda de 5,1% de registro de novos casos no país. Em 2016, o Rio Grande do Sul (RS) apresentou a segunda maior taxa de detecção de AIDS no país com 31,8 casos/100 mil habitantes. Em Porto Alegre (POA), a taxa de novos casos foi de 65,9 casos/100 mil habitantes, valor superior ao dobro da taxa do RS (BRASIL, 2017).

Primeiramente, PVHA apresentavam uma condição aguda de doença, decorrente do rápido desfecho após o diagnóstico devido à ausência de tratamento. Assim, com o início do uso da TARV, ocorreu uma mudança de perfil e controle da doença onde

as PVHA passaram a conviver com uma doença com características crônicas. Isso devido ao controle da doença através da supressão da carga viral, diminuição das internações hospitalares, redução das complicações causadas por doenças oportunistas e, consequentemente, aumento da sobrevida de PVHA (Freiberg *et al*., 2016; Taylor *et al.,* 2018).

No entanto, a TARV e as alterações causadas pela infecção do HIV apresentaram um grande impacto nas alterações metabólicas e composição corporal, como: lipodistrofia, dislipidemia, resistência insulínica, disfunção endotelial, hipertensão arterial sistêmica (HAS), elevação de marcadores inflamatórios, produção de radicais livres pela liberação espécies reativas de oxigênio (ERO) (Nordell *et al*., 2014; Leach *et al*., 2015; O'Brien *et al*., 2016; Vancampfort *et al*., 2016; Strijdom *et al*., 2017). Associado e/ou decorrente dessas alterações, PVHA apresentam altas taxas de sedentarismo e baixos escores de qualidade de vida (O'Brien *et al*., 2016).

Assim, em virtude dessa série de alterações fisiológicas, PVHA apresentam elevado risco para doença cardiovascular (DCV). No entanto, o elevado risco cardiovascular em PVHA é uma soma dos seguintes fatores: 1) efeitos crônicos da infecção pelo HIV; 2) uso prolongado de TARV; 3) diferenças de características clínicas e dados sociodemográficos, além de fatores de risco tradicionais a todas as pessoas (Currier *et al*., 2008; Ngu *et al*., 2018). Além disso, a presença de fatores como: contaminação pelo vírus da hepatite C e uso de drogas ilícitas contribuem para o aumento da DCV (Freiberg *et al*., 2016).

Outro aspecto que contribui para a presença de fatores de risco para DCV é a alta taxa de sedentarismo em PVHA, pois ocorrem alterações musculares que associadas à falta de condicionamento físico causam dor e fadiga (Jaggers *et al*., 2014; O'Brien *et al*., 2016; Vancampfort *et al*., 2016; Berner *et al*., 2017). Assim, a diminuição da atividade física é consequência da infecção crônica e sarcopenia em PVHA em uso de TARV, tendo como correlações importantes para inatividade física indicadores característicos da infecção do HIV, como: contagem de linfócitos T CD4+ e carga viral (High *et al*., 2005; Oursler *et al*., 2009).

Neste sentido, sabe-se que PVHA apresentam risco cardiovascular elevado quando comparado a sujeitos saudáveis, principalmente na incidência de infarto agudo do miocárdio (IAM) e acidente vascular encefálico (Mosepele *et al*., 2017).

Sendo que os fatores de risco para DCV permanecem elevados mesmo com supressão da replicação viral e em PVHA jovens (Petoumenos *et al*., 2014; Phan *et al*., 2017). Em vista do elevado risco cardiovascular, sugeriu-se que a doença cardíaca é o principal responsável não relacionada à AIDS pela morbimortalidade em PVHA (Balsam *et al*., 2015; Maggi *et al*., 2017).

Ainda, a síndrome metabólica é uma alteração frequente encontrada em PVHA. Sendo caracterizada por alterações na composição corporal e metabólicas que elevam o risco cardiovascular. Os critérios que constituem a referida síndrome são: acúmulo de gordura visceral, elevada concentração de triglicerídeos, redução no HDL, HAS e elevada concentração de glicemia na corrente sanguínea (Grundy *et al*., 2005; Ngu *et al*., 2018).

No entanto, a principal complicação causada pelo elevado risco cardiovascular é o IAM (Triant *et al*., 2007). Nesse contexto, foi apresentado que a incidência de IAM em 1000 pessoas/ano foi 11,13 (95% CI 9,58 – 12,68) em PVHA e 6,98 (95% CI 6,89 – 7,06) em sujeitos saudáveis (Triant *et al*., 2007). O referido estudo mostrou aumento do risco relativo de 1,75 de IAM em PVHA comparado a sujeitos saudáveis após o controle de fatores de risco tradicionais para IAM (Triant *et al*., 2007). Contudo, sabe-se que idade avançada, tabagismo, histórico prévio de DCV, sexo masculino, diabetes prévia, aumento do colesterol total e triglicerídeos aumentam o risco de IAM em PVHA (Law *et al*., 2006).

A publicação do *Data Collection on Adverse Events of Anti-HIVA Drugs* (D:A:D) com seguimento de 6 anos de exposição apresentou a ocorrência de aumento relativo da incidência de IAM em 26% por ano de exposição a TARV (Group DCoAEoA-HDS, 2003). Além disso, dentre os fatores de risco cardíaco, o principal fator de risco para IAM foi a dislipidemia (RR 3,65; (95% CI 2,59 – 5,19; $p < 0.0001$) após controle da idade, raça, gênero e outros fatores de risco tradicionais (Triant *et al*., 2007).

Além disso, a infecção pelo HIV promove hiperativação do sistema imune e uma inflamação crônica, contribuindo para a formação de aterosclerose identificada com o sinal da disfunção endotelial, sendo esse um fator importante para o prognóstico da DCV (Wilk *et al*., 2013; Mazzuca *et al*., 2016; Iantorno *et al*., 2017). Somado a isso, a disfunção endotelial é um marcador precoce para a doença arterial coronariana e a doença arterial periférica, sendo que a redução do óxido nítrico tem

papel principal no desenvolvimento de aterosclerose (Wilk *et al*., 2013; Hansen *et al*., 2017). No entanto, é uma disfunção reversível pela ação de diversos tipos de tratamento (medicamentoso e/ou não medicamentoso), além de mudanças do estilo de vida (Balsam *et al*., 2015).

As PVHA apresentam alterações no endotélio vascular devido à ativação de células resultantes do processo inflamatório causado pela infecção pelo HIV. A integridade vascular depende do equilíbrio entre o mecanismo de dano e o reparo celular, sendo que a lesão do vaso sanguíneo está associada a altos níveis de circulação das células endoteliais (Mazzuca *et al*., 2016). Assim, sugeriu-se que os principais fatores relacionados à aterosclerose foram: aumento nos níveis de colesterol total, sobrepeso ou obesidade e HAS (Wilk *et al*., 2013).

Ainda nesse contexto, já foi mostrado que altas concentrações de proteína C reativa (PCR), interleucina 6 (IL-6), fator da necrose tumoral (TNF-α), fibrinogênio, molécula de adesão intercelular solúvel (*soluble intercellular adhesion molecule* - sICAM) e molécula de adesão das células vasculares solúveis (*soluble vascular cell adhesion molecule* - sVCAM) causam ativação e dano endotelial (Mazzuca *et al*., 2016).

Para a avaliação da função endotelial, a maioria dos estudos utiliza a ultrassonografia, sendo um método operador dependente e que necessita de ampla experiência do operador (Wilk *et al*., 2013). No entanto, a tonometria arterial periférica por hiperemia reativa (*reactive hyperaemia peripheral arterial tonometry* - RHPAT) é um método não invasivo para avaliação da função endotelial que avalia o comportamento da microcirculação, caracterizada por ser um método rápido, de fácil aplicação e avaliador independente (Wilk *et al*., 2013; Balsam *et al*., 2015). A avaliação ocorre durante a oclusão da artéria braquial por cinco minutos. Além disso, o *software* realiza a comparação simultânea com o lado contralateral não ocluído simultaneamente. A oclusão causa uma isquemia momentânea que expressa o grau de alteração do tônus arterial definida pelo índice de hiperemia reativa (*reactive hyperaemia índex* – RHI), considerando função endotelial normal RHI superior a 1,67 (Wilk *et al*., 2013; Balsam *et al*., 2015; Hansem *et al*., 2017).

A disfunção endotelial já foi demonstrada em PVHA. Inclusive, através da avaliação pelo RHI, mostrando que 35% das PVHA apresentavam disfunção endotelial, sendo que o uso crônico de TARV e dados demográficos foram

independentes para o diagnóstico de disfunção endotelial (Balsam *et al*., 2015). Além disso, já foi verificado que a responsividade endotelial aumenta quando ocorre redução dos marcadores inflamatórios (Dysangco *et al*., 2017). No entanto, sugeriu-se que a disfunção endotelial em PVHA pode estar associada a outras alterações cardíacas que não apenas os ligados aos efeitos deletérios decorrentes de biomarcadores inflamatórios, contagem T CD4+ e carga viral (Sinha *et al*., 2016; Dysangco *et al*., 2017).

Nesse sentido, a infecção pelo HIV mostra associação direta através da replicação viral ou indireta, pelo uso de TARV, no sistema inflamatório pela ativação imune crônica causando a deteriorização do sistema cardiovascular (Gori *et al*., 2016). Os monócitos são os principais mediadores da imunidade inata, ligados ao processo de infecções crônicas virais (Schechter et al., 2017). Por isso, a homeostase entre citocinas pró-inflamatórias e anti-inflamatórias é fundamental, uma vez que biomarcadores inflamatórios são preditores de morbimortalidade em PVHA em virtude da replicação viral (Nordell *et al*., 2014; Sinha *et al*., 2016; Manion *et al*., 2017). Apesar do uso de TARV reduzir a replicação viral, há manutenção de um processo inflamatório que apresenta impacto no sistema cardiovascular (Schechter et al., 2017).

Ainda, sabe-se que marcadores pro-inflamatórios como TNF-α, IL-6, interleucina 10 (IL-10), monócito quimiotático da proteína-1 (*monocyte chemoattractant protein* 1 - MCP-1) e o receptor antagonista da interleucina 1 (IL-1ra) estão elevados em PVHA resultante de alterações, como: lipodistrofia e dislipidemia (Charles *et al*., 2011; Gori *et al*., 2016; Pedro *et al*., 2017; Viskovic *et al*., 2018). Outro biomarcador importante é a interleucina 1-beta (IL1β) que tem relação com a preservação do sistema imune e, quando em concentrações elevadas, parece proteger PVHA de efeitos causados por coinfecções como tuberculose (Schechter et al., 2017; Thobakgale *et al*., 2017).

Nesse contexto, já foi mostrado que esses marcadores pró-inflamatórios estão associados com pior desempenho em avaliações de função endotelial, onde o TNF-α mostrou associação significativa com a disfunção microvascular em PVHA (Sinha *et al*., 2016). Um estudo comparou PVHA que não apresentaram evento fatal comparado à PVHA que apresentaram efeito fatal decorrente doença cardíaca mostrou elevado nível de IL-6 [1,8 (1,2 – 2,8); 3,1 (1,5 – 3,5)], respectivamente

(Nordell *et al*., 2014). No entanto, ocorre uma grande dificuldade em avaliação do perfil inflamatório em PVHA pela ausência de valores de referência para essa população uma vez que a infecção pelo HIV causa um processo inflamatório crônico (Pedro *et al*., 2017).

Outro preditor de mortalidade em PVHA que é independente de fatores relacionados ao HIV, como: contagem de linfócitos T CD4+, carga viral e inflamação é o estresse oxidativo (Masiá *et al*., 2016). A ERO é a definição referente ao oxigênio com alta capacidade reativa que quando liberadas em excesso, causam alterações celulares imunes e/ou morte celular (Deshmane *et al*., 2009; Ivanov *et al*., 2016; Aboutaleb *et al*., 2017). Nas fases do processo que envolve a replicação do HIV no meio intercelular, ocorre a liberação de ERO. Por isso, a infecção pelo HIV influencia o estresse oxidativo em virtude de uma desregulação que causa a liberação de ERO e induz uma disfunção mitocondrial podendo até mesmo causar neurodegeneração em PVHA (Deshmane *et al*., 2009).

O nitrito é considerado um dos principais mediadores do meio intra e extracelular e responsável por funções fundamentais de caráter endotelial, como manutenção do tônus vascular. Nesse sentido, quando ocorre a diminuição na concentração de nitritos, há uma procura para a ligação com a oxi-hemoglobina que está sendo oxidada para o encontro com o nitrato causando uma reação pró-oxidante levando à liberação de radicais livres (Hathazi *et al*., 2018). Outro importante marcador é a substância reativa do ácido tiobarbitúrico (*thiobarbituric acid reative susbstance* – TBARS) que se apresenta influenciado por fatores que tradicionalmente contribuem para o risco cardiovascular incluindo o comportamento lipídico, glicêmico e obesidade (Okauchi *et al*., 2011).

Outros aspectos que sofrem grande impacto em PVHA é a qualidade de vida e a elevada incidência de depressão. Essa relação ocorre desde o processo de diagnóstico, resultantes do preconceito ainda existente associado a fatores fisiológicos sobre efeito da infecção pelo HIV (Ivanov *et al*., 2016; Karkashadze *et al*., 2017). As PVHA que utilizam TARV e apresentam elevada contagem de linfócitos T CD4+ apresentaram melhor relação social e melhor escore de qualidade de vida quando comparados à PVHA sem tratamento com TARV (Karkashadze *et al*., 2017). Além desses aspectos, também influenciam a qualidade de vida a idade,

inatividade física e nível socioeconômico (Karkashadze *et al*., 2017; Quiles *et al*., 2017).

Por isso, a qualidade de vida em PVHA deve ser verificada por meio de instrumentos que avaliem diferentes aspectos que são capazes de influenciar a qualidade de vida. O instrumento de qualidade de vida (*Quality of Life questionnaire – HAT-Qol*), validado para a população brasileira, avalia nove domínios: função geral, satisfação com a vida, preocupações com a saúde, preocupações financeiras, preocupações com a medicação, aceitação do HIV, preocupações com o sigilo, confiança profissional e função sexual (Soárez *et al*., 2009). Assim, quanto maior o escore obtido em cada domínio, menor o impacto do HIV na qualidade de vida de PVHA (Soárez *et al*., 2009; Medeiros *et al*., 2017).

Em vista do elevado fator de risco para DCV, foi sugerido intervenções para a redução desses fatores de risco em PVHA (Petoumenos *et al*., 2014). No entanto, a inserção de drogas adicionais para esse controle, pode causar efeitos adversos e elevar o risco para outros problemas, além de causar interação medicamentosa (Law *et al*., 2006). Assim, já está bem documentado na literatura, a utilização de programas de exercício físico em doenças crônicas como alternativa não medicamentosa para controle de fatores de risco cardiovascular, além de influenciar na mudança de estilo e qualidade de vida de PVHA (Leach *et al*., 2015; O'Brien *et al*., 2016; Berner *et al*., 2017).

Nesse sentido, quando observamos os efeitos do exercício físico, verificamos que os dados antropométricos são os parâmetros que apresentam melhora em todos os estudos após a prática de um protocolo de treinamento físico (Leach *et al*., 2015). Associados a isso, estudos clínicos e revisões sistemáticas mostraram que o exercício físico é capaz de alterar diversos fatores, como: composição corporal, capacidade funcional, variáveis cardíacas, função metabólica, perfil inflamatório, estresse oxidativo, função endotelial, parâmetros imunológicos e qualidade de vida em PVHA (Pereira *et al*., 2013; Ezema *et al*., 2014; Jaggers *et al*., 2014; Leach *et al*., 2015; O'Brien *et al*., 2016; Ostman *et al*., 2017; Oursler *et al*., 2018). No entanto, os efeitos do exercício físico sobre algumas variáveis ainda necessita de melhor entendimento (Pedro *et al*., 2017).

Quando observado os efeitos específicos do treinamento aeróbio em PVHA, verificou-se melhora na composição corporal, saúde cardiovascular e perfil

metabólico (Garcia *et al*., 2014; Ostman *et al*., 2017). Além disso, sugeriu-se que os protocolos de treinamento aeróbio devem ser realizados por, pelo menos, 20 minutos com uma frequência de 3-5 vezes/semana e intensidade de moderada à alta (O'Brien *et al*., 2016). Ainda, mostrou ser segura a prática de exercício físico em moderada/alta intensidade em PVHA com medicação estável (O'Brien *et al*., 2016).

Associado, foi apresentado que o exercício físico é capaz de melhorar parâmetros de estresse oxidativo sugerindo uma melhora nas complicações causadas pelo HIV e uso de TARV, além de reestabelecer a homeostase no combate à liberação de ERO (Garcia *et al*., 2014).

No entanto, já foi sugerido que para PVHA o mínimo significativo para alteração clínica do VO_{2max} após treinamento aeróbico de alta intensidade deve ser 3,6 mL/kg/min (Oursler *et al*., 2018). Assim, para monitoramento e obtenção da intensidade segura de treinamento, o teste de esforço cardiopulmonar é o padrão ouro para avaliação da capacidade funcional tanto em sujeitos saudáveis quanto em sujeitos com doença crônica (Carvalho *et al*., 2011; O'Brien *et al*., 2016).

Baseados em todas as alterações apresentadas em PVHA em diferentes sistemas e sabendo que qualquer acréscimo de drogas para combater essas alterações podem causar ainda mais danos e toxicidade, o exercício físico é uma opção na tentativa de redução dessas alterações. Por isso, apresentamos os resultados de efeito do treinamento aeróbio nas variáveis supracitadas no artigo 1, intitulado: "***Aerobic training improves functional capacity, cardiovascular risk factors, quality of life and modulates the inflammatory and oxidative stress markers in people living with HIV"***.

Além disso, PVHA apresentam alterações no sistema nervoso autônomo (SNA). Em 1987, Craddock *et al.,* sugeriu pela primeira vez alterações no SNA quando publicou a ocorrência de síncope em quatro de cinco PVHA após aspirações pulmonares (Craddock *et al*., 1987). Sugeriu-se que a infecção pelo HIV estaria associada com a neuropatia autonômica, semelhante a pacientes diabéticos, aumentando o risco de parada cardiorrespiratória em PVHA durante procedimentos invasivos (Rogstad *et al*., 1999).

A avaliação do SNA pode ser realizada através da avaliação da variabilidade da frequência cardíaca (VFC). A VFC é um método não invasivo de avaliação da atividade do sistema nervoso cardíaco e geralmente descreve as

variações entre batimentos cardíacos consecutivos identificando o “complexo QRS” que sofre constante influência do SNA simpático e do SNA parassimpático (Nenna *et al*., 2017; Von Rosenberg *et al*., 2017; Shiraishi *et al*., 2018). Quando avaliamos separadamente os constituintes do SNA, verificamos que o SNA simpático tende a elevar a frequência cardíaca (FC) e apresenta uma resposta mais lenta quando comparado ao SNA parassimpático que causa uma influência para que ocorra uma redução da FC (Nenna *et al*., 2017).

Por isso, tanto o SNA simpático quanto o SNA parassimpático devem estar equilibrados para que não ocorram alterações drásticas da FC, podendo ocasionar uma parada cardiorrespiratória. Além disso, sabe-se que a VFC está associada com a morbi-mortalidade em pacientes após o IAM (Shiraishi *et al*., 2018).

A VFC pode ser analisada através de 3 modelos diferentes: domínio do tempo através do desvio padrão de todos os intervalos NN (*standart deviation of all NN intervals* - NN); desvio padrão de todos os intervalos RR (*standart deviation of the RR intervals* - SDNN); quadrado das diferenças entre as adjacentes dos intervalos RR (*square of the differences between adjacent RR intervals* - RMSSD) e intervalo sucessivo de RR que diferem mais do que 50 ms dividido pelo número total de intervalos RR (*intervals differing by more than 50 ms* - pNN50); domínio da frequência: é dividido em alta frequência (*high frequency* - HF), baixa frequência (*low frequency* - LF) e a relação LF/HF; domínio não-linear (Nenna *et al*., 2017; Rosenberg *et al*., 2017; Shiraishi *et al*., 2018). Sendo utilizado para a construção do segundo artigo apenas dos 2 primeiros domínios supracitados.

No entanto, ainda pouco se sabe sobre qual o impacto das disfunções autonômicas nas disfunções cardíacas e na morbimortalidade de PVHA (Spierer *et al*., 2007). Sabe-se da relação entre disfunção autonômica e sedentarismo, onde a disfunção autonômica estava presente: 20% em baixo nível de atividade física; 40% em moderado nível de atividade física e 60% no grupo sedentário dentre as PVHA avaliadas (Kocher *et al*., 2015).

Assim, sugeriu-se que a implementação de programas de treinamento aeróbio podem melhorar a performance do SNA em PVHA (Spierer *et al*., 2007). Ao nosso conhecimento, até o presente momento, não existe publicação onde foram avaliados efeitos crônicos de um protocolo de treinamento físico na função autonômica de PVHA. Por isso, apresentamos no artigo 2, intitulado *“***Aerobic training improve the**

autonomic function of people living with HIV – A pilot study*”*, sobre os efeitos do treinamento aeróbio na função autonômica de PVHA.

Apesar do aumento de risco cardiovascular em PVHA ser independente do sexo, percebemos que grande parte dos estudos sobre fatores de risco cardiovascular e exercício físico, são realizados com PVHA do sexo masculino (Peteoumenos *et al*., 2014; Womack *et al*., 2014; O'Brien *et al*., 2016; Masiá *et al*., 2016; Baker *et al*., 2017; Cortés *et al*., 2017). Isso acontece em virtude das alterações limitadas a homens e mulheres sendo um importante diferencial o componente hormonal, além de alterações na distribuição de gordura (Womack *et al*., 2014; Cortés *et al*., 2017; Zanni *et al*., 2017; Hatleberg *et al*., 2018).

Assim, foi apresentado que após análise de fatores específicos ligados ao sexo, tanto mulheres quanto homens apresentavam risco cardiovascular elevado, sendo que 60% das mulheres e 40% dos homens apresentavam sobrepeso ou obesidade (Kaplan *et al*., 2007). Associados a isso, outros dados mostraram que 13,8% das PVHA apresentaram risco moderado para DCV e apenas 2,7% apresentavam alto risco cardiovascular (Glass *et al*., 2006).

Quando observamos pesquisas realizadas com mulheres, percebemos grande referência ao período pré e pós menopausa, devido, principalmente, a concentração de estrogênio (Womack *et al*., 2014; Cortés *et al*., 2017; Zanni *et al*., 2017; Hatleberg *et al*., 2018). Nesse sentido, mostrou-se que a média de idade de evento cardiovascular entre mulheres infectadas pelo HIV foi 49,3 anos (13.5; 95% CI 10.1 - 18.1), e 52,1 anos (5,3; 95% CI 3,9 – 7,3) quando comparadas a mulheres não portadoras do HIV (Womack *et al*., 2014). Assim, a redução da contagem de linfócitos T CD4+ e a menopausa, combinados com a redução de estrogênio circulante, estão associados ao aumento do risco cardiovascular (Womack *et al*., 2014; Cortés *et al*., 2017).

Entre PVHA, há aumento do risco cardiovascular associado ao aumento da idade (Mosepele *et al*., 2017). Nesse sentido, mostrou-se que a incidência de eventos cardíacos 1000 pessoas/ano foi de 3,5 eventos, onde 90% dos sujeitos eram homens com média de idade de 48 anos (Law *et al*., 2006).

Além disso, o instrumento mais publicado para avaliação do risco cardiovascular é o escore de Framingham proposto pela *American Heart Association* e *American College of Cardiology* que avalia do risco de evento coronário na próxima década de

vida (Kannel *et al*., 1984). O instrumento avalia os seguintes critérios: idade, colesterol total, HDL, pressão arterial sistólica, diabetes e tabagismo para ambos os sexos, mas com diferentes pontuações. Assim, quando observamos o critério idade, percebe-se grande diferença de pontuação entre mulheres no período pré-menopausa quando comparados a homens na mesma faixa etária (Kannel *et al*., 1984; Glass *et al*., 2006; Law *et al*., 2006; Womack *et al*., 2014; Cortés *et al*., 2017).

Baseados nessas alterações de comportamento e diferenças fisiológicas entre homens e mulheres no risco cardiovascular, escrevemos o artigo 3, intitulado "***Presence of cardiovascular risk despite control of disease among men and women with HIV using antiretroviral therapy - a cross-sectional study Cardiovascular risk in PLWH"***, onde realizamos análises ligadas ao sexo entre variáveis clássicas de risco cardiovascular e escore de Framingham, além de marcadores inflamatórios e estresse oxidativo.

Referências Bibliográficas

ABOUTALEB N, ZARRATI M, CHESHMAZAR E, SHOORMASTI RS, RAZMPOOSH E, NASIRINEZHAD F. Association between the circulating leptin levels and the biomarkers of oxidative stress and inflammation among Iranian overweight and obese adults. **Med J Islam Repub Iran**. 2017;31:81 doi: 10.14196/mjiri.31.81.

BALSAM P, MIKUŁA T, PELLER M, SUCHACZ M, PUCHALSKI B, KOŁTOWSKI Ł, et al. Evaluation of endothelial function and arterial stiffness in HIV-infected patients: a pilot study. **Kardiol Pol.** 2015;73(5):344-51.

BAKER JV, SHARMA S, ACHRA AC, BERNARDINO JI, BOGNER JR, DUPREZ D, et al. Changes in Cardiovascular Disease Risk Factors With Immediate Versus Deferred Antiretroviral Therapy Initiation Among HIV-Positive Participants in the START (Strategic Timing of Antiretroviral Treatment) Trial. **J Am Heart Assoc.** 2017;26(5): pii: e004987. doi: 10.1161/JAHA.116.004987.

BARRÉ-SINOUSSI F, ROSS AL, DELFRAISSY JF. Past, present and future: 30 years of HIV research. **Nat Rev Microbiol.** 2013;11(12):877-83.

BERNER K, MORRIS L, BAUMEISTER J, LOUW Q. Objective impairments of gait and balance in adults living with HIV-1 infection: a systematic review and meta-analysis of observational studies. **BMC Musculoskeletal Disord.** 2017;18:325. doi: 10.1186/s12891-017-1682-2.

CARVALHO EEVd, COSTA DC, CRESCÊNCIO JC, SANTI GLD, PAPA V, MARQUES F, et al. Heart failure: comparison between six-minute walk test and cardiopulmonary test. **Arq Bras Car**. 2011;97:59-64.

CHARLES BA, DOUMATEY A, HUANG H, ZHOU J, CHEN G, SHRINER D, et al. The roles of IL-6, IL-10, and IL-1RA in obesity and insulin resistance in African-Americans. **J Clin Endo Metabol.** 2011;96(12):E2018-E22.

CRADDOCK C, BULL R, PASVOL G, PROTHEROE A, HOPKIN J. Cardiorespiratory arrest and autonomic neuropathy in AIDS. **Lancet.** 1987;2(8549):16-8.

CORTÉS YI, REAME N, ZEANA C, JIA H, FERRIS DC, SHANE E, et al. Cardiovascular risk in HIV-infected and uninfected postmenopausal minority women: use of the framingham risk score. **J Womens Health.** 2017;26(3):241-8.

CURRIER JS, LUNDGREN JD, CARR A, KLEIN D, SABIN CA, SAX PE, et al. Epidemiological evidence for cardiovascular disease in HIV-infected patients and relationship to highly active antiretroviral therapy. **Circulation.** 2008;118(2):e29-e35.

DESHMANE SL, MUKERJEE R, FAN S, DEL VALLE L, MICHIELS C, SWEET T, ET AL. Activation of the oxidative stress pathway by HIV-1 Vpr leads to induction of hypoxia-inducible factor 1α expression. **J Biol Chem**. 2009;284(17):11364-73.

DYSANGCO A, LIU Z, STEIN JH, DUBÉ MP, GUPTA SK. HIV infection, antiretroviral therapy, and measures of endothelial function, inflammation, metabolism, and

oxidative stress. **PloS One**. 2017;12(8) e0183511. doi: 10.1371/journal.pone.0183511. eCollection 2017.

EZEMA C, ONWUNALI A, LAMINA S, EZUGWU U, AMAEZE A, NWANKWO M. Effect of aerobic exercise training on cardiovascular parameters and CD4 cell count of people living with human immunodeficiency virus/acquired immune deficiency syndrome: A randomized controlled trial. **Niger J Clin Pract**. 2014;17(5):543-8.

FREIBERG MS, SO-ARMAH K. HIV and cardiovascular disease: we need a mechanism, and we need a plan. **Am Heart Assoc.** 2016; 4(3):e003411. doi: 10.1161/JAHA.116.003411.

FRIIS-MØLLER N, SABIN CA, WEBER R, D'ARMINIO MONFORTE A, EL-SADR WM, REISS P, et al. Combination antiretroviral therapy and the risk of myocardial infarction. **N Engl J Med.** 2003;349(21):1993-2003.

GARCIA A, FRAGA GA, VIEIRA JR RC, SILVA CMS, TROMBETA JCDS, NAVALTA JW, et al. Effects of combined exercise training on immunological, physical and biochemical parameters in individuals with HIV/AIDS. **J Sports Sci.** 2014;32(8):785-92.

GLASS T, UNGSEDHAPAND C, WOLBERS M, WEBER R, VERNAZZA P, RICKENBACH M, et al. Prevalence of risk factors for cardiovascular disease in HIV-infected patients over time: the Swiss HIV Cohort Study. **HIV Med**. 2006;7(6):404-10.

GORI E, MDULUZA T, NYAGURA M, STRAY-PEDERSEN B, GOMO ZA. Inflammation-modulating cytokine profile and lipid interaction in HIV-related risk factors for cardiovascular diseases. **Ther Clin Risk Manag**. 2016;12:1659-66.

GRUNDY SM, CLEEMAN JI, DANIELS SR, DONATO KA, ECKEL RH, FRANKLIN BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. **Circulation**. 2005;112(17):2735-52.

HANSEN AS, BUTT JH, HOLM-YILDIZ S, KARLSSON W, KRUUSE C. Validation of repeated endothelial Function Measurements Using endoPaT in stroke. **Front Neurol.** 2017;8:178. doi: 10.3389/fneur.2017.00178. eCollection 2017.

HATHAZI D, SCURTU F, BISCHIN C, MOT A, ATTIA AA, KONGSTED J, et al. The Reaction of Oxy Hemoglobin with Nitrite: Mechanism, Antioxidant-Modulated Effect, and Implications for Blood Substitute Evaluation. **Molecules.** 2018;23(2): pii: E350. doi: 10.3390/molecules23020350.

HATLEBERG CI, RYOM L, EL-SADR W, MOCROFT A, REISS P, DE WIT S, et al. Gender differences in the use of cardiovascular interventions in HIV-positive persons; the D: A: D Study. **J Int AIDS Soc.** 2018;21(3). doi: 10.1002/jia2.25083.

HIGH KP, BRADLEY S, LOEB M, PALMER R, QUAGLIARELLO V, YOSHIKAWA T. A new paradigm for clinical investigation of infectious syndromes in older adults:

assessment of functional status as a risk factor and outcome measure. **Clin Infect Dis**. 2005;40:114-22.

IANTORNO M, SCHÄR M, SOLEIMANIFARD S, BROWN TT, MOORE R, BARDITCH-CROVO P, et al. Coronary artery endothelial dysfunction is present in HIV-positive individuals without significant coronary artery disease. **AIDS**. 2017;31(9):1281-9.

IVANOV AV, VALUEV-ELLISTON VT, IVANOVA ON, KOCHETKOV SN, STARODUBOVA ES, BARTOSCH B, et al. Oxidative stress during HIV infection: mechanisms and consequences. **Oxid Med Cell Longev**. 2016;2016:8910396.

JAGGERS JR, PRASAD VK, DUDGEON WD, BLAIR SN, SUI X, BURGESS S, et al. Associations between physical activity and sedentary time on components of metabolic syndrome among adults with HIV. **AIDS Care**. 2014;26(11):1387-92.

KANNEL WB, ABBOTT RD. Incidence and prognosis of unrecognized myocardial infarction: an update on the Framingham study. **N Engl J Med.** 1984;311(18):1144-7.

KAPLAN RC, KINGSLEY LA, SHARRETT AR, LI X, LAZAR J, TIEN PC, et al. Ten-year predicted coronary heart disease risk in HIV-infected men and women. **Clin Infec Dis**. 2007;45(8):1074-81.

KARKASHADZE E, GATES MA, CHKHARTISHVILI N, DEHOVITZ J, TSERTSVADZE T. Assessment of quality of life in people living with HIV in Georgia. **Int J STD AIDS**. 2017;28(7):672-8.

KOCHER MH, HETZLER RK, SHIKUMA CM, KIMURA IF, STICKLEY CD, LINDSEY RA, et al. Autonomic function is associated with fitness level in HIV-infected individuals. **Jacobs J AIDS HIV**. 2015;1(1). pii: 005.

LAW M, FRIIS-MØLLER N, EL-SADR W, WEBER R, REISS P, D'ARMINIO MONFORTE A, et al. The use of the Framingham equation to predict myocardial infarctions in HIV-infected patients: comparison with observed events in the D: A: D Study. **HIV Med.** 2006;7(4):218-30.

LEACH L, BASSETT S, SMITHDORF G, ANDREWS BS, TRAVILL AL. A Systematic Review of the Effects of Exercise Interventions on Body Composition in HIV+ Adults. **Open AIDS J.** 2015;9:66-79.

LIU H, YANG Z, HUANG L, QU W, HAO H, LI L. Heart-rate variability indices as predictors of the response to vagus nerve stimulation in patients with drug-resistant epilepsy. **Epilepsia**. 2017;58(6):1015-22.

MAGGI P, BELLACOSA C, LEONE A, VOLPE A, RICCI ED, LADISA N, et al. Cardiovascular risk in advanced naïve HIV-infected patients starting antiretroviral therapy: Comparison of three different regimens-PREVALEAT II cohort. **Atherosclerosis**. 2017; 263:398-404.

MANION M, ANDRADE BB, DERSIMONIAN R, GU W, RUPERT A, MUSSELWHITE LW, et al. Country of residence is associated with distinct inflammatory biomarker signatures in HIV-infected patients. **J Virus Erad**. 2017:24-33.

MASIÁ M, PADILLA S, FERNÁNDEZ M, RODRÍGUEZ C, MORENO A, OTEO JA, et al. Oxidative stress predicts All-Cause mortality in HIV-Infected patients. **PloS One**. 2016;11(4): e0153456. doi: 10.1371/journal.pone.0153456. eCollection 2016.

MAZZUCA P, CARUSO A, CACCURI F. HIV-1 infection, microenvironment and endothelial cell dysfunction. **New Microbiol.** 2016;39:163-73.

MEDEIROS RCDSC, MEDEIROS JAD, SILVA TALD, ANDRADE RDD, MEDEIROS DCD, ARAÚJO JDS, et al. Quality of life, socioeconomic and clinical factors, and physical exercise in persons living with HIV/AIDS. **Rev Saude Publica**. 2017;51:66. doi: 10.1590/S1518-8787.2017051006266.

MOSEPELE M, HEMPHILL LC, PALAI T, NKELE I, BENNETT K, LOCKMAN S, et al. Cardiovascular disease risk prediction by the American College of Cardiology (ACC)/American Heart Association (AHA) Atherosclerotic Cardiovascular Disease (ASCVD) risk score among HIV-infected patients in sub-Saharan Africa. **PloS One.** 2017; 12(2):e0172897. doi: 10.1371/journal.pone.0172897. eCollection 2017.

NENNA A, LUSINI M, SPADACCIO C, NAPPI F, GRECO SM, BARBATO R, et al. Heart rate variability: a new tool to predict complications in adult cardiac surgery. **J Geriatr Cardiol.** 2017;14(11):662-8.

NGU RC, CHOUKEM S-P, DIMALA CA, NGU JN, MONEKOSSO GL. Prevalence and determinants of selected cardio-metabolic risk factors among people living with HIV/AIDS and receiving care in the South West Regional Hospitals of Cameroon: a cross-sectional study. **BMC Res Notes**. 2018; 11(1):305. doi: 10.1186/s13104-018-3444-0.

NORDELL AD, MCKENNA M, BORGES ÁH, DUPREZ D, NEUHAUS J, NEATON JD. Severity of cardiovascular disease outcomes among patients with HIV is related to markers of inflammation and coagulation. **J Am Heart Assoc.** 2014;3(3):e000844. doi: 10.1161/JAHA.114.000844.

O'BRIEN KK, TYNAN A-M, NIXON SA, GLAZIER RH. Effectiveness of aerobic exercise for adults living with HIV: systematic review and meta-analysis using the Cochrane Collaboration protocol. **BMC Infect Dis**. 2016; 17(1):268. doi: 10.1186/s12879-017-2342-8.

OKAUCHI Y, KISHIDA K, FUNAHASHI T, NOGUCHI M, OGAWA T, OKITA K, et al. Cross-sectional and longitudinal study of association between circulating thiobarbituric acid-reacting substance levels and clinicobiochemical parameters in 1,178 middle-aged Japanese men-the Amagasaki Visceral Fat Study. **Nutri Metab.** 2011;8(1):82. doi: 10.1186/1743-7075-8-82.

OSTMAN C, SMART N, MORCOS D, DULLER A, RIDLEY W, JEWISS D. The effect of exercise training on clinical outcomes in patients with the metabolic syndrome: a

systematic review and meta-analysis. **Cardiovasc Diabetol**. 2017;16:110. doi: 10.1186/s12933-017-0590-y.

OURSLER KK, KATZEL LI, SMITH BA, SCOTT WB, RUSS DW, SORKIN JD. Prediction of Cardiorespiratory Fitness in Older Men Infected with the Human Immunodeficiency Virus: Clinical Factors and Value of the Six-Minute Walk Distance. **J Am Geriatr Soc**. 2009;57(11):2055-61.

OURSLER KK, SORKIN JD, RYAN AS, KATZEL LI. A pilot randomized aerobic exercise trial in older HIV-infected men: Insights into strategies for successful aging with HIV. **PloS One.** 2018;13(6):e0198855. doi: 10.1371/journal.pone.0198855. eCollection 2018.

PHAN BAP, WEIGEL B, MA Y, SCHERZER R, LI D, HUR S, et al. Utility of 2013 American College of Cardiology/American Heart Association Cholesterol Guidelines in HIV-Infected Adults With Carotid Atherosclerosis. **Cir Cardiovasc Imaging**. 2017; 10(7). pii: e005995. doi: 10.1161/CIRCIMAGING.116.005995.

PEDRO RE, CANDIDO N, GUARIGLIA DA, MELO BP, BERTOLINI DA, PERES SB, et al. Exercise improves cytokine profile in HIV-infected people: A randomized clinical trial. **Cytokine**. 2017;99:18-23.

PEREIRA DS, MATEO ECC, DE QUEIROZ BZ, ASSUMPÇÃO AM, MIRANDA AS, FELÍCIO DC, et al. TNF-α, IL6, and IL10 polymorphisms and the effect of physical exercise on inflammatory parameters and physical performance in elderly women. **Age (Dordr)**. 2013;35(6):2455-63.

PETOUMENOS K, REISS P, RYOM L, RICKENBACH M, SABIN C, EL-SADR W, et al. Increased risk of cardiovascular disease (CVD) with age in HIV-positive men: a comparison of the D: A: D CVD risk equation and general population CVD risk equations. **HIV Med.** 2014;15(10):595-603.

QUILES NN, CICCOLO JT, GARBER CE. Association Between Physical Activity, Depression, and Diabetes in Urban-Dwelling People Living with HIV. **J Assoc Nurses AIDS Care**. 2017;28(6):838-48.

ROGSTAD KE, SHAH R, TESFALADET G, ABDULLAH M, AHMED-JUSHUF I. Cardiovascular autonomic neuropathy in HIV infected patients. **Sex Transm Infect**. 1999;75(4):264-7.

SCHECHTER ME, ANDRADE BB, HE T, RICHTER GH, TOSH KW, POLICICCHIO BB, et al. Inflammatory monocytes expressing tissue factor drive SIV and HIV coagulopathy. **Sci Transl Med**. 2017;9(405): pii: eaam5441. doi: 10.1126/scitranslmed.aam5441.

SECRETARIA DE VIGILÂNCIA EM SAÚDE – Ministério da Saúde [homepage na internet]. Brasil: Boletim Epidemiológico HIV AIDS 2017 [atualizada em 2017; acesso em 2018 Abr 15]. Disponível em http://www.aids.gov.br/pt-br/pub/2017/boletim-epidemiologico-hivaids-2017.

SHIRAISHI Y, KATSUMATA Y, SADAHIRO T, AZUMA K, AKITA K, ISOBE S, et al. Real-Time Analysis of the Heart Rate Variability During Incremental Exercise for the Detection of the Ventilatory Threshold. **J Am Heart Assoc**. 2018;7. pii: e006612. doi: 10.1161/JAHA.117.006612.

SINHA A, MA Y, SCHERZER R, HUR S, LI D, GANZ P, et al. Role of T-Cell Dysfunction, Inflammation, and Coagulation in Microvascular Disease in HIV. **J Am Heart Assoc**. 2016;5(12): pii: e004243. doi: 10.1161/JAHA.116.004243.

SOÁREZ PCD, CASTELO A, ABRÃO P, HOLMES WC, CICONELLI RM. Brazilian-Portuguese translation and validation of the HIV/AIDS-Targeted Quality of Life Instrument. **Rev Panam Salud Publica**. 2009; 25:69-73.

SPIERER DK, DEMEERSMAN RE, KLEINFELD J, MCPHERSON E, FULLILOVE RE, ALBA A, et al. Exercise training improves cardiovascular and autonomic profiles in HIV. **Clin Auton Res**. 2007;17(6):341-8.

STRIJDOM H, DE BOEVER P, WALZL G, ESSOP MF, NAWROT TS, WEBSTER I, et al. Cardiovascular risk and endothelial function in people living with HIV/AIDS: design of the multi-site, longitudinal EndoAfrica study in the Western Cape Province of South Africa. **BMC Infect Dis**. 2017;17(1):41.doi: 10.1186/s12879-016-2158-y.

TAYLOR G. Rolling out HIV antiretroviral therapy in sub-Saharan Africa: 2003-2017. **Can Commun Dis Rep.** 2018;44(2):68-70.

THOBAKGALE C, NAIDOO K, MCKINNON LR, WERNER L, SAMSUNDER N, KARIM SA, et al. Interleukin 1-Beta (IL-1β) Production by Innate Cells Following TLR Stimulation Correlates With TB Recurrence in ART-Treated HIV-Infected Patients. **J Acquir Immune Defic Syndr**. 2017;74(2):213-20.

TRIANT VA, LEE H, HADIGAN C, GRINSPOON SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. **J Clin Endocrinol Metab**. 2007;92(7):2506-12.

UNAIDS data [homepage na internet]. Geneve: Joint United Nations Programme on HIV/AIDS (UNAIDS) [atualizada em 2017; acesso em 2018 Abr 15]. Disponível em http://www.unaids.org/en/resources/documents/2017/2017_data_book.

VANCAMPFORT D, MUGISHA J, ROSENBAUM S, FIRTH J, DE HERT M, PROBST M, et al. Cardiorespiratory fitness levels and moderators in people with HIV: A systematic review and meta-analysis. **Prev Med**. 2016;93:106-14.

VIŠKOVIĆ K, LEPEJ SŽ, GORENEC A, GRGIĆ I, LUKAS D, ZEKAN Š, et al. Cardiovascular markers of inflammation and serum lipid levels in HIV-infected patients with undetectable viremia. **Sci Rep**. 2018;8(1):6113. doi: 10.1038/s41598-018-24446-4.

VON ROSENBERG W, CHANWIMALUEANG T, ADJEI T, JAFFER U, GOVERDOVSKY V, MANDIC DP. Resolving ambiguities in the LF/HF ratio: LF-HF

scatter plots for the categorization of mental and physical stress from HRV. **Front Physiol**. 2017;8:360. doi: 10.3389/fphys.2017.00360. eCollection 2017.

WILK G, OSMENDA G, MATUSIK P, NOWAKOWSKI D, JASIEWICZ-HONKISZ B, IGNACAK A, et al. Endothelial function assessment in atherosclerosis: comparison of brachial artery flow-mediated vasodilation and peripheral arterial tonometry. **Pol Arch Med WeWn**. 2013;123(9):443-52.

WOMACK JA, CHANG C-CH, SO-ARMAH KA, ALCORN C, BAKER JV, BROWN ST, et al. HIV infection and cardiovascular disease in women. **J Am Heart Assoc**. 2014;3(5): e001035. doi: 10.1161/JAHA.114.001035.

ZANNI MV, FITCH K, RIVARD C, SANCHEZ L, DOUGLAS PS, Grinspoon S, et al. Follow YOUR Heart: development of an evidence-based campaign empowering older women with HIV to participate in a large-scale cardiovascular disease prevention trial. **HIV Clinical Trials**. 2017;18(2):83-91.

2. Objetivos

2.1Objetivo Geral

Avaliar o risco cardiovascular e verificar o efeito do treinamento aeróbio nas variáveis de risco cardiovascular, variabilidade da frequência cardíaca e qualidade de vida em PVHA.

2.2 Objetivos Específicos

Os objetivos específicos serão apresentados abaixo conforme a divisão dos artigos desenvolvidos nessa tese:

Artigo 1

O objetivo do artigo 1 foi avaliar o efeito de 24 sessões de treinamento aeróbio em PVHA em uso de TARV nas seguintes variáveis:

- Capacidade funcional pelo consumo máximo de oxigênio;
- Função endotelial pelo índice de hiperemia reativa;
- Dados antropométricos pela massa corporal, circunferência abdominal e circunferência do quadril;
- Perfil lipídico (LDL, HDL, triglicerídeos e colesterol total) e glicêmico (glicemia);
- Contagem de linfócitos T CD4+;
- Estresse oxidativo por nitrito, TBARS e Tiol;
- Perfil inflamatório por meio de TNF-α, MCP-1, IL-1β, IL-1ra, IL-6 e IL-10;
- Instrumento de qualidade de vida focado em HIV/AIDS.

Artigo 2

O objetivo apresentado no estudo 2 foi avaliar a variabilidade da frequência cardíaca e realizar um estudo piloto verificando os efeitos do treinamento aeróbio no domínio do tempo e no domínio da frequência em PVHA, sendo avaliado as seguintes variáveis:

- Domínio do tempo: desvio padrão de todos os intervalos NN; quadrado das diferenças entre as adjacentes dos intervalos RR; desvio padrão de todos os intervalos RR;
- Domínio da frequência: baixa frequência; alta frequência; relação baixa frequência/alta frequência.
- Correlacionar os domínios da VFC com variáveis relacionadas ao HIV e perfil lipídico.

Artigo 3

O objetivo do artigo 3 foi avaliar o risco cardiovascular entre homens e mulheres vivendo com HIV em uso de TARV, sendo avaliado as variáveis a seguir:

- Capacidade funcional pelo consumo máximo de oxigênio;
- Função endotelial pelo índice de hiperemia reativa;
- Dados antropométricos pela massa corporal, circunferência abdominal e circunferência do quadril;
- Perfil lipídico (LDL, HDL, triglicerídeos e colesterol total) e glicêmico (glicemia);
- Contagem de linfócitos T CD4+;
- Estresse oxidativo por nitrito, TBARS e Tiol;
- Perfil inflamatório por meio de TNF-α, MCP-1, IL-1β, IL-1ra, IL-6 e IL-10;
- Escore de Framingham.

Os artigos que contemplam os referidos objetivos são apresentados a seguir:

3. Artigo 1

Aerobic training improves functional capacity, cardiovascular risk factors, quality of life and modulates the inflammatory and oxidative stress markers in people living with HIV

Artigo a ser submetido ao periódico – *Journal of Exercise Rehabilitation.*

Aerobic training improves functional capacity, cardiovascular risk factors, quality of life and modulates the inflammatory and oxidative stress markers in people living with HIV

Running Title: Aerobic training in cardiovascular risk and QoL in PLWH

Candissa Silva da Silva[1,2], Luis Fernando Deresz[3], Gilson Pires da Silva[1,2], Letícia Mignoni[1], Giovana de Marchi Castelli[1], Alessandra Peres[1,4], Pedro Dal Lago[1,2]

Department of Physical Therapy, Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, Brazil

Corresponding author at: UFCSPA, Sarmento Leite, 245, CEP: 90050-170, Porto Alegre, RS, Brazil. Tel.: +55 51 3303 8796; fax: +55 51 3303 8793.

E-mail adresses: pdallago@pq.cnpq.br, pdallago@ufcspa.edu.br (P. Dal Lago)

1. Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA). Porto Alegre- Brazil

2. Graduation Program in Health Sciences -UFCSPA. Porto Alegre- Brazil

3. Universidade Federal de Juiz de Fora, Campus Governador Valadares. Governador Valadares – Brazil.

4. Research Center. Methodist University Center IPA. Porto Alegre, Brazil.

Abstract

Purpose: People living with HIV (PLWH) in use antiretroviral therapy (ARV) present high incidence of cardiovascular events, prevalence of sedentary lifestyle and low quality of life (QoL). However, the performance of exercise training may influence these variables. Thus, the aim of this study was to evaluate the effects of aerobic training program on functional capacity, endothelial function, inflammatory markers and oxidative stress and QoL in PLWH.

Methods: This quasi-experimental study with 15 PLWH in ARV (8 PLWH completed the training protocol and 7 PLWH were included by intention to treat analysis) with undetectable viral load (< 40 copies/mL) participated of 24 sessions of aerobic training (40 min/day in a frequency of 3x/week for 8 weeks). Were evaluated pre and post aerobic training: anthropometric measurements, functional capacity (VO_{2max}), endothelial function (EndoPAT), lipid and glycemic profile, oxidative stress (nitrite, TBARS and thiol), inflammatory profile (TNF-α, MCP-1, IL-1β, IL-1ra, IL-6, IL-10) and quality of life (HAT-QoL).

Results: There was a decrease in weight ($p = 0.02$), abdominal circumference ($p = 0.01$), hip circumference ($p = 0.02$), triglycerides ($p = 0.001$) glucose ($p = 0.001$), total cholesterol ($p = 0.02$), and TBARS ($p = 0.001$). Moreover, exercise training increased CD4+ T-cell ($p = 0.03$), nitrite ($p = 0.02$), IL-1ra ($p = 0.02$), IL-10 ($p = 0.001$) and improvement of the HAT-Qol scores.

Conclusions: 24 aerobic training sessions have an impact on the reduction of cardiovascular disease risk factors, promotes modeling of inflammatory markers and oxidative stress and improve quality of life in PLWH.

Key Words: HIV, Aerobic Training, Functional Capacity, Inflammation, Quality of Life

Introduction

The introduction of antiretroviral (ARV) regimens has had a profound impact on the natural history of human immunodeficiency virus (HIV) infection and has changed the course of the disease. People living with HIV (PLWH) often present physical and mental changes associated with disease progression, ARV use and age (1). ARV reduced mortality rates, increased life expectancy and improved quality of life (QoL) in this population (2-6). However, it has caused numerous changes in several systems, including higher risk cardiovascular disease (CVD) with an in PLWH, than the general population (2, 7, 8). Associated with this, present lipodystrophy, increased risk of metabolic syndrome (MS) and the production of pro-inflammatory cytokines by immune cells, contributing to the formation of atherosclerosis (2, 5, 6, 9, 10).

Several studies have shown that CVD is the most common cause of morbidity and mortality in non-AIDS-related in PLWH and is considered an independent risk factor for HIV (2, 5-7, 11). A study showed that the relative risk of acute myocardial infarction (AMI), comparing HIV with no-HIV, were 2.98 (95% CI 2.33-3.75; $p < 0.0001$) (10). Endothelial dysfunction is evaluated as a marker of atherosclerosis, being present in 35% of PLWH (11, 12). This marker correlates with severity and extent of coronary sclerosis and a predictor of coronary event, but with reversibility characteristic (2, 7, 12).

Due to the constant inflammatory process caused by viral replication, it was found higher levels of tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6) and interleukin-10 (IL-10) in PLWH, and interleukin-1β (IL-1β) is associated with hypothalamic activation and is correlated with increased physiological stress (5). Also, PLWH present changes in body composition, as a decreased in body mass index (BMI) and lipodystrophy, causing pain and muscle fatigue, a low level of daily physical activity, increasing cardiovascular risk and early death (13-16).

Structural and inflammatory muscle abnormalities may impair the muscle's ability to draw or use oxygen during exercise causing physical limitation (14). Study showed that PLWH has reduced aerobic capacity when compared to predicted values (14). Already published that supervised aerobic training performed 3-5 times a week performed with moderate intensity is safe and effective in PLWH with drug adherence and stable clinically with controlled viral load (VL) and CD4+ T-cell (6, 15, 16). The practice of physical activity is a determinant for QoL in PLWH and reduction of cardiometabolic risk (3, 13, 16).

Few studies have been conducted directing the effects of physical exercise on inflammatory cytokine, and oxidative stress markers, reversibility of endothelial dysfunction and functional capacity in PLWH and the published results remain controversial and conflicting due to several factors that influence body composition and factors of cardiovascular risk (4, 5, 14). Thus, the aim of this study was to evaluate the effects of 24 sessions aerobic training program on functional capacity, endothelial function, anthropometric measurements, lipid and glycemic profile, oxidative stress, inflammatory profile and QoL in PLWH using ARV.

Methods

Setting

The present quasi-experimental study was conducted with 210 PLWH of both genders, aged 18–75 years. They were recruited from the Department of Infectious Diseases of the Irmandade da Santa Casa de Misericórdia de Porto Alegre (ISCMPA), Rio Grande do Sul in the period from March 2015 to December 2017. The study was approved by the Ethics Committee of the Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA) (nº 797.649/14). Before data collection, the patients signed an informed consent form.

Participants

Inclusion criteria were: confirmed diagnosis of HIV disease, men and women, aged over 18 years, use of ARV for 6 consecutive months, undetectable viral load (VL) (< 40 copies/mL) and level of physical activity classified as sedentary according to IPAQ (17). The exclusion criteria are shown in figure 1.

Personal and Anthropometric Data

The logistics of the study is presented in figure 2. Personal data contained questions about age, smoking, associated diseases, medication use, time for HIV diagnosis, drug scheme and time of medication use. All this information was confirmed with the data recorded in medical records.

For anthropometric assessments, all tests were performed 3 times, and the average was used for analysis. Body mass (kg) and height (meters) were determined by a semi-analytical scale (Welmy, Brazil), and a stadiometer attached (Welmy, Brazil). To measure the abdominal circumference (AC), an inelastic tape was used at the midpoint between the iliac crest and the outer face of the last rib. The hip circumference (HC) was measured at the level of the upper anterior iliac spine (18).

Laboratory Tests

Blood samples were obtained from each patient after 12 hours of fasting. A trained investigator performed a 10 mL collection of venous blood into the antecubital vein. The collected blood sample was transferred to a tube containing heparin (6 mL). The samples were centrifuged (1500g, 10 minutes, 22°C), aliquoted and frozen at -20°C for further analysis. Blood glucose, total cholesterol (TC) and triglycerides were determined enzymatically. HDL was determined by immunoinhibition and insulin dosed by chemiluminescence. The MS was defined following National Cholesterol Education Program Adult Treatment Panel Definition (19). The number of CD4+T-cell and VL data were collected collected from patient's medical records pre and post training protocol.

The Nitrite/Nitrate (NOx) concentrations were analyzed on a microplate reader (SpectraMax M2e, USA) with the specified wavelength at 540 nm, and the results were expressed as μM/L (20). Thiobarbituric acid reactive substances (TBARS) concentrations were analyzed following a technique previously described by Ohkawa *et al.* (21). Samples were analyzed on a microplate reader at 532 nm, and the results were expressed as μM MDA/L. Total thiols were analyzed using the reagent 5-5'-dithio-bis (2-nitrobenzoic acid) (22).

Serum concentrations of Interleukin-1β (IL-1β), IL-1ra, IL-6 and IL-10, Monocyte Chemoattractant Protein-1 (MCP-1), TNF-α (Ebioscience, Thermo Fisher Scientific, USA) were quantified by enzyme-linked immuno sorbent assay (ELISA) following the manufacturer's recommendations. The intra-assay coefficient of variation was always <5%.

Cardiopulmonary exercise testing (CPX)

CPX was performed using an electric gradient treadmill protocol (Centurion 300, Micromed, Brazil) in a laboratory with temperature control (18-22ºC) and relative humidity (40-60%). The test started an initial velocity of 3 km/h and no inclination for all study

participants. The load test was designed to obtain VO_{2peak} within 8 to 12 minutes, followed by 1 minute of active recovery (speed and incline similar to the initial test data) and 5 minutes of passive recovery. The test was terminated after verification of the following circumstances: a) request of the participant due to extreme tiredness and/or perception of the intense sensation of dyspnea; (b) peak respiratory exchange ratio RER> 1.1 and c) VO_2 plateau was reached even with increasing workload (22). Ventilatory and metabolic parameters were collected by respiration using Metalyzer 3B (Cortex, Germany) and were analyzed after the mean of the data in 8 respiratory cycles. The average of the last 30s data points from the test were used to determine the VO_{2peak} and HR_{max} (23).

Endothelial Function

Patients were instructed not to use caffeine, tobacco, alcohol, antioxidants, and non-steroidal medications for at least 12 hours before evaluation. The EF response was evaluated through pulse tonometry (EndoPAT2000, Itamar Medical, Israel).

The digital pulse amplitude was measured by placing a sensor on the tip of both index fingers with the patient in the supine position. After verification of the signal for 10 minutes at the basal position, the flow was stopped for a period of 5 minutes by insufflation of a cuff (50 mmHg above diastolic blood pressure (DBP) or above 200 mmHg) (12). The degree of arterial tone changes in response to ischemia was expressed as the reactive hyperemia index (RHI), the normal endothelial function was defined as RHI > 1.67 (12).

Quality of Life Questionnaire

We used the questionnaire HAT-QoL validated for PLWH in Brazil (24). The questionnaire has 34 questions, distributed in 9 domains (3, 24). In each domain the score was (0-100), and the higher the score means the lower the impact of HIV infection is the QoL of PLWH (3).

Aerobic Training

The training was conducted on a non-inclined treadmill 3 times/ week, totaling 24 sessions. The training protocol is shown in figure 2, was composed as follows: 5 minutes acceleration; 30 minutes of training with the load determined by the CPX and 5 minutes of deceleration (25).The HR corresponded to 60-65% of VO_{2max} is considered moderate/high intensity and HR corresponded to 75-80% of VO_{2max} is high intensity (26). As the sensation of dyspnea and tiredness referred to by the Borg scale (27).

Statistical analysis

The data were compared pre and post-training. Statistical analysis was performed using SPSS statistics software version 18. We used the intention to treat methodology with repetition of the baseline data from the initial evaluation. The Shapiro Wilk test was applied to verify the normality of the data. The data that presented normal distribution were presented in mean and standard deviation and those that did not present normal distribution have a median and interquartile presentation, being also considered the presentations of frequency when necessary. In data with normal distribution will be applied paired t-test. For the difference between frequencies was used the Fischer test. The level of statistical significance will be considered, $p < 0.05$.

Results

Fifteen PLWH, 4 female, and 11 (63.6%) men were analyzed. Regarding the associated diseases: 46.6% had depression, 33.3% had systemic arterial hypertension, and 6.7% had chronic obstructive pulmonary disease. The study participants had the following drug regimens: 2 nucleoside reverse transcriptase inhibitors (NRTIs) + 1 inhibitor of non-nucleoside reverse transcriptase (NNRTI) drug (n = 9); 2 NRTIs + 1 protease inhibitor (PI) (n = 3) and 3 NRTIs + 1 PI (n = 3).

Previous to the training protocol, 10 (66.6%) patients had MS and after training remained only to 3 (20%) patients (p = 0.02), being presented improvement in the following parameters according to individual analysis of the study participants: PLWH 1 (glucose and systolic blood pressure - SBP); PLWH 2 (triglycerides and AC); PLWH 3 (glucose); PLWH 4 (glucose); PLWH 5 (SBP); PLWH 6 (without modified parameters); PLWH 7 (AC).

The anthropometric data, disease characteristics and lipid and glycemia profile are available in table 1. All participants remained with undetectable VL < 40 copies/mL. There was a significant decreased in BMI, AC, HC, triglycerides, glycemia, and total cholesterol levels. Moreover, there was an increase in CD4+ T-cell.

Figure 2 presents pre and post training results with the increase in VO_{2max} (p = 0.01); anti-inflammatory cytokines: increase of IL-1ra (p = 0.02) and IL-10 (p = 0.001); oxidative stress markers: increase of nitrite (p = 0.02) and decrease in TBARS (p = 0.001).

Figure 3 shows the QoL of the HAT-QoL, with general function (p = 0.02) and concern with medication (p = 0.03) in the domains that showed a statistically significant improvement.

Before the training, 11 (68.7%) PLWH had ED (RHI < 1.67) and after the training 9 (56.2%) (p = 0.70) PLWH had a higher value than the reference. There was no significant change in the values of the natural logarithm (lnRHI) (p = 0.29) and augmentation index (AI) (p = 0.53).

Discussion

The present study was able to show that 24 sessions of aerobic training improve cardiovascular risk factors and has a positive impact on the functional capacity, risk factors for CVD, oxidative stress, inflammatory profile, and QoL of PLWH in ARV use. During the training protocol, there was no change in doses and/or medications for the treatment of associated diseases. In addition, although new classes and drugs were available in ARV protocols Brazil during the study, only NNRTI, NRTI and PI were used in this study.

Previous studies have presented a wide variety of methodologies regarding the required number of training sessions for the beneficial effects of PLWH training programs. Leach *et al.* (28) showed that aerobic and/or strength training in PLWH ranged from 6 to 24 weeks, with 12-week programs with 3-5 sessions/week being most common (28). However, the option was made for 8 weeks due to the high failure rates of training protocols in this population, trying to reduce the dropout rate. The present study presented values of adherence to the program similar to that found in the systematic review of Leach *et al*. (0-76%) (28). From the tests carried out on the first day until the protocol was completed, only (53.3%) of the participants remained and the sample consisted mostly of men (73.3%) similar to the data presented in the systematic review by O'Brien *et al.*(16) who reported that there is a loss in the external validity of the results for applicability in women.

PLWH have high lipid and glycemic and TC levels. A study showed that only walking 3 days/week can reduce TC levels (29), being these traditional risk factors for CVD (16, 29). The results in the present study corroborate these findings, where we find reduction of TC ($p = 0.02$), besides other important variables such as glycemic profile ($p = 0.001$), body weight ($p = 0.04$), AC ($p = 0.001$) and HC ($p = 0.02$) were reduced. However, we did not observe a significant effect on the increase in HDL ($p = 0.24$), similar to the study by Bonato *et al.* (29). This may have occurred since the decrease in HDL is observed during the inflammatory process and a consequence of the increase in the cellular catabolism that may have been

associated to the present study due to the intensity of training performed (30). Since it has been suggested in previous studies that diabetes and dyslipidemia are independent cardiovascular risk factors associated with the event of AMI in PLWH and showed that diabetes mellitus is associated with low level of physical activity (1, 10).

In our study, there was a significant increase in VO_{2max} ($p = 0.01$) as in the randomized clinical trial showed an increase in VO_{2max} after aerobic training protocol ($p = 0.0001$) (31). Moreover, some studies showed an increase in VO_{2max} when associated with aerobic and strength training (16, 28, 32). Thus, we can verify that the realization of only one type of training is already capable of impacting PLWH functional capacity. Already well documented in the literature that the VO_{2max} is the gold-standard in the evaluation of cardiorespiratory fitness and improvement in VO_{2max} may suggest a strategic effect in the reduction of cardio-metabolic risk among PLWH (13, 16). This is because it has been published that the practice of moderate intensity exercise for 15 minutes is able to reduce all causes of mortality and increase life expectancy by 3 years compared to inactive people (33).

Few studies have evaluated the exercise-induced effects of oxidative stress in PLWH. However, strong evidence has already been presented that regular exercise is able to regulate endogenous antioxidants not only in muscle and that increased the reactive oxygen species elicited by moderate intensity exercise may lead to beneficial adaptations such as increased oxidative capacity in muscle (34). It is known that under normal physiological conditions, nitrite is derived from the oxidation of nitric oxide, can be absorbed by the erythrocyte and vasculature (35, 36). Our study showed increase in nitrite ($p = 0.02$). This may have occurred due to increased oxygen demand during exercise and/or the high intensity load of the proposed training.

Regarding nitrite, it is known that in high doses can cause nitrosative stress and tissue damage, but at low dosages has beneficial regulatory effect on vasodilatation, glucose

uptake and immune function (34). It is still unclear whether nitrite is able to attenuate the deleterious effects of pathological cardiovascular processes (35). Thus, it was observed that nitrite has the capacity to modulate reactive oxygen species. However, there is no distinct threshold between the damaging effect and the beneficial effect on PLWH.

There was a decrease in TBARS, in addition to these results being similar to another study unpublished by our research group and as reported in the study by Lima *et al.* (37) with 20 weeks of PLWH training and a decrease in TBARS ($p = 0.001$). But, and in the study by Deresz *et al.*(4), there was no effect on TBARS in the analysis of acute training in PLWH. It's suggested that only the chronic effects of physical training can reduce TBARS value.

Innate cytokines induced by acute HIV infection may contribute directly to CD4+ T-cell apoptosis (38). Our study showed an increase in the CD4+ T-cell ($p = 0.04$), suggesting an improvement in the immunological profile in PLWH. Previous studies have shown that an increase in CD4+ T-cell occurs in moderate-intensity aerobic training (29, 31). Although these data are not well defined in the literature. Our finding must be associated with those PLWH participating in the study being clinically stable and disease controlled demonstrated by the presence of undetectable VL. Thus, aerobic training may have only been a potentiator of increased CD4+ T-cell. A pilot study found that 2 mechanisms may be associated with the effects of physical training on inflammatory profile: reduction of body fat and immunomodulatory effects caused by contraction of the skeletal muscle (29).

The increase in viremia in primary HIV infection is associated with the orderly sequence of rapid elevation in plasma cytokines and more sustained increase of TNF-α and MCP-1 and after the proinflammatory increase including IL-6 and, more slowly, the peak IL-10 (38). However, high levels of IL-10 are associated with secondary infections and disease progression, with an increase in the presence of opportunistic diseases in PLWH (5, 30). Although we did not find statistical significance, we obtained reduction of important

proinflammatory markers and that have a strong relation with endothelial function IL-6 and TNF-α, which are cytokines that are influenced by physical exercise (39). Increases in plasma IL-1ra concentrations have a pivotal anti-inflammatory role after an exercise session, blocking the receptor of pro-inflammatory IL-1 (40). Thus, the systematic exercise performed in our study induces a progressive increase in immunoregulatory cytokines, such as IL-1ra and IL-10 (39).

The increase of IL-ra may have been due to physical exercise in leptin, which has direct effects on monocytes, resulting in an increase in IL-1ra secretion (41). .Furthermore, studies have shown that elevated pro-inflammatory levels are related to increased cardiovascular risk by contributing to the pathogenesis of atherosclerosis (42, 43). One study showed that IL-10 stimulates the absorption of cholesterol from modified lipoproteins and the efflux of cholesterol from the cell (30). So the increase of IL-10 may have been one of the factors that contributed to cholesterol reduction in our study.

Thus, the changes in the cytokine profile observed in our study may be due to weight loss observed after exercise training. In fact, reductions of IL-6 and TNF-α were observed after 16-weeks of aerobic or strength training in PLWH (44). Also, one study has shown that the greatest difficulty is to determine the normal cytokine values for PLWH since the inflammatory condition mediated by the HIV itself and other factors interferes with inflammatory and proinflammatory cytokines (5).

Further, inflammation, metabolic changes, and oxidative stress are predictors of endothelial dysfunction, and in the case of PLWH, there is still the sum of the effects of ARV (45). Like CVD is a major cause of mortality in PLWH, many studies have been conducted on the effects of endothelial function on PLWH (11, 45-47). Although not significant, our study showed a decrease endothelial dysfunction in PLWH after the training program. Neither we detected a large number of PLWH with a presence of endothelial dysfunction in the baseline

evaluation (n=11), and at the end, 9 PLWH remained with endothelial dysfunction. However, the improvement was observed in the 2 PLWH who completed the training protocol, suggesting that the practice of regular physical exercise may aid in the improvement of endothelial function. This may have occurred as a result of endothelial regeneration and neovascularization promoted by regular exercise training (34). Associated with this, we observed in the present study decreased, although not statistically significant, proinflammatory cytokines (IL-6 and TNF-α) and a significant increase in the anti-inflammatory IL-10 that may help improved the endothelial function.

Moreover, most of the studies involving evaluation of EF in PLWH used methods of evaluation of brachial artery dilation with macrovascular evaluation using ultrasound (US) (45, 46, 48). However, in the present study we chose to perform endothelial function measurement by EndoPat, since the result is an independent operator, besides being a quick and easy to apply test (12, 45).

Quiles *et al.*, showed that approximately 60% of participants had 1 or 2 physical or mental health conditions diagnosed (depression, HAS, diabetes, angina, AMI, stroke and CVD) and half of the associated diseases are related to depression (1). Which is similar to our study, where 46.6% of the patients presented a diagnosis of depression and this may be one of the factors that have contributed to some participants abandoning the training program (49). Moreover is has been reported that depression is a risk factor for cardiovascular disease (50). Because depression is also influenced by proinflammatory markers, besides that HIV disease progression, having depression can significantly increase plasma VL (49, 50).

O'Brien *et al.*, has already been able to show that physical training improves PLWH QoL (16). In addition to a sedentary lifestyle in PLWH, the lower aerobic fitness of this population are related to the low perception of general function and satisfaction with life in a questionnaire that evaluates QoL (3). QoL assessment is essential for the rehabilitation

process and of great importance for understanding the behaviour and life of PLWH (14). In our study, of the 9 domains evaluated, the aspects of general function ($p = 0.02$) and concern with medication ($p = 0.03$) were those that presented statistical significance. The improvement in health status influences on QoL as presented in a study that showed that the domain of health concern is related to CD4+ T-cell count and that the higher the socioeconomic level of the patients and the level of physical activity, the better the QoL score (3).

The main limitations of our study are the small sample of patients who completed the training protocol, the difficulty of obtaining values considered normal for this population in the variables studied, and did not have a PLWH control group.

In conclusion, the present study showed that 24 sessions of aerobic training can significantly modify not only classic parameters of CVD such as VO_{2max}, lipid profile, glycemic profile, and anthropometric measures as important and fundamental parameters for homeostasis, oxidative stress, inflammatory profile and influence on the improvement of QoL of PLWH in the use of ARV. Therefore, we suggest that regular practice of physical exercise should be considered as alternative non-drug treatment to reduce the effects of chronic HIV infection in PLWH.

Conflict of interest

The authors declared they not have anything to disclose regarding conflict of interest with respect to this manuscript.

Acknowledgments

This study was funded by grants from the Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS).

References

1. Quiles NN, Ciccolo JT, Garber CE. Association Between Physical Activity, Depression, and Diabetes in Urban-Dwelling People Living with HIV. J Assoc Nurses AIDS Care. 2017;28(6):838-48.

2. Maggi P, Bellacosa C, Leone A, Volpe A, Ricci ED, Ladisa N, et al. Cardiovascular risk in advanced naïve HIV-infected patients starting antiretroviral therapy: Comparison of three different regimens-PREVALEAT II cohort. Atherosclerosis. 2017; 263:398-404.

3. Medeiros RCDSC, Medeiros JAD, Silva TALD, Andrade RDD, Medeiros DCD, Araújo JDS, et al. Quality of life, socioeconomic and clinical factors, and physical exercise in persons living with HIV/AIDS. Rev Saude Publica. 2017;51:66. doi: 10.1590/S1518-8787.2017051006266.

4. Deresz L, Sprinz E, Kramer A, Cunha G, De Oliveira A, Sporleder H, et al. Regulation of oxidative stress in response to acute aerobic and resistance exercise in HIV-infected subjects: a case–control study. AIDS care. 2010;22(11):1410-7.

5. Pedro RE, Candido N, Guariglia DA, Melo BP, Bertolini DA, Peres SB, et al. Exercise improves cytokine profile in HIV-infected people: A randomized clinical trial. Cytokine. 2017;99:18-23.

6. Jaggers JR, Prasad VK, Dudgeon WD, Blair SN, Sui X, Burgess S, et al. Associations between physical activity and sedentary time on components of metabolic syndrome among adults with HIV. AIDS care. 2014;26(11):1387-92.

7. Strijdom H, De Boever P, Walzl G, Essop MF, Nawrot TS, Webster I, et al. Cardiovascular risk and endothelial function in people living with HIV/AIDS: design of the multi-site, longitudinal EndoAfrica study in the Western Cape Province of South Africa. BMC Infect Dis. 2017;17(1):41.doi: 10.1186/s12879-016-2158-y.

8. Fuchs SC, Alencastro PR, Ikeda MLR, Barcellos NT, Wolff FH, Brandão A, et al. Risk of coronary heart disease among HIV-infected patients: a multicenter study in Brazil. The Scientific World Journal. 2013;2013:163418. doi: 10.1155/2013/163418. eCollection 2013.

9. Dubé MP, Shen C, Mather KJ, Waltz J, Greenwald M, Gupta SK. Relationship of body composition, metabolic status, antiretroviral use, and HIV disease factors to endothelial dysfunction in HIV-infected subjects. AIDS Res Hum Retroviruses. 2010;26(8):847-54.

10. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. J Clin Endocrinol Metabol. 2007;92(7):2506-12.

11. Dysangco A, Liu Z, Stein JH, Dubé MP, Gupta SK. HIV infection, antiretroviral therapy, and measures of endothelial function, inflammation, metabolism, and oxidative stress. PloS one. 2017;12(8):e0183511.

12. Balsam P, Mikuła T, Peller M, Suchacz M, Puchalski B, Kołtowski Ł, et al. Evaluation of endothelial function and arterial stiffness in HIV-infected patients: a pilot study. Kardiol Pol. 2015;73(5):344-51.

13. Vancampfort D, Mugisha J, Rosenbaum S, Firth J, De Hert M, Probst M, et al. Cardiorespiratory fitness levels and moderators in people with HIV: A systematic review and meta-analysis. Prev Med. 2016;93:106-14.

14. Gomes Neto M, Conceição CS, Ogalha C, Brites C. Aerobic capacity and health-related quality of life in adults HIV-infected patients with and without lipodystrophy. Braz J Infect Dis. 2016;20(1):76-80.

15. Sullivan K, Shikuma CM, Chow D, Cornelius E, Romine RK, Lindsey RA, et al. Aerobic Fitness Levels and Validation of a Non Exercise VO2max Prediction Equation for HIV-Infected Patients on HAART. HIV Clin Trials. 2014;15(2):69-77.

16. O'Brien KK, Tynan A-M, Nixon SA, Glazier RH. Effectiveness of aerobic exercise for adults living with HIV: systematic review and meta-analysis using the Cochrane Collaboration protocol. BMC Infect Dis. 2016; 17(1):268. doi: 10.1186/s12879-017-2342-8.

17. Committee IR. Guidelines for data processing and analysis of the International Physical Activity Questionnaire (IPAQ)–short and long forms. 2005.

18. Romancini JLH, Guariglia D, Nardo Jr N, Herold P, Pimentel GGdA, Pupulin ÁRT. Levels of physical activity and metabolic alterations in people living with HIV/AIDS. Rev Bras Med Esp. 2012;18(6):356-60.

19. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome. Circulation. 2005;112(17):2735-52.

20. Miranda KM, Espey MG, Wink DA. A rapid, simple spectrophotometric method for simultaneous detection of nitrate and nitrite. Nitric oxide. 2001;5(1):62-71.

21. Ohkawa H, Ohishi N, Yagi K. Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. Anal Biochem. 1979;95(2):351-8.

22. Ellman GL. Tissue sulfhydryl groups. Arc Biochem Biophysics. 1959;82(1):70-7.

23. Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher GF, et al. Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. Circulation. 2010;122(2):191-225.

24. SOÁREZ PCD, CASTELO A, ABRÃO P, HOLMES WC, CICONELLI RM. Brazilian-Portuguese translation and validation of the HIV/AIDS-Targeted Quality of Life Instrument. Rev Panam Salud Publica. 2009; 25:69-73.

25. Hand GA, Phillips KD, Dudgeon WD, William Lyerly G, Larry Durstine J, Burgess SE. Moderate intensity exercise training reverses functional aerobic impairment in HIV-infected individuals. AIDS care. 2008;20(9):1066-74.

26. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee I-M, et al. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc. 2011;43(7):1334-59.

27. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc. 1982;14(5):377-81.

28. Leach L, Bassett S, Smithdorf G, Andrews BS, Travill AL. Suppl 1: M3: a systematic review of the effects of exercise interventions on body composition in HIV+ adults. Open AIDS J. 2015;9:66-79.

29. Bonato M, Galli L, Passeri L, Longo V, Pavei G, Bossolasco S, et al. A pilot study of brisk walking in sedentary combination antiretroviral treatment (cART)-treated patients: benefit on soluble and cell inflammatory markers. BMC Infect Dis. 2017;17(1):61. doi: 10.1186/s12879-016-2095-9..

30. Gori E, Mduluza T, Nyagura M, Stray-Pedersen B, Gomo ZA. Inflammation-modulating cytokine profile and lipid interaction in HIV-related risk factors for cardiovascular diseases. Ther Clin Risk Manag. 2016;12:1659-66.

31. Ezema C, Onwunali A, Lamina S, Ezugwu U, Amaeze A, Nwankwo M. Effect of aerobic exercise training on cardiovascular parameters and CD4 cell count of people living with human immunodeficiency virus/acquired immune deficiency syndrome: A randomized controlled trial. Niger J Clin Pract. 2014;17(5):543-8.

32. Ortmeyer HK, Ryan AS, Hafer-Macko C, Oursler KK. Skeletal muscle cellular metabolism in older HIV-infected men. Physiol Rep. 2016;4(9). pii: e12794. doi: 10.14814/phy2.12794.

33. Eijsvogels TM, Thompson PD. Exercise is medicine: at any dose? Jama. 2015;314(18):1915-6.

34. Fiuza-Luces C, Garatachea N, Berger NA, Lucia A. Exercise is the real polypill. Physiology. 2013;28(5):330-58.

35. Omar SA, Webb AJ. Nitrite reduction and cardiovascular protection. J Mol Cell Cardiol. 2014;73:57-69.

36. Rifkind JM, Mohanty JG, Nagababu E, Salgado MT, Cao Z. Potential Modulation of Vascular Function by Nitric Oxide and Reactive Oxygen Species Released from Erythrocytes. Front Physiol. 2018; 9:690. doi: 10.3389/fphys.2018.00690. eCollection 2018.

37. Lima AH, Correia MA, Soares AH, Farah BQ, Forjaz CL, Silva AS, et al. Acute effects of walking and combined exercise on oxidative stress and vascular function in peripheral artery disease. Clin Physiol Funct Imaging. 2018;38(1):69-75.

38. Stacey AR, Norris PJ, Qin L, Haygreen EA, Taylor E, Heitman J, et al. Induction of a striking systemic cytokine cascade prior to peak viremia in acute human immunodeficiency virus type 1 infection, in contrast to more modest and delayed responses in acute hepatitis B and C virus infections. J Virol. 2009;83(8):3719-33.

39. Pareja-Galeano H, Garatachea N, Lucia A. Exercise as a polypill for chronic diseases. Prog Mol Biol Transl Sci. 2015; 135:497-526.

40. Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. Nat Rev Immunol. 2011;11(9):607-15.

41. Meier CA, Bobbioni E, Gabay C, Assimacopoulos-Jeannet Fo, Golay A, Dayer J-M. IL-1 receptor antagonist serum levels are increased in human obesity: a possible link to the resistance to leptin? J Clin Endocrinol Metabol. 2002;87(3):1184-8.

42. Bestawros M, Chidumayo T, Blevins M, Canipe A, Bala J, Kelly P, et al. Increased systemic inflammation is associated with cardiac and vascular dysfunction over the first 12

weeks of antiretroviral therapy among undernourished, HIV-infected adults in Southern Africa. J AIDS Clin Res. 2015;6(3). pii: 431.

43. Nordell AD, McKenna M, Borges ÁH, Duprez D, Neuhaus J, Neaton JD. Severity of cardiovascular disease outcomes among patients with HIV is related to markers of inflammation and coagulation. Severity of cardiovascular disease outcomes among patients with HIV is related to markers of inflammation and coagulation. J Am Heart Assoc. 2014;3(3):e000844. doi: 10.1161/JAHA.114.000844.

44. Lindegaard B, Hansen T, Hvid T, Van Hall G, Plomgaard P, Ditlevsen S, et al. The effect of strength and endurance training on insulin sensitivity and fat distribution in human immunodeficiency virus-infected patients with lipodystrophy. J Clin Endocrinol Metab. 2008;93(10):3860-9.

45. Sinha A, Ma Y, Scherzer R, Hur S, Li D, Ganz P, et al. Role of T-Cell Dysfunction, Inflammation, and Coagulation in Microvascular Disease in HIV. J Am Heart Assoc. 2016;5(12): pii: e004243. doi: 10.1161/JAHA.116.004243.

46. Moerland M, Kales A, Schrier L, Van Dongen M, Bradnock D, Burggraaf J. Evaluation of the EndoPAT as a tool to assess endothelial function. Int J Vasc Med. 2012;2012:904141. doi: 10.1155/2012/904141.

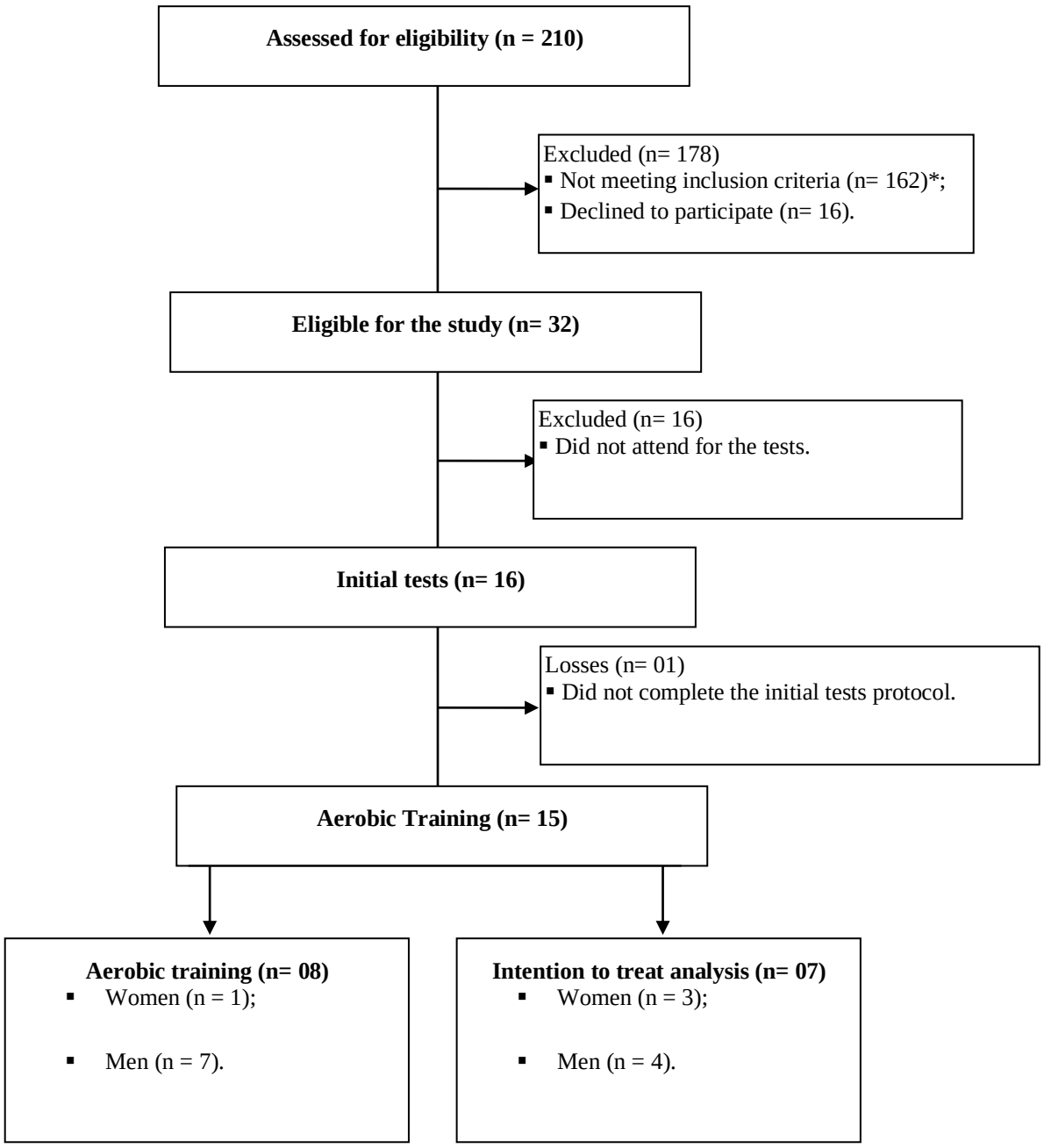
47. Wilk G, Osmenda G, Matusik P, Nowakowski D, Jasiewicz-Honkisz B, Ignacak A, et al. Endothelial function assessment in atherosclerosis: comparison of brachial artery flow-mediated vasodilation and peripheral arterial tonometry. Polish Arc Int Med. 2013;123(9):443-52.

48. Hansen AS, Butt JH, Holm-Yildiz S, Karlsson W, Kruuse C. Validation of repeated endothelial Function Measurements Using endoPaT in stroke. Front Neurol. 2017;8:178. doi: 10.3389/fneur.2017.00178.

49. Rivera-Rivera Y, Vázquez-Santiago FJ, Albino E, Sánchez MdC, Rivera-Amill V. Impact of depression and inflammation on the progression of HIV disease. J Clin Cell Immunol. 2016;7(3). pii: 423.

50. Rozanski A, Blumenthal JA, Davidson KW, Saab PG, Kubzansky L. The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: the emerging field of behavioral cardiology. J Am Coll Cardiol. 2005;45(5):637-51.

Figure 1: Flow diagram of the patients who performed the aerobic training protocol.



*Co-infection with hepatitis C virus (n=86), hepatitis B virus (n=7), diagnosed with psychological disorders (n=6), cardiac abnormalities (n=6), adherence to therapy (n=6), human T-lymphotropic virus (n=5), motor changes (n=5), pregnancy (n=3), Chagas disease (n=2), cognitive impairment (n=2), severe anemia (n=2) illicit drug use (n=1),visually impaired (n=1) and 30 people living with HIV had 2 or more of these associated changes.

Figure 2: Logistics of the study and aerobic training.

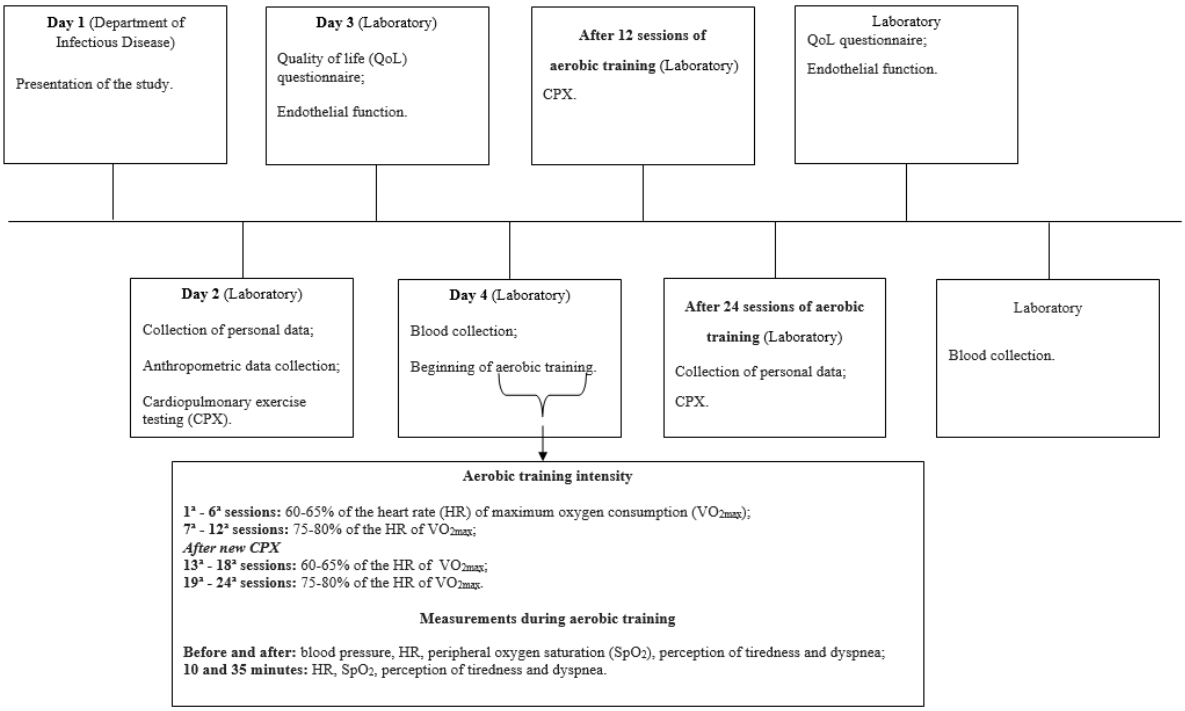
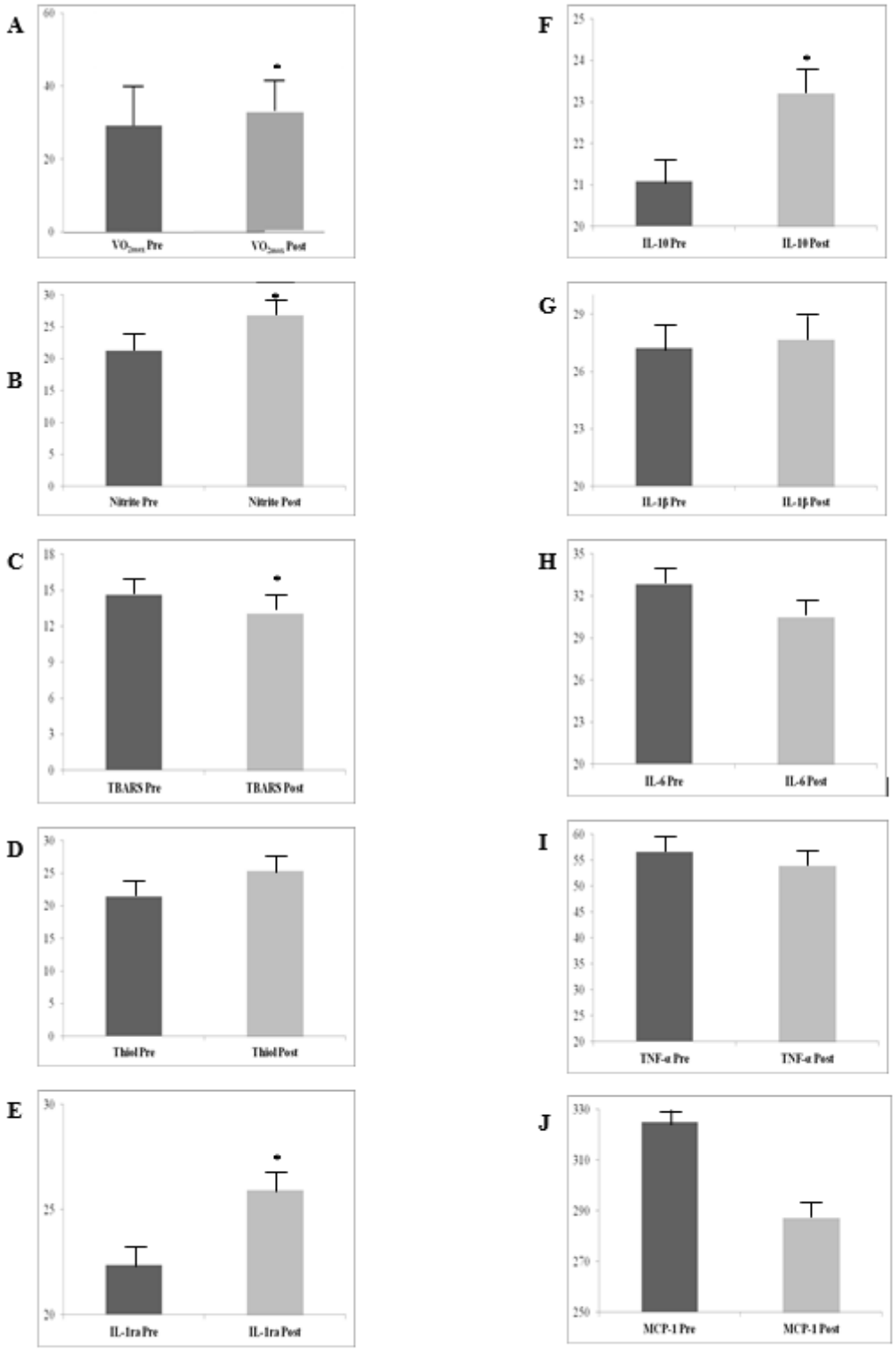
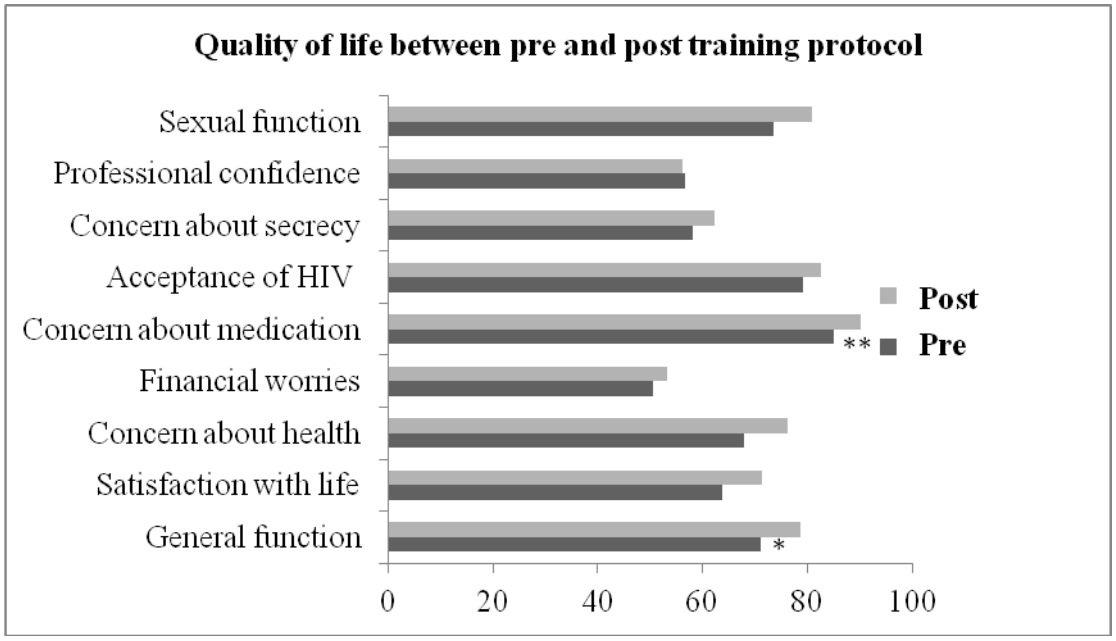


Figure 3: Comparison functional capacity, oxidative stress and inflammatory profile.



Note: **A–J)** Applied paired t test. **A)** Functional capacity. **B-D)** Oxidative stress markers. **E-J)** Inflammatory profile. **A)** VO_{2max}: maximum oxygen consumption; * p = 0.01. **B)** * p = 0.02. **C)** TBARS: thiobarbituric acid reactive substances; * p = 0.001. **E)** IL-1ra: interleukin-1 receptor antagonist; p = 0.02. **F)** IL-10: interleukin-10; * p = 0.001. **G)** IL-1β: interleukin 1 beta. **H)** IL-6: interleukin 6. **I)** TNF-α: tumor necrosis factor. **J)** MCP-1: monocyte chemotactic protein-1.

Figure 4: Data from the nine domains in the quality of life pre and post training protocol.



Note: Fischer test. * p = 0.02. ** p = 0.03.

Table 1: Demographic, anthropometric and clinical data.

	Pre	**Post**	p value*
Woman/Men	4/11	-	NA
Age (years)	46.73 ± 10.04	-	NA
Weight (kg)	79.51 ± 10.79	78.46 ± 10.37	0.02
Height (m)	1.69 ± 0.08	-	NA
BMI (kg/m^2)	27.87 ± 3.45	27.47 ± 3.40	0.01
Abdominal circumference (cm)	98.87 ± 11.67	96.67 ± 12.33	0.01
Hip circumference (cm)	99.67 ± 8.91	98.67 ± 9.11	0.02
HIV diagnosis (months)	45 (8 – 182)	-	NA
Time of medication (months)	44 (6 – 180)	-	NA
CD4+Tcell (cell/mm^3)	549.33 ± 117.53	560.67 ± 116.90	0.03
Triglycerides (mg/dL)	234.07 ± 61.64	207.00 ± 56.18	0.001
Glucose (mg/dL)	115.87 ± 17.82	109.53 ± 19.61	0.001
HDL (mg/dL)	41.27 ± 5.16	42.20 ± 3.93	0.12
LDL (mg/dL)	162.80 ± 74.13	151.20 ± 72.93	0.09
Total cholesterol (mg/dL)	252.13 ± 78.12	231.67 ± 82.74	0.02

Note: Data are expressed as mean ± standard deviation or median (minimum – maximum). BMI: body mass index. *Paired t test. NA: not applied.

4. Artigo 2

Aerobic training improve the autonomic function of people living with HIV – A pilot study

Artigo a ser submetido ao periódico – *Clinical Autonomic Research*.

Clinical Autonomic Research

Aerobic training improve the autonomic function of people living with HIV – A pilot study

Candissa Silva da Silva[1,2], Luis Fernando Deresz[3], Gilson Pires da Silva[1,2], Letícia Mignoni[1], Giovana de Marchi Castelli[1], Pedro Dal Lago[1,2]

Department of Physiotherapy, Federal University of Health Sciences of Porto Alegre, Porto Alegre, Brazil

Corresponding author at: UFCSPA, Sarmento Leite, 245, CEP: 90050-170, Porto Alegre, RS, Brazil. Tel.: +55 51 3303 8796; fax: +55 51 3303 8793.

E-mail addresses: pdallago@pq.cnpq.br, pdallago@ufcspa.edu.br (P.D. Lago)

1. Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA). Porto Alegre- Brazil
2. Post-Graduation Program in Health Sciences -UFCSPA. Porto Alegre- Brazil
3. Universidade Federal de Juiz de Fora, Campus Governador Valadares. Governador Valadares – Brazil.

Abstract

Purpose – the heart rate variability (HRV) is altered in people living with HIV (PLWH). The objective of the study is to evaluate the effects of aerobic training (AT) on HRV in PLWH.

Methods – 8 PLWH participated in the 24 sessions of AT with evaluation of HRV by EndoPat. Time domain and the frequency domain data were evaluated before and after the training.

Results – when comparing pre and post training data, there was an increase in NN ($p < 0.001$), SDNN ($p < 0.001$), RMSSD ($p < 0.001$), LF ($p = 0.03$) and HF ($p = 0.02$). There were correlations between SDNN pre and post x CD4+T-cell pre and post ($p = 0.03$), SDNN x HDL pre ($p = 0.04$), SDNN x HDL post (0.03), time of diagnosis x HF (0.02) and time of medication x HF ($p = 0.01$).

Conclusions – AT may improve HRV in PLWH.

Keywords: heart rate variability; people living with HIV; aerobic training; autonomic nervous system

INTRODUCTION

The autonomic nervous system (ANS) plays a key role in cardiovascular homeostasis. ANS is often evaluated by tests based on the power of spectral analysis of heart rate variability (HRV) by the time domain and frequency domain (1, 2). Sympathetic predominance contributes to increased blood pressure and reduced arterial compliance, increased risk of acute myocardial infarction (AMI) and high mortality rates (3). Previous studies have shown that people living with HIV (PLWH) had a decrease in HRV indicating parasympathetic dysfunction (4, 5).

Associated with this, PLWH present high sedentary rates and increased risk of a cardiovascular event when compared to the general population (6, 7). Another study suggested that a sedentary lifestyle is associated with the reduction of arterial distension and negative regulation of baroreceptors (3). In addition, the presence of autonomic dysfunction (AD) in 60% of the sedentary PLWH and a positive correlation between the level of physical activity and variables of HRV (8). Another factor that contributes to a deficient autonomic profile is the immunosuppression present in PLWH (3). The objective of the present study was to evaluate the effects of aerobic training (AT) on HRV in PLWH.

METHODS

Subjects

The present pilot study was conducted with PLWH of both genders, aged 18–75 years. They were recruited from the Department of Infectious Diseases of the Santa Casa de Misericórdia de Porto Alegre, Rio Grande do Sul. The study was approved by the Ethics Committee of the Universidade Federal de Ciências da Saúde de Porto Alegre (nº 797.649/14). Prior to data collection, the patients signed an informed consent form. Inclusion criteria were: confirmed diagnosis of HIV disease, undetectable viral load (VL), both sex, aged over 18 years. Subjects with co-infection, motor abnormalities, cardiopulmonary alterations, pregnancy, use of illicit drugs, failure to adhere to treatment and cognitive and/or mental impairment that impeded application of the test were excluded from the study.

Anthropometric and Clinical Data

Body mass (kg) and height (meters). Blood glucose, total cholesterol (TC) and triglycerides, HDL, LDL, CD4+T-cell and VL data were collected from patient's medical records pre and post-training.

Cardiopulmonary Exercise Testing (CPX)

CPX was performed using an electric gradient treadmill protocol (Centurion 300, Micromed, Brazil). Started with the velocity of 3 km/h. Being the test programmed to obtain the maximum oxygen consumption (VO_{2max}) between 8 and 12 minutes with 1 minute of deceleration and 5 minutes of rest. The test was finalized when peak respiratory exchange ratio RER> 1.1 or VO_{2max} plateau was reached even with increasing workload or request of the participant (22). Ventilatory and metabolic parameters were collected by respiration using Metalyzer 3B (Cortex, Germany). The average of the last 30s data points from the test were used to determine the VO_{2peak} and HR_{max} (9). The test was applied at the beginning, after 12 training sessions, and at the end.

Heart Rate Variability (HRV)

Patients were instructed not to use stimulants, antioxidants, and non-steroidal medications for at least 12 hours prior to evaluation. The HRV response was evaluated through pulse tonometry (EndoPAT2000, Itamar Medical, Caesarea Israel). The digital pulse amplitude was measured by placing a sensor on the tip of both index fingers with the patient in the supine position. The verification of the signal for 10 minutes at the basal position. The amplitude of the pulse response was recorded electronically in both index fingers and digitally analyzed by the computerized system (Itamar Medical, Caesarea Israel). In the domain time: successive beats (NN), Standard Deviation of NN (SDNN) and Root Mean Square of the Successive Differences (RMSSD); the frequency domain Low Frequency (LF) and High Frequency (HF).

Aerobic Training (AT)

The AT occurred 3 times/week until a total of 24 sessions. Each session was composed of: 5 minutes warm-up; 30 minutes of exercise with the load determined by the CPX; 5 minutes of cool-down (10). From session 1ª – 6ª the training load was the HR corresponded to 60-65% of VO_{2max} is considered moderate/high intensity and session 7ª – 12ª the training load was the HR corresponded to 75-80% of VO_{2max} is high intensity (11). The exercise intensity was adjusted in the 13th session based on new CPX.

Statistical analysis

Statistical analysis was performed using SPSS version 18. The data that presented normal distribution were presented in mean and standard deviation and those that did not present normal distribution have a median and interquartile presentation. In data with normal distribution will be applied paired t test. Correlations will be

performed with the application of the Pearson coefficient. The level of statistical significance will be considered, $p < 0.05$.

RESULTS

Fifteen patients were eligible to participate in the study and 8 (7 men) completed the training protocol and were analyzed. The mean age was 49.50 ± 10.76 years and time of diagnosis was 82.5 (12-182) months and time of medication 82.5 (10-180) months. When the pre and post training values were compared, the following significantly reduced: weight 80.55 ± 12.53 x 78.58 ± 11.90 (p = 0.02); triglycerides 234.38 ± 62.54 x 183.63 ± 35.88 (p < 0.001); glucose 111.38 ± 12.91 x 99.50 ± 10.18 (p < 0.001); TC 217.63 ± 55.31 x 179.25 ± 27.10 (p = 0.02). Being the following variables with significant increase: CD4+T-cell 580.63 ± 121.93 x 596.88 ± 111.93 (p = 0.02); VO_{2max} 28.49 ± 8.98 x 35.30 ± 5.40 (p = 0.01). All PLWH who participated in the training had undetectable VL < 40 copies/mL.

Figure 1 shows an increase in the time domain variables: NN (p < 0.001); SDNN (p < 0.001); RMSSD (p < 0.001); and in the frequency domain LF (p = 0.03) and HF (p = 0.02) after the AT. Figure 2 shows strong correlations between time domain variables and CD4+T-cell and HDL; and frequency domain variables with time of diagnosis and time of disease.

DISCUSSION

The present pilot study was able to show that 24 sessions of AT are capable of altering the HRV in PLWH. To our knowledge, this is the first study to evaluate the chronic effects of an AT protocol on HRV in PLWH. This because many studies have been using HRV as a primary endpoint and it is being considered as a strong predictor of prognosis in the cardiology scenario through the evaluation of the ANS (12). Also, studies have shown that the reduction of HRV is indicative of impairment of vagal control and alteration of the sympatovagal balance (13).

The decrease in HRV is associated with dysfunction of cardiac markers of the ANS and high risks of ventricular arrhythmias and mortality after AMI (12). However, it is still contradictory the information on the extent to which AD is capable of affecting morbidity and mortality, mainly by alterations in cardiovascular function (3, 13, 14). However, it is already well documented in the literature classic factors that contribute to the risk of cardiovascular disease (CVD), such as lipid e glycemic alterations, decreased immunologic capacity and a sedentary lifestyle. Thus, it is known the benefits of AT in classic CVD risk factors in both healthy individuals and individuals with chronic diseases. Limberg *et al.*, found an association between HRV variables and episodes of hypoglycemia in diabetic patients, although we did not find a significant relationship between these variables, we observed improvement of both variables after the training period (13).

In the present study, in addition to an improvement in the classic CVD risk factors, we also observed a significant improvement in VO_{2max} demonstrating an improvement in PLWH functional capacity. Kocher *et al.* showed a positive correlation between VO_{2max} and time domain variables of HRV indicating that AT promotes HRV increment and showed a positive correlation between VO_{2max} and parasympathetic tone (8). Although our study did not find a strong correlation between VO_{2max} and HRV variables, probably due to the small sample size, we obtained improvement in VO_{2max} and an increase in HRV variables. Probably, our findings of improvement in HRV variables corroborate with that suggested by Spierer *et al.*, who referred to the component of improvement and increase of arterial compliance through the arterial complement and stimulation of the α-adrenergic component that decreases HR during exercise and increases baroreflex sensitivity by preserving the compliant components of the artery through aerobic practice (3).

Associated with this justification, the same study reported that a sensitive baroreflex results in responses to spontaneous changes in pressure and increased stimulation of parasympathetic nerve fibers (3). Thus, HIV improves autonomic function simply by adopting an active lifestyle (8). In addition, we found significant correlations between time domain and frequency domains with immunological match variables in PLWH. The CD4+T-cell are a primary factor to verify the immunological function and staging of the disease in PLWH. Although PLWH had an undetectable VL from the beginning of the protocol, there was a significant increase in CD4+T-cell positively correlated with SDNN both before and after termination of the protocol. Thus, a previous study suggested that dynamic two-way communication occurs between the nervous system and the immune system with a significant impact on the sympathetic nervous system (3). Spierer *et al.*, showed that the findings of parasympathetic modulation in response to improved aerobic fitness may shed light on the relationship between the autonomic profile of individuals and their immune status (3).

Askgaard *et al.*, showed a negative correlation between time domain and medication time (5). In addition, there were inverse correlations between HF and other markers of disease progression, suggesting that the longer the time of diagnosis and the time of medication, the lower the HF, probably due to the

immunological decline caused by the progression of the disease associated with the toxicity of the medications. Askgaard *et al*. suggest that hypercholesterolemia causes greater damage to SNA in HIV (5). Once that the lipid profile control in PLWH is performed in order to prevent the development of AD (5). We obtained a correlation between SDNN and HDL in both pre and post training measurements. The main limitation of our study is sample size and we do not currently have a PLWH control group.

CONCLUSIONS

It is suggested that HRV is related to immune function and the present study showed that AT is capable of improving HRV suggesting an improvement in ANS and a reduction in the influence of this system's impairment on PLWH cardiac function.

Conflict of interest

The are no relevant conflicts of interest to disclose.

Acknowledgments

This study was funded by grants from the Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS).

References

1. Rahman F, Pechnik S, Gross D, Sewell L, Goldstein DS (2011) Low frequency power of heart rate variability reflects baroreflex function, not cardiac sympathetic innervation. Clin Auton Res 21(3):133-41.

2. Liu H, Yang Z, Huang L, Qu W, Hao H, Li L (2017) Heart-rate variability indices as predictors of the response to vagus nerve stimulation in patients with drug-resistant epilepsy. Epilepsia 58(6):1015-22.

3. Spierer DK, DeMeersman RE, Kleinfeld J, McPherson E, Fullilove RE, Alba A, et al. (2007) Exercise training improves cardiovascular and autonomic profiles in HIV Clin Auton Res 17(6):341-8.

4. Lebech AM, Kristoffersen US, Mehlsen J, Wiinberg N, Petersen CL, Hesse B, et al. (2007) Autonomic dysfunction in HIV patients on antiretroviral therapy: studies of heart rate variability. Clin Physiol Funct Imaging 27(6):363-7.

5. Askgaard G, Kristoffersen US, Mehlsen J, Kronborg G, Kjaer A, Lebech AM (2011). Decreased heart rate variability in HIV positive patients receiving antiretroviral therapy: importance of blood glucose and cholesterol. PLoS One 6(5):e20196.

6. Maggi P, Bellacosa C, Leone A, Volpe A, Ricci ED, Ladisa N, et al. (2017) Cardiovascular risk in advanced naïve HIV-infected patients starting antiretroviral therapy: Comparison of three different regimens-PREVALEAT II cohort. Atherosclerosis 263: 398-404.

7. Strijdom H, De Boever P, Walzl G, Essop MF, Nawrot TS, Webster I, et al. (2017) Cardiovascular risk and endothelial function in people living with HIV/AIDS: design of the multi-site, longitudinal EndoAfrica study in the Western Cape Province of South Africa. BMC Infect Dis 17(1):41. doi: 10.1186/s12879-016-2158-y.

8. Kocher MH, Hetzler RK, Shikuma CM, Kimura IF, Stickley CD, Lindsey RA, et al. (2015) Autonomic function is associated with fitness level in HIV-infected individuals. Jacobs J AIDS/HIV 1(1). pii: 005.

9. Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher GF, et al. (2010) Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. Circulation 122(2):191-225.

10. Hand GA, Phillips KD, Dudgeon WD, William Lyerly G, Larry Durstine J, Burgess SE (2008) Moderate intensity exercise training reverses functional aerobic impairment in HIV-infected individuals. AIDS care 20(9):1066-74.

11. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee I-M, et al. (2011) Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc 43(7):1334-59.

12. Nenna A, Lusini M, Spadaccio C, Nappi F, Greco SM, Barbato R, et al. Heart rate variability: a new tool to predict complications in adult cardiac surgery (2017). J Geriatr Cardiol 14(11):662-68.

13. Limberg JK, Dube S, Kuijpers M, Farni KE, Basu A, Rizza RA, et al. (2015) Effect of hypoxia on heart rate variability and baroreflex sensitivity during hypoglycemia in type 1 diabetes mellitus. Clin Auton Res 25(4):243-50.

14. Shiraishi Y, Katsumata Y, Sadahiro T, Azuma K, Akita K, Isobe S, et al. (2018) Real-Time Analysis of the Heart Rate Variability During Incremental Exercise for the Detection of the Ventilatory Threshold. J Am Heart Assoc 7(1). pii: e006612. doi: 10.1161/JAHA.117.006612.

Figure 1: Heart rate variability pre and post aerobic training.

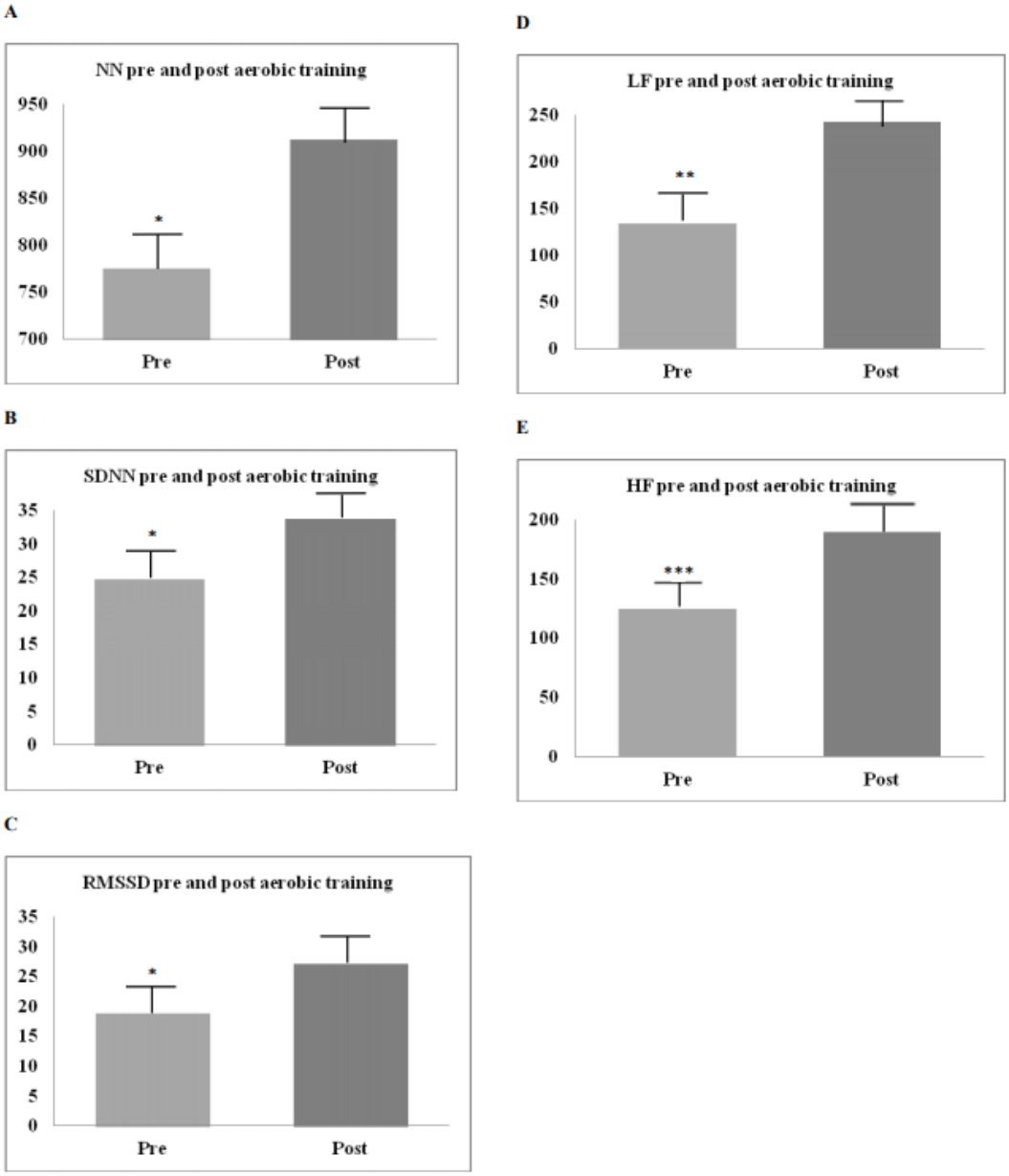


Fig 1: For all groups (mean ± SD). *(A)* Standard deviation of all NN intervals (NN). *(B)* Standart deviation of the RR intervals (SDNN). *(C)* Squares of the differences between adjacent RR intervals (RMSSD). *(D)* Low frequency (LF). *(E)* High frequency (HF). For all groups applied paired t test. * $p < 0.001$. ** $p = 0.03$. *** $p = 0.02$.

Figure 2: Correlation of HRV with clinical parameters.

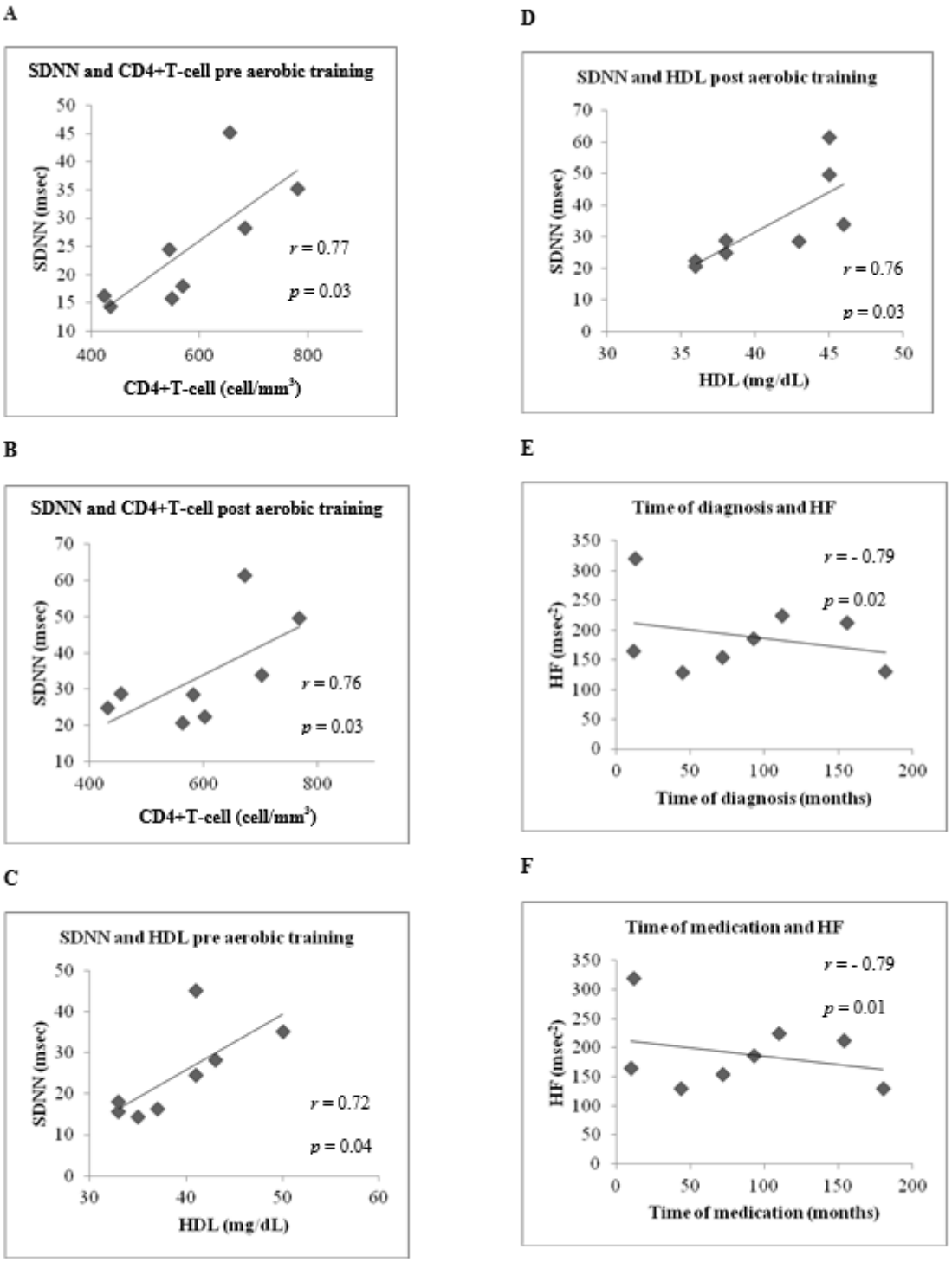


Fig 2: Heart rate variability (HRV). *(A, B, C)* Standart derivation of the RR intervals (SDNN). *(E,F)* High frequency (HF). For all groups applied correlations of the Pearson coefficient.

5. Artigo 3

Presence of cardiovascular risk despite control of disease among men and women with HIV using antiretroviral therapy - a cross-sectional study

Artigo a ser submetido ao periódico – Arquivos Brasileiros de Cardiologia*.

* Para facilitar a leitura, as legendas foram colocadas juntamente às figuras.

Presence of cardiovascular risk despite control of disease among men and women with HIV using antiretroviral therapy - a cross-sectional study

Running Title: Cardiovascular risk in PLWH

Risco cardiovascular entre homens e mulheres vivendo com HIV em uso de terapia antirretroviral e com controle da doença – estudo transversal*

Título Resumido: Risco cardiovascular em PVHA

Keywords: HIV. Cardiovascular disease. ARV. Endothelial function.

Palavas-chave: HIV. Doença cardiovascular. ARV. Função endotelial.

*Autores: Candissa Silva da Silva, Luis Fernando Deresz, Gilson Pires da Silva, Letícia Mignoni, Giovana de Marchi Castelli, Alessandra Peres, Pedro Dal Lago.

Abstract

Introduction: People living with HIV (PLWH) present high cardiovascular risk even with suppression of viral load.

Objective: The aim of this study is to assess the cardiovascular risk between men and women living with HIV taking antiretroviral therapy.

Methods: The cross-sectional study included sixteen PLWH with 11 men and 5 women. Cardiovascular risk variables were evaluated through anthropometric measurements, functional capacity (VO_{2max}), metabolic syndrome (MS), endothelial function (EndoPAT), lipid and glycemic profile, oxidative stress (nitrite, TBARS and thiol), inflammatory profile (TNF-α, MCP-1, IL-1β, IL-1ra, IL-6, IL-10) and score of Framingham.

Results: All women and 55% of men evaluated had endothelial dysfunction. In addition, 80% of the women had MS. In both women and men, have high in lipid profile, for women: triglycerides (226.20 ± 83.87); LDL (183.40 ± 99.77); total cholesterol (TC) (271.40 ± 109.84) and men triglycerides (231.27 ± 54.39); LDL (151.73 ± 58.31); TC (240.64 ± 58.97). It was obtained a strong correlation IL-1ra and abdominal circumference of all subjects ($p = 0.02$) and men ($p < 0.001$); in women MCP-1 and LDL ($p = 0.04$); IL-6 and VO_{2max} ($p = 0.01$). In addition to strong correlations among women with oxidative stress markers such as TBARS and glucose ($p = 0.04$); thiol and CD_4 T-cell ($p = 0.04$). The variables that are correlated among men were nitrite and age ($p < 0.001$). Further, women present higher Framingham score when compared to men.

Conclusions: Despite undetectable viral load, PLWH present altered variables that contribute to a high cardiovascular risk.

Introduction

With the advent of antiretroviral therapy (ART), people living with HIV (PLWH) have control of the disease with decreased viral replication, number of hospitalizations and reduction of mortality rates (1, 2). However, there is a growing number of PLWH that present high mortality rates due to cardiovascular disease (CVD) (1-4). This increase in CVD is due not only to traditional factors, such as age, genetic and family history, but also HIV infection itself and the use of ART (3, 5, 6). Therefore, many studies with PLWH have been using the Framingham score to assess cardiovascular risk in 10 years (7-9). Studies have shown an increased risk of acute myocardial infarction (AMI) in PLWH regardless of these factors when compared to healthy subjects (5, 10). Thus, the cohort study showed an increased relative risk of AMI of 1.75 compared to PLWH with healthy subjects after adjustments of traditional risk factors (10). In addition, it has been suggested that HIV infection increases the absolute risk of CVD by around 1.2 to 2-fold (5).

Among the main changes that contribute to this increase in cardiovascular risk are: increased body fat levels, dyslipidemia, insulin resistance, inflammatory markers, oxidative stress, metabolic syndrome (MS), formation of atherosclerosis and sedentary lifestyle (2, 3, 6, 11-13). In addition, there is influence of specific factors such as age and others linked to sex, such as hormones and immune responsiveness (6, 7, 14).

Moreover, there were independent association of oxidative stress and death in PLWH, independent of disease-related factors such as CD_4 T-cell, viral load (VL), and inflammation (15). Moreover, oxidative stress may play an important role in the development of the asymptomatic phase of the disease in stages prior to the development of Acquired Immunodeficiency Syndrome (AIDS) (16). Combined with this, inflammatory biomarkers associated with chronic inflammation are also correlated with morbidity and mortality in PLWH and are related with CVD (17-19). The primary aim of this study was to evaluate

cardiovascular risk factors in PLWH in ART use and, secondly, to correlate risk factors for cardiovascular disease among PLWH women and men in ART use.

Methods

Setting

The present cross-section study was conducted with 16 PLWH of both genders, aged 18–75 years. They were recruited from the Department of Infectious Diseases of the Irmandade da Santa Casa de Misericórdia de Porto Alegre (ISCMPA), Rio Grande do Sul in the period from March 2015 to December 2017. The study was approved by the Ethics Committee of the Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA) (nº 797.649/14). Before data collection, the patients signed an informed consent form.

Participants

Inclusion criteria were: confirmed diagnosis of HIV disease in men and women, undetectable VL (< 40 copies/mL) and aged over 18 years. Subjects with co-infection, motor abnormalities, cardiopulmonary alterations, pregnancy, use of illicit drugs, failure to adhere to the treatment, severe anaemia, and cognitive and/or mental impairment that impeded application of the test were excluded from the study.

Evaluation protocols

Anthropometric Data

A qualified professional performed all anthropometric evaluations, collecting three times all measures, and the mean was used for analysis. Body mass (kg) and height (meters) were determined by a semi-analytical scale (Welmy, Santa Barbara D'Oeste, Brazil), with capacity for 200 kg and a stadiometer attached (Welmy, Santa Barbara D'Oeste, Brazil) with an accuracy of 0.1 kg and 0.005 cm, respectively. To measure the abdominal circumference (AC), an inelastic tape was used at the midpoint between the iliac crest and the outer face of the last rib. The hip circumference (HC) was measured at the level of the upper anterior iliac spine (20).

Laboratory Tests

Were collected by a trained investigator 10 ml of blood, subsequently transferred to a tube containing heparin (6 mL). The samples were centrifuged (1500g, 10 minutes, 22°C), aliquoted and frozen at -20°C for further analysis.

The Nitrite/Nitrate (NOx) concentrations were analyzed according to the technique described by the study Miranda *et al.* (21) and analyzed on a microplate reader (SpectraMax M2e, USA) with the specified wavelength at 540 nm, and the results were expressed as μM/L. Thiobarbituric acid reactive substances (TBARS) concentrations were analyzed following a technique previously described by Ohkawa *et al.* (22). Samples were analyzed on a microplate reader at 532 nm, and the results were expressed as μM MDA/L. Total thiols were analyzed according to the methodology described by Ellman *et al.* (23) using the reagent 5-5'-dithio-bis (2-nitrobenzoic acid).

Serum concentrations of Interleukin-1β (IL-1β), IL-1ra, IL-6 and IL-10, Monocyte Chemoattractant Protein-1 (MCP-1), TNF-α (Ebioscience, Thermo Fisher Scientific, USA) were quantified by enzyme-linked immuno sorbent assay (ELISA) following the manufacturer's recommendations. The intra-assay coefficient of variation was always <5%.

The blood glucose, total cholesterol (TC), triglycerides, HDL, LDL, CD_4 T-cell and VL data were collected from patient's medical records. The MS was defined following National Cholesterol Education Program Adult Treatment Panel Definition (24). To calculate the Framingham score, we used age, TC, HDL, systolic blood pressure values, diabetes (> 126 mg/dL) and smoking data (13, 25).

Cardiopulmonary exercise test (CPX)

In the laboratory with temperature control (18-22ºC) and relative humidity (40-60%) was performed the CPX using an electric gradient treadmill protocol (Centurion 300, Micromed, Brazil). For all participants, the test started with a speed of 3 km/h and no

inclination. The load test was designed to obtain VO_{2peak} within 8 to 12 minutes, followed by 1 minute of active recovery (speed and incline similar to the initial test data) and 5 minutes of passive recovery. The speed and slope gradually increased according to the maximum limit tolerated by the participant. The test was terminated when the participant reported maximal exhaustion; VO_2 plateau was reached even with increasing workload (22). The Metalyzer 3B (Cortex, Germany) was used to measure the ventilatory and metabolic parameters. The average of the last 30 seconds of the test were used to determine the VO_{2peak} and HR_{max} (26).

Endothelial Function

Patients were instructed not to use caffeine, tobacco, alcohol, antioxidants, and non-steroidal medications for at least 12 hours before evaluation. The endothelial function response was evaluated through pulse tonometry with the participant in the supine position (EndoPAT2000, Itamar Medical, Caesarea Israel). The digital pulse amplitude was measured by placing a sensor on the tip of both index fingers. After verification of the signal for 10 minutes at the basal position, the flow was stopped for a period of five minutes by insufflating a cuff (50 mmHg above diastolic blood pressure (DBP) or above 200 mmHg) positioned on the forearm, following the pressure release of the cuff occurred an increase in the flow inducing the reactive hyperaemia (27). The amplitude of the pulse response was recorded electronically in both index fingers and digitally analyzed by a computerized system (Itamar Medical). The degree of arterial tone changes in response to ischemia was expressed as reactive hyperemia index (RHI), the normal endothelial function was defined as RHI > 1.67 (27).

Statistical analysis

Statistical analysis was performed using SPSS statistics software version 18. The Shapiro-Wilk test was applied to verify the normality of the data. Data with normal distribution is shown in mean and standard deviation and those that did not present normal

distribution appear as a median and interquartile, with the corresponding frequencies when necessary. In data with normal distribution was applied independent t-test. For the difference between frequencies was used the Fischer test and Chi-square test. Correlations were performed with the application of the Pearson coefficient. The level of statistical significance considered is $p < 0.05$.

Results

Two hundred and ten PLWH were selected for evaluation (fig. 1). We screened a total of 16 PLWH. Of these, 11 (69%) were men. All PLWH had undetectable VL and were not smokers. The PLWH were treated with the following drug regimens: 2 nucleoside reverse transcriptase inhibitors (NRTIs) associated with a 1 inhibitor of non-nucleoside reverse transcriptase (NNRTI) drug (n = 9; 7 men); 2 NRTIs + 1 inhibitor protease (IP) (n = 4; 2 men) and 3 NRTIs + 1 IP (n = 3; 2 men). Of the total number of patients evaluated, 11 (69%) had abnormal endothelial function (RHI < 1.67), 6 (55%) men and 4 women (100%), being that 1 participant women did not perform the endothelial function test.

Table 1 shows demographic, anthropometric and clinical data of PLWH. When observed the separation by sex, we detected differences between the variables in weight ($p = 0.02$); height ($p = 0.02$); time of diagnosis ($p = 0.01$) and time of medication ($p = 0.03$). We observed that most PLWH have MS, especially women (80%). Table 2 presents data of inflammatory markers and oxidative stress with statistical significance between the sex in the TBARS ($p = 0.04$).

The correlations are shown in figure 2. We showed strong correlations between inflammatory markers such as IL-1ra and abdominal circumference of all subjects ($p = 0.02$) and men ($p < 0.001$); in women MCP-1 with LDL ($p = 0.04$); IL-6 and functional capacity ($p = 0.01$). In addition to strong correlations among women with oxidative stress markers such as TBARS and glucose ($p = 0.04$); thiol and CD4 T-cell ($p = 0.04$). The variables that are correlated among men were nitrite and age ($p < 0.001$).

Table 3 showed the cardiovascular risk in 10 years according to the Framingham score, showing that women present higher cardiovascular risk.

Discussion

This cross-sectional study carried out with PLWH presents cardiovascular risk variables between men and women that demonstrate control of the disease evolution and, consequently, undetectable VL. These variables were based on different modalities that contribute to increase cardiovascular risk, such as sex, lipid and glucose profile, immunological variables, inflammatory markers, oxidative stress, functional capacity and endothelial function.

Our study had among the participants preponderance of men (69%). Although 51% of PLWH in the world are women, the majority of studies evaluating cardiovascular risk in PLWH were performed with men (3, 5, 9, 14, 15, 28-30). Previous studies have shown that regardless of sex, suppression of VL reduces cardiovascular risk (4, 28). However, it has already been shown that risk of CVD remains increased in PLWH with undetectable viral load when compared to healthy subjects (12). Probably because the traditional risk factors for CVD increase with the time of ART exposure (8). In addition, none of the participants in the present study were smokers, which favors the reduction of cardiovascular risk (5). Furthermore, all participants had an undetectable VL. According Law *et al*., when evaluating the Framingham score, nonsmoking patients presented a 4.1% risk of AMI when compared to a 9% risk of AMI smokers (8). The majority of participants in our study had abnormal endothelial function, especially among women (100%). This result probably reflects the fact that the women in our study had a lower CD4 T-cell and increased variables that influence endothelial function, described in other studies such as glucose, LDL, TC and MS, besides the age close to pre menopause period (1, 28).

This study showed high TC in both men and women, which may be related to the drug regimen. Whereas been shown that the increase in TC is associated with the use of PI and NNRTI classes of drugs, widely present in the therapeutic regimen of our patients (31). In

addition, our study presents the majority of participants with MS, 80% of the women and 63.6% of the men. These findings corroborate Muyahja *et al.,* where the majority of the participants had MS apart of age and gender factors, however, they showed that women had a higher risk for CVD (29). The lipid alterations presented in our study in both sex may be linked to hepatic alterations, oxidative stress and toxicity of ART (mainly caused by PIs in LDL binding), beyond genetic factors (3).

Other factors that contribute to increased cardiovascular risk are inflammatory markers and oxidative stress that are altered in PLWH, probably due to chronic infection caused by HIV (15, 28-30). Despite the influence of ART on oxidative stress, it has already been suggested that oxidative stress is an additional predictor of mortality regardless of HIV-related factors such as CD4 T-cell, VL and inflammatory markers (15). Although all the PLWH of the present study have suppressed VL, oxidative stress remains altered and may contribute to the cardiovascular risk. When we observed the correlations, we found a negative association between nitrite and age among men, which may be the cause of impairment in endothelial function, due to the decrease of nitrite with aging.

Furthermore, the assessment and control of inflammatory profile in PLWH becomes important, as it has already been verified that HIV influences the inflammatory process and increases the risk of CVD (19, 30). Our study shows a deregulation between inflammatory and pro-inflammatory markers. In women, elevation of TNF-α and IL-6 may be related to the reduction of estrogen with the advent of age and proximity to menopause period (30). However, in men, despite elevated inflammatory markers, Manion *et al*., suggested that a more coordinated response of these markers occurs (19). Although VO_{2max} is higher in men as expected, it is strongly correlated with IL-6 in women, probably because of the influence of age among these variables (30).

The higher cardiovascular risk in women in the Framingham score corroborates findings from studies suggesting increased cardiovascular risk in women even after adjustments of non-HIV related variables (9, 28). Probably, due to hormonal changes (30, 31). However, some studies inquiry these findings and report a higher cardiovascular risk in men (7, 8). In addition, our study presented only 2 PLHA (1 woman, 1 men) with a high cardiovascular risk with a Framingham score > 10. These data corroborate the multicentric study carried out in Brazil that showed that only 4.5% of PLHA in southern Brazil had a Framingham score ≥ 10 (9).

Nevertheless, there are several questions between not taking into account female-related factors that influence cardiovascular variables such as gestation, menopause, hormone count and contraceptives (1). But, although several studies use the Framingham score for cardiovascular risk assessment in PLWH, there is a great controversy about the validity of these findings since this evaluation methodology does not take into account pathophysiological mechanisms that increase cardiovascular risk and are related to HIV (28, 30). In addition, it was suggested that this score underestimates the risk of AMI in PLWH and, showing a specific score for PLWH (7, 8).

The present study presents as a strong limitation the size of the sample, mainly among women, not presenting a control group of healthy subjects paired by age to control the variables and we did not control the hormonal variables, mainly estrogen. Furthermore, the inclusion criteria imposed for realization the tests (subjects with co-infection, motor abnormalities, cardiopulmonary alterations, pregnancy, use of illicit drugs, failure to adhere to treatment, severe anaemia, and cognitive and/or mental) may limit the external validity of the sample. However, there are confounding factors for cardiovascular risk: coinfections, use of illicit drugs, lack of adherence to treatment and cardiovascular problem prior to the diagnosis of HIV. Already the other exclusion factors, could cause PLWH safety at risk mainly during

the CPX. However, we conclude that despite the control of viral replication, PLWHA present high cardiovascular risk factors with a difference between men and women, but in common with increasing age.

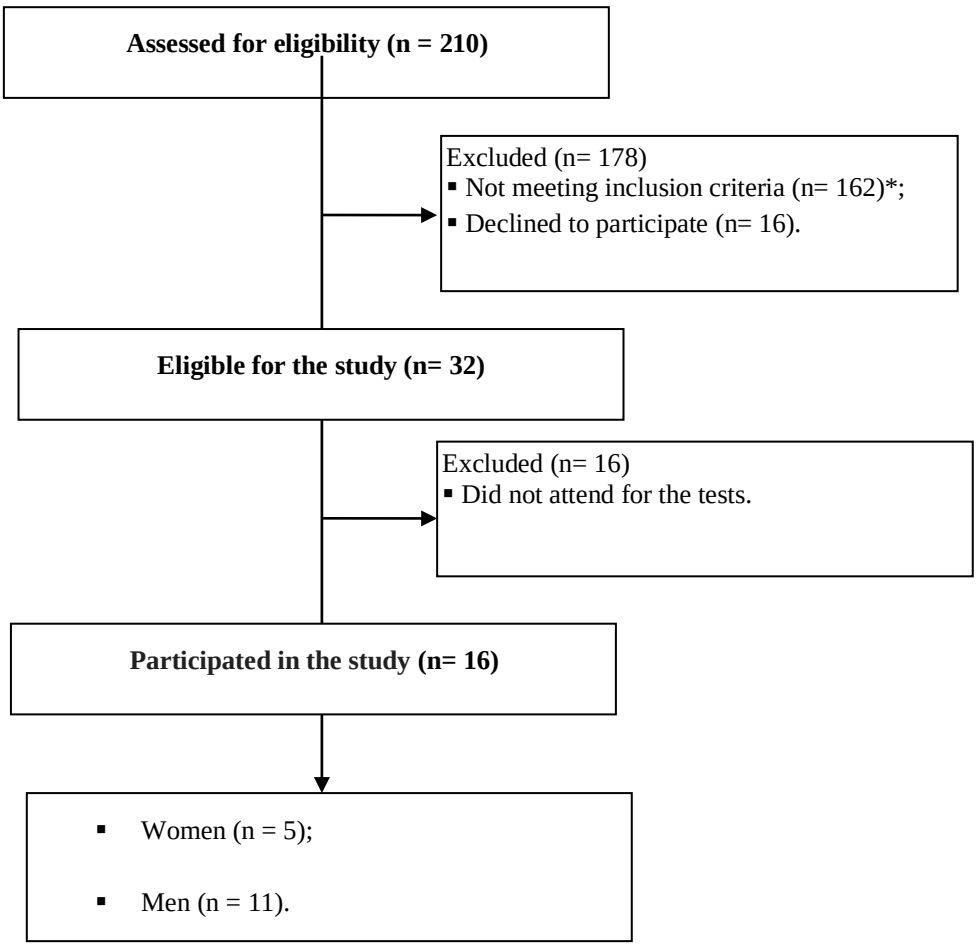
Conflict of interest

All authors: no conflicts.

Acknowledgments

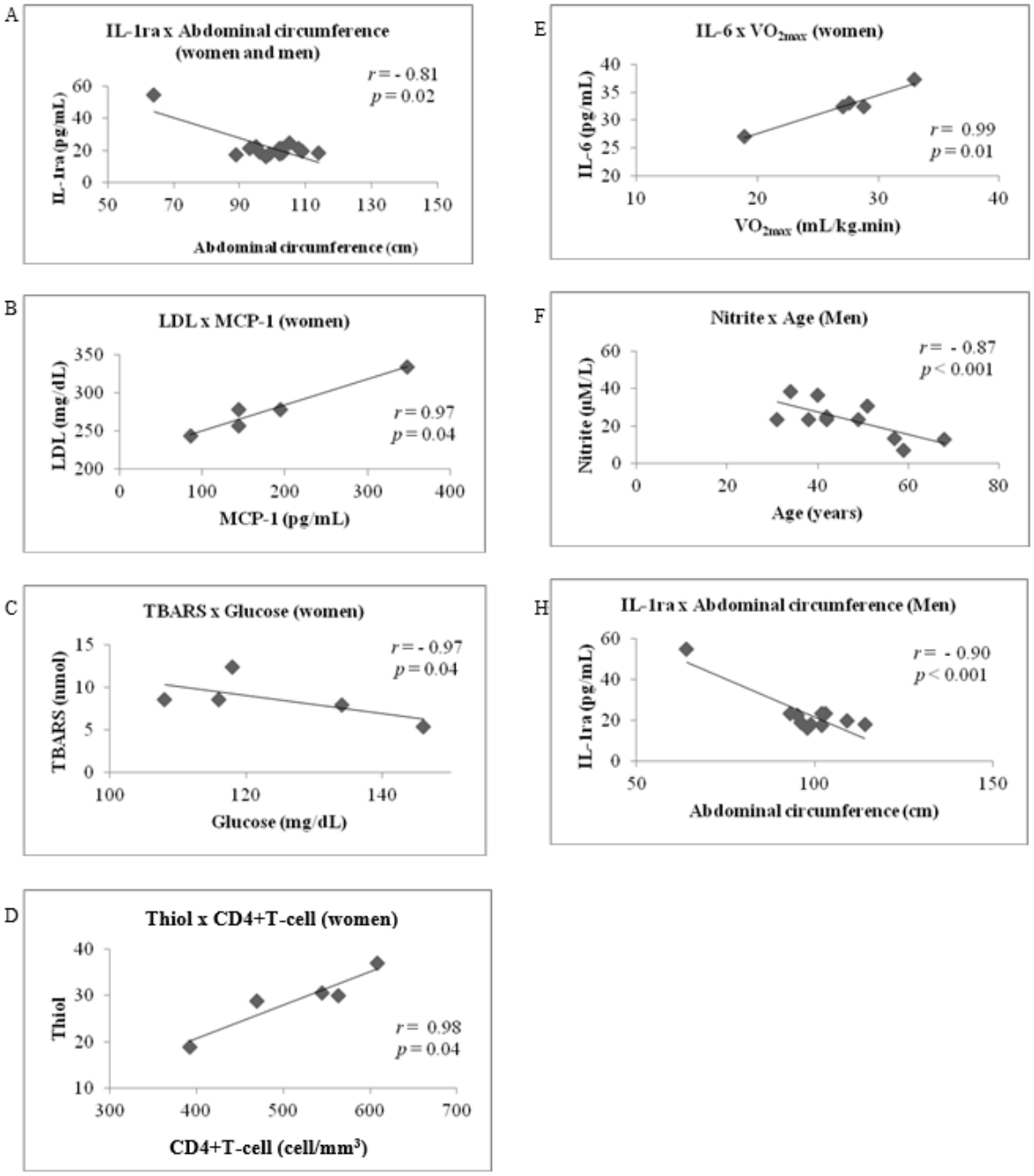
This study was funded by grants from the Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS).

Figure 1: Flow diagram of the patients.



*Co-infection with hepatitis C virus (n=86), hepatitis B virus (n=7), diagnosed with psychological disorders (n=6), cardiac abnormalities (n=6), adherence to therapy (n=6), human T-lymphotropic virus (n=5), motor changes (n=5), pregnancy (n=3), Chagas disease (n=2), cognitive impairment (n=2), severe anemia (n=2) illicit drug use (n=1),visually impaired (n=1) and 30 people living with HIV had 2 or more of these associated changes.

Figure 2: Correlations between inflammatory profile, oxidative stress and clinical variables.



Note: A and G) IL-1ra: interleukin-1 receptor antagonist. B) MCP-1: monocyte chemotactic protein-1. C) TBARS: thiobarbituric acid reactive substances. E) IL-6: interleukin 6. VO_{2max}: maximum oxygen consumption. A, B, C, D, E, F, and G was applied correlations of the Pearson coefficient.

Table 1: Demographic, anthropometric and clinical data.

	Woman (n = 5)	**Men** (n = 11)	p value*
Age (years)	45.0 ± 7.52	46.45 ± 11.43	0.38
Weight (kg)	69.76 ± 8.04	82.02 ± 11.30	0.02
Height (m)	1.61 ± 0.08	1.72 ± 0.06	0.02
BMI (kg/m^2)	26.85 ± 3.84	27.71 ± 3.87	0.34
Abdominal circumference (cm)	102.40 ± 7.73	97.73 ± 12.76	0.19
Hip circumference (cm)	101.80 ± 7.92	98.27 ± 9.13	0.23
HIV diagnosis (months)	14 (12 – 156)	70 (8 – 176)	0.01†
Time of medication (months)	14 (10 – 105)	70 (6 – 176)	0.03†
CD4+T-cell (cell/mm^3)	515.28 ± 85.20	554.27 ± 125.50	0.48
Triglycerides (mg/dL)	226.20 ± 83.87	231.27 ± 54.39	0.91
Glucose (mg/dL)	124.40 ± 15.32	114.18 ± 14.69	0.25
HDL (mg/dL)	42.60 ± 3.29	41.0 ± 5.78	0.50
LDL (mg/dL)	183.40 ± 99.77	151.73 ± 58.31	0.54
Total cholesterol (mg/dL)	271.40 ± 109.84	240.64 ± 58.97	0.58
MS	4 (80%)	7 (63.6%)	0.42‡
VO_{2max} [ml/(kg.min)]	27.07 ± 5.13	29.84 ± 8.76	0.44

Note: Data are expressed as mean ± standard deviation or median (minimum – maximum). BMI: body mass index. MS: metabolic syndrome. VO_{2max}: maximum oxygen consumption. *Unpaired t test. †Wilcoxon test. ‡Chi-square test.

***Table 2**:* Data of inflammatory markers and oxidative stress.

	Woman (n = 5)	**Men** (n = 11)	p value*
Nitrite (µM/L)	15.62 ± 7.73	23.41 ± 11.62	0.25
TBARS (nmol)	8.55 ± 3.54	16.89 ± 5.57	0.04
Thiol	28.8 ± 9.27	18.61 ± 12.71	0.20
TNF-α	53.5 ± 6.14	57.70 ± 10.90	0.45
MCP-1 (pg/mL)	278.16 ± 49.32	342.59 ± 169.04	0.36
IL-1β (pg/mL)	21.36 ± 2.42	29.43 ± 19.85	0.29
IL-1ra (pg/mL)	20.10 ± 3.89	23.24 ± 12.92	0.54
IL-6 (pg/mL)	32.49 ± 5.19	32.99 ± 9.43	0.91
IL-10 (pg/mL)	19.05 ± 5.19	16.89 ± 6.14	0.46

Note: Data are expressed as mean ± standard deviation. TBARS: thiobarbituric acid reactive substances TNF-α: tumor necrosis factor. MCP-1: monocyte chemotactic protein-1. IL-1β: interleukin 1 beta. IL-1ra: interleukin-1 receptor antagonist. IL-6: interleukin 6. IL-10: interleukin 10. *Independent t test.

Table 3: Cardiovascular risk by the Framingham score.

Woman	Framingham score
1	2
2	3
3	32
4	6
5	2
Men	
1	11
2	7
3	3
4	3
5	3
6	7
7	5
8	7
9	8
10	7
11	2

References

1 Hatleberg CI, Ryom L, EL-Sadr W, Mocroft A, Reiss P, De Wit S, et al. Gender differences in the use of cardiovascular interventions in HIV-positive persons; the D: A: D Study. J Int AIDS Soc. 2018;21(3). doi: 10.1002/jia2.25083.

2 Maggi P, Bellacosa C, Leone A, Volpe A, Ricci ED, Ladisa N, et al. Cardiovascular risk in advanced naïve HIV-infected patients starting antiretroviral therapy: Comparison of three different regimens-PREVALEAT II cohort. Atherosclerosis. 2017; 263:398-404.

3 Baker JV, Sharma S, Achra AC, Bernardino JI, Bogner JR, Duprez D, et al. Changes in Cardiovascular Disease Risk Factors With Immediate Versus Deferred Antiretroviral Therapy Initiation Among HIV-Positive Participants in the START (Strategic Timing of Antiretroviral Treatment) Trial. J Am Heart Assoc. 2017;26(5): pii: e004987. doi: 10.1161/JAHA.116.004987.

4 Mosepele M, Hemphill LC, Palai T, Nkele I, Bennett K, Lockman S, et al. Cardiovascular disease risk prediction by the American College of Cardiology (ACC)/American Heart Association (AHA) Atherosclerotic Cardiovascular Disease (ASCVD) risk score among HIV-infected patients in sub-Saharan Africa. PloS One. 2017; 12(2):e0172897. doi: 10.1371/journal.pone.0172897. eCollection 2017.

5 Petoumenos K, Reiss P, Ryom L, Rickenbach M, Sabin C, El-Sadr W, et al. Increased risk of cardiovascular disease (CVD) with age in HIV-positive men: a comparison of the D: A: D CVD risk equation and general population CVD risk equations. HIV Med. 2014;15(10):595-603.

6 Currier JS, Lundgren JD, Carr A, Klein D, Sabin CA, Sax PE, et al. Epidemiological evidence for cardiovascular disease in HIV-infected patients and relationship to highly active antiretroviral therapy. Circulation. 2008; 118(2):e29-e35.

7 Kaplan RC, Kingsley LA, Sharrett AR, Li X, Lazar J, Tien PC, et al. Ten-year predicted coronary heart disease risk in HIV-infected men and women. Clin Infec Dis. 2007;45(8):1074-81.

8 Law M, Friis-Møller N, El-Sadr W, Weber R, Reiss P, D'Arminio Monforte A, et al. The use of the Framingham equation to predict myocardial infarctions in HIV-infected patients: comparison with observed events in the D: A: D Study. HIV Med. 2006;7(4):218-30.

9 Fuchs SC, Alencastro PR, Ikeda MLR, Barcellos NT, Wolff FH, Brandão A, et al. Risk of coronary heart disease among HIV-infected patients: a multicenter study in Brazil.

Scientific World Journal. 2013; 2013:163418. doi:10.1155/2013/163418. eCollection 2013.

10 Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. J Clin Endocrinol Metab. 2007;92(7):2506-12.

11 Dubé MP, Shen C, Mather KJ, Waltz J, Greenwald M, Gupta SK. Relationship of body composition, metabolic status, antiretroviral use, and HIV disease factors to endothelial dysfunction in HIV-infected subjects. AIDS Res Hum Retroviruses. 2010;26(8):847-54.

12 Phan BAP, Weigel B, Ma Y, Scherzer R, Li D, Hur S, et al. Utility of 2013 American College of Cardiology/American Heart Association Cholesterol Guidelines in HIV-Infected Adults With Carotid Atherosclerosis. Cir Cardiovasc Imaging. 2017; 10(7). pii: e005995. doi: 10.1161/CIRCIMAGING.116.005995.

13 Ngu RC, Choukem S-P, Dimala CA, Ngu JN, Monekosso GL. Prevalence and determinants of selected cardio-metabolic risk factors among people living with HIV/AIDS and receiving care in the South West Regional Hospitals of Cameroon: a cross-sectional study. BMC Res Notes. 2018; 11(1):305. doi: 10.1186/s13104-018-3444-0.

14 Zanni MV, Fitch K, Rivard C, Sanchez L, Douglas PS, Grinspoon S, et al. Follow YOUR Heart: development of an evidence-based campaign empowering older women with HIV to participate in a large-scale cardiovascular disease prevention trial. HIV Clinical Trials. 2017;18(2):83-91.

15 Masiá M, Padilla S, Fernández M, Rodríguez C, Moreno A, Oteo JA, et al. Oxidative stress predicts All-Cause mortality in HIV-Infected patients. PloS One. 2016;11(4): e0153456. doi: 10.1371/journal.pone.0153456. eCollection 2016.

16 Sharma B. Oxidative stress in HIV patients receiving antiretroviral therapy. Curr HIV Res. 2014;12(1):13-21.

17 Sinha A, Ma Y, Scherzer R, Hur S, Li D, Ganz P, et al. Role of T-Cell Dysfunction, Inflammation, and Coagulation in Microvascular Disease in HIV. J Am Heart Assoc. 2016;5(12): pii: e004243. doi: 10.1161/JAHA.116.004243.

18 Nordell AD, Mckenna M, Borges ÁH, Duprez D, Neuhaus J, Neaton JD. Severity of cardiovascular disease outcomes among patients with HIV is related to markers of inflammation and coagulation. J Am Heart Assoc. 2014;3(3):e000844. doi: 10.1161/JAHA.114.000844.

19 Manion M, Andrade BB, Dersimonian R, Gu W, Rupert A, Musselwhite LW, et al. Country of residence is associated with distinct inflammatory biomarker signatures in HIV-infected patients. J Virus Erad. 2017:24-33.
20 Romancini JLH, Guariglia D, Nardo Jr N, Herold P, Pimentel GGdA, Pupulin ÁRT. Levels of physical activity and metabolic alterations in people living with HIV/AIDS. Rev Bras Med Esp. 2012;18(6):356-60.
21 Miranda KM, Espey MG, Wink DA. A rapid, simple spectrophotometric method for simultaneous detection of nitrate and nitrite. Nitric oxide. 2001;5(1):62-71.
22 Ohkawa H, Ohishi N, Yagi K. Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. Anal Biochem. 1979;95(2):351-8.
23 Ellman GL. Tissue sulfhydryl groups. Arch Biochem Biophys. 1959;82(1):70-7.
24 Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation. 2005;112(17):2735-52.
25 Kannel WB, Abbott RD. Incidence and prognosis of unrecognized myocardial infarction: an update on the Framingham study. N Engl J Med. 1984;311(18):1144-7.
26 Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher GF, et al. Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. Circulation. 2010;122(2):191-225.
27 Balsam P, Mikuła T, Peller M, Suchacz M, Puchalski B, Kołtowski Ł, et al. Evaluation of endothelial function and arterial stiffness in HIV-infected patients: a pilot study. Kardiol Pol. 2015;73(5):344-51.
28 Womack JA, Chang C-Ch, So-Armah KA, Alcorn C, Baker JV, Brown ST, et al. HIV infection and cardiovascular disease in women. J Am Heart Assoc. 2014;3(5): e001035. doi: 10.1161/JAHA.114.001035.
29 Muyanja D, Muzoora C, Muyingo A, Muyindike W, Siedner MJ. High prevalence of metabolic syndrome and cardiovascular disease risk among people with HIV on stable ART in Southwestern Uganda. AIDS Patient Care STDS. 2016;30(1):4-10.
30 Cortés YI, Reame N, Zeana C, Jia H, Ferris DC, Shane E, et al. Cardiovascular risk in HIV-infected and uninfected postmenopausal minority women: use of the framingham risk score. J Women's Health. 2017;26(3):241-8.

31 Glass T, Ungsedhapand C, Wolbers M, Weber R, Vernazza P, Rickenbach M, et al. Prevalence of risk factors for cardiovascular disease in HIV-infected patients over time: the Swiss HIV Cohort Study. HIV Med. 2006;7(6):404-10.

6. Conclusões

Os artigos provenientes da presente tese foram elaborados com objetivo de identificar os fatores de risco cardiovascular, VFC e a qualidade de vida em PVHA e verificar os efeitos do treinamento aeróbio nessas variáveis.

O artigo 1 foi planejado com a finalidade de verificar o efeito do treinamento aeróbio, realizado em moderada e alta intensidade, na capacidade funcional, fatores de risco cardiovascular, estresse oxidativo, perfil inflamatório e qualidade de vida em PVHA. Os resultados encontrados indicaram melhora na capacidade funcional, redução de medidas antropométricas como massa corporal, circunferência abdominal, circunferência do quadril, redução de marcadores lipídicos e glicêmicos, modulação de marcadores de estresse oxidativo e de perfil inflamatórios, além de melhora nos escores de qualidade de vida. Somados a isso, apresentaram influência na função endotelial e no aumento da contagem de linfócitos T CD4+. O referido estudo mostrou que o exercício aeróbio de moderada e alta intensidade pode ser um recurso seguro no tratamento não medicamentoso para a redução de fatores de risco cardiovascular e melhora da qualidade de vida em PVHA.

O artigo 2 foi desenvolvido para testar a hipótese de que o treinamento aeróbio crônico é capaz de melhorar a VFC, tanto no domínio do tempo quanto no domínio da frequência em PVHA. O estudo mostrou que após 24 sessões de treinamento aeróbio, PVHA apresentaram aumento nas variáveis de domínio do tempo: NN, SDNN e RMSSD e, no domínio da frequência: LF e HF. Porém, não existem valores de referência para esses domínios em PVHA. Além disso, a pesquisa apresentou fortes correlações de alguns domínios da VFC com variáveis relacionadas ao tempo de infecção com HIV e perfil lipídico. Assim, o estudo sugeriu que o treinamento aeróbio, através da melhora da VFC, pode influenciar a melhorar do SNA em PVHA. No entanto, por se tratar de um estudo piloto, existe como limitação o reduzido tamanho amostral. Recomendamos que esse protocolo seja mantido e novos pacientes sejam incluídos para uma avaliação mais detalhada dessas variáveis.

O artigo 3 apresentou a avaliação do risco cardiovascular entre homens e mulheres vivendo com HIV. A pesquisa mostrou que PVHA com adesão à TARV e carga viral indetectável, apresentam risco cardiovascular. O presente estudo avaliou diferentes variáveis, sendo possível realizar correlações entre os fatores de risco cardiovascular, além de apresentar essas associações ligadas ao sexo. Através

disso, podemos verificar que mesmo com o controle da replicação viral, existe presença de risco cardiovascular com algumas diferenças entre mulheres e homens e que mulheres apresentam risco mais elevado através do escore de Framingham quando comparado aos homens.

Associados os resultados dos 3 artigos, verificamos que o risco cardiovascular elevado é presente em PVHA mesmo com controle da replicação viral verificado através da carga viral indetectável. Além disso, mostrou que o exercício aeróbio de moderada e alta intensidade é um método seguro para a redução do risco cardiovascular e melhora a qualidade de vida em PVHA. Assim, sugerimos a recomendação do treinamento aeróbio contínuo como alternativa de tratamento não medicamentoso para controle dos riscos cardiovasculares em PVHA.

ANEXOS

Anexo A – Termo de Consentimento Livre e Esclarecido

UNIVERSIDADE FEDERAL DE CIÊNCIAS DA SAÚDE DE PORTO ALEGRE

Termo de Consentimento Livre e Esclarecido dos Pacientes

Você está sendo convidado a participar do projeto de pesquisa intitulado "Efeitos de diferentes modalidades de treinamento físico sobre a capacidade funcional e qualidade de vida relacionada à saúde de pacientes portadores do HIV em uso de terapia antirretroviral" desenvolvido pela aluna de doutorado Candissa Silva orientada pelo Prof. Drº Pedro Dal Lago. Esta pesquisa tem como orientação ética os requisitos da Resolução 466/12, do Ministério da Saúde, que regulamenta pesquisas que envolvem seres humanos**.** O projeto tem como objetivo avaliar os efeitos do treinamento físico em fatores de risco cardiovasculares, capacidade funcional e qualidade de vida de pacientes portadores do HIV. Este estudo justifica-se pela importância de proporcionar aos indivíduos uma avaliação detalhada e acompanhamento do sistema cardiopulmonar e um treinamento físico supervisionado.

Para este estudo, você receberá um número que será sorteado, pelo computador, para ver em qual grupo de treinamento você fará parte. Os treinamentos serão realizados por 8 semanas, com uma frequência de 3 vezes por semana, no laboratório de Fisioterapia da Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA). Os grupos são divididos da seguinte forma: 1) Treino em esteira; 2) Treinamento de força; 3) Treinamento associado (esteira e força); 4) Grupo Controle (nesse grupo, você ficará sendo supervisionado por 8 semanas, sem fazer nenhum tipo dos exercícios propostos). Após esse tempo, você será sorteado para um dos grupos de treinamento. As avaliações serão realizadas antes do início do treinamento e no final de 8 semanas. Caso você seja fumante, terá que realizar um teste que determinará se você participará ou não da pesquisa. Para a realização desse teste, você encherá bem os pulmões e na sequência, soltará todo o ar com as narinas ocluídas por um clipe nasal. Para seguir o teste, você utilizará 4 doses de um medicamento broncodilatador.

Após a entrevista com seus dados pessoais, você responderá a um questionário de múltipla escolha que vai avaliar o seu índice de qualidade de vida. Em outro dia, você caminhará em uma esteira com a velocidade aumentando de acordo com o seu desempenho, até o tempo máximo de 12 minutos. Haverá ainda outro teste em que, seu braço sofrerá uma pressão por 5 minutos realizada por manguito semelhante o da verificação da pressão arterial. Para realizar esses testes, será pedido pelo menos 12 horas antes da hora marcada para essas aferições, você evite de fumar, ingerir álcool e cafeína (que está presente em alguns refrigerantes, café e chás).

Além disso, você realizará um teste para verificar a carga de força para os treinamentos com um peso nas mãos e pernas. Além dos exames laboratoriais de rotina realizados no laboratório da Santa Casa, você também fará na UFCSPA uma coleta para verificar valores de marcadores inflamatórios e estresse oxidativo. Todos os procedimentos realizados para coletar o sangue serão executados de acordo com as normas de segurança vigentes. No transcorrer ou após os exercícios poderão ocorrer alguns desconfortos como cansaço, cãibra e dores musculares que, tornar-se-ão menos frequentes e intensos, à medida que se exercite. Caso ocorra alguma alteração, você será acompanhado por um dos pesquisadores até a emergência do

sistema único de saúde da Santa Casa de Porto Alegre. Os benefícios dos exercícios físicos grandes e podem variar de intensidade de indivíduo para indivíduo, você poderá apresentar: melhora no controle lipídico e glicêmico, menor sensação de cansaço, melhora da força muscular, controle dos fatores de risco cardiovascular, aumento da massa muscular e melhora na qualidade de vida. Para complementar os dados da pesquisa, serão coletados do seu prontuário do hospital os resultados do seu último exame laboratorial. Sua identidade será preservada sob qualquer hipótese, mesmo durante a divulgação da pesquisa. Você não terá nenhuma despesa pela participação na pesquisa. Os dados da pesquisa ficarão sobre a responsabilidade do Prof. Drº Pedro Dal Lago por um período de 5 anos. Após este período, todos esses dados serão incinerados.

Pelo presente Termo de Consentimento Livre e Esclarecido, declaro que estou de acordo em participar deste projeto de pesquisa, livre de qualquer constrangimento, pois fui informado de forma clara e detalhada dos objetivos, da justificativa, dos procedimentos aos quais serei submetidos, dos riscos, desconfortos e benefícios. Autorizo a utilização dos resultados dos meus testes e dados do meu prontuário clínico para publicação da pesquisa em meios científicos. Fui igualmente informado da garantia de receber a qualquer pergunta ou dúvida esclarecimento sobre a pesquisa, e da liberdade de retirar meu consentimento a qualquer momento, sem que haja prejuízo na continuidade do meu tratamento no Setor de Infectologia da Santa Casa.

Ciente e de acordo com o que foi anteriormente exposto, eu _____, RG número_____ estou de acordo em participar desta pesquisa, assinando este consentimento em duas vias, ficando com a posse de uma delas e a outra em posse do pesquisador.

Porto Alegre, _____ de _____ de 201__.

_____
Assinatura

_____
Prof. Drº Pedro Dal Lago
Pesquisador Responsável

_____
Dda. Candissa Silva da Silva
Co-pesquisadora

Contato:

- Prof. Drº Pedro Dal Lago: Universidade Federal de Ciências da Saúde de Porto Alegre. Rua Sarmento Leite, nº 245; CEP 90050-170, Centro, Porto Alegre. Anexo 1, sala 308. Telefone (51) 3303 – 8796. E-mail: pdallago@ufcspa.edu.br
- Comitê de Ética da UFCSPA: Universidade Federal de Ciências da Saúde de Porto Alegre (6º andar). Rua Sarmento Leite, nº 245; CEP 90050-170, Centro, Porto Alegre. Telefone (51) 3303–8700.
-Fisioterapeuta Candissa Silva da Silva: (51) 8180-7288. E-mail: candissa_my@yahoo.com.br

Anexo B – Aprovação no Comitê de Ética em Pesquisa

UNIVERSIDADE FEDERAL DE CIÊNCIAS DA SAÚDE DE PORTO ALEGRE

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: EFEITOS DE DIFERENTES MODALIDADES DE TREINAMENTO FÍSICO SOBRE A CAPACIDADE FUNCIONAL E QUALIDADE DE VIDA RELACIONADA À SAÚDE DE PACIENTES PORTADORES DO HIV EM USO DE TERAPIA ANTIRRETROVIRAL

Pesquisador: Pedro Dal Lago

Área Temática:

Versão: 3

CAAE: 34231613.0.0000.5345

Instituição Proponente: Universidade Federal de Ciências da Saúde de Porto Alegre

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 926.355

Data da Relatoria: 17/12/2014

Apresentação do Projeto:

Projeto vinculado ao PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA SAÚDE desta Universidade, em nível de Doutorado.

Objetivo da Pesquisa:

Comparar os efeitos dos diferentes tipos de treinamento: aeróbio, força e combinado na capacidade funcional, na função endotelial, no perfil inflamatório, no estresse oxidativo e na qualidade de vida relacionada à saúde em portadores do HIV em uso de TARV.

Avaliação dos Riscos e Benefícios:

Riscos: No transcorrer ou após os exercícios poderão ocorrer alguns desconfortos como cansaço, câibra e dores nos músculos que, tornar-se-ão menos frequentes e intensos, à medida que se exercite. Benefícios: Redução de risco cardiovascular e melhora na qualidade de vida, consequente do aumento na capacidade funcional proporcionada pela realização de exercícios físicos supervisionados.

Comentários e Considerações sobre a Pesquisa:

Alterações sugeridas foram realizadas.

Endereço: Rua Sarmento Leite ,245
Bairro: **CEP:** 90.050-170
UF: RS **Município:** PORTO ALEGRE
Telefone: (513)303 -8804 **E-mail:** cep@ufcspa.edu.br

Considerações sobre os Termos de apresentação obrigatória:

Termos apresentados.

Recomendações:

Aprovação.

Conclusões ou Pendências e Lista de Inadequações:

Sem pendências.

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

Considerações Finais a critério do CEP:

De acordo com o parecer do Relator.

PORTO ALEGRE, 23 de Dezembro de 2014

Assinado por:
Julia Fernanda Semmelmann Pereira Lima
(Coordenador)

Anexo C – Normas do Periódico *Journal of Exercise Rehabilitation*

JER Journal of Exercise Rehabilitation

Instructions for Author

pISSN 2288-176X
eISSN 2288-1778
http://www.e-jer.org

Established in 2005
Revised on April 15, 2013

Manuscripts for submission to the Journal of Exercise Rehabilitation should be prepared according to the following instructions. For issues not addressed in these instructions, the author is referred to the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication" (http://www.icmje.org/).

CHARACTERISTICS AND CATEGORIES OF MANUSCRIPTS

1. Contents and Classifications of Manuscript

Journal of Exercise Rehabilitation is the official journal of the Korean Society of Exercise Rehabilitation, being published six times a year. Its formal abbreviation is "J Exer Rehabil". The types of manuscripts include research articles, review articles, and articles invited by the Editorial Board. Journal of Exercise Rehabilitation contains 6 sections: Basic research on exercise rehabilitation, Clinical research on exercise rehabilitation, Exercise rehabilitation pedagogy, Exercise rehabilitation education, Exercise rehabilitation psychology, and Exercise rehabilitation welfare.

Only articles that are scientifically identified and theoretically, originally developed as the results of new, significant, and recent studying on the medical information and knowledge associated with the above-mentioned fields and that were conducted ethically and complied with policies of management of the Korean Society of Exercise Rehabilitation can be published in this Journal. Articles that have been already published or submitted for publication elsewhere cannot be submitted to this journal, and articles that have been published in this journal cannot be published elsewhere without permission. The Korean Society of Exercise Rehabilitation has all the copyrights of all the manuscripts that have been submitted and permitted for publication in this Journal.

2. Author Contributions

Authors are required to make clear of their contribution to their manuscript in cover letter. To be listed as an author one should have contributed substantially to all three categories established by the International Committee of Medical Journal Editors (ICMJE): 1) conception and design, or acquisition, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published (www.icmje.org/index. html). The ICMJE further states that acquisition of funding, the collection of data, or general supervision of the research group, by themselves, do not justify authorship. Individuals who have contributed substantially to some but not all of the three categories, or in other areas, should be listed in Acknowledgments. In principle, we do not allow the addition of authors or the changes of the first or the corresponding author after our initial decision to accept the manuscript for publication. Written causes of changing should be submitted when the authors of a manuscript is changed, approval of the Editorial board is needed when the first author or corresponding author is changed, and approval of the Chief Editor is needed when other authors is changed before acceptance of the submitted manuscript. If an author wishes to be removed from the byline, he or she should submit a signed letter indicating his or her wish to be deleted from the list of authors. The change in the order in the byline requires a letter from all authors indicting agreement with the same.

3. Language

This Journal will accept manuscripts written in English only. The abstract should be written in English and English medical terms are based on International Continence Society (ICS) terminology, the recent edition as the report of Standardization Sub-committee of the ICS. Other terms are based on English-Korean Ko-

rean-English Medical Terminology, published by the Korean Medical Association.

REGULATIONS ON ETHICS

The Journal adheres to the ethical guidelines for research and publication described in *Good Publication Practice Guidelines for Medical Journals* (http://kamje.or.kr./publishing_ethics.html) and *Guidelines on Good Publication* (http://publicationethics.org/static/1999/1999pdf13.pdf).

1. Registration of Clinical Trial Research

Any research that deals with a clinical trial should be registered with a primary national clinical trial registration site such as http://ncrc.cdc.go.kr/cris, or other sites accredited by WHO or the International Committee of Medical Journal Editors.

2. Disclosure of Conflict of Interest

Conflict-of-Interest Statement

A conflict of interest may exist when an author (or the author's institution or employer) has financial or personal relationships or affiliations that could bias the author's decisions of the manuscript. Authors are expected to provide detailed information about all relevant financial interests and relationships or financial conflicts, particularly those present at the time the research was conducted and through publication, as well as other financial interests (such as patent applications in preparation), that represent potential future financial gain. All disclosures of any potential conflicts of interest, including specific financial interests and relationships and affiliations (other than those affiliations listed in the title page of the manuscript) relevant to the subject of their manuscript will be disclosed by the corresponding author on behalf of each coauthor, if any, as part of the submission process. Likewise, authors without conflicts of interest will be requested to state so as part of the submission process. If authors are uncertain about what constitutes a relevant financial interest or relationship, they should contact the editorial office. Failure to include this information in the manuscript will prohibit commencement of the review process of the manuscript. For all accepted manuscripts, each author's disclosures of conflicts of interest and relevant financial interests and affiliations and declarations of no such interests will be published. The policy requesting disclosure of conflicts of interest applies for all manuscript submissions. If an author's disclosure of potential conflicts of interest is determined to be inaccurate or incomplete after publication, a correction will be published to rectify the original published disclosure statement. Authors are also required to report detailed information regarding all financial and material support for the research and work, including but not limited to grant support, funding sources, and provision of equipment and supplies as part of the submission process. For all accepted manuscripts, each author's source of funding will be published.

Funding/Support and Role of Sponsor

All financial and material support for the research and work will be requested to be clearly and completely identified as part of the submission process (Cover Letter). The specific role of the funding organization or sponsor in each of the following should be specified: "design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript." The corresponding author is responsible for acknowledging this on the authorship form at the time of submission.

3. Examination on Ethics

Personal information with which a patient's identity can be established cannot be published with any forms including texts, photos, and pedigree. When personal information of patients is critical as scientific data, it should be stated clearly that the purpose of the study and mental & physical damages that can be done during the participation to the study were sufficiently explained for and written contents were submitted by the participants or their caregivers. In a study of an experiment for human subjects, it should be reported that the experiment complied with the ethics criteria of institutions reviewing ethics of experiment on human body or local "Ethics Committee on Clinical Experiments" and Declaration of Helsinki. The data for explanation such as photos should not include names, English initials, and hospital numbers of patients. In cases of animal experiments, it should be stated clearly that the processes complied with regulations of in-

stitutions or national research committee related to breeding and using laboratory animals or the NIH Guide for the Care and Use of Laboratory Animals. If necessary, it can be required to submit written consents and approvals of ethics committee.

4. Originality and Duplicate Publication

Manuscripts that have been already published elsewhere or in this journal should not be published. When a similar article has been already elsewhere or in this journal, its copy should be submitted with the relevant manuscript. The editorial Board of the Korean Society of Exercise Rehabilitation will decide whether the relevant manuscript is duplicately published and examine whether it can be published in this Journal.

MANUSCRIPTS PREPARATION

1. Review Articles

Review article was selected as a significant theme from areas relevant to neurologic field and whose authors were selected and referred on the basis of articles published in this or other journals. The submitted manuscript should be decided to be published via reviewing of the Editorial Board. The length of the manuscript should not exceed 5,000 words except for the cover, tables, figures, and references. The works in the references should not exceed 100.

2. Research Articles

The manuscript for original articles should be organized in the following order: 1) title page, 2) abstract and keywords, 3) introduction, 4) materials and methods, 5) results, 6) discussion, 7) conflict of interest, 8) acknowledgments (if necessary), 9) references, 10) tables, 11) figures and photos, and 12) legends.

The manuscript should be provided in MS Word file (doc), double spaced on 212 × 297 mm (A4 size) with 2.5 cm margins at the top, bottom, and left margin.

The length of the manuscript should not exceed 5,000 words except for the cover, tables, figures, and references. No more than 50 references can be cited. All manuscript pages are to be numbered consecutively, beginning with the title page as page 1. The use of acronyms and abbreviations is discouraged and should be kept to a minimum. When used, they are to be defined where first used, followed by the acronym or abbreviation in parentheses. Abbreviations are not allowed in the title. The names and locations (city, state, nation) of manufacturers of equipment and non-generic drugs should be given. When quoting from other sources, give a reference number in bracket after the author's name or at the end of the quotation.

3. Editorials

Editorials are invited perspectives on an area of exercise or rehabilitation, dealing with fields of research, current medical interests, fresh insights and debates.

GENERAL GUIDELINES FOR MANUSCRIPTS

1. Title Page

The title page should include the article title, name(s) of author(s), and institutional affiliations in English, and corresponding author and other footnotes. The author(s) should type the original and running title (less than 60 characters) in the title page directly. When there are several authors with different affiliations, the main institute should be recorded first and others be expressed as superscripts like 1, 2, 3, etc. next to the name of the relevant author and then the name of the affiliation in order. The corresponding author should present the name, affiliation, address, zip code, and contact details (such as Tel, Fax, and E-mail).

2. Abstract and Keywords

The abstract should be brief descriptions of the manuscript, containing 250 words. The abstract should be a structured one which includes purpose, methods, results, and conclusions. A list of keywords, with a maximum of six items in English, should be included at the end of the abstract. The selection of keywords should be based on Medical Subject Heading (MeSH) of Index Medicus, and each keywords should begin with a capital letter. Do not use abbreviations or reference citations.

3. Introduction

The introduction should address the purpose of the study briefly and concisely, and include background reports only related to the

purpose of the study.

4. Materials and Methods

The design, subjects, and methods should be described in order. When patients are the subjects, the properties, inclusion criteria, and exclusion criteria of the populations should be clarified. Particular chemicals or equipment should be clarified of the names of the suppliers, the cities, the states, and the nations according to unified forms. Explanation of the experimental methods should be sufficient for repetition by other researchers, though methods that had been reported in detail may be described briefly by citation of references. However, new methods or modifications of previously published methods should be described enough for other researchers to represent. The methods of statistical verification on the results should be clarified.

5. Results

The authors should describe clearly and logically their significant findings of observations or results corresponding to the purpose of the study, following the order in the methods. The authors should avoid overlapping descriptions by figures or tables and by main text, describing important results only.

It should be clear which statistical test is associated with each P-value reported. Rarely used statistical techniques should be described. Medians and percentiles (such as quartiles) are preferred over means and standard deviations (or standard errors) when analyzing asymmetric data, especially when nonparametric statistics are calculated. Fractions (e.g., 5/10) should accompany percentages. In randomized clinical trials, consider reporting separate analyses with confounding variables included. If sample sizes differ between groups when patients are randomized, randomized, reasons should be provided.

6. Discussion

Important or new findings from the results of the study should be emphasized and the consequent conclusions are described, while repetition of the contents in the introduction and the results should be avoided. The authors are needed to describe the significance and limitations of the study and directions for the further studies, comparing with the results of the other related studies. Conclusion should be included in the discussion part. The conclusions should include a comprehensive description of the judgment or thoughts of the authors being induced from the results and discussion sections and corresponding to the purpose of the study mentioned in the introduction. The simple summary or overlapped array of the results should be avoided. An addition of directions for further studies or expected effects should be avoided if possible.

7. Conflict of Interest

The corresponding author of an article is asked to inform the Editor of the authors' potential conflicts of interest possibly influencing their interpretation of data. A potential conflict of interest should be disclosed in the manuscript even when the authors are confident that their judgments have not been influenced in preparing the manuscript. Such conflicts may be financial support or private connections to pharmaceutical companies, political pressure from interest groups, or academic problems (e.g., employment/affiliation, grants or funding, consultancies, stock ownership or options, royalties, or patents filed, received, or pending).

8. Acknowledgments

When necessary, acknowledgments shall be provided for those who contributed to the studying but were insufficient to be considered authors. The acknowledgments should express appreciation for the concrete roles of the contributors in the studying (e.g., data collection, financial assistance, statistical processing, and experimental analysis), and the authors should notify them that their names will be included in the acknowledgements for their advanced consents.

9. References

Abbreviations for the literature shall be based on the Index Medicus (see http://www.ncbi.nlm.nih.gov/sites/entrez?db=journals). All authors are listed in the reference list.

The description of the journal reference follows the below description. For more on references, refer to the "Citing Medicine: the NLM Style Guide for Authors, Editors, and Publishers (http://www.nlm.nih.gov/citingmedicine)."

Journal Article:

- Ferro JM. Update on intracerebral haemorrhage. J Neurol 2006; 253:985-999.
- Kramer AF, Erickson KI. Capitalizing on cortical plasticity: influence of physical activity on cognition and brain function. Trends Cogn Sci 2007;11:342-348.
- Kim BK, Shin MS, Lee HH, Sung YH, Kim H. Swimming alleviates streptozotocin-induced short-term memory impairment in rats. J Exer Rehabil 2012;8:273-284.
- Guise AI, Chen F, Zhang G, See W. The effects of physiological estrogen concentration on the immune response of urothelial carcinoma cells to bacillus Calmette-Guerin. J Urol 2010 Nov 13 [Epub]. DOI: S0022-5347(10)04540-4.

Book:

- Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA, editors. Campbell-Walsh urology. 9nd ed. Philadelphia: Saunders; 2007.

Book Chapter:

- Klein Ea, Platz EA, Thompson IM. Epidemiology, etiology, and prevention of prostate cancer. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA, editors. Campbell-Walsh urology. 9nd ed. Philadelphia: Saunders; 2007. p. 2854-73.

Website:

- Whitmore K. Sexual pain in men and women with IC/PBS and chronic pelvic pain [Internet]. Bristol: International Continence Society; c2010 [cited 2010 Dec 20]. Available from: https://www.icsoffice.org/News. aspx?NewsID=22.

10. Tables

Tables should be written as "Table" in the text and be described briefly in English, left-aligned. All the abbreviations used should be described under the tables or figures. The first letter of the title of a table should be a capital letter, and do not use a period if the description is not a complete sentence. The table should be included one in a page as double space, written clearly and briefly. No vertical or horizontal lines are allowed to be included within a table. Title all tables and number them with Arabic numerals at the top of them, and table footnotes or description should be given markers in the order of [a, b), c) –

11. Figures

Figures should be written as "Fig." in the text. The minimum requirements for digital resolution are:

- 1,200 DPI/PPI for black and white images, such as line drawings or graphs.
- 300 DPI/PPI for picture-only photographs.
- 600 DPI/PPI for photographs containing pictures and line elements, i.e., text labels, thin lines, arrows.

12. Text Style, Numbers and Units

If foreign-language words are needed, capital and small letters should be clarified: in principal, proper nouns, place names, and names of persons should be written with capital letter as the first letter and then small letters for the rest. When translated words are insufficient in conveying meanings, the translated term will be presented with the original term within parenthesis for the first time and then the translated term only can be used. Numbers should be written with Arabic numerals. The measurements of length, height, weight, and volume shall be recorded with the metric system (meters, grams, and liters), temperature shall be recorded with centigrade, and blood pressure shall be recorded with mmHg. The hematological or clinical test measurements shall be recorded on the basis of common units or the system of the International Units (SI).

SUBMISSION OF MANUSCRIPT

All the manuscripts are submitted via the electronic article submission system of the website of the Journal of Exercise Rehabilitation (http://www.e-jer.org) with written consents containing all the authors' signatures on copyright transfer. When the publication is approved by the Editorial Board after reviewing, one final version of the manuscript of the article and the file containing all the contents should be finally submitted to the Editorial Board via the Internet article submission system.

The submission day of a manuscript shall be the day when the manuscript is submitted, the author(s) is finally approved, and is

delivered to the Editorial Board, and the day of decision of the publication shall be the day when the manuscript is completed of its reviewing and is decided to be published.

Detailed information on manuscript submission and journal edition is provided in the "Online System Guide" in the website. More information on using the system can be inquired using the below-mentioned address.

REVIEW OF MANUSCRIPTS

1. Editorial Board

The Editorial Board deals with all the works for accepting and editing manuscripts. A manuscript that is not complied with the regulations for submission can be suggested to be adjusted or be reserved to be published, or can be adjusted by the Board, if necessary, without affecting the original contents. A manuscript with sufficient errors in form or misspellings or the one that is not complied with the regulations for submission can be rejected of acceptance and the author(s) will be notified. In case of reviewer(s)'s request, submission of data can be required for the author(s) via the decision of the Editorial Board.

2. Reviewing and Publication of Manuscripts

All the submitted manuscripts shall be conducted of peer review of three professionals on the basis of the regulations for article reviewing of the Korean Society of Exercise Rehabilitation, and be decided of its publication after reviewing of the Editorial Board. When the reviewing decisions are different each other, the selection of the relevant manuscript shall be decided after re-reviewing of the Board. A manuscript shall be considered of relinquishment of its publication when it won't be submitted within two months of notifying the decision of the reviewing without specific reason. A selected manuscript shall be decided of its order of publication by consideration of its type and the day of deciding its publication by the Editorial Board.

Anexo D – Normas do Periódico *Clinical Autonomic Research*

Instructions for Authors

Manuscript types

Research Articles are full-length reports of original research. They should contain no more than 3000 words, excluding references, and must be accompanied by an abstract of 250 words or less. References should be limited to 50. Tables and figures should be limited to 6.
Short Communications are original data communicated in no more than 1700 words, excluding references, and should be accompanied by an abstract no longer than 150 words. References should be limited to 15. Tables and figures should be limited to 2.
Review Articles and Editorials may be submitted by authors after discussing the topic of the proposed review with the Editors. Unsolicited contributions are also welcome. Both solicited and unsolicited contributions will be submitted for peer review. Review Articles should contain no more than 5000 words, excluding references, and must be accompanied by an abstract of 250 words or less. References should be limited to 80. Tables and figures should be limited to 8.
Letters to the Editor are encouraged. Case reports and Autonomic Images can be submitted as Letters. Letters may report new or important observations or provide comments or criticisms pertaining to developments in understanding autonomic function. Letters may also comment on papers previously published in this journal. Criticism of published work must be objective and supported by experimental data, and any such letter accepted for publication will be shown to the author(s) of the original paper, who will be invited to submit a reply for publication in the same issue. Letters should follow the normal presentation style of the journal. They should contain less than 1000 words and one table and/or one illustration, and may include up to 5 references. Although every effort is made to avoid mistakes, they occasionally occur. Letters that point out errors in previous issues will be published in the Department of Errors and the author will be acknowledged.

MANUSCRIPT SUBMISSION

Manuscript Submission

Submission of a manuscript implies: that the work described has not been published before; that it is not under consideration for publication anywhere else; that its publication has been approved by all co-authors, if any, as well as by the responsible authorities – tacitly or explicitly – at the institute where the work has been carried out. The publisher will not be held legally responsible should there be any claims for compensation.

Permissions

Authors wishing to include figures, tables, or text passages that have already been published elsewhere are required to obtain permission from the copyright owner(s) for both the print and online format and to include evidence that such permission has been granted when submitting their papers. Any material received without such evidence will be assumed to originate from the authors.

Online Submission

Please follow the hyperlink “Submit online” on the right and upload all of your manuscript files following the instructions given on the screen.

TITLE PAGE

Title Page

The title page should include:

- The name(s) of the author(s)
- A concise and informative title
- The affiliation(s) and address(es) of the author(s)
- The e-mail address, and telephone number(s) of the corresponding author
- If available, the 16-digit ORCID of the author(s)

Abstract

Please provide a structured abstract of 150 to 250 words which should be divided into the following sections:

- Purpose (stating the main purposes and research question)
- Methods
- Results
- Conclusions

Keywords

Please provide 4 to 6 keywords which can be used for indexing purposes.

TEXT

Text Formatting

Manuscripts should be submitted in Word.

- Use a normal, plain font (e.g., 10-point Times Roman) for text.
- Use italics for emphasis.
- Use the automatic page numbering function to number the pages.
- Do not use field functions.
- Use tab stops or other commands for indents, not the space bar.
- Use the table function, not spreadsheets, to make tables.
- Use the equation editor or MathType for equations.
- Save your file in docx format (Word 2007 or higher) or doc format (older Word versions).

Manuscripts with mathematical content can also be submitted in LaTeX.

- LaTeX macro package (zip, 182 kB)

Headings

Please use no more than three levels of displayed headings.

Abbreviations

Abbreviations should be defined at first mention and used consistently thereafter.

Footnotes

Footnotes can be used to give additional information, which may include the citation of a reference included in the reference list. They should not consist solely of a

reference citation, and they should never include the bibliographic details of a reference. They should also not contain any figures or tables.
Footnotes to the text are numbered consecutively; those to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data). Footnotes to the title or the authors of the article are not given reference symbols.
Always use footnotes instead of endnotes.

Acknowledgments

Acknowledgments of people, grants, funds, etc. should be placed in a separate section on the title page. The names of funding organizations should be written in full.

REFERENCES

Citation

Reference citations in the text should be identified by numbers in square brackets. Some examples:
1. Negotiation research spans many disciplines [3].
2. This result was later contradicted by Becker and Seligman [5].
3. This effect has been widely studied [1-3, 7].

Reference list

The list of references should only include works that are cited in the text and that have been published or accepted for publication. Personal communications and unpublished works should only be mentioned in the text. Do not use footnotes or endnotes as a substitute for a reference list.
The entries in the list should be numbered consecutively.

- Journal article

  Gamelin FX, Baquet G, Berthoin S, Thevenet D, Nourry C, Nottin S, Bosquet L (2009) Effect of high intensity intermittent training on heart rate variability in prepubescent children. Eur J Appl Physiol 105:731-738. https://doi.org/10.1007/s00421-008-0955-8

  Ideally, the names of all authors should be provided, but the usage of “et al” in long author lists will also be accepted:

  Smith J, Jones M Jr, Houghton L et al (1999) Future of health insurance. N Engl J Med 965:325–329

- Article by DOI

  Slifka MK, Whitton JL (2000) Clinical implications of dysregulated cytokine production. J Mol Med. https://doi.org/10.1007/s001090000086

- Book

  South J, Blass B (2001) The future of modern genomics. Blackwell, London

- Book chapter

  Brown B, Aaron M (2001) The politics of nature. In: Smith J (ed) The rise of modern genomics, 3rd edn. Wiley, New York, pp 230-257

- Online document

  Cartwright J (2007) Big stars have weather too. IOP Publishing PhysicsWeb. http://physicsweb.org/articles/news/11/6/16/1. Accessed 26 June 2007

- Dissertation

  Trent JW (1975) Experimental acute renal failure. Dissertation, University of California

Always use the standard abbreviation of a journal's name according to the ISSN List of Title Word Abbreviations, see

- ISSN.org LTWA

If you are unsure, please use the full journal title.
For authors using EndNote, Springer provides an output style that supports the formatting of in-text citations and reference list.

- EndNote style (zip, 2 kB)

Authors preparing their manuscript in LaTeX can use the bibtex file spbasic.bst which is included in Springer's LaTeX macro package.

TABLES

- All tables are to be numbered using Arabic numerals.
- Tables should always be cited in text in consecutive numerical order.
- For each table, please supply a table caption (title) explaining the components of the table.
- Identify any previously published material by giving the original source in the form of a reference at the end of the table caption.
- Footnotes to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data) and included beneath the table body.

Anexo E – Normas do Periódico Arquivos Brasileiros de Cardiologia

Normas para Publicação

1. Os Arquivos Brasileiros de Cardiologia (Arq Bras Cardiol) são uma publicação mensal da Sociedade Brasileira de Cardiologia, indexada no Cumulated Index Medicus da National Library of Medicine e nos bancos de dados do MEDLINE, EMBASE, LILACS, Scopus e da SciELO com citação no PubMed (United States National Library of Medicine) em inglês e português.

2. Ao submeter o manuscrito, os autores assumem a responsabilidade de o trabalho não ter sido previamente publicado e nem estar sendo analisado por outra revista. Todas as contribuições científicas são revisadas pelo Editor-Chefe, pelo Supervisor Editorial, Editores Associados e pelos Membros do Conselho Editorial. Só são encaminhados aos revisores os artigos que estejam rigorosamente de acordo com as normas especificadas. Os trabalhos também são submetidos à revisão estatística, sempre que necessário. A aceitação será na originalidade, significância e contribuição científica para o conhecimento da área.

3. Seções

3.1. Editorial: todos os editoriais dos Arquivos são feitos através de convite. Não serão aceitos editoriais enviados espontaneamente.

3.2. Carta ao Editor: correspondências de conteúdo científico relacionadas a artigos publicados na revista nos dois meses anteriores serão avaliadas para publicação. Os autores do artigo original citado serão convidados a responder.

3.3. Artigo Original: os Arquivos aceitam todos os tipos de pesquisa original na área cardiovascular, incluindo pesquisas em seres humanos e pesquisa experimental.

3.4. Revisões: os editores formulam convites para a maioria das revisões. No entanto, trabalhos de alto nível, realizados por autores ou grupos com histórico de publicações na área serão bem-vindos. Não serão aceitos, nessa seção, trabalhos cujo autor principal não tenha vasto currículo acadêmico ou de publicações, verificado através do sistema Lattes (CNPQ), Pubmed ou SciELO. Eventualmente, revisões submetidas espontaneamente poderão ser reclassificadas como “Atualização Clínica” e publicadas nas páginas eletrônicas, na internet (ver adiante).

3.5. Comunicação Breve: experiências originais, cuja relevância para o conhecimento do tema justifique a apresentação de dados iniciais de pequenas séries, ou dados parciais de ensaios clínicos, serão aceitos para avaliação.

3.6. Correlação Anátomo-Clínica: apresentação de um caso clínico e discussão de aspectos de interesse relacionados aos conteúdos clínico, laboratorial e anátomo-patológico.

3.7. Correlação Clínico-Radiográfica: apresentação de um caso de cardiopatia congênita, salientando a importância dos elementos radiográficos e/ou clínicos para a consequente correlação com os outros exames, que comprovam o diagnóstico. Ultima-se daí a conduta adotada.

3.8. Atualização Clínica: essa seção busca focar temas de interesse clínico, porém com potencial de impacto mais restrito. Trabalhos de alto nível, realizados por autores ou grupos com histórico de publicações na área serão aceitos para revisão.

3.9. Relato de Caso: casos que incluam descrições originais de observações clínicas, ou que representem originalidade de um diagnóstico ou tratamento, ou que ilustrem situações pouco frequentes na prática clínica e que mereçam uma maior compreensão e atenção por parte dos cardiologistas serão aceitos para avaliação.

3.10. Imagem Cardiovascular: imagens clínicas ou de pesquisa básica, ou de exames complementares que ilustrem aspectos interessantes de métodos de imagem, que esclareçam mecanismos de doenças cardiovasculares, que ressaltem pontos relevantes da fisiopatologia, diagnóstico ou tratamento serão consideradas para publicação.

3.11. Ponto de Vista: apresenta uma posição ou opinião dos autores a respeito de um tema científico específico. Esta posição ou opinião deve estar adequadamente fundamentada na literatura ou em sua experiência pessoal, aspectos que irão ser a base do parecer a ser emitido.

4. Processo de submissão: os manuscritos deverão ser enviados via internet e sistema, disponível no endereço: http://www.arquivosonline.com.br/2013/submissao

5. Todos os artigos devem vir acompanhados por uma carta de submissão ao editor, indicando a seção em que o artigo deva ser incluído (vide lista acima), declaração do autor de que todos os coautores estão de acordo com o conteúdo expresso no trabalho, explicitando ou não conflitos de interesse* e a inexistência de problemas éticos relacionados.

6. Todos os manuscritos são avaliados para publicação no menor prazo possível, porém, trabalhos que mereçam avaliação especial para publicação acelerada ("fast-track") devem ser indicados na carta de submissão ao editor.

7. Os textos e as tabelas devem ser editados em word e as figuras e ilustrações devem ser anexados em arquivos separados, na área apropriada do sistema. Figuras devem ter extensão JPEG e resolução mínima de 300 DPI. As Normas para Formatação de Tabelas, Figuras e Gráficos encontram-se em http://www.arquivosonline.com.br/publicacao/informacoes_autores.asp / http://publicacoes.cardiol.br/pub_abc/autor/pdf/manual_de_formatacao_abc.pdf

8. Conflito de interesses: quando existe alguma relação entre os autores e qualquer entidade pública ou privada que pode derivar algum conflito de interesse, essa possibilidade deve ser comunicada e será informada no final do artigo. Enviar a Declaração de Potencial Conflito de Interesses para revista@cardiol.br, colocando no assunto número do artigo. Acesse: http://www.arquivosonline.com.br/pdf/conflito_de_interesse_abc_2013.pdf

9. Formulário de contribuição do autor: o autor correspondente deverá completar, assinar e enviar por e-mail (revista@cardiol.br – colocar no assunto número do artigo) os formulários, explicitando as contribuições de todos os participantes, que serão informadas no final do artigo. Acesse: http://www.arquivosonline.com.br/pdf/formulario_contribuicao_abc_2013.pdf

10. Direitos Autorais: os autores dos artigos aprovados deverão encaminhar para os Arquivos, previamente à publicação, a declaração de transferência de direitos autorais assinada por todos os coautores (preencher o formulário da página http://publicacoes.cardiol.br/pub_abc/autor/pdf/Transferencia_de_Direitos_Autorais.pdf e enviar para revista@cardiol.br, colocando no assunto número do artigo).

11. Ética

11.1. Os autores devem informar, no texto e/ou na ficha do artigo, se a pesquisa foi aprovada pela Comissão de Ética em Pesquisa de sua instituição em consoante à Declaração de Helsinki.

11.2. Nos trabalhos experimentais envolvendo animais, os autores devem indicar se os procedimentos seguidos seguiram os padrões éticos do comitê responsável por experimentação humana (institucional e nacional) e da Declaração de Helsinki de 1975, revisada em 2008. Se houver dúvida quanto à realização da pesquisa em conformidade com a Declaração de Helsinki, os autores devem explicar as razões para sua abordagem e demonstrar que o corpo de revisão institucional explicitamente aprovou os aspectos duvidosos do estudo. Ao relatar experimentos com animais, os autores devem indicar se as diretrizes institucionais e nacionais para o cuidado e uso de animais de laboratório foram seguidas.

11.3. Nos trabalhos experimentais envolvendo seres humanos, os autores devem indicar se os procedimentos seguidos seguiram os padrões éticos do comitê responsável por experimentação humana (institucional e nacional) e da Declaração de Helsinki de 1975, revisada em 2008. Se houver dúvida quanto à realização da pesquisa em conformidade com a Declaração de Helsinki, os autores devem explicar as razões para sua abordagem e demonstrar que o corpo de revisão institucional explicitamente aprovou os aspectos duvidosos do estudo. Estudos realizados em humanos devem estar de acordo com os padrões éticos e com o devido consentimento livre e esclarecido dos participantes conforme Resolução 196/96 do Conselho Nacional de Saúde do Ministério da Saúde (Brasil), que trata do Código de Ética para Pesquisa em Seres Humanos e, para autores fora do Brasil, devem estar de acordo com Comittee on Publication Ethics (COPE).

12. Ensaios clínicos

12.1. O International Committee of Medical Journal Editors (ICMJE) e a Organização Mundial da Saúde (OMS) acredita que é importante promover uma base de dados de estudos clínicos

abrangente e disponível publicamente. O ICMJE define um estudo clínico como qualquer projeto de pesquisa que prospectivamente designa seres humanos para intervenção ou comparação simultânea ou grupos de controle para estudar a relação de causa e efeito entre uma intervenção médica e um desfecho relacionado à saúde. As intervenções médicas incluem medicamentos, procedimentos cirúrgicos, dispositivos, tratamentos comportamentais, mudanças no processo de atendimento, e outros.

12.2. O número de registo do estudo deve ser publicado ao final do resumo. Serão aceitos qualquer registro que satisfaça o ICMJE, ex. http://clinicaltrials.gov/. A lista completa de todos os registros de ensaios clínicos pode ser encontrada no seguinte endereço: http://www.who.int/ictrp/network/primary/en/index.html.

12.3. Os ensaios clínicos devem seguir em sua apresentação as regras do CONSORT STATEMENT. Acesse http://www.consort-statement.org/consort-statement/

13. Citações bibliográficas: os Arquivos adotam as Normas de Vancouver – Uniform Requirements for Manuscripts Submitted to Biomedical Journal (www.icmje.org).

14. Idioma: os artigos devem ser redigidos em língua portuguesa (com a ortografia vigente) e/ou inglês.

14.1. Para os trabalhos que não possuírem versão em inglês ou que essa seja julgada inadequada pelo Conselho Editorial, a revista providenciará a tradução sem ônus para o(s) autor(es).

14.2. Caso já exista a versão em inglês, tal versão deve ser enviada para agilizar a publicação.

14.3. As versões inglês e português serão disponibilizadas na íntegra no endereço eletrônico da SBC (http://www.arquivosonline.com.br) e da SciELO (www.scielo.br), permanecendo à disposição da comunidade internacional.

15. Avaliação pelos Pares (peer review): todos os trabalhos enviados aos ABC serão submetidos à avaliação inicial dos editores, que decidirão, ou não, pelo envio a revisão por pares (peer review), todos eles pesquisadores com publicação regular em revistas indexadas e cardiologistas com alta qualificação (Corpo de Revisores dos ABC http://www.arquivosonline.com.br/conselhoderevisores/).

15.1. Os autores podem indicar até cinco membros do Conselho de Revisores para análise do manuscrito submetido, assim como podem indicar até cinco revisores para não participar do processo.

15.2. Os revisores tecerão comentários gerais sobre o manuscrito e decidirão se esse trabalho deve ser publicado, corrigido segundo as recomendações, ou rejeitado.

15.3. Os editores, de posse dos comentários dos revisores, tomarão a decisão final. Em caso de discrepâncias entre os revisores, poderá ser solicitada uma nova opinião para melhor julgamento.

15.4. As sugestões de modificação dos revisores serão encaminhadas ao autor principal. O manuscrito adaptado às novas exigências será reencaminhado aos revisores para verificação.

15.5. Em casos excepcionais, quando o assunto do manuscrito assim o exigir, o Editor poderá solicitar a colaboração de um profissional que não conste do Corpo de Revisores.

15.6. Os autores têm o prazo de trinta dias para proceder às modificações solicitadas pelos revisores e submeter novamente o artigo. A inobservância desse prazo implicará na retirada do artigo do processo de revisão.

15.7. Sendo aceitos para revisão, os pareceres dos revisores deverão ser produzidos no prazo de 30 dias.

15.8. As decisões serão comunicadas por mensagem do Sistema de Envio de Artigos e e-mail.

15.9. As decisões dos editores não serão discutidas pessoalmente, nem por telefone. As réplicas deverão ser submetidas por escrito à revista.

15.10. Limites de texto: a contagem eletrônica de palavras deve incluir a página inicial, resumo, texto, referências e legenda de figuras/tabelas.

Quadro 1: Limites permitidos (nº) e estrutura dos artigos submetidos à publicação no Int J Cardiovasc Sci.

	Artigo Original	Editorial	Artigo de Revisão Atualização Clínica	Relato de Caso	Comunicação Breve	Ponto de Vista	Carta ao Editor	Imagem	Correlações
Nº máx. de autores	10	2	4	6	8	8	3	5	4
Título (caracteres incluindo espaços)	150	120	150	120	120	120	120	120	120
Título reduzido (caracteres incluindo espaços)	50	50	50	50	50	50	50	50	50
Resumo (nº máx. de palavras)	250	---	250	---	250	---	---	---	---
Nº máx. de palavras (incluindo referências)	5000	1500	6500	1500	1500	5500	500	250	800
Nº máx. de referências	40	15	80	10	10	20	5	---	10
Nº máx. de tabelas + figs + vídeo	8	2	8	2	2	2	1	1	1

AO=Artigo Original; AR=Artigo de Revisão; AA= Artigo de Atualização; CP=Comunicação Preliminar; RC=Relato de Caso; PV=Ponto de Vista; IC=Imagem Cardiovascular
Resumo[1] - resumo organizado de forma estruturada, em cabeçalhos: Fundamentos – Objetivos – Métodos – Resultados – Conclusões
Resumo [2] - organizado de forma cursiva

15.11. Orientações Estatísticas

15.11.1. O uso adequado dos métodos estatísticos bem como sua correta descrição é de suma importância para a publicação nos Arquivos Brasileiros de Cardiologia. Desta forma, a seguir, são apresentadas orientações gerais aos autores sobre as informações que devem ser fornecidas no artigo referente à análise estatística (para maiores detalhes, sugerimos a leitura das orientações estatísticas do European Heart Journal).

1) Sobre a amostra: • Detalhamento tanto da população de interesse quanto dos procedimentos utilizados para definição da amostra do estudo.

2) Dentro do tópico Métodos, criação de um subtópico direcionado exclusivamente à descrição da análise estatística efetuada no estudo, contendo: • Forma de apresentação das variáveis contínuas e/ou categóricas: para variáveis contínuas com distribuição normal, apresentação da média e desvio-padrão e, para as com distribuição não normal, apresentar através de mediana e intervalos interquartis. Já para as variáveis categóricas, as mesmas devem ser apresentadas através de números absolutos e percentagens, com os respectivos intervalos de confiança; • Descrição dos métodos estatísticos utilizados. Na utilização de métodos estatísticos mais complexos, deve ser fornecida uma literatura de referência para os mesmos; • Como regra, os testes estatísticos devem sempre ser bilaterais ao invés de unilaterais; • Nível de significância estatística adotado; e • Especificação do software empregado nas análises estatísticas e sua respectiva versão.

3) Em relação à apresentação dos resultados obtidos após as análises estatísticas:

• Os principais resultados devem sempre ser descritos com seus respectivos intervalos de confiança; • Não repetir no texto do artigo dados já existentes em tabelas e figuras; • Ao invés de apresentar tabelas muito extensas, utilizar gráficos como alternativa de modo a facilitar a leitura e entendimento do conteúdo; • Nas tabelas, mesmo que o p-valor não seja significativo, apresentar o respectivo valor em vez de "NS" (por exemplo, p = 0,29 em vez de NS).

16. Os artigos deverão seguir a seguinte ordem: 16.1. Página de título 16.2. Texto 16.3. Agradecimentos 16.4. Legendas de figuras 16.5. Tabelas (com legendas para as siglas) 16.6. Referências

16.7. Primeira Página:

16.7.1. Deve conter o título completo do trabalho de maneira concisa e descritiva, em português e inglês, assim como um título resumido (com até 50 caracteres, incluindo espaços) para ser utilizado no cabeçalho das demais páginas do artigo;

16.7.2. Devem ser incluídos de três a cinco descritores (palavras-chave), assim como a respectiva tradução para as keywords (descriptors). Os descritores devem ser consultados nos sites: http://decs.bvs.br/, que contém termos em português, espanhol e inglês ou www.nlm.nih.gov/mesh, para termos somente em inglês;

16.8. Segunda Página:

16.8.1. Resumo (até 250 palavras): o resumo deve ser estruturado em cinco seções quando se tratar Artigo Original, evitando abreviações e observando o número máximo de palavras. No caso de Artigo de Revisão e Comunicação Breve, o resumo não é estruturado, respeitando o limite máximo de palavras. Não cite referências no resumo:

• Fundamento (racional para o estudo); • Objetivos; • Métodos (breve descrição da metodologia empregada); • Resultados (apenas os principais e mais significativos); • Conclusões (frase(s) sucinta(s) com a interpretação dos dados). Obs.: Os Relatos de Caso não devem apresentar resumo.

16.9. Texto para Artigo Original: deve ser dividido em introdução, métodos, resultados, discussão e conclusões.

16.9.1. Introdução:

16.9.1.1. Não ultrapasse 350 palavras.

16.9.1.2. Faça uma descrição dos fundamentos e do racional do estudo, justificando com base na literatura.

16.9.2. Métodos: descreva detalhadamente como foram selecionados os sujeitos da pesquisa observacional ou experimental (pacientes ou animais de experimentação, incluindo o grupo controle, quando houver), incluindo idade e sexo.

16.9.2.1. A definição de raças deve ser utilizada quando for possível e deve ser feita com clareza e quando for relevante para o tema explorado.

16.9.2.2. Identifique os equipamentos e reagentes utilizados (incluindo nome do fabricante, modelo e país de fabricação, quando apropriado) e dê detalhes dos procedimentos e técnicas utilizadas de modo a permitir que outros investigadores possam reproduzir os seus dados.

16.9.2.3. Justifique os métodos empregados e avalie possíveis limitações.

16.9.2.4. Descreva todas as drogas e fármacos utilizados, doses e vias de administração.

16.9.2.5. Descreva o protocolo utilizado (intervenções, desfechos, métodos de alocação, mascaramento e análise estatística).

16.9.2.6. Em caso de estudos em seres humanos, indique se o trabalho foi aprovado por um Comitê de Ética em Pesquisa e se os pacientes assinaram termo de consentimento livre e esclarecido.

16.9.3. Resultados: exibidos com clareza, subdivididos em itens, quando possível, e apoiados em número moderado de gráficos, tabelas, quadros e figuras. Evitar a redundância ao apresentar os dados, como no corpo do texto e em tabelas.

16.9.4. Discussão: relaciona-se diretamente ao tema proposto quando analisado à luz da literatura, salientando aspectos novos e importantes do estudo, suas implicações e limitações. O último período deve expressar conclusões ou, se pertinentes, recomendações e implicações clínicas.

16.9.5. Conclusões

16.9.5.1. Ao final da sessão “Conclusões”, indique as fontes de financiamento do estudo.

17. Agradecimentos: devem vir após o texto. Nesta seção, é possível agradecer a todas as fontes de apoio ao projeto de pesquisa, assim como contribuições individuais.

17.1. Cada pessoa citada na seção de agradecimentos deve enviar uma carta autorizando a inclusão do seu nome, uma vez que pode implicar em endosso dos dados e conclusões.

17.2. Não é necessário consentimento por escrito de membros da equipe de trabalho, ou colaboradores externos, desde que o papel de cada um esteja descrito nos agradecimentos. 18. Referências: os Arquivos seguem as Normas de Vancouver.

18.1. As referências devem ser citadas numericamente, por ordem de aparecimento no texto e apresentadas em sobrescrito.

18.2. Se forem citadas mais de duas referências em sequência, apenas a primeira e a última devem ser digitadas, separadas por um traço (Exemplo: 5-8).

18.3. Em caso de citação alternada, todas as referências devem ser digitadas, separadas por vírgula (Exemplo: 12, 19, 23). As abreviações devem ser definidas na primeira aparição no texto.

18.4. As referências devem ser alinhadadas à esquerda.

18.5. Comunicações pessoais e dados não publicados não devem ser incluídos na lista de referências, mas apenas mencionados no texto e em nota de rodapé na página em que é mencionado.

18.6. Citar todos os autores da obra se houver seis autores ou menos, ou apenas os seis primeiros seguidos de et al, se houver mais de seis autores.

18.7. As abreviações da revista devem estar em conformidade com o Index Medicus/Medline – na publicação List of Journals Indexed in Index Medicus ou por meio do site http://locatorplus.gov/.

18.8. Só serão aceitas citações de revistas indexadas. Os livros citados deverão possuir registro ISBN (International Standard Book Number).

18.9. Resumos apresentados em congressos (abstracts) só serão aceitos até dois anos após a apresentação e devem conter na referência o termo “resumo de congresso” ou “abstract”.

19. Política de valorização: os editores estimulam a citação de artigos publicados nos Arquivos.

20. Tabelas: numeradas por ordem de aparecimento e adotadas quando necessário à compreensão do trabalho. As tabelas não deverão conter dados previamente informados no texto. Indique os marcadores de rodapé na seguinte ordem: *, †, ‡, §, //,¶, #, **, ††, etc. O Manual de Formatação de Tabelas, Figuras e Gráficos para Envio de Artigos à Revista ABC está no endereço: http://publicacoes.cardiol.br/pub_abc/autor/pdf/manual_de_formatacao_abc.pdf

21. Figuras: as figuras submetidas devem apresentar boa resolução para serem avaliadas pelos revisores. As legendas das figuras devem ser formatadas em espaço duplo e estar numeradas e ordenadas antes das Referências. As abreviações usadas nas ilustrações devem ser explicitadas nas legendas. O Manual de Formatação de Tabelas, Figuras e Gráficos para Envio de Artigos à Revista ABC está no endereço: http://publicacoes.cardiol.br/pub_abc/autor/pdf/manual_de_formatacao_abc.pdf

22. Imagens e vídeos: os artigos aprovados que contenham exames (exemplo: ecocardiograma e filmes de cinecoronariografia) devem ser enviados através do sistema de submissão de artigos como imagens em movimento no formato MP4 com codec h:264, com peso de até 20 megas, para serem disponibilizados no site http://www.arquivosonline.com.br e nas revistas eletrônicas para versão tablet.

23. Os autores não são submetidos à taxa de submissão de artigos e de avaliação.