UNIVERSIDADE FEDERAL DE SÃO CARLOS
CENTRO DE CIÊNCIAS BIOLÓGICAS E DA SAÚDE
PROGRAMA DE PÓS-GRADUAÇÃO EM FISIOTERAPIA

VICTOR RIBEIRO NEVES

ESTUDO DA DINÂMICA DA FREQUÊNCIA CARDÍACA DO REPOUSO AO EXERCÍCIO FÍSICO EM PACIENTES COM DOENÇA ARTERIAL CORONARIANA

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Orientadora: Prof[a]. Dr[a]. Aparecida Maria Catai

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VICTOR RIBEIRO NEVES

PRIMEIRO ESTUDO:

Análise linear e não linear da variabilidade da frequência cardíaca na doença arterial coronariana

Linear and nonlinear analysis of heart rate variability in coronary disease

SEGUNDO ESTUDO:

Dinâmica da frequência cardíaca no pós-exercício em pacientes com doença arterial coronariana com e sem diabetes tipo 2

Heart rate dynamics after exercise in cardiac patients with and without type 2 diabetes

Orientadora: Prof[a]. Dr[a]. Aparecida Maria Catai

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Dedicatória

Dedico essa tese...

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(2º Timóteo Cap 2 Vers 22)

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RESUMO

O estudo da variabilidade da frequência cardíaca (VFC) tem sido utilizado para avaliar o controle autonômico da frequência cardíaca de diferentes populações, tanto em condições de repouso quanto durante a realização de exercício físico. A redução da modulação autonômica cardíaca tem sido observada em pacientes com doença arterial coronariana (DAC), sendo que, a progressão da DAC para o infarto agudo do miocárdio (IAM), pode estar relacionada a um desequilíbrio simpatovagal. A VFC tem sido tradicionalmente avaliada por métodos lineares, entretanto, nos últimos anos, alguns métodos não lineares têm fornecido dados adicionais os quais não são identificados pela análise linear. Assim, o primeiro estudo teve o objetivo de comparar a VFC de pacientes com DAC com e sem IAM com saudáveis da mesma faixa etária por meio da análise linear (análise espectral) e não-linear [Entropia de Shannon (ES), entropia condicional (EC) e análise simbólica (AS)]. Foram selecionados 56 homens que foram divididos em 3 grupos: saudável (n=19, 57±4), DAC (n=20, 56±10) e DAC-IAM (n=19, 54±12). Não houve diferença entre os grupos com relação a modulação autonômica cardíaca avaliada com os métodos linear (análise espectral) e não-linear (SA, ES e EC). Esses resultados podem ser devidos ao uso de betabloqueador, angioplastia coronariana, a capacidade física dos indivíduos saudáveis bem como o protocolo utilizado. Conclui-se que, nas condições estudadas, os métodos de análise utilizados não mostraram diferenças na modulação autonômica cardíaca entre os grupos estudados. Por outro lado, a DAC pode estar acompanhada de diabetes tipo 2 (DT2), que é uma doença que agrava o comprometimento da modulação autonômica cardíaca. Outro método usado para esse trabalho, foi estudo da resposta da frequência cardíaca e da sua variabilidade no período de recuperação e após o exercício físico. Há evidências que a recuperação após o exercício é uma fase vulnerável a vários eventos cardiovasculares. Portanto, o segundo estudo teve o objetivo de avaliar a regulação autonômica de pacientes com DAC com e sem DT2 na condição pós-exercício. Foram avaliados 132 pacientes divididos em 2 grupos: DAC (n=68, 61±5 anos) e DAC+DT2 (n=64, 62±5 anos) os quais foram submetidos a um teste cardiopulmonar sintoma limitado. Os resultados do segundo estudo indicam que os pacientes do grupo DAC+DT2 apresentaram uma atraso na FC de recuperação no pós-exercício quando comparados com aqueles do grupo DAC. Entretanto, após o ajuste com índice de massa corporal, capacidade física e medicação, as diferenças observadas entre os grupos em relação a FC de recuperação, desapareceram. Portanto,

os resultados do segundo estudo sugerem que a perda do controle autonômico da FC no pós exercício observado nos pacientes DAC+DT2 pode estar mais relacionado a baixa capacidade física e a obesidade que a DT2 por si mesma.

ABSTRACT

The study of heart rate variability (HRV) has been used to assess the cardiac autonomic control in different population both on the supine position and during exercise test. The reduction of cardiac autonomic control has been observed in coronary artery disease (CAD) patients, since the progression of CAD to acute myocardial infarction (AMI) can be related with symphatovagal imbalance. The HRV has been traditionally assessed by linear methods, but in recent years, the use of some nonlinear methods has provided additional data, which does not uncovered by linear analysis. Thereby, the first study had the aim to compare the HRV of CAD patients with and without AMI (CAD-AMI) with health-matched controls by linear (spectral analysis) and nonlinear (Shannon entropy, conditional entropy and symbolic analysis). Fifty-six men were divided into three groups: healthy (n=19, 57±4 years), CAD (n=20, 56±10 years) and CAD-AMI (n=19, 54±12 years). There was no difference between the groups regarding cardiac autonomic modulation by linear (spectral analysis) and nonlinear (Shannon entropy, conditional entropy and symbolic analysis). These results may be due to beta-blocker use, coronary angioplasty, exercise capacity of healthy subjects and methodology this study. Thereby, in studied conditions, methods of analysis used showed no difference in cardiac modulation between groups. On the other hand, CAD can be to take together type 2 diabetes (T2D), which is a disease that worsens the impairment of cardiac autonomic modulation. Other method used in this study, is assessment the behavior of hear rate response and variability in the phase recovery after physical exercise. Therefore, the incidence of cardiovascular events is higher in CAD patients with type 2 diabetes (CAD+T2D) than in CAD patients without T2D. There is increasing evidence that the recovery phase after exercise is a vulnerable phase for various cardiovascular events. However, the second study had the aim to assess the autonomic regulation of CAD patients with and without T2D during post-exercise condition. One-hundred-two patients were divided into two groups: CAD (n=68, 61±5 years) e DAC+DT2 (n=64, 62±5 years), which underwent cardiopulmonary exercise testing. The result of second study indicated that DAC+T2D patients had a higher delay of heart rate recovery in comparison with DAC patients without T2D. However, there no differences between the groups in heart rate recovery after adjustment for exercise capacity, body mass index and medications. Thereby, the result of this second study suggesting impairment of cardiac autonomic control after exercise in diabetic patients compared

with non-diabetic patients is more closely related to low exercise capacity and obesity than to T2D itself.

LISTA DE ILUSTRAÇÕES

Primeiro Estudo:

Figura 1: Fluxograma da amostra dos pacientes com doença arterial coronariana (DAC) sem e com infarto do miocárdio (DAC-IAM) e saudável. DPOC, doença pulmonar obstrutiva crônica; CRVM, cirurgia de revascularização do miocárdio; AVC, acidente vascular cerebral; AV, atrioventricular; ICP, intervenção coronariana percutânea..... **28**

Segundo Estudo:

Figura 1: Exemplo da frequência cardíaca de recuperação, mostrada com ajuste linear dos dados de FC durante os primeiros 60 segundos após a interrupção do exercício, para dois pacientes (com e sem diabetes tipo 2), com similar idade e frequência cardíaca máxima. A reta foi calculada pelo modelo linear usando a média de cinco intervalos R-R (convertidos para valores de FC em bpm como 60.(média dos intervalos R-R em ms/100^{-1}) no pico do esforço e nos pontos de 15, 30 e 60 segundos após a interrupção do exercício.....……..... **48**

LISTA DE TABELAS

Primeiro Estudo

Tabela 1: Características dos grupos saudável, pacientes com doença arterial coronariana (DAC) sem e com infarto do miocárdio (DAC-IAM)..... **32**

Tabela 2: Dados clínicos, angiográficos, fatores de risco e medicações dos grupos doença arterial coronariana (DAC) sem e com infarto do miocárdio (DAC-IAM)..... **33**

Tabela 3: Entropia de Shannon (SE), entropia condicional (EC) e análise simbólica e espectral da variabilidade da frequência cardíaca dos grupos saudável, com doença arterial coronariana (DAC) sem e com infarto do miocárdio (DAC-IAM)..... **34**

Tabela 4: Correlações entre os índices da análise simbólica (padrões 0V%, 1V%, 2LV% e 2ULV%) e Entropia de Shannon [índice de complexidade (IC) e índice de complexidade normalizada (ICN)], para os grupos saudável, doença arterial coronariana (DAC) sem e com infarto do miocárdio (DAC-IAM)..... **39**

Segundo Estudo:

Tabela 1: Características dos pacientes..... **50**

Tabela 2: Capacidade física máxima e frequência cardíaca de recuperação..... **51**

Tabela 3: Valores médios das análises linear e não linear da variabilidade da frequência cardíaca antes do exercício (5 min) e na condição pós–exercício, de 3 a 8 minutos, na posição supina..... **53**

LISTA DE ABREVIATURAS

ACTP	Angioplastia coronariana transluminal percutânea
AF	Alta frequência
AFun	Alta frequência em unidade normalizada
AS	Análise simbólica
BF	Baixa frequência
BFun	Baixa frequência em unidade normalizada
BF/AF	Razão entre baixa frequência e alta frequência
CRI	Índice cronotrópico
DAC	Doença arterial coronariana
DT2	Diabetes tipo 2
EC	Entropia condicional
ES	Entropia de Shannon
FC	Frequência cardíaca
FC_{rec}	Frequência cardíaca de recuperação
FC_{rec120}	Frequência cardíaca de recuperação nos 120 segundos
FC_{rec15}	Frequência cardíaca de recuperação nos 15 segundos
FC_{rec30}	Frequência cardíaca de recuperação nos 30 segundos
FC_{rec60}	Frequência cardíaca de recuperação nos 60 segundos
$FC_{slope60}$	Ajuste linear da frequência cardíaca nos primeiros 60 segundos após o exercício
HbA1c	Hemoglobina glicosilada
IAM	Infarto agudo do miocárdio
IC	Índice de complexidade
ICN	Índice de complexidade normalizado
iRR	Intervalo R–R
MET	Equivalente metabólico
RMSSD	Raiz quadrada da somatória da diferença entre os intervalos RR e seu adjacente, elevada ao quadrado, dividido pelo número de intervalos RR num determinado período, menos um
SDNN	Desvio padrão dos intervalos R-R
VFC	Variabilidade da frequência cardíaca
V_E	Ventilação

VO_2	Consumo de oxigênio
VO_{2peak}	Pico do consumo do oxigênio
W	Watt

SUMÁRIO

1. CONTEXTUALIZAÇÃO……... 18

2. PRIMEIRO ESTUDO……. 23

2.1. RESUMO…… 24

2.2. INTRODUÇÃO…….. 25

2.3. METODOLOGIA……..... 26

2.3.1. SUJEITOS……... 26

2.3.2. PROCEDIMENTOS EXPERIMENTAIS…… 29

2.3.3. PROTOCOLO EXPERIMENTAL……... 29

2.4. ANÁLISES DE DADOS…… 30

2.4.1. ANÁLISE ESPECTRAL DA VFC……. 30

2.4.2. ENTROPIA DE SHANNON……..…….. 30

2.4.3. ANÁLISE SIMBÓLICA……..…… 31

2.4.4. ENTROPIA CONDICIONAL…… 31

2.5. ANÁLISE ESTATÍSTICA..…….. 31

2.6. RESULTADOS……..……. 32

2.7. DISCUSSÃO..……. 37

2.7.1. LIMITAÇÃO…… 40

2.8. AGRADECIMENTOS.……. 41

3. SEGUNDO ESTUDO…….. 42

3.1. RESUMO……..…….…….. 43

3.2. INTRODUÇÃO…..…….…… 44

3.3. MATERIAIS E MÉTODOS….……. 45

3.3.1. PACIENTES E PROTOCOLO DE ESTUDO……... 45

3.3.2. TESTE CARDIOPULMONAR…….….. 46

3.3.3. VARIABILIDADE FREQUÊNCIA CARDÍACA...…..……...……. 48

3.4. ESTATÍSTICA…….....…….……..……. 49

3.5. RESULTADOS.……..……. 49

3.5.1. POPULAÇÃO DO ESTUDO.…….. 49

3.5.2. TESTE CARDIOPULMONAR……... 51

3.5.3. FREQUÊNCIA CARDÍACA E SUA VARIABILIDADE…… 52

3.6. DISCUSSÃO.……. 53

3.6.1. DINÂMICA DA FC NO PÓS-EXERCÍCIO..……...…. 54

3.6.2. RESPOSTA DA FC AO EXERCÍCIO MÁXIMO..…….. 54

3.6.3. VARIABILIDADE DA FREQUÊNCIA CARDÍACA…...…… 55

3.6.4. LIMITACOES DO ESTUDO..…...……. 56

3.6.5. APLICACÃO CLINICA…..……...……. 56

3.6.6. CONCLUSÃO……...…..…….. 57

3.7. AGRADECIMENTOS..……...……... 57

4. CONSIDERAÇÕES FINAIS…….. 58

5. OUTRAS ATIVIDADES REALIZADAS DURANTE O PERÍODO DO DOUTORADO……. 60

5.1. Participação em outros projetos no Laboratório de Fisioterapia Cardiovascular..... 60

5.2. Atividades relacionadas ao estágio de doutorado sanduíche..... 61

5. REFERÊNCIAS……... 63

ANEXO A……. 74

ANEXO B……. 97

ANEXO C……. 105

ANEXO D……. 114

ANEXO E……. 136

ANEXO F……. 141

ANEXO G……. 144

ANEXO H……. 148

ANEXO I……... 153

1. CONTEXTUALIZAÇÃO

1. CONTEXTUALIZAÇÃO

A doença cardiovascular continua sendo uma das principais causas de morte nos países desenvolvidos e no mundo. A prevalência da doença arterial coronariana (DAC) varia de 5% a 8% na população economicamente ativa acima de 40 anos e é responsável por quase 32% dos óbitos no Brasil (Polanczyk e Ribeiro, 2009). Estilo de vida sedentário, obesidade, dislipidemia e diabetes são os principais fatores de risco para doenças cardiovasculares (Piegas *et al.*, 2003; Avezum *et al.*, 2009; Chow *et al.*, 2010). Ainda, dentre as doenças cardiovasculares, o infarto agudo do miocárdio (IAM) é uma das maiores causas de morbidade e mortalidade, principalmente no Brasil. (Piegas *et al.*, 2003; Avezum *et al.*, 2009; Polanczyk e Ribeiro, 2009).

Além dos fatores de riscos bem conhecidos, como a obesidade e o tabagismo, a diabetes tipo 2 é outra doença que também está relacionada ao estilo de vida sedentário. O surgimento dessa patologia está diretamente relacionado com a obesidade e, consequentemente, aumenta o risco do surgimento de doenças cardiovasculares (Avezum *et al.*, 2009; Polanczyk e Ribeiro, 2009). Portanto, o estilo de vida sedentário e os maus hábitos alimentares, podem favorecer o aparecimento do diabetes mellitus (Tentolouris *et al.*, 2008).

Vários trabalhos têm apresentado os efeitos fisiopatológicos da DAC sobre o organismo e a sua relação com o sistema nervoso autonômico cardíaco (Wennerblom *et al.*, 2000; Montano *et al.*, 2009; Routledge *et al.*, 2010). Esta patologia pode favorecer o aumento da atividade simpática e/ou redução da atividade vagal sobre o coração (Wennerblom *et al.*, 2000; Hautala *et al.*, 2009; Montano *et al.*, 2009) e, portanto, deflagrar arritmias malignas que podem levar a morte súbita (Taskforce, 1996). Além disso, esta disfunção autonômica pode levar ao aumento da formação de gordura corporal, à maior sobrecarga renal com alta concentração plasmática de catecolaminas na urina, à disfunção barorreflexa, ao aumento da pressão arterial e frequência cardíaca ao repouso, e finalmente, à redução da variabilidade da frequência cardíaca (Tentolouris *et al.*, 2008), variável amplamente empregada no estudo do controle autonômico sobre o coração (Taskforce, 1996).

Assim, a variabilidade da frequência cardíaca (VFC) é uma medida simples, não-invasiva e altamente reprodutível na avaliação da função do sistema nervoso autonômico cardíaco simpático e parassimpático (Taskforce, 1996; Kleiger *et al.*, 2005; Montano *et al.*, 2009). Indivíduos que apresentam uma maior VFC de

repouso, possuem uma maior habilidade do sistema nervoso autonômico cardíaco e do nodo sinusal em responder dinamicamente as alterações ambientais, e isso geralmente é indicativo de um coração saudável. Do contrário, uma VFC reduzida pode indicar uma incapacidade ou atenuação do sistema nervoso autonômico ou do nodo sinusal se adaptar as respostas oriundas do meio externo (Catai *et al.*, 2002; Kleiger *et al.*, 2005; Hautala *et al.*, 2009; Montano *et al.*, 2009). A relevância do estudo do controle autonômico da frequência cardíaca para a cardiologia clínica vem desde o final da década de 1980, quando os resultados do dano da função autonômica foram observados com o objetivo de predizer a mortalidade entre pacientes com DAC que tinham sofrido um IAM (Kleiger *et al.*, 1987; Bigger *et al.*, 1988).

O estudo da VFC pode ser realizado por meio de metodologias lineares e não lineares. Das metodologias lineares utilizadas, as mais conhecidas são as medidas do domínio do tempo e da frequência. Os métodos no domínio do tempo são calculados, a partir de métodos estatísticos, e fornecem os seguintes índices: SDNN, desvio padrão dos intervalos R-R; RMSSD, raiz quadrada da somatória da diferença entre os intervalos RR e seu adjacente elevado ao quadrado, dividido pelo número de intervalos RR num determinado período, menos um. Esses índices avaliam a variabilidade total e a modulação vagal, respectivamente (Antila, 1979; Kleiger *et al.*, 2005). Já o método no domínio da freqüência, utilizando-se a análise espectral, decompõe a série temporal em componentes oscilatórios fundamentais por meio da transformada rápida de Fourier ou do modelo autorregressivo. Assim, a análise da densidade da potência espectral fornece a informação básica de como a potência é distribuída como uma função da frequência. As principais bandas espectrais são: a) alta frequência (AF – varia de 0,15 a 0,4 Hz), que corresponde à modulação respiratória e é um indicador da modulação vagal sobre o coração; b) baixa frequência (BF – varia de 0,04 a 0,15 Hz), que representa a interação simpatovagal, com predomínio da modulação simpática, portanto, utilizada como um marcador da modulação simpática; e c) muito baixa frequência (MBF – varia de 0 a 0,04 Hz), que parece estar relacionada ao sistema renina-angiotensina-aldosterona, termorregulação e tônus vasomotor periférico, mas a sua explicação fisiológica não está claramente definida (Montano *et al.*, 1994; Kleiger *et al.*, 2005; Montano *et al.*, 2009).

A associação do valor prognóstico dos índices VFC com as doenças cardiovasculares tem sido amplamente estudada. Um estudo clássico observou que a VFC reduzida poderia ser um importante preditor de eventos cardiovasculares

subsequentes em pacientes com DAC ou insuficiência cardíaca congestiva (Tsuji *et al.*, 1996). Outro estudo avaliou os índices espectrais dos intervalos RR de curta duração (de 2 a 15 min) em 715 pacientes duas semanas após o IAM e observaram que esses índices são excelentes preditores de toda causa de mortalidade e morte súbita cardíaca. Ainda, foi observado que o índice AF pode ser considerado um importante preditor de evento isquêmico (Liao *et al.*, 1997).

No entanto, os métodos não lineares da VFC têm despertado forte interesse nos últimos anos, pois eles revelam informações complementares de uma série temporal quando comparados com os métodos lineares, mas os mecanismos fisiológicos por trás dessas metodologias ainda são pouco conhecidos. Diferentemente dos métodos lineares, esses métodos objetivam avaliar a qualidade e não a magnitude do sinal (Huikuri *et al.*, 2009). Há vários algoritmos de análise não linear para avaliar a complexidade da frequência cardíaca. Por exemplo, a entropia de Shannon (ES) fornece informações adicionais sobre a distribuição da sequência de batimentos (padrões) em uma série de intervalos RR (Porta *et al.*, 2001). Além disso, a análise simbólica (AS) pode distinguir esses padrões e relacioná-los a modulação simpática e parassimpática (Guzzetti *et al.*, 2005; Porta, Tobaldini*, et al.*, 2007). A entropia condicional (EC) fornece informações da organização do batimento cardíaco, i.e., se essa sequência de batimentos repete-se no tempo ou não (Porta, Faes*, et al.*, 2007). Além disso, os índices de complexidade e da dinâmica simbólica da VFC têm sido utilizados em diversas populações (Porta, Faes*, et al.*, 2007; Kunz *et al.*, 2011; Perseguini *et al.*, 2011; Porta *et al.*, 2011; Takahashi *et al.*, 2011). De acordo com esses estudos, a menor complexidade e o desequilíbrio simpato-vagal podem estar relacionados com o aumento da idade, a insuficiência cardíaca crônica, e a doença arterial coronariana (Porta, Faes*, et al.*, 2007; Kunz *et al.*, 2011; Perseguini *et al.*, 2011; Porta *et al.*, 2011; Takahashi *et al.*, 2011).

Portanto, o primeiro estudo foi realizado com o objetivo de avaliar a variabilidade da frequência cardíaca por meio de análises linear (espectral) e não lineares, como a análise simbólica (SA), entropia de Shannon (ES) e entropia condicional (EC), em pacientes com DAC e IAM.

Conjuntamente ao estudo da VFC em repouso, o estudo do comportamento da FC durante o exercício físico também tem sido utilizado para avaliar a integridade do sistema nervoso autonômico durante um período de estresse fisiológico. Sabidamente, o teste de exercício físico máximo além de fornecer

informações referentes a capacidade física, pode fornecer importantes informações sobre as respostas da FC e sua relação com doenças cardiovasculares, como a DAC, e o diabetes mellitus (Hautala *et al.*, 2009; Routledge *et al.*, 2010). Além disso, o estudo da dinâmica da FC durante o período de recuperação tem fornecido importante informação prognóstica para o surgimento de arritmias e morte súbita, principalmente nos primeiros minutos após a interrupção do exercício, pois essas alterações da resposta da FC no pós exercício podem estar relacionadas ao desequilíbrio simpatovagal (Siscovick *et al.*, 1982; Siscovick *et al.*, 1984; Albert *et al.*, 2000; Von Klot *et al.*, 2008).

Dessa forma o segundo estudo foi realizado afim de avaliar a dinâmica da FC durante a realização do exercício e na fase de recuperação pós-exercício em pacientes com DAC com e sem diabetes. Pressupunha-se que os resultados desse estudo possibilitaria maior precisão na prescrição de exercício físico para essa população, tendo em vista que a fisioterapia, se utiliza de exercícios físicos, como importante recurso no tratamento e prevenção dessa patologia.

Os estudos desenvolvidos são apresentados a seguir: o primeiro estudo foi submetido ao periódico *Clinical Autonomic Research* e o segundo estudo publicado no periódico *Frontiers in Physiology*. Os textos originais estão apresentados nos anexos A e B, respectivamente.

2. PRIMEIRO ESTUDO

(Versão do artigo em português)

ANÁLISE LINEAR E NÃO LINEAR DA VARIABILIDADE DA FREQUENCIA CARDÍACA NA DOENÇA CORONARIANA

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2. PRIMEIRO ESTUDO

ANÁLISE LINEAR E NÃO LINEAR DA VARIABILIDADE DA FREQUÊNCIA CARDÍACA NA DOENÇA CORONARIANA

2.1. Resumo

A doença arterial coronariana (DAC) e o infarto agudo do miocárdio (IAM) estão associados com a redução da variabilidade da frequência cardíaca (VFC). **Objetivo:** O objetivo do estudo foi comparar a VFC de pacientes com e sem IAM com indivíduos saudáveis por meio da análise linear (análise espectral) e não-linear (entropia de Shannon (ES), entropia condicional (EC) e análise simbólica (AS)). **Métodos:** Cinquenta e seis homens foram divididos em três grupos: saudável (n = 19, 57 ± 4 anos), DAC (n = 20, 56 ± 10 anos) e DAC-IAM (n = 19, 54 ± 12 anos). Os intervalos RR foram registrados em repouso na posição supina durante 10 minutos por meio de um monitor cardíaco (Polar ®S810i). Uma série temporal de 250 batimentos foi selecionada para analisar a variância, ES, EC (índice de complexidade (IC), IC normalizado (ICN)), AS (padrões 0V, 1V, 2LV e 2ULV) e análise espectral. O padrão 0V e o padrão 2ULV refletem a modulação simpática e vagal, respectivamente. Foi realizado o teste ANOVA de um fator (ou Kruskal-Wallis, quando apropriado) e a correlação de Pearson. **Resultados:** O grupo DAC apresentou maior massa e índice de massa corporal que o grupo DAC-IAM, mas nenhuma diferença foi observada entre os grupos saudável e DAC-IAM. Com relação à análise espectral, AS, ES, IC e NCI, a diferença entre os grupos não atingiram significância estatística. Os padrões 0V e 2ULV tiveram correlação significativa com ES, IC e ICN para os três grupos. **Interpretação:** Não houve nenhuma diferença entre os grupos em relação a modulação autonômica cardíaca pela análise espectral, ES, EC e AS. A inexistência de diferenças entre os grupos avaliadas pela análise linear e não linear da VFC de repouso podem ser devidos a terapia beta-bloqueadora, angioplastia coronariana, capacidade física dos indivíduos saudáveis e o protocolo de avaliação utilizado.

Palavras-chaves: Variabilidade da frequência cardíaca; Sistema nervoso autonômico; Infarto Agudo do Miocárdio; Doença arterial coronariana; Análise simbólica; Entropia condicional.

2.2. Introdução

A progressão da doença arterial coronariana (DAC) para o infarto agudo do miocárdio (IAM) pode estar relacionada ao desequilíbrio simpatovagal (Taskforce, 1996; Routledge *et al.*, 2010). Alguns trabalhos têm mostrado que a maior modulação simpática observada em pacientes com DAC com IAM pode levar a arritmias e morte súbita (Taskforce, 1996; Montano *et al.*, 2009). Ainda, as alternâncias elétricas e as arritmias ventriculares podem estar associadas com uma maior redução da variabilidade da frequência cardíaca (VFC) em pacientes com IAM recente (Liew, 2010) mesmo sendo submetidos à angioplastia coronariana (Pelicano *et al.*, 2006).

A VFC avaliada por meio de métodos lineares e não lineares tem sido utilizada para descrever a interação fisiológica entre o coração e o sistema nervoso autonômico (Taskforce, 1996; Huikuri *et al.*, 2009; Voss *et al.*, 2009). Nos últimos anos, os métodos não lineares têm revelado algumas modificações da dinâmica da frequência cardíaca que não são observadas pelos métodos lineares, como a análise espectral (Porta, Faes*, et al.*, 2007; Porta, Tobaldini*, et al.*, 2007; Huikuri *et al.*, 2009; Voss *et al.*, 2009).

Vários estudos têm mostrado o desbalanço autonômico em pacientes com DAC e IAM pelos métodos lineares, como a análise espectral (Taskforce, 1996; Sztajzel, 2004; Montano *et al.*, 2009; Routledge *et al.*, 2010). Entretanto, os métodos não lineares não estão ainda bem estabelecidos para essa população e, portanto, esses métodos podem fornecer informações adicionais sobre o controle autonômico cardíaco de pacientes com DAC com e sem IAM.

Há vários algoritmos de análise não linear para avaliar a complexidade da frequência cardíaca. Por exemplo, a entropia de Shannon (ES) fornece informações sobre a distribuição da sequência de batimentos (padrões) em uma série de intervalos RR (Porta *et al.*, 2001). Ainda, a análise simbólica pode distinguir esses padrões e relacioná-los a modulação simpática e parassimpática (Guzzetti *et al.*, 2005; Porta, Tobaldini*, et al.*, 2007). A entropia condicional (EC) fornece informações da organização do batimento cardíaco, i.e., se essa sequência de batimentos repete-se no tempo ou não (Porta, Faes*, et al.*, 2007).

Sendo assim, a hipótese do presente estudo foi que o desbalanço autonômico cardíaco nos pacientes com doença arterial coronariana com e sem IAM (Taskforce, 1996; Sztajzel, 2004; Montano *et al.*, 2009) poderia ser detectado pela ES,

EC e AS, obtidas de uma série de curta duração da VFC. Adicionalmente, seria esperado que os pacientes coronarianos com IAM apresentassem complexidade reduzida, maior modulação simpática e menor modulação vagal da VFC do que os coronarianos sem IAM e os indivíduos saudáveis.

Portanto, o objetivo do estudo foi comparar a VFC de indivíduos saudáveis, coronarianos com e sem IAM por meio das análises lineares e não lineares.

2.3. Metodologia

2.3.1. Sujeitos

Esse estudo descritivo transversal foi realizado no período de 2008 a 2011 e incluiu pacientes com DAC com e sem IAM e indivíduos saudáveis do gênero masculino. Este trabalho foi realizado na Santa Casa de Misericórdia de São Carlos e no Laboratório de Fisioterapia Cardiovascular do Núcleo de Pesquisa em Exercício Físico da Universidade Federal de São Carlos (São Carlos, Brasil), respectivamente. Este estudo foi executado de acordo com a Declaração de Helsinki e aprovado pelo Comitê de Ética em Pesquisa em Seres Humanos da Universidade Federal de São Carlos, São Carlos, SP, Brasil (protocolos números 387/2008 e 160/2010). Todos os voluntários e pacientes foram informados sobre os objetivos do estudo, protocolo experimental e assinaram um termo de consentimento pós-informado.

Foram avaliados 222 indivíduos de acordo com as seguintes condições clínicas: sujeitos saudáveis (n = 23) (grupo Saudável) e pacientes com DAC (n = 199). Todos os voluntários do grupo saudável, foram considerados aparentemente saudáveis com base na avaliação clínica e exame físico, testes laboratoriais, eletrocardiograma de 12 derivações e teste ergométrico clínico, conduzido por um cardiologista. O grupo saudável também foi submetido a um teste cardiopulmonar sintoma-limitado para avaliar a capacidade física pelo consumo de oxigênio obtido no pico do esforço (VO_{2pico}).

Os critérios de exclusão do grupo saudável foram: indivíduos com hipertensão arterial, diabetes, lesões neurológicas, doenças cardiovasculares, pulmonares e músculo-esquelética, tabagismo, usuários de drogas e etilismo.

Os pacientes com DAC foram divididos em dois grupos: grupo DAC (n = 91), sujeitos que tinham a doença arterial coronariana documentada por angiografia coronariana e sem história de IAM; e grupo DAC-IAM (n = 108), sujeitos que tinham a doença arterial coronariana documentada por angiografia, e sofrido o

primeiro infarto agudo do miocárdio, Killip I ou II, com supra desnivelamento do segmento ST há menos de 24 horas. Todos os pacientes do grupo DAC-IAM foram submetidos a angioplastia coronariana transluminal percutânea (ACTP) primária ou eletiva com sucesso e sem qualquer complicação.

Os critérios de exclusão dos pacientes do grupo DAC foram: pacientes com hipertensão arterial (níveis pressóricos > 180/100 mmHg), fibrilação atrial, arritmias ventriculares malignas, batimentos ventriculares ectópicos complexos, taquicardia supraventricular ou sinusal (maior que 120 bpm), bloqueio atrioventricular de 2^{o} e 3^{o}, implante de marca-passo, sinais de baixo débito cardíaco ou falência ventricular, hipotensão e insuficiência cardíaca, debilidade, febre, insuficiência respiratória, doença pulmonar obstrutiva crônica, sequelas de acidente vascular cerebral, amputação de membro inferior, estenose aórtica severa, idade > 35 e < 75 anos, severa lesão de tronco de coronária esquerda (>50%) ou cirurgia de revascularização do miocárdio prévia. Ainda, foram excluídos os pacientes do grupo DAC-IAM que apresentaram IAM complicado, dor torácica pós-IAM, re-infarto ou admissão hospitalar 48 horas pós-IAM.

Dos 222 indivíduos avaliados inicialmente, apenas 58 preencheram os critérios de inclusão e exclusão e foram distribuídos nos diferentes grupos: DAC (n = 20, 56 ± 10 anos), DAC-IAM (n = 20, 54 ± 12 anos) e saudável (n = 19, 57 ± 4 anos).

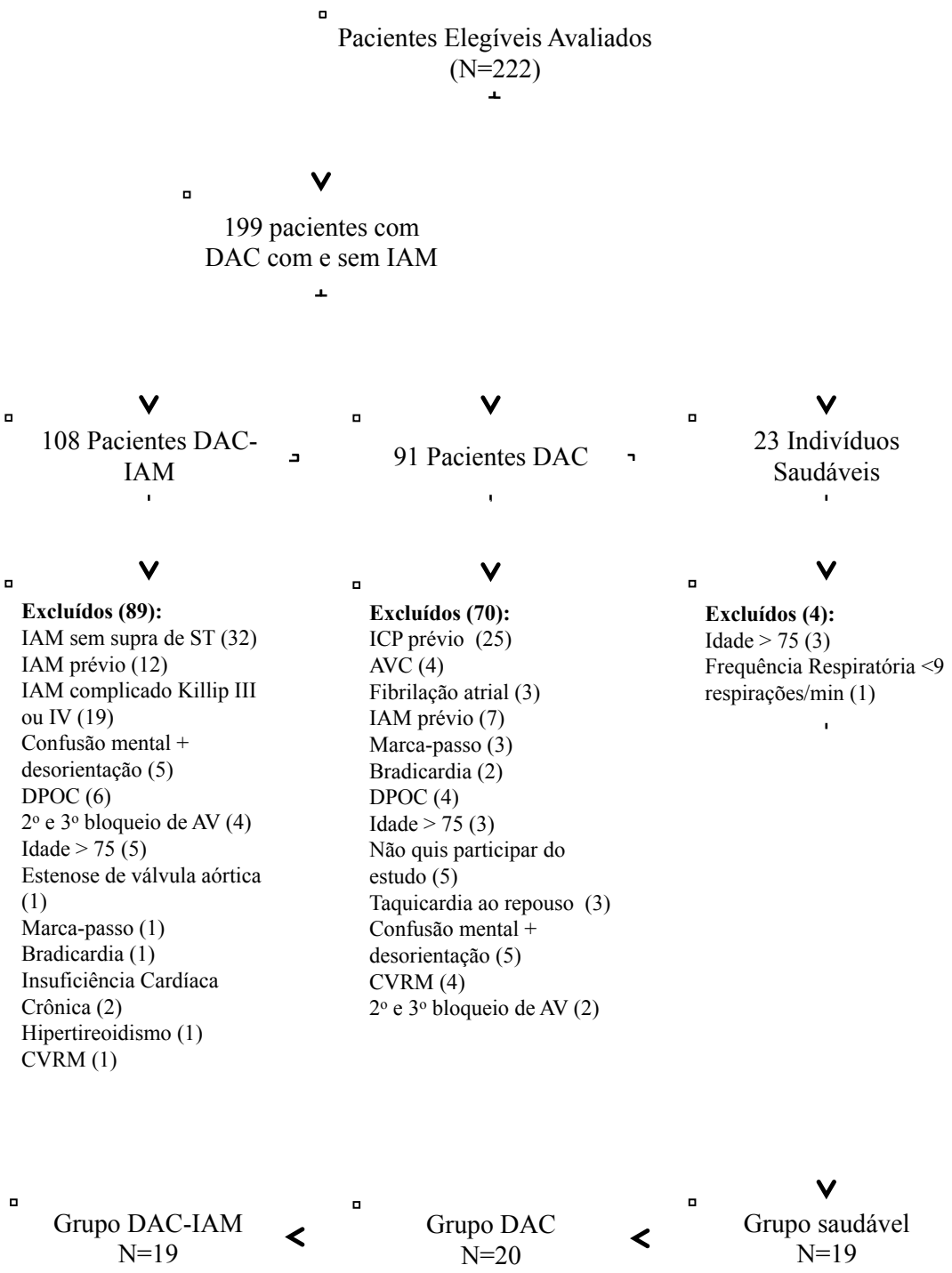

Figura 1: Fluxograma da amostra dos pacientes com doença arterial coronariana (DAC) sem e com infarto do miocárdio (DAC-IAM) e saudável.

DPOC, doença pulmonar obstrutiva crônica: CVRM, cirurgia de revascularização do miocárdio; AVC, acidente vascular cerebral; AV, atrioventricular; ICP, intervenção coronariana percutânea.

2.3.2. Procedimentos experimentais

Os grupos saudável e DAC foram instruídos a evitar bebidas alcoólicas e com cafeína, bem como a realização de qualquer exercício extenuante no dia, antes da realização do protocolo. Adicionalmente, eles foram instruídos a terem uma alimentação leve pelo menos 2 horas antes do protocolo experimental. No dia do experimento, os voluntários e os pacientes foram entrevistados e examinados antes do teste para verificar se eles estavam em boas condições de saúde e/ou clinicamente estáveis. Os experimentos foram realizados em uma sala climatizada (21-24^{o}C) com umidade relativa do ar de 40-60%. Antes de realizar os experimentos, os voluntários foram familiarizados com os equipamentos e os procedimentos experimentais a fim de reduzir a ansiedade. Além disso, os pacientes do grupo DAC foi avaliado 7 dia após a realização do cateterismo cardíaco.

Em relação ao grupo DAC-IAM, o protocolo experimental foi realizado na Unidade Coronariana do Hospital local com média de 22 ± 5 horas depois da admissão e de 12 a 24 horas após o diagnóstico de IAM. Antes de iniciar o protocolo, foram realizadas avaliações clínicas baseadas nos exames físico, clínico e testes laboratoriais (concentração de enzima CK-MB, contagem sanguínea total, raio-X de tórax, ECG de 12 derivações e angiografia coronariana). Os pacientes também foram familiarizados com a equipe e o procedimento experimental a fim de reduzir a ansiedade na Unidade Coronariana.

2.3.3. Protocolo Experimental

Todos os indivíduos permaneceram em repouso com respiração espontânea por um período de 10 minutos na posição supina. Após esse período, iniciaram-se os registros dos intervalos R-R, por mais um período de 10 minutos. No início e no final do experimento, foram realizadas as medidas de pressão arterial pelo método auscultatório.

Os intervalos R-R (iRR) foram registrados durante o repouso na posição supina por meio de sistema de telemetria digital que consiste de um transmissor posicionado no tórax do paciente e de um monitor de FC (Polar® S810i; Polar Electro Oy, Kempele, Finland) (Loimaala *et al.*, 1999; Soares *et al.*, 2005). Este sistema detecta a despolarização ventricular que corresponde às ondas R do eletrocardiograma, com uma taxa de amostragem de 500 Hz e um resolução temporal

de 1 ms (Ruha *et al.*, 1997), e foi previamente validado (Loimaala *et al.*, 1999). Os sinais foram transmitidos para um receptor e depois para o computador para uma posterior análise.

2.4. Análise dos dados

A sequência de iRR com 250 batimentos e com maior estabilidade foi selecionada para cada sujeito. A mesma sequência foi utilizada para as análises linear e não-linear. Ainda, a média e a variância dos iRR também foram calculadas.

2.4.1. Análise espectral da VFC

A análise da VFC no domínio da frequência foi realizada por meio de modelo autorregressivo (Pagani *et al.*, 1986; Malliani *et al.*, 1991) aplicado aos dados da sequência dos iRR previamente selecionados. Foram considerados dois componentes espectrais: baixa frequência (BF - de 0.04 a 0.15 Hz) e alta frequência (AF - de 0.15 a 0.50 Hz), pois eles representam melhor a modulação simpática e parassimpática, respectivamente (Taskforce, 1996). Os componentes espectrais foram expressos em unidades normalizadas (BFun e AFun) e a razão BF/AF. A normalização consistiu da divisão da potência de um dado componente espectral (AF ou BF) pela potência total menos a potência abaixo de 0,04 Hz, e multiplicando a razão por 100 (Malliani *et al.*, 1991). Todos os voluntários apresentaram frequências respiratórias dentro da variação da banda AF (de 0.15 a 0.50 Hz), i. é., maior que 9 respirações por minuto.

2.4.2. Entropia de Shannon

Os iRR foram transformados dentro de uma sequência de símbolos (números) que variam de 0 a 5. Em seguida, foi realizada a construção dos padrões de uma sequência de 3 batimentos. A distribuição dos padrões foi calculada pela entropia de Shannon (ES). Este índice descreve a forma da distribuição dos padrões. A ES é alta se a distribuição é plana (todos os padrões são identicamente distribuídos e a série transporta o máximo de informação). Por outro lado, a ES é baixa se um subconjunto de padrões é mais comum, enquanto outros estão ausentes ou são pouco frequentes, como em uma distribuição Gaussiana (Porta *et al.*, 2001).

2.4.3. Análise Simbólica

Para executar a análise simbólica (AS), todos os padrões foram agrupados em quatro famílias, descritas a seguir: (a) padrões sem variação (0V: todos os símbolos são iguais, i.e. 2,2,2 ou 4,4,4); (b) padrões com uma variação (1V: 2 símbolos consecutivos são iguais e um símbolo é diferente, i.e. 4,2,2 ou 4,4,3); (c) padrões com duas variações similares (2LV: 3 símbolos que formam uma rampa ascendente ou descendente, i.e. 5,4,2 ou 1,3,4); (d) 2 variações diferentes (2ULV: 3 símbolos que formam um pico ou um vale, i.e. 4,1,2 ou 3,5,3). A taxa de ocorrência de cada padrão é definido como 0V%, 1V%, 2LV%, e 2ULV% (Porta, Tobaldini*, et al.*, 2007). Onde 0V% e 2ULV% podem ser considerados marcadores da modulação simpática e vagal, respetivamente (Porta, Tobaldini*, et al.*, 2007).

2.4.4 Entropia condicional

De acordo com Porta et al (Porta, Faes*, et al.*, 2007), entropia condicional (EC) mede a quantidade de informação por uma nova amostra que não pode ser obtida a partir de uma sequência L de valores. A EC é avaliada pelo índice de complexidade (IC). Adicionalmente, para calcular IC normalizada (IC), este foi normalizado pela ES dos intervalos RR e varia de 0 (informação nula) a 1 (informação máxima). Quanto maior o IC e o ICN, maior é a complexidade e menor a regularidade da série (Porta, Faes*, et al.*, 2007).

2.5. Análise Estatística

Para verificar a distribuição dos dados foi aplicado o teste Kolmogorov-Smirnov. O teste X^2 foi usado para variáveis categóricas, tais como medicamentos e fatores de risco entre os grupos DAC e DAC-IAM. O teste *ANOVA* de uma via com *post-hoc* de *Bonferroni* (ou teste Kruskal-Wallis, análise de variância de uma via por *ranks* com correção de *Dunn,* quanto apropriado) foi utilizado para comparar as características antropométricas, idade, média e variância dos iRR e índices espectrais, ES, IC, ICN e índices simbólicos. A correlação de Pearson foi calculada para os padrões 0V%, 1V%, 2LV% e 2ULV% e os índices de complexidade (ES, IC e ICN). Todos os dados foram apresentados em média±DP, e o nível de significância foi de $p<0.05$. A análise estatística foi realizada com o software Sigma Plot para Windows versão 11.0.

2.6. Resultados

As características dos grupos estão apresentadas na Tabela 1. Massa corporal e índice de massa corpórea (IMC) foram maiores no grupo DAC que no grupo DAC-IAM ($p<0.05$), mas nenhum diferença foi encontrada o grupo saudável e DAC e entre o grupo saudável e DAC-IAM. Nenhuma diferença na idade e na altura foi encontrada entre os grupos.. A capacidade física máxima do grupo saudável foi considerada de baixa (n=8) a regular (n=11) (VO_{2pico} = 26 ± 5 mL/kg/min) de acordo com a *American Heart Association* (Cooper e Storer, 2001).

Tabela 1: Características dos grupos saudável, pacientes com doença arterial coronariana sem (DAC) e com infarto do miocárdio (DAC-IAM).

	Saudável	**DAC**	**DAC-IAM**
	n=18	n=20	n=19
Idade (anos)	57±4	56 ±10	54±12
Massa corporal (kg)	72±8	81±16†	71±10
Estatura (cm)	168±5	171±7	168±7
IMC (kg/m^2)	26±2	28±4†	25±3

Valores estão em média±DP. IMC, índice de massa corporal; DAC, doença arterial coronariana; IAM, infarto agudo do miocárdio. $^{\dagger}p<0.05$ entre os grupos DAC *vs* DAC-IAM.

Os fatores de risco, dados angiográficos e medicações dos grupos DAC e DAC-IAM estão apresentados na Tabela 2. Houve significativamente mais pacientes em uso de betabloqueador no grupo DAC-IAM que no grupo DAC (100% e 95%, respectivamente). O grupo DAC-IAM apresentou uma percentagem significativamente maior de pacientes com obstrução da artéria descendente anterior >50% que os do grupo DAC (89% e 45%, respectivamente).

Tabela 2: Dados clínicos, angiográficos, fatores de risco e medicações dos grupos doença arterial coronariana (DAC) sem e com infarto do miocárdio (DAC-IAM).

Variáveis	DAC	DAC-IAM
N	20	19
Fatores de risco		
Tabagismo	7 (35%)	13 (68%)
Hipertensão Arterial	9 (45%)	6 (32%)
História familiar de DAC	3 (15%)	5 (26%)
Diabetes mellitus	3 (15%)	2 (11%)
Estilo de vida sedentário	8 (40%)	8 (42%)
Dislipidemia	9 (45%)	8 (42%)
Nº. de artérias obstruídas		
Sem obstrução	3(15%)	1(5%)
Uma artéria	10(50%)	8(42%)
Duas artérias	3(15%)	3(16%)
Três artérias	4(20%)	7(37%)
Obstrução >50%		
Artéria descendente anterior	9(45%)†	17(89%)
Artéria coronária direita	8(40%)	8(42%)
Artéria circunflexa	10(50%)	9(47%)
Medicações		
Betabloqueadores	11 (55%)†	19 (100%)
Inibidores da ECA	13 (65%)	9 (47%)
Hipolipemiantes	12 (60%)	10 (53%)
Aspirina	16 (80%)	19 (100%)
Antiagregante plaquetário	8 (40%)†	18 (95%)

Valores em número absoluto (frequência de ocorrência). IMC, índice de massa corporal; DAC, doença arterial coronariana; IAM, infarto agudo do miocárdio. †$p<0,05$ entre DAC *vs* DAC-IAM.

No grupo DAC-IAM, 5 pacientes tiveram infarto de parede inferior e 14 infarto de parede anterior. Dezoito pacientes foram submetidos a angioplastia transluminal percutânea primária com sucesso. Somente um paciente do grupo DAC-IAM foi submetido a angioplastia coronariana devido ao vaso espasmo. No grupo DAC, somente um paciente foi submetido a angioplastia.

Os resultados das análises linear e não linear estão apresentadas na tabela 3. Não houve nenhuma diferença nas variáveis lineares e não lineares entre os grupos.

Tabela 3: Entropia de Shannon (SE), entropia condicional (EC) e analise simbólica e espectral da variabilidade da frequência cardíaca dos grupos saudável, com doença arterial coronariana (DAC) sem e com infarto do miocárdio (DAC-IAM)

	Saudável	**DAC**	**DAC-IAM**
Variância (iRR ms^2)	1452±1309	859±1014	1199±1559
Média dos iRR (ms)	972±148	959±208	906±180
Análise espectral			
BF (ms^2)	545±495	299±504	325±515
AF (ms^2)	220±237	241±293	177±246
BFun	64,13±23,59	46,74±26,15	59,99±19,33
AFun	35,34±23,51	50,19±29,08	35,03±17,91
BF/AF	3,25±3,08	2,70±4,83	2,80±2,62
Analise Simbólica			
0V%	26,15±12,05	26,56±13,08	23,21±14,24
1V%	48,38±3,50	45,83±4,88	45,66±6,64
2LV%	9,07±5,37	9,21±5,97	7,95±3,95
2ULV%	16,40±8,01	18,39±8,01	23,18±11,50
Entropia			
ES	3,34±0,34	3,41±0,44	3,54±0,42
ICN	0,71±0,10	0,73±0,09	0,74±0,11
IC	0,99±0,15	1,02±0,17	1,09±0,21

Valores em média±DP. DAC, doença arterial coronariana; IAM, infarto agudo do miocárdio; iRR, intervalo RR; ES, entropia de Shannon; ICN, índice de complexidade normalizado; IC, índice de complexidade.

A tabela 4 mostra as correlações entre os índices da AS e a entropias (ES, IC e ICN). Todos os grupos mostraram uma correlação negativa significativa entre o padrão 0V% e ES, IC, e ICN. Em contrapartida, o grupo saudável teve uma correlação significativa entre o padrão 2ULV% e ES, IC e ICN. Para o grupo DAC, houve uma moderada correlação com ICN e uma fraca correlação com ES e IC. No grupo DAC-IAM, houve uma moderada correlação entre o índice 2ULV e todos os índices de complexidade. Adicionalmente, houve uma correlação significante

moderada entre 2LV% e todos os índices no grupo saudável. Houve uma moderada correlação entre 2LV%, ES e IC no grupo DAC. Finalmente, houve moderada correlação significante entre ES, ICN, IC e 2LV% no grupo DAC-IAM.

2.7 Discussão

O principal achado do estudo foi que nenhuma diferença foi observada entre os grupos (DAC, DAC-IAM e saudável) nem para análise linear (variância, média e análise espectral) e nem para análise não-linear (análise simbólica, entropia de Shannon e entropia condicional).

A análise espectral é um método mais tradicional e bem estabelecido que a análise simbólica, uma vez que as bandas de frequência estão relacionadas com a modulação simpática e parassimpática (Taskforce, 1996; Montano *et al.*, 2009). Porém, este método tem algumas limitações pois este pode ser muito sensível a definição de bandas (baixa frequência, de 0,04 a 0,15 Hz e alta frequência, de 0,15 a 0,5 Hz). Além disso, os índices espectrais em unidades normalizadas (AFun e BFun) são úteis em condições caracterizadas por alterações recíprocas da modulação simpatovagal, isto é, o aumento da modulação simpática corresponde a um igual redução da modulação vagal (Porta, Tobaldini*, et al.*, 2007). Porta *et al* (2007) propôs a AS, onde os padrões seriam divididos em quatro famílias. Este de análise pode detectar alterações autonômicas não recíprocas, isto é, quando o aumento da modulação simpática não corresponde a redução da modulação vagal (Porta, Tobaldini*, et al.*, 2007)

Alguns estudos tem comparado a análise espectral com a simbólica. Tobaldini *et al* (2009) mostrou que a AS foi mais apropriada para descrever as alterações da dinâmica da frequência cardíaca e da regulação cardiovascular modelos animais com insuficiência cardíaca (Tobaldini, Porta*, et al.*, 2009). Porta *et al* (2007) avaliou a modulação autonômica durante o teste de inclinação em prancha ortostática (*graded head-up tilt*) pela AS e análise espectral e encontrou que AS foi capaz de descrever condições caracterizadas pelas alterações recíprocas de diferentes magnitudes (Porta, Tobaldini*, et al.*, 2007). Por outro lado, Perseguini *et al* (2011), estudando homens e mulheres idosos em resposta a alteração postural, descreveu que a análise espectral poderia melhor revelar diferenças intergrupos nas alterações reciprocas na FC que AS (Perseguini *et al.*, 2011). Entretanto, o presente estudo mostra que nem a análise espectral e nem a simbólica foram capazes de encontrar diferenças entre os três grupos (DAC, DAC-IAM e saudável).

Vários estudos mostraram que pacientes com doenças cardíacas, principalmente aqueles com infarto agudo do miocárdio, apresentaram uma maior modulação simpática e/ou menor modulação vagal avaliada pela análise espectral

(Taskforce, 1996; Kleiger *et al.*, 2005; Montano *et al.*, 2009; Routledge *et al.*, 2010). Lombardi *et al* (1996) estudaram a VFC durante as primeiras horas (de 1 à 6 horas) do IAM e observaram que pacientes com infarto de parede anterior tinham uma maior hiperatividade simpática que aqueles com infarto de parede inferior (Lombardi *et al.*, 1996). Interessantemente, em nosso estudo, nenhuma diferença na análise espectral foi encontrada entre o grupo DAC-IAM e os outros grupos. Os resultados podem ser devidos a vários fatores: 1) todos os pacientes do grupo DAC-IAM e metade do grupo DAC estava em uso de betabloqueador; 2) todos os pacientes do grupo DAC-IAM foram submetidos a angioplastia com sucesso; 3) a avaliação do grupo DAC-IAM foi realizada em uma fase precoce do infarto do miocárdio, de 12 a 24 horas após o evento.

Os mesmos fatores também se aplicam aos nossos resultados da análise simbólica. Kunz *et al* (2011) mostrou que pacientes com DAC com estenose significante (≥ 50%) tem um aumento do padrão 0V% e uma redução do padrão 2ULV% em comparação com os pacientes DAC sem estenose significante (< 50%) e indivíduos saudáveis (Kunz *et al.*, 2011). Entretanto, esses autores incluíram pacientes com IAM (> 6 meses depois do evento) e pacientes com cirurgia de revascularização do miocárdio. Além do mais, todos os pacientes não estavam em uso de betabloqueador, ao contrário dos pacientes do grupo DAC-IAM desse estudo.

Com relação a análise simbólica, era esperado que os grupos DAC e DAC-IAM apresentassem maior padrão 0V% e menor padrão 2ULV% em comparação ao grupo saudável. O padrão 2ULV é descrito como sequências alternantes “curto-longo-curto” ou “longo-curto-longo” dos ciclos cardíacos, e essas alterações muito rápidas dos iRR parecem esta sobre o controle da modulação vagal em indivíduos saudáveis (Guzzetti *et al.*, 2005; Porta, Tobaldini*, et al.*, 2007). Porém, em condições patológicas, este tipo de sequência pode estar relacionada a mecanismos não estritamente sob o comando do sistema nervoso autônomo (Kodama *et al.*, 2004). Por exemplo, em ratos com insuficiência cardíaca, o 2ULV pode está ligado à instabilidades elétricas, tais como alternância mecânicas ou de pulsos (Tobaldini, Montano*, et al.*, 2009; Tobaldini, Porta*, et al.*, 2009). Esse tipo de fenômeno pode gerar resultados aparentemente paradoxais. Porta et al (Porta, Faes*, et al.*, 2007) observou este fato em pacientes com insuficiência cardíaca que apresentou maior padrão 2ULV% que indivíduos saudáveis durante o período do dia. Este

mesmo fenômeno pode ter contribuído para nenhuma diferenciação do índice 2ULV entre os grupos saudável, DAC e DAC-IAM.

A respeito do ES e EC, era esperado que grupo saudável apresentasse sequências de padrões mais irregular e imprevisível e a distribuição dos padrões pudesse ser mais diferente que os grupos DAC e DAC-IAM. Kunz *et al* (2011) observaram que pacientes com DAC, independentemente do nível de estenose da artéria coronária (> ou < 50%) apresentaram uma menor ES que os indivíduos saudáveis. Entretanto, os pacientes desse estudo não estavam em uso de betabloqueador e ainda foram incluídos aqueles com IAM prévio e/ou submetidos a cirurgia de revascularização do miocárdio. Takahashi *et al* (2011) observaram uma redução da IC e da ICN em homens de meia idade em comparação com jovens, mas a ES permaneceu inalterada. Portanto, estes padrões tinham a mesma distribuição, mas estas sequências de padrões formados era mais regular e previsível, então reduzindo a IC e a ICN. Em nosso estudo, nem a EC (os índices IC ou ICN) e nem a ES foram diferente entre os grupos. Sendo assim, os dados desse estudo sugerem que a complexidade cardíaca foi similar entre os grupos.

É importante destacar que foi observado uma moderada a forte correlação entre os padrões 0V% e 2ULV% e todos os índices de complexidade, principalmente ES e ICN para todos os grupos. De acordo com Tobaldini *et al* (2009), o índice 2ULV também pode ser considerado uma potente medida da complexidade (regularidade) da dinâmica cardíaca. Entretanto, nenhuma diferença foi encontrada entre os grupos para os índices da análise simbólica, ES, IC e ICN.

O betabloqueador e a angioplastia são importantes terapias no tratamento de pacientes com IAM e DAC uma vez que eles podem alterar o controle autonômico cardíaco (Airaksinen *et al.*, 1994; Malfatto *et al.*, 1996; Lampert *et al.*, 2003; Malfatto *et al.*, 2005). Airaksinen *et al* (1994) estudaram os efeitos do metoprolol e atenolol em pacientes com DAC estável em comparação com o grupo placebo. Foi observado que o betabloqueador induziu um aumento da modulação vagal (maior AF) e uma redução da modulação simpática (menor BF). Lampert *et al* (2003) observaram que a terapia betabloqueadora aumentou a AF em pacientes com IAM. Soares *et al* (2005) observaram que os indivíduos saudáveis apresentaram maior AF que pacientes com DAC, mas somente um paciente desse grupo estava em uso de betabloqueador. Neste estudo todos os pacientes do grupo DAC-IAM e 55% do grupo

DAC estavam em uso de betabloqueador, o qual poderia explicara similaridade dos resultados entre os grupos.

Malfatto *et al* (2005) estudaram pacientes com IAM de parede anterior que foram submetidos angioplastia coronariana primária e pacientes IAM com nenhuma reperfusão e observaram que pacientes com IAM que foram submetidos a angioplastia primária apresentaram um melhor balanço simpatovagal (isto é, menor BF/AF) logo após o IAM (Malfatto *et al.*, 2005). Em um outro estudo, a angioplastia primária realizada com um tempo < 12 horas após-IAM resultou em um resposta bifásica da VFC, e finalmente levando a uma significante recuperação dos parâmetros da VFC que indicou uma recuperação significante da VFC, uma ativação vagal e uma retirada simpática (Bonnemeier *et al.*, 2000). Em nosso estudo, todo os pacientes do grupo DAC-IAM foram submetidos a angioplastia coronariana com sucesso. Portanto, tomados em conjunto, betabloqueador e angioplastia coronariana podem ter contribuído com esses resultados.

Adicionalmente, a baixa capacidade física dos indivíduos saudáveis observada pelo VO_{2pico} pode ter influenciado o sistema nervoso autonômico, pois trabalho prévio mostra que indivíduos com baixa capacidade física apresentam uma menor modulação vagal que indivíduos com boa capacidade física (Hautala *et al.*, 2009). De fato, o grupo saudável do presente estudo mostrou capacidade física aeróbia de baixa a regular e isto pode ser mais um dos fatores que pode ter contribuído com os resultados do presente estudo.

Sendo assim, a conclusão do nosso estudo foi que o grupo saudável, DAC e DAC-IAM não apresentaram diferenças em relação ao controle autonômico e complexidade da dinâmica cardíaca pelas análises linear (analise espectral) e não linear [analise simbólica, entropia de Shannon e entropia Condicional (índice de complexidade (IC) e IC normalizado (ICN)]. Este resultado pode ser devido a terapia betabloqueadora, a angioplastia coronariana no grupo DAC-IAM e a capacidade física dos indivíduos saudáveis.

2.7.1 Limitação

A primeira limitação do estudo foi que nenhuma intervenção foi aplicada para estimular um resposta autonômica cardíaca (alteração postural, exercício físico, etc.) o que limitam a possibilidade de compreender uma possível alteração na dinâmica de ativação/desativação do sistema autonômico cardíaco.

Segundo, somente os indivíduos saudáveis foram submetidos ao teste cardiopulmonar máximo para determinar o consumo máximo de oxigênio devido a impossibilidade de submeter os pacientes em uma fase precoce do infarto ao teste cardiopulmonar. Além do mais, embora a utilização de betabloqueador possa ter interferido nos resultados dos pacientes CAD-IAM, a cessação dessa medicação é impossível, uma vez que é terapia de escolha (Antman *et al.*, 2004).

2.8. AGRADECIMENTOS

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3. SEGUNDO ESTUDO

(VERSÃO EM PORTUGUÊS)

DINÂMICA DA FREQUÊNCIA CARDÍACA NO PÓS-EXERCÍCIO EM PACIENTES COM DOENÇA ARTERIAL CORONARIANA COM E SEM DIABETES MELLITUS TIPO 2

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3. SEGUNDO ESTUDO

DINÂMICA DA FREQUÊNCIA CARDÍACA NO PÓS-EXERCÍCIO EM PACIENTES COM DOENÇA ARTERIAL CORONARIANA COM E SEM DIABETES TIPO 2

3.1. Resumo

Objetivo: A incidência de eventos cardiovasculares é maior em pacientes com doença arterial coronariana (DAC) com diabetes tipo 2 (DT2) que naqueles sem DT2. Há evidências que a fase de recuperação logo após o exercício é vulnerável a eventos cardiovasculares. A hipótese desse trabalho foi que a regulação autonômica difere em pacientes com DAC com e sem DT2 durante a fase de recuperação pós-exercício. **Métodos:** Teste máximo sintoma-limitado em cicloergômetro foi realizado em 68 pacientes DAC com DT2 (grupo DAC+DT2) (idade 61±5 anos, 78% homens, fração de ejeção 67±8%, 100% betabloqueados) e 64 pacientes DAC sem DT2 (grupo DAC) (idade 62±5 anos, 80% homens, fração de ejeção 64±8, 100% betabloqueados). A frequência cardíaca (FC) de recuperação após o exercício foi calculada ajustando-se uma reta aos dados da FC durante os primeiros 60 segundos após o térmico do exercício na posição supina (FCR_{slope}). Os intervalos R-R foram analisados pelos métodos no domínio do tempo e da frequência e *detrended fluctuation* (α_1). **Resultados:** O índice de massa corporal (IMC) foi 30±4 *vs.* 27±3 $kg \cdot m^2$ ($p < 0.001$); capacidade física máxima, 6.5±1.7 vs. 7.7±1.9 METs ($p < 0.001$); FC máxima, 128 ± 19 vs. 132±18 bpm (p = ns); e FCR_{slope}, -0.53±0.17 vs. -0.62±0.15 batimento/seg (p = 0.004), para os grupos DAC+DT2 e DAC, respectivamente. Nenhuma diferença foi observada entre os grupos na FCR_{slope} depois de ajustar para METs, IMC e medicação (ANCOVA, p=0.228 para DT2 e, por exemplo, p=0.030 para METs). Pacientes DAC+DT2 tem uma maior FC em repouso que os pacientes DAC (57±10 vs. 54±6 bpm, respectivamente, p = 0,030), mas nenhuma outra diferença foi observada na dinâmica da FC ao repouso ou na condição pós-exercício. **Conclusão:** A FC de recuperação está lentificada nos pacientes DAC+DT2, o que sugere uma redução da modulação vagal e/ou aumento da atividade simpática após o exercício. Entretanto, a atenuação da FC de recuperação após o exercício nos coronarianos diabéticos quando comparados com os coronarianos não diabéticos está mais intimamente relacionado a baixa capacidade física e a obesidade que pela própria DT2.

Palavras chaves: frequência cardíaca de recuperação, diabetes tipo 2, regulação autonômica

3.2. Introdução

A incidência de eventos cardiovasculares é maior em pacientes com doença arterial coronariana (CAD) com diabetes tipo 2 (DT2) que em pacientes coronarianos sem DT2 (Haffner *et al.*, 1998; Junttila *et al.*, 2010), mas os mecanismos fisiológico ou fisiopatológico que causam essas diferenças não são bem conhecidos. A disautonomia autonômica é um mecanismo que pode resultar em um aumento no número de eventos cardiovasculares em pacientes coronarianos com DT2 (Okada *et al.*, 2010; Pop-Busui *et al.*, 2010; Lanza *et al.*, 2011). O controle autonômico pode ser estudado por meio de diferentes métodos em laboratório, testes em condições ambulatoriais tais como os testes de mudança postural (*passive head-up tilt test*) e o de preensão manual (*hand grip*) (Montano *et al.*, 1994; Kiviniemi *et al.*, 2009; Hautala *et al.*, 2010; Junttila *et al.*, 2010) ou medidas ambulatoriais da variabilidade da frequência cardíaca (VFC) e da pressão arterial (Pagani *et al.*, 1985; Kleiger *et al.*, 1987; Piira *et al.*, 2011). O estudo da regulação autonômica antes e depois do exercício também tem sido utilizado em condições fisiológicas (Yamamoto *et al.*, 1991; Gregoire *et al.*, 1996; Tulppo *et al.*, 1998; Junttila *et al.*, 2010) e clínicas (Cole *et al.*, 1999; Cole *et al.*, 2000; Jouven e Ducimetiere, 2000; Jouven *et al.*, 2005; Kiviniemi *et al.*, 2011).

Há evidências que a fase de recuperação após exercício é uma fase vulnerável a vários eventos cardiovasculares. Estudos *case-crossover* têm mostrado que o exercício como gatilho do infarto agudo do miocárdio não está limitado ao tempo de realização do exercício físico, mas se estende por um certo período de tempo depois do término da atividade física (Siscovick *et al.*, 1982; Siscovick *et al.*, 1984; Albert *et al.*, 2000; Von Klot *et al.*, 2008). Semelhantemente, o risco de morte súbita está transitoriamente aumentado nos 30 minutos depois de um exercício vigoroso, e os episódios de fibrilação atrial são mais frequentes após a realização de exercício físico que antes (Siscovick *et al.*, 1982; Siscovick *et al.*, 1984; Coumel, 1994; Albert *et al.*, 2000; Huikuri, 2008). Medidas da função autonômica numa fase precoce de recuperação após o exercício tem fornecido importante informação prognóstica. Por exemplo, a lentificação da FC de recuperação avaliada de 1 a 2 minutos após o exercício mostrou-se capaz de predizer eventos cardiovasculares na

população geral e em vários estudos de grupos de pacientes e de experimentação animal (Cole *et al.*, 1999; Lauer e Froelicher, 2002; Nissinen *et al.*, 2003; Jouven *et al.*, 2005; Smith *et al.*, 2005). Recentemente, nós mostramos que a co-ativação dos ramos do sistema nervoso autonômico, simpático e parassimpático, pode ocorrer durante o período da fase de recuperação do exercício (Tulppo *et al.*, 2011), o qual pode ser usado para explicar parcialmente o agrupamento de vários eventos cardiovasculares na fase de recuperação do exercício.

Sendo assim, o presente estudo foi desenhado para avaliar o comportamento da dinâmica da FC durante o exercício e na fase de recuperação em pacientes DAC com e sem DT2, pareado pela idade, fração de ejeção (FE) e gênero. A hipótese foi que a regulação autonômica medida pela FC de recuperação e pelos métodos da VFC, são diferentes nos pacientes com DAC com e sem DT2, principalmente na condição pós-exercício.

3.3. Materiais e Métodos

3.3.1. Pacientes e protocolo de estudo

O presente estudo foi realizado no Departamento de Exercício e Fisiologia Médica, Instituto Verve (Oulu, Finlândia) e no Hospital Universitário de Oulu. Os pacientes foram selecionados da base de dados do estudo multicêntrico ARTEMIS (*Innovation to Reduce Cardiovascular Complications of Diabetes at the Intersection* – Inovação para Redução de Complicações Cardiovasculares da Diabetes) os quais tinham DAC estável sem diabetes tipo 2 (DT2) (grupo DAC, n = 64) e com DT2 (grupo DAC+DT2, n = 68). Os critérios de exclusão foram a incapacidade de realizar o teste cardiopulmonar sintoma-limitado, angina instável no período de recrutamento, idade maior que 75 anos, infarto do miocárdio recente (< 6 meses), nefropatia severa, insuficiência cardíaca, revascularização do miocárdio agendada durante o período do estudo, neuropatia autonômica diabética, demência, alcoolismo ou usuário de drogas ilícitas ou qualquer condição que poderia prejudicar a capacidade do indivíduo de assinar o termo de consentimento pós-informado. A DAC foi avaliada e documentada pela angiografia coronária e a DT2 foi verificada pelo teste oral de tolerância a glicose de acordo com as atuais recomendações (WHO, 1999). O estudo foi executado de acordo com a Declaração de Helsinki e o trabalho foi aprovado pelo Comitê de Ética em Pesquisa do *Northern Ostrobothnia Hospital District* (Oulu, Finlândia).

Os testes laboratoriais foram realizados no Departamento de Exercício e Fisiologia Médica em Verve (Oulu, Finlândia). Os pacientes foram orientados a não comer ou consumir bebidas com cafeína por 3 horas antes dos testes. A realização de exercício físico e o uso de álcool foi proibido por 24 horas antes do teste. O eletrocardiograma de 12 derivações (ECG) e os intervalos RR (iRR) foram coletados durante 10 minutos ao repouso na posição supina antes do exercício, durante o exercício e durante 10 minutos logo após a interrupção do exercício na posição supina. Os pacientes respiraram espontaneamente em todas as fases do protocolo experimental. Os iRR foram analisados nos últimos 5 minutos do período de repouso, em cada carga de trabalho com duração de aproximadamente 1 minuto, e finalmente, do 3^{o} ao 8 ^{o} após o término do exercício durante o período de recuperação. Uma amostra sanguínea capilar foi obtida antes da realização do teste físico para analisar a concentração de HbA1c (Afinion™ AS100, Axis-Shield PoC AS, Oslo, Noruega).

3.3.2. Teste Cardiopulmonar

Todos os pacientes foram submetidos ao teste incremental máximo em cicloergômetro (Monark Ergomedic 839 E; Monark Exercise AB, Vansbro, Suécia). Eles começaram a pedalar com uma carga inicial de 30 Watts por um período de 2 minutos. O incremento da carga de trabalho foi de 10 watts para mulheres e 15 watts para homens a cada minuto até a exaustão. Os pacientes mudaram da posição sentada sobre o cicloergômetro para a posição supina sobre a maca logo após o término do teste por um período aproximadamente de 30 segundos. Finalmente, os pacientes foram orientados a não falar ou mover-se durante o período de recuperação, somente se fosse necessário.

A ventilação (V_E) e as trocas gasosas (M909 Ergoespirometer, Medikro, Kuopio, Finlândia) foram medidas e registradas como o valor médio a cada minuto. O maior valor médio do consumo de oxigênio (VO_2) foi expresso como o pico do consumo de oxigênio (VO_{2pico}). A carga máxima de trabalho (W) e o equivalente metabólico (METs) máximo foram calculados como a média da carga de trabalho e do METs durante o último minuto do teste. O eletrocardiograma foi monitorado e registrado por meio de um eletrocardiógrafo de 12 derivações (GE Healthcare, Cam-14, Waukesha, WI, EUA) e ao mesmo tempo, os intervalos R-R foram registrados por meio de um gravador Polar com uma taxa de amostragem de 1000 Hz (Polar Electro, Kempele, Finlândia). A pressão arterial foi medida por meio

de um esfigmomanômetro eletrônico (Tango, Sun-Tech, Raleigh, NC, EUA) em repouso e durante o exercício. Todos os pacientes foram encorajados a alcançar a carga de trabalho máxima sintoma-limitado, e o exercício era interrompido se a depressão do segmento ST do traçado eletrocardiográfico fosse >0.2 mV.

A resposta cronotrópica (IRC) ao exercício foi calculada a partir seguinte equação: IRC = 100 · (FC máxima – FC repouso) · (220 – idade – FC repouso)$^{-1}$ (Kiviniemi *et al.*, 2011), e a FC de reserva (FC_{res}) como: FC_{res} = FC máxima – FC repouso. A FC de recuperação (FC_{rec}) foi calculada como a modificação a partir da FC máxima à FC_{rec} no 15^{o}, 30^{o}, 60^{o} e 120^{o} segundos após o término do exercício. A FC máxima foi calculada como a média dos 5 intervalos R-R antes do término do exercício. Semelhantemente, os valores da FC de recuperação foi calculado como a média dos 5 intervalos R-R no tempo de 15 (FC_{rec15}), 30 (FC_{rec30}), 60 (FC_{rec60}) e 120 (FC_{rec120}) segundos após o término do exercício durante o período de recuperação. Os dados de iRR foram obtidos a partir do gravador Polar utilizado durante todo o teste. Adicionalmente, o ajuste da FC durante os 60 segundos depois do término do exercício ($FC_{slope60}$) foi calculada por um modelo linear a partir dos valores dos intervalos R-R (convertido para bpm) obtidas da FC máxima e na FC no tempo de 15, 30 e 60 segundos após o exercício (Figura 1).

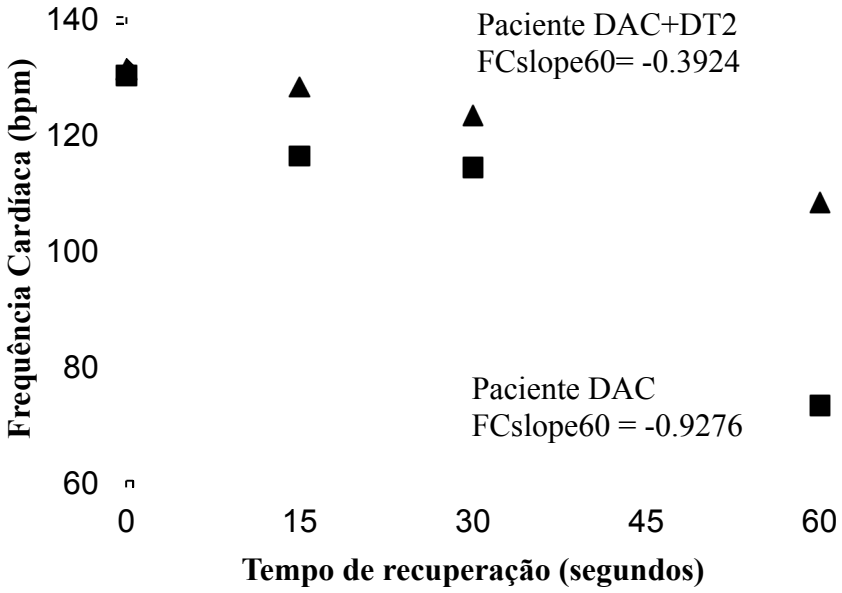

Figura 1. Exemplo da frequência cardíaca de recuperação, mostrada com ajuste linear dos dados de FC durante os primeiros 60 segundos após a interrupção do exercício, para dois pacientes (com e sem diabetes tipo 2), com similar idade e frequência cardíaca máxima. A inclinação foi calculada pelo modelo linear usando a média de cinco intervalos R-R (convertidos para valores de FC em bpm como 60.(média dos intervalos R-R em ms/100^{-1}) no pico do esforço e nos pontos de 15, 30 e 60 segundos após a interrupção do exercício.

3.3.3. Variabilidade da Frequência Cardíaca

Antes de analisar a VFC, todos os iRR foram editados manualmente afim de excluir todos os batimentos prematuros e ruídos, o qual correspondem a <8% em cada sujeito. O traçado eletrocardiográfico foi utilizado durante a edição dos iRR para confirmar a origem sinusal dos batimentos. Um modelo autorregressivo foi utilizado para estimar a densidade da potência espectral da VFC após a retirada de um componente linear (*dentreding)* (Huikuri *et al.*, 1996; Tulppo *et al.*, 1996). A potência espectral foi calculada como a área sobre as duas bandas de frequência: baixa frequência (BF, 0.04-0.15 Hz) e alta frequência (AF, 0.15-0.4 Hz). Os detalhes da análise espectral foi descrito previamente (Taskforce, 1996). O método da *Detrended Fluctuation Analysis* (DFA) foi usado para calcular as propriedades da correlação fractal dos intervalos R-R (Peng *et al.*, 1995; Iyengar *et al.*, 1996). Nesse estudo, a escala exponencial (α-1) de curta duração (4-11 batimentos) foram calculados baseados em experimentos prévios (Makikallio *et al.*, 1996).

3.4. Análise estatística

Os dados foram apresentados como média±SD. A distribuição normal dos dados foi avaliada pelo teste *Kolmogorov-Smirnov*. O teste *t* não pareado foi usado para calcular as diferenças no índices de variabilidade entre os grupos. O teste X^2 foi usado para as variáveis categóricas. ANOVA de dois fatores (tempo x grupo) foi usado para avaliar o efeito pós o exercício na FC_{rec} (FC_{rec15}, FC_{rec30}, FC_{rec60} e FC_{rec120}) acompanhado pelo *pos-hoc* (teste *t* não pareado). Análise de covariância (ANCOVA) foi usada para comparar a FC_{rec} entre pacientes DAC com e sem DT2. A DT2 foi usado como fator fixo e MET máximo, IMC e medicações como (nitratos e antagonista dos canais de cálcio) foram adicionados como covariáveis de ajuste do resultado. Os dados foram analisados através do software SPSS (SPSS 19, SPSS Inc, Chicago, EUA). Um valor de p <0,05 foi considerado estatisticamente significante.

3.5. Resultados

3.5.1. População de estudo

As características da população do estudo, incluindo a comparação entre os grupos DAC e DAC+DT2, estão apresentados na Tabela 1. A composição corporal do grupo DAC+DT2, isto é, massa corporal (p <0.001), circunferência da cintura (p<0.001)**,** IMC (p<0.001) e HbA1c (p<0.001) foram estatisticamente diferentes do grupo DAC. Entretanto, pressão arterial, fração de ejeção, história de infarto e revascularização ou fumantes não foram diferentes entre os grupos. A medicação também não diferiu entre os grupos, com exceção para os antagonistas do canais de cálcio, nitratos e antiabético oral que foram mais comuns no grupo DAC+DT2 que no grupo DAC.

Tabela 1: Características dos pacientes.

	DAC+DT2 n=68	DAC n=64	*P*
Gênero (M/F)	15/53	13/51	*p*=0,488
Idade (anos)	61±5	62±5	*p*=0,514
Altura (cm)	171±7	171±8	*p*=0,678
Massa corporal (kg)	89±15	80±12	*p*<0,001
Cintura (cm)	105±12	94±10	*p*<0,001
Quadril (cm)	105±10	99±6	*p*<0,001
Cintura/quadril	1,00±0,07	0,95±0,07	*p*<0,001
IMC ($kg \cdot m^{-2}$)	30±4	27±3	*p*<0,001
HbA1c (%)	6,0±0,7	5,5±0,2	*p*<0,001
PAS (mmHg)	138±18	136±16	*p*=0,672
PAD (mmHg)	82±10	82±8	*p*=0,875
História de IAM			
NSST	18 (26%)	19 (30%)	*p*=0,469
SST	13 (19%)	14 (21%)	*p*=0,662
Revascularização			
CRM	14 (21%)	13 (28%)	*p*=0,506
ACTP	42 (67%)	27 (59%)	*p*=0,426
Fumantes ativos	3 (4%)	8 (12%)	*p*=0,147
FEVE (%)	67±8	65±8	*p*=0,107
Medicação			
Anticoagulantes	66 (97%)	63 (98%)	*p*=1,000
Beta-bloqueadores	68 (100%)	64 (100%)	*p*=1,000
Antagonista do canal de cálcio	20 (29%)	9 (14%)	*p*=0,037
IECA	31 (46%)	23 (36%)	*p*=0,291
AT2	13 (19%)	14 (22%)	*p*=0,830
Diuréticos	26 (38%)	15 (23%)	*p*=0,090
Estatina	63 (93%)	57 (89%)	*p*=0,553
Insulina	10 (7 %)	0 (0%)	*p*=0,001
Antidiabéticos orais	50 (74%)	0 (0%)	*p*<0,001
Nitratos	28 (41%)	8 (13%)	*p*<0,001
Antiarrítmicos	1 (1%)	1 (1%)	*p*=1,000

Dados apresentados em média±DP. IMC, índice de massa corporal; HbA1c, hemoglobina glicosilada; PAS, pressão arterial sistólica; PAD, pressão arterial diastólica; FC, frequência cardíaca; IAM, infarto agudo do miocárdio; NSST, sem supra desnivelamento do segmento ST; SST, supra desnivelamento do segmento ST; revascularização, pacientes que receberam pelo menos um dos procedimentos (CRM, cirurgia de revascularização do miocárdio ou ACTP, angioplastia coronariana transluminal percutânea); FEVE, fração de ejeção de ventrículo esquerdo; IECA, inibidor da enzima conversora da angiotensina; AT2, bloqueador do receptor da angiotensina II; DAC, grupo de pacientes com doença arterial coronariana sem diabetes tipo 2; DAC+DT2, grupo de pacientes com doença arterial coronariana com diabetes tipo 2.

3.5.2. Teste cardiopulmonar

Os resultados do teste cardiopulmonar dos pacientes coronarianos diabéticos e não diabéticos estão apresentados na Tabela 2. A potência máxima atingida foi menor (p<0.001) no grupo DAC+DT2, mas a FC máxima ficou no mesmo nível comparativamente com o grupo DAC (Tabela 2). Não houve nenhuma diferença entre os grupos na prevalência da depressão do segmento ST (>0.1mV) durante o teste físico. Entretanto, houve diferença significativa nos vários parâmetros que mostram o resposta da FC durante e após o exercício entre os grupos.

Tabela 2. Capacidade física máxima e frequência cardíaca de recuperação.

	DAC+DT2 n=68	DAC n=64	*P*
Carga máxima (Watts)	139±41	155±43	p=0,033
METs máximo	6,5±1,7	7,7±1,9	p<0,001
VO_{2pico}			
$ml \cdot kg^{-1} \cdot min^{-1}$	21,6±5,8	25,9±6,5	p<0,001
$L \cdot min^{-1}$	1,89±0,52	2,05±0,58	p=0,101
Depressão ST máxima >1 mm	32 (47%)	57 (49%)	p=0,228
FC máxima (bpm)	128±19	132±18	p=0,178
FC de reserva (bpm)	70±20	78±18	p=0,027
IRC (bpm)	69±18	75±17	p=0,057
FC de recuperação			
15 seg (bpm)	10,9±4,6	10,8±5,0	p=0,376
30 seg (bpm)	15,8±7,0	17,8±6,9	p=0,098
60 seg (bpm)	32,7±10,5	37,8±9,7	p=0,006
120 seg (bpm)	44,3±13,4	48,9±11,1	p=0,037
Slope 60 (batimentos/seg)	-0,53±0,17	-0,62±0,14	p=0,004

Dados apresentados em média±DP. METs, equivalente metabólico; VO_{2pico}, pico do consumo de oxigênio; FC, frequência cardíaca; IRC, índice da resposta cronotrópica ao exercício máximo; DAC, grupo de pacientes com doença arterial coronariana sem diabetes tipo 2; DAC+DT2, grupo de pacientes com doença arterial coronariana com diabetes tipo 2.

A FC_{res} foi menor (p=0.027) e IRC tendeu a ser menor (p=0.057) no grupo DAC+DT2 que no grupo DAC. A DT2 modificou a FC_{rec} no pós exercício (principal efeito de interação entre tempo x grupo p=0.037). Os pacientes do grupo DAC+DT2 tinham FC_{rec60} (p=0.006), FC_{rec120} e $FC_{slope60}$ (p=0.004) mais lentificada comparativamente com os pacientes do grupo DAC (Tabela 2). Entretanto, não houve diferença entre os grupos para as seguintes varáveis: FC_{res}, IRC, FC_{rec60}, FC_{rec120} ou

$FC_{slope60}$ depois de ajustar para METs máximo, IMC e medicação, isto é, FC_{Rec60} ANCOVA p=0.223, p=0.061, p=0.387 e p=0.094 para diabetes, METs, IMC e antagonista do canal de cálcio, respectivamente. Os valores de p correspondentes para FC_{rec120} foi p=0.980, p=0.001, p=0.451 e p=0.006 e para $FC_{slope60}$ p=0.228, p=0.030, p=0.404 e p=0.079 para diabetes, METs, IMC e antagonista do canal de cálcio, respectivamente. Os nitratos não modificaram as respostas da FC entre os grupos em nenhuma condição. A Figura 1, apresenta um exemplo de $FC_{slope60}$ para coronariopatas diabéticos e não diabéticos.

3.5.3. Frequência cardíaca e sua variabilidade

A FC e a VFC antes e após o exercício em ambos os grupos estão apresentados na Tabela 3. Cinco pacientes diabéticos foram excluídos da análise devido ao significante número de extra-sístoles ou artefatos nos iRR. Um paciente não diabético foi excluído devido à presença de extra-sístoles durante e após o exercício e um outro paciente também foi excluído pelo mesmo motivo na condição pós exercício.

Tabela 3. Valores médios das análises lineares e não lineares da variabilidade da frequência cardíaca antes do exercício (5 min) e na condição pós exercício de 3 a 8 minutos após o exercício, na posição supina.

	CAD+T2D n=63	CAD n=63	*P*-level
Pré-exercício 5 min			
FC (bpm)	57±10	54±6	*p*=0,030
SDNN (ms)	36±19	36±21	*p*=0,969
AF power (ms^2)	299±353	479±1347	*p*=0,490
BF power (ms^2)	385±521	409±563	*p*=0,940
BF/AF ratio	1,81±1,71	1,47±1,34	*p*=0,210
α-1	1,04±0,27	0,99±0,26	*p*=0,280
Pós-exercício 5 min	n=63	n=62	
FC (bpm)	76±10	75±10	*p*=0,765
SDNN (ms)	29±12	28±17	*p*=0,386
AF (ms^2)	102±172	114±246	*p*=0,268
BF (ms^2)	162±212	175±352	*p*=0,608
BF/AF	2,8±2,3	3,9±3,9	*p*=0,257
α-1	1,18±0,30	1,24±0,28	*p*=0,277

Dados em média±DP. FC, frequência cardíaca; SDNN, desvio padrão dos intervalos R-R; AF, alta frequência; BF, baixa frequência; BF/AF, razão entre as bandas de baixa e de alta frequência; α-1, *fractal scaling exponent* dos intervalos R-R; DAC, grupo de pacientes com doença arterial coronariana sem diabetes tipo 2; DAC+DT2, grupo de pacientes com doença arterial coronariana com diabetes tipo 2.

Os pacientes diabéticos apresentaram uma maior FC na condição de repouso que os pacientes não diabéticos (*p*=0.030), mas nenhuma outra diferença foi observada entre os grupos durante o exercício nos níveis de 40%, 60% ou 80% do VO_{2pico}, i. e., FC foi 92±12 *vs*. 95±14 bpm (*p*=0.099) e α_1 1.02±0.37 *vs.* 1.02±0.32 (*p* = 0.93) no nível de 61%±5% e 61%±5% do VO_{2pico} para diabéticos e não diabéticos, respectivamente.

3.6. Discussão

O presente estudo mostrou que a resposta da FC de recuperação no pós exercício foi mais lenta nos pacientes do grupo DAC+DT2 que nos pacientes do grupo DAC, e isto sugere uma perda da modulação vagal ou aumento da atividade simpática logo após a interrupção do exercício em pacientes com DAC+DT2. A FC de recuperação reduzida nos pacientes diabéticos foi mais evidente no primeiro minuto após o exercício, documentado pelos índices FC_{rec60} e $FC_{slope60}$. Entretanto, a atenuação da FC de recuperação logo após o exercício nos pacientes coronarianos

diabéticos comparativamente com os pacientes coronarianos não diabéticos estava mais relacionada a baixa capacidade física e obesidade que a DT2 por si mesma. Avaliados conjuntamente, estes achados sugerem que o atraso da FC de recuperação logo após o exercício máximo nos pacientes com DT2 pode ser reversível por meio de programas de prevenção e tratamento clínico, incluindo, por exemplo, exercício físico regular e controle da massa corporal.

3.6.1. Dinâmica da FC no pós-exercício

A complexa interação entre a regulação simpática e vagal da FC durante o exercício é organizada em um modelo recíproco, isto é, o aumento da atividade simpática é acompanhada pela redução da atividade vagal sobre o coração durante o exercício dinâmico (Robinson *et al.*, 1966; Maciel *et al.*, 1986; Orizio *et al.*, 1988; Yamamoto *et al.*, 1991; Tulppo *et al.*, 1996; Tulppo *et al.*, 1998). Entretanto, este comportamento recíproco está alterado durante o período de recuperação após o exercício devido as diferenças temporais no padrão de recuperação dos ramos autonômicos na condição pós-exercício. Uma rápida restauração da modulação vagal ocorre logo após o término do exercício (Imai *et al.*, 1994; Goldberger *et al.*, 2006; Martinmaki e Rusko, 2008; Tulppo *et al.*, 2011). Em contrapartida, o sistema nervoso simpático parece apresentar um maior período de latência para retornar aos valores basais após a interrupção do exercício, e isto resulta em uma hiperatividade simpática de longa duração (Ray, 1993; Tulppo *et al.*, 2011). Conjuntamente, essas alterações na regulação autonômica podem resultar em uma dupla ativação dos ramos simpático e parassimpático do sistema nervoso autonômico no pós-exercício (Tulppo *et al.*, 2011). Estas alterações na atividade autonômica na condição de pós-exercício pode explicar parcialmente os achados clínicos, desde que, particularmente, a fase de recuperação do exercício pode ser considerada como uma fase vulnerável para vários eventos cardiovasculares (Siscovick *et al.*, 1982; Siscovick *et al.*, 1984; Albert *et al.*, 2000; Von Klot *et al.*, 2008).

É bem conhecido que os coronariopatas diabéticos apresentam um maior risco para eventos cardiovasculares que aqueles sem DT2. O desbalanço autonômico no pós exercício é um mecanismo em potencial, já que a lenta FC de recuperação após o exercício também tem sido associada com eventos cardiovasculares em várias populações clínicas e subclínicas (Cole *et al.*, 1999; Lauer e Froelicher, 2002; Nissinen *et al.*, 2003; Jouven *et al.*, 2005). No presente estudo, a FC de recuperação

de um a dois minutos após o exercício foi o único marcador da atividade autonômica diferenciando coronariano diabético e não diabético pareados pela idade, gênero, e fração de ejeção para todos com medicação otimizada, incluindo beta-bloqueador. Visto que ocorre uma complexa interação ocorre na fase inicial depois do exercício, é difícil identificar a diferença na FC de recuperação entre coronariano diabéticos e não diabéticos devido a perda da ativação vagal ou aumento da atividade simpática ou ambos. Adicionalmente, as catecolaminas circulantes tem um importante contribuição para a hiperatividade simpática pós exercício (Krock e Hartung, 1992), mas no presente estudo infelizmente, não medimos as catecolaminas circulantes (epinefrina e norepinefrina). Em terceiro lugar, como um novo achado do presente estudo, não houve nenhuma diferença entre os grupos de pacientes na FC de recuperação depois de ajustar os dados para METs e IMC. Esses achados destacam que o treinamento físico e manutenção da massa corporal como um potente tratamento para melhorar a FC de recuperação nos pacientes coronarianos diabéticos. Além disso, os antagonistas do canais de cálcio modificaram a FC_{rec} principalmente 2 minutos após o exercício. Pacientes que normalmente fazem uso de antagonistas de canais de cálcio tem hipertensão arterial mais severa que pode estar associada com o atraso da FC_{rec}(Carnethon *et al.*, 2011).

3.6.2. Resposta da FC ao exercício máximo

A medida da resposta cronotrópica da FC ao exercício tem sido usada particularmente para avaliar a influência simpática sobre o coração e tem sido mostrado ser um potente preditor de mortalidade cardíaca em populações assintomáticas (Azarbal *et al.*, 2004; Gulati *et al.*; Jouven *et al.*, 2005; Savonen *et al.*, 2006; Kiviniemi *et al.*, 2011; Lanza *et al.*, 2011) e em pacientes com diversas cardiopatias (Myers *et al.*, 2007; Savonen *et al.*, 2008; Kiviniemi *et al.*, 2011). No presente estudo, a FC de reserva foi menor e a IRC ajustada para idade apresentou uma tendência a ser menor no grupo CAD+DT2 que no grupo DAC. Entretanto, não houve nenhuma diferença entre os grupos depois de ajustado para nível de aptidão física e IMC.

3.6.3. Variabilidade da Frequência Cardíaca

A diabetes tipo 2 tem mostrado capaz de reduzir a VFC e a sensibilidade barorreflexa avaliadas em pacientes diabéticos sem DAC (Masaoka *et al.*, 1985;

Frattola *et al.*, 1997). Estudos prévios mostram que a DT2 não apresentaram nenhuma redução adicional na sensibilidade barorreflexa entre pacientes com DAC (Wykretowicz *et al.*, 2005) ou na VFC entre pacientes diabéticos com insuficiência cardíaca congestiva ou DAC (Burger e Aronson, 2001; Kiviniemi *et al.*, 2010). Também no presente estudo, os índices da VFC de curta duração no repouso ou na condição pós-exercício não foram capazes de diferenciar os coronariopatas com e sem DT2. Primeiro, todos os pacientes foram cuidadosamente pareados pela idade, gênero, FE e quanto ao uso de betabloqueador, pois já é conhecido os seus efeitos sobre a VFC e que podem parcialmente explicar os nosso achados. Segundo, a medida da VFC em condições laboratoriais não são tão bem reprodutíveis quanto os registros de 24 horas (Huikuri *et al.*, 1990; Tulppo *et al.*, 1998) e pode ser influenciada pelo efeito "*jaleco branco*", em alguns pacientes (Grassi *et al.*, 1999). Em terceiro lugar, particularmente o alto nível de norepinefrina circulante na condição pós exercício pode resultar em alteração abrupta na dinâmica dos intervalos R-R os quais não são identificados pelos métodos de VFC utilizados (Tulppo *et al.*, 1998). Ao contrário das medidas da VFC no repouso ou poucos minutos após o exercício, uma mudança rápida e acentuada da ativação dos ramos autonômicos nos primeiros segundos com a mudança do domínio simpático para a restauração vagal, leva a uma redução da FC após o exercício (Tulppo *et al.*, 2011). O comportamento da regulação autonômica inicialmente após exercício máximo é o maior candidato para explicar as diferenças na FC de recuperação entre os grupos diabéticos e não diabéticos.

3.6.4. Limitações do Estudo

Por razoes éticas, as medidas do presente estudo foram executadas com manutenção da prescrição medicamentosa mantida por razões éticas pois é bem conhecido o efeito de retirada ou cessação do betabloqueador. Entretanto, os presentes resultados terão mais implicações práticas quando as análises são realizadas no período que os pacientes estão sob o uso de suas medicações.

3.6.5. Aplicação Clínica

Baseado no presente estudo, é importante enfatizar o papel do exercício físico na manutenção da boa função do condicionamento cardiovascular, melhorando a performance física e na perda de peso. Embora todos os pacientes estivessem com a medicação otimizada, é importante destacar que a modificação de hábitos de vida,

como a prática regular de exercícios físicos e a reeducação alimentar deveriam receber a mesma importância como os medicamentos usados para a prevenção (Chow *et al.*, 2010).

3.6.6. Conclusão

O atraso da FC de recuperação nos pacientes coronarianos diabéticos comparados com os pacientes coronarianos não diabéticos, pode estar relacionado a diminuição da atividade vagal e/ou aumento da atividade simpática depois do exercício. Entretanto, a atenuação da FC de recuperação incialmente pós-exercício nos pacientes coronarianos diabéticos está intimamente mais relacionada a capacidade física e obesidade que a DT2 *per si*.

3.7. Agradecimentos

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4. Considerações Finais

4. Considerações Finais

Os estudos apresentados mostraram o uso de ferramentas simples e de baixo custo para avaliar a resposta dinâmica da FC e de sua variabilidade tanto durante o repouso quanto durante o teste de exercício físico máximo e na recuperação após o exercício, em distintas populações com doença cardiovascular com e sem infarto agudo do miocárdio e com e sem diabetes mellitus tipo 2.

O primeiro estudo mostrou o uso da análise não linear para avaliar a complexidade da dinâmica da frequência cardíaca em pacientes com doença cardiovascular com e sem infarto do miocárdio. Embora não encontramos encontrado nenhuma diferença entre os grupos, que pode ser devida à angioplastia coronariana nos pacientes com IAM, ao uso de betabloqueador, à capacidade física do grupo saudável e ao protocolo utilizado (avaliação somente realizada na postura supina), o uso da análise simbólica e de entropias tem mostrado utilidade na avaliação da modulação autonômica cardíaca e da complexidade, respectivamente, de uma série temporal de curta duração em ambientes diferentes, como ambulatório e unidade coronariana.

No segundo estudo, utilizamos diferentes índices para avaliar o comportamento dinâmico da FC e de sua variabilidade durante e após o exercício físico. É importante destacar que este foi o primeiro estudo que avaliou a resposta da FC de pacientes com doença arterial coronariana com e sem diabetes tipo 2. E que o atraso da FC de recuperação observado nos pacientes com DAC associada ao diabetes tipo 2 foi devido à obesidade e a baixa capacidade do que a diabetes por si mesma.

Para a fisioterapia, o presente trabalho contribui da seguinte forma: 1) possibilitar o estudo do controle autonômico cardíaco de pacientes por meio de uma coleta simples e de curta duração da VFC em uma unidade coronariana ou terapia intensiva; 2) na prescrição de exercício físico que pode ser realizado para a população de pacientes com doença arterial coronariana com ou sem diabetes tipo 2 focando melhoria na capacidade física e na redução de massa corporal.

Ainda, o controle da fase de recuperação pós o exercício tem grande importância pois ela pode fornecer informações sobre a efetividade e segurança do tratamento fisioterapêutico empregado naqueles pacientes com alto risco de um evento cardiovascular.

5. OUTRAS ATIVIDADES REALIZADAS DURANTE O PERÍODO DO DOUTORADO

Durante o período de realização do Doutorado (2008-2011), foram desenvolvidas outras atividades relacionadas à participação em outros projetos de pesquisa do Laboratório de Fisioterapia Cardiovascular/NUPEF e ao doutorado sanduíche realizado no Instituto Verve de Pesquisa (*Verve Research)*.

5.1. Participação em outros projetos do Laboratório de Fisioterapia Cardiovascular.

A participação no projeto de pesquisa "Avaliação cardiorrespiratória e da variabilidade da frequência cardíaca de pacientes com infarto do miocárdio submetidos a intervenção fisioterapêutica: fases I e II da reabilitação cardiovascular" que resultou no artigo: *"Effects of progressive exercise during phase I cardiac rehabilitation on the heart rate variability of patients with acute myocardial infarction"* publicado no periódico *Disability and Rehabilitation* (Anexo C), no qual sou co-autor *e a* participação do "*16th International World Physical Therapy Congress*" dos dias 20 à 23 de junho com a apresentação do seguinte trabalho *"Effect of Early Cardiovascular Physiotherapy on Respiratory Sinus Arrhythmia in Patients with Acute Myocardial Infarction",* desenvolvido no Lab. de Fisioterapia Cardiovascular-UFSCar (Anexo G)

Participação do projeto de pesquisa "Avaliação cardiorrespiratória, da limitação ventilatória e da variabilidade da freqüência cardíaca de pacientes com infarto do miocárdio submetidos a intervenção fisioterapêutica na fase II da reabilitação cardiovascular" resultou no artigo "*Relationship between inspiratory muscle capacity and peak exercise tolerance in postmyocardial*" aceito para publicação no periódico Heart & Lung, no qual sou co-autor (Anexo E).

Co-orientação informal do trabalho de graduação "Avaliação da cinética da frequência cardíaca e do consumo de oxigênio em homens saudáveis", realizado pelo aluno Thomas Beltrame. Esse trabalho teve o objetivo de avaliar a cinética da frequência cardíaca e do consumo de oxigênio de homens saudáveis em esteira ergométrica em diferentes cargas de trabalho.

5.2. Atividades relacionadas ao estágio de doutorado sanduíche.

De 31 de julho de 2010 a 26 de julho de 2011, realizei estágio no Departamento de Exercício e Fisiologia Médica do Instituto Verve de Pesquisa e o Departamento de Medicina Interna da Universidade de Oulu/Finlândia, sob a tutoria do Prof. Dr. Mikko Tulppo (ANEXO H). Neste período realizei diversas atividades, entre as quais:

1 - Participei da análise e do processamento de dados do projeto multicêntrico intitulado "Predição e prevenção de eventos cardiovasculares em pacientes diabéticos – Aplicação de Novas tecnologias" (*Prediction and prevention of cardiovascular events in diabetic patients – Applications of novel technology*") como parte do projeto multicêntrico "Inovação para Redução de Complicações Cardiovasculares da Diabetes - ARTEMIS" ("*ARTEMIS - Innovation to Reduce Cardiovascular Complications of Diabetes at the Intersection*") entre a Universidade de Oulu – Oulu/Finland e Verve Research

2 - Processamento e a análise da variabilidade da frequência cardíaca de 24 horas de duração; análise da variação da pressão arterial; análise da sensibilidade barorreflexa; registro domiciliar de longa duração do sistema nervoso autonômico pela variabilidade da frequência cardíaca e análise dos mesmos.

3 – Análise dos dados durante o repouso e exercício, o qual foi utilizado um software específico para o cálculo da dinâmica fractal da frequência cardíaca (detrend flutation analysis - DFA), Poincaré Plot, por meio meio de vetores de duas dimensões para avaliação quantitativa da FC e a entropia aproximada que avalia a complexidade. Sendo todos índices não lineares da VFC.

4 – Acompanhamento na Clinica de Reabilitação Cardíaca dos pacientes do projeto ARTEMIS.

5 - Participação no projeto intitulado "*Association of heart rate dynamics during exercise and recovery to vascular function in coronary artery disease*" do Prof. Dr. Antti Kiviniemi que avalia o fluxo sanguíneo da artéria carótida por meio do ecocardiograma.

6 - Participação do grupo de discussões relacionadas ao projeto multicêntrico ARTEMIS.

7 - Participação do "EuroPrevent Congress 2010" realizado na cidade de Genebra/Suiça organizado pela *European Association for Cardiovascular Prevention and Rehabilitation* (Associação Européia de Prevenção e Reabilitação

Cardiovascular). No congresso, apresentei o estudo "*Chronotropic response and heart rate recovery after exercise in cardiac patients with and without type 2 diabetes*", desenvolvido no Instituto Verve de Pesquisa, Oulu, Finlândia, o qual foi publicado no periódico European Journal of Cardiovascular Prevention & Rehabilitation 2011 18:S27, 2011 (Anexo F)

8 - Em junho/2011, participei do *CBCS/ESC Summer School on Cardiovascular Sciences: 'From Basic Mechanisms to Clinical Application* dos dias 12 à 16, Sophia Antipolis, France.

A participação em todas as atividades desenvolvidas no período do meu doutorado contribuiu de forma significativa para a minha formação acadêmica, científica e pessoal. Destaco a fundamental importância do trabalho realizado em equipe, considerando todos os membros do Laboratório de Fisioterapia Cardiovascular/NUPEF/UFSCar, como também os pesquisadores do Departamento de Exercício e Fisiologia Médica do Instituto Verve, especialmente ao Prof. Dr. Mikko Tulppo, ao Prof. Dr. Arto Hautala e ao Prof. Dr. Antti Kiviniemi.

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ANEXO A

Victor R Neves; Anielle C M Takahashi; Michele D B Santos-Hiss; Antti M Kiviniemi; Mikko P Tulppo; Silvia C G Moura; Marlus Karsten; Audrey Borghi-Silva; Alberto Porta; Nicola Montano; Aparecida M Catai. **Linear and nonlinear analysis of heart rate variability in coronary disease.** Artigo submetido ao periódico *Clinical Autonomical Research*.

Clinical Autonomic Research

Linear and nonlinear analysis of heart rate variability in coronary disease

--Manuscript Draft--

Manuscript Number:	
Full Title:	Linear and nonlinear analysis of heart rate variability in coronary disease
Short Title:	Autonomic control in coronary disease
Article Type:	Research Article
Keywords:	Heart rate variability; Symbolic analysis; Conditional entropy; Acute Myocardial Infarction; Coronary Artery Disease
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Abstract:	Coronary artery disease (CAD) and acute myocardial infarction (AMI) are associated with a reduction of heart rate variability (HRV). Objective: The aim of this study was to compare the HRV of CAD patients with and without AMI (CAD-AMI) with health-matched controls by linear (spectral analysis) and nonlinear [Shannon entropy (SE), conditional entropy (CE) and symbolic analysis (SA)] analysis. Methods: Fifty-six men were divided into three groups: healthy (n=19, 57±4 years), CAD (n=20, 56±10 years) and CAD-AMI (n=19, 54±12 years). The RR intervals were recorded at rest in the supine position for 10 min with a HR monitor (Polar ®S810i). A series of 250 beats was selected to analyze variance, spectral analysis, SE, CE [complexity index (CI), normalized CI (NCI)] and SA (0V, 1V, 2LV and 2ULV patterns), as well as 0V (no significant variation) and 2ULV (two significant unlike variations), which reflect sympathetic and vagal modulation, respectively. One-way ANOVA (or the Kruskal-Wallis test when appropriate) and Pearson correlation were used. Results: The CAD group had higher body mass index and weight than the CAD-AMI group, but no differences were found between the healthy and AMI groups. There were no differences between the groups regarding linear and nonlinear analysis. The 0V and

	2ULV patterns were significantly correlated with the SE, CI and NCI of the three groups. Interpretation: There was no difference between the groups regarding cardiac autonomic modulation by linear and nonlinear methods, which may be due to beta-blocker use, coronary angioplasty and the exercise capacity of healthy subjects.

Coversheet

Dear Editor,

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*Manuscript

Linear and nonlinear analysis of heart rate variability in coronary disease

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Short title: Autonomic control in coronary disease

Abstract

Coronary artery disease (CAD) and acute myocardial infarction (AMI) are associated with a reduction of heart rate variability (HRV). **Objective:** The aim of this study was to compare the HRV of CAD patients with and without AMI (CAD-AMI) with health-matched controls by linear (spectral analysis) and nonlinear [Shannon entropy (SE), conditional entropy (CE) and symbolic analysis (SA)] analysis. **Methods:** Fifty-six men were divided into three groups: healthy (n=19, 57±4 years), CAD (n=20, 56±10 years) and CAD-AMI (n=19, 54±12 years). The RR intervals were recorded at rest in the supine position for 10 min with a HR monitor (Polar ®S810i). A series of 250 beats was selected to analyze variance, spectral analysis, SE, CE [complexity index (CI), normalized CI (NCI)] and SA (0V, 1V, 2LV and 2ULV patterns), as well as 0V (no significant variation) and 2ULV (two significant unlike variations), which reflect sympathetic and vagal modulation, respectively. One-way ANOVA (or the Kruskal-Wallis test when appropriate) and Pearson correlation were used. **Results:** The CAD group had higher body mass index and weight than the CAD-AMI group, but no differences were found between the healthy and AMI groups. There were no differences between the groups regarding linear and nonlinear analysis. The 0V and 2ULV patterns were significantly correlated with the SE, CI and NCI of the three groups. **Interpretation:** There was no difference between the groups regarding cardiac autonomic modulation by linear and nonlinear methods, which may be due to beta-blocker use, coronary angioplasty and the exercise capacity of healthy subjects.

Keywords: Heart rate variability; Symbolic analysis; Conditional entropy; Acute Myocardial Infarction; Coronary Artery Disease; Autonomic nervous system.

Introduction

The progression of coronary artery disease (CAD) to acute myocardial infarction (AMI) may be related to sympathovagal imbalance [1,2]. Studies have reported that the higher sympathetic modulation observed in CAD patients with and without AMI may be a main cause of arrhythmia and sudden death [1,3]. Additionally, electrical alternans and ventricular arrhythmias may be associated with decreased heart rate variability (HRV) in patients soon after AMI [4] and even after coronary angioplasty [5].

Linear and nonlinear methods of HRV analysis have been used to describe the physiological interaction between heart period and the autonomic nervous system [1,6,7]. In recent years, the nonlinear method has revealed certain heart period changes that cannot be observed by spectral analysis [8,6,7]. Although a number of studies have demonstrated autonomic imbalance in CAD and AMI patients with linear methods (spectral analysis) [3,1], the nonlinear method has not yet been well-established for use with this population. Thus, nonlinear methods may provide additional information about cardiac autonomic control in CAD patients with and without AMI.

There are several algorithms of nonlinear analysis for assessing the complexity of heart period, such as Shannon Entropy (SE), which provides information about the distribution of sequences of beats (patterns) in RR interval series [9]. Symbolic analysis can also distinguish between these patterns and relate them to sympathetic and parasympathetic modulation [8,10]. Conditional entropy (CE) provides information about heartbeat organization, i.e., whether cardiac beat sequences repeat over time or not [11].

Therefore, the hypothesis of the present study was that cardiac autonomic imbalance in CAD patients with and without AMI [1,3] could be detected by symbolic analysis (SA), Shannon entropy (SE) and conditional entropy (CE) obtained from short-period HRV. Additionally, it was expected that CAD-AMI patients would present higher sympathetic and lower vagal modulation and less HRV complexity than CAD patients and healthy subjects.

Thus, the aim of this study was to compare HRV in healthy subjects and CAD patients with and without AMI by means of linear and nonlinear methods.

Methods

Subjects

This descriptive, cross-sectional study included male CAD patients with and without AMI and healthy males. It was carried out in both a local hospital and the Laboratory of Cardiovascular Physiotherapy of the Department of Physiotherapy of the Federal University of São Carlos (São Carlos, Brazil). The study followed Declaration of Helsinki guidelines and was approved by the Human Research Ethics Committee of the Federal University of São Carlos, São Carlos, SP, Brazil (protocol number 160/2010). All participants were informed about the study's objectives and experimental protocol and signed an informed consent form.

A total of 222 men in the following clinical conditions were evaluated: healthy subjects (n =23) (Healthy group) and coronary artery disease patients (CAD) (n = 199). The determination of health was based on clinical and physical examinations, laboratory tests, a standard electrocardiogram (ECG) and a maximum exercise test conducted by a physician. The healthy group also underwent a cardiopulmonary test to assess exercise capacity according to maximal oxygen consumption (VO_{2max}).

Exclusion criteria for healthy subjects included: arterial hypertension, diabetes, chronic obstructive pulmonary disease, neurological injuries, cardiovascular, respiratory diseases, musculoskeletal diseases, smoking or habitual drinking.

The coronary artery disease patients were subdivided into the following two groups: a CAD group (n = 91), whose coronary artery disease had been documented by coronary angiography but who had no history of myocardial infarction, and a CAD-AMI group (n = 108) whose coronary artery disease had been documented by coronary angiography and who had recently suffered their first non-complicated myocardial infarction (12 to 24 hours post-cardiac event) with ST-segment elevation. The CAD-AMI group included only patients who had undergone a successful primary or elective percutaneous transluminal coronary angioplasty with no complications.

Exclusion criteria for CAD patients with and without AMI included: hypertension with levels above 180/100 mmHg, atrial fibrillation, malignant ventricular arrhythmias, complex ectopic ventricular beats, supraventricular or sinus tachycardia (greater than 120 beats per minute), 2° and 3° AV block, pacemaker, signs of low cardiac output or ventricular failure, hypotension and heart failure, debility, fever, respiratory insufficiency, chronic obstructive pulmonary disease, illegal drug use, stroke sequelae, lower limb amputation, severe aortic stenosis or severe left main coronary injury (>50%) or

prior coronary artery bypass graft surgery. Additional exclusion criteria for CAD-AMI patients were complicated AMI, AMI without ST-segment elevation, symptoms of post-AMI chest pain, re-infarction or hospital admission more than 48 hours after the AMI event.

Although 222 subjects were originally evaluated, only 58 were not excluded, being distributed as follows: CAD (n = 20), CAD-AMI (n = 19) and healthy (n = 19) group (Figure 1).

Insert Fig. 1

Experimental procedures

The participants were instructed to avoid caffeinated and alcoholic beverages as well as strenuous exercise on the day before the test protocol. They were also instructed to have a light meal at least 2 hours prior to the test. On the day of the experiment, the participants were interviewed and examined before the test to verify if they were in good health and/or clinically stable. The experiments were carried out in climate-controlled conditions (21–24°C) with relative air humidity of 40–60%. To reduce anxiety, the volunteers were familiarized with the equipment and the experimental procedures prior to carrying out the experiment.

The experimental protocol for the CAD-MI group was carried out in the hospital's Coronary Care Unit 22±5 h after admission and 12 to 24 h after the cardiac event. Before beginning the protocol, clinical and physical examinations and laboratory tests ($CK\text{-}_{MB}$ enzyme concentration, total blood count, chest X-ray, standard ECG and coronary angiography) were carried out.

Experimental protocol

The volunteers remained at rest for 10 minutes in the supine position and were instructed to breathe spontaneously. At the beginning and end of the experiment, the blood pressure of all volunteers was measured by the auscultatory method.

With the volunteer in the supine position, instantaneous R-R intervals (RRi) were recorded using a digital telemetry system that consisted of a transmitter placed on the patient's chest and a HR monitor (Polar® S810i; Polar Electro Oy, Kempele, Finland) [12,13]. This previously validated [13] system detects ventricular depolarization, corresponding to the *R* wave on the electrocardiogram, at a

sampling rate of 500 Hz and a temporal resolution of 1 ms [14]. The signals were transmitted to a receiver and then to a computer for subsequent analysis.

Data analysis

The RRi sequence length (n=250 beats) with the greatest stability was selected for each subject. The same sequence was used for both analyses (linear and nonlinear). The mean and standard deviation of the RRi were calculated.

HRV spectral analysis

Frequency domain analysis was performed using an autoregressive model [15,16] on previously-selected RRi sequences. Two main spectral components were considered: low frequency (LF - from 0.04 to 0.15 Hz) and high frequency (HF - from 0.15 to 0.50 Hz), which represent sympathetic and vagal modulations, respectively [1]. The spectral components were expressed as normalized units (LFnu and HFnu) and ratio (LF/HF). Normalization consisted of dividing the power of a given spectral component (HF or LF) by the total power minus the power below 0.04 Hz and multiplying this ratio by 100 [15]. All the volunteers presented a respiratory rate in the HF range.

Shannon Entropy

The RRi series were transformed into a sequence of numbers (symbols) ranging from 0 to 5 and organized into 3 beat sequences from which patterns were observed. The shape and distribution of these patterns was calculated with Shannon entropy (SE). The SE is large if the distribution is flat (all patterns are identically distributed and the series carries the maximum amount of information). However, if there is a subset of more probable patterns, while others are missing or infrequent (e.g., in a Gaussian distribution), the SE is small [9].

Symbolic Analysis

Symbolic analysis was carried out by grouping the patterns into four families as follows: (a) no variation (0V: all the symbols are equal, i.e. 2,2,2 or 4,4,4); (b) one variation (1V: 2 consecutive symbols are equal and the remaining symbol is different, i.e. 4,2,2 or 4,4,3); (c) two like variations (2LV: the 3 symbols form an ascending or descending ramp, i.e. 5,4,2 or 1,3,4); and (d) two unlike

variations (2ULV: the three symbols form a peak or a valley, i.e. 4,1,2 or 3,5,3). The rate of occurrence for each pattern is defined as 0V%, 1V%, 2LV%, and 2ULV%. It has been observed that 0V% and 2ULV% can function as markers of sympathetic and vagal modulation, respectively [8].

Conditional Entropy

According to Porta et al. [11], conditional entropy (CE) measures the amount of information carried by the most recent sample of patterns that cannot be derived from a sequence of L past values. CE is assessed with the complexity index (CI). We normalized this index with the Shannon entropy of the RRi to obtain a normalized CI (NCI) that expresses complexity in terms of dimensionless units. This index ranges from 0 (null information) to 1 (maximum information). The larger both indexes are, the greater the complexity and the lower the regularity.

Statistical analysis

Normal Gaussian distribution of the data was verified with the Kolmogorov-Smirnov goodness-of-fit test. The Chi-square test was used to compare categorical variables such as medications and risk factors between CAD and CAD-AMI groups. One-way ANOVA with Bonferroni correction (or the Kruskal-Wallis test with Dunn correction, when appropriate) was used to compare the anthropometric characteristics, RRi mean, spectral indexes and variance, SE, CI, NCI and symbolic indexes. The Pearson Correlation test was calculated for the 0V%, 1V%, 2LV% and 2ULV% patterns and the complexity indexes (SE, CI and NCI). All data are presented as mean ± SD, and the significance level was set at $p < 0.05$. The statistical analysis was carried out with Sigma Plot for Windows v11.0.

Results

The characteristics of each group are presented in Table 1. Weight and body mass index (BMI) were higher in CAD than in the CAD-AMI group ($p<0.05$), but no differences were found between healthy and CAD groups or between healthy and CAD-AMI groups. No difference in height or age were found between the groups. The maximal exercise capacity of the healthy group was from

low (n=8) to regular (n=11) (VO_{2max} was 26±5 mL/kg/min) according to American Heart Association criteria [17].

Insert Table 1

The comorbidities, angiographic data and medications of the CAD and CAD-AMI groups are presented in Table 2. There were more patients on beta-blocker therapy in CAD-AMI than CAD (100% and 55%, respectively). The CAD-AMI group presented a significantly higher percentage of patients with anterior descending artery obstruction >50% than the CAD group (89% and 45%, respectively).

Insert Table 2

In the CAD-AMI group, 5 patients had inferior wall infarction and 14 had anterior wall infarction. Eighteen patients had undergone successful percutaneous transluminal coronary angioplasty (PTCA). Only one patient in the CAD-AMI group had not undergone PTCA due to vasospasm. In the CAD group, only one patient had undergone PTCA.

The results of the nonlinear and linear analysis are presented in Table 3. There were no linear or nonlinear variable differences between the groups.

Insert Table 3

Table 4 shows the correlations between the types of SA (SE, CI and NCI). All groups showed a significant negative correlation between 0V% and SE, CI and NCI. On the other hand, there was a significant correlation between 2ULV% patterns and SE, CI and NCI in the healthy group. For the CAD group, there was a significant moderate correlation with NCI and a weak correlation with SE and CI. In CAD-MI, there was a significant moderate correlation between 2ULV% and all variables. In addition, there was a significant moderate correlation between 2LV% and all indexes in the healthy group. There was a significant moderate correlation between 2LV%, SE and CI in the CAD group. Finally, there was a significant moderate correlation between SE, NCI, CI and 2LV% in the CAD-MI group.

Insert Table 4

Discussion

The main finding of this study was that no differences were found between the groups (CAD, CAD-AMI and Healthy) for either linear (variance, mean and spectral analysis) or nonlinear analysis (symbolic analysis, SE, CI and NCI).

Spectral analysis is more traditional and well-established than symbolic analysis, since the frequency bands are related to sympathetic and parasympathetic modulation [1]. Nevertheless, this method has some limitations in that it may be sensitive to band definition (low frequency, from 0.04 to 0.15 Hz and high frequency, from 0.15 to 0.50 Hz). Indeed, normalized unit spectral indexes (HFnu and LFnu) are useful in conditions characterized by reciprocal changes in symphatovagal modulation, e.g., an increase in sympathetic modulation corresponding to an equal decrease of vagal modulation [8]. Thus, to overcome the limitations of spectral analysis, Porta et al. [11] proposed SA, whose patterns are divided into four families. This type of analysis can detect nonreciprocal autonomic change, e.g., when increased sympathetic modulation does not correspond to reduced vagal modulation [8].

A number of studies have compared spectral analysis to SA. Tobaldini et al., [18] showed that SA seems more suitable than spectral analysis for describing alterations of heart period dynamics and cardiovascular regulation in an animal model of heart failure. Porta et al., [8] assessed cardiac autonomic modulation during graded head-up tilt with SA and spectral analysis and found that SA was suitable for describing conditions characterized by reciprocal changes of different magnitudes. On the other hand, Perseguini et al. [19], studying elderly men and women in response to postural change, reported that spectral analysis could better reveal intergroup differences in reciprocal HR changes than SA. Nevertheless, neither spectral analysis nor symbolic analysis detected differences between the three groups in the present study (CAD, CAD-AMI and Healthy).

Several studies have shown that patients with cardiac disease, especially those with acute myocardial infarction, have higher sympathetic modulation and/or lower vagal modulation when evaluated by spectral analysis [3,1]. Lombardi et al. [20] studied the HRV of patients shortly after an AMI (from 1 to 6 hours) and observed that those with anterior wall infarction had higher sympathetic

modulation than patients with inferior wall infarction. Interestingly, no difference in spectral analysis was found between CAD-AMI and the other groups. These results could be due to several factors: 1) all of the CAD-AMI group and half of the CAD group were on beta-blocker therapy; 2) all CAD-AMI patients had undergone successful coronary angioplasty; 3) and the CAD-AMI group assessment was carried out in a very early phase, from 12 to 24 hours after the myocardial infarction event.

The same factors also apply to our symbolic analysis results. Kunz et al. [21] showed that CAD patients with significant stenosis (≥ 50%) had an increased 0V% pattern and a reduced 2ULV% pattern compared to CAD patients without significant stenosis (<50%) and healthy subjects. However, these authors included patients >6 months after an AMI event and patients with myocardial revascularization. Moreover, not all the patients were on beta-blocker therapy, unlike the CAD-AMI group this study.

With regard to symbolic analysis, it was expected that the CAD and CAD-AMI groups would have higher 0V% and lower 2ULV% than the healthy group. The 2ULV pattern is described as alternating sequences of short-long-short or long-short-long heart periods, and these very fast changes appear to be under vagal control in healthy subjects [8,10]. Nevertheless, in pathological conditions, this kind of sequence might be related to mechanisms not strictly under autonomic nervous system control [22]. For example, in rats with heart failure, 2ULV may be linked to cardiac electrical instabilities such as mechanoelectrical interactions or pulsus alternans [23,18]. Such phenomena can generate apparently paradoxical results. Porta et al. [11] observed this fact in heart failure patients who showed a higher 2ULV% pattern than healthy subjects during the daytime. These same phenomena may have contributed to the lack of distinction in 2ULV% pattern between the healthy, CAD and CAD-AMI groups.

Concerning SE and CE, it was expected that the healthy group would have sequences of more irregular and unpredictable patterns and that the pattern distribution would be different from CAD and CAD-AMI. Kunz et al. [21] observed that CAD patients, independently of coronary artery obstruction level (> or < 50%), had lower SE than healthy subjects. However, these patients were not on beta-blocker therapy and those with previous AMI and/or cardiac surgery were not excluded, as previously mentioned. Takahashi et al. [24] observed decreases in CI and NCI in an older healthy group compared to a younger group, but the SE remained unchanged. Thus, these patterns had the same distribution, but formed more regular and predictable sequences, including decreased CI and NCI. In our study, neither

CE (CI and NCI) nor SE differed between the three groups, which suggests that their cardiac complexity was similar.

It is worth noting that a moderate to strong correlation was observed between 0V% and 2ULV% patterns and all complexity indexes, especially SE and NCI, for all groups. According to Tobaldini et al. [23], 2ULV% could also be regarded as a powerful measure of the regularity (or complexity) of the heart period. However, we found no differences between the groups regarding symbolic analysis indexes (SE, CI and NCI).

Beta-blockers and angioplasty are important therapies for patients with AMI and CAD since they can change cardiac autonomic control [25-27]. Airaksinen et al. [27] observed the effects of metoprolol and atenolol on stable CAD patients compared to a placebo group. They observed that beta-blockers induced an increase in vagal modulation (higher HF) and a reduction in sympathetic modulation (lower LF). Lampert et al. (2003) observed that beta-blocker therapy improved HF in patients with AMI. Soares et al. [13] observed that healthy subjects had higher HF than CAD patients, but only one CAD patient was on beta-blocker therapy. In this study all of the CAD-AMI patients and 55% of the CAD patients were on beta-blocker therapy, which could explain the similarity of results between these groups.

Malfatto et al. [25] studied patients with anterior wall AMI who had undergone primary coronary angioplasty and AMI patients with no reperfusion and observed that the AMI patients who had undergone coronary angioplasty had better sympathovagal balance (i.e., lower LF/HF) soon after AMI [25]. In another study, primary coronary angioplasty carried out > 12 hours after an AMI event resulted in a biphasic HRV response that led to a significant recovery of HRV parameters, including vagal activation and sympathetic withdrawal [28]. In our study, the entire CAD-AMI group had undergone successful coronary angioplasty. Thus, taken together, beta-blocker therapy and coronary angioplasty could have contributed to our results.

Additionally, the low exercise capacity indicated by the healthy subjects' VO_{2max} may have influenced their autonomic nervous system since subjects with low exercise capacity have lower vagal modulation than subjects with good exercise capacity [29]. Indeed, the healthy group showed low to regular aerobic capacity, which could be a further contributing factor to our results.

In conclusion, we found that the healthy, CAD and CAD-AMI groups did not differ regarding cardiac autonomic modulation or complexity according to linear (spectral analysis) and nonlinear

methods [symbolic analysis, Shannon entropy and Conditional entropy (CI and NCI)]. This may have been due to the beta-blocker therapy and coronary angioplasty of CAD-AMI group and the exercise capacity of the healthy subjects.

Limitation

The first limitation of this study is that no intervention was applied to stimulate a cardiac autonomic response (postural changing, physical exercise, etc.) which narrows the possibility of understand a possible changing in activation/deactivation dynamic of cardiac autonomic nervous system. Secondly, only the healthy subjects underwent cardiopulmonary exercise testing to determine maximal oxygen consumption due to the impossibility of such testing with patients in a very early phase of AMI. Furthermore, although beta-blocker therapy may have interfered in the results of the AMI patients, its cessation is another impossibility since it is a mandatory therapy [30].

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Conflict of interest The authors declared no conflict of interest.

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Table 1: Characteristics of healthy subjects and coronary artery disease patients with and without acute myocardial infarction.

	Healthy	**CAD**	**CAD-AMI**
	n=19	n=20	n=19
Age (years)	57±4	56 ±10	54±12
Weight (kg)	72±8	81±16†	71±10
Height (cm)	168±5	171±7	168±7
BMI (kg/cm^2)	26±2	28±4†	25±3

Values are mean±SD. BMI, body mass index; CAD, coronary artery disease group; AMI, acute myocardial infarction group. $^{\dagger}p<0.05$ CAD vs. AMI.

Table 3: Heart rate variability spectral analysis, Shannon entropy, conditional entropy and symbolic analysis of healthy subjects and coronary artery disease patients with and without acute myocardial infarction.

	Healthy	**CAD**	**CAD-AMI**
Linear Analysis			
Variance (RRi ms^2)	1452±1309	859±1014	1199±1559
RRi Mean (ms)	972±148	959±208	906±180
Spectral analysis			
HF (ms^2)	545±495	299±504	325±515
LF (ms^2)	220±237	241±293	177±246
LFnu	64.13±23.59	46.74±26.15	59.99±19.33
HFnu	35.34±23.51	50.19±29.08	35.03±17.91
LF/HF	3.25±3.08	2.70±4.83	2.80±2.62
Nonlinear Analysis			
Symbolic analysis			
0V%	26.15±12.05	26.56±13.08	23.21±14.24
1V%	48.38±3.50	45.83±4.88	45.66±6.64
2LV%	9.07±5.37	9.21±5.97	7.95±3.95
2ULV%	16.40±8.01	18.39±8.01	23.18±11.50
Shannon entropy	3.34±0.34	3.41±0.44	3.54±0.42
Conditional Entropy			
NCI	0.71±0.10	0.73±0.09	0.74±0.11
CI	0.99±0.15	1.02±0.17	1.09±0.21

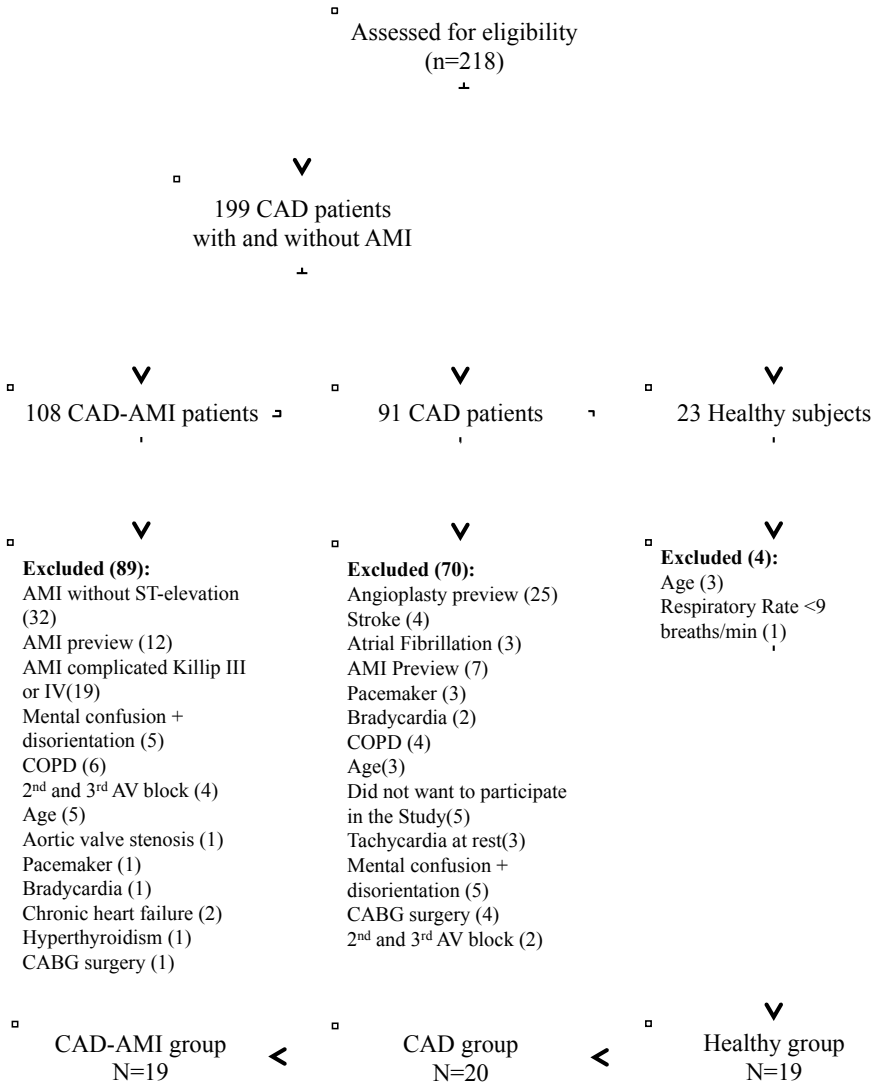
Values are expressed as mean±SD. CAD, coronary artery disease group; CAD-AMI, coronary artery disease with acute myocardial infarction group; RRi, RR interval; HF, high frequency; LF, low frequency; HFun, high frequency normalized unity; LFun, low frequency normalized unity; 0V%, patterns with no variations; 1V%, patterns with one variation; 2LV%, patterns with two like variations; 2ULV%, patterns with two unlike variations; NCI, normalized complexity index; CI, complexity index. No difference was found between groups with ANOVA.

Table 4: Correlations between symbolic index (0V%, 1V%, 2LV% and 2ULV% patterns) and Shannon Entropy (SE), complexity index (CI) and normalized complexity index (NCI) for healthy subjects and coronary artery disease patients (CAD) without and with acute myocardial infarction (AMI).

Correlations	**Healthy**			**CAD**			**CAD-AMI**		
	SE	**NCI**	**CI**	**SE**	**NCI**	**CI**	**SE**	**NCI**	**CI**
0V%	*r*=-0.909	*r* = -0.733	*r* = -0.892	*r* = -0.790	*R* = -0.617	*r* = -0.696	*r* = -0.820	*r* = -0.811	*r* = -0.780
	P < 0.00*	*P* < 0.00*	*P* < 0.00*	*P* < 0.00*	*P* < 0.00*	*P* = 0.00*	*P* < 0.00*	*P* < 0.00*	*P* < 0.00*
1V%	*r* = -0.193	*r* = 0.118	*r* = 0.096	*r* = 0.325	*r* = 0.082	*r* = 0.230	*r* = 0.140	*r* = 0.148	*r* = 0.147
	P = 0.415	*P* = 0.622	*P* = 0.686	*P* = 0.174	*P* = 0.737	*P* = 0.344	*P* = 0.567	*P* = 0.546	*P* = 0.547
2LV%	*r* = 0.719	*r* = 0.751	*r* = 0.791	*r* = 0.765	*r* = 0.365	*r* = 0.623	*r* = 0.607	*r* = 0.675	*r* = 0.619
	P < 0.00*	*P* < 0.00*	*P* < 0.00*	*P* < 0.00*	*P* = 0.124	*P* < 0.00*	*P* < 0.00*	*P* < 0.00*	*P* < 0.00*
2ULV%	*r* = 0.737	*r* = 0.629	*r* = 0.717	*r* = 0.533	*r* = 0.647	*r* = 0.529	*r* = 0.727	*r* = 0.686	*r* = 0.668
	P < 0.00*	*P* < 0.00*	*P* < 0.00*	*P* < 0.00*	*P* < 0.00*	*P* < 0.02*	*P* < 0.00*	*P* < 0.00*	*P* < 0.00*

* *P* < 0.05

Fig 1 Distribution diagram of the coronary artery disease patients (CAD group), CAD patients with acute myocardial infarction (CAD-AMI group) and healthy subjects. CAD, coronary artery disease; AMI, acute myocardial infarction; COPD, coronary obstruction pulmonary disease; AV, atrioventricular; CABG, coronary artery bypass graft.


Assessed for eligibility
(n=218)
199 CAD patients
with and without AMI
108 CAD-AMI patients
91 CAD patients
23 Healthy subjects
Excluded (89):
AMI without ST-elevation (32)
AMI preview (12)
AMI complicated Killip III or IV(19)
Mental confusion + disorientation (5)
COPD (6)
2nd and 3rd AV block (4)
Age (5)
Aortic valve stenosis (1)
Pacemaker (1)
Bradycardia (1)
Chronic heart failure (2)
Hyperthyroidism (1)
CABG surgery (1)
Excluded (70):
Angioplasty preview (25)
Stroke (4)
Atrial Fibrillation (3)
AMI Preview (7)
Pacemaker (3)
Bradycardia (2)
COPD (4)
Age(3)
Did not want to participate in the Study(5)
Tachycardia at rest(3)
Mental confusion + disorientation (5)
CABG surgery (4)
2nd and 3rd AV block (2)
Excluded (4):
Age (3)
Respiratory Rate <9 breaths/min (1)
CAD-AMI group
N=19
CAD group
N=20
Healthy group
N=19

ANEXO B

Victor R Neves; Antti M Kiviniemi; Arto J Hautala; Jaana Karjalainen; Olli-Pekka Piira; Aparecida M Catai; Timo H Mäkikallio; Heikki V Huikuri; Mikko P Tulppo. **Heart rate dynamics after exercise in cardiac patients with and without type 2 diabetes.** Artigo publicado no periódico *Frontiers in Physiology*.

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Heart rate dynamics after exercise in cardiac patients with and without type 2 diabetes

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Purpose: The incidence of cardiovascular events is higher in coronary artery disease patients with type 2 diabetes (CAD + T2D) than in CAD patients without T2D. There is increasing evidence that the recovery phase after exercise is a vulnerable phase for various cardiovascular events. We hypothesized that autonomic regulation differs in CAD patients with and without T2D during post-exercise condition. **Methods:** A symptom-limited maximal exercise test on a bicycle ergometer was performed for 68 CAD + T2D patients (age 61 ± 5 years, 78% males, ejection fraction (EF) 67 ± 8, 100% on β-blockade), and 64 CAD patients (age 62 ± 5 years, 80% males, EF 64 ± 8, 100% on β-blockade). Heart rate (HR) recovery after exercise was calculated as the slope of HR during the first 60 s after cessation of exercise (HRR_{slope}). R–R intervals were measured before (5 min) and after exercise from 3 to 8 min, both in a supine position. R–R intervals were analyzed using time and frequency methods and a detrended fluctuation method (α_1). **Results:** BMI was 30 ± 4 vs. 27 ± 3 kg m^2 ($p < 0.001$); maximal exercise capacity, 6.5 ± 1.7 vs. 7.7 ± 1.9 METs ($p < 0.001$); maximal HR, 128 ± 19 vs. 132 ± 18 bpm (p = ns); and HRR_{slope}, −0.53 ± 0.17 vs. −0.62 ± 0.15 beats/s ($p = 0.004$), for CAD patients with and without T2D, respectively. There was no differences between the groups in HRR_{slope} after adjustment for METs, BMI, and medication (ANCOVA, $p = 0.228$ for T2D and, e.g., $p = 0.030$ for METs). CAD + T2D patients had a higher HR at rest than non-diabetic patients (57 ± 10 vs. 54 ± 6 bpm, $p = 0.030$), but no other differences were observed in HR dynamics at rest or in post-exercise condition. **Conclusion:** HR recovery is delayed in CAD + T2D patients, suggesting impairment of vagal activity and/or augmented sympathetic activity after exercise. Blunted HR recovery after exercise in diabetic patients compared with non-diabetic patients is more closely related to low exercise capacity and obesity than to T2D itself.

Keywords: heart rate recovery, type 2 diabetes, autonomic regulation

INTRODUCTION

The incidence of cardiovascular events is higher in coronary artery disease patients (CAD) with type 2 diabetes (T2D) than in CAD patients without T2D (Haffner et al., 1998; Junttila et al., 2010), but the physiological or pathophysiological mechanisms causing these differences are not well known. Altered autonomic regulation is one potential mechanism resulting in the increased number of cardiovascular events in CAD + T2D patients (Okada et al., 2010; Pop-Busui et al., 2010; Lanza et al., 2011). Autonomic regulation can be studied using various methods at the laboratory, or ambulatory condition tests such as passive head-up tilt and handgrip tests (Montano et al., 1994; Tulppo et al., 2001, 2005; Fu et al., 2002), or ambulatory heart rate (HR) variability and blood pressure measurements (Pagani et al., 1985; Kleiger et al., 1987; Piira et al., 2011). Analysis of autonomic regulation during and after exercise has also been used in various physiological (Yamamoto et al., 1991; Gregoire et al., 1996; Tulppo et al., 1996, 1998b) and clinical settings (Cole et al., 1999, 2000; Jouven and Ducimetiere, 2000; Jouven et al., 2005; Kiviniemi et al., 2011).

There is increasing evidence that the recovery phase after exercise is a vulnerable phase for various cardiovascular events. Case-crossover studies have shown that exercise as a trigger of acute myocardial infarction is not limited to the time of exercise, but extends for a certain time period after cessation of physical activity (Siscovick et al., 1982, 1984; Albert et al., 2000; von Klot et al., 2008). Similarly, the risk of sudden cardiac death is transiently increased in the 30-min after vigorous exercise, and atrial fibrillation episodes occur more commonly after rather than before exercise (Siscovick et al., 1982, 1984; Coumel, 1994; Albert et al., 2000; Huikuri, 2008). Measurement of autonomic function in the very early phase of recovery after exercise has also provided prognostic information. For example, delayed HR recovery 1–2 min after exercise has been shown to predict cardiovascular events in the general population and in various patient groups and animal studies (Cole et al., 1999; Lauer and Froelicher, 2002; Nissinen et al., 2003; Jouven et al., 2005; Smith et al., 2005). Recently, we have shown that co-activation of both autonomic arms may occur during the recovery phase of exercise (Tulppo et al., 2011), which

may partly explain the clustering of various cardiovascular events in the recovery phase of exercise.

The present research was designed to study the behavior of HR dynamics during exercise and in the recovery phase of exercise in CAD patients with and without T2D, matched for age, ejection fraction (EF), and sex. We hypothesized that autonomic regulation, measured by HR recovery and HR variability methods, differs in CAD patients with and without T2D, particularly during post-exercise condition.

MATERIALS AND METHODS

SUBJECTS AND STUDY PROTOCOL

The present study was conducted in the Department of Exercise and Medical Physiology at Verve (Oulu, Finland) and Oulu University Hospital, and the patients were selected from patients in the ARTEMIS (Innovation to Reduce Cardiovascular Complications of Diabetes at the Intersection) study database who had stable CAD without ($n = 64$) and with T2D ($n = 68$). The exclusion criteria were inability to perform the exercise stress test, unstable angina at the time of recruitment, advanced age (>75 years), a recent (<6 months) myocardial infarction, severe nephropathy, heart failure, scheduled cardiac revascularization therapy, T2D diagnosed less than 6 months from the beginning of study, diabetes autonomic neuropathy, dementia, alcoholism, drug abuse, or any condition that could impair the subject's capacity to give informed consent. CAD was documented by coronary angiography and T2D was verified by oral glucose tolerance test according to current recommendations (WHO, 1999). The study was performed according to the Declaration of Helsinki, the local committees of research ethics in the Northern Ostrobothnia Hospital District (Oulu, Finland) approved the protocol, and all the subjects gave written informed consent.

The laboratory measurements were performed in the Department of Exercise and Medical Physiology at Verve (Oulu, Finland). The patients were not allowed to eat or consume caffeine for 3 h before the tests. Physical exercise and use of alcohol were prohibited for 24 h before testing. Electrocardiography (ECG) and R–R intervals were collected for 10 min at supine rest, during exercise, and 10 min after exercise in supine position. Breathing was spontaneous in all phases. A capillary blood sample was obtained for analysis of HbA1c concentration before testing (Afinion™ AS100, Axis-Shield PoC AS, Oslo, Norway).

EXERCISE STRESS TEST

The patients performed an incremental maximal test on a bicycle ergometer (Monark Ergomedic 839 E; Monark Exercise AB, Vansbro, Sweden), starting at 30 W with the work rate increasing at a rate of 10 and 15 W every 1 min until exhaustion for females and males, respectively. The patients moved to the supine position within 30 s after cessation of exercise. The patients were not allowed to move or talk during the recovery phase.

Ventilation (V_E) and gas exchange (M909 Ergospirometer, Medikro, Kuopio, Finland) were measured and reported as the mean value for every minute. The highest 1-min mean value of oxygen consumption was expressed as the peak oxygen consumption (VO_{2peak}). Maximal workload (W) and maximal METs were calculated as average workload and METs during the last 1 min of the test. ECG was monitored and recorded using a standard 12-lead ECG (GE Healthcare, Cam-14, Waukesha, WI, USA) and at the same time R–R intervals were recorded with a Polar R–R recorder with a sampling frequency of 1,000 Hz (Polar Electro, Kempele, Finland). Blood pressure was measured with an electronic sphygmomanometer (Tango, Sun-Tech, Raleigh, NC, USA) at rest and during exercise testing. The patients were encouraged to reach a symptom-limited maximal workload, and exercise was stopped if ST depression was >0.2 mV.

The maximal HR was calculated as a mean value of 5 R–R intervals before cessation of exercise from Polar R–R interval data and converted to maximal HR in beats/min with the following equation: maximal HR (beats/min) = 60·(mean R–R interval in ms/1000)$^{-1}$. The chronotropic response to exercise was calculated by chronotropic response index (CRI) with the following equation: CRI = 100·(maximal HR − resting HR)·(220 − age − resting HR)$^{-1}$ (Kiviniemi et al., 2011), and HR reserve as maximal HR − resting HR. HR recovery values were calculated as mean values of 5 R–R intervals around the time points of 15 (HRR_{15}), 30 (HRR_{30}), 60 (HRR_{60}), and 120 (HRR_{120}) s after cessation of exercise from Polar data. Thereafter, HR recovery (beats/min) was calculated as the change in HR from maximal HR to recovery HR at the time points of 15, 30, 60, and 120 s after cessation of exercise. The slope of HR during the 60-s after cessation of exercise (HRR_{slope}) was calculated by linear model using above described HR values at the maximum and 15, 30, and 60 s time points (**Figure 1**).

HEART RATE VARIABILITY

R–R intervals were analyzed from the last 5-min period at rest, at every load during exercise (1-min periods), and from 3 to 8 min (5-min) after exercise. Before HR variability analysis (using

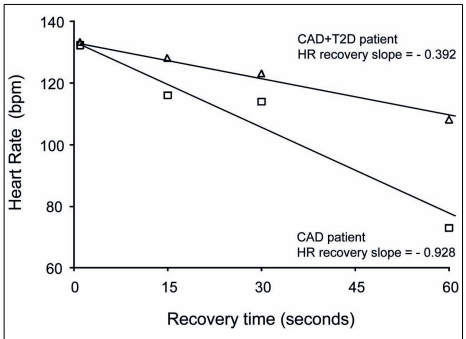

FIGURE 1 | Example of heart rate recovery as the slope of heart rate during the first 60 s after cessation of exercise for two patients (with and without type 2 diabetes) with similar age and maximal heart rate. The slope was calculated by linear model using mean values of 5 R–R intervals [converted to the HR values in beats/min as 60·(mean R–R interval in ms/100)$^{-1}$] at maximum and around the time points of 15, 30, and 60 s after cessation of exercise.

Polar R–R data), all of the R–R intervals were edited manually to exclude all premature beats and noise, which accounted for <8% in every subject. ECG data was used during the editing to confirm sinus origin of the beats. An autoregressive model was used to estimate the power spectrum densities of HR variability after period level detrending (Huikuri et al., 1996; Tulppo et al., 1996). The power spectra were quantified by measuring the area under two frequency bands: LF power (0.04–0.15 Hz) and HF power (0.15–0.4 Hz). Details of the spectrum analyses have been described previously elsewhere (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Detrended fluctuation analysis (DFA) method was used to calculate fractal-like correlation properties of the R–R interval data (Peng et al., 1995; Iyengar et al., 1996). In this study the short-term (4–11 beats) scaling exponent (α-1) was calculated based on previous experiments (Mäkikallio et al., 1996).

STATISTICS

The data were presented as mean ± SD. The normal Gaussian distribution of the data was verified with the Kolmogorov–Smirnov goodness-of-fit test (z value > 1.0). For repeated measurements of post-exercise HR recovery (HRR_{15}, HRR_{30}, HRR_{60}, HRR_{120}), two-factor ANOVA (time × group) was used to assess main effects followed by *post hoc* comparison (unpaired t-test). Significant *post hoc* differences in HR recovery between the groups were adjusted for maximal METs, BMI, and medications (calcium antagonists and nitrates) using ANCOVA. For other variables, the unpaired Student's t-test was used to assess the differences between CAD and CAD + T2D groups in normally distributed data. The Mann–Whitney U-test was used to assess the difference in HR variability indices between groups. The Chi-square test was used for categorical variables. The data were analyzed using SPSS software (SPSS 19.0, SPSS Inc., Chicago, USA). A p-value < 0.05 was considered statistically significant.

RESULTS

STUDY POPULATION

The characteristics of the study population, including comparisons between diabetic and non-diabetic patients, are given in **Table 1**. The diabetic patients' body composition, e.g., weight ($p < 0.001$), waist circumference ($p < 0.001$), BMI ($p < 0.001$), and HbA1c ($p < 0.001$) differed from that of the non-diabetic patients. However, blood pressure, EF, history of infarction, and revascularization or smoking did not differ between the diabetic and non-diabetic patients (**Table 1**). Medication did not differ between the groups, except that calcium antagonists, nitrates, and antidiabetics were more common among the diabetic than the non-diabetic patients (**Table 1**).

Table 1 | Characteristics of patients.

	CAD + T2D ($n = 68$)	CAD ($n = 64$)	p-Level
Sex (F/M)	15/53	13/51	$p = 0.488$
Age (years)	61 ± 5	62 ± 5	$p = 0.514$
Height (cm)	171 ± 7	171 ± 8	$p = 0.678$
Weight (kg)	89 ± 15	80 ± 12	$p < 0.001$
Waist (cm)	105 ± 12	94 ± 10	$p < 0.001$
Hip (cm)	105 ± 10	99 ± 6	$p < 0.001$
Waist/Hip ratio	1.00 ± 0.07	0.95 ± 0.07	$p < 0.001$
BMI (kg m^{-2})	30 ± 4	27 ± 3	$p < 0.001$
HbA1c (%)	6.0 ± 0.7	5.5 ± 0.2	$p < 0.001$
SBP (mmHg)	138 ± 18	136 ± 16	$p = 0.672$
DBP (mmHg)	82 ± 10	82 ± 8	$p = 0.875$
HISTORY OF AMI			
NSTEMI	18 (26%)	19 (30%)	$P = 0.469$
STEMI	13 (19%)	14 (21%)	$p = 0.662$
REVASCULARIZATION			
CAGB	14 (21%)	13 (28%)	$p = 0.506$
PCI	42 (67%)	27 (59%)	$p = 0.426$
Current smokers	3 (4%)	8 (12%)	$p = 0.147$
LVEF (%)	67 ± 8	65 ± 8	$p = 0.107$
MEDICATION			
Anticougulants	66 (97%)	63 (98%)	$p = 1.000$
Beta blockers	68 (100%)	64 (100%)	$p = 1.000$
Calcium antagonists	20 (29%)	9 (14%)	$p = 0.037$
ACEI	31 (46%)	23 (36%)	$p = 0.291$
AT2	13 (19%)	14 (22%)	$p = 0.830$
Diuretics	26 (38%)	15 (23%)	$p = 0.090$
Statin	63 (93%)	57 (89%)	$p = 0.553$
Insulines	10 (7%)	0 (0%)	$p = 0.001$
Oral antidiabetics	50 (74%)	0 (0%)	$p < 0.001$
Nitrates	28 (41%)	8 (13%)	$p < 0.001$
Arrhythmia	1 (1%)	1 (1%)	$p = 1.000$

Values are mean ± SD. BMI, body mass index; HbA1c, Glycosylated hemoglobin; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; AMI, acute myocardial infarction; NSTEMI, no-ST segment elevation myocardial infarction; STEMI, ST segment elevation myocardial infarction; revascularized, the patients who had at least one of the procedures (CABG, coronary artery by-pass grafting or PCI, Percutaneus coronary intervention); LVEF, left ventricular ejection fraction; ACEI, angiotensin conversion enzyme inhibitor; AT2, angiotensin II receptor blocker; CAD, coronary artery disease group; CAD + T2D, coronary artery disease with type 2 diabetes.

HR RESPONSE TO MAXIMAL EXERCISE

The results of the maximal exercise test, including comparisons between diabetic and non-diabetic patients, are given in **Table 2**. Maximal exercise capacity was lower ($p < 0.001$) in the diabetes patients, but maximal HR ($p = 0.178$) was at the same level compared with the non-diabetic patients (**Table 2**). HR reserve was smaller ($p = 0.027$) and CRI tended to be smaller ($p = 0.057$) in the diabetic patients than in the non-diabetic patients. However, there were not significant differences between groups in HR reserve or CRI after adjustment for maximal METs, BMI, and medication, e.g., for HR reserve ANCOVA $p = 0.686$, $p < 0.001$, $p = 0.126$, and $p = 0.169$ for diabetes, Mets, BMI, and calcium antagonists, respectively. There was no difference between the groups in the prevalence of ST segment depression >0.1 mV during the exercise test.

HR RECOVERY

Type 2 diabetes modified post-exercise HR recovery (main effect for time × group interaction $p = 0.037$). The diabetic patients had

Table 2 | Maximal exercise capacity and heart rate recovery.

	CAD+T2D ($n=68$)	CAD ($n=64$)	p-Level
Max load (W)	139 ± 41	155 ± 43	$p=0.033$
Max METs	6.5 ± 1.7	7.7 ± 1.9	$p<0.001$
MAX VO2PEAK			
ml kg^{-1} min^{-1}	21.6 ± 5.8	25.9 ± 6.5	$p<0.001$
l min^{-1}	1.89 ± 0.52	2.05 ± 0.58	$p=0.101$
Max ST depression > 1 mm	32 (47%)	57 (49%)	$p=0.228$
Max HR (bpm)	128 ± 19	132 ± 18	$p=0.178$
HR reserve (bpm)	70 ± 20	78 ± 18	$p=0.027$
CRI (bpm)	69 ± 18	75 ± 17	$p=0.057$
HR RECOVERY			
15 s (bpm)	10.9 ± 4.6	10.8 ± 5.0	$p=0.376$
30 s (bpm)	15.8 ± 7.0	17.8 ± 6.9	$p=0.098$
60 s (bpm)	32.7 ± 10.5	37.8 ± 9.7	$p=0.006$
120 s (bpm)	44.3 ± 13.4	48.9 ± 11.1	$p=0.037$
Slope 60 (beats/s)	−0.53 ± 0.17	−0.62 ± 0.14	$p=0.004$

Values are mean ± SD. METs, metabolic equivalents; VO_2peak, peak uptake oxygen; HR, heart rate; CRI, maximal chronotropic response index.

Table 3 | Average values of linear and non-linear heart rate variability before exercise (5 min) and in post-exercise condition from 3 to 8 min after exercise, both in supine position.

	CAD+T2D	CAD	p-Level
Pre-exercise 5 min	**$n=63$**	**$n=63$**	
HR (bpm)	57 ± 10	54 ± 6	$p=0.030$
SDNN (ms)	36 ± 19	36 ± 21	$p=0.969$
HF power (ms^2)	299 ± 353	479 ± 1347	$p=0.490$
LF power (ms^2)	385 ± 521	409 ± 563	$p=0.940$
LF/HF ratio	1.81 ± 1.71	1.47 ± 1.34	$p=0.210$
α-1	1.04 ± 0.27	0.99 ± 0.26	$p=0.280$
Post-exercise 5 min	**$n=63$**	**$n=62$**	
HR (bpm)	76 ± 10	75 ± 10	$p=0.765$
SDNN (ms)	29 ± 12	28 ± 17	$p=0.386$
HF power (ms^2)	102 ± 172	114 ± 246	$p=0.268$
LF power (ms^2)	162 ± 212	175 ± 352	$p=0.608$
LF/HF ratio	2.8 ± 2.3	3.9 ± 3.9	$p=0.257$
α-1	1.18 ± 0.30	1.24 ± 0.28	$p=0.277$

Values are mean ± SD. HR, heart rate; SDNN, SD of normal-to-normal R–R intervals; HF, high frequency power of R–R intervals; LF, low frequency power of R–R intervals; α-1, fractal scaling exponent of R–R intervals.

delayed HRR_{60} ($p=0.006$), HRR_{120} ($p=0.037$), and HRR_{slope} ($p=0.004$) compared with the non-diabetic patients (**Table 2**). However, there were not significant differences between groups in HRR_{60}, HRR_{120}, or HRR_{slope} after adjustment for maximal METs, BMI, and medication, e.g., for HRR_{60} ANCOVA $p=0.223$, $p=0.061$, $p=0.387$, and $p=0.094$ for diabetes, Mets, BMI, and calcium antagonists, respectively. The corresponding p values for HRR_{120} were $p=0.980$, $p=0.001$, $p=0.451$, and $p=0.006$ and for HRR_{slope} $p=0.228$, $p=0.030$, $p=0.404$, and $p=0.079$ for diabetes, Mets, BMI, and calcium antagonists, respectively. Nitrates did not modify HR behavior between groups at any condition. Examples of HRR_{slope} for non-diabetic and diabetic subjects are shown in **Figure 1**.

HR AND HR VARIABILITY AT REST, DURING SUBMAXIMAL EXERCISE AND AFTER EXERCISE

Heart rate and HR variability before and after exercise, including comparisons between diabetic and non-diabetic patients, are given in **Table 3**. Five diabetic patients were excluded from the analysis due to the significant number of extra systoles or technical artifacts in the R–R interval data. One non-diabetic patient was excluded due to the extra systoles in both pre- and post-exercise conditions and one in post-exercise condition due to the same reason.

The diabetic patients had a higher HR in resting condition than the non-diabetic patients ($p=0.030$), but no other differences were observed at rest or in post-exercise condition (**Table 3**). HR or HR variability did not differ between the groups during submaximal exercise at the levels of 40, 60, or 80% of maximal oxygen uptake, e.g., HR was 92 ± 12 vs. 95 ± 14 bpm ($p=0.099$) and α_1 1.02 ± 0.37 vs. 1.02 ± 0.32 ($p=0.93$) at the level of 61 ± 5% and 61 ± 5% of maximal oxygen uptake for diabetic and non-diabetic patients, respectively.

DISCUSSION

The present study showed that post-exercise HR recovery was slower in CAD + T2D patients than in CAD patients, suggesting an impairment of vagal modulation and/or augmented sympathetic activity initially after exercise for diabetic patients. The impaired HR recovery in diabetic patients was the most obvious 1 min after exercise, documented by HRR_{60} and HRR_{slope} indices. However, blunted HR recovery initially after exercise in diabetic patients compared with non-diabetic patients was more closely related to low exercise capacity and obesity than to T2D itself. Taken together, these findings suggest that delayed HR recovery after exercise in T2D patients may be reversible through prevention and treatment, including, e.g., regular exercise and weight management.

POST-EXERCISE HR DYNAMICS

The interplay between sympathetic and vagal regulation of HR during exercise is organized in a reciprocal fashion, i.e., increased sympathetic activity is accompanied by decreased vagal activity in the heart during dynamic exercise (Robinson et al., 1966; Maciel et al., 1986; Orizio et al., 1988; Yamamoto and Hughson, 1991; Tulppo et al., 1996, 1998b). However, this reciprocal behavior is altered in the recovery phase after exercise due to temporal differences in the recovery pattern of the autonomic arms in post-exercise condition (Tulppo et al., 2011). A rapid restoration of vagal activity occurs after cessation of exercise (Imai et al., 1994; Goldberger et al., 2006; Martinmaki and Rusko, 2008; Tulppo et al., 2011). On the contrary, the sympathetic nervous system seems to have a longer latency to return to the baseline after cessation of exercise, resulting in long-lasting hyperactivity of sympathetic activity (Ray, 1993; Tulppo et al., 2011). Taken together, these changes in autonomic regulation may result in dual activation of the sympathetic and vagal arms in post-exercise condition

(Tulppo et al., 2011). These changes in autonomic activity in post-exercise condition may partly explain the clinical findings, since particularly the recovery phase of exercise has been shown to be a vulnerable phase for various cardiovascular events (Siscovick et al., 1982, 1984; Albert et al., 2000; von Klot et al., 2008).

It is well known that CAD + T2D patients are at a higher risk for cardiac events than CAD patients without diabetes. Altered autonomic regulation in post-exercise condition is one potential mechanism, since slow HR recovery after exercise has also been associated with cardiovascular events in various clinical and subclinical populations (Cole et al., 1999; Lauer and Froelicher, 2002; Nissinen et al., 2003; Jouven et al., 2005). In the present study, HR recovery from 1 to 2 min after exercise was the only marker of autonomic activity separating diabetic and non-diabetic cardiac patients matched with age, sex, and EF all in optimal medications, including β-blockade. Since a complex interaction of autonomic regulation occurs in the initial phase after exercise, it is difficult to detect the difference in HR recovery between diabetic and non-diabetic patients due to impaired vagal activation or augmented sympathetic activation or both. Also circulating catecholamines have an important contribution for the sympathetic post-exercise hyperactivity (Krock and Hartung, 1992), but unfortunately we did not measure epinephrine or norepinephrine in the present study. Thirdly, as a novel finding of the present study, there were no differences between patients groups in HR recovery after adjustment for METs and BMI. These findings emphasized regular exercise training and weight management as potential treatments to improve post-exercise HR recovery in CAD + T2D patients. Importantly, also calcium antagonists modified HR recovery particularly 2 min after exercise. Patients with calcium antagonists usually have more severe hypertension which is associated with delayed HR recovery (Carnethon et al., 2011).

HR RESPONSE TO MAXIMAL EXERCISE

Measurement of the chronotropic response of HR to exercise has been used to assess particularly sympathetic influence on the heart and it has been shown to be a powerful predictor of cardiac mortality in both asymptomatic populations (Azarbal et al., 2004; Gulati et al., 2005; Jouven et al., 2005; Savonen et al., 2006; Kiviniemi et al., 2011) and in patients with various cardiac diseases (Myers et al., 2007; Savonen et al., 2008; Kiviniemi et al., 2011). In the present study HR reserve was lower and the maximal chronotropic response adjusted for age (CRI) tended to be lower in CAD + T2D patients than in CAD patients without diabetes. However, there were no differences between patients groups in these indices after adjustment for fitness and BMI.

HR VARIABILITY

Type 2 diabetes has been shown to decrease HR variability and baroreflex sensitivity in T2D patients without CAD (Masaoka et al., 1985; Frattola et al., 1997). There are previous studies where T2D has shown no additional decrease in baroreflex sensitivity among patients with CAD (Wykretowicz et al., 2005) or in HR variability among T2D patients with heart failure or CAD (Burger and Aronson, 2001; Kiviniemi et al., 2010). Also in the present study the short-term HR variability indices measured at resting or post-exercise condition were not able to separate CAD patients with and without T2D. There are several potential explanations for these findings. First, the populations are carefully matched according to age, sex, EF, and β-blockade which all are known to effect on HR variability and may partly explain the present findings. Secondly, short-term HR variability measures at laboratory condition are not so well reproducible than 24-h recordings (Huikuri et al., 1990; Tulppo et al., 1998b) and may be influenced by "white coat" effects in some subjects (Grassi et al., 1999). Thirdly, high level of circulating norepinephrine particularly in post-exercise condition may results in abrupt changes in beat-to-beat R–R interval dynamics which are not detected by used HR variability methods (Tulppo et al., 1998a). On the contrary to HR variability measurements at rest or few minutes after exercise, rapid and marked changes occurs in both autonomic arms in tens of seconds from sympathetic dominance to restoration of vagal activity resulting decreased HR after exercise (Tulppo et al., 2011). The unique behavior of autonomic regulation initially after maximal exercise is the major candidate to explain differences in HR recovery between diabetic and non-diabetic patient groups.

STUDY LIMITATIONS

The measurements of the present study were performed under continued prescribed medication because of ethical reasons and the well known withdrawal effect of beta-block cessation. However, the present results will have more practical implications when the analyses are performed at a time when the patients are on their normal medication.

CLINICAL APPLICATIONS

Based on the present study, it is important to emphasize the role of physical exercise in maintaining good cardiovascular function, improving physical performance, and losing weight. Although all the patients were on optimized medication, it is important to underscore that behavioral modification, exercises, and diet should be given priority similar to other preventive medications (Chow et al., 2010).

CONCLUSION

Heart rate recovery 1 min after exercise is the most powerful index separating CAD patients with and without T2D in the modern treatment era, beyond short-term HR variability measurements at rest, during exercise, or in post-exercise condition. HR recovery is delayed in CAD + T2D patients compared with CAD patients without T2D, suggesting impairment of vagal activity and/or augmented sympathetic activity after exercise. However, blunted HR recovery initially after exercise in diabetic patients compared with non-diabetic patients is more closely related to exercise capacity and obesity than to T2D itself.

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ANEXO C

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RESEARCH PAPER

Effects of progressive exercise during phase I cardiac rehabilitation on the heart rate variability of patients with acute myocardial infarction

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Abstract

Purpose. Heart rate variability (HRV) decreases after an acute myocardial infarction (AMI) due to changes in cardiac autonomic balance. The purpose of the present study, therefore, was to evaluate the effects of a progressive exercise protocol used in phase I cardiac rehabilitation on the HRV of patients with post-AMI.

Material and methods. Thirty-seven patients who had been admitted to hospital with their first non-complicated AMI were studied. The treated group (TG, $n = 21$, age $= 52 \pm 12$ years) performed a 5-day programme of progressive exercise during phase I cardiac rehabilitation, while the control group (CG, $n = 16$, age $= 54 \pm 11$ years) performed only respiratory exercises. Instantaneous heart rate (HR) and RR interval were acquired by a HR monitor (Polar® S810i). HRV was analysed by frequency domain methods. Power spectral density was expressed as normalised units (nu) at low (LF) and high (HF) frequencies, and as LF/HF.

Results. After 5 days of progressive exercise, the TG showed an increase in HFnu (35.9 ± 19.5 to 65.19 ± 25.4) and a decrease in LFnu and LF/HF (58.9 ± 21.4 to 32.5 ± 24.1; 3.12 ± 4.0 to 1.0 ± 1.5, respectively) in the resting position ($p < 0.05$). No changes were observed in the CG.

Conclusions. A progressive physiotherapeutic exercise programme carried out during phase I cardiac rehabilitation, as supplement to clinical treatment increased vagal and decreased sympathetic cardiac modulation in patients with post-AMI.

Keywords: *Acute myocardial infarction, cardiac rehabilitation, heart rate variability*

Introduction

Analysis of beat-to-beat heart rate variability (HRV) provides a simple, reproducible, and non-invasive method for quantifying the influence of the autonomic nervous system on the heart and, consequently, for identifying the presence of autonomic imbalance [1,2]. In general, HRV is analysed by time and frequency domain methods [2–5], which allow the characterisation of some conditions and/or diseases that affect cardiac autonomic control [3].

It is well established that autonomic imbalance plays an important role in the pathophysiology of cardiovascular diseases [6]. In patients with myocardial infarction, sympathetic hyperactivity has been shown to occur soon after the acute event [7]. Therefore, these patients have low HRV, which is characterised by decreased cardiac vagal modulation and consequent sympathetic predominance [8–10]. Because of its prognostic value, HRV has been used in several clinical trials with coronary artery disease (CAD) patients as an index for clinical outcome

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[11]. The literature has reported that reduced HRV is an important predictor for arrhythmic complications [1,2,8,9], as well as an independent mortality predictor associated with other post-acute myocardial infarction (AMI) risk factors (i.e., reduced ejection fraction and increased resting HR) [8–10,12].

On the other hand, a recent meta-analysis showed that HRV increases significantly in response to pharmacological interventions, biobehavioural treatments and exercise training in patients with CAD [11]. Although the exercise training in phase II outpatient cardiac rehabilitation improves the HRV of patients with CAD [13,14] and myocardial infarction [14,15], little is known about the effects of progressive exercise applied during phase I cardiac rehabilitation on the cardiac autonomic modulation of patients with post-AMI. Considering that cardiopulmonary rehabilitation provides significant improvement in health outcomes, reduced hospital admissions and length of hospitalisation, maintenance of the patient's functional level, and improvement in quality of life and overall risk factor control through lifestyle change [16,17], it is possible that progressive exercise in the early phase of recovery could bring additional benefits to patients with post-AMI. Therefore, we hypothesised that progressive exercise during phase I cardiac rehabilitation in addition to clinical intervention might aid in the recuperation of cardiac autonomic balance in patients with post-AMI. Thus, the purpose of the present study was to evaluate the effects of phase I cardiac rehabilitation on the HRV of patients with post-AMI.

Methods

Subjects

One hundred and sixty-two patients (both genders) with AMI were admitted to the Coronary Care Unit (CCU) of a local hospital during the periods November 2004 through November 2005 and September 2006 through April 2007. Only fifty-nine (mean age: 53-years old) fulfilled the inclusion criteria, i.e., having suffered their first non-complicated AMI with ST-segment elevation. The exclusion criteria were as follows: a history of previous AMI, complicated AMI, AMI without ST-segment elevation, signs and/or symptoms of post-AMI chest pain or re-infarction, presence of diabetes mellitus associated with cardiac autonomic dysfunction, persistence of altered pressure response (refractory hypertension with levels greater than 180/100 mmHg), atrial fibrillation, malignant ventricular arrhythmias, complex ectopic ventricular beats, supraventricular or sinus tachycardia (greater than 120 beats per minute), 2° and 3° AV block; pacemaker implantation; signs of low output or ventricular failure, hypotension and heart failure; debility, fever, respiratory insufficiency, chronic obstructive pulmonary disease, illegal drug consumption, sequelae of stroke, lower limb amputation, severe aortic stenosis, severe left main coronary injury (>50%), prior coronary artery bypass graft surgery, inability to progress to next protocol step and hospital entry at least 48 h after the AMI event.

Initially, 59 patients were evaluated during the first day of hospitalisation, but only 40 were followed until hospital discharge. Because of noise in the electrocardiogram (ECG) signal, three patients were excluded before the data analysis. Thus, a total of 37 patients were studied, of which 16 belonged to control group (CG, 54 $\pm$ 11 years old) and 21 to the treatment group (TG, 52 $\pm$ 12 years old) (Figure 1). Among this sample, seven (19%) were submitted to thrombolyze with streptokinase (STK), 24 (65%) were submitted to primary percutaneous transluminal coronary angioplasty (PTCA) and six (16%) were treated with neither STK nor PTCA due to delayed admission to hospital (12 h after the beginning of chest pain). During hospitalisation, all patients were submitted to cardiac catheterisation, and 34 (92%) were successfully treated with PTCA (primary or elective).

Procedures

In accordance with the Helsinki Declaration, all patients were informed of the experimental procedures and signed an informed consent form approved by the Ethics Committee of the local institution (Process no. 023/2004 and no. 232/2006).

Clinical evaluations were based on daily clinical and physical examinations and laboratory tests, including: CK-MB enzyme concentration, total blood count, clinical biochemical screening (glucose), chest X-ray, and standard ECG, as well as cardiac catheterisation.

Experiments were always carried out in the afternoon. The patients were followed over 5 days, starting in the CCU (first two days) and concluding in the ward (remaining four days). The experimental protocol was initiated 22 $\pm$ 5 h after CCU admission for both groups, as recommended by Antman et al. [18]. Both groups were daily submitted to a standard protocol that included 10 min of rest in supine position followed by 4 min of respiratory exercises. During the resting period, the patients were always instructed to quietly relax, breathe spontaneously and remain awake. The respiratory exercises were done in the supine position and included diaphragmatic breathing pattern and deep breathing pattern. These respiratory exercises were only performed to

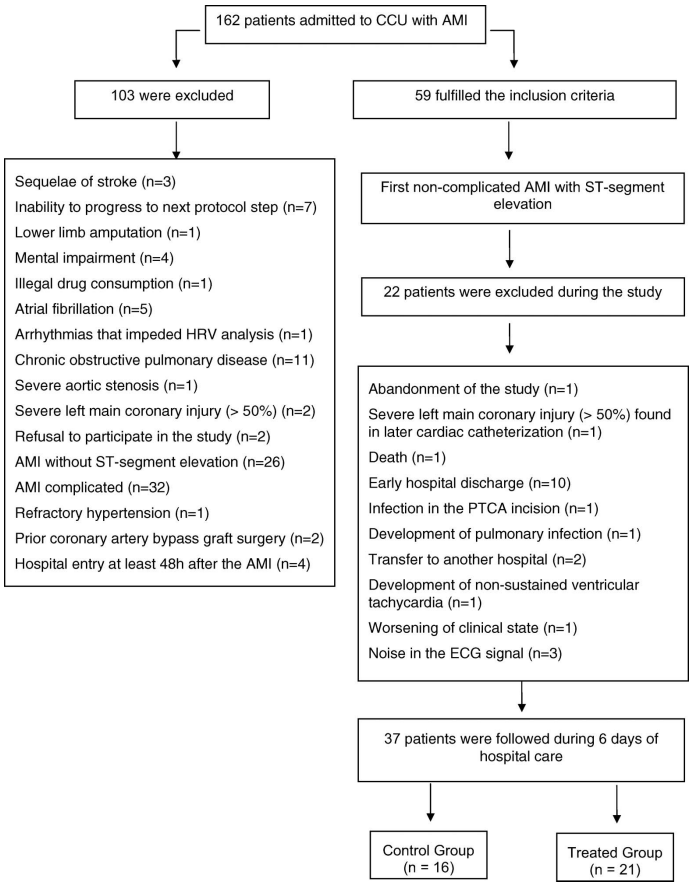

Figure 1. Flow diagram accounting for sample loss.

avoid possible pulmonary complication due to bed rest and hospitalisation. In addition, TG performed 5 days of phase I cardiac rehabilitation that consisted of a 5-step exercise programme, progressing from active assisted movements on the first day after AMI to walking in the final days of hospitalisation. This intervention was performed and supervised by a team of physical therapists.

The progression of TG through the exercise protocol was based on a daily clinical evaluation of each patient. Walking intensity was set at 20 beats per min above standing rest heart rate [16]. Additionally, if any signs and/or symptoms appeared during the progressive exercise training such as fatigue, chest pain, dyspnea, cyanosis, pallor, tachycardia (>120 beats per min), bradycardia, complex arrhythmias (i.e., those causing electrical and hemodynamic instability) or hypotension, the session was interrupted. However, none of these signs or symptoms occurred.

The instantaneous HR and RR interval were recorded during both standard and progressive exercise protocols with a digital telemetry system consisting of a transmitter placed on the patient's chest and a HR monitor (Polar® S810; Polar Electro Oy, Kempele, Finland). The system detects ventricular

depolarisation, corresponding to the R wave on the ECG, with a sampling rate of 500 Hz and a temporal resolution of 1 ms [19], and has been previously validated by Loimaala et al. [20]. After recording, the signals were transmitted to a receiver and interface connected to a computer for subsequent analysis. Additionally, blood pressure (BP) was measured each day by the auscultatory method before, during and after the standard and progressive exercise protocols. The medication dosage was noted daily and was not changed during the investigation in order to prevent any influence on the variables studied.

Heart rate variability

HR and RR interval data were obtained on the first (T0) and the sixth day of hospitalisation (T5) (i.e., after five days of progressive exercise training) during a 10-min period while subjects were in the resting supine position. Frequency domain analysis of HRV was performed with an autoregressive algorithm [21,22], which was applied to stable 256 RR interval series. The power spectral density was calculated for each RR series. Three spectral components were obtained: very low frequency (VLF), from 0 to 0.03 Hz; low frequency (LF), from 0.03 to 0.15 Hz; and high (HF), from 0.15 to 0.4 Hz. The spectral components were expressed in absolute (ms^2) and normalised units and as low/high frequency ratio (LF/HF). Normalisation was computed by dividing the absolute power of a given spectral component (low or high frequency component) by the total power minus the power of the component, with a frequency range between 0 and 0.03 Hz (very low frequency), and then multiplying this ratio by 100 [21,22].

Statistical analysis

Data are reported as mean ± SE. Subject characteristics, medication dosages, HR, SBP, DBP and resting HRV indices at baseline (T0 = 1st day) were compared between groups using the *t*-test for independent samples. After that, the effect of time (T0 compared with T5 = 6th day), group (control compared with treated) and the interaction between time and group effects were evaluated by two-way ANOVA for repeated measures. When an interaction between time and group effects was found, the Student–Newman–Keuls Method was performed. Finally, intragroup analysis was performed using the paired *t*-test. These statistical analyses were carried out using Sigma Stat for Windows, version 2.03. The level of significance was set at $p < 0.05$.

Results

In each group studied, the autonomic heart rate modulation of patients with post-AMI was similar when divided by gender (male and female), ejection fraction (preserved and reduced), AMI topography (anterior and posterior) and clinical intervention received (with STK, without STK and with primary PTCA). Data were, therefore, pooled according to each condition (control or treatment). The patients' characteristics are presented in Table I. No differences were found between CG and TG for these variables.

Medications

All administered medications were recommended in the ACC/AHA Guidelines [18] and the dosage of those that could affect HRV (*β*-blockers and angiotensin-converting enzyme-ACE inhibitors) was unchanged from the first (T0) to the sixth day of hospitalisation (T5) for both groups.

Heart rate, blood pressure, respiratory frequency, mean R–R and variance

In both groups, resting HR and systolic blood pressure (SBP) were high and mean R–R was lower

Table I. Patient characteristics.

Characteristics	Control group ($n = 16$)	Treatment group ($n = 21$)
Gender (male/female)	13/3	17/4
Age (years)	54 ± 11	52 ± 12
Weight (kg)	73 ± 15	72 ± 12
Height (cm)	165 ± 7	168 ± 7
BMI (kg/m^2)	27 ± 5	26 ± 3
Coronary heart disease risk factors		
Smoking	11 (69%)	13 (62%)
Hypertension	8 (50%)	8 (38%)
Family history of CAD	9 (56%)	5 (24%)
Diabetes mellitus	1 (6%)	3 (14%)
Overweight and obesity	10 (62%)	11 (52%)
Hyperlipidaemia	13 (81%)	9 (43%)
Sedentary	7 (44%)	10 (48%)
Stress	12 (75%)	14 (67%)
Infarction topography		
Anterior	8 (50%)	14 (67%)
Inferior	8 (50%)	7 (33%)
Medications		
B-blockers	15 (94%)	15 (71%)
ACE inhibitors	16 (100%)	9 (43%)
Lipid-lowering	12 (75%)	14 (67%)
Aspirin	15 (94%)	20 (95%)
Ticlopidine/Clopidogrel	15 (94%)	19 (90%)

BMI, body mass index; CAD, coronary artery disease; ACE, angiotensin-converting enzyme.

on the first day than the sixth day (time effect, $p < 0.05$). No additional effects (group and interaction) were observed for these variables. Diastolic blood pressure (DBP) was higher in TG than in CG (group effect, $p < 0.05$), but remained within the normal range (<80 mmHg). The variance of R–R intervals and respiratory frequency presented no significant effects (time, group or interaction). Only TG patients showed a lower SBP at discharge than on their first day of hospitalisation ($p < 0.05$) (Table II).

Heart rate variability

All HRV indices presented a time effect ($p < 0.05$), suggesting that these indices changed during hospitalisation. Additionally, LFnu, HFnu and LF/HF were influenced by an interaction between time (T0 *vs*. T5) and group (control group *vs*. treated group) ($p < 0.05$). Thus, the progressive exercise protocol was able to decrease the LFnu and LF/HF ratio, as well as increase the HFnu in TG ($p < 0.05$). For CG, however, the HRV indices remained unchanged (Table II). Intragroup changes were observed only in TG, which presented a higher HFnu and a lower LFnu and LF/HF at discharge (day 6) than on the first day of hospitalisation ($p < 0.05$) (Table II).

Discussion

These results demonstrate that five days of progressive exercise improves vagal modulation and decreases sympathovagal balance while in the resting supine condition in patients with post-AMI. Considering that attenuated HRV is an independent risk marker of premature morbidity and mortality among patients with CAD [11], the present findings indicate that, when applied as a supplement to clinical treatment, progressive exercise contributes a protective effect during early recovery from AMI.

The imbalance in autonomic cardiac function that accompanies an AMI can be observed up to 6 months after the event [9]. This fact can be attributed to ventricular remodelling, which is divided into two phases: early, which occurs within hours of AMI onset, and late, which occurs 72 h after onset. Early ventricular remodelling is characterised by infarct expansion, which results in ventricular rupture or aneurism. Later remodelling involves the entire left ventricle (LV) and is associated with progressive dilatation, LV architecture alteration and myocyte hypertrophy, causing increasing wall stress and damage to contractile function. Disturbances in circulatory hemodynamics activate the sympathetic adrenergic system, which stimulates catecholamine synthesis and activates the rennin–angiotensin–aldosterone system [23]. An increase in afferent sympathetic activity would cause reflex inhibition of vagal activity, leading to sympathetic modulation predominance on the sinus node [24]. Consequently, the structural alterations observed in post-infarction LV remodelling can cause persistently reduced HRV [23,24].

Abe et al. [24], studying patients after reperfused first anterior AMI, verified that an HRV index (SDNN) was independently associated with LV end-systolic volume index. These authors suggested that autonomic alteration consequent to post-infarction LV remodelling might result in depressed HRV

Table II. Cardiovascular and respiratory variables with heart rate variability data during resting supine condition for both groups studied.

	CG ($n = 16$)		TG ($n = 21$)		p Values		
	T0	T5	T0	T5	T	G	I
Cardio-vascular and respiratory variables							
HR (bpm)	71 ± 2.0	62 ± 2.0	69 ± 1.7	66 ± 1.7	$p = 0.006$	NS	NS
SBP (mmHg)	108 ± 3.3	100 ± 3.3	110 ± 2.9*	103 ± 2.9	$p = 0.029$	NS	NS
DBP (mmHg)	68 ± 2.3	67 ± 2.3	76 ± 2.0	71 ± 2.0	NS	$p = 0.042$	NS
RF (resp/min)	19 ± 3.4	18 ± 2.8	19 ± 3.1	20 ± 2.5	NS	NS	NS
Time domain							
Mean (ms)	865 ± 0.15	981 ± 0.14	898 ± 0.1	942 ± 0.2	$p = 0.02$	NS	NS
Variance (ms^2)	120 ± 12.2	109 ± 8.6	113 ± 15	60 ± 4.6	NS	NS	NS
Frequency domain							
LF (nu)	51.4 ± 21.0	54.4 ± 22.4	58.9 ± 21.4*	32.5 ± 24.1	$p = 0.012$	NS	$p = 0.002$
HF (nu)	39.9 ± 19.4	39.3 ± 23.0	35.9 ± 19.5*	65.2 ± 25.4	$p = 0.036$	$p = 0.005$	$p = 0.024$
LF/HF	2.2 ± 1.7	2.6 ± 2.3	3.1 ± 4.0*	1.0 ± 1.5	$p = 0.0034$	$p = 0.003$	$p = 0.004$

CG: control group; TG: treatment group; T0 = control condition (1st day); T5 = after 5 days of cardiovascular physiotherapy treatment (6th day); HR: heart rate; SBP: systolic blood pressure; DBP diastolic blood pressure; RF: respiratory frequency; LF: low frequency; HF: high frequency; nu: normalised units; ANOVA two way: *T* = time effect (T0 *vs*. T5); G = group effect (control group *vs*. treated group); I = interaction between group and time effects.
**t*-test: significant difference T0 *vs*.T5 for TG.

[23,24], which can persist for weeks or months after the AMI [9,23]. On the other hand, some studies have demonstrated that exercise training does not accelerate [25,26] or may even attenuate the progression of ventricular remodelling after AMI [27]. Although functional and structural changes in the left ventricle were not evaluated in the present study, it is unlikely that short-term exercise training, i.e., five days of progressive exercise, would be able to attenuate ventricular remodelling. In addition, available data on the benefits of exercise with respect to post-MI ventricular remodelling have come from studies carried out during phase II–III cardiac rehabilitation, in which patients were submitted to six months of moderate-intensity exercise [27,28]. Considering the points discussed above, the improvement in autonomic imbalance observed in TG was probably mediated by mechanisms other than an attenuation of ventricular remodelling.

It is also important to note that there are some factors responsible for HRV recovery in post-AMI: the spontaneous recuperation of HRV without medication in the months following the event [29,30]; the use of β-blockers (class I in AMI treatment) [18] and angiotensin-converting enzyme (ACE) inhibitors [3,31,32] and the association between β-blockade therapy and exercise training in phase II cardiac rehabilitation [15]. Lurje et al. [31] observed that β-blockade therapy increases HRV in patients with post-AMI. The authors followed up patients for 3 months (from the 3rd to 6th month after the event) and did not detect any additional increase in HRV, with medication dosages unaltered during the study. Similarly, Carpeggiani et al. [33] evaluated 349 patients with post-AMI who had been admitted to CCU and observed no HRV changes between their admission (HFnu = 27, LFnu = 54 and LF/HF = 3) and their discharge (HFnu = 29, LFnu = 57 and LF/HF = 3) (13 ± 7 days). Moreover, these patients received no physiotherapeutic intervention, and their doses of β-blockers and ACE inhibitors remained unchanged. Therefore, our results agree with these authors, since no changes were observed in any HRV index of CG patients between the first day (i.e., 22 h after hospital admission) and discharge on the sixth day. Only the treated group, who performed progressive exercise training in addition to pharmacological treatment, showed modifications in HRV indices. Thus, considering the studies previously cited and the fact that our patients were under the influence of β-blockers and ACE inhibitors, whose dosage remained unaltered during the study, the improvement of HRV observed in TG at discharge could be seen as a consequence of the progressive exercise protocol.

The positive effect of physical exercise on cardiac autonomic modulation appears to involve adaptations in peripheral and central neural pathways [13]. Habitual exercise results in increased compliance in large arteries, which would act to augment pressure stimulus transductions, afferent responsiveness and, as consequence, baroreflex sensitivity [34]. Since arterial stiffness and baroreflex dysfunction would tend to reinforce sympathetic hyperactivity and potentially contribute to reduced HRV, associated improvements in HRV due to exercise training could be the result of both greater blood vessel distensibility and better signal transduction in barosensitive areas [35]. Besides its well-known influence on vascular homeostasis, nitric oxide may also be involved in cardiac autonomic control, since it exerts a facilitatory effect on afferent-mediated baroreflex activity in the central nervous system and also increases central and peripheral vagal neuronal activity [36]. However, the effects of exercise training on nitric oxide-mediated increases in vagal activity need further investigation. While it cannot be assumed that neuronal nitric oxide synthesis is influenced by physical exercise, accumulating scientific research data indicate that nitric oxide may modulate the vascular effects of physical training [36]. Hambrecht et al. [37] observed significant attenuation of coronary vasoconstriction in response to acetylcholine and shear stimuli in patients with CAD, suggesting an enhancement in the ability of the vascular endothelium to synthesize nitric oxide. Nevertheless, we can only speculate about the mechanisms by which exercise could be associated with increased HRV, mainly because most of the positive results came from studies involving greater periods and intensities of physical training [14,38,39] than those here presented. There is strong evidence that increased vagal modulation protects the heart against arrhythmias induced by cardiac electrophysiological imbalance [40]. The present findings showed that progressive exercise applied during early recovery from AMI decreased sympathovagal balance, which is a protective factor against cardiovascular complications.

The literature reports that bed rest causes a decrease in physical capacity, muscular tone, orthostatic tolerance and increased HR response to exercise [41]. Physiotherapeutic intervention by means of progressive exercise in phase I cardiac rehabilitation is an effort to decrease deleterious bed rest effects, evaluate the clinical response to increasing effort, establish the intensity of daily activities, reduce the length of hospitalisation and reduce cardiopulmonary complications [16,17,41]. Consequently, the progressive exercise protocol involves postural changes associated with a gradual increase in effort intensity, allowing early mobilisation of the bedridden patient (1st day) and preparing patients for a return to daily activities after discharge (6th day). In the present study, we observed that patients

gradually adapted to each protocol stage, since they performed progressively higher intensity exercise in different postures. Finally, none of the TG patients showed signs and/or symptoms of exercise intolerance at any stage of progressive exercise training, and no clinical intercurrence was observed.

The present study has some limitations. First, bidimensional echocardiography was not performed due to logistical problems and, consequently, the process of ventricular remodelling could not be analysed. Second, due to the sample loss during the study, the final number of patients studied in each group was small. However, the number was sufficient to detect differences in HRV after the progressive exercise programme.

Conclusion

The present findings suggest that, as a supplement to clinical intervention, a progressive physiotherapeutic exercise protocol carried out during phase I cardiac rehabilitation caused an increase in vagal modulation and a decrease in sympathetic modulation and sympathovagal balance in the resting supine condition. Furthermore, the implemented progressive exercise protocol was well-tolerated by the patients and cause neither signs nor symptoms of exercise intolerance.

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ANEXO D

Laura Maria Tomazi Neves; Marlus Karsten; Victor Ribeiro Neves; Thomas Beltrame; Audrey Borghi-Silva; Aparecida Maria Catai. **Relationship between inspiratory muscle capacity and peak exercise tolerance in post-myocardial infarction patients.** Artigo aceito no periódico *Heart & Lung*.

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Date: Jul 28, 2011
To: "Laura Maria Tomazi Neves" lmtomazi@hotmail.com
From: "Heart & Lung" heartlungjournal@gmail.com
Subject: Your Submission

Ms. Ref. No.: HL-D-10-00162R3
Title: Relationship between inspiratory muscle capacity and peak exercise tolerance in post-myocardial infarction patients.
Heart & Lung: The Journal of Acute and Critical Care

Dear lmtomazi,

I am pleased to inform you that your manuscript "Relationship between inspiratory muscle capacity and peak exercise tolerance in post-myocardial infarction patients." has been accepted for publication in Heart & Lung: The Journal of Acute and Critical Care.

Thank you for submitting your work to Heart & Lung: The Journal of Acute and Critical Care.

Yours sincerely,

Dr. Nancy Redeker, PhD, RN, FAHA, FAAN
Editor

Ardis O'Meara
Editorial Office
Heart & Lung: The Journal of Acute and Critical Care

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***2) Title Page (including Author info and Acknowledgements)**

TITLE PAGE

Relationship between inspiratory muscle capacity and peak exercise tolerance in post-myocardial infarction patients.

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ABSTRACT

Objective: To evaluate inspiratory muscle endurance in post-myocardial infarction patients without respiratory muscle weakness and its correlation with peak exercise capacity. **Methods:** Ten recent post-myocardial infarction patients (RIG), nine less recent post-myocardial infarction (LIG) and twelve healthy subjects (CG) underwent a cardiopulmonary exercise test and a respiratory endurance protocol. ANOVA with post-hoc Dunn comparisons was used to contrast performances on all tests and Pearson's correlation was used to determine associations between variables. **Results:** RIG presented lower maximal incremental pressure and oxygen consumption than CG ($p<0.01$).There was a positive correlation between peak oxygen uptake and both maximal inspiratory pressure (0.68, $p<0.001$) and maximal incremental pressure (0.65, $p<0.001$) in RIG. **Conclusions**: Recent post-myocardial infarction patients exhibit lower maximal incremental pressure, which is related to peak exercise capacity. This novel relationship in functional capacity can indicate the need to improve muscle endurance in these patients even in the absence of inspiratory muscle weakness.

Key-word: Aerobic Exercise; Pulmonary Function Tests; Respiratory Muscles; Respiratory Endurance; Coronary Artery Disease.

Word Count

Abstract: 150
Text: 4313

ORIGINAL ARTICLE

Introduction

Following myocardial infarction, individuals may exhibit reduced exercise tolerance, expressed by reduced peak oxygen uptake during dynamic exercise (VO_{2peak}), and dyspnea, with a significant reduction in aerobic capacity and quality of life as well as an increasingly sedentary lifestyle.[1] (Square 1) Exercise limitation in this population is related to either dyspnea or lower limb fatigue.[2-7] The severity of these symptoms is associated with exercise intensity and the functional capacity.[2,3,5,6] The development of dyspnea involves various neurological processes, including nervous system control of ventilation, respiratory mechanics, respiratory gas exchange and the elastic (strength and endurance) and inelastic properties of respiratory muscles.[8]

Insert Square 1

During exercise, the functional capacity of the respiratory muscle for tolerating the overload imposed by increases in ventilatory demand can be affected by biochemical, morphological, inflammatory and functional alterations,[3,8,9,10] which impacts on exercise performance. Strength and endurance are components of respiratory muscle capacity, which are expressed as maximal inspiratory pressure (MIP) and respiratory muscle endurance (time [Tlim] or pressure [PTH_{MAX}]), respectively. MIP under 60% of predicted values indicates respiratory muscle weakness[3,9,11,12] which may contribute to reduced inspiratory airflow and a subsequent feeling of dyspnea upon exertion, which has been observed both in healthy subjects and patients with chronic diseases, including cardiovascular disease.[1,3,9,11,12]

Endurance is the ability to sustain a load for a period of time: it is a predominant characteristic of the respiratory muscles and is influenced by respiratory muscle strength.[13,14] Respiratory muscle strength and endurance seem to be closely related in a number of circumstances, and respiratory muscle training for both strength and endurance can have an effect on exercise tolerance.[3,10,15,16] However, to our knowledge, it is has not been well established whether the strength and endurance of respiratory muscles are associated with exercise capacity in patients with recent or chronic myocardial infarction. In healthy individuals as well as in those with heart failure, respiratory muscle endurance is a determinant of respiratory muscle fatigue, which is correlated with exercise tolerance.[3,10] Therefore, the primary

aim of the present study was to evaluate respiratory muscle endurance and its association with peak exercise capacity in post-myocardial infarction patients with preserved respiratory muscle strength.

Methods

A descriptive, cross-sectional study was conducted in post-myocardial infarction patients (Killip grade I and II) and carried out at the Laboratory of Cardiovascular Physical Therapy of the Nucleus of Research in Physical Exercise of the Department of Physical Therapy of the *Universidade Federal de São Carlos,* Brazil. The study was approved by the Human Ethics Committee of the *Universidade Federal de São Carlos, B*razil, under the protocol number 353/2009, in compliance with the Declaration of Helsinki . All participants were informed about the objectives of the study and signed an informed consent form after confirming their willingness to participate.

Two groups of post-myocardial infarction patients (35-65 years of age) that had been diagnosed with one episode of myocardial infarction were formed: a recent infarction group (RIG, n=10) made up of individuals having suffered myocardial infarction in the previous 45 days and a less recent infarction group (LIG, n=09) made up of individuals who had suffered a myocardial infarction at least six months prior to the study. Both groups were submitted to either chemical (chemical thrombolysis) or mechanical (percutaneous transluminal coronary angioplasty) myocardial reperfusion. A control group (CG, n=12) consisting of apparently healthy individuals was matched for age, body mass and height to the other groups. The rationale for including individuals with recent and less recent myocardial infarction was to determine the possible influence of recovery time following myocardial infarction on the variables studied (aerobic capacity, respiratory muscle strength and endurance) considering the occurrence of ventricular remodeling up to six months after myocardial infarction.

As well as the aforementioned characteristics, the following inclusion criteria were established: a sufficient cognitive level for understanding the test routine and an absence of musculoskeletal, joint, respiratory, neurological or vascular disorders. The following exclusion criteria were employed: a body mass index ≥ 35 kg/m^2; systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥ 90 mmHg (at rest); a functional capacity ≤ 4 metabolic equivalents; ST-segment depression > 2 mm; angina during exercise; an exercise-induced

decrease in systolic blood pressure ≥ 15 mmHg; sustained ventricular arrhythmia; supraventricular arrhythmia that compromises cardiac function; moderate or severe valve disease; a fixed-frequency pacemaker; uncontrolled diabetes; moderate or severe obstructive lung disease; and the difficulty to perform a self-assessment of effort using the Borg scale.

All procedures were carried out in the morning at the Laboratory of Cardiovascular Physical Therapy under appropriate conditions of temperature (20-22ºC) and humidity (40-60%). Subjects were submitted to familiarization with the procedures, the technical personnel, and the equipment and materials involved. They were instructed to avoid both caffeinated and alcoholic beverages as well as any strenuous exercise on the day before as well as the morning of the test protocol. They were also instructed to have a light meal at least 2 hours prior to the tests. On the day of the experiment, the subjects were interviewed and examined before the test to determine if they were in good health, had slept properly the night before and that the controlling conditions (heart rate and systemic blood pressure) were within normal limits.

Clinical and functional evaluation

All volunteers were interviewed to assess clinical information and receive clearance from the cardiologist to participate safely in the study. For such, the participants completed a) a physical exam of at-rest cardiovascular and respiratory parameters, b) a pulmonary function test – slow and forced vital capacity and maximal voluntary ventilation[17] (CPX-D, Medical Graphics, St Paul, MN, USA), c) a resting 12-derivation electrocardiogram in the supine position (Schiller, AT1, Altgasse, Switzerland) and a clinical treadmill stress test, carried out by a cardiologist with the help of a physical therapist.

Cardiopulmonary exercise test

On a previous day of cardiopulmonary exercise testing, all subjects identified their maximal walking velocity on a treadmill, which was defined as the maximal comfortable walking cadence before having to run. This procedure consisted of 0.5 km/h (0.3 mph) increases every 30 s, starting at 2.4 km/h (1.5 mph) with no slope, until either the subject complained of discomfort or the researcher observed it. The cardiopulmonary exercise test was performed on a treadmill (Master ATL, Inbramed, Porto Alegre, Brazil) using a ramping protocol. The protocol consisted of a four-minute warm-up (2.4 km/h [1.5 mph], no slope), followed by an incremental increase in velocity during three minutes until the previously identified individual maximal walking velocity was met. After this period, 0.5% increases in elevation were implemented every

15 s. The test was terminated when the subject presented signs and/or symptoms of fatigue. The test was followed by one minute of active recovery (2.4 km/h [1.5 mph], no slope) and two minutes of passive recovery. Ventilatory and metabolic parameters were monitored and registered breath-by-breath (CPX-D/BreezeSuite 6.4.1, Medical Graphics, St Paul, USA) and were analyzed after averaging the data over the eight breath-to-breath respiratory cycles. The cardiopulmonary exercise test system was calibrated before each test, first for airflow (volumetric flow calibration) and then for gas analysis (O_2 and CO_2).[18] The electrocardiogram was continuously monitored, and subjects heart rates were recorded with a digital telemetry system (Polar® S810i; Polar Electro Oy, Kempele, Finland). The acquired heart rate data were transmitted to a computer for subsequent analysis. Blood pressure was assessed every two minutes, and perceived exertion was rated with the Borg scale. The anaerobic threshold, which represents the transition from a predominance of aerobic to anaerobic metabolism, was identified by three independent evaluators using the ventilatory method.[18,19] Oxygen uptake at the anaerobic threshold was identified at this point. The highest oxygen uptake observed in the last 30 seconds of exercise was defined as VO_{2peak}.[19]

Evaluation of respiratory muscle strength and endurance

Respiratory muscle strength was assessed by the indirect method, using a pressure transducer (MVD-300, Globalmed, Porto Alegre, Brazil).[15] The values used to define MIP were those observed in the first second after peak pressure.[20] Static pressure values <60% of the predicted value were considered indicative of respiratory muscle weakness.[12,21] Additionally, to determine inspiratory muscle endurance, an incremental test was employed in which patients breathed continuously through a mouthpiece connected to a linear inspiratory load resistor (Power Breath®, IMT Technologies Ltda, Birmingham, UK) (Figure 1). The test began with an initial load of 50% MIP followed by 10% MIP increments every 3 min until the patient was unable to continue breathing.[13] The test was discontinued when the individual failed to achieve the load in three consecutive inspirations. The greatest inspiratory pressure that the subject was able to sustain for at least 1 min (PTH_{MAX}) was taken as the measure for inspiratory muscle endurance.[12,15] In the second part of the protocol, a constant inspiratory load equivalent to 80% PTH_{MAX} was employed, and the time elapsed until task failure was defined as respiratory muscle endurance time (Tlim).

Insert Figure 1

Statistical analysis

Data were analyzed using STATISTICA 7 (StatSoft. Inc., Oklahoma, USA). Based on the results of the pilot study (n=4), we estimated that a sample size of five individuals in each group would have a power of 80% to detect a 20 cmH_2O difference in endurance pressure (PTH_{MAX}). The level of significance was set at 5%. Data with normal distribution (Shapiro-Wilk test) are presented as mean±SD; data with non-normal distribution are expressed as median and maximum and minimum values; nominal variables are expressed as frequency and percentage of occurrence. Baseline data were compared with one-way ANOVA (Tukey post-hoc) and categorical data were analyzed with the chi-square test. Univariate analysis was performed with two-way ANOVA to determine the possible influence of body mass index, smoking status and β-blockers on respiratory muscle strength (MIP), endurance (PTH_{MAX} and Tlim) and aerobic capacity (VO_{2peak}) in all groups. Intragroup data on respiratory function were analyzed using Kruskal-Wallis ANOVA (Dunn's post-hoc test) and from aerobic capacity using one-way ANOVA (Tukey's post-hoc test). Pearson's correlation coefficient was used to evaluate associations between MIP, PTH_{MAX}, Tlim and VO_{2peak}.

Results

Patients

The post-myocardial infarction patients were identified and recruited from the Coronary Unit of the *Santa Casa de Misericórdia de São Carlos* by direct approach (RIG) during the admittance or from the data base (LIG). Control group volunteers were identified and recruited from the School Health Unit of *Universidade Federal de São Carlos*: the screening of both groups was carried out according the diagram below (Figure 2).

Insert Figure 2

Clinical and functional evaluation

The sample consisted of middle-aged men (50±8 years) who had similar anthropometric characteristics except for body mass index, which was lower in the CG than LIG. Regarding risk factors, the post-myocardial infarction groups were similar in family history of cardiovascular disease, dyslipidemia and stress. The lowest frequencies of cardiovascular risk factors occurred in the CG, where there was an absence of hypertension, diabetes mellitus, dyslipidemia, sedentary lifestyle and class I obesity (body mass index between 35 and 39.9 Kg/m^2).[22] Ex-

smokers who had quit either before or upon having a myocardial infarction event were included in the smoker category, provided that they had consumed ≥ 30 pack-years. For all groups, spirometric values were within the range predicted, with no difference among groups.[17] In the post-myocardial infarction groups, the type of myocardial infarction, type of interventional procedure and drugs used were similar, with a predominance of inferior infarction and low use of statins and clopidogrel in LIG (Table 1). Among the post-myocardial infarction patients, the mean time elapsed between infarction and inclusion in the study was 28 (range: 23 to 39) days in RIG and 561 (range: 221 to 883) days in the LIG. All RIG and LIG subjects had preserved ventricular function with a left ventricular ejection fraction greater than 50%, according to ventriculography.

Insert Table 1

Univariate analysis was performed with two-way ANOVA to determine the possible influence of body mass index, smoking status and β-blockers on the respiratory muscle strength (MIP), endurance (PTH_{MAX} and Tlim) and aerobic capacity (VO_{2peak}) tests in all groups. No interaction was found between these factors on MIP, Tlim, PTH_{MAX} and VO_{2peak} (Table 2), which confirms that neither smoking, body mass index nor the use of β-blockers influenced the respiratory and aerobic tests.

Insert Table 2

Cardiopulmonary exercise test

During the cardiopulmonary exercise test, VO_{2peak} (absolute and corrected for body mass), duration of cardiopulmonary exercise test, speed, grade and the metabolic equivalent level achieved at peak exercise were higher in the CG than RIG and LIG (Table 3).

Insert Table 3

Evaluation of respiratory muscle strength and endurance

The MIP of all subjects was greater than 60% of the predicted value, based on reference values (Table 2).[21] There were no statistically significant differences among groups for absolute and percentage of predicted MIP values. In contrast, regarding respiratory muscle endurance values, PTH_{MAX} was 20% lower in the RIG than in the CG during the incremental load protocol. The Tlim was similar among groups during the constant load protocol.

Correlations

There was positive correlation between MIP and VO_{2peak} as well as between PTH_{MAX} and VO_{2peak} (Figure 3; Table 2). There was positive correlation between Tlim and VO_{2peak} only in LIG (Table 2).

Insert Figure 3

Discussion

These data provide the first evidence that, despite normal respiratory muscle strength, respiratory muscle endurance appears to be reduced during the incremental inspiratory test and is associated with peak exercise capacity in recent myocardial and later infarction patients.

Inspiratory muscle strength and endurance

The MIP of all subjects was greater than 60% of the predicted value, based on reference values. Only subjects with normal respiratory muscle strength were included in the present study in order to reduce the influence of low respiratory muscle strength on respiratory endurance.[14] It is believed that the individuals reached their maximal respiratory endurance capacity and could not continue to generate the target pressure to release the air flow. At the time of test failure during the highest load applied, the individuals experienced a sensation of suffocation.[23] A difference in the absolute PTH_{MAX} value was detected between RIG and CG. In a study carried out by Jones et al. (1985) involving healthy subjects, tolerance pressure during the endurance test (75 cmH_2O) was lower than PTH_{MAX} found in the LIG and CG in the present investigation, which was reached at approximately 90 cmH_2O.[23]

A reduced Tlim is the most common finding among individuals with an airflow limitation of muscular origin.[13,10] However, the considerable variation in Tlim may have contributed to the non-reduction of respiratory muscle endurance. In a study on patients with heart failure involving similar methods, Tlim also presented a large variation among individuals, although other differences in respiratory muscle endurance were observed.[10] Moreover, the RIG may have presented a similar Tlim to CG due to the use of a lower workload in the endurance test at constant load.

Considering that the mean time elapsed between infarction and inclusion in the study was 28 days in RIG and 561 days in LIG, our findings only allow speculation regarding mechanisms that might explain the reduction in respiratory muscle endurance in RIG. Following myocardial infarction, the cardiovascular and muscular systems undergo physiological, mechanical and neurohumoral changes in order to adapt to the new condition.[3] Soon after a

myocardial event, however, the majority of individuals haven't yet return to their daily activities and thus usually adopt a more sedentary life style. In contrast, LIG had sufficient time to return to a more active life style, which could have helped adapt the entire body, including the respiratory muscles, to a higher tolerance of effort tests.[1,5]

Functional capacity

Lower exercise tolerance is a frequent characteristic of cardiac patients who have undergone a minimally invasive intervention (angioplasty), but there is a trend toward an increase in exercise tolerance particularly among those who have also undergone cardiovascular exercise programs.[2,24-27] The exercise tolerance of this post- myocardial infarction sample was greater than that found in other studies on cardiovascular disease.[10,28,29] We believe that this difference is due to the preserved ejection fraction in the individuals in the present study, as well as to the fact that our sample was relatively young and had a lower body mass index. Although demographic trends suggest that patients admitted to the hospital with cardiovascular disease are older and have associated comorbidities[1], our sample was composed of a relatively young post-myocardial infarction population with fewer comorbidities, which may have minimized the influence of various possible physiological changes that occur in pulmonary, muscular and cardiovascular systems during the aging process on aerobic performance.[1,3,5,9]

A previous study with cardiac patients also found a positive correlation between respiratory muscle strength and exercise tolerance (r=0.39, p<001).[5] Studies on respiratory muscle endurance mainly focus on elite athletes and individuals with chronic obstructive pulmonary disease. Regarding heart patients, however, we found only a single study by Dall'Ago et al. (2006), in which a correlation of 0.62 (p<0.01) was observed between respiratory muscle endurance and exercise tolerance in individuals with heart failure after they had undergo inspiratory muscle training.[10] In the present study, the moderate correlation between PTH_{MAX} and VO_{2peak} (r=0.65) indicates a possible interaction of respiratory muscle endurance to exercise tolerance in post- myocardial infarction similar as others cardiovascular diseases.[10]

These findings suggest that the reduced respiratory muscle endurance in RIG was related to a lower ability for maintaining inspiratory muscle contraction in situations of increased ventilatory and circulatory demand.[6,30,31] Thus, we consider that the reduction in respiratory muscle endurance in RIG could be associated with lower exercise tolerance, even among post-

myocardial infarction patients with preserved ventricular function, when there are a greater circulatory and ventilatory demand.[3,31,32]

Study limitation

Although this sample may not represent the usual clinical population, it represents those at the peak of productivity who are most affected by myocardial infarction. Women were not included in this study because there were very few women in the recent period of myocardial infarction at the time of data collection. Older individuals were also excluded because of the higher prevalence of comorbidities (ex: COPD and dementia), which can affect the results. The cross-sectional design of the study did not allow monitoring the evolution of inspiratory capacity in the recent and less recent periods of the same patient. Our findings were limited by a lack of validated respiratory muscle endurance rates and ratios, which prevented a more detailed evaluation. Moreover, the Power Breath® did not supply a conversion formula for the pressure load given in cmH_2O to units of mass (grams) limited the comparison of our results with other.

Clinical implications

Our findings suggest that reduced respiratory muscle endurance is associated to peak oxygen uptake in recent uncomplicated post-myocardial infarction patients, with preserved respiratory muscle strength at rest, resulting in a clinically relevant reduction on exercise capacity. Such aspects have not been investigated previously, and now allow a better understanding of possible limiting factors for dynamic exercise capacity in post-myocardial infarction patients. These findings indicate the importance of evaluating respiratory muscles, especially with regard to endurance, in post-myocardial infarction patients in consequence of its relationship with aerobic capacity, which is the principal component of exercise tolerance. The treatment in patients in the recent post-MI phase should also focus on improving inspiratory muscle capacity since hospitalization. This information can assist professionals involved in post-myocardial infarction in managing exercise prescription more appropriately, using new specific training methods. Further studies involving populations of different age ranges and gender are encouraged in order to obtain a better understanding of the function of respiratory muscles with respect to cardiac, respiratory and metabolic behavior during respiratory muscle endurance testing. Future studies should also include the investigation into the use of respiratory muscle endurance values in post-myocardial infarction patients as a possible predictor of post-discharge outcomes.

Conclusion

In this descriptive, cross-sectional study with recent and less recent post-myocardial infarction patients without inspiratory muscles weakness, a reduction in endurance incremental pressure and cardiopulmonary capacity was observed in the recent infarction patients in comparison with the control group. In addition, respiratory muscle endurance is associated with peak oxygen uptake. This novel relationship in functional capacity impairment may indicate the need to improve inspiratory muscle capacity in these patients even without inspiratory muscle weakness.

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Table 1

Table 1: Anthropometric characteristics, risk factors for cardiovascular disease, spirometric values, characteristics of topography of infarction and drug therapy used.

Characteristics	RIG (n=10)	LIG (n=9)	CG (n=12)
Anthropometric			
Age (years)	48±8	51±6	50±9
Body mass (Kg)	80±10	83±15	76±11
Height (m)	1.7±0.1	1.7±0.1	1.8±0.1
BMI (Kg/m^2)	28±4	29±4[a]	24±3
Risk factors for CVD			
Ex-Smokers	5 (50%)[b]	4 (44%)	1 (8%)
Hypertension	3 (30%)[b]	6 (67%)[c]	0
Family history of CVD	9 (90%)	7 (78%)	9 (75%)
Diabetes	3 (30%)[b]	5 (56%)[c]	0
Obesity (grade I)	3 (30%)[b]	4 (44%)[c]	0
Dyslipidemia	4 (40%)	5 (56%)	3 (25%)
Sedentary lifestyle	6 (60%)[b]	1 (11%)	0
Stress	8 (80%)	6 (67%)	8 (67%)
Spirometry			
MVV (L/s)	152±28	150±27	175±26
Nº of obstructed arteries			
Uni-arterial	5 (50%)	5 (56%)	-
Bi-arterial	3 (30%)	2 (22%)	-
Tri-arterial	2 (20%)	2 (22%)	-
Interventional procedure			
CT	1 (10%)	2 (22%)	-
PTCA	9 (90%)	7 (78%)	-
Infarct site			
Anterior	4 (40%)	3 (33%)	-
Inferior	6 (60%)	3 (33%)[d]	-
Lateral	0	3 (33%)	-
Drugs			
β-blockers	8 (80%)	6 (67%)	-
ACE inhibitors	4 (40%)	5 (56%)	-
Hypolipidemic	9 (90%)	4 (44%)[d]	-
Aspirin	9 (90%)	9 (100%)	-
Clopidogrel	7 (70%)	0[d]	-

CVD: cardiovascular disease; RIG: recent post-myocardial infarction group; LIG: less recent post-myocardial infarction group; CG: control group; BMI: body mass index; ACE: angiotensin I converting enzyme; MVV: maximal voluntary ventilation; CT: chemical thrombolysis; PTCA: percutaneous transluminal coronary angioplasty; $p<0.05$ by one-way ANOVA with Tukey post-hoc (CG x LIG)[a]; $p<0.05$ by chi-square test among (CG x RIG)[b], (CG x LIG)[c] and (RIG x LIG)[d].

Table 2

Table 2: Influence of factors **(**smoking, use of β-blocker and body mass index) on respiratory muscle strength (MIP), endurance (PTH_{MAX} and Tlim) and aerobic capacity (VO_{2peak}) for recent post-myocardial infarction group (RIG), less recent post-myocardial infarction group (LIG) and control group (CG).

Factors	MIP		PTH_{MAX}		Tlim		VO_{2peak}	
	G	G*F	G	G*F	G	G*F	G	G*F
BMI	0,02*	0,16	<0,01*	0,11	0,41	0,78	<0,01*	0,70
Ex-smokers	0,55	0,79	0,13	0,75	0,89	0,13	<0,01*	0,33
β-blockers	0,05*	0,31	0,08	0,91	0,71	0,73	0,11	0,95

The values in the table represent the p-value of univariate analysis by two-way ANOVA, considering the group (RIG, LIG and CG), factor (ex-smokers, use of β-blocker and body mass index) or group versus factor influence on MIP, PTH_{MAX}, Tlim and VO_{2peak}. MIP: maximal inspiratory pressure; PTH_{MAX}: maximum pressure generated against a progressively increasing inspiratory threshold load; Tlim: respiratory muscle endurance time; VO_{2peak}: peak oxygen uptake; G: group interaction by two-way ANOVA; BMI: body mass index; G*F: group and factor interaction by two-way ANOVA; *p≤0.05 by two-way ANOVA.

Table 3

Table 3: Evaluation of RMS, RME, cardiopulmonary capacity and correlation matrice for recent post-myocardial infarction group (RIG), less recent post-myocardial infarction group (LIG) and control group (CG).

Values	RIG (n=10)	LIG (n=9)	CG (n=12)	α	β
RMS					
MIP (cmH_2O)	87 (60-125)	99 (92-123)	100 (74-165)	0.16	0.47
RME					
PTH_{MAX} (cmH_2O)	71 (54-112)	87 (68-111)	90 (67-149)*	0.01	0.75
Tlim (s x 10)	130 (72-180)	180 (60-180)	180 (108-180)	0.07	0.79
CPX					
Duration (s)	641±67	718±128	828±78§	<0.01	0.99
Grade (%)	15±4	15±4	19±2§	0.04	0.80
Speed (km/h)	5.9±0.3	6.1±0.5	10.9±0.5§	<0.01	0.99
VO_{2peak} (mL/min)	2069±433	2268±391	2899±340§	<0.01	0.99
VO_{2peak} ($mL.Kg^{-1}.min^{-1}$)	27±6	28±6	38±4§	<0.01	0.87
METS	6.7±1.7	6.7±1.7	9.5±0.9§	<0.01	0.99
Dyspnea (CR10)	6.4±2.8	7.3±2.3	6.3±2.6	0.99	0.11
RPE (CR10)	5.0±3.2	6.2±2.9	4.9±3.4	0.99	0.11
Correlations$^{¥}$					
MIP X VO_{2peak}	r=0.68	r=0.61^{ns}	r=0.61	-	-
PTH_{MAX} X VO_{2peak}	r=0.65	r=0.67	r=0.51^{ns}	-	-
Tlim X VO_{2peak}	r=-0.38^{ns}	r=0.82	r=0.55^{ns}	-	-

RMS: respiratory muscles strength; RME: respiratory muscles endurance; MIP: maximal inspiratory pressure; PTH_{MAX}: maximum pressure generated against a progressively increasing inspiratory threshold load; CPX: cardiopulmonary exercise test; MET: metabolic equivalent; RPE: perception effort rate (Borg); VO_{2peak}: peak oxygen uptake; *p<0.05 in comparison with CG and RIG by Kruskal-Wallis ANOVA (Dunn post-hoc); §p<0.05 in comparison with CG and RIG and LIG by one-way ANOVA (Tukey post-hoc); $^{¥}$Pearson's correlation between RMS and RME with VO_{2peak} (mL/min); ns: not-significant Pearson's correlation (p>0.05).

Square 1

Abbreviations and Acronyms

Aerobic capacity: maximum amount of oxygen the body can use during intense exercise, which express the functional capacity of the cardiorespiratory system.
CG: control group.
Endurance: the ability of muscles to exert for a long period of time (minutes or hours depending of exercise type).
Exercise tolerance: intensity and/or time of physical exercise which the individual be able to do with moderate symptoms of fatigue.
Functional capacity: evaluation that focuses on major physical tolerance abilities related to musculoskeletal strength, endurace, speed and flexibility.
LIG: less recent post-myocardial infarction group
MIP: maximal inspiratory pressure.
PTH_{MAX}: maximum pressure generated against a progressively increasing inspiratory threshold load.
Strength: the ability of the muscles to exert force.
RIG: recent post-myocardial infarction group.
Tlim: respiratory muscle endurance time.
VO_{2peak}: peak oxygen uptake.

Figure 1

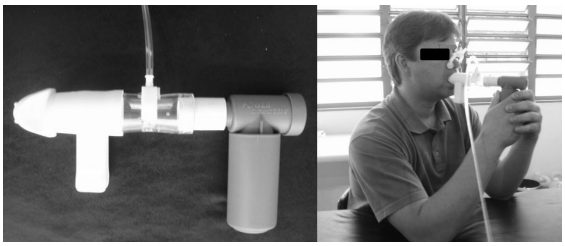

Figure 1: Ilustration of the inspiratory muscles testing equipment (Power Breath®, IMT Techonologies Ltd, Birmingham, UK) and demonstration of the use position.

Figure 2

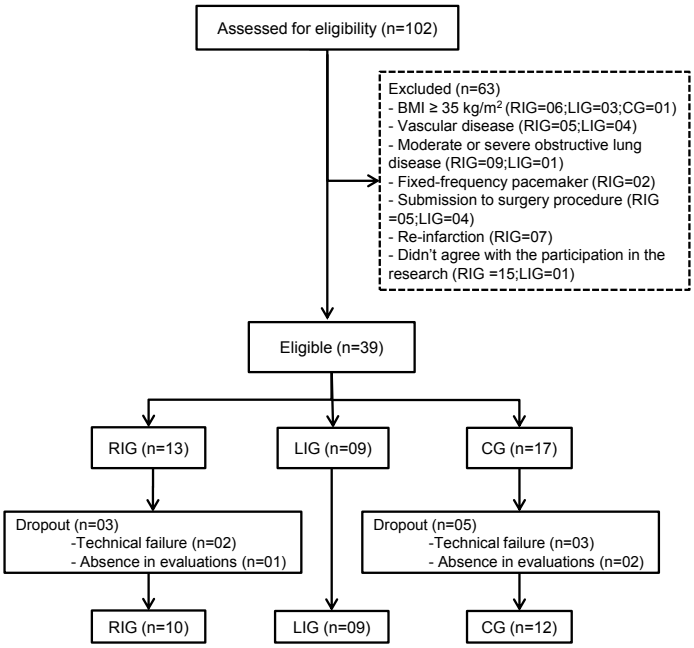

Figure 2: Diagram of sample distribution for recent post-myocardial infarction group (RIG), less recent post-myocardial infarction group (LIG) and control group (CG).

Figure 3

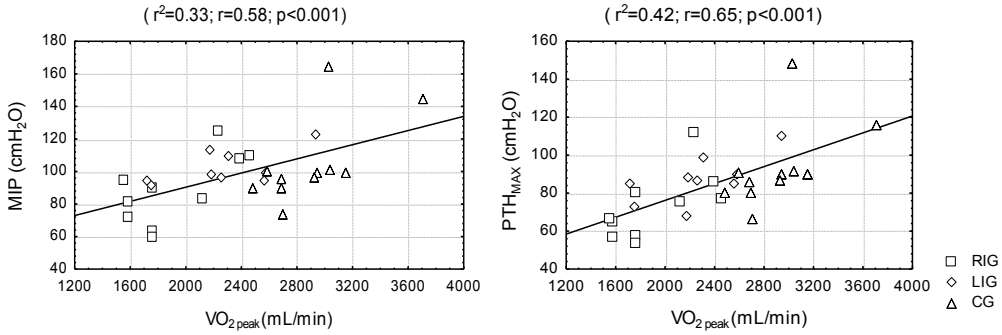

Figure 3: Ilustration correlation of MIP (cmH_2O), PTH_{MAX} (cmH_2O) and VO_{2peak} (mL/min) for recent post-myocardial infarction group (RIG), less recent post-myocardial infarction group (LIG) and control group (CG).

Figure legends

Figure legends

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ANEXO E

Neves VR, Kiviniemi AM, Hautala AJ, Karjalainen J, Catai AM, Huikuri HV, Tulppo MP. **Effects of exercise training on heart rate recovery in coronary artery disease patients.** In: International Society Autonomic Neuroscience Congress, 2011, Búzios, Brasil. Clinical Autonomic Research and Autonomic Neuroscience: Basic and Clinical: **Springer, 2011.**

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PROGRAM

Special Issue
1st Joint Meeting of the International Society for Autonomic Neuroscience and the American Autonomic Society

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Campinas, Campinas, Brazil), F.A. Cunha, F. Porto (Physical Activity and Health Promotion Laboratory (LABSAU), Physical Education and Sports Institute, State University of Rio de Janeiro, Rio de Janeiro, Brazil; Physical Education and Sports Institute, State University of Rio de Janeiro, Rio de Janeiro, Brazil), J.L. Gurgel (Physical Activity and Health Promotion Laboratory (LABSAU), Physical Education and Sports Institute, State University of Rio de Janeiro, Rio de Janeiro, Brazil; Physical Education Institute, Fluminense Federal University, Niterói, Rio de Janeiro, Brazil), P.T.V. Farinatti (Physical Activity and Health Promotion Laboratory (LABSAU), Physical Education and Sports Institute, State University of Rio de Janeiro, Rio de Janeiro, Brazil; Graduate Program in Physical Activity Sciences of the Salgado de Oliveira University, Rio de Janeiro, Brazil)

Background/aims: Altered autonomic nervous system activity has been reported in patients with overweight or obesity. In other words, obese subjects had lower HF values at resting and demonstrated altered cardiovascular hemodynamics and reflex control during exercise and recovery than lean subjects. An attenuated decrease in heart rate after exercise, or heart rate recovery (HRR), has been shown to predict mortality. In NIRS studies, the prefrontal cortex has been more activated during and post aerobic exercise. To investigate whether the manipulation of brain excitability by transcranial direct current stimulation (tDCS) modulates the parasympathetic reactivation after submaximal isocaloric exercise, the effect of tDCS on left dorsolateral prefrontal cortex (DLPFC) in young obese subjects was evaluated.

Methods: The heart rate variability (HRV) parameters (HR recovery; LF_{LOG}, HF_{LOG} and LF/HF_{LOG}) was assessed in 09 subjects [5 males: 26.6 ± 3.8 yr; 102 ± 29 kg; 174.4 ± 7.7 cm; 33.2 ± 7.5 kg/m^2; 3.1 ± 0.8VO_{2REST}; 29.5 ± 7VO_{2MAX}: 69.2 ± 9.4HR_{REST}; 177.8 ± 4.5HR_{MAX}; 282.8 ± 29.4W_{MAX} and 04 females: 23 ± 4.1 yr; 82.5 ± 6.5 kg; 173.4 ± 3.2 cm; 27.4 ± 1.8 kg/m^2; 2.8 ± 0.9VO_{2REST}; 23.5 ± 4.5VO_{2MAX}: 72.5 ± 1.3HR_{REST}; 185 ± 4.1HR_{MAX}; 182.1 ± 43.8W_{MAX}] before and immediately after randomized anodic or sham tDCS and aerobic isocaloric exercise sessions (70%VO_{2MAX}; ~200 kcal.sessão^{-1}).

Results: After anodal tDCS, parasympathetic reactivation (HF_{LOG}) increased ($P<0.01$) and sympatho-vagal balance (LF/HF_{LOG}) decreased ($P<0.01$) until 30 min of recovery period. However, the sympathetic activity (LF_{LOG}) did not change during the 30-min recovery period in anodic or sham condition ($P>0.05$).

Conclusion: tDCS applied on left DLPFC significantly enhanced the parasympathetic modulation and the sympatho-vagal balance after 30 min of recovery period.

Keywords: tDCS; heart rate recovery; autonomic activity; vagal-related indexes; aerobic training.

Financial Support: This study was partially supported by CNPq and FAPERJ grants.

doi:10.1016/j.autneu.2011.05.222

P.208 Effects of exercise training on heart rate recovery in coronary artery disease patients

V.R. Neves (Federal University of São Carlos, Department of Physiotherapy, São Carlos, SP, Brazil), A.M. Kiviniemi, A.J. Hautala, J. Karjalainen (Verve Research, Department of Exercise and Medical Physiology, Finland), A.M. Catai (Federal University of São Carlos, Department of Physiotherapy, São Carlos, SP, Brazil), H.V. Huikuri (University of Oulu, Division of Cardiology, Department of Internal Medicine, Finland), M.P. Tulppo (Verve Research, Department of Exercise and Medical Physiology, Finland)

Introduction: Delayed heart rate (HR) recovery after exercise is an independent predictor of cardiovascular events in coronary artery disease patients (CAD). However, the effect of exercise training on HR recovery in CAD patients with and without type 2 diabetes (T2D) is not well known. We hypothesized that home-based exercise training improves HR recovery among CAD patients with and without T2D.

Methods: 79 CAD patients having optimized medication, including β-blockade, (44 CAD + T2D, age 62 ± 4 years, 9 females and 35 CAD, age 62 ± 5 years, 8 females) underwent six-months home-based exercise training program according to current guidelines. HR recovery at 15, 30, 60 and 120 s after maximal bicycle ergometer test was analyzed. ANOVA for repeated measures with (time × group) was performed for maximal oxygen uptake and HR recovery variables.

Results: Maximal oxygen uptake increased similarly in both groups from 27.6 ± 6.7 to 28.7 ± 6.4 and from 21.9 ± 5.9 to 23.3 ± 6.6 ml/kg/min ($p<0.01$ for both) for CAD and CAD + T2D, respectively. Maximal HR did not change after exercise training (135 ± 16 vs. 136 ± 17 bpm and 127 ± 16 vs. 129 ± 16 bpm, for CAD and CAD + T2D, respectively, $p=$ ns for both). HR recovery 120 s improved after exercise training similarly in CAD and CAD + T2D from 51 ± 11 to 55 ± 14 beats ($p=0.036$) and from 44 ± 14 to 48 ± 14 beats ($p=0.038$), respectively. Across all patients, the change in HR recovery 120 s correlated positively with the change in maximal oxygen uptake in relative (ml/kg/min, $r=0.23$, $p=0.038$) and absolute units (L/min, $r=0.28$, $p=0.014$). HR recovery 15, 30 or 60 s did not change significantly after exercise training. There was no time × group interaction in maximal oxygen uptake or HR recovery.

Conclusion: Six-months home-based exercise training improves cardiorespiratory fitness and HR recovery similarly in both CAD and CAD + T2D patients. The change in HR recovery is associated with the change in cardiorespiratory fitness.

Keywords: heart rate recovery, maximal oxygen uptake, cardiac patients, autonomic nervous system, diabetes mellitus

Financial Support: CNPq.

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P.209 Reduced heart rate variability in the diabetic heart is reversed by inhibition of glycogen synthase kinase 3β activity

C.M. Welzig (Medical University of South Carolina — Neurosciences, USA), Y. Zhang, H.-J. Park, K. Picard, J.B. Galper (Tufts Medical Center — Molecular Cardiology Research Institute, Boston, MA, USA)

Decreased heart rate variability (HRV) associated with diabetic autonomic neuropathy is a risk factor for sudden death. Parasympathetic stimulation of the heart involves acetylcholine activation of the G protein-coupled K+ channel, (GIRK1)2/(GIRK4)2. We have previously demonstrated that expression of GIRK1 is decreased in the hearts of the Type I diabetic Akita mouse in association with a marked decrease in the negative chronotropic effect of the acetylcholine analog carbamylcholine. Increased Glycogen synthase kinase 3β (GSK3β), whose activity is inhibited by phosphorylation in response to insulin, has recently been implicated in the pathogenesis of

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P.209 Reduced heart rate variability in the diabetic heart is reversed by inhibition of glycogen synthase kinase 3β activity

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This is to certify that

Victor Ribeiro Neves

attended the 1st Meeting of the International Society for Autonomic Neuroscience and the American Autonomic Society - Búzios, Rio de Janeiro, Brazil - September 12-16, 2011.

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Congress Chairman

ANEXO F

Neves V R; Takahashi A C M; Santos-Hiss M D B; Karsten M; Verzola R M M; Borghi-Silva A; Catai A M. **Effect of early cardiovascular physiotherapy on respiratory sinus arrhythmia in patients with acute myocardial infarction.** In: World Physical Therapy Congress 2011, Amsterdã, Holanda. Physiotherapy, v. 97, Suppl. S1, p. eS877.

tively). ET reduced the complexity of heart rate variability evaluated by SE only in the training group (TG: 3.57 ± 0.37–3.30 ± 0.43) and remain similar to control group (CG 3.42 ± 0.36–3.40 ± 0.19).
Conclusions: The eccentric strength training for healthy older men has improved the muscle force but had a negative effect on the complexity of heart rate variability.
Implications: This fact has an important clinical impact on the elderly, because the reduced in the complexity it can be associated with higher cardiovascular risk.
Keywords: Ageing; Eccentric training; Shanon Entropy
Funding acknowledgements: This work was supported by Fundação de Amparo à Pesquisa do Estado de São Paulo (06/52860-0 to A.C.M.T. and 05/54838-9 to A.M.C.), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (PDEE/1228/08-0 to A.C.M.T.).
Ethics approval: This study was approved by the Ethics Committee of our Institution (098/05).

Research Report Poster Display
Number: RR-PO-301-8-Wed Wednesday 22 June 12:00
RAI: Exhibit Halls 2 & 3

EFFECT OF EARLY CARDIOVASCULAR PHYSIOTHERAPY ON RESPIRATORY SINUS ARRHYTHMIA IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

Neves V.R.[1,2], Takahashi A.C.M.[1], Santos-Hiss M.D.B.[1], Karsten M.[1], Verzola R.M.M.[2], Borghi-Silva A.[1], Catai A.M.[1]
[1]Federal University of São Carlos, Physiotherapy, São Carlos, Brazil, [2]Federal University of São Carlos, Physiology Sicences, São Carlos, Brazil

Purpose: To evaluate the effect of early cardiovascular physiotherapy associated with inspiratory muscle training (IMT) on respiratory sinus arrhythmia (RSA) magnitude in inpatients with acute myocardial infarction (AMI).
Relevance: RSA measured by expiration/inspiration ratio (*E/I*) and inspiration–expiration difference of heart rate variation (ΔIE) is reduced after AMI.
Participants: It was evaluated one hundred and forty-nine AMI patients (of both genders) who were admitted to the Coronary Care Units (CCU) of the involved hospitals. Only fifty-nine fulfilled the inclusion criteria, which were: a non-complicated AMI with ST-segment elevation, undergoing a primary or elective percutaneous transluminal coronary angioplasty, and compliance with the medication regimen prescribed by their physician.
Methods: They were divided in two groups: treated group (5 days of progressive exercise training associated with IMT-TG) (14 males, 5 females, 50 ± 9 years old) and control group (CG) (11 males, 3 females, 52 ± 11 years old) without physiotherapeutic intervention. The RR intervals obtained in the RSA test on 1st and 6th days were used to calculate the RSA. The maximal inspiratory pressure (PImax) was obtained on the 2nd and 6th days. The IMT was carried out from the 2nd to the 6th days and was composed of 3 sets of 10 forced inspirations for 3 s each in 40% of PImax.
Analysis: The expiration/inspiration (E/I) ratio from the mean value of the longest R–R interval obtained during the expiration phase divided by the mean value of the shortest R–R interval obtained during the inspiration phase. The inspiration–expiration difference (ΔIE) was derived from the difference between the mean value for the highest HR obtained during the inspiration phase and the mean value of the lowest HR obtained during the expiration phase of deep breathing test.
Results: PImax significantly increased ($p < 0.05$) from 78 ± 25 cm H_2O (2nd day) to 101 ± 25 cm H_2O (6thday) in TG group. However, ΔIE decreased significantly in both groups (TG: 13 ± 8–10 ± 5 bpm; CG: 11 ± 5–8 ± 3 bpm).
Conclusions: The progressive exercise training associated with IMT can produce enhance of inspiratory muscle strength without positively influence in RSA index in AMI patients.
Implications: The early progressive training exercise performed in CCU with TG was well-tolerated and safe for this population. Nevertheless, this specific early short-term protocol did not modify the RSA indexes in these patients.
Keywords: Cardiovascular physiotherapy; Muscle inspiratory training; Acute myocardial infarction
Funding acknowledgements: Fundação de Amparo a Pesquisa do Estado de São Paulo (FAPESP) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).
Ethics approval: The research was approved by Ethics Committee of the Federal University of São Carlos (Process no 387/2008).

Research Report Poster Display
Number: RR-PO-311-5-Wed Wednesday 22 June 13:00
RAI: Exhibit Halls 2 & 3

THE EFFECTS OF A POSTPARTUM EDUCATION PROGRAM ON SYMPTOMS AND HEALTHCARE SEEKING BEHAVIORS IN NEW MOTHERS

Neville C.[1], Irion J.[2], Mallinson T.[3], Abraham K.[4]
[1]Brooks Rehabilitation, Women's Health Rehabilitation, Jacksonville, FL, United States, [2]University of South Alabama, Department of Physical Therapy, Mobile, AL, United States, [3]University of Southern California, Division of Occupational Science and Occupational, Los Angeles, CA, United States, [4]Shenandoah Univeristy, Division of Physical Therapy, Winchester, VA, United States

Purpose: The purpose of this study is to determine whether an educational packet given to postpartum women will influ-

World Physical Therapy 2011
16th International WCPT Congress
20-23 June 2011 Amsterdam Holland

This is to certify that

Victor Ribeiro Neves

presented

Research report poster display number RR-PO-301-8-Wed

EFFECT OF EARLY CARDIOVASCULAR PHYSIOTHERAPY ON RESPIRATORY SINUS ARRHYTHMIA IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

at the 16th International Congress of the
World Confederation for Physical Therapy on

22 June 2011

Marilyn Moffat
WCPT President
World Confederation for Physical Therapy

Chair, International Scientific Committee
World Confederation for Physical Therapy

Ref: Wed-12:0

ANEXO G

VR Neves, HV Huikuri, AM Kiviniemi, AJ Hautala, AM Catai, OP Piira, TH Mäkikallio, MP Tulppo. **Chronotropic response and heart rate recovery after exercise in cardiac patients with and without type 2 diabetes.** In: EuroPrevent Congress 2011, 14 a 16 de abril, Genebra, Suiça. European Journal of Cardiovascular Prevention & Rehabilitation: **SAGE**.

European Journal of Cardiovascular Prevention & Rehabilitation
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European Association for Cardiovascular Prevention and Rehabilitation
EACPR
European Association for Cardiovascular Prevention and Rehabilitation
A Registered Branch of the ESC

P203

Omega-3 fatty acids exert multiple cardioprotection in male and female hypertensive rats.

N Tribulova[1], J Radosinska[1], B Bacova[1], M Mitasikova[1], V Knezl[2], P Weismann[3], J Slezak[1]

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Topic: Hypertension (Exercise & Translational Science)

Objective: It is well known that omega-3 fatty acids (omega-3 FA) reduce the incidence of cardiovascular diseases and sudden cardiac death. However, mechanisms involved are still not fully elucidated. Aim of this study was, therefore, to investigate cardioprotective and antiarrhythmic effects of omega-3 FA in aged spontaneously hypertensive rats (SHR) and possible cellular mechanisms of their actions.

Design and Method: Male and female 14-months-old SHR fed with omega-3 FA (Vesteralens, Norway, 40 mg/day for 2 months) were compared with untreated ones. Blood pressure was registered at the beginning and end of the experiment. Ventricular tissues from treated and untreated SHR hearts were processed for 'in situ' detection of selected enzymes activity, immunodetection of gap junctional cell-to-cell coupling protein, connexin-43 and ultrastructure examination. Susceptibility of the heart to electrically-induced ventricular fibrillation was tested using Langendorff model of isolated perfused heart.

Key results: Omega-3 FA supplementation resulted in 1/ significant decline of systolic blood pressure by 10%-12% in male and female SHR; 2/ enhancement of energetic metabolism enzymes activity, such as succinic dehydrogenase, beta-hydroxybutyrate dehydrogenase and glycogen pshosporylase; 3/ increase of capillary density with enhanced activity of alkaline phosphatase while decreased dipeptidyl peptidase-4 activity; 4/ suppression of sustained ventricular fibrillation by 57% (male) and 67% (female) despite presence of myocardial hypertrophy, fibrosis and abnormal connexin-43 distribution; 5/ significant increase of connexin-43 expression and its phosphorylation; 6/ preservation of subcellular and cell-to-cell junctions integrity.

Conclusions: Aged male and female SHR benefit from omega-3 FA supplementation particularly due to suppression of life-threatening arrhythmias. It appears that preservation of cardiomyocyte integrity and up-regulation of connexin-43 to improve myocardial cell-to-cell communication and synchronization via gap junction connexin channels is most likely a key mechanism in lethal arrhythmia suppression.

P204

Chronotropic response and heart rate recovery after exercise in cardiac patients with and without type 2 diabetes

VR Neves[1], HV Huikuri[2], AM Kiviniemi[1], AJ Hautala[1], AM Catai[3], OP Piira[2], TH Makikallio[2], MP Tulppo[1]

[1]Department of Exercise and Medical Physiologic, Verve Research, Oulu, Finland, [2]Institute of Clinical Medicine, University of Oulu, Oulu, Finland, [3]Universidade Federal de São Carlos, São Carlos, Brazil

Topic: Diabetes Type 1/2 (Exercice & Translational Science)

Purpose: The incidence of cardiovascular events is higher in coronary artery disease patients (CAD) with type 2 diabetes (T2D) than CAD patients without T2D. A poor chronotropic response of heart rate (HR) to maximal exercise (CRI) and delayed HR recovery after exercise both predict cardiovascular events in various populations. The differences in these variables between cardiac patients with and without T2D are not known. We hypothesized that HR response to exercise and recovery differs in CAD patients with and without T2D matched for age, sex and ejection fraction (EF).

Methods: CRI was calculated as 100 · (peak HR− resting HR) · (220 − age − resting HR)-1 and HR recovery as a slope of HR during the first 60 sec after cessation of exercise. Sixty three CAD patients with T2D (age 62±5 years, 78 % males, EF 67±8, maximal ST-depression during exercise -0.11±0.05 mV and 100% on β-blocking medication) and forty six CAD patients without T2D (age 62±5 years, 82 % males, EF 64±8, maximal ST-depression during exercise -0.12±0.04 mV and 100% on β-blocking medication) underwent maximal bicycle ergometer test until exhaustion.

Results: The BMI was 30±4 and 27±3 kg·m2 ($p<0.001$), maximal exercise capacity 6.5±1.7 vs. 7.8±1.9 METs ($p<0.001$) and maximal HR 128±19 vs. 132±18 bpm ($p=ns$) for CAD patients with and without T2D. CRI was 70±19 vs. 75±16 bpm ($p=ns$) and HR recovery -0.53±0.17 vs. -0.62±0.15 beats/sec ($p=0.012$) for CAD patients with and without T2D, respectively. The difference between CAD patients with and without T2D in HR recovery vanished after adjustment for METs (ANCOVA $p=0.007$, and $p=0.120$ for METs and diabetes, respectively), and also after adjustment for BMI (ANCOVA $p=0.021$, and $p=0.144$ for BMI and diabetes, respectively).

Conclusion: The chronotropic response to the maximal exercise is similar in CAD patients on optimal medication with and without T2D. However, post-exercise heart rate recovery, as an index of autonomic interaction, is delayed in CAD patients with T2D compared with CAD patients without diabetes suggesting impairment of vagal activity and/or augmented sympathetic activity in post-exercise condition for diabetes patients. Blunted HR recovery after exercise is more closely related to impaired exercise capacity and obesity than to T2D itself.

P205

Insulin resistant diabetic rats benefit from omega-3 fatty acids supplementation

J Radosinska[1], B Bacova[1], V Dosenko[2], H Lin[3], I Imanaga[3], N Tribulova[1]

[1]Slovak Academy of Sciences, Institute for Heart Research , Bratislava, Slovak Republic, [2]Bogomoletz Institute of Physiology, Kyiv, Ukraine, [3]Fukuoka University, School of Medicine, Fukuoka, Japan

Topic: Diabetes Type 1/2 (Exercice & Translational Science)

Background: Contractile dysfunction and heart rhythm disturbances are frequent complications of diabetes mellitus in human whereby our previous studies using insulin-deficient rats suggest that abnormal cell-to-cell communication due to hyperphosphorylation of connexin-43 (Cx43) channels can be involved. Goal of this study was to investigate whether myocardial Cx43 mRNA and protein expression are altered in insulin-resistant rats and whether diabetic rats may benefit from omega-3 fatty acids (omega-3 FA) supplementation.

Design and Methods: Experiments were conducted on male adult spontaneously diabetic Goto-Kakizaki rats and age-matched healthy Wistar-Clea rats. Animals were divided into un-treated and treated for 2month with omega-3 FA (Vesteralens, Norway, 200mg/kg/day). At the end of experiments biometrical and biochemical parameters of all rats were registered. Left ventricular heart tissues were used for determination of Cx43 mRNA and protein expression using real time PCR and Western blotting. Isoform-specific protein kinase C (PKC) phosphorylation of Cx43 was analysed by immunoblotting.

Key results: Blood glucose, cholesterol and triglycerides were increased in diabetic rats while significantly reduced due to treatment with omega-3 FA. Body and heart weights were lower in diabetic compared to healthy rats and these parameters were not affected by omega-3 FA. Myocardial Cx43 mRNA level was higher in diabetic than non-diabetic rats and omega-3 FA caused its marked increase in both groups. Ratio of phosphorylated to non-phosphorylated Cx43 protein was lower in diabetic versus healthy rats. In contrast, a significant elevation of phosphorylated forms of Cx43 was detected upon omega-3 FA in diabetic and to lesser extent in healthy rat heart ventricles. It was associated with increased expression of PKC epsilon.

Conclusions: Rats with type 2 diabetes benefit from omega-3 FA supplementation due to up-regulation of Cx43. This may affect intercellular communication and consequently heart function and its susceptibility to malignant arrhythmias.

P206

Antiarrhythmic potential of omega-3 fatty acids and atorvastatin in rats suffering from hypertriglyceridemia.

B Bacova[1], J Radosinska[1], V Knezl[2], M Barancik[2], J Slezak[2], N Tribulova[1]

[1]Slovak Academy of Sciences, Institute for Heart Research , Bratislava, Slovak Republic, [2]Slovak Academy of Sciences, Institute of Experimental Pharmacology & Toxicology, Bratislava, Slovak Republic

Topic: Lipid Disorders (Exercice & Translational Science)

Dyslipidemia is a risk factor for cardiovascular diseases that increase incidence of sudden cardiac death presumably due to ventricular fibrillation (VF). Since omega-3 polyunsaturated fatty acids (omega-3 FA) and lipid-lowering drugs statins were shown to possess antiarrhythmic potential, the aim of this work was to examine their effects on threshold for VF and myocardial cell-to-cell coupling protein connexin-43 (Cx43) in experimental model of dyslipidemia.

Methods: Hypertrigliceridemic (HTG) and age-matched healthy Wistar rats were divided to six groups: 1) Wistar rats untreated 2) Wistar rats feed with omega-3 FA (400mg/kg) for 2 month. 3) Wistar rats treated with Atorvastatin (0.5mg/kg) for 2 month. 4) HTG rats untreated. 5) HTG rats fed with omega-3 FA (400mg/kg) for 2 month. 6) HTG rats treated with Atorvastatin (ATO, 0.5mg/kg) for 2 month. At the end of experiment ventricular tissues from each group were processed for both in situ immunodetection of Cx43 to reveal its cardiomyocyte distribution and western blotting of Cx43 to assess its expression and phosphorylation. Isolated perfused heart model was used to test VF threshold starting with 1sec burst of electrical rectangular pulses at 100 pulses/sec, 1ms in duration at 15mA. When sustained VF was not induced after repetitive 5 stimuli, the stimulus intensity was increased in 5 mA steps.

Results: showed that both ATO and omega-3 FA reduced elevated blood pressure, TG and heart rate in HTG rats. VF threshold of the latter was less than in normal Wistar rats, i.e. 15mA vs 25mA. Omega-3 FA supplementation and ATO treatment resulted in a significant increase of VF threshold in HTG (to 40mA and 45mA respectively) and Wistar rat hearts as well. Abnormal cardiomyocyte distribution of Cx43-positive gap junctions, i.e. increased number of gap junctions on lateral surfaces was not eliminated by the treatment of HTG rats. However, abnormally elevated phosphorylation of Cx43 was significantly decreased in HTG rat hearts due to the treatment.

It is concluded that omega-3 FA and Atorvastatin have the potential to protect the heart against malignant arrhythmias while modulation of cell-to-cell coupling protein connexin-43 is most likely involved in their anti-arrhythmic effects.

EUROPEAN SOCIETY OF CARDIOLOGY®

EuroPRevent 2011

14 April - 16 April 2011, Geneva - Switzerland

CERTIFICATE OF ATTENDANCE

The European Board for Accreditation in Cardiology (EBAC) has granted

Mr Victor NEVES

15 external CME credits for participation in the

EuroPRevent 2011

in Geneva - Switzerland

from Thursday 14 April to Saturday 16 April

Ben Hainsworth

Congresses and Meetings Division Director
European Society of Cardiology

EBAC®

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Irish Cardiac Society
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ANEXO H

Declaração de realização de estágio de doutorado sanduiche no período de 1 de agosto de 2010 a 30 de julho de 2011 e do plano de atividades realizado no Departamento de Exercício e Fisiologia Médica, Verve Research, Oulu/Finlândia enviada pelo Prof. Dr. Mikko Tulppo. Processo: CNPq/SWE – 200630/2010.

CNPq
Conselho Nacional de Desenvolvimento Científico e Tecnológico

Ministério da Ciência e Tecnologia
GOVERNO FEDERAL

7357582794463569

Victor Ribeiro Neves
Núcleo de Pesquisa em Exercício Físico - NUPEF
13565-905 - Sao Carlos - SP - Brasil

Diretoria de Ciências Agrárias, Biológicas e da Saúde
Coordenacao-Geral do Programa de Pesquisa Em Saude
Coordenacao do Programa de Pesquisa em Saude
PROGRAMA BASICO DE FISIOTERAPIA E TERAPIA OCUPACIONAL

Ofício SN/CGEFO/CNPq Brasília, 21 de maio de 2010

Processo número 200630/2010-5 (Novo) Comitê Assessor MS Modalidade SWE

Inst.: University Of Oulu/Finlândia

Em aditamento a mensagem eletrônica na qual lhe foi comunicada a concessão de uma bolsa de estudos no exterior, vimos informar-lhe os benefícios, prazos e condições da referida bolsa, em conformidade com as normas em vigor no CNPq.

Modalidade: Doutorado Sanduiche no Exterior
Vigência: 01/08/2010 até 31/07/2011
Mês de remessa da documentação para análise quanto à renovação (se pertinente): Abril

Benefícios:

Mensalidade: EUR 1.300,00 (valor-base: EUR 1.300,00)

Seguro-Saúde: EUR 840,00

Auxílio Instalação (parte fixa): EUR 1.300,00

Passagens aéreas para o trecho: Brasil/Sao Carlos/Finlândia/Oulu

CONDIÇÕES

1 - A implementação da bolsa está condicionada a assinatura e devolução da Procuração e do Termo de Compromisso, para o seguinte endereço:

CNPq
Conselho Nacional de Desenvolvimento Científico e Tecnológico

Ministério da Ciência e Tecnologia

GOVERNO FEDERAL

TO WHOM IT MAY CONCERN

Brasilia, May 21, 2010

We hereby certify that the CNPq - Conselho Nacional de Desenvolvimento Científico e Tecnológico, of the Ministry for Science and Technology of Brazil, has granted a scholarship for 12 months to Victor Ribeiro Nevee to pursue Split Fellowship Program starting in August/2010 up to July/2011 at University Of Oulu

This scholarship consists of:

Monthly stipend of EUR 1.300,00

Transportation between: Brasil/Sao Carlos/Finlândia/Oulu

Health insurance fees up to EUR 840,00

Monica Rebello de Oliveira
Coordenadora-Geral de Fomento - CGEFO
PO Nº 084/2010

Serviço de Bolsas Individuais no Exterior - SEBIE

SEPN 509, Térreo

CEP 70750-501 - Brasília - DF

2 - No caso de Doutorado Pleno, se houver acompanhamento de dependentes, acréscimo ao valor-base da mensalidade só será implementado durante a permanência dos mesmos em sua companhia por um período superior a 9 (nove) meses. A entrada dos dependentes no país de destino deverá ser comprovada no prazo de 60 (sessenta) dias pela apresentação dos bilhetes de passagem utilizados e cópia dos passaportes contendo os vistos de entrada naquele país. O não atendimento desta condição acarretará a imediata dedução do acréscimo por dependentes e o desconto dos valores já creditados.

3 - No prazo de 60 (sessenta) dias contados a partir da data de embarque, V.Sa deverá encaminhar ao CNPq seu bilhete de passagem juntamente com o comprovante de matrícula na instituição para a qual teve sua bolsa aprovada (obrigatório para o doutorado pleno) ou declaração da instituição/orientador atestando o início das atividades para as outras modalidades. Deverá, ainda, enviar para o e-mail sebie@cnpq.br o seu endereço definitivo e informar na página do CNPq na Internet os dados bancários no exterior, no endereço http://folhadepagamento.cnpq.br/dadosbancarios/. O atendimento a estas exigências é imprescindível para a manutenção do pagamento das mensalidades.

4 - No prazo de 60 (sessenta) dias após a data de recebimento do adiantamento para o seguro-saúde, o bolsista deverá apresentar cópia da apólice, devidamente quitada, contendo o valor pago, o período coberto e nome dos dependentes segurados. Caso isto não ocorra, o CNPq deduzirá o valor adiantado.

OBSERVAÇÃO IMPORTANTE: O pagamento das mensalidades no exterior é efetuado trimestralmente, nos meses de Janeiro, Abril, Julho e Outubro de cada ano civil, mediante depósito em conta bancária do bolsista, conforme o cronograma abaixo:

- **janeiro/fevereiro/março, crédito entre os dias 20 e 31 de janeiro**
- **abril/maio/junho, crédito entre os dias 20 e 30 de abril**
- **julho/agosto/setembro, crédito entre os dias 20 e 31 de julho**
- **outubro/novembro/dezembro, crédito entre os dias 20 e 31 de outubro**

O bolsista não incluído no cronograma acima, terá seu pagamento efetivado em folha suplementar.

Caso V. Sa. tenha recebido outro ofício com a mesma finalidade, solicitamos desconsiderá-lo.

Atenciosamente

Monica Rebello de Oliveira

Coordenadora-Geral de Fomento - CGEFO

PO Nº 084/2010

verve

Letter of Reference

1. Student: Victor Ribeiro Neves
2. Period: 01/08/2010 to 30/07/2011, fulltime (40 hours/week)
3. Site: Department of Exercise and Medical Physiology, Verve, Oulu Finland.
4. Supervisor: Adj. Prof Mikko Tulppo, PhD
5. Project title: Study of autonomic modulation in patients with heart coronary diseases and acute myocardial infarction.
6. Summary of activities:

   Victor Ribeiro Neves has been involved in clinical research and teaching programs in our laboratory. I am responsible for project that involves the acute responses and chronic modification of different regulatory systems to the physical exercise in cardiovascular patients with and without type II diabetes.

   The main activities of Victor Ribeiro Neves in the study were as following:

   1. Learning new methodologies including e.g., nonlinear heart rate variability methods, baroreflex analysis methods and time-frequency spectral analysis technique of cardiovascular signals.
   2. Performing laboratory measurements in cardiac patients together with other laboratory staff including: anthropometrics, maximal oxygen uptake measurements, beat-to-beat heart rate variability measurements, continuous blood pressure measurements, continuous respiratory frequency measurements, hand grip testing and passive head-up testing by tilt table.
   3. Analyzing following parameters by our custom made softwares: 24-hour R-R intervals editing and analyzing time-frequency domain variables as well as nonlinear variables including approximate entropy and detrended fluctuation analysis. Short-term heart rate variability editing side by side with ECG and analyzing data by our softwares named Hearts and Kubios. Analyzing physical activity data collected by novel Polar PA device. Analyzing data by Excel, Power point and SPSS softwares. Preparing scientific oral and poster presentations.
   4. Writing a scientific manuscript.

Based on my one year experience Victor Ribeiro Neves is very hardworking and innovative person and his social skills are excellent.

Oulu, Finland 20.11.2011

Mikko Tulppo, Adjunct Professor, PhD
Director of the Department of Exercise and Medical Physiology
Verve
P.O. Box 404, FIN-90101 Oulu, Finland
Tel. +358 20 757 4750 ,
E-mail: Mikko.Tulppo@Verve.fi

ANEXO I

Termo de Aprovação do Comitê de Ética em Pesquisa em Seres Humanos da UFSCAr

UNIVERSIDADE FEDERAL DE SÃO CARLOS
COMITÊ DE ÉTICA EM PESQUISA EM SERES HUMANOS
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cephumanos@power.ufscar.br http://www.propg.ufscar.br

CAAE 2751.0.000.135-08

Título do Projeto: ANÁLISE DA VARIABILIDADE DA FREQÜÊNCIA CARDÍACA E DA PROTEÍNA C-REATIVA DE PACIENTES COM INFARTO AGUDO DO MIOCÁRDIO SUBMETIDOS À INTERVENÇÃO FISIOTERAPÊUTICA

Classificação: Grupo III

Pesquisadores (as): Victor Ribeiro Neves, Profa. Dra. Aparecida Maria Catai (orientadora)

Parecer Nº. 160/2010

1. Normas a serem seguidas

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

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

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

• Eventuais modificações ou emendas ao protocolo devem ser apresentadas ao CEP de forma clara e sucinta, identificando a parte do protocolo a ser modificada e suas justificativas. Em caso de projetos do Grupo I ou II apresentados anteriormente à ANVISA, o pesquisador ou patrocinador deve enviá-las também à mesma, junto com o parecer aprobatório do CEP, para serem juntadas ao protocolo inicial (Res. 251/97, item III.2.e).

• Relatórios parciais e final devem ser apresentados ao CEP, inicialmente em ___/____/____ e ao término do estudo.

2. Avaliação do projeto

O Comitê de Ética em Pesquisa em Seres Humanos da Universidade Federal de São Carlos (CEP/UFSCar) analisou o projeto de pesquisa acima identificado e considerando os pareceres do relator, do revisor e do consultor *ad hoc* DELIBEROU:

Trata-se de avaliação de proposta de aditamento. Este projeto foi anteriormente aprovado por este CEP/UFSCar conforme Parecer nº 387/2008, de 19/09/2008.

O aditamento tem como objetivo avaliar o comportamento da Variabilidade da freqüência cardíaca (VFC) pré e pós angioplastia coronariana, em pacientes com diagnóstico clínico de insuficiência coronariana, encaminhados eletivamente para o procedimento e comparar ao

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comportamento desta variável em pacientes durante infarto agudo do miocárdio, submetidos à mesma terapêutica.

Acreditamos que o autor deva levar em consideração que pacientes encaminhados para cineangiocoronariografia e angioplastia coronariana de maneira eletiva, conforme proposto, provavelmente apresentarão maior VFC, quando comparado ao grupo de pacientes encaminhados ao procedimento em vigência de síndrome coronariana aguda, pois nesta última situação certamente haverá predomínio do tônus simpático devido ao estresse emocional e dor quase sempre presentes nesta situação.

Outro fato a ser considerado é a provável diferença do tratamento medicamentoso utilizado nos dois grupos, devido a influência que algumas drogas (estatinas, betabloqueadores, BRA,IECA ...) podem exercer sobre a VFC.

Com relação à segurança dos pacientes, acreditamos que a proposta colocada no aditamento, atende às exigências ética e científicas fundamentais previstas na Resolução 196/96, do Conselho Nacional de Saúde, pois o método de coleta dos dados e análise da VFC é realizado de forma não invasiva.

3. Conclusão:

Em razão do acima exposto, considera-se a presente proposta de aditamento aprovada.

São Carlos, 18 de maio de 2010.

Profa. Dra. Cristina Paiva de Sousa
Coordenadora do CEP/UFSCar

Impresso em 18/5/2010 22:22:08

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CAAE 2751.0.000.135-08

Título do Projeto: ANÁLISE DA VARIABILIDADE DA FREQÜENCIA CARDÍACA E DA PROTEÍNA C-REATIVA DE PACIENTES COM INFARTO AGUDO DO MIOCÁRDIO SUBMETIDOS À INTERVENÇÃO FISIOTERAPÊUTICA
Classificação: Grupo III
Pesquisadores (as): Victor Ribeiro Neves, Profª Drª Aparecida Maria Catai (orientadora)

Parecer Nº. 387/2008

1. Normas a serem seguidas

• O sujeito da pesquisa tem a liberdade de recusar-se a participar ou de retirar seu consentimento em qualquer fase da pesquisa, sem penalização alguma e sem prejuízo ao seu cuidado (Res. CNS 196/96 – Item IV.1.f) e deve receber uma cópia do Termo de Consentimento Livre e Esclarecido, na íntegra, por ele assinado (Item IV.2.d).
• O pesquisador deve desenvolver a pesquisa conforme delineada no protocolo aprovado e descontinuar o estudo somente após análise das razões da descontinuidade pelo CEP que o aprovou (Res. CNS Item III.3.z), aguardando seu parecer, exceto quando perceber risco ou dano não previsto ao sujeito participante ou quando constatar a superioridade de regime oferecido a um dos grupos da pesquisa (Item V.3) que requeiram ação imediata.
• O CEP deve ser informado de todos os efeitos adversos ou fatos relevantes que alterem o curso normal do estudo (Res. CNS Item V.4). É papel do pesquisador assegurar medidas imediatas adequadas frente a evento adverso grave ocorrido (mesmo que tenha sido em outro centro) e enviar notificação ao CEP e à Agência Nacional de Vigilância Sanitária – ANVISA – junto com seu posicionamento.
• Eventuais modificações ou emendas ao protocolo devem ser apresentadas ao CEP de forma clara e sucinta, identificando a parte do protocolo a ser modificada e suas justificativas. Em caso de projetos do Grupo I ou II apresentados anteriormente à ANVISA, o pesquisador ou patrocinador deve enviá-las também à mesma, junto com o parecer aprobatório do CEP, para serem juntadas ao protocolo inicial (Res. 251/97, item III.2.e).
• Relatórios parciais e final devem ser apresentados ao CEP, inicialmente em ___/___/___ e ao término do estudo.

2. Avaliação do projeto

O Comitê de Ética em Pesquisa em Seres Humanos da Universidade Federal de São Carlos (CEP/UFSCar) analisou o projeto de pesquisa acima identificado e considerando os pareceres do relator e do revisor DELIBEROU:

A proposta de estudo apresentada atende às exigências éticas e científicas fundamentais previstas na Resolução 196/96, do Conselho Nacional de Saúde.

3. Conclusão:
Projeto aprovado

São Carlos, 19 de setembro de 2008.

Profa. Dra. Cristina Paiva de Sousa
Coordenadora do CEP/UFSCar