

**UNIVERSIDADE DE BRASÍLIA
FACULDADE DE CEILÂNDIA
PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS
E TECNOLOGIAS EM SAÚDE**

**Viabilidade da Avaliação Ambulatorial da Pressão Parcial do Dióxido de
Carbono Expirado (PetCO₂) em Repouso pela Capnografia em
Insuficiência Cardíaca.**

Alexandra Corrêa Gervazoni Balbuena de Lima

**BRASÍLIA
2017**

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Viabilidade da Avaliação Ambulatorial da Pressão Parcial do Dióxido de Carbono Expirado (PetCO₂) em Repouso pela Capnografia em Insuficiência Cardíaca.

Tese de Doutorado apresentada a Faculdade de Ceilândia da Universidade de Brasília como requisito parcial á obtenção do Título de Doutor em Ciências e Tecnologias em Saúde.

Área de Concentração: Promoção, Prevenção e Intervenção em Saúde.

Linha de Pesquisa: Saúde, Funcionalidade, Ocupação e Cuidado.

Orientador: Prof. Dr. Gerson Cipriano Jr.

BRASÍLIA

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“Não é o quanto fazemos, mas quanto Amor colocamos naquilo que fazemos.

Não é o quanto damos, mas quanto Amor colocamos em dar.”

Madre Teresa de Calcutá

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RELAÇÃO DE SIGLAS, SÍMBOLOS E ABREVIATURAS

PetCO₂ – Pressão Parcial de Oxigênio Expirado

TCPE – Teste Cardiopulmonar de Exercício

PetCO₂^{TCPE} – Pressão Parcial de Oxigênio Expirado medida durante o teste cardiopulmonar de exercício

IC – Insuficiência Cardíaca

PetCO₂^{CAP} – Pressão Parcial de Oxigênio Expirado medida não invasivamente pela capnografia

CF da NYHA – Classificação funcional da *New York Heart Association*

PAS – Pressão arterial sistólica

FC – Frequência cardíaca

FEVE - Fração de ejeção do ventrículo esquerdo

VO₂ pico - Consumo de oxigênio no pico do exercício

Slope VE/VCO₂ - Inclinação da relação ventilação minuto e produção de dióxido de carbono

ICC – Coeficiente de Correlação Intraclasse

LA - Limiar anaeróbico

PCR - Ponto de compensação respiratório

IC – Intervalo de Confiança

EtCO₂ – *End-tidal Carbon Dioxide*

HF – *Heart Failure*

RESUMO

Introdução: A pressão parcial do dióxido de carbono no final da expiração (PetCO₂) avaliada durante o teste cardiopulmonar de exercício (PetCO₂^{TCPE}) já está estabelecida como um importante fator prognóstico na insuficiência cardíaca (IC). A PetCO₂ avaliada por meio da capnografia (PetCO₂^{CAP}) em diferentes cenários clínicos (ex: Unidade de Terapia Intensiva, neurocirurgia, em atendimento pré-hospitalar, em reanimação cardiopulmonar) está associada com alterações do débito cardíaco. Todavia, o comportamento da PetCO₂^{CAP} na IC ainda não foi descrito.

Objetivos: Estudo 1) avaliar a confiabilidade e concordância da PetCO₂^{CAP} na IC; Estudo 2) determinar o valor prognóstico da PetCO₂^{CAP} em IC para morte cardíaca ou transplante cardíaco no primeiro ano de seguimento.

Métodos: Pacientes com IC realizaram medidas seriadas da PetCO₂^{CAP}, seguidas por um TCPE sintoma limitado. Os pacientes foram acompanhados em relação a morte cardíaca e transplante dentro do período de 1 ano.

Resultados: Foram incluídos na análise 158 pacientes com IC (idade média de 56.1 ± 12.7 anos, 69% homens, 35% etiologia isquêmica, classificação funcional III da *New York Heart Association* de 64% [CF da NYHA], fração de ejeção do ventrículo esquerdo [FEVE] de 37.8 ± 14.9%, consumo de oxigênio no pico do exercício [VO₂ pico] de 13.6 ± 5.5 ml.kg⁻¹.min⁻¹, e inclinação da relação ventilação minuto e produção de dióxido de carbono [*Slope* VE/VCO₂] de 35.9 ± 12.3). A PetCO₂^{CAP} apresentou uma excelente associação entre as medidas (r > 0.90; p < 0.0001), e elevada uniformidade (Intervalo de Confiança Intraclasse [ICC], 0.983; Intervalo de Confiança [IC] 95%, 0.991-0.995; p < 0.001). A PetCO₂^{CAP} foi capaz de predizer 94% da PetCO₂^{TCPE} repouso, apesar de uma correlação moderada entre as variáveis (r = 0.41; p < 0.0001). A PetCO₂^{CAP} foi menor quanto pior a classe funcional da NYHA (p < 0.0001). Foram acompanhados 125 pacientes (16 eventos em 1 ano), que apresentaram a PetCO₂^{CAP} reduzida (PetCO₂^{CAP}, 29.4 ± 6.9 mmHg; p = 0.05) em relação ao grupo sem eventos. O melhor ponto de corte da PetCO₂^{CAP} para

morte cardíaca e transplante foi ≤ 38 mmHg (Qui-Quadrado, 6.91; hazard ratio, 0.145; IC 95%, 0.019- 1.096; $p = 0.03$), com sensibilidade de 93% e especificidade de 67%, e valor preditivo negativo de 98%.

Conclusões: A capnografia mostrou ser uma ferramenta estável para a medida da $P_{et}CO_2$ e capaz de discriminar pacientes com risco de eventos.

Palavras chaves: Insuficiência Cardíaca; Pressão Parcial Expirada de Gás-Carbônico, Capnografia, Confiabilidade, Mortalidade Cardiovascular.

Abstract

Introduction: End-tidal expiratory carbon dioxide pressure (EtCO₂) assessed during the cardiopulmonary exercise testing (EtCO₂^{CPX}) is already established as an important prognostic factor in heart failure (HF) patients. EtCO₂ evaluated by capnography (EtCO₂^{CAP}) is associated with changes in cardiac output and prognosis variable in different clinical settings (ex. Intensive Care Unit, neurosurgery, abdominal aortic aneurysm correction surgery, prehospital care, cardiopulmonary resuscitation). However, the behavior of EtCO₂^{CAP} non-invasively measured has not yet been described in HF.

Objectives: Study 1) evaluate the reliability and agreement of EtCO₂^{CAP} in HF; Study 2) determine the prognostic value of EtCO₂^{CAP} in HF for cardiovascular death and urgent cardiac transplantation in one-year follow-up.

Methods: HF patients performed serial measurements of EtCO₂^{CAP}, followed by a symptom-limited CPX. HF subjects were followed during one-year for cardiac death or cardiac transplantation.

Results: One hundred and fifty-eight HF patients (mean age 56.1 ± 12.7 years, 69% men, 35% ischemic etiology, 64% New York Heart Association functional class III [NYHA FC], 37.8 ± 14.9% left ventricular ejection fraction [LVEF], 13.6 ± 5.5 ml.kg⁻¹.min⁻¹ oxygen consumption at the peak of the exercise [VO₂ peak], and 35.9 ± 12.3 Slope of ratio of minute ventilation and carbon dioxide production [VE / VCO₂ Slope]) were evaluated. The EtCO₂^{CAP} presented an excellent association between the measures (r > 0.90; p < 0.0001) and higher reliability (intraclass confidence interval [ICC], 0.983; 95% confidence interval [CI], 0.991-0.995; p < 0.001). The EtCO₂^{CAP} predicted 94% of resting EtCO₂^{CPX}, although a moderate correlation between them (r = 0.41; p < 0.0001). EtCO₂^{CAP} was lower as worst NYHA FC (p < 0.0001). One hundred and twenty-five patients were followed (16 events during one-year). The event-group presented reduced EtCO₂^{CAP} (29.4 ± 6.9mmHg; p = 0.05). The best threshold point of EtCO₂^{CAP} was ≤38mmHg (X² = 6.91; Hazard Ratio, 0.145; 95% CI 0.019-1.096;

p = 0.03), with 93% sensitivity, 67% specificity and 98% negative predictive value.

Conclusions: Our study is pioneer in evaluating EtCO₂^{CAP} non-invasively in HF patients. Noninvasive capnography was a stable tool for the measurement of EtCO₂ and was capable of discriminating HF patients with one-year risk of cardiovascular death and transplantation.

Key words: Heart Failure; Carbon-Dioxide, Capnography, Reliability, Agreement, Mortality

1. INTRODUÇÃO GERAL:

A presente tese foi redigida na modalidade de artigos científicos, em uma abordagem de artigos verticais ou sequenciais, de acordo com as Normas para Preparo da Dissertação ou da Tese para Obtenção do Título de Mestre ou de Doutor do Programa de Pós-Graduação em Ciências e Tecnologias em Saúde da Universidade de Brasília, sendo composta pelos seguintes elementos:

- Introdução geral, com contextualização e apresentação da contribuição do estudo à literatura científica, justificativa e os objetivos propostos;
- Dois artigos científicos, apresentados conforme as normas específicas dos periódicos para os quais foram submetidos (os artigos foram retirados na integrada devido a proteção de direitos autorais);
- Discussão geral e conclusões;
- Como apêndice, constam o Termo de Consentimento Livre e Esclarecido (TCLE); uma relação com as contribuições científicas ao longo do período de Doutorado; e um relatório das atividades realizadas durante o Programa de Doutorado Sanduíche no Exterior (PDSE);
- Em anexo, estão apresentados o Parecer Consubstanciado do Comitê de Ética em Pesquisa da Faculdade de Ciências da Saúde da Universidade de Brasília (CEP-FS/UnB); e as normas de publicação dos periódicos aos quais foram submetidos os artigos científicos, o Qualis dos periódicos e os comprovantes de submissão.

1.1 CONTEXTUALIZAÇÃO:

A insuficiência cardíaca (IC) é a via final comum da maioria das doenças que acometem o coração, sendo um dos mais importantes desafios clínicos atuais na área da saúde. Trata-se de um problema epidêmico em progressão

(1). Embora sua terapêutica tenha evoluído substancialmente nos últimos vinte anos, o prognóstico da doença ainda pode ser considerado desfavorável. No Brasil, segundo o DATASUS, do Ministério da Saúde, pode-se estimar que cerca de 6,4 milhões de brasileiros sofram de IC (2). A taxa de mortalidade anual média dos pacientes internados no Sistema Único de Saúde (SUS) é de 6% a 7% para pacientes em estágio inicial (Classe Funcional I *NYHA*), e de 30% a 40% para aqueles estágios finais (Classe Funcional IV *NYHA*), adequadamente tratados. Com isso, os custos de tratamento são crescentes, caracterizando a IC como um importante problema de saúde pública mundial (1, 2).

Ao longo das duas últimas décadas, o teste de exercício cardiopulmonar de exercício (TCPE) tem sido amplamente utilizado para ajudar a estabelecer a gravidade da doença e estimar o prognóstico em pacientes com IC. O parâmetro mais comumente avaliado no TCPE é o consumo de oxigênio no pico do exercício (VO_2 pico) (3). Contudo, as limitações ao uso do VO_2 pico para predição do prognóstico foram amplamente descritas; estes incluem uma incapacidade de determinar o esforço "máximo" em alguns pacientes, sua dependência da motivação, sua utilidade prognóstica questionável entre os pacientes que se enquadram em um intervalo intermediário ($10-18 \text{ ml.kg}^{-1}.\text{min}^{-1}$) (4-6) e uma discordância entre o VO_2 pico e o desempenho ventricular e a gravidade da doença (7, 8).

Mais recentemente, as respostas do TCPE que refletem a ineficiência ventilatória durante o exercício tem demonstrado um excelente desempenho prognóstico na IC. Esses parâmetros incluem a inclinação da relação entre a ventilação e a produção de dióxido de carbono (*Slope* VE/VCO_2), a cinética de VO_2 no início do exercício ou na recuperação, a inclinação da eficiência de absorção de oxigênio (OUES), um padrão de ventilação periódica e uma redução pressão parcial de CO_2 no final da expiração ($PetCO_2$) (9-11).

Com base em estudos realizados na unidade de terapia intensiva (UTI), a $PetCO_2$ reduzido tem sido relacionado à redução de débito cardíaco (12-15). A eliminação de dióxido de carbono, e, por conseguinte, a $PetCO_2$, diminui, quando o fluxo de sangue para os pulmões é reduzido. Shibutani *et al* (16), encontraram que a $PetCO_2$ em repouso foi significativamente correlacionada com alterações no débito cardíaco durante a cirurgia ($r=0,82$, $p<0,01$). Wahba

et al (17), encontraram que a PetCO₂ em repouso, medido antes e após a cirurgia cardíaca eletiva, foi efetivamente capaz de detectar alterações no índice cardíaco ($r=0,75$, $p<0,001$). Em um modelo intubado/sedado, resultados de Idris *et al* (18), sugerem que a PetCO₂ em repouso é capaz de refletir com precisão o débito cardíaco em uma ampla faixa de taxas de fluxo, incluindo as taxas de fluxo muito baixas. Asplin *et al* (19), encontraram que valores na PetCO₂ em repouso iniciais mais elevados foram capazes de prever o retorno a circulação espontânea em pacientes que sofreram parada cardíaca. Por fim, em pacientes submetidos à cirurgia em estado crítico, Domsky *et al* (20), relataram uma taxa de mortalidade de 55% em pacientes com uma PetCO₂ em repouso menor ou igual a 28 mmHg. Este foi comparado com uma taxa de mortalidade de 17% para aqueles pacientes com uma PetCO₂ em repouso maior que 28 mmHg.

A partir dessas investigações, a PetCO₂ surgiu como uma medida que pode ser de particular valor prognóstico em pacientes com IC (21, 22). A PetCO₂ se correlacionou com capacidade funcional e débito cardíaco durante o exercício, com sensibilidade 92% e especificidade de 42% para valores de PetCO₂ em repouso inferior a 33mmHg (23). O PetCO₂ no limiar anaeróbico abaixo de 36mmHg mostrou associação independente com eventos cardiovascular (sensibilidade 77% e especificidade 69%) (24) e forte associação com *Slope* VE/VCO₂ ($r=0.78$, $p<0.001$)(25). De fato, tanto em repouso como durante o exercício, a PetCO₂ avaliada durante o TCPE demonstrou ser um importante preditor de risco para eventos adversos em IC (24, 26). Inclusive, a PetCO₂ reduzida seria um preditor de risco ainda mais poderoso do que o pico VO₂ (24). Em pacientes portadores de IC com fração de ejeção reduzida, a PetCO₂, em repouso e durante o exercício, adiciona valor prognóstico a avaliação desse grupo de pacientes (27). À luz de estudos recentes que demonstram que PetCO₂ avaliada durante o TCPE é um forte marcador de prognóstico e a capacidade de medir a PetCO₂ de maneira não invasiva a partir da capnografia desenhamos o estudo atual.

1.2. HIPÓTESE:

A hipótese principal desse estudo é que, relacionando o conhecimento prévio de que a redução do débito cardíaco está associada a marcante intolerância ao exercício (28, 29) e que a redução da PetCO₂ avaliada pelo TCPE possui valor prognóstico em pacientes com diagnóstico de IC (26, 27, 30), assim acreditamos que a PetCO₂ em repouso medida pela capnografia apresentaria comportamento semelhante. Logo, em pacientes portadores de IC a PetCO₂ avaliada pela capnografia terá um valor reduzido e estará associada com uma pior classe funcional de acordo com a *NYHA*, uma elevação de *Slope VE/VCO₂*, uma redução do *VO₂* e uma maior número de eventos cardiovasculares (ex: morte cardíaca, transplante de urgência).

Para testar as hipóteses, foram realizados dois estudos, como se segue:

- Estudo 1: **“Spontaneously Breathing Capnography in Chronic Heart Failure Patients: Reliability, Agreement and Validity Study of Partial Pressure of End-tidal Carbon Dioxide.”**

Nesse estudo de coorte prospectiva, avaliamos se a PetCO₂ medida pela capnografia seria uma medida confiável, avaliando a sua confiabilidade e a sua concordância com a PetCO₂ medida pelo TCPE em diferentes pontos (em repouso, no limiar anaeróbico, no ponto de compensação respiratório e no pico do exercício). Além da validação da sua capacidade de diferenciar pacientes em diferentes classes funcionais pela classificação funcional da *NYHA*. Este estudo foi desenhado segundo o Consenso para Estudos de Confiabilidade e Concordância (Guidelines for Reporting Reliability and Agreement Studies – GRRAS) (31).

- Estudo 2: **“Non-invasive Resting Capnography in Chronic Heart Failure Patients: End-tidal Carbon Dioxide as a new prognostic factor on Heart Failure.”**

Nessa coorte prospectiva, os pacientes que realizaram a capnografia e o TCPE foram acompanhados por um período de um 1 ano com relação a eventos cardiovasculares – morte cardíaca ou transplante cardíaco de

urgência. Nesse estudo, procuramos avaliar se a PetCO₂ avaliada pela capnografia apresentaria capacidade de predizer eventos cardiovasculares, se poderia ser determinado um ponto de corte, assim como foi feito para a PetCO₂^{TCPE} em repouso (PetCO₂^{TCPE} repouso ≤ 33mmHg)(23) e no limiar anaeróbico (PetCO₂^{TCPE}LA ≤ 36mmHg)(24).

1.3. OBJETIVOS:

Objetivo Geral

Avaliar o padrão de comportamento da variável PetCO₂ em repouso pela capnografia, comparar com a medida da PetCO₂ durante o teste cardiopulmonar e determinar se a PetCO₂ pela capnografia seria capaz de se correlacionar com eventos cardiovasculares em uma coorte prospectiva com acompanhamento de 1 ano

Objetivos Específicos:

- Determinar se a PetCO₂ em repouso seria uma variável estável e confiável em pacientes com IC.
- Determinar se a PetCO₂ em repouso seria equivalente a PetCO₂ medida pelo TCPE em diferentes pontos.
- Determinar se a PetCO₂ em repouso medida pela capnografia estaria associada com a diferentes parâmetros prognósticos (VO₂ pico, *Slope* VE/VCO₂).
- Determinar se a PetCO₂ avaliada pela capnografia seria capaz de diferenciar pacientes em diferentes estágios clínicos (ex: CF da NYHA).

3. DISCUSSÃO GERAL E CONCLUSÕES:

3.1 INTEGRAÇÃO DAS PARTES DA PROJETO

A $\text{PetCO}_2^{\text{CAP}}$ tem sido associada a redução do débito cardíaco em uma variedade de situações experimentais e clínicas, incluindo a UTI, no choque cardiogênico e durante a cirurgia (32-34). Nos pacientes com IC, a medida da PetCO_2 durante a realização do teste cardiopulmonar, mostrou ser um parâmetro importante para avaliação e prognóstico cardiovascular (23-27, 30). Contudo, a confiabilidade da medida da $\text{PetCO}_2^{\text{CAP}}$, a sua correlação com a medida realizada durante o TCPE e a sua associação com eventos cardiovasculares ainda não foi descrita em pacientes com IC.

A hipótese inicial era que a PetCO_2 medida pela capnografia seria uma medida equivalente a PetCO_2 medida durante o TCPE, porém esse não foi o achado do nosso estudo. Em nosso estudo, a $\text{PetCO}_2^{\text{CAP}}$ medida de forma não invasiva em pacientes com IC foi uma variável estável com elevada confiabilidade intraclassa. A $\text{PetCO}_2^{\text{CAP}}$ já havia sido descrita como uma medida confiável de forma não invasiva em pacientes saudáveis (35, 36), possuindo segundo nosso estudo padrão de comportamento semelhante em pacientes com IC. A $\text{PetCO}_2^{\text{CAP}}$ mostrou correlação com as diferentes medidas da $\text{PetCO}_2^{\text{TCPE}}$, mas concordância moderada com as medidas da $\text{PetCO}_2^{\text{TCPE}}$ no LA e no PCR. Os valores da $\text{PetCO}_2^{\text{CAP}}$ do nosso estudo foram semelhantes aos encontrados em outros estudos que avaliaram a $\text{PetCO}_2^{\text{TCPE}}$ em repouso (26, 27), mas os nossos pacientes apresentaram valores reduzidos de $\text{PetCO}_2^{\text{TCPE}}$ em repouso.

Variabilidade nas medidas feitas em um mesmo indivíduo pode ser atribuída a diferenças na técnica de medida. A técnica de medida da $\text{PetCO}_2^{\text{CAP}}$ é por via *side-stream*, onde o sensor está colocado de gás carbônico está localizado no monitor, logo distante do paciente. E cada aparelho tem uma regra de correção para ajustar a medida adquirida pelo aparelho. A $\text{PetCO}_2^{\text{TCPE}}$ é medida por via *main-stream*, onde o sensor está localizado na célula de coleta da amostra de gases, bem próximo a boca do paciente (37, 38). Contudo, o comportamento da $\text{PetCO}_2^{\text{TCPE}}$ no nosso estudo foi dentro do esperado durante o TCPE, aumentando até o LA e o PCR e em seguida caindo

até o pico do exercício(13, 23), confirmando a qualidade da nossa medida de $\text{PetCO}_2^{\text{TCPE}}$. Wasserman et al(39) sugere que a redução do PetCO_2 no pico do exercício é causada por alterações na relação ventilação perfusão, devido a vasoconstrição pulmonar e grande redução na perfusão pulmonar associada na pressão venosa elevada. Além disso, nossa descoberta de uma $\text{PetCO}_2^{\text{TCPE}}$ de repouso significativamente menor poderia ser explicado pelo aumento do gradiente $\text{PaCO}_2\text{-PETCO}_2$ devido ao aumento do VD/VT , conforme relatado em casos de insuficiência cardíaca congestiva (40), e no nosso estudo a maioria dos pacientes apresentavam classe funcional C ou D de Weber.

Por outro lado, em nosso estudo, outros mecanismos provavelmente estavam envolvidos porque $\text{PetCO}_2^{\text{CAP}}$ foi maior do que a esperada, já que a $\text{PetCO}_2^{\text{CAP}}$ foi coletada em posição supina e a $\text{PetCO}_2^{\text{TCPE}}$ em posição sentada. Estudo realizado durante neurocirurgia com coleta da PetCO_2 em diferentes posições demonstrou que a PetCO_2 em posição supina pode ser até 4mmHg superior a PetCO_2 em posição sentada ou em pé(41). A posição sentada contribui para a redistribuição do fluxo sanguíneo para as bases pulmonares e cria a zona I de West (capilares pulmonares colapsados com altos índices ventilação-perfusão) (42). Portanto, com base em nossos resultados, podemos inferir, mas não estabelecer, que apesar das medidas não serem concordantes e não ser possível substituir a coleta da $\text{PetCO}_2^{\text{TCPE}}$ pela coleta da $\text{PetCO}_2^{\text{CAP}}$, seria possível pela análise dos gráficos de Bland-Altman supor um erro padrão que pode ser subtraído do valor de $\text{PetCO}_2^{\text{CAP}}$ para determinação do $\text{PetCO}_2^{\text{TCPE}}$ em repouso e no pico do exercício (média da diferença 4,15mmHg e 3,20mmHg, respectivamente).

Pacientes com insuficiência cardíaca avançada possuem um débito cardíaco reduzido e um aumento da ventilação devido ao aumento do espaço morto durante o exercício (40, 43). O PetCO_2 durante o exercício é significante reduzido em pacientes classe funcional III *NYHA* (25, 27). Myers *et al* (25) demonstrou que PetCO_2 no pico do exercício está relacionado com o VO_2 pico em pacientes com IC, mas a relação entre PetCO_2 e o VO_2 pico foi fraca ($r = 0.355$). Observamos que a $\text{PetCO}_2^{\text{CAP}}$ identificou pacientes com capacidade funcional reduzida e ineficiência ventilatória e desempenho cardíaco reduzido durante o exercício. As implicações clínicas desses resultados incluem o fato

de que a $\text{PetCO}_2^{\text{CAP}}$ pode complementar outras respostas da avaliação clínica e de exercício no acompanhamento de pacientes com IC.

Usando a resposta da $\text{PetCO}_2^{\text{CAP}}$ identificamos pacientes com ICC em alto risco de desfechos adversos. O ponto de corte da $\text{PetCO}_2^{\text{CAP}}$ de 38mmHg apresentou um valor preditivo negativo de 83%, demonstrando que valores reduzidos da $\text{PetCO}_2^{\text{CAP}}$ estão associados com menores chance de sobrevida. Contudo, a monitorização da $\text{PetCO}_2^{\text{CAP}}$ de forma isolada não pode ser utilizada para prever eventos em pacientes com IC. Nos demonstramos que em pacientes com IC o uso de parâmetros ambulatoriais simples (ex: PAS em repouso associada a medida da $\text{PetCO}_2^{\text{CAP}}$) poderia auxiliar na triagem de indivíduos com maior ou menor risco de eventos.

Pacientes diagnosticados com IC são normalmente atendidos em ambiente ambulatorial para avaliação da sua estabilidade clínica e ajuste de medicamentos. Nesse ambiente, várias medidas de repouso, incluindo CF da *NYHA*, ecocardiograma, eletrocardiograma, pressão arterial e marcadores inflamatórios e neurohormonais têm sido utilizadas para auxiliar no diagnóstico e manuseio de descompensações clínicas (1, 44). O nosso estudo sugere considerar a incorporação da $\text{PEtCO}_2^{\text{CAP}}$ a avaliação desses pacientes. A natureza não-invasiva, rápida e de baixo custo da aquisição da $\text{PEtCO}_2^{\text{CAP}}$ torna essa variável promissora na avaliação da IC, principalmente em ambientes onde recursos mais avançados podem ser limitados.

Nossos dados sugerem que a simples medida da $\text{PetCO}_2^{\text{CAP}}$ pode auxiliar na triagem de pacientes portadores de IC com maior ou menor risco de eventos. Isso é de extrema relevância em países onde o tempo de espera para realização de um ecocardiograma ou de um teste cardiopulmonar pode ser longo, ou onde os custos para dosagem de peptídeo natriurético não são cobertos pelos provedores de saúde. Todavia, é importante colocar que os autores recomendam fortemente a realização do teste cardiopulmonar na avaliação de pacientes candidatos a transplante cardíaco e implante de dispositivos externos, como preconizado nas diretrizes nacionais e internacionais.

3.2. DETALHES DA EXECUÇÃO DO PROJETO

As avaliações foram realizadas na Universidade de Brasília (UnB), no campus da Ceilândia, no Laboratório de Biofísica e Fisiologia. O laboratório de Biofísica e Fisiologia da UnB encontra-se equipado com todos os materiais de segurança padronizados pela Sociedade Brasileira de Cardiologia (SBC) (45).

Pacientes portadores de IC foram recrutados de ambulatórios de IC da região do Distrito Federal e Entorno, mediante indicação de médicos cardiologistas para realização de teste cardiopulmonar de exercício. Os pacientes foram avaliados do ponto de vista clínico por um único médico avaliador cardiologista – pesquisador responsável pela pesquisa, assim como a execução e interpretação do teste cardiopulmonar de exercício. Antes de cada teste cardiopulmonar, os pacientes realizaram a medida do PetCO₂ em repouso pela capnografia, com auxílio de alunos da graduação de fisioterapia vinculados ao Programa de Iniciação Científica (PIBIC) e alunos de pós-graduação de mestrado e doutorado do programa de pós-graduação em Ciências e Tecnologias em Saúde.

O seguimento desses pacientes foi realizado por entrevista telefônica a cada três meses a partir da data da realização da capnografia e do TCPE pelo pesquisador e por alunos da graduação de fisioterapia vinculados ao PIBIC.

O projeto contribuiu na formação de discentes de pós-graduação, graduação e iniciação científica promovendo como resultados a elaboração de artigos científicos. Portanto, a partir da divulgação dos resultados deste estudo por meio de artigos científicos, de apresentação em congressos e simpósios, este projeto favoreceu a prática clínica baseada em evidências.

Todos os pacientes que participaram do estudo foram convidados a participar e vários participaram e participam do Programa Extensão de Reabilitação Cardiopulmonar Supervisionada e Não-Supervisionada desenvolvido na Faculdade da Ceilândia da Universidade de Brasília.

3.3 CONCLUSÃO

A investigação proposta determinou que a $\text{PetCO}_2^{\text{CAP}}$ é um método confiável e reprodutível pelo qual o risco aumentado de eventos adversos pode ser facilmente avaliado em pacientes com insuficiência cardíaca. A coleta e interpretação da $\text{PetCO}_2^{\text{CAP}}$ não requer treinamento avançado, permitindo às diversas profissões ligadas a saúde obter e usar esta medida. Esta informação objetiva pode ser utilizada para identificar pacientes com risco aumentado de eventos adversos e a auxiliar nas decisões de tratamento.

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Apêndice A – Termo de Consentimento Livre e Esclarecido (TCLE)



Universidade de Brasília – UnB
Faculdade de Ceilândia – FCE

Termo de Consentimento Livre e Esclarecido – TCLE

Convidamos o(a) Senhor(a) a participar do projeto de pesquisa “**Avaliação Ambulatorial da Pressão Parcial do Dióxido de Carbono Expirado (PETCO₂) e desenvolvimento de Software de predição clínica em indivíduos para pacientes com Insuficiência Cardíaca**”, sob a responsabilidade do pesquisador **Alexandra Corrêa Gervazoni Balbuena de Lima**. O projeto irá fazer avaliações da função cardíaca e pulmonar – exame físico, eletrocardiograma, ecocardiograma, teste de esforço, teste de função pulmonar, coleta de gases expirados em repouso e de sangue, nos próximos dois anos, em indivíduos portadores de insuficiência cardíaca, determinando quais os fatores que foram mais frequentes naqueles indivíduos que internaram ou que morreram por causa cardíaca. A partir desses dados, será desenvolvido um programa de computador para determinar o risco de uma pessoa com insuficiência cardíaca apresentar complicações sérias da doença.

Os objetivos desta pesquisa são: **avaliar o padrão de comportamento dos gases expirados em repouso, e comparar com outros métodos de avaliação da capacidade cardiorrespiratória e cardiovascular; desenvolver um programa de predição clínica em indivíduos com diagnóstico de insuficiência cardíaca.**

O(a) senhor(a) receberá todos os esclarecimentos necessários antes e no decorrer da pesquisa e lhe asseguramos que seu nome não aparecerá sendo mantido o mais rigoroso sigilo pela omissão total de quaisquer informações que permitam identificá-lo(a)

A sua participação se dará por meio de **realização de avaliações seriadas da função cardíaca e pulmonar no laboratório de Biofísica e Fisiologia da Faculdade de Ceilândia da Universidade de Brasília** com um tempo estimado de **90 a 120 minutos em 3 visitas consecutivas e no período de 12 a 24 meses após as avaliações será feito contato telefônico para saber sobre o seu estado de saúde**. As avaliações realizadas serão:

1. Visita 1:
 - a. Avaliação médica onde serão feitas perguntas sobre o seu problema de coração, os medicamentos utilizados e procedimentos já feitos; e exame médico com medida da pressão arterial, da frequência cardíaca e ausculta do seu coração e pulmão;
 - b. Eletrocardiograma – exame em repouso que avalia a parte elétrica do coração;
 - c. Ecocardiograma: exame de ultrassom realizado deitado com a utilização de um gel, com objetivo de avaliar a função do coração.
2. Visita 2:
 - a. Capnografia: exame realizado em repouso, onde é colocado um cateter no nariz e realizada a avaliação da respiração por 3 minutos;
 - b. Espirometria - exame que avalia a função pulmonar, a partir de um sopro forte repetido 3 vezes;
 - c. Manuvacuometria - exame que avalia a força muscular respiratória, a partir de um sopro forte repetido 3 vezes.
 - d. Teste Cardiopulmonar de Exercício com carga incremental: exame de esforço, em bicicleta, com aumento progressivo da carga da bicicleta, com uma máscara para coleta de gases, onde os batimentos cardíacos, pressão arterial e a respiração serão avaliados até o máximo de esforço que o paciente conseguir.

3. Visita 3:

- a. Coleta de sangue para dosagem do BNP: coleta de um pouco de sangue
- b. Teste Cardiopulmonar de Exercício com carga constante: exame de esforço, em bicicleta, com a mesma carga do início ao fim, com uma máscara para coleta de gases, onde os batimentos cardíacos, pressão arterial e a respiração serão avaliados até o máximo de tempo que o paciente conseguir.
- c. Avaliação da Função Vascular pelo método NIRS - o aparelho avalia em repouso por meio de luz infravermelha quantidade de oxigênio no músculo.

Os riscos decorrentes de sua participação na pesquisa são estão **associados com a realização dos exames** e serão tomadas todas as medidas para que o(a) Senhor(a) não seja submetido a qualquer dano:

1) Eletrocardiograma - o gel e a colocação peras para a realização do exame pode causar desconforto e discreto hematoma na pele do paciente. Para minimizar esse incômodo, o paciente será esclarecido sobre o procedimento e será utilizado gel condutor específico para o procedimento;

2) Teste cardiopulmonar de exercício com carga incremental e carga constante - o paciente será orientado sobre o exame que será realizado; o exame será realizado por médico cardiologista habilitado e experiente, em ambiente com temperatura e imunidade adequadas, com equipamento completo para realizar as manobras de reanimação cardiorrespiratória e transporte por Ambulância do Campus da FCE ou do SAMU para emergência do Hospital Regional da Ceilândia; a máscara será adaptada conforme o tamanho do rosto do paciente da maneira mais confortável possível; serão utilizados eletrodos descartáveis; o manguito do aparelho de pressão será ajustado conforme circunferência do braço do paciente; o exame será realizado em bicicleta, sendo excluído o risco de queda em caso de mal-estar ou fadiga extrema, já que o paciente se encontra sentado. O exame será realizado conforme as orientações da Diretriz de Teste Ergométrico da Sociedade Brasileira de Cardiologia;

3) Ecocardiograma - o paciente será orientado quanto o procedimento a ser realizado, o procedimento será realizado por profissional experiente e habilitado para o mesmo, gel condutor adequado será utilizado para o exame. O exame será realizado conforme as orientações da Sociedade Brasileira de Cardiologia;

4) Espirometria e Manuvacuometria- o paciente será orientado quanto ao procedimento, o exame será realizado por profissional experiente, com material descartável, exame realizado segundo as normativas da Sociedade Americana Cirurgia Torácica (ATS);

5) Coleta do PetCO₂ em repouso através de capnografia - será utilizado cateter individualizado e descartável para cada indivíduo e cada coleta;

6) Coleta de sangue para dosagem do BNP - os riscos relativos a coleta de sangue são o desconforto associado a punção sanguínea e hematoma no local de punção sanguínea. Para minimizar os riscos as coletas serão realizadas por profissional da FCE experiente em coleta de sanguínea com material descartável;

7) Avaliação da Função Vascular pelo método NIRS – o paciente será orientado quanto ao procedimento.

Se você aceitar participar, estará contribuindo para que **um exame barato e indolor possa ser utilizado para a melhora no diagnóstico e acompanhamento dos pacientes portadores de IC.**

O(a) Senhor(a) pode se recusar a responder (ou participar de qualquer procedimento) qualquer questão que lhe traga constrangimento, podendo desistir de participar da pesquisa em qualquer momento sem nenhum prejuízo para o(a) senhor(a). Sua participação é voluntária, isto é, não há pagamento por sua colaboração.

Todas as despesas que você tiver relacionadas diretamente ao projeto de pesquisa (tais como, passagem para o local da pesquisa, alimentação no local da pesquisa ou exames para realização da pesquisa) serão cobertas pelo pesquisador responsável. O(a) Senhor(a) ficará com o resultado de todos os exames realizados.

Caso haja algum dano direto ou indireto decorrente de sua participação na pesquisa, você poderá ser indenizado, obedecendo-se as disposições legais vigentes no Brasil.

Os resultados da pesquisa serão divulgados na **Defesa de Doutorado do Programa de Pós-Graduação em Ciências e Tecnologias da Saúde da Faculdade da Ceilândia / Universidade de Brasília** podendo ser publicados posteriormente. Os dados e materiais serão utilizados somente para esta pesquisa e ficarão sob a guarda do pesquisador por um período de cinco anos, após isso serão destruídos.

Se o(a) Senhor(a) tiver qualquer dúvida em relação à pesquisa, por favor telefone para: **Alexandra Corrêa Gervazoni Balbuena de Lima – telefone: na Faculdade da Ceilândia / Universidade de Brasília no telefone (61) 9975-1658.**

Este projeto foi Aprovado pelo Comitê de Ética em Pesquisa da Faculdade de Ciências da Saúde (CEP/FS) da Universidade de Brasília. O CEP é composto por profissionais de diferentes áreas cuja função é defender os interesses dos participantes da pesquisa em sua integridade e dignidade e contribuir no desenvolvimento da pesquisa dentro de padrões éticos. As dúvidas com relação à assinatura do TCLE ou os direitos do participante da pesquisa podem ser esclarecidas pelo telefone (61) 3107-1947 ou do e-mail cepfs@unb.br ou cepfsunb@gmail.com, horário de atendimento de 10:00hs às 12:00hs e de 13:30hs às 15:30hs, de segunda a sexta-feira. O CEP/FS se localiza na Faculdade de Ciências da Saúde, Campus Universitário Darcy Ribeiro, Universidade de Brasília, Asa Norte.

Este documento foi elaborado em duas vias, uma ficará com o pesquisador responsável e a outra com o Senhor(a).

Nome / assinatura

Pesquisador Responsável
Nome e assinatura

Brasília, ____ de _____ de _____.

Apêndice B – Contribuições Científicas

MANUSCRITOS SUBMETIDOS (PRIMEIRO AUTOR)

1. **Lima, ACGB**, Silva FMF, Missias AA, Sousa RF, Ramalho SHR, Nakano EY, Cipriano GFB, Cahalin LP, Cipriano Jr G. *Spontaneously Breathing Capnography in Chronic Heart Failure Patients: Reliability, Agreement and Validity Study of Partial Pressure of End-tidal Carbon Dioxide.*
2. **Lima, ACGB**, Silva FMF, Missias AA, Sousa RF, Ramalho SHR, Nakano EY, Cipriano GFB, Cahalin LP, Cipriano Jr G. *Non-invasive Resting Capnography in Chronic Heart Failure Patients: End-tidal Carbon Dioxide as a new prognostic factor on Heart Failure.*

MANUSCRITOS SUBMETIDOS (AUTOR COLABORADOR)

1. Lima FV, Chiappa GR, Ramalho SHR, **Lima ACGB**, Souza FS, Cahalin LP, Durigan JL, Castro I, Cipriano Jr G. *Resistance Exercise Enhances Oxygen Uptake without Worsening Cardiac Function in Patients with Systolic Heart Failure: A Systematic Review and Meta-Analysis.* Accepted on Heart Failure Reviews in October 11th, 2017.
2. Thomaz SR, Teixeira FA, **Lima ACGB**, Cahalin LP, Cipriano Jr G. *Acute effect of Osteopathic Manipulative Treatment focusing on myofascial release upon the resistive index and blood pressure in heart failure patients: a randomised clinical trial.* Accepted on Journal of Bodywork & Movement Therapies in July 20th, 2017.
3. Thomaz SR, Teixeira FA, **Lima ACGB**, Ramalho SHR, Nakata CH, Silva FMF, Cipriano Jr G, Cahalin LP. *Circuit Resistance Training Improves Exercise Tolerance, Muscle Strength, Quality of Life, and Depression in Heart Failure Patients.*
4. Campos FVS, Silva ML, Teixeira FA, Silva VM, Lima ACGB, Arena R, Cahalin LP, Cipriano GFB, Cipriano Jr G. *Effects of Cervicothoracic Transcutaneous Electrical Nerve Stimulation in Cardiovascular Response and Muscle Performance during Leg Resistance Exercise in Ischemic HF.*

MANUSCRITOS EM ELABORAÇÃO (PRIMEIRO AUTOR)

1. Lima **ACGB**, Silva, ML, Silva VZM, Giollo Jr LT, Silva AP, Vilela-Martin JF, Chiappa GR, Cipriano Jr G. *Vascular Peripheric Differences in Patients with Chagas Versus Ischemic Heart Failure.*

RESUMOS APRESENTADOS EM CONGRESSOS E PUBLICADOS EM PERIÓDICOS INDEXADOS (PRIMEIRO AUTOR)

1. Lima **ACGB**, Silva, ML, Silva VZM, Giollo Jr LT, Silva AP, Vilela-Martin JF, Chiappa GR, Cipriano Jr G. *Vascular Peripheric Differences in Patients with Chagas Versus Ischemic Heart Failure.* *Medicine & Science in Sports & Exercise.* 49(5S):817. DOI: 10.1249/01.mss.0000519189.68608.61
2. Lima **ACGB**; Silva FMF; Teixeira FMT; Silva ML; Missias AA; Furtado R; Ramalho SHR; Staufer F; Cipriano Jr G. *Capnography in spontaneously breathing chronic heart failure patients: resting partial pressure of end-tidal carbon dioxide a new non-invasive factor on heart failure.* *European Journal of Heart Failure* (2017) **19** (Suppl. S1) 13. doi:10.1002/ejhf.833
3. Lima **ACGB**, Silva FMF, Teixeira FM, Nakata CH, Thomaz SR, Missias AA, Ramalho SHR, Melo PF, Freitas LAO, Cipriano Jr G. *Novel cardiac rehabilitation program modalities - high intensity interval training (HIIT) and circuit resistance training (CRT) - improve cardiorespiratory fitness with safety and compliance.* *European Journal of Preventive Cardiology.* 2017, Volume 24, Issue 1_suppl, S 149.
4. Lima, **ACGB**; Silva, ML; Martorelli, AS; Souza, FS; Pereira, MC; Cipriano, GFB; Carmo, JC; Ferreira, E; Cipriano Jr, G. *Effect of electrical muscle stimulation on cardiorespiratory and skeletal muscle capacity in individuals with moderate and severe heart failure.* *Journal of Cardiopulmonary Rehabilitation & Prevention.* 2015, 35(4):286-294.
5. Lima, **ACGB**; Otto, MEB; Silva, ML; Neves, LMT; Silva, VZM; Arena, R; Cipriano Jr, G. *Comparação de Parâmetros Ergoespirométricos e a Função do Ventrículo Direito em Paciente com Insuficiência Cardíaca Avançada e Baixa Capacidade Funcional de Etiologia Isquêmica e*

- Chagásica*. Arq Bras Card. 2014, 103 (Sup 1): 28.
6. **Lima, ACGB**; Otto, MEB; Silva, ML; Neves, LMT; Silva, VZM; Arena, R; Cipriano Jr, G. *Parâmetros Ventilatórios em Teste Cardiopulmonar de Exercício na Insuficiência Cardíaca Avançada de Etiologia Isquêmica e Chagásica*. Arq Bras Card. 2014, 103 (Sup 1): 84.
7. **Lima, ACGB**; Otto, MEB; Silva, ML; Neves, LMT; Silva, VZM; Arena, R; Cipriano Jr, G. *O exercício aeróbico muda a função vascular em pacientes com insuficiência cardíaca chagásica, mas não em pacientes com insuficiência cardíaca isquêmica*. Arq Bras Card. 2014, 103 (Sup 1): 85.

RESUMOS APRESENTADOS EM CONGRESSOS E PUBLICADOS EM PERIÓDICOS INDEXADOS (AUTOR COLABORADOR)

1. Nakata CH, Teixeira FA, Ramalho SHR, **Lima ACGB**, Cipriano Jr G. *Acute effects of Ganglionic electrical stimulation on flow-mediated vasodilation in healthy men*. Can J Cardiol. Volume 32, Issue 10, Supplement 1, Page 221.
DOI: <http://dx.doi.org/10.1016/j.cjca.2016.07.352>

TRABALHOS APRESENTADOS EM CONGRESSOS

69º Congresso da Sociedade Brasileira de Cardiologia 2014

Brasília, Brasil. 26 a 29 setembro, 2014.

1. **Lima, ACGB**; Otto, MEB; Silva, ML; Neves, LMT; Silva, VZM; Arena, R; Cipriano Jr, G. *Comparação de Parâmetros Ergoespirométricos e a Função do Ventrículo Direito em Paciente com Insuficiência Cardíaca Avançada e Baixa Capacidade Funcional de Etiologia Isquêmica e Chagásica*. Tema Livre Oral (Apresentado)
2. **Lima, ACGB**; Otto, MEB; Silva, ML; Neves, LMT; Silva, VZM; Arena, R; Cipriano Jr, G. *Parâmetros Ventilatórios em Teste Cardiopulmonar de Exercício na Insuficiência Cardíaca Avançada de Etiologia Isquêmica e Chagásica*. Pôster (Apresentado)
3. **Lima, ACGB**; Otto, MEB; Silva, ML; Neves, LMT; Silva, VZM; Arena, R;

Cipriano Jr, G. *O exercício aeróbico muda a função vascular em pacientes com insuficiência cardíaca chagásica, mas não em pacientes com insuficiência cardíaca isquêmica.* Pôster (Apresentado)

AACVPR 30th Annual Meeting 2015

Washington DC, Estados Unidos. 09 a 12 Setembro, 2015.

1. **Lima, ACGB**; Silva, ML; Martorelli, AS; Souza, FS; Pereira, MC; Cipriano, GFB; Carmo, JC; Ferreira, E; Cipriano Jr, G. *Effect of electrical muscle stimulation on cardiorespiratory and skeletal muscle capacity in individuals with moderate and severe heart failure.* Tema Livre Oral (Apresentado)

23º Congresso Nacional da SBC/DERC 2016

Rio de Janeiro, Brasil. 01 a 03 Janeiro, 2016.

1. **Lima, ACGB**; Silva, FMF; Teixeira, FA; Nakata, CH; Thomaz, SR; Missias, AA; Ramalho, SHR; Silva, ML; Staufer, F; Melo, PF; Freitas, LAO; Cipriano Jr, G. *O efeito da reabilitação cardíaca no volume atrial esquerdo em pacientes portadores de insuficiência cardíaca.* Tema Livre Oral (Apresentado)

Europevent 2017

Málaga, Espanha. 19 a 21 Abril, 2017.

1. **Lima, ACGB**; Silva, FMF; Teixeira, FA; Nakata, CH; Thomaz, SR; Missias, AA; Ramalho, SHR; Silva, ML; Staufer, F; Melo, PF; Freitas, LAO; Cipriano Jr, G. *Novel cardiac rehabilitation program modalities - high intensity interval training (HIIT) and circuit resistance training (CRT) - improve cardiorespiratory fitness with safety and compliance.* Pôster (Apresentado)

Heart Failure 2017 / 4th World Congress on Acute Heart Failure

Paris, França. 29 abril a 02 maio, 2017.

1. **Lima, ACGB**; Silva, FMF; Teixeira, FA; Missias, AA; Furtado, R; Ramalho, SHR; Silva, ML; Cipriano Jr, G. *Capnography in Spontaneously*

Breathing Chronic Heart Failure Patients: Resting Partial Pressure of End-tidal Carbon Dioxide a new non-invasive prognostic factor on Heart Failure. Pôster Comentado (Apresentado)

ACSM Annual Meeting 2017

Denver, Estados Unidos. 31 maio a 03 junho, 2017.

1. **Lima, ACGB**; Silva, ML; Silva, VZM; Giollo Jr, LT; Chiappa, GR; Vilela-Martin, JF; Silva, APX; Cipriano Jr, G. *Vascular Peripheric Differences in Patients with Chagas Versus Ischemic Heart Failure.* Pôster (Apresentado)

FINANCIAMENTO

O presente projeto foi realizado com recursos do edital Universal do Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq); do edital Fundação de Amparo a Pesquisa do Distrito Federal (FAP-DF); e da empresa Nonin Medical.

A autora realizou Programa de Doutorado Sanduíche no Exterior com recursos da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES, PDSE - 88881.134474/2016-01).

Apêndice C – Programa de Doutorado Sanduíche no Exterior (PDSE)

LOCAL

University of Miami

Department of Physical Therapy, Miller School of Medicine

Miami, Florida, Estados Unidos

PERÍODO

14 de junho de 2017 a 28 de setembro de 2017.

PROCESSO

CAPES, PDSE - 88881.134474/2016-01

CO-ADVISOR

Prof. Dr. Lawrence P. Cahalin

Professor / Research Health Scientist

Clinical Focus

Dr. Cahalin is Board Certified in Cardiopulmonary Physical Therapy. He has 33 years of clinical experience in physical therapy. His clinical practice has focused on independent exercise testing, cardiac and pulmonary rehabilitation, physical therapy for patients with end-stage heart and lung disease before and after heart or lung transplantation, and breathing retraining.

Research Focus

Dr. Cahalin has an interest and expertise in exercise testing, exercise training, and assessment of functional capacity. He also has a strong interest and expertise in the testing and training of the respiratory muscles in both healthy subjects and patients with heart and lung disease. His training in both physical therapy and gerontology has provided him with clinical and research skills to better appreciate and understand the effects of aging in older adults with and without heart and lung disease. He is particularly interested in understanding and implementing methods to promote favorable health

behaviors in adults. Much of his work has examined the dynamic interaction between the cardiac and pulmonary systems at rest and during exercise with the goal of improving diagnoses, functional performance, and quality of life. He has made significant contributions to science and clinical research addressing (1) the safety of exercise testing, (2) the clinical utility of the 6-minute walk test in heart failure and end-stage lung disease, (3) inspiratory muscle testing and training in heart failure, (4) the clinical utility of heart rate recovery during maximal and submaximal exercise, and (5) promoting the development and implementation of worksite health and wellness programs as vehicles to prevent non-communicable disease and provide cardiac rehabilitation.

ATIVIDADES REALIZADAS

Lab Meetings – Reuniões para discussão dos dados a serem analisados, estratégias estatísticas e de artigos relevantes a pesquisa realizada.

CURSOS REALIZADOS

1. Accelerated English Conversation Advanced

Miami Dade College, Miami – Flórida – Período 03/07/17 a 24/08/17

Os alunos devem ser capazes de contribuir para grandes discussões em grupo ou em sala de aula, bem como pequenas discussões em grupo, mas também precisam conhecer as regras tácitas de *turn-taking*, estratégias linguísticas para participar e lidar com conversas de barra lateral, sugestões verbais e não verbais, e marcadores de polidez adequados. Carga horária: 72 horas.

2. Accent Reduction Intermediate

Miami Dade College, Miami – Flórida – Período 03/07/17 a 24/08/17

Os estudantes melhoram a pronúncia do inglês americano, incluindo o estresse, o ritmo e a entonação. A estrutura fonética dos sons das vogais é sistematicamente analisada, e os alunos são treinados na pronúncia correta destes sons e padrões em contexto. Carga horária: 72 horas.

Anexo A – Parecer Consubstanciado do Comitê de Ética em Pesquisa da Faculdade de Ciências da Saúde da Universidade de Brasília – CEP/FS-UnB



FACULDADE DE CIÊNCIAS DA SAÚDE DA UNIVERSIDADE DE BRASÍLIA - CEP/FS-UNB



PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Avaliação Ambulatorial da Pressão Parcial do Dióxido de Carbono Expirado (PETCO₂) e desenvolvimento de Software de predição clínica em indivíduos para pacientes com Insuficiência Cardíaca.

Pesquisador: Alexandra Corrêa Gervazoni Balbuena de Lima **Área Temática:Versão:** 2CAAE: 50414115.4.0000.0030

Instituição Proponente: PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS E TECNOLOGIAS EM **Patrocinador Principal:** Financiamento Próprio

DADOS DO PARECER Número do Parecer: 1.385.215

Apresentação do Projeto:

A insuficiência cardíaca (IC) e a via final comum da maioria das doenças que acometem o coração, sendo um dos mais importantes desafios clínicos atuais na área da saúde. Trata-se de um problema epidêmico em progressão. Embora sua terapêutica tenha evoluído substancialmente nos últimos vinte anos, o prognóstico da doença ainda pode ser considerado desfavorável. No Brasil, segundo o DATASUS, do Ministério da Saúde, pode-se estimar que cerca de 6,4 milhões de brasileiros sofram de IC. A taxa de mortalidade anual média dos pacientes internados no Sistema Único de Saúde (SUS) e de 6% a 7% para pacientes em estágio inicial (Classe Funcional I NYHA), e de 30% a 40% para aqueles estágio final (Classe Funcional IV NYHA), adequadamente tratados. Com isso, os custos de tratamento são crescentes, caracterizando a IC como um importante problema de saúde pública mundial.

Dentre as variáveis mais importantes para avaliação e monitoramento destes pacientes,

destacam-se a fração de ejeção do ventrículo esquerdo (FE, %) 5 avaliada por meio da ecografia, inclinação da relação ventilação e produção de gás carbônico (VE/VCO₂ Slope) e Consumo Máximo de Oxigênio (VO₂, mL O₂.Kg⁻¹.min⁻¹) avaliados por meio do teste cardiopulmonar e dentre os biomarcadores de prognóstico o peptídeo natriurético cerebral (BNP). Estas medidas têm diferentes níveis de acurácia prognóstica e nenhuma é considerada padrão-ouro universal.

Quanto ao débito cardíaco para os tecidos, sabe-se que o metabolismo oxidativo é o principal meio pelo qual o organismo humano gera energia para realizar trabalho e, assim, efetuar suas atividades. Desta forma, o estudo da cinética de O₂ envolve os possíveis mecanismos fisiológicos da resposta dinâmica do consumo de oxigênio ao exercício e sua recuperação subsequente. Fatores como VO₂ máximo, VO₂ necessário para realização de exercício submáximo, e a taxa em que ele aumenta na transição para um exercício de maior exigência metabólica, até atingir um platô em seu valor máximo, influenciam na tolerância a atividade física de um indivíduo. Medidas da cinética do VO₂ têm sido uma importante ferramenta para avaliar as disfunções e o mecanismo em que as disfunções ocorrem, em diferentes doenças crônicas. A cinética do consumo de oxigênio durante o exercício de carga constante em diferentes intensidades permite caracterizar os domínios moderado, pesado e severo do exercício. Em exercício de intensidade constante, o perfil da resposta do VO₂, analisada por ajustes exponenciais, apresenta as fases cardiodinâmica, fundamental e lenta. A ocorrência do componente lento (CL) tem sido associada a fatores como recrutamento de fibras do tipo II e acúmulo de metabolitos, como lactato, íons H⁺, fosfato inorgânico e ADP. O CL expressa uma redução da eficiência muscular e tem sido associado a menor tolerância às atividades de vida diária. Complementando a avaliação cardiorrespiratória, a avaliação da extração de oxigênio nos músculos periféricos auxilia no melhor entendimento da influência do comportamento metabólico na limitação da capacidade cardiorrespiratória. A espectroscopia por infravermelho (Near InfraRed Spectrophotometry - NIRS) é uma técnica não invasiva que avalia o monitoramento da saturação de oxigênio nos tecidos através da detecção de mudanças na absorção de tecidos de dois comprimentos de onda (850 e 760 nm), refletindo a oxigenação relativa de hemoglobina e mioglobina. As mudanças na saturação de oxigênio do músculo esquelético durante um exercício incremental detectado pelo NIRS refletem uma redução na oferta de oxigênio e início precoce do metabolismo anaeróbico em pacientes com IC crônica (ICC). Os pacientes com ICC sistólica apresentam uma desoxigenação muscular mais precoce, tanto em musculatura periférica quanto musculatura respiratória, em comparação com indivíduos sedentários saudáveis, indicando um início precoce do metabolismo anaeróbico.

Na avaliação cardiorrespiratória, o VO₂ pico é severamente reduzido em pacientes com IC e a resposta ventilatória ao exercício tem se demonstrado o melhor marcador prognóstico nesta população. Dessa forma, a maioria das pesquisas de valor prognóstico nos pacientes com IC tem sido direcionada para medidas obtidas durante o exercício. Com a exceção de uma quantidade limitada de pesquisas, a avaliação prognóstica de variáveis ventilatórias em repouso é limitada. A partir dessas investigações, a PetCO₂ em repouso surgiu como uma medida que pode ser de particular valor prognóstico em pacientes com IC. A maioria dos dados que demonstram a ligação entre a função cardíaca e a PetCO₂ em repouso, dão suporte para a sua utilização rotineira em pacientes com IC, além da literatura anestésica e intensivista. A eliminação de dióxido de carbono, e, por conseguinte, a PetCO₂, diminui, quando o fluxo de sangue para os pulmões é reduzido. Várias investigações demonstraram uma relação

significativa entre a PetCO₂ em repouso e débito cardíaco em um grupo de pacientes submetidos a correção de aneurisma da aorta abdominal. Shibutani et al encontraram que a PetCO₂ em repouso foi significativamente correlacionada com alterações no débito cardíaco durante a cirurgia ($r^2 = 0,82$, $p < 0,01$). Wahba et al encontraram que a PetCO₂ em repouso, tomadas antes e após a cirurgia cardíaca eletiva, foi efetivamente capaz de detectar alterações no índice cardíaco ($r = 0,75$, $p < 0,001$). Em um modelo intubado / sedado, resultados de Idris et al sugerem que a PetCO₂ em repouso é capaz de refletir com precisão o débito cardíaco em uma ampla faixa de taxas de fluxo, incluindo as taxas de fluxo muito baixas. Em 23 indivíduos estavam em parada cardíaca, Garnett et al relataram um aumento imediato e significativo na PetCO₂ em repouso nos 10 indivíduos que tiveram um retorno da circulação espontânea. Asplin et al encontraram valores na PetCO₂ em repouso iniciais mais elevados foram capazes de prever o retorno a circulação espontânea em 27 pacientes que sofrem parada cardíaca. Por fim, em um grupo de 100 pacientes submetidos a cirurgia em estado crítico, Domsy et al relataram uma taxa de mortalidade de 55% em pacientes com um PETCO₂ em repouso menor ou igual a 28 mmHg. Este é comparado com uma taxa de mortalidade de 17% para aqueles pacientes com uma PetCO₂ em repouso maior que 28 mmHg.

A especificidade das variáveis de prognóstico dos indivíduos com IC permanece com várias lacunas na sua compreensão, e isso é um determinante para a condução do tratamento e para decisão do prognóstico clínico. Reconhecendo que a redução da capacidade funcional, demonstrada pelo VO₂ reduzido, esta associada com uma marcante intolerância ao exercício, até o momento, não há análise prospectiva do valor prognóstico da PetCO₂ em repouso em pacientes com diagnóstico de IC compensada. A PetCO₂ em repouso pode ser facilmente medida, tanto no ambiente hospitalar e ambulatorial, praticamente sem risco para o paciente, fazendo a sua investigação particularmente custo-efetiva. Nosso objetivo será avaliar o padrão de comportamento da variável PetCO₂ em repouso e a comparação desta variável com outros métodos de predição clínica da capacidade cardiorrespiratória e cardiovascular bem como o desenvolvimento de um software capaz de otimizar com eficácia a predição de diagnóstico de IC compensada.

Objetivo da Pesquisa:

Objetivo Principal

Avaliar o padrão de comportamento da variável PetCO₂ em repouso, e comparar com outros métodos padrão-ouro de avaliação da capacidade cardiorrespiratória e cardiovascular. Objetivos Secundários 1) Determinar o valor prognóstico do PetCO₂, obtida durante o repouso; 2) Desenvolver um software multi-paramétrico de predição clínica em indivíduos com diagnóstico de IC compensada.

Avaliação dos Riscos e Benefícios:

Os riscos relativos a pesquisa estão associados com a realização das intervenções que serão realizadas: 1) Eletrocardiograma - exame não invasivo, de baixo risco, onde o gel e a colocação das pernas para a realização do exame pode causar desconforto e discreto hematoma na pele do paciente. Para minimizar esse incômodo, os pacientes serão esclarecidos sobre o procedimento e será utilizado gel condutor específico para o procedimento. 2) Teste

cardiopulmonar de exercício com carga incremental e carga constante - exame não invasiva, onde será realizado um teste de esforço máximo, em bicicleta, com uma máscara para coleta de gases, com o paciente monitorizado com eletrocardiograma de 12 derivações e da pressão arterial com aparelho de pressão arterial aneróide. Para minimizar os riscos envolvidos com o teste de esforço cardiopulmonar, o indivíduo será orientado sobre o exame que será realizado; o exame será realizado por médico cardiologista habilitado e experiente, em ambiente com temperatura e imunidade adequadas, com equipamento completo para realizar as manobras de reanimação cardiorrespiratória e cerebral (desfibrilador externo automático, medicamentos, bala de oxigênio) e transporte por ambulância do Campus da FCE ou do SAMU para emergência do Hospital Regional da Ceilândia; a máscara será adaptada conforme o tamanho do rosto do paciente da maneira mais confortável possível; serão utilizados eletrodos descartáveis e hipoalérgicos; o manguito do aparelho de pressão será ajustado conforme circunferência do braço do paciente; o exame será realizado em cicloergômetro sendo excluído o risco de queda em caso de mal-estar ou fadiga extrema, já que o paciente se encontra sentado e o exame é interrompido quando o paciente para de pedalar. A interrupção do exame será realizada conforme as orientações da Diretriz de Teste Ergométrico da Sociedade Brasileira de Cardiologia. 3) Ecocardiograma - exame não invasivo para avaliação por meio de ultrassom do coração. Para reduzir o risco envolvido ao procedimento, o indivíduo será orientado quanto o procedimento a ser realizado, o procedimento será realizado por profissional experiente e habilitado para o mesmo, gel condutor adequado será utilizado para o exame.

4) Espirometria - exame que avalia a função pulmonar. Para minimizar os riscos, o indivíduo será orientado quanto ao procedimento, o exame será realizado por profissional experiente, com material descartável, exame realizado segundo as normativas da Sociedade Americana Cirurgia Torácica (ATS).

5) Manuvacuometria - exame que avalia a força muscular respiratória. Para minimizar os riscos, o indivíduo será orientado quanto o procedimento, o exame será realizado por profissional experiente, o material será esterilizado após cada avaliação, exame realizado segundo as normativas da ATS.

6) Coleta do PetCO₂ em repouso através de capnografia - coleta do PetCO₂ em repouso. Para minimizar os riscos relativos ao procedimento será utilizado cateter individualizado e descartável para cada indivíduo e cada coleta.

7) Coleta de sangue para dosagem do BNP. Os riscos relativos a coleta de sangue são o desconforto associado a punção sanguínea, hematoma no local de punção sanguínea. Para minimizar os riscos as coletas serão realizadas por profissional da FCE experiente em coleta de sanguínea com material descartável.

8) Avaliação do metabolismo oxidativo muscular pelo método NIRS - o aparelho de NIRS avalia por meio de luz infravermelha a presença de Hg oxidada x não oxidada no músculo avaliado, refletindo a chegada e liberação de oxigênio no músculo. A avaliação é indolor, não-invasiva, podendo gerar leve desconforto relacionado a colocação do aparelho.

Comentários e Considerações sobre a Pesquisa:

A presente pesquisa é referente ao projeto de Doutorado em Ciências e Tecnologias em Saúde da Faculdade de Ceilândia da Universidade de Brasília da pesquisadora Alexandra Correa Gervazoni Balbuena de Lima sob a orientação do professor Dr. Gerson Cipriano Jr. Trata-se de uma pesquisa qualitativa que tem como objetivo avaliar o padrão de comportamento da variável PetCO₂ em repouso, e comparar com outros métodos padrão-ouro de avaliação da capacidade cardiorrespiratória e cardiovascular.

Para isso, a equipe de pesquisa irá recrutar os participantes por meio da indicação de médicos cardiologistas e folhetos publicados nos ambulatórios de IC da região do Distrito Federal e Entorno. Todos os exames serão realizados na Universidade de Brasília (UnB), no campus da Ceilândia, no Laboratório de Biofísica e Fisiologia.

O projeto e o TCLE estão redigidos de maneira clara, permitindo a avaliação ética por parte deste CEP. A pesquisadora faz uma avaliação de risco e benefício seguindo as normas da Resolução CNS/MS 466/2012. Na avaliação de risco do Teste cardiopulmonar de exercício com carga incremental e carga constante, a possibilidade de necessitar de uma reanimação cardiorrespiratória e cerebral (com desfibrilador externo automático, medicamentos, bala de oxigênio) e transporte por ambulância do Campus da FCE ou do SAMU para emergência do Hospital Regional da Ceilândia. Como a população em questão já é considerada uma população de alto risco, a realização desse tipo de exame fora do ambiente hospitalar já é considerado de risco. É necessário que os pesquisadores considerem a realização desses procedimentos em ambiente hospitalar ou mesmo que haja garantia da presença de transporte imediato em situação de emergência.

Considerações sobre os Termos de apresentação obrigatória:

Documentos analisados para emissão do presente parecer: 1- Informações Básicas do Projeto: "PB_INFORMACOES_BASICAS_DO_PROJETO_549953.pdf", postado em 18/12/2015; 2- Carta resposta ao CEP: Carta_Resposta_ao_CEP.pdf, postado em 18/12/2015.

Recomendações:

Não se aplica.

Conclusões ou Pendências e Lista de Inadequações:

A pesquisadora faz uma avaliação de risco e benefício seguindo as normas da Resolução CNS/MS 466/2012. Na avaliação de risco do "Teste cardiopulmonar de exercício com carga incremental e carga constante", há possibilidade de necessitar de uma reanimação cardiorrespiratória e cerebral (com desfibrilador externo automático, medicamentos, bala de oxigênio) e transporte por ambulância do Campus da FCE ou do SAMU para emergência do Hospital Regional da Ceilândia. Como a população em questão já é considerada uma população de alto risco, a realização desse tipo de exame fora do ambiente hospitalar já é considerado de risco. É necessário que os pesquisadores considerem a realização desses procedimentos em ambiente hospitalar ou mesmo que haja garantia da presença de transporte imediato em situação de emergência. Solicitam-se esclarecimentos e/ou adequação. Documentação pertinente devesse ser anexada, se for o caso. PENDÊNCIA ATENDIDA. A pesquisadora responsável garantiu a presença de todo equipamento necessário para o

atendimento imediato do paciente no laboratório de pesquisa e garantiu que a FCE dispõe de uma ambulância para o transporte dos pacientes, caso seja necessário. Dessa forma não existem óbices éticos.

Considerações Finais a critério do CEP:

De acordo com a Resolução 466/12 CNS, itens X.1.- 3.b. e XI.2.d, os pesquisadores responsáveis deverão apresentar relatórios parcial semestral e final do projeto de pesquisa, contados a partir da data de aprovação do protocolo de pesquisa.

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

BRASILIA, 07 de Janeiro de 2016

Assinado por:

Keila Elizabeth Fontana (Coordenador)

Anexo B – Normas de publicação do periódico, Qualis na área Interdisciplinar referente ao Estudo 1 - “Spontaneously Breathing Capnography in Chronic Heart Failure Patients: Reliability, Agreement and Validity Study of Partial Pressure of End-tidal Carbon Dioxide.”



INTERNATIONAL JOURNAL OF CARDIOLOGY

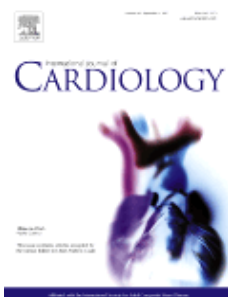
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AUTHOR INFORMATION PACK

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Prof. Paolo Camici has now become new Editor-in-Chief of this journal (click [here](#) for more information). **Manuscripts submitted before 5 September will be finalized by Prof. Andrew Coats, former Editor-in-Chief.**

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Cardiologists, cardiac surgeons, pediatric cardiologists, researchers in cardiovascular diseases.

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2016: 6.189 © Thomson Reuters Journal Citation Reports 2017

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GUIDE FOR AUTHORS

Introduction

The International Journal of Cardiology is a global journal of cardiology, cardio-metabolic and vascular sciences. Articles reporting clinical observations and interventions, experimental studies and theoretical concepts are all welcome provided they are of major scientific importance and clinical relevance. The journal covers all aspects of cardiology from genes to populations. The journal commissions high quality review articles from distinguished authors. Submission of a manuscript to this journal gives the publisher the right to publish that paper if it is accepted. Manuscripts may be edited to improve clarity and expression

ANNOUNCEMENT

Professor Paolo G. Camici, MD, FESC, FACC, FAHA, FRCP has taken over from Professor Andrew J.S. Coats (Joint Academic Vice-President, Monash University, Australia AND University of Warwick, United Kingdom) as Editor-in-Chief of the International Journal of Cardiology in September 2016. Having worked for many years in prestigious Universities and hospitals both in the UK and Italy, with a wealth of experience as Consultant, Clinician Scientist, Program Director, Lecturer, Examiner, Society Fellow, Working Group Chairman and member of multiple Editorial Boards, Professor Camici's current position is Professor of Cardiology and Consultant Cardiologist at the Vita-Salute University San Raffaele, in Milan, Italy. He is also Director of the University's Cardiology Training program.

Professor Camici has appointed a prestigious new Editorial Board consisting of five Deputy Editors (Prof. Domenico Cianflone, Prof. Perry Elliott, Prof. Juan Carlos Kaski, Prof. Peter J. Schwartz and Dr. Ornella Rimoldi). The goal of this new team is to create a unique forum for international investigators that can offer an exciting alternative to the main Journals of the European and American Cardiology Societies. In addition to original papers, we are launching a range of new manuscript types, including Consensus and Position Papers, Systematic Reviews and Meta-analyses, and Brief Reports.

INTRODUCTION

The International Journal of Cardiology is a global journal of cardiology that welcomes the following types of articles:

Original articles Text in these articles should not exceed **3,500** words, **50** references and **4** tables/figures. Additional

references and/or methods will be published online only.

This category includes the following types of articles:

Original clinical research studies, basic science/translational research papers:

International Journal of Cardiology publishes articles highlighting all aspects of cardiovascular disease, including original clinical studies in the fields of clinical investigation, pharmacotherapy, genetics,

cardiovascular imaging, intervention, structural heart disease, etc.- clinical trials, meta-analyses, pathophysiological investigations, experimental studies with clinical relevance and state-of-the-art papers. Cardiovascular basic science research studies with a strong clinical translational component will be considered for publication. Basic science papers usually depict research carried out in experimental animals, cells, or tissue. The abstract section of these papers should include a paragraph or two (**50-75** words) describing the translational aspect of the work.

Consensus and Position Papers _____

Usually produced by recognized institutions or working groups these articles provide expert opinion on topical issues in cardiovascular medicine and related disciplines which are of high interest and potential value for the practicing cardiologist as well as regulatory agencies, national and international societies and Society in general. These articles generally deal with issues that are not specifically covered by current international guidelines and therefore constitute unmet needs.

Systematic reviews and meta-analyses

These manuscripts are systematic assessments of the evidence available in the medical literature regarding specific issues, including pathophysiological mechanisms, diagnosis, prognosis, disease treatment, preventative management, etc. An established methodology exists for the production of these articles. For advice on systematic review preparation consult the Cochrane Reviewers' Handbook.

Short communication

Short communication should contain original data as per the description given under "original articles" but their length should not exceed **1,500** words; **20** references; **2** figures/tables. Case reports are not acceptable under this category. This manuscript category may include clinical studies/high quality observational work - either clinical or experimental - reflecting novel preliminary findings or results of studies that can be summarised in under 1500 words. These articles may be hypothesis generating and/or able to stimulate research in a specific area. A structured abstract (around 200 words) is required and the article should be structured in the same fashion as original papers. Illustrative figures are welcome.

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Editorial articles are commissioned by the Editor-in-Chief and aim to provide brief expert views on specific manuscripts published in a given IJC issue. These articles should contain a max. of **1,000** words; **10** references; **1** figure/table

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PREPARATION OF MANUSCRIPTS: Original articles and Short communication should be structured as following:

Divide the manuscript into the following sections: Title page, Structured Abstract, Key words (3-6), Introduction, Methods, Results, Discussion, Acknowledgments, References. The editors will consider the

use of other sections if more suitable for certain manuscripts. Type double-spaced. The Title Page should include: 1. The title (not to exceed 25 words) 2. The full list of authors and for each author a numbered footnote. The footnote should state the author's academic affiliation and the following statement of authorship: "This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation". Any author unable to make this statement must instead state their specific contribution to the manuscript. 3. Corresponding author and contact details 4. Acknowledgement of grant support 5. Any potential conflicts of interest, including related consultancies, shareholdings and funding grants 6. A list of up to 6 keywords The Next Page Should Include:

A Structured Abstract, of no more than 250 words. As this may be the only part of the article read by some readers it must include sufficient detail for an adequate summary of the whole manuscript. The preferred subheadings are Background, Methods, Results and Conclusions, although a merged Methods and Results subheading is also permitted if this permits more economical expression. The Next Page should commence the main article subdivided into the following sections:

The Introduction should be brief and set out why the study has been performed along with a review of relevant previous work only where essential.

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Área de Avaliação:

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ISSN:

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Título:

 INTERNATIONAL JOURNAL OF CARDIOLOGY (PRINT)

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0167-5273	INTERNATIONAL JOURNAL OF CARDIOLOGY (PRINT)	MEDICINA I	A1

Anexo C – Normas de publicação do periódico, Qualis na área Interdisciplinar e comprovante de submissão do manuscrito referente ao Estudo 2 - “Non-invasive Resting Capnography in Chronic Heart Failure Patients: End-tidal Carbon Dioxide as a new prognostic factor on Heart Failure.”

EUROPEAN JOURNAL OF HEART FAILURE

Author Guidelines

REQUIRED FORMS

European Journal of Heart Failure requests that all authors complete: [An ICMJE Conflicts of Interest disclosure form. An Author Contribution form](#)

INTRODUCTION

Thank you for your interest in *European Journal of Heart Failure*. Please consult the following instructions for help in preparing your manuscript, and feel free to contact us with any questions. To ensure fast peer review and publication, manuscripts that do not adhere to the following instructions will be returned to the corresponding author for technical revision before undergoing peer review. We look forward to your submission.

AIMS AND SCOPE

The *European Journal of Heart Failure* is the international journal of the Heart Failure Association of the European Society of Cardiology dedicated to the advancement of knowledge in the field of heart failure. The journal publishes reviews and editorials in order to improve the understanding, prevention, investigation and treatment of heart failure. Molecular and cellular biology, pathology, physiology, electrophysiology, pharmacology, as well as the clinical, social and population sciences all form part of the discipline that is heart failure. Accordingly, submission of manuscripts on basic, clinical and population sciences is invited. Original contributions on nursing, care of the elderly, primary care, health economics and other specialist fields related to heart failure are also welcome.

HEART NETWORK

The *European Journal of Heart Failure* participates in the HEART Network which is a network of Editors from most cardiovascular journals. Information is exchanged between Editors on a regular basis. The network has recently approved a common ethics standard.

Its purpose is to ensure transparency and honesty in the scientific process that promotes ethical conduct in performance and publication of research.

The following will be considered as parts of this process:

- a. Disclosure of potential conflicts of interest for all involved in the performance of research and in the evaluation and publication process of a manuscript. Relevant relationships with commercial interests should be disclosed according to the guidelines of the journal's sponsoring society, or, when no such guidelines exist, according to those of the AHA, ACC, or ESC.
- b. Establish thorough review processes particularly alert to discovering scientific fraud and data falsification, redundant or duplicate publication, and plagiarism, and to adopt a uniform standard of dealing with authors guilty of fraudulent practices.

- c. To maintain confidentiality and embargos where appropriate.
- d. To create uniform criteria to establish authorship. To qualify for authorship, individuals must have made substantial contributions to the intellectual content of the paper in at least one of the following areas: conceived and designed the research, acquired the data, analysed and interpreted the data, performed statistical analysis, handled funding and supervision, drafted the manuscript, or made critical revision of the manuscript for important intellectual content. Authors must give final approval of the version to be submitted and any revised version to be published. For multi-centre trials, individuals who accept direct responsibility for the manuscript should fully meet the criteria for authorship defined above and contributors not meeting these criteria should be acknowledged.
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- g. Noting compliance with institutional review board requirements and, when appropriate, approved laboratory procedures for animal research, and that the research conforms to the ethical standards of the *Declaration of Helsinki*, the *Geneva Declaration*, the *Belmont Report*, and *Good Clinical Practices* from the FDA, and the submission conforms to the *International Committee of Medical Journal Editors (ICMJE): Uniform Requirements for Manuscripts Submitted to Biomedical Journals: writing and editing for biomedical publication* (*Haematologica* 2005; **89**:264).

PRE-SUBMISSION

1. Editorial Review and Acceptance

The acceptance criteria for all papers are the quality and originality of the research and its significance to our readership. Except where otherwise stated, manuscripts are double-blind peer reviewed by two anonymous reviewers and the Editor. Final acceptance or rejection rests with the Editorial Board, who reserves the right to refuse any material for publication.

Manuscripts should be in a clear, concise and direct style. Where contributions are judged as acceptable for publication on the basis of content, the Editor and the Publisher reserve the right to modify typescripts to eliminate ambiguity and repetition and improve communication between author and reader. If extensive alterations are required, the manuscript will be returned to the author for revision.

2. Pre-submission Resources

2.1. Author Services

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2.2. Pre-submission English-language Editing

Authors for whom English is a second language are advised to consider having their manuscript professionally edited before submission to improve the English, and to ensure the paper is clearly written in standard, scientific English language appropriate to the discipline. This can be undertaken by a service such as the Wiley English Language Editing Service, at <http://wileyeditingservices.com>. Please note that using the Wiley English Language Editing Service does not guarantee that your paper will be accepted by this journal, and all services are paid for and arranged by the author.

3. Manuscript Preparation

3.1. Manuscript Categories and Criteria

The *European Journal of Heart Failure* accepts the following categories of articles:

Research Articles

These should not exceed 3500 words (excluding references, tables and figures) and may include up to a maximum of 6 figures and/or tables and up to 30 references. Research articles should be divided into the following sections: (1) Title page, (2) Abstract and up to six Keywords, (3) Introduction, (4) Methods, (5) Results, (6) Discussion, (7) Acknowledgements, (8) Funding, (9) Conflict of interest, (10) References, (11) Figure legends, (12) Appendices, (13) Tables, (14) Figures. The Abstract should be divided into the following sections 'Aims', 'Methods and results' and 'Conclusion'; it should not exceed 250 words.

Reviews(1)

The *European Journal of Heart Failure* publishes a limited number of scholarly, comprehensive review papers. Reviews should not exceed 3500 words. They should summarise and critically evaluate research in the subject area, and should discuss implications for the future. Reviews have unstructured abstracts with no headings, which should not exceed 250 words and may include up to 45–50 references. Please see below for systematic reviews.

Systematic Reviews

These reviews should follow the format of research articles (refer to the section, 'Research Articles'). These should be submitted as a research article during the submission process.

Editorials

All editorials should be limited to 1500 words (excluding references), with a maximum of 15 references. They do not require an abstract and may include one table and/or one figure. In particular, the addition of one figure would be welcome and could add to the understanding and attractiveness of the article. The following different categories of editorials may be considered:

- **Editorial comment.** Written upon invitation by the Editor, it is a comment to a research article and should discuss its results, compare them with the current literature and give a personal interpretation of the study.
- **Viewpoint.** This is a commentary on a topical item. It may be invited or not. When we receive more viewpoints regarding a similar topic they may be gathered under the category of "Different viewpoints" in the index page. However, their labelling will remain "viewpoint" in the title page so that they may be considered alone.
- **Opinion Piece.** This has to be written by one single author and have possibly controversial content and opinions.
- **In the News.** This is a single author comment on recent event or trial.
- **From opinion to evidence.** This is an expert opinion and can be written by multiple authors. It must be based on facts and be evidence based. Differently from the other categories of editorials, it may reach 2000 words and 30 references.

Short Reports

These reports should not exceed 1500 words and should comprise a Background section (≈100 words), Aims (≈50 words), Methods (≈300 words), Results (300 words) and Conclusion (250 words). The editorial team reserves the right to decide which of the tables/figures submitted are necessary. A structured abstract not exceeding 250 words is also required for Internet purposes.

Letters to the Editor

Letters to the Editor may regard comments to an article published in our journal in the previous months. These letters should have a maximum of 3 authors, should not exceed 400 words and have a maximum of 5 references, including one reference to the article that they are about. We may ask for a reply to the authors of the original article and the letter and its reply be published together.

Research Letters

Letters based on original research findings are also allowed. The letter may include up to 1000 words, including a maximum of 8 references, and one figure and/or Table. Research letters should have no abstract and no sub-headings. However, a short description of methods, results and conclusions is required.

Case Reports

These reports should not exceed 1200 words. Case reports should include an unstructured Abstract with no subheadings (not exceeding 100 words), an Introduction, a Description of the case(s) under the heading, 'Case Report' and a Discussion of the findings in the context of current practice.

Study Design

These should not exceed 3500 words (excluding references, tables, and figures) and may include up to a maximum of 6 figures and/or tables and up to 30 references. Study design papers should be divided into the following sections: (1) Title page, (2) Abstract and up to six Keywords, (3) Introduction, (4) Study Design, (5) Discussion, (6) Acknowledgements, (7) Funding, (8) Conflict of Interest, (9) References, (10) Figure legends, (11) Appendices, (12) Tables, (13) Figures. The Abstract should be divided into the following sections 'Aims', 'Methods', and 'Conclusion'; it should not exceed 250 words.

Book Reviews

Book reviews may include up to 800 words, including a maximum of 3 references. They should have no abstract and no sub-headings.

3.2. Manuscript Format and Structure**General Format**

Prepare your manuscript text using a Word processing package (save in .doc or .rtf format). Submissions of text in the form of PDF files are not permitted. Manuscripts should be double-spaced, including text, tables, legends and references.

Number each page. Please avoid footnotes; use instead, and as sparingly as possible, notes within brackets. Enter text in the style and order of the journal. Type references in the correct order and style of the journal. Type unjustified, without hyphenation, except for compound words (where two words are joined to form a new word e.g. end-systolic, non-infarcted). Type headings in the style of the journal. Use the TAB key once for paragraph indents. Where possible use Times New Roman for the text font and Symbol for Greek and special characters. Use the word processing formatting features to indicate bold, italic, Greek, maths, superscript and subscript characters. Clearly identify unusual symbols and Greek letters. Differentiate between the letter O and zero; the letters l and I; and the number 1.

Check the final copy of your paper carefully, as any spelling mistakes and errors may be translated into the typeset version.

Style and Spelling

Oxford English spelling should be used. Authors whose first language is not English are requested to have their manuscripts checked carefully before submission. This will help expedite the review process and avoid confusion.

Abbreviations

Abbreviations of standard SI units of measurement only should be used.

Ethics

Declaration of Helsinki: The authors should state their study complies with the *Declaration of Helsinki*, that the locally appointed ethics committee has approved the research protocol and that informed consent has been obtained from the subjects (or their guardians).

ARRIVE Guidelines: The contribution of animal research in enabling better health for man and animals is incontrovertible and *EJHF* is committed to the publication of research studies which use animal models, but demands the same rigorous attention to detail as in clinical trials. Failure to describe research methods and to report results appropriately has scientific and ethical implications for the entire research process and the reputation of those involved in it.

Experiments involving animals should be appropriately designed, correctly analysed and then transparently reported, to both increase the validity of the results, and maximise the scientific gain. A minimum amount of relevant information must be included in manuscripts published in this journal to ensure that the methods and results of a study can be reviewed, analysed and repeated. *EJHF* will therefore refer to the *ARRIVE (Animals in Research: Reporting In Vivo Experiments) Guidelines* as the basis for the process of reviewing manuscripts of research involving animals.

These guidelines were generated by The National Centre for the Replacement, Refinement and Reduction of Animals in Research, which is an independent scientific organisation, established by the UK Government, in consultation with scientists, statisticians, journal editors and research funders.

DNA Sequences and GenBank Accession Number

For each and every gene accession number cited in an article, authors should type the accession number in bold, underlined text. Letters in the accession number should always be capitalised. Example: (GenBank accession nos. **AI631510**, **AI631511**, **AI632198** and **BF223228**), a B-cell tumor from a chronic lymphatic leukemia (GenBank accession no. **BE675048**), and a T-cell lymphoma (GenBank accession no. **AA361117**).

3.3. Parts of the Manuscript

Title Page

The title page should include the following: (1) the title, (2) the name(s) of authors, (3) the institution(s) where work was performed, (4) the position, institution and location of all authors, (5) the telephone number, fax number and e-mail address of the corresponding author, (6) the institutional affiliations of the authors (including corporate appointments) should be acknowledged in a footnote, (7) total words count.

Abstract and Keywords

All abstracts may not contain more than 250 words and should be submitted as a separate file. The abstract should be formatted with the following heading: (1) Aims, (2) Methods and Results, (3) Conclusion.

A maximum of six keywords may be submitted.

Introduction

This section should provide a rationale for conducting the study within the context of previous work by other authors.

Methods

This section should be sufficiently detailed to enable repetition of the study by other investigators. If pertinent, the section may be divided into headed subsections. For animal studies, this section should contain a statement that, "The investigation conforms to the *Guide for the Care and Use of Laboratory Animals* published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1985)". Human studies should contain a statement that, "The investigation conforms with the principles outlined in the *Declaration of Helsinki*" (*Br Med J* 1964; ii: 177). In addition details of the ethics committee approval procedures and a statement that all subjects gave written informed consent to participate in the study should be included.

Results

If pertinent, the section may be divided into headed subsections. For presentation of data, figures are preferred to tables. Data should not be duplicated in both figures and tables. Extensive numerical data should be presented in legends to the figures rather than in the main body of text. SI units should be used throughout.

Discussion

Four manuscript pages should in general be enough to compare and interpret the findings of the study with regard to previous work by (other) authors. This section should also contain 1–4 paragraphs dealing with topics that are beyond the scope of the study. Limitations to the study should also be discussed.

Figures

General information about graphics:

- All figures should be submitted as separate files.
- Supply figures at final size widths: **84 mm** (single column), **176 mm** (double column) or **125 mm** (intermediate), and containing all parts.
- Label parts clearly using capital letters (e.g. A, B, C etc.).
- Use sans serif, Type 1/OpenType/TrueType fonts for labels (preferably Arial), and Times (New) Roman if serif fonts are required.
- Ensure all lettering/lines are clear and that photographic images are neither blurred nor fuzzy.
- Ensure that all figures are clearly labelled and match the sequence in the text.
- Submit either PDF/EPS (line art) or TIFF (halftone/photographs) files only.
- PDF/EPS files should be saved with fonts embedded (and with a TIFF preview if possible).
- Black and white photographic images should be supplied as 'grayscale'.
- Colour images should be supplied as RGB (not CMYK).
- For scanned images, the scanning resolution (at final image size, see above for a guide to sizes) should be as follows to ensure adequate reproduction:
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