TESE DE DOUTORADO

Yôga e o treinamento de técnicas respiratórias em pacientes com insuficiência cardíaca com fração de ejeção preservada: Ensaio Clínico Randomizado

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O que nos dá o direito de supor que sabemos tanto, que nossa narrativa cósmica não está profundamente incompleta? A ciência funciona bem quando busca descobrir o que já existe; porém, não pode determinar com autoridade absoluta aquilo que não existe. A única coisa que podemos afirmar com certeza absoluta é que temos muito a aprender, que encontraremos muitas surpresas pela frente.

- Marcelo Gleiser,

A ilha do Conhecimento

SUMÁRIO

LISTA DE SIGLAS

AHA= American Heart Association

ARA= Antagonistas do Receptor da Angiotensina II

DAC= Doença Arterial Coronariana

Dif a-v O_2 = Diferença arteriovenosa de Oxigênio

ECR= Ensaio Clínico Randomizado

FA = Fibrilação Atrial

FE= Fração de Ejeção

FMR= Fraqueza Muscular Respiratória

FR= Frequência Respiratória

HAS= Hipertensão Arterial Sistêmica

IC = Insuficiência Cardíaca

IC-FEP= Insuficiência Cardíaca com Fração de Ejeção Preservada

IC-FER= Insuficiência Cardíaca com Fração de Ejeção Reduzida

IECA= Inibidores da Enzima de Conversão da Angiotensina

IMC= Índice de Massa Corpórea

MET= Equivalente Metabólico

NOS= Óxido Nítrico Sintase

NT-próBNP= Fragmento \n-Terminal do Peptídeo Natriurético tipo B

PImax= Presssão Inspiratória Máxima

Pthmax= Pressão máxima sustentada por 1 min (teste incremental)

RSA = Arritmia \Sinusal Ventilatória

TCPE = Teste Cardiopulmonar de Esforço

TC6m = Teste de caminhada de 6 minutos

TMR = Treinamento Muscular Respiratório

VFC= Variabilidade da Frequência Cardíaca

VO_{2pico} = Consumo de O_2 de pico

RESUMO

Pacientes com Insuficiência cardíaca com fração de ejeção preservada (IC-FEP) e intolerância aos esforços estão associados a piores prognósticos, podendo apresentar fraqueza muscular inspiratória (FMI), alterações hemodinâmicas e autonômicas, com consequente impacto na qualidade de vida. Portanto, o presente ensaio clínico randomizado (ECR) foi conduzido para testar a hipótese de que um programa de 8 semanas de yôga e técnicas de respiração específicas com diferentes ritmos ventilatórios pudesse estar associados à melhora nas respostas musculares inspiratórias, capacidade funcional, características distintas do sistema nervoso autônomo, peptídeos natriuréticos, medições ecocardiográficas e qualidade de vida em pacientes com IC-FEP, com e sem FMI. Foram randomizados trinta e dois (32) pacientes com diagnóstico prévio de ICFEP, fração de ejeção (FE) ≥50%, disfunção diastólica de grau I-III, classe funcional II-III, idades entre 45-75 anos, ambos os gêneros, advindos dos ambulatórios de IC de dois hospitais, para grupos yôga (Y=11 pacientes) ou treinamento de técnicas respiratórias (TR=11 pacientes) e grupo controle (C=10 pacientes), com tratamento medicamentoso padrão e sem alterações de rotina durante ECR. Os principais resultados foram aumento de força muscular respiratória no grupo yôga e modificações autonômicas no grupo de intervenção com técnicas respiratórias. Não foram encontradas alterações significativas na capacidade funcional e nos parâmetros de função diastólica. Os benefícios encontrados no presente estudo devem ser confirmados em estudos maiores e com avaliação de desfechos clínicos para que se possa considerar a indicação destas intervenções em pacientes com IC-FEP.

ABSTRACT

Patients with heart failure with preserved ejection fraction (HFpEF) have intolerance to efforts and may present inspiratory muscle weakness (IMW), hemodynamic and autonomic changes, consequently impacting quality of life and prognosis. Therefore, this randomized controlled trial (RCT) was conducted to test the hypothesis that an 8-week yoga program and specific breathing techniques with different ventilatory rhythms might be associated with improved inspiratory muscle responses, functional capacity, autonomic nervous system, natriuretic peptides, echocardiographic measurements and quality of life in HFpEF patients , with and without IMW. Thirty-two (32) patients with previous diagnosis of HFpEF, ejection fraction $\geq 50\%$, diastolic dysfunction I-III, functional class II-III, ages 45-75 years, of both genders, from outpatient clinics of two university hospitals were included in the study. Patients were randomized to yoga groups (Y = 11 patients) or respiratory techniques training (RT = 11 patients) and control group (C = 10 patients), with standard drug treatment and no routine changes during the study. The main results included increased respiratory muscle strength in the yogic group and improvement in autonomic parameters in the intervention group with respiratory techniques. There were no significant changes in functional capacity and diastolic function parameters. The benefits found in the present study should be confirmed in larger studies evaluating clinical outcomes so that these interventions might be recommended to HFpEF patients.

I INTRODUÇÃO

A Organização Mundial de Saúde definiu que a insuficiência cardíaca (IC) é uma das prioridades entre as enfermidades crônicas que necessitam de atenção dos setores de saúde em todo o mundo. Apesar dos progressos médicos, a prevalência da doença aumentou nas últimas 5 décadas e, ainda hoje, a mortalidade pode ultrapassar 50% em 5 anos, a partir do momento do seu diagnóstico (1), que quando estabelecido, implica em limitações físicas sucessivas, alterando substancialmente a qualidade de vida dos pacientes que progridem para morbidade e mortalidade significativas.

1.2 Epidemiologia

No Brasil, segundo dados do Ministério da Saúde, em 1995 (Datasus) havia 2 milhões de pacientes com IC e 240 mil novos casos diagnosticados anualmente, sendo a principal causa de internação hospitalar por doença cardiovascular no país (2). Nos EUA e no Brasil, atualmente, cerca de 300 mil indivíduos por ano morrem por causa direta ou indiretamente associada à IC, sendo que em pacientes oligossintomáticos o risco de morte é de 5 a 10%(3).

Dados atualizados da American Heart Association (AHA) estimam prevalência de 5,1 milhões de indivíduos com IC somente nos Estados Unidos, no período de 2007-2012. As projeções mostram que a prevalência da IC aumentará 46% de 2012-2030, resultando em mais de 8 milhões de pessoas acima dos 18 anos de idade com esse diagnóstico. A prevalência em ascensão se deve provavelmente ao aumento da expectativa de vida, uma vez que a IC acomete de forma preponderante faixas etárias mais elevadas(4).

Outros estudos epidemiológicos mostram que a IC com fração de ejeção preservada (IC-FEP) é responsável pela maioria dos casos novos em IC. Embora a IC-FEP já tenha sido vista como uma doença de menor gravidade que a IC com fração de ejeção reduzida (IC-FER), dados atuais mostram sua importância clínica pelo incremento

na mortalidade anual de 5% a 8% (comparado a 10% a 15% da IC-FER)(5). Além disso, outros estudos mais recentes relataram que a proporção de casos incidentes de IC-FEP aumentou de 47,8% em 2000-2003 para 56,9% em 2004-2007 e para 52,3% em 2008-2010(6).

Em outros estudos observacionais com dados de prevalência específicos para idade e gênero, foram relatadas maiores porcentagens de mulheres do que homens em coortes com IC-FEP, descrevendo que o gênero feminino apresenta maior risco no desenvolvimento da doença, conforme aumento de idade, quando comparadas aos homens (Figura 1).
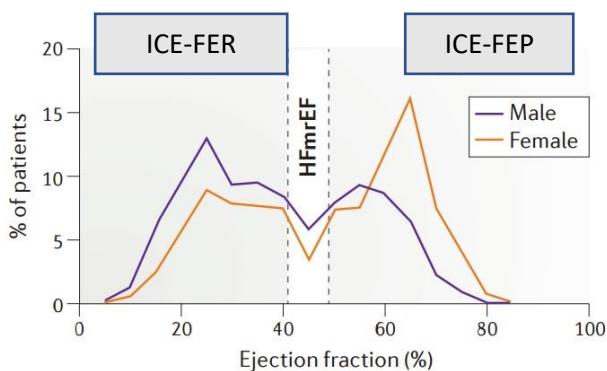
Figura 1- Distribuição da incidência de IC (1.223 pacientes) em homens e mulheres conforme fração de ejeção. (adaptado de Dunlay, S. M. et al, 2012)(7)

1.3 Mecanismos fisiopatológicos na IC

A definição da síndrome de IC em termos clínicos representa a soma de múltiplas alterações mecanísticas, anatômicas, funcionais e biológicas que, em conjunto, interagem de uma forma extremamente complexa sustentada por fatores ambientais e genéticos(8). Na classificação da doença existem fatores diferenciais e terminologias conceituais que incluem insuficiência cardíaca direita ou/e esquerda, de fração reduzida ou/e preservada e de progressão aguda ou crônica(9-11).

A IC resulta inicialmente da disfunção do ventrículo esquerdo como consequência de qualquer doença primária do miocárdio que estimule mecanismos compensatórios à manutenção de funções hemodinâmicas pela perfusão adequada tecidual. Sistemas de compensação pressóricos e de manutenção do débito cardíaco passam por ajustes de resposta ventricular a um aumento de pré-carga e concomitante

ganho na força de contração (mecanismo de Frank- Starling), que resultam, ambos, em hipertrofia do ventrículo com ausência ou presença de dilatação e ativação simpática neuro-hormonal(12, 13). Apesar dos benefícios hemodinâmicos iniciais, a prolongada ativação neuro-humoral está associada à progressão do remodelamento cardíaco e aos piores prognósticos em IC(14). Ademais, a hipervolemia mediará a liberação de peptídeos natriuréticos atriais e ventriculares, induzindo à natriurese e diurese que alteram conteúdos volumétricos intravascular, ventricular e de pré-carga(15).   O rim exerce papel importante pela retenção de água e sódio (Na^+) e redução da filtração glomerular que ocorre na IC como consequência das modificações de PA, das contrações de arteríolas pré- glomérulo em resposta às ativações das vias adrenergéticas e de síntese de angiotensina II(12, 13, 16, 17). Estes mecanismos de ação renal são complexos e respondem tanto pelas características endócrinas e autócrinas deste órgão, como pela redução da pressão de perfusão, podendo causar a retenção hídrica e salina concomitante à diminuição do índice de filtragem e de entrega de Na^+ ao néfron associado à atividade direta da angiotensina II na reabsorção tubular de água e na ativação de hormônio antidiurético (ADH).

Ainda, novos fatores metabólicos, imunológicos e moleculares vêm sendo associados à progressão da doença evidenciando tais interações ao remodelamento cardíaco e à disfunção endotelial. Estudos recentes têm sugerido que alterações miocárdicas estejam diretamente relacionadas às expressões genéticas e às estruturas proteicas contráteis(16, 18).

1.4   Insuficiência Cardíaca com Fração de Ejeção Preservada (IC-FEP):

A IC-FEP, usualmente caracterizada por função sistólica normal (FE ≥50 %) e moderada à severa disfunção diastólica tem apresentado maior prevalência entre as doenças cardiovasculares (DCV). Esta disfunção cardíaca permite ser definida como a incapacidade do ventrículo esquerdo em manter pressões normais de enchimento e pode resultar de anormalidades durante uma ou mais fases da diástole(19). As anormalidades da função diastólica ventricular contribuem para as manifestações clínicas de pacientes com comprometimento da função sistólica. A presença de disfunção diastólica isolada (IC-FEP), sem comprometimento sistólico, apresenta sintomas semelhantes à IC-FER, porém, com algumas peculiaridades.

Outra característica da IC-FFEP é sua associação a diversas comorbidades, incluindo as não cardiovasculares. Pacientes com IC-FEP parecem ter idade mais avançada, apresentam maior índice de fibrilação atrial/ flutter, hipertensão e re-hospitalizações mais prevalentes, quando comparados aos pacientes com IC-FER(20). Recentemente, estudo descreveu condições clínicas favoráveis à apresentação de IC-FEP, como presença de obesidade/sobrepeso, diabetes/ síndrome metabólica, hipertensão arterial sistêmica (HAS), doença arterial coronariana (DAC) e disfunção renal(21)

Existem evidências de que na população com IC-FEP a mortalidade aumenta com a progressão da gravidade da disfunção diastólica, independente da idade, do gênero e da FEVE. Quando comparados à função diastólica normal, pacientes com disfunção leve (déficit de relaxamento – grau 1) aumentaram 8,3 vezes a mortalidade, enquanto aqueles com disfunção de grau moderado (pseudonormal – grau II) comparados à pacientes mais graves (restritivo reversível – grau III; restritivo irreversível – grau IV), apresentaram aumento de risco 10,2 vezes maior(22).

Os mecanismos neuro-humorais como o sistema renina-angiotensina-aldosterona (SRAA), sistema periférico autonômico simpático, vasopressina e endotelina levam ao aumento da vasoconstrição e à retenção de sódio (Na^+) e água, consequente aumento da volemia, podem estar hiperativados em boa parte dos pacientes com IC-FEP. O remodelamento do VE e a disfunção em IC-FEP envolve hipertrofia, destruição de miócitos e fibrose intersticial por fatores patológicos mecânicos, genéticos e neuro-hormonais que alteram proliferação celular, morfologia e homeostase ventricular em uma intrincada rede de sinalizações moleculares. Entre essas vias, a abordagem da interação L-arginina- óxido nítrico parecem interessantes no esclarecimento de mecanismos de inflamações sistêmicas e celulares no remodelamento em IC-FEP(23). Historicamente, a presença de óxido nítrico (NO) configurava efeitos atmosféricos de tempestades eletromagnéticas e produto inerente à poluição automotiva. Atualmente, a realidade do NO aparece como resultado promissor da síntese do aminoácido L-arginina de importante função no organismo de mamíferos, através de família de enzimas que contém agrupamento "heme", as NO sintases(24-26).

1.4.1   Avaliação diagnóstica da IC-FEP:

O diagnóstico da IC leva em conta uma complexa caracterização das desordens retrogradas hemodinâmicas associadas à origem da doença, suas manifestações funcionais, celulares, clínicas e laboratoriais. As principais manifestações que fundamentam o diagnóstico clínico são dispneia combinada à fadiga o que, invariavelmente, limitam a tolerância à esforços, favorece a retenção hídrica e ao aparecimento de edema pulmonar e/ou periférico. A ortopnéia e a tosse noturna, bem como a dispneia paroxística noturna (DPN) podem participar deste processo de falência cardíaca, em quadros de descompensação da IC. Nas classificações diagnósticas das últimas diretrizes da sociedade europeia de cardiologia (ESC), são 3 os tipos de IC conforme a fração de ejeção do ventrículo esquerdo (FEVE), podem adicionar melhorias quanto às peculiaridades patológicas associadas às pressões de enchimento e esvaziamento ventricular e especificidade para o tratamento de cada disfunção. Nesta última diretriz, a inclusão de um novo subgrupo na classificação da FEVE entre 40-49% descrita como insuficiência cardíaca com fração de ejeção limítrofe (IC-FEL), categoriza a "área cinza" com fatores distintos entre classificações de IC-FER (FEVE <40%) e de IC-FEP (FEVE ≥50%).

O ecocardiograma é uma modalidade diagnóstica que empresta informações determinantes à classificação pela FE, morfologia do VE, espessura das paredes cardíacas, avaliação da função valvar, presença de DAC e medidas ecocardiográficas adicionais de pré e pós carga, além de velocidades de enchimento e índices volumétricos (E/e')(27-29).

Uma ferramenta diagnóstica para acompanhamento agudo e crônico em IC é o peptídeo natriurético cerebral (BNP) que pode possibilitar diagnóstico precoce além de prognosticar pacientes durante o tratamento(30) (Figura 2). Ademais, o bnp ou/e NT-proBNP podem auxiliar no diagnóstico diferencial da dispneia secundária às DPOCs, à obesidade e ao déficit de relaxamento comum ao processo natural de envelhecimento(31, 32). Assim, a disfunção diastólica pode estar ausente em alguns casos de IC-FEP e, por outro lado, nem sempre a presença confere tal diagnóstico. Pela prevalência na grande maioria dos casos diagnosticados, o déficit de relaxamento do VE permanece sendo o foco fisiopatológico da síndrome(33).
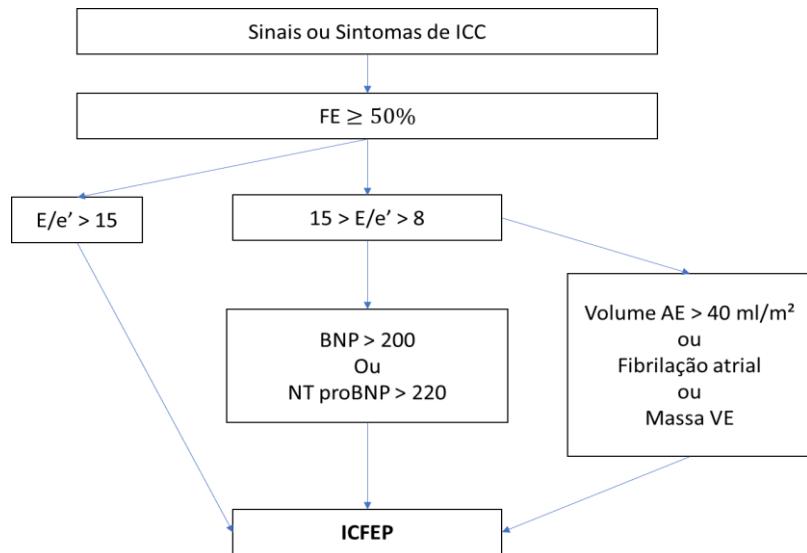
AE, átrio esquerdo; Massa VE index, massa do VE indexada;

Figura 2- Diagnóstico em IC-FEP (Paulus, WJ et al. Eur J Heart Fail 2007).

O teste de esforço com analise de gases ventilatórias (ergoespirometria) avalia tolerância ao esforço, prognóstico e capacidade no consumo máximo ou pico de oxigênio (VO_{2max} ou VO_{2pico}). O teste cardiopulmonar de esforço (TCPE) ou ergometria com análise indireta, permitem verificar e prescrever possibilidades de exercícios estruturados, além de contribuir à decisão de outras terapêuticas a serem adotadas no manejo de pacientes.

1.4.2   Tratamento da IC- FEP

As terapias correntes para IC reúnem estratégias para melhorar a qualidade de vida, aumentar a tolerância ao exercício e reduzir morbidade e mortalidade. Diferentemente do IC-FER, na IC-FEP, ainda não há estudos comprovando classes de medicamentos que interfiram na evolução natural da doença(34).

O tratamento disponível deve ser direcionado ao alívio sintomático e controle de comorbidades, como controle pressórico e glicêmico, diureticoterapia na congestão, controle da frequência cardíaca na presença de fibrilação atrial, perda ponderal e atividade física. No entanto, sabe-se que o controle das principais doenças responsáveis pela disfunção diastólica tem mostrado evolução favorável dessa patologia. Assim, o

tratamento da HAS, diabetes, DAC, prevenção e reversão da hipertrofia cardíaca e atenuação ou prevenção da fibrose miocárdica são metas no tratamento(35, 36).

Outros objetivos são controlar sintomas através da redução da congestão venosa e da frequência cardíaca e, como anteriormente citado, o controle do ritmo também pode ser benéfico em pacientes com fibrilação atrial selecionados. Aliado a estas e outras formas de tratamento, o objetivo comum deve acompanhar a melhora da qualidade de vida e da funcionalidade do indivíduo. Neste contexto, as alterações no fluxo sanguíneo periférico e propriedades musculares esqueléticas intrínsecas, limitantes à contração muscular, podem ser mecanismos funcionais modificáveis pelo exercício físico terapêutico na IC(37). Durante o exercício, o músculo esquelético exige maior fornecimento de oxigênio do que em repouso. Em adultos saudáveis, 85% do fluxo sanguíneo total é direcionado para músculo esquelético envolvido no trabalho contrátil(38).

Nesse contexto terapêutico, torna-se essencial que novas terapias- incluindo exercício físico e tratamentos específicos, sejam avaliadas por seu impacto em desfechos clinicamente importantes como morte e hospitalização em pacientes com insuficiência cardíaca(39)

1.4.3 Capacidade funcional dos pacientes com IC-FEP:

Estudos descrevem que alguns indivíduos com IC apresentam alterações no sistema músculo-esquelético(40) que envolvem funcionalidade e capacidade de deslocamento. A capacidade funcional destes pacientes é normalmente avaliada pelo teste de caminhada de 6 minutos (TC-6), pela ergoespirometria (TCPE) e ergometria, que reforçam a classe funcional e prognóstico destes pacientes pela capacidade de gerar trabalho e, comumente, pelo grau de intolerância ao exercício.

O TC-6 avalia a distância percorrida pelos pacientes no período de seis minutos, sendo que o paciente poderá andar no seu ritmo e, se necessário, parar para descansar. Esse teste também é bom preditor do VO$_2$ máximo e marcador independente de mortalidade cardiovascular.

O TCPE avalia de maneira direta o consumo máximo de oxigênio no pico do esforço (VO$_{2máx}$) e reflete a capacidade funcional aeróbica do paciente correlacionada, diretamente, com a mortalidade cardiovascular. Funcionalmente, VO$_2$ máximo é preditor

de alto risco cardiovascular e indicação de transplante cardíaco (abaixo de 10 -12 ml/kg/min) bem como identifica pacientes com IC de menor risco (acima de 18 ml/kg/min)(41-43). Estes fatores vêm sendo associando os piores prognósticos aos decréscimos na qualidade de vida dos pacientes com IC-FEP(44).

Sujeitos saudáveis em altas cargas de trabalho, demonstraram em estudo que capacidade do coração para fornecer sangue e oxigênio é eventualmente excedido e, simpaticamente, a vasoconstrição mediada pelos efeitos da vasodilatação, preserva o equilíbrio hemodinâmico, mesmo testes máximos e cargas de trabalho com níveis elevados de intensidade(45). Em IC-FER, estudo sobre alterações circulatórias antes e depois de treinamento físico, relatou que a capacidade funcional destes pacientes depende tanto do desempenho cardíaco central, como da perfusão vascular mediada pela utilização periférica de oxigênio(37, 38). Em IC-FEP, alterações hemodinâmicas em subgrupo de estudo pós treinamento aeróbico foram relatadas pelo aumento discreto do débito cardíaco apontando a Dif a-v O_2 como mecanismo principal para melhorias funcionais de pacientes idosos avaliados(46).

1.4.4 Treinamento em pacientes IC-FEP

A incapacidade de gerar trabalho em IC vem sendo também associada, muitas vezes, à insuficiência ventilatória muscular que pode promover alterações de fluxo contínuo no transporte de gases e contribuir à dispneia e fadiga periférica precoce. Outros achados sobre treinamento em modelo animal, evidenciaram que a IC-FEP induz a significativas alterações moleculares, mitocondriais e histológicas no diafragma e soleo que foram atenuadas na presença de exercícios estruturados(47). Neste contexto do exercício em IC, a maioria dos trabalhos que envolvem o treinamento muscular respiratório - normalmente com equipamentos, baseiam-se em evidências no tratamento em pacientes com doença pulmonar obstrutiva crônica (DPOC), insuficiência renal e também na insuficiência cardíaca(40, 48, 49).

A força muscular respiratória é usualmente medida por meio da pressão inspiratória máxima (PI_{max}) e da pressão expiratória máxima (PE_{max}), em cmH_2O(48). Após a realização da medida, se o indivíduo atingir um valor menor do que 70% do previsto para a sua PI_{max}, considera-se que ele apresenta fraqueza muscular inspiratória (FMI), com prevalência marcante em pacientes com IC-FER e IC-FEP(50). Para a

restauração da força em indivíduos com fraqueza muscular inspiratória, o treino muscular inspiratório realizado com equipamentos é utilizado na reabilitação cardiopulmonar.[56] Este treino resulta em um aumento na força e resistência muscular respiratória em geral, no consumo máximo de oxigênio (VO$_2$), capacidade funcional, respostas respiratórias ao exercício e melhora na qualidade de vida(51, 52).

O treinamento muscular inspiratório com técnicas apropriadas às características fisiopatológicas em questão, podem vir a ser aproveitadas para fortalecimento da musculatura ventilatória, mesmo em pacientes que apresentam dispneia importante em repouso (classe IV) ou dispneia frequentemente provocada pelo exercício (classe III)(40).

A avaliação da condição simpático- vagal de pacientes em treinamento físico convencional e em treinamento muscular respiratório, pré e pós exercício, parece somar em resultados crônico-adaptativos às respostas ao treinamento aeróbico conduzido de forma regular. Nesta direção de evidências, devem ser investigadas outras estratégias de treinamento que mobilizem o tratamento secundário de IC-FEP.

1.5. Yôga e IC:

Estudos recentes com terapia de Yôga têm pontuado evidências quanto às questões de restauração da força muscular respiratória(53), consumo máximo de oxigênio(53-55), aptidão física(55), variações autonômicas(56, 57), marcadores inflamatórios(54, 58), controle de stress(59-61) e qualidade de vida(55, 58, 62, 63) em pacientes com Insuficiência Cardíaca(55, 58, 62), na reabilitação cardíaca(64-66), no controle da Pressão Arterial(57, 59, 67, 68), na DPOC(69) e no desempenho físico(54) e respiratório(53).

Na IC, evidências vêm sendo descritas quanto aos benefícios do yôga que, independentes da perda de peso, aumentou a capacidade de exercício em 20% (VO$_{2max}$), Qualidade de vida (QV), marcadores inflamatórios (IL-6, hs- CRP), um precursor do óxido nítrico (EC-SOD), e flexibilidade que foram significativos em população norte-americana, afrodescendentes, após 8 semanas de intervenção, quando comparado com um grupo de pacientes com IC que receberam cuidados médicos padrão(62). Os pacientes

estudados foram, predominantemente, com diagnóstico de IC-FER (19 pacientes: grupo yôga, 1 paciente com IC-FEP; grupo controle: total de 18 e somente 1 com ICFEP).

Em meta análise foi demonstrado que o yôga na reabilitação de pacientes com IC obteve resultados eficazes, com base principal no aumento do VO_{2pico} acima de 10% após programas de intervenções cardiovasculares, representado manejo aliado a um bom prognóstico em pacientes com IC(70). A média do VO_{2pico} em dois estudos analisados foi de 15,85 mL.kg^{-1}.min^{-1} antes da intervenção e de 19,05 mL.kg^{-1}.min^{-1} após intervenções com yôga.

Foi demonstrado que um VO_{2pico} mínimo de 15 mL·kg^{-1}·min^{-1} em mulheres e 18 mL.kg^{-1}.min^{-1} em homens em torno de 85 anos supre as necessidades fisiológicas para uma vida autônoma e independente (e.g. para a realização de atividades diárias com gasto metabólico semelhante à jardinagem e subir e descer escadas)(71, 72). Esta mesma revisão sistemática, indicou melhorias de 24,1% na QV dos grupos com intervenção de yôga. A QV é um resultado clínico importante pelo impacto resultante para o processo de reabilitação. As modificações na QV também estão relacionadas ao bem - estar físico e mental do paciente e podem ser consideradas nas melhorias evidenciadas no desempenho de qualidades físicas e vice-versa.

Além disso, já foi amplamente demonstrado que o yôga promove melhora de distúrbios mentais importantes, tais como ansiedade e depressão, e melhora a capacidade de exercício dos pacientes(73). Nos estudos analisados, a média da QV através do questionário Minnesota: Living with Heart Failure Questionnaire (MLFHQ) foi de 37,5 antes da intervenção e de 28,45 no pós-teste, o que descreve significativo queda de 9 pontos na escala. Arnold e cols. observaram que a diferença mínima clinicamente importante e utilizando o MLFHQ é de 5 pontos. Neste item, a variação foi semelhante ao resultado de uma meta-análise anterior, que incluiu seis ensaios clínicos randomizados envolvendo pacientes com IC submetidos às atividades físicas comuns(74). Os autores consideram que, pelo fato de ser baixa a adesão de pacientes com IC à treinamentos físicos convencionais, a investigação de novas estratégias é importante no contexto de reabilitação cardíaca.

Em estudo recente que avaliou a efetividade, factibilidade e segurança de um programa de 4 semanas de treinamento muscular inspiratório (TMI) de alta intensidade, em pacientes com IC, concluiu que o exercício respiratório foi eficaz na diminuição da fraqueza e na fadiga dos músculos envolvidos, promovendo melhorias na disfunção

ventilatória dos pacientes. Neste contexto, a Fraqueza muscular inspiratória (FMI) foi postulada como fator de prognóstico em IC e, o TMI de alta intensidade, importante na meta terapêutica do tratamento(75).

Na relação com exercícios respiratórios específicos (*pranayàmas*) que comumente são realizados como parte de alguns métodos clássicos de yôga, estudo sobre efeito agudo de sessão (40 min.) de técnica com manipulação nasal (*anuloma pranayàma*) foi realizado em população saudável, intercalando respiração com narina direita (RNYB-com bloqueio nasal esquerdo), respiração com narina esquerda (LNYB-com bloqueio nasal direito), respiração alternada (ANYB- bloqueios nasais alternando narina D/E) e respiração consciente (BAW- sem bloqueio nasal). As avaliações incluíram variabilidade da frequência cardíaca (VFC), condutância da pele, amplitude do pletismograma do dedo, taxa de respiração e pressão sanguínea. Após RNYB houve um aumento significativo na pressão sistólica, diastólica e média. Em contraste, as pressões sistólicas e diastólicas diminuíram após ANYB, enquanto a pressão sistólica e média foram menores após LNYB. Assim, as práticas unilaterais de respiração com manipulação nasal do yôga parecem influenciar a pressão arterial de diferentes maneiras. Estes efeitos sugerem possíveis aplicações terapêuticas destas técnicas ventilatórias do yôga(56).

Em outro estudo sobre técnicas de respiração do yôga muito lenta, informações valiosas foram relatadas sobre mecanismos de regulação do sistema nervoso autônomo que normalmente não estão disponíveis para seres humanos com hábitos respiratórios comuns. Este artigo apresentou resultados de oito sessões de Nadi Shodhana Pranayàma praticadas a uma taxa de uma (1) respiração por minuto. Foram caracterizadas medidas estatísticas e espectrais da variabilidade da frequência cardíaca antes, durante e após os exercícios. Alterações significativas incluíram aumento das VFC na respiração lenta e diminuição nas médias dos intervalos RR (959,3- 904,1 ms). Alterações proeminentes do exercício respiratório lento incluíram aumento significativo da arritmia sinusal respiratória (RSA) e relação de baixa e alta frequência (BF / AF) além da diminuição de frequência respiratória (FR), quando comparado ao estado antes do exercício. A frequência máxima de baixa frequência (BF) diminuiu de 0,0919 Hz para 0,07125 Hz (t (7) = -3,255, p <0,01), indicando a diminuição do ritmo respiratório médio de 5,5 respirações / min para 4,3 respirações / min. Além disso, no estado após o exercício,

desapareceram frequências espectrais de VFC e aumento significativo de BF / AF de 14,33 para 50,93 o que remete à função vagal predominante(76).

II Justificativa e Objetivos do estudo

Uma vez que a IC-FEP tem elevada prevalência e impacto, mas poucas estratégias terapêuticas especificas, faz-se necessário o estudo de intervenções nesta população. Ainda, há escassez de estudos que esclareçam mecanismos para possíveis benefícios do exercício na disfunção diastólica, em especial onde a comparação de diferentes estratégias possa ser realizada. Por outro lado, o yôga vem surgindo como uma opção terapêutica com benefícios comprovados em diversos cenários. Justifica-se, assim, a investigação dos efeitos da terapia do yôga e de técnicas respiratórias específicas no manejo muscular inspiratório e funcional em pacientes com diagnóstico prévio de IC-FEP.

No presente estudo, avaliamos os efeitos das posturas físicas do yôga somado a uma condução respiratória (yôga ativo: posturas acompanhadas da respiração intensa e conduzida clássica do Ashtanga Yôga: *Ujjay*) e somente respiratório (yôga passivo: técnicas respiratórias com menor FR – adaptado da técnica *Anuloma Pranayàma*, sem mobilidade corporal significativa) sobre avaliações de força muscular inspiratória, capacidade funcional, aptidão cardiorrespiratória e variabilidade cardíaca, além da qualidade de vida destes pacientes.

2.1 Objetivos

2.1.1 Geral:

Verificar os efeitos do Yôga e de Técnicas respiratórias na resposta muscular inspiratória em indivíduos com Insuficiência Cardíaca Congestiva com Fração de Ejeção Preservada (IC-FEP).

2.1.2. Específicos:

Associar e avaliar respostas dos treinamentos, Yôga e Técnicas respiratórias, na força muscular inspiratória, resistência muscular respiratória, capacidade funcional, QV, BNP, variáveis ecocardiográficas e características distintas de modulação autonômica em pacientes com IC-FEP.

2.2 Hipóteses:

2.2.1 H_0: Intervenções com yôga e/ou técnicas respiratórias não alteram parâmetros cardioventilatórios, funcionais e QV de pacientes com IC-FEP.

2.2.2 H_1: Intervenções com yôga e/ou técnicas respiratórias alteram parâmetros cardioventilatórios, funcionais e QV de pacientes com IC-FEP.

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ARTIGO I - YÔGA AND BREATHING TECHNIQUES TRAINING IN PATIENTS WITH HEART FAILURE AND PRESERVED EJECTION FRACTION: Study Protocol for a randomized clinical trial**

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Abstract

Background

Current therapies for heart failure (HF) bring together strategies to improve quality of life and exercise tolerance, as well as to reduce morbidity and mortality. Some HF patients present changes in the musculoskeletal system and inspiratory muscle weakness, which may be restored by inspiratory muscle training, thus increasing respiratory muscle strength and endurance, maximum oxygen consumption (VO2), functional capacity, respiratory responses to exercise, and quality of life. Yôga therapies have been shown to improve quality of life, inflammatory markers, and VO2 peak in HF patients, mostly with reduced ejection fraction. However, the effect of different yôga breathing techniques in patients with HF with preserved ejection fraction (HFpEF) has yet to be assessed.

Methods/Design

A PROBE (prospective randomized open blinded endpoint) parallel-group trial will be conducted at two specialized HF clinics. Adult patients previously diagnosed with HFpEF will be included. After signing informed consent and performing pre-test intervention, patients will be randomized into 3 groups: (1) Yôga – active breathing technique; (2) Yôga's passive breathing technique – pranayama; or (3) Control group (standard pharmacological treatment). Follow-up will be of 8 weeks (16 sessions). The post-intervention tests will be performed at the end of intervention period for analysis of outcomes. Interventions will occur continuously according to patients' enrollment. Main outcomes include respiratory muscular resistance and cardiorespiratory responses. A total of 33 patients are expected to be enrolled.

The present protocol was written in accordance with SPIRIT guideline and completing the SPIRIT checklist.

Discussion

This trial shall be the first to assess the effects of a non-pharmacologic intervention, Yôga and specific breathing techniques, in the cardiorespiratory function, autonomic system, and quality of life in patients with HFpEF.

Trial registration number

REBEC Identifier: **RBR-64mbnx** (19 August 2012).

Clinical Trials Register: **NCT03028168**

Keywords

Yôga, Respiratory techniques, Heart Failure with Preserved Ejection (HFpEF), randomized controlled trial, autonomic system, maximal inspiratory pressure, and oxygen uptake consumption.

Background

Many HF patients have limited physical activity due to early fatigue and dyspnea, which have been associated with low oxygen consumption and inspiratory muscle dysfunction, suggesting that physical deconditioning and respiratory muscle weakness might be underlying attenuated increased ventilation during hyperpnoea [1].

Over the last years, it has been observed and recognized that reduced performance capacity may be due to some additional factors that might be connected to the limited exercise response. Some studies have focused on the role of maximal inspiratory pressure (PI_{max}) and endurance of inspiratory muscles, which have been associated to low quality of life and worse clinical prognosis[2,3,4]. In a randomized, placebo-controlled trial in patients with heart failure with reduced ejection fraction (HFrEF) and inspiratory muscle weakness (IMW), inspiratory muscle training markedly improved inspiratory muscle strength and endurance, with increments in submaximal and maximal functional capacity, as well as in quality of life. In addition, Heart rate variability (HRV) also decreases with cardiovascular diseases and might result from a direct central up-regulation of cardiovagal activity, or as a secondary effect of baroreceptor activation or of changes in respiration [5].

Less attention, however, has been paid to respiration, despite evidence that breathing characteristics (frequency, amplitude, and regularity) markedly affect beat-to-beat cardiovascular variability [6,7,8]. Within this context, Yogic breathing might combine abdominal, thoracic, and clavicular breathing phases to maximize breathing volume and thus increase oxygen uptake. It has been reported that very slow and moderately slow Yogic breathing creates a significant change in HRV frequency bands during and after exercise in health men and women [9,10]. Recently, study reported the comparative effectiveness of several forms of lifestyle modifications and found smoking cessation and yôga to be the most effective forms of cardiovascular disease prevention [11].

Furthermore, Yôga techniques without breathing control have shown to improve oxygen consumption in patients with HF, mostly HFrEF [12]. However, almost half of HF patients present with heart failure with preserved EF (HFpEF), and less studies have been performed in those patients. It has been recently demonstrated that HFpEF induces significant molecular, mitochondrial, histological, and functional alterations in the diaphragm and soleus, which were attenuated by exercise training [13]. In cardiac disease and aging, several authors have shown a significant reduction in HR variability in the frequency ranges associated with breathing, by using spectral analysis of HR and respiration [14, 15].

Therefore, the present randomized clinical trial (RCT) will be conducted in order to test the hypothesis that an 8-week program of yôga and specific breathing techniques with different ventilatory rhythms could be associated with improvement in inspiratory muscle responses, functional capacity, distinct features of the autonomic nervous system, natriuretic peptides, echocardiographic measurements, and quality of life in patients with HFpEF, with and without IMW.

Methods/Design

Study design

A PROBE (prospective randomized open blinded endpoint) parallel-group trial with three groups will be conducted at two specialized HF clinics (HF Clinic at Hospital de Clínicas de Porto Alegre, and the HF Ambulatory at Hospital ULBRA-Mãe de Deus, Canoas, RS). Subjects will be blinded for intervention while investigators will be blinded for endpoints and analysts will be blinded for groups but not endpoints.

Inclusion and exclusion criteria

Adult patients with a diagnosis of HFpEF, functional capacity class II and III, who are being treated at a specialized HF clinic will be eligible. HF diagnosis will be established by clinical history (signs and symptoms), echocardiographic findings (left ventricular ejection fraction $\geq 50\%$) [16] and medical records confirming management for HF, aged 45 to 75 years.

Exclusion criteria are unstable angina, myocardial infarction, or cardiac surgery within the previous three months; active orthopedic or infectious disease; treatment with steroids, hormones, or cancer chemotherapy. The exclusion criteria are pulmonary disease (forced vital capacity<80% of predicted and/or forced expiratory volume in 1 s <70% of predicted) (5, 17), significant mitral or aortic valve diseases, history of exercise-induced asthma, and active smoking. After recruitment, the discontinuous criteria are HFpEF decompensated, more than two consecutive missing in the intervention groups and if subject manifest intention to discontinue at any moment of the study.

Heart Failure Clinic and team approach

The two HF clinics participating in this trial are staffed by a multidisciplinary team of cardiologists, physical educators, physiotherapists, and nurses. On average, the patients will start the protocols as soon as they finalize preclinical testing and will be randomized either to one of the intervention groups, or to the control group. To improve adherence to the study, the team maintains telephone contact to reinforce the subject's participation and confirm attendance at scheduled tests, interventions, or to understand the reasons for possible faults. The two centers have facilities that enable the realization of Yoga interventions to be done in this study.

Sample size

Based on previous studies, sample size was calculated using inspiratory muscle pressure as an endpoint [5, 12, 17,18,19, 20, 21]. Considering a difference between treatments of 15 cmH$_2$O and a standard deviation (SD) of 12 cmH$_2$O in the PI$_{max}$, with α=0.05 and power of 80%, 9 patients would have to be included per group. Considering potential loss of follow-up in the order of 10%, the sample set at 11 patients per group.

Study protocol

Eligible patients will be initially evaluated by medical history, physical examination, resting electrocardiogram, two-dimensional echocardiogram, protocols of pulmonary function and inspiratory muscle function, cardiopulmonary exercise testing (CPET), 6-min walk test, Minessota quality of life (QoL), NT-proBNP e HRV frequencies (Holter 24h). All of these evaluations will be explained in details in the appropriate sections. These records and subject's personal information will be kept securely stored in HCPA facility with access only to assistants and investigators.

After signing informed consent and pre-test intervention, patients will be randomized into 3 groups as follows (Figure 1):

Yôga – active breathing technique. Active protocol with yôga body movements (*àsanas*) performed along with respiratory technique without contentions, current and vigorous(*ujjayi*), observing respiratory frequency (RF) of 15- 20 respiratory cycles per minute (rcpm). Session should last around 45 minutes.

Yôga's passive breathing technique – *pranàyama*. Passive protocol, seated patient, no significant body movements. Yoga breathing technique, with alternate nostril breathing (*viloma pranàyama*), uses diaphragmatic breathing, both current and combined to inspiratory and expiratory retentions, observing slow RF, between 5-8 rcpm. Session will last approximately 45 minutes. A standardized 7-minute final relaxation will be performed and will be common to both study intervention protocols.

Control group (standard pharmacological treatment). Patients will be oriented to keep their pharmacological routine and daily activities, with no structured exercises. They will have to return to the hospital for post-testing after 8 weeks from randomization. After final assessment, all patients, including control group, will be invited to participate in the study breathing activities at the outpatient wards of this trial.

Intervention will take 8 weeks (16 sessions). The post-intervention tests will be performed at the end of the intervention period for evaluation of endpoints. To ensure data security, will be stored in principal investigator and study coordinator computer and added to virtual drive. Access to data will be allowed to researchers, study coordinators, doctors and statisticians. Interventions will occur at specific facilities in HCPA (Physiatrist sector) and in ULBRA University Hospital (Clinical School) according to patients' enrollment. Registration of protocol deviation and adverse events involving subject's participants in clinical studies in the HCPA is recorded in the system Strategic Adviser (SA), available in Hospital intranet. Deviations and adverse events occurring at HU-Ulbra-Mãe de Deus will be recorded in the same system from HCPA. The auditing procedures are random or by indication of the Ethical Committee for research analysis.

Pulmonary Function Inspiratory muscle function testing will be performed using a pressure transducer (MVD-500 V.1.1 Microhard System, Globalmed, Porto Alegre, Brazil), connected to a system with two unidirectional valves (DHD Inspiratory Muscle Trainer, Chicago, Illinois). Maximal static inspiratory pressure will be determined in deep inspiration from residual volume against an occluded airway, with a minor air leak

(2mm). The highest pressure of six measurements will be used for analysis. The PImax measurement will be performed at rest, and on the 5th and 10th minute after CPET. Predicted values will be corrected for age, gender, and weight (14). Additionally, for the determination of inspiratory muscle endurance, an incremental test will be used in which patients will breathe continuously through a mouthpiece connected to a measure device. The patients will use an initial load of 50% of PImax, and increments of 10% of PImax will be added every 3 min until the patient is unable to continue breathing. The greatest inspiratory pressure that the subject is able to sustain for at least 1 min (Pthmax) will be taken as the measure for inspiratory muscle endurance, and will be expressed as a percentage of maximal inspiratory pressure (Pthmax/PImax). In the second part of the protocol, subjects will breathe against a constant inspiratory submaximal load equivalent to 80% Pthmax, and the time elapsed to task failure will be defined as the inspiratory endurance time. The Powerbreathe K5 will be used for patients with IMW and for those with normal ventilatory fraction, for age and gender [15, 16].

Six-minute walk test. The maximum distance covered during the walk test will be used to assess submaximal functional capacity [22]. Patients will self-grade their degree of dyspnea during the test using the Borg scale [23].

Cardiopulmonary exercise testing. Maximal functional capacity will be evaluated using an incremental exercise test, with expired gas analysis, on a treadmill (INBRAMED10200, Porto Alegre, Brazil), using a ramp protocol, starting at a speed of 2.4 km·h -1 and 2% slope, with 20-s increments of speed (0.1 to 0.2 km·h^{-1}) and 60-s increments in slope (0.5% to 1.0%), to reach volitional fatigue at approximately 10 min. Twelve-lead electrocardiographic tracings are obtained every minute (Nihon Khoden Corp., Tokyo, Japan). Blood pressure will be measured every 2 min with a standard cuff sphygmomanometer. Metabolic and ventilator variables will be measured during and after exercise by 20-s mean aliquots, by a computer-aided gas analyzer (Total Metabolic Analysis System, TEEM 100, Aero Sport, Ann Arbor, Michigan), previously validated [24]. Peak oxygen uptake (VO$_2$peak) will be considered the highest value of VO2 calculated in a 20-second-period exercise. Maximal circulatory power will be calculated as the product of VO2 peak and peak systolic pressure [25] During incremental exercise, oxygen uptake will be plotted against the logarithm of total ventilation, and the OUES will be determined [26].

Quality of life. Quality of life (QoL) will be assessed using the Minnesota Living With Heart Failure Questionnaire [27]. We will analyze overall scores as well as the separate effects of physical and psychological perceptions of QoL.

HRV analysis. Twenty-four-hour ECG recordings will be obtained with a SEER Light digital recorder (GE Medical Systems Information Technologies, Milwaukee, WI). The recorded data will be analyzed using a MARS 8000 analyzer (Marquete Medical Systems, Milwaukee, WI) [28,29]. In short, time domain and frequency domain analyses of HRV will be performed according to recommendations from the European Society of

Cardiology and North American Society of Pacing and Electrophysiology [30]. For time domain analysis, the following 24-h indices will be calculated: mean of all normal RR intervals, SD of all normal RR intervals, root mean square of successive differences of adjacent RR intervals, and percentage of successive differences between normal adjacent RR intervals above 50 ms. For frequency domain analysis, the following spectral components will be calculated: low frequency (0.04–0.15 Hz), high frequency (0.15–0.5 Hz), and low-to-high frequency ratio. Spectral components will be expressed in absolute values (ms^2Hz) and in normalized units. Heart rate spectral analysis and time domain indices will be calculated using 5-min segments, at rest, during active breathing (*ujjayi*), and passive breathing (*pranàyama).*

BNP and NT-proBNP. BNP test: Natriuretic peptide type B (Brain), clinical specimen byserum, with chemiluminescence analysis method (ADVIA CENTAURSIEMENS); NT-proBNP test: N-terminal precursor of natriuretic peptide type B (Brain) proBNP, clinical specimen by serum, sandwich-type electrochemiluminescence analysis method (COBAS E601-ROCHE). Since this trial will be done at two centers, both methods will be used. However, the same biomarker (either BNP or NT-proBNP) will be employed for pre- and post-tests in any given patient.

Echocardiography. Usual and additional echocardiographic measures, such as volumetric gradients and diastolic parameters will be analyzed in the selection of eligible patients (Ejection Fraction calculated by Teichholz method-EF$\geq$ 50%) [16] and after intervention by using two-dimensional echocardiograms (PHILIPS IEE 33).

Randomization

Patients who meet the eligibility criteria shall be invited to take part in the study, and those who accept it will provide written informed consent. After finalizing the tests before intervention, the investigator shall inform the biostatistics center at Hospital de Clínicas de Porto Alegre, which is in charge of the randomization list. Participants will be allocated to Yôga (Y) or Respiratory (R) or Control group (C) in a 1:1:1 ratio using a pre-generated simple randomization list.

Sociodemographic and clinical variables

A structured questionnaire will be filled for all study participants for recording sociodemographic data and clinical parameters (age, gender, education, current occupation or previous occupation when retired, daily routine, etiology and duration of HF, presence of comorbidities such as hypertension, atrial fibrillation and aortic or mitral valve disease, history of smoking and alcohol consumption, medications, hospitalizations, previous illnesses, presence of angina, stent placements, history of acute myocardial infarction, New York Heart Association (NYHA) functional class, echocardiographic data). Weight, height and body mass index (BMI) [31], vital signs and electrocardiogram at rest will be evaluated in the first and last CPET.

Patients should be instructed to keep their activities of daily living (ADLs) and eating routine, as established on the date of enrollment. Any change in pharmacological management should also be reported and recorded in the study.

Endpoints

The primary endpoints are inspiratory muscle strength by measuring maximal inspiratory pressure (PImax) and peak VO2.

Secondary endpoints include**:**

(a) Vagal activity in resting and exercising HRV); (b) QoL Minnesota scores as a specific inventory for patients with HF**;** (c) Functional capacity **(NYHA** Classification); (d) Volumetric ratios of LA and diastolic pressure gradients on echocardiography**;** (e) Changes in BNP/NT-proBNP tests between pre- and post-interventions**.**

Independent/ exposure variables and confounding

In both intervention groups - in the presence and absence of body movements, the main independent variable includes respiratory management with different rhythms.

The impact of each management over the trial endpoints must be controlled to confounders: concomitant physical exercise or co–intervention, and changes during intervention on medications or non-pharmacological treatment,

Statistical analysis

Continuous variables shall be expressed as means and standard deviations if normally distributed or medians and quartiles otherwise. Categorical variables shall be expressed as absolute and relative frequencies. Depending on the distribution of variables, baseline characteristics and the effect of the trial intervention shall be compared by means of Student's *t*-test or the Mann-Whitney *U* test (for continuous variables) or Pearson's chi-square test (for categorical variables). Correlation coefficient (Pearson or Spearman) will be used to assess associations.

The effect of interventions on the continuous variables will be compared using an analysis of variance (ANOVA) for repeated measures (two way) or ANCOVA, between and within groups and a post-hoc analysis will be performed with the Tukey test. For categorical responses a logistical regression will be performed to control factors and covariables. Data will be adjusted for subgroup parameters when appropriated. A *P* value <0.05 (two-tailed) shall be considered statistically significant. All statistical analyses shall be carried out in Statistical Package for the Social Sciences (SPSS) 19.0, Chigago, Illinois.

	Study Period				
	Enrolment	*Allocation*	*Post-allocation* *(16 sessions: 2 Sessions/week)*		*Close-out*
TIMEPOINT	*-t_1*	**0**	*m_1*	*m_2*	*t_x*
ENROLMENT					
Eligibility screen	X				
Informed consent	X				
Allocation		X			
INTERVENTIONS					
Yoga's active breathing technique			→————————————→		
Yoga's passive breathing technique – *pranayama*			→————————————→		
Control group			→————————————→		
ASSESSMENTS					
Pulmonary Function	X				X
Six-minute walk test	X				X
Cardiopulmonary exercise testing	X				X
Quality of life	X				X
HRV analysis	X				X
BNP and NT-pro-BNP	X				X
Echocardiography	X				X

Discussion

Patients with HFpEF have poor functional capacity despite preserved systolic function, and little has been added to the treatment of those patients. Recent work indicates that patients with restrictive ventilation, poor functional capacity or peripheral abnormalities have more symptoms of exercise intolerance. Therapeutic strategies are needed to improve exercise tolerance by targeting the integrated functions of these systems [32].

This trial shall assess the effects of Yôga and specific breathing techniques in inspiratory muscle responses, VO2 peak, distinct features of the autonomic nervous system, biomarkers and QoL in patients with HFpEF. If this non-pharmacologic specific intervention happens to improve cardiorespiratory function and several functional parameters in patients with HFpEF, a new possibility of treatment would be available for this group of patients.

Trial status

This trial is currently in the patient recruitment and intervention stages. Thus far, 20 patients have been enrolled, 18 of whom have completed the trial.

List of abbreviations

HFpEF=Heart Failure with Preserved Ejection

CPET =Cardiopulmonary Exercise Testing

IMT =Inspiratory Muscle Training

IMW = Ispiratory Muscle Weakness

PImax =Maximal static Inspiratory Pressure

Pthmax =Maximal Inspiratory Pressure sustainedfor 1 min during incremental test

R = Respiratory Exchange Ratio

/t slope= Kinetics during recovery

$T_{1/2}$ = Time required for 50% from peak

VE =Minute ventilation

VCO_2= Carbon dioxide output

VE/VCO_2 - slope =Relationship between change in VE

and VCO_2during incremental exercise

VO_2=Oxygen uptake

OUES = Oxygen uptake efficiency slope

RSA= Respiratory Sinus Arrhythmia

HRV= Heart Rate Variability

RF = Respiratory Frequency

Declarations

Ethical Approval and Consent to participate

All participants will read and sign an informed consent form before entering the study. All collaborators were trained to introduce, show and take questions about the informed consent, exams to be taken and eventually discomforts associated to interventions before the signature of the informed consent. The study protocol has been approved by the HCPA Institutional Review Board (protocol number 11-0069) and will

be conducted in accordance with the principles of the Declaration of Helsinki and in compliance with the Brazilian legal and regulatory framework for research involving human subjects.

This protocol was registered in the ClinicalTrial.gov under identifier number NCT03028168 (16 January 2017) and in the Brazilian Records of Clinical Trials (REBEC) with the identifier number: RBR-64mbnx (19 August 2012) and the last update was made on 02 September 2013.

The ethical bodies from Hospital de Clínicas de Porto Alegre (IRB 00000921) and from Hospital ULBRA-Mãe de Deus (Registration Number at Plataforma Brasil: 5349) are listed in the additional file 6.

For patient safety, they will be followed up after the end of the protocol in the outpatient services of the Hospital de Clínicas of Porto Alegre and the University Hospital ULBRA-Mãe de Deus.

Consent for publication

The consent of publications was included in the consent to participate.

Availability of supporting data

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

CPL conceived the study, is performing the Yôga intervention, protocol training and drafted the manuscript. LCD conceived the study, and will hold electrocardiographic analysis. RSM designed the study and drafted the manuscript, and will conduct spectral analyzes of HRV. PJVC and GC designed the study, drafted the manuscript and will perform metabolic and ventilation analysis. FFM and DSS designed the study, collaborated with the manuscript, and will perform collections and interventions. LSPG drafted the manuscript and will conduct statistical analyses. AB conceived, directed the study and drafted the manuscript. All authors have read and approved the final manuscript. JPR, *in memoriam*, was the founder and great supporter of this study

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Author's information

Not applicable

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Figures title and legends

Fig. 1 Flowchart of study participation and intervention

Fig. 2 Schedule of enrolment, interventions, and assessments.

Additional Files

File Name: additional file 1

File format: PDF

Title data: Informed Consent

Description data: Informed Consent of Participants – Portuguese version (Termo de Consentimento Livre e Esclarecido – TCLE) and translated version.

File Name: additional file 2

File format: PDF

Title data: List of ethical bodies

Description data: List of member of the ethical bodies from Hospital ULBRA/Mãe de Deus and Hospital de Clínicas de Porto Alegre.

File Name: additional file 3

File format: PDF

Title data: Institutional declaration

Description data: Institutional declaration attesting author's affiliation.

File Name: additional file 4

File format: PDF

Title data: SPIRIT Checklist

Description data: Spirit Checklist of the protocol study.

File Name: additional file 5

File format: PDF

Title data: SPIRIT Figure

Description data: Spirit figure of the protocol study.

ARTIGO II - YOGA AND BREATHING TRAINING IN PATIENTS WITH HEART FAILURE AND PRESERVED EJECTION FRACTION: a randomized clinical trial

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Abstract

Background: Patients with heart failure with preserved ejection fraction (HF-PEF) and physical effort intolerance are associated with worse prognoses, and may present inspiratory muscle weakness (IMF), hemodynamic and autonomic changes, with a consequent impact on quality of life. Yoga is known to have significant benefits on cardiovascular health. However, the effects of yoga and breathing techniques on HFpEF have not been reported**. Objectives:** The purpose of this study was to examine the impact of yoga breathing techniques training on maximum inspiratory pressure (PImax), functional capacity, Pro-Bnp, quality of life (QoL), Heart Rate Variability (HRV) and diastolic parameters. **Methods:** Randomized clinical trial (RCT). Thirty-two patients (45-75 years old), with standard drug treatment and no changes in the routine, were randomized to the yoga group (Y = 11), Breathing techniques (BT=11) or the control group (C = 10) in order to test the hypothesis that an 8-week program of yoga and specific breathing techniques with different ventilatory rhythms might be associated with improvement in inspiratory muscle responses, functional capacity, distinct features of the autonomic nervous system, natriuretic peptides, echocardiographic measurements, and quality of life in HFpEF patients, with and without IMW. **Results:** Data were analyzed using the Generalized Estimates equation model (GEE- GZLM). Yoga training and breathing techniques training improved PImax (63.5 ± 5 vs 83 ± 8, p<0,001 and 55 ± 8 vs 74 ± 8, p<0,001, respectively). Yoga training also results in 46% improvement in inspiratory muscle strength (43 ± 6 vs 62 ± 7, p<0,05), in marked interaction (group-time). Breathing techniques increase heart rate variability (HRV) (827.6 ± 46.7 vs 936 ± 51.4, p<0,05). **Conclusions:** In HFpEF patients with and without IMF, yoga training with physical postures and faster conducted breathing promoted increased respiratory muscle strength. Yoga RT training with slower-conducted ventilation showed an increase in clinically relevant vagal activity. There was neither improvement in the functional capacity of these patients nor in parameters of diastolic function. (Yoga and breathing

techniques training in patients with heart failure and preserved ejection fraction, Identifier: **NCT03028168).**

Key Words: Yoga, Breathing techniques, Heart Failure.

INTRODUCTION

Most patients with heart failure (HF) have limitations on physical activities due to the occurrence of dyspnea and peripheral muscle fatigue (1). Many of them show respiratory muscle weakness (RMW) and/or deconditioning of skeletal muscles, which are involved in the metabolic dynamics of the global movement as well as, possibly, in increased work of the ventilatory muscles during hyperpnea (2). In this context, additional factors, such as a decrease in resistance and maximal inspiratory pressure (PImax), are associated with decreased capacity response to exercise in patients with HF. In addition, changes in those parameters are also associated with worsening of quality of life and disease progression (3, 4). Several indicators such as inadequate ventilatory responses to exercise (5), presence of periodic ventilation (6) and delayed recovery after maximal effort are associated with greater severity in HF (7). Heart rate variability (HRV) may also be decreased in these patients, which suggests direct central regulation of cardiovagal activity, or a secondary effect of baroreceptor activation that is subject to ventilatory changes (8). Inspiratory muscle training (IMT) appears to have satisfactory effects on functional class, inspiratory muscle strength and endurance, with increases in submaximal and maximal functional capacity and quality of life in HF patients with reduced ejection fraction (HFrEF) (4, 9-11). However, little attention has been paid to ventilation, although evidence that breathing characteristics (frequency, amplitude and regularity) markedly affect beat-to-beat cardiovascular variability (8, 12, 13).

A study has recently compared the efficacy of various lifestyle modifications and ranked smoking cessation and adherence to yoga programs among the most effective changes in cardiovascular disease prevention (14).

In physical work and specific respiratory techniques, the Yoga ventilatory control, characterized by complete diaphragmatic mobilization during the abdominal, thoracic and clavicular phases, may optimize respiratory volume and thus increase alveolar ventilation and perfusion. In addition, it has been reported that very slow and moderately slow yoga breathing creates significant changes in the frequency bands of heart rate variability (HRV) during and after exercise in healthy men and women (15, 16). Other studies have reported that yogic techniques without respiratory control improve oxygen uptake and inflammatory markers in HF patients, especially in HFrEF (17, 18).

Almost half of the patients diagnosed with HF have preserved ejection fraction (HFpEF), yet few patients with these distinct clinical and functional characteristics have been included in these studies using yogic techniques, and none of them exclusively with HFpEF. This condition, associated with several comorbidities and with a shortage of defined pharmacological treatment, induces significant molecular, mitochondrial, histological and functional changes in the diaphragm and soleus, which were attenuated by physical exercise (1).

Therefore, this study was conducted to test the hypothesis that an 8-week yogic program and specific Breathing techniques with different ventilatory rhythms may be primarily associated with improvements in inspiratory muscle responses, functional capacity and with the distinct characteristics of the autonomic nervous system, natriuretic peptides, echocardiographic measurements and quality of life in patients with HFPEF, with and without RMW.

METHODS

Patients and design.

The present study is a prospective, randomized, controlled trial with blinded outcome assessment. The study was registered in the Brazilian clinical trials platform - REBEC (RBR-64 mbnx) and in the international directory of clinical trials - Clinical Trials (NCT03028168).

Patients with previous diagnosis of HFpEF (EF ≥50%) were allocated to participation and, as an inclusion criterion, resulting from recruitment through the cardiology outpatient clinics of the Hospital de Clínicas de Porto Alegre (HCPA) and

ULBRA University Hospital (HU-ULBRA). Exclusion criteria were unstable angina, hospitalization due to decompensation, myocardial infarction or cardiac surgery in the previous three months, infectious disease, presence of cardiac pacemaker, severe valve disease, treatment with steroids, hormones or chemotherapy, severe prior lung disease (19). Individuals with history of exercise-induced asthma, smokers or alcoholics were not recruited as well as those who did not comply with the inclusion criteria or who did not sign the informed consent form.

Personal data such as name, telephone, date of birth, age, gender, occupation, residential address, outpatient clinic and responsible doctor, comorbidities (clinical history), smoking status, education, ethnicity were recorded.

In the clinical file, the individual's degree of dyspnea during rest and their level of intolerance to stress were classified according to the classification of the New York Heart Association (20).

Interventions

The therapeutic intervention was associated with two different Breathing techniques and one control group with no exercise therapy.

(1) Yoga Group (Y): Breathing frequency around 15-18 Breathing cycles per minute (crpm), combined with yogic protocol movements with active postures (àsanas) (patient with body movement - protocol 1);

(2) Breathing Technique Group (BT): Isolated Breathing, frequency around 5-8 crpm, with alternating nasal manipulation, according to protocol of Respiratory techniques of yoga (anuloma Prânayama) with immobile postures (sitting patient - protocol 2); assessment of the effects aimed in this study was performed after eight weeks of these specific trainings. On average, the sessions lasted between 45 minutes and 1 hour, twice a week.

(3) Control group (C): (standard pharmacological treatment): Patients were instructed to maintain routines of daily living, medications, and exercise during the two-month follow-up. Medication changes in the period were reported.

Before and after intervention, with an 8-week follow-up period and 16 sessions distributed twice a week, the patients in the 3 groups performed a routine of tests, requested by the cardiologist in charge to follow the treatment evolution.

Tests.

Assessment of anthropometric measures:

Body weight (kg) and height (cm) were measured; body mass index (BMI): calculated from the Body Mass Index formula (BMI = weight/height2: kg/m2) (21).

Exercise tolerance test:

The maximum incremental exercise test was performed on a treadmill (Imbramed) with a ramp protocol, with an initial velocity of 2.4 km.h-1, a 2% incline, and an increase in velocity every 20 s (0.1 a 0.2 mh-1) until spontaneous fatigue occurs. Blood pressure was measured every 2 minutes with a sphygmomanometer. Heart rate (HR) was determined using the R-R interval from 12 electrocardiogram leads. The variables of the maximum incremental exercise test were indirectly calculated by the equation (velocity x 0.1) + (slope/100 x 1.8 x velocity) + 3.5/3.5 to designate effort in METS, and $VO_{2 / Kg / min}$ by the formula (velocity x 0.1) + 3.5 + (velocity x slope x 0.9)/weight, using body mass (kg) of data baseline and post-intervention (22). According to Clinical Statements and Guidelines – AHA, the standard exercise tolerance test (ETT), without ventilatory assessments, can also be used to assess functional dynamics in older adults. The METs calculated from standard ETT showed that even this relatively less intricate measure of functional capacity (FC) was a powerful predictor of mortality in adults with and without heart failure (23).

VO_{2peak} was defined as the highest value achieved during the test for 20 seconds.

Six-Minute Walk Test (TC-6):

The submaximal functional capacity was recorded by means of the TC-6, in which the greatest distance that the individual walked within a fixed time interval of six minutes was measured (24). Subjects were instructed to perform the test according to the attached protocol.

BP and Respiratory rate (RR) were measured at the beginning and end of the test. The HR, peripheral oxygen saturation (measured by digital oximeter) and the BORG dyspnea scale were recorded at the beginning of the test, every minute and at the end of the test. The predicted distance for the individual was estimated using Enright and Sherrill's equations (25).

Respiratory Testing

Respiratory muscle strength:

Respiratory muscle strength was determined using the PImax and PEmax measurements and the MVD-300 manovacuometer (Microhard System, Globalmed, Porto Alegre, Brazil). During the procedure, the patients remained seated at rest, upright, their nostrils occluded with a nasal clip and their mouths properly set in the mouthpiece, avoiding air leaks. To measure PEmax, the individual was asked to inhale at the level of total lung capacity (TLC), followed by a maximal expiratory effort. PImax was obtained by performing an inspiration, using TLC, generating maximal inspiratory effort. The patient performed three to six attempts on the test, and the evaluator was instructed to record all the values obtained for PImax and PEmax (cmH_2O). When choosing PImax and PEmax values, the evaluator recorded the highest value obtained by the individual, provided that it was not higher than 10% of the second highest value. During the evaluation, the evaluator strongly encouraged the individual to give his or her maximum using incentive phrases. During the test, when a patient's predicted PImax value was <70%, according to gender and age, it was considered as a decrease in inspiratory muscle strength or inspiratory muscle weakness (IMW) (26).

Progressive load test of inspiratory muscles:

The inspiratory muscle strength was determined using the modified progressive loading protocol of Martyn et al (27). Inspiration was initiated with a loading of 50% of

PImax, and the loading increased 10% of the PImax every three minutes. The patient ventilated continuously until the inspiratory valve of the equipment could not be opened.

The resistance index will be determined by the maximal sustained inspiratory pressure (MSIP) for at least 60 seconds in the last stage, and will be expressed as a percentage of the maximal inspiratory pressure (MSIP/PImax) (28).

At each stage, heart rate (HR), Respiratory rate (RR), oxygen saturation by pulse oximetry (Sp) (Datex-Ohmeda, 3800 Oximeter, Louisville, USA) and the dyspnea index by the perception scale of BORG will be monitored.

Constant load test:

To test the inspiratory muscle strength, the patient ventilated against 80% of MSIP for the maximum tolerated time. The improvement in the individual's performance was evaluated by the total duration of the test (29).

Heart rate variability analysis

Heart rate variability indices were calculated from twenty-four-hour ECG recordings obtained with a SEER Light digital recorder (GE Medical Systems Information Technologies, Milwaukee, WI). The recorded data were analyzed using a MARS 8000 analyzer (Marquete Medical Systems, Milwaukee, WI) as previously described (30). In short, time domain indices were calculated according to recommendations of the European Society of Cardiology and North American Society of Pacing and Electrophysiology (31). The following 24-h indices were calculated: mean of all normal RR intervals, SD of all normal RR intervals, root mean square of successive differences of adjacent RR intervals, and percentage of successive differences between normal adjacent RR intervals above 50 ms (RR, pNN50, RR, rMSSD, SDNN). Only patients in sinus rhythm were included.

Quality of Life Questionnaire:

Quality of life (QOL) was assessed using the Minnesota Living With Heart Failure questionnaire (32). Overall scores as well as the separate effects of physical and psychological perceptions on QOL were analyzed.

BNP and Pro- BNP:

Due to adherence to the method of modified analysis at the hospital of origin, two different methodologies were used to measure BNP. Initially, blood samples of the natriuretic peptide type B (BNP), clinical sample by serum, with chemiluminescence analysis method (ADVIA CENTAURSIEMENS).

The N-terminal precursor test of B-type natriuretic peptide (NT-proBNP) was adopted using the sandwich-type electrochemiluminescence analysis (COBAS E601-ROCHE). In the pre- and post- tests, the same biomarker (BNP or NT-proBNP) was employed (33, 34). Classifications were analyzed for the diagnosis of HFPEF and for comparison after the interventional treatment. For the analysis of the two methodologies, the variables were transformed into a Z-scale in order to set same metric values. For each method, the mean and standard deviation were calculated by the formula $Z = x_i - \bar{x} / s_i$, where "i" is the subject, "x" is the BNP value observed, "$\bar{X}$" is the BNP mean of the method, and "s" is standard deviation of each method.

Echocardiogram:

The usual and additional echocardiographic measurements, such as volumetric gradients and diastolic parameters, were analyzed in the selection of eligible patients (LVEF calculated using the Teichholz method - EF≥50%) (35) and using two-dimensional echocardiograms after the intervention (PHILLIPS IEE 33).

Sample size

Based on previous studies, sample size was calculated using inspiratory muscle pressure as an endpoint (4, 19 ,26, 29, 36,37). Considering a difference between treatments of 15 cmH2O and a standard deviation (SD) of 12 cmH$_2$O in the PImax, with α=0.05 and power of 80%, 9 patients would have to be included per group. Considering potential loss of follow-up in the order of 10%, the sample was set at 11 patients per group.

Statistical analysis.

The data were analyzed using the Generalized Estimating Equations (GEE-GZLM), specific for repeated measurements, to compare the effects (means) across the 3 groups and the two times, in addition to the group * time interaction. GEE Matrix of robust estimator covariance and exchangeable labor correlation matrix was used in the

normal distribution with identity binding function. When significant, the factors under study were compared by Bonferroni's post-hoc test. Correlations were described by the Spermann test. The Statistical Package for Social Sciences (version 18.0, SPSS, Chicago, Illinois) was used in this analysis.
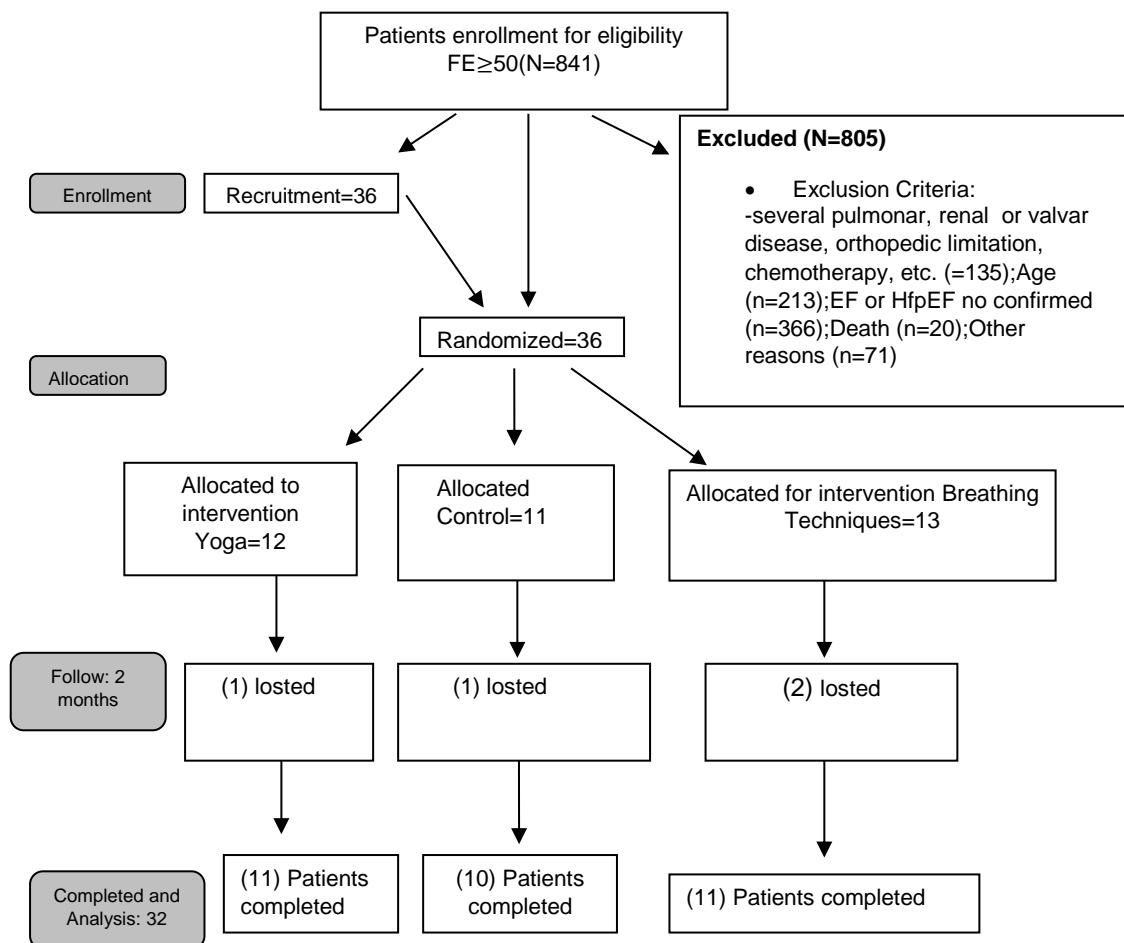
Figure 1 - Flow diagram of study.

RESULTS

Patients. Between August 2012 and March 2017, 841 patients with HF were screened for the study. After verification of the inclusion and exclusion criteria, 42 patients were recruited; however, because of additional exclusions, only 36 were randomized. Among the 12 patients randomized to the "Yoga group"- Y, 1 did not complete the training protocol because of personal problems. Among the 13 patients

allocated to "Breathing Techniques group"- BT, 1 was excluded because of excessive absences in protocol, and 1 developed HFrEF criteria. Among the 11 patients allocated to "Control Group"- C, one did not complete pre-protocol tests. Therefore, 32 patients completed the protocols and the tests (Figure 1).

Table 1 - Baseline characteristics of patients randomized to Yoga, Breathing techniques, Control group

	Y (n=11)	BT (n=11)	C (n=10)
Characteristics			
Gender, female/male	10|01	06|05	06|04
Age (years)	67 ± 6	65 ± 8	62 ± 6
Body mass index (kg/m²)	33,9 ± 5	32,7 ± 8	33,8 ± 5
Obesity	7 (63,6)	5 (45,5)	8 (80)
Sedentary	9 (81,8)	7 (63,6)	6 (60)
Functional class (NYHA)			
I	0	1	0
II	6 (54,5)	6 (54,5)	10 (100)
III	5 (45,4)	4 (36,6)	0 (0)
Etiology of Heart Failure			
Ischemic	5 (45,4)	2 (25)	1 (10)
Non ischemic	6 (54,5)	9 (90)	8 (80)
AF	6 (54,5)	0 (0)	4(50)
Mitral failure	3 (37,5)	2 (25)	2 (33)
Hypertension	11 (100)	9 (90)	9 (90)
Diabetes	3 (27,3)	5 (45)	3 (30)
Dyslipidemia	9 (81,8)	8 (72,7)	7 (70)
Ejecion Fraction %	68,7 ± 1,7	67 ± 1,5	66,7 ± 2,1
PI_{max}	63,8 ± 21	53,9 ±31	65,2 ± 28
PI_{max} predicted %	64,2 ± 11	78,3 ± 21	84,6 ± 18
HR peak	125,1 ± 8,9	123,9 ± 6,9	133,4 ± 7,9
Drugs (n)			
Beta blokers	8 (72,7)	8 (72,7)	7 (70)
ACEI	8 (72,7)	5 (45,5)	8 (80)
Digitalic	4 (36,4)	1 (9,1)	0 (0)
Diuretics	10 (90,9)	6 (54,5)	7 (70)
Antiplatelets	7 (63,6)	5 (50)	6 (66,7)

Inspiratory muscle function tests.

After 16 weeks, yoga and respiratory exercises induced marked improvement in PImax (20 cm H_2O for Y group, 19 cm H_2O for BT group, and 6 cm H_2O for C group) (Figure 2). Although sustained inspiratory muscle strength significantly increased in the Y group at the end of the incremental load test (Pthmax), Pthmax/PImax (%) function increased in the BT group (18 cmH_2O); while this may be clinically relevant, it is not statistically significant. PImax presented increased, markedly higher means in the BT group (p <0.05) at minute 5 after maximal effort (62 cmH_2O; 66 cmH_2O for group Y, 69 cmH_2O; 78 cmH_2O for group BT and 62 (66 cmH_2O, 71 cmH_2O for group Y, 66 cmH_2O, 77 cmH_2O for 49 group BT and 61 cmH_20, 65 cmH_2O) after the intervention period.

Table 2 - Inspiratory muscle function testing data at baseline and post training compared by among the yoga, breathing techniques and control

	Y			BT			C		
	Baseline	Follow-up	Δ	Baseline	Follow-up	Δ	Baseline	Follow-up	Δ
PImax	63 ± 5	83 ± 8	20 (6 to 31)†	55 ± 8	74 ± 8	19 (0,01 to 37)†	65 ± 8	71 ± 9	6 (-3 to 16)†
PEmax	70 ± 7	77 ± 9	8 (-2 to 18)	80 ± 13	101 ± 14	21 (-1 to 43)	95 ± 11	87 ± 8	-8 (-20 to 5)
PImax 5 (min)	62 ± 5	66 ± 6	4 (-6 to 15)‡	69 ± 7	78 ± 9	9 (-2 to 20)‡	62 ± 8	67 ± 8	5 (-1 to 12)‡
PImax 10 (min)	66 ± 7	71 ± 8	5 (-7 to 17)	66 ± 8	77 ± 9	11 (1 to 22)	61 ± 7	65 ± 8	4 (-4 to 11)
Pthmax	43 ± 6	62 ± 7	19 (7 to 29)*	40 ± 7	54 ± 5	14 (1 to 27)	49 ± 6	51 ± 6	2 (-2 to 5)
Pthmax/Pimax	74 ± 5	75 ± 6	1 (-14 to 15)	61 ± 10	78 ± 3	18 (-6 to 41)	77 ± 4	72 ± 3	-5 (-14 to 4)
Endurance time	544 ± 85	690 ± 62	147 (-54 to 348)	556 ± 73	428 ± 45	-129 (-287 to 30)	643 ± 79	508 ± 85	-135 (-335 to 65)

Date expressed as mean ± SD. Δ, difference from follow-up and baseline; PI_{max}, maximum inspiratory pressure; PE_{max}, maximum expiratory pressure; PI 5 (min), PI 10 (min), maximum inspiratory pressure at 5 and 10 min after maximal exercise; Pth_{max}, maximum inspiratory pressure and time sustained for incremental test. * p<0,05 for group-time interaction; † p<0,001 for time comparison; ‡ p<0,05 for time comparison. d

The endurance time sustained in the inspiratory muscle presented a statistical trend (p=0.07) and the yoga group reached a higher mean when compared to the respiratory techniques group in post-training (Table 2). As to PImax, a statistical difference was observed in the post-intervention period (p <0.001), where mean values were higher in all groups; they were significant in Y and BT, but not in the control group (0.196) (Figure 1).

Pth max
65
60
55
50
45
40
35
30
25
20
1   —Y   —BT   —C   2

PI max 10 min
80
75
70
65
60
55
50
1   —Y   —BT   —C   2

PI max 5 min
80
75
70
65
60
55
50
1   —Y   —BT   —C   2

PI max
85
80
75
70
65
60
55
50
1   —Y   —BT   —C   2
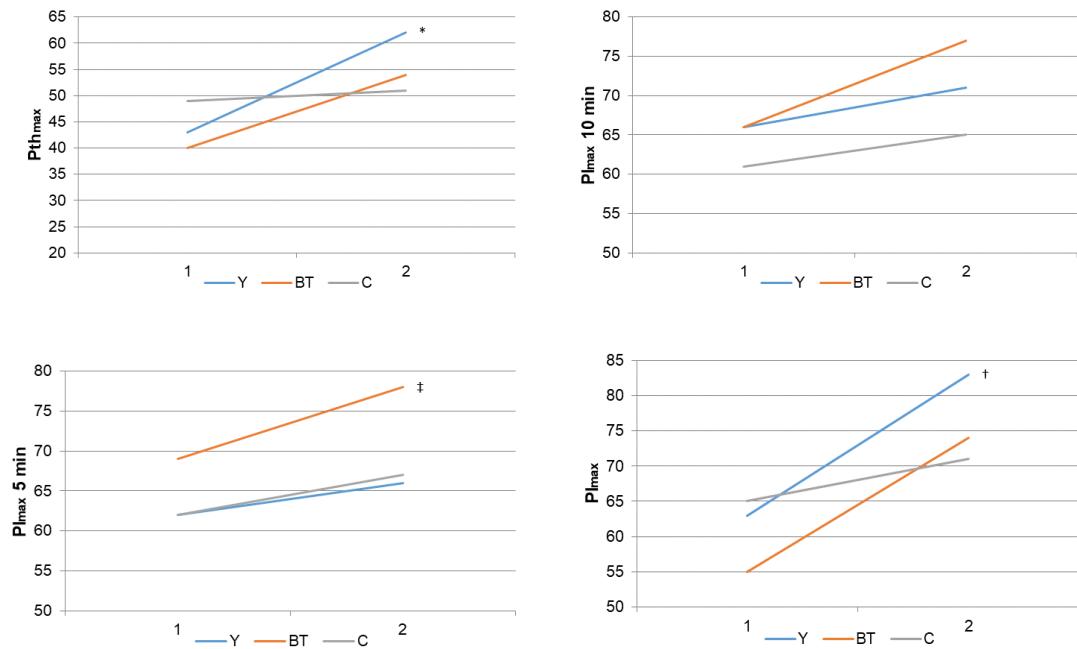
Data expressed as mean ± SD. * p<0,05 for group-time interaction; † p<0,001 for time comparison; ‡ p<0,05 for time comparison

Figure 2 – Main outcome at baseline and follow-up.

Exercise Capacity.

There were no serious adverse events related during exercise stress testing. No significant differences were observed for the evaluated exercise stress parameters (Table 3). However, a moderate and significant correlation was observed (r=0.41; p<0.05) between VO_2 (kg/ml/min) and PImax (cmH_2O) in post-training, regardless of the group.

Table 3 - Exercise stress testing data at baseline and post-training period compared across the groups (yoga, breathing techniques, and control groups)

	Y			BT			C		
	Baseline	Follow-up	Δ	Baseline	Follow-up	Δ	Baseline	Follow-up	Δ
VO2 (ml/min)	1391 ± 29	1417 ± 36	25 (-52 to 103)	1392 ± 44	1429 ± 54	37 (-58 to 132)	1470 ± 32	1469 ± 31	-1 (-76 to 75)
VO2 (ml/kg/min)	18 ± 1	19 ± 1	1 (-0,3 to 1,5)	17 ± 1	17 ± 1	0,3 (-0,6 to 1,4)	17 ± 1	17 ± 1	0,2 (-0,5 to 1)
METS	6,7 ± 0,3	6,9 ± 0,3	0,2 (-0,4 to 0,9)	6,7 ± 0,4	7,1 ± 0,5	0,4 (-0,5 to 1,2)	7,4 ± 0,3	7,4 ± 0,3	-0,01 (-0,7 to 0,7)
HR peak (beats/min)	125,1 ± 8,9	119 ± 7,4	-5,5 (-29,5 to 18,2)	123,9 ± 6,9	128 ± 5,5	5 (-3,5 to 12,3)	133,4 ± 7,9	133,2 ± 8,4	-0,2 (-8,5 to 8,1)
SBP (mm Hg)	171 ± 7	166 ± 8	-5 (-22 to 13)*	192 ± 5	171 ± 8	-21 (-34 to -7)*	182 ± 6	173 ± 6	'-9 (-23 to 4)*

Date expressed as mean ± SD. Δ, difference from follow-up and baseline. VO_2, oxygen consumption; METS, metabolic equivalents; HR, heart rate; SBP, systolic blood pressure. * p<0,05 for time comparison
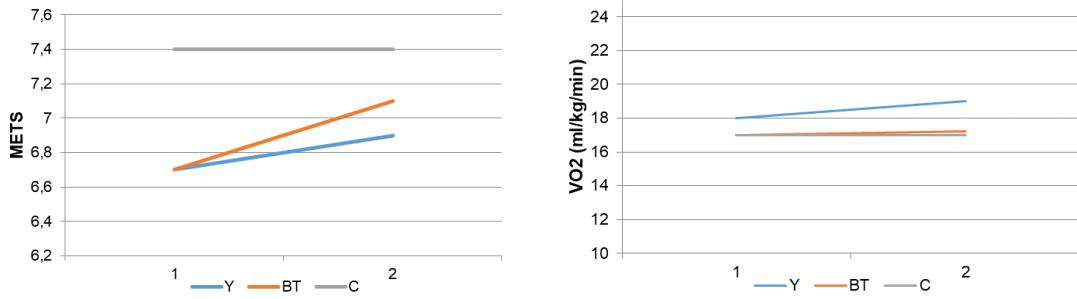
Data expressed as mean ± SD. VO₂, oxygen consumption; METS, metabolic equivalents.

Figure 3- Exercise stress testing data at baseline and follow-up.

Autonomic responses. The time domain parameters of HRV, including mean RR interval (p = 0.000), NN50 count divided by the total number of all NN intervals (pNN50) (p = 0.02), and square root of the mean of the sum of the squares of differences between adjacent NN intervals (rMSSD) (p = 0.04) increased in the Breathing Techniques group, when compared to the other groups or to the time of intervention (Table 4). In the frequency domain analysis, power of low-frequency (LF), power of high frequency (HF) as well as in the time domain, the standard deviation variable of all NN intervals (SDNN) did not attain statistical significance (Figure 4).

Table 4 – Distribution of time domain means throughout 24h in Yoga Group, Breathing Techniques Group, and Control Group

	Y			BT			C		
	Baseline	Follow-up	Δ	Baseline	Follow-up	Δ	Baseline	Follow-up	Δ
RR	916,9 ± 46,4	870,5 ±41,2	-46,4 (-122 to 19)	827,6 ± 46,7	936 ±51,4	108,4 (36 to 180,7)†	866,3 ± 49,5	811,8 ± 35,7	54,5 (-117,6 to 8,7)
SDNN	152 ± 21	131 ± 10	-21 (-58 to 15)	109 ± 12	119 ± 10	10 (1 to 17)	110 ± 5	119 ± 8	9 (-0,2 to 18)
RMSSD	38 ± 6	44 ± 7	6 (-8 to 20)	28 ± 2	33 ± 3	5 (0,5 to 7)*	25 ± 2	27 ± 3	2 (-6 to 9)
PNN50	14 ± 5	19 ± 6	5 (-4 to 13)	7 ± 1	10 ± 2	3 (-,0,04 to 6)*	3 ± 0,6	6 ± 2	3 (-2 to 6)

RR: interval variability; pNN50 (%): SD of all normal RR intervals; rMSSD: square root of the mean of the sum of the squares of differences between adjacent NN intervals; SDNN: standard deviation of all NN intervals. Values are expressed as mean ± SD. *p<0,05 for different means in comparisons; † p< 0,05 for group-time interaction.
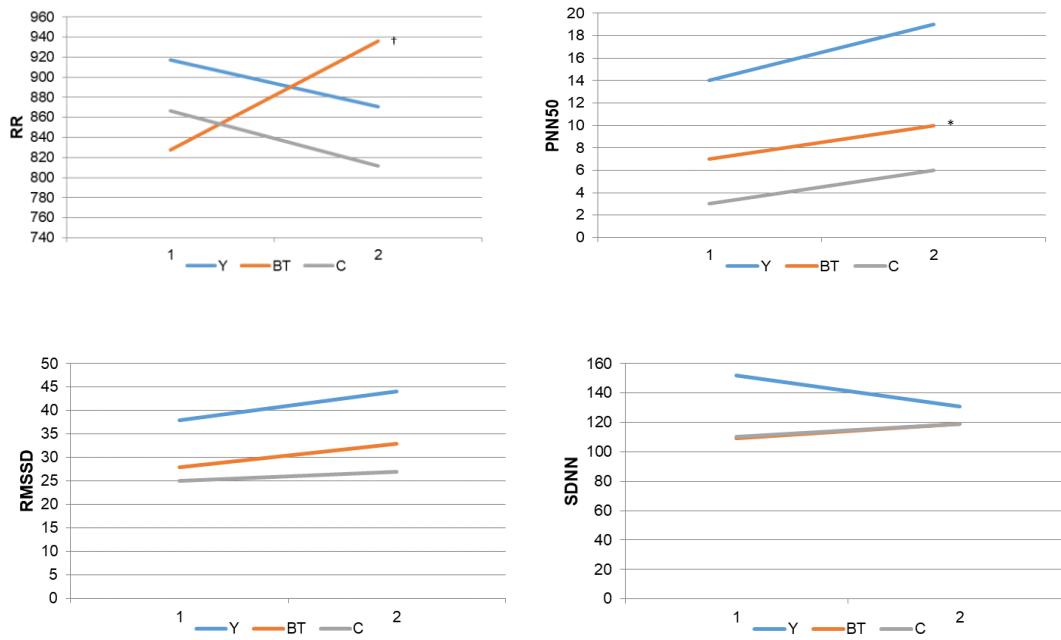
Values are expressed as mean ± SD. Δ, difference from follow-up and baseline, * p<0,05 for different means in comparisons; for different means in comparison; † p <0.001 for group-time interaction.

Figure 4- HRV parameters (RR, PNN50, rMSSD, SDNN) outcomes at baseline and follow-up.

Other outcomes. On the 6-minute walk test, all patients, regardless of the group, showed shorter distances at baseline for gender, age, and body weight. After training, the mean meters covered increased in groups Y, BT, and C, with respective Δ, 45m, 28m and 44m (Table 5).

Table 5 – Other Secondary Outcomes at Baseline and Follow-up

	Y			BT			C		
	Baseline	Follow-up	Δ	Baseline	Follow-up	Δ	Baseline	Follow-up	Δ
TC-6	387 ± 12	432 ± 22	45 (8 to 82)*‡	442 ± 31	471 ± 22	29 (-8 to 66)‡	453 ± 33	497 ± 21	44 (-32 to 121)§‡
Expected distance	421 ± 10	425 ± 11	4 (-2 to 10)	454 ± 16	452 ± 16	-2 (-8 to 5)	457 ± 16	492 ± 37	35 (-35 to 105)
HR (baseline)	64 ± 3	62 ± 3	-2 (-8 to 3)	70 ± 3	67 ± 3	-3 (-7 to 2)	69 ± 3	70 ± 5	1 (-6 to 9)
HR (end)	92 ± 9	84 ± 3	-9 (-27 to 10)	99 ± 7	87 ± 6	-12 (-28 to 4)	93 ± 9	101 ± 8	8 (-8 to 24)
Borg	6 ± 05	5 ± 0,4	-1 (-2 to -0,06)‡	7 ± 0,4	7 ± 0,5	-0,5 (-1 to 0,8)‡	7 ± 0,4	7 ± 0,5	-0,3 (-2 to 1)‡
BNP	0,5 ± 0,4	0,8 ± 0,4	0,3 (-0,24 to 0,9)	-0,4 ± 0,2	-0,3 ± 0,2	0,1 (-0,13 to 0,36)	-0,4 ± 0,2	0,3 (-0,2 to 0,8)	0,3 (-0,2 to 0,8)
Echocardiography									
Ø A (mm)	3,1 ± 0,1	31 ± 0,07	0,05 (-0,1 to 0,2)	3,3 ± 0,1	3,2 ± 0,1	-0,1 (-0,1 to 0,05)	3,4 ± 0,1	3,5 ± 0,1	0,1 (-0,004 to 0,13)
Ø LA (mm)	4,3 ± 0,1	4,2 ± 0,1	-0,1 (-0,2 to 0,1)	4,2 ± 0,1	4,3 ± 0,1	0,1 (-0,02 to 0,2)	4,1 ± 0,03	4,1 ± 0,07	0,02 (-0,1 to 0,1)
Ø LVEDD (mm)	4,9 ± 0,1	4,7 ± 0,1	-0,2 (-0,3 to 0,05)	4,7 ± 0,1	4,4 ± 0,1	-0,3 (-0,5 to 0,02)	4,9 ± 0,1	5 ± 0,1	0,1 (-0,2 to 0,3)
Ø LVESD (mm)	3 ± 0,1	2,8 ± 0,1	-0,2 (-0,004 to 0,3)	29 ± 0,1	2,8 ± 0,1	-0,1 (-0,2 to 0,04)	3,1 ± 0,1	3,2 ± 0,1	0,1 (-0,2 to 0,3)
EF (%)	68,7 ± 1,7	70,2 ± 2	1,5 (2,1 to -5,1)	67 ± 1,5	65,7 ± 1,3	-1,3 (-3,3 to 0,8)	66,7 ± 2,1	65,7 ± 2,8	-1 (-6,6 to 4,5)
LVM (g)	202 ± 15	189 ± 13	-13 (-28 to 3)	213 ± 26	216 ± 31	3 (-16 to 21)	228 ± 8	217 ± 16	-11 (-42 to 21)
mass/body surface	111 ± 6	107 ± 7	-4 (-12 to 2)	111 ± 10	108 ± 13	-3(-11 to 6)	114 ± 7	121 ± 9	7 (-3 to 17)
E/e'	12 ± 1,4	12 ± 1,5	0,05 (-0,09 to 1,1)	10 ± 0,9	10 ± 0,8	0,1 (-0,7 to 0,9)	10 ± 1,1	11 ± 1,5	1 (-0,8 to 2,3)

Values are expressed as mean ± SD. Δ, difference from follow-up and baseline. HR, heart rate; Borg, subjective effort scale; BNP, brain natriuretic peptide, Ø A, aortic diameter; Ø LA, left atrium diameter; Ø LVEDD, left ventricle end diastolic diameter; Ø LVESD, left ventricle end systolic diameter, EF, ejection fraction; LVM, left ventricle mass; E/e', early diastolic peak velocity and diastolic peak velocities of the mitral annulus ratio. * p<0.05 for different means in comparisons; † p<0.001 for time comparison; ‡ p<0.05 for time comparison.

The outcomes related to Borg, BNP and echocardiography showed no differences across the groups. MLHF scores results decreased in the 3 groups; however, in group Y, Δ showed higher reduction (-17.6), followed by BT group (-10.3) and C group (-4.2). As to physical and emotional domains, group Y showed higher score decrease (respectively -8; -6); group BT (-4; -1) and group C (-3; -1) showed similar reduction. (Table 5).

Table 6- Quality of life scores

	Y			BT			C		
	Baseline	Follow-up	Δ	Baseline	Follow-up	Δ	Baseline	Follow-up	Δ
Emotional	15 ± 7	9 ± 2	-6 (-9 to -3)*†	7 ± 6	6 ± 1	-1 (-3 to 1)†	$1- \pm 5$	7 ± 2	-3 (-6 to 0)†
Physical	$19 \pm 2,9$	$11 \pm 2,2$	-9 (2,2 to 14,1)†	$16 \pm 3,3$	$12 \pm 2,7$	-4 (0,8 to 37,4)	$18 \pm 3,6$	$15 \pm 3,2$	-3 (1,9 to 16,3)
MLHF	$43,5 \pm 5,2$	$25,9 \pm 3,5$	-17,6 (-30 to -4)†	$38 \pm 5,6$	$27,7 \pm 4,8$	10,3 (-18,7 to -1,8)‡	$36,4 \pm 5,5$	$32,2 \pm 2,9$	-4,2 (-15,3 to 6,9)

Values are expressed as mean ± SD. Δ, difference from follow-up and baseline. MLHF, Minnesota living with heart failure scores.
* p<0.05 for different means in comparisons; † p<0.001 for time comparison; ‡ p<0.05 for time comparison.

Subgroup analysis.

IMW. The Respiratory variables were adjusted by IMW. After adjustment, data have not changed significantly, confirming IMW independence to the Respiratory outcomes obtained.

Diabetes in autonomic analyses. The adjustment for diabetes in the autonomic model showed no difference when compared to previous analyses. In addition, in SDNN analysis, there was a group*time interaction trend (p=0.06) that was not shown before remission in diabetes.

DISCUSSION

In this randomized clinical trial conducted in HFpEF patients, yoga and Breathing techniques for a two-month training period improved inspiratory muscle strength and endurance as well as heart rate variability, regardless of factors that decrease ventilatory or autonomic efficiency, such as weak inspiratory muscles and presence of diabetes. There was no difference in functional capacity and diastolic function parameters. QoL tended to have a better post-intervention emotional response in group Y.

Traditionally, yoga is a complex physical practice associated with specific ventilatory techniques (38). At present, it has been recommended in risk reduction

programs (14) and cardiovascular rehabilitation (39), and its outcomes include well-being, cognitive and motor benefits, positive effects in the treatment of hypertension (38), inflammatory markers (18), and functional capacity of HFrEF patients (17).

In HFpEF patients, these functional and neuromuscular qualities are still poorly reported in the acute or adaptive response to yogic physical and/or breathing practices. However, the clinical and semiologic aspects of HFpEF consider exercise intolerance as forceful when compared to other cardiovascular diseases (40) since it presents variable degrees of pulmonary/systemic congestion (41), functional capacity limitations, autonomic vagal dysfunction, and significant chronotropic incompetence. A study on the pathophysiological paradigm in HFpEF suggested that comorbidities associated with the syndrome such as SAH, DM, COPD, iron deficiency and obesity would be potential inducers of inflammatory states and tissue oxidative stress (42). These processes act on the coronary and systemic microvascular endothelium, determining less bioavailability of nitric oxide, with a possible reduction of the arterial reserve, to the hemodynamic increases triggered by the exercise (43). These limitations might explain a profile of a higher clinical stability toward small efforts (short duration) or at rest, but a poor performance during continuous exercise, related to aerobic metabolism and to the worst prognoses by the functional class associated with a low rate on peak oxygen uptake.

In a review of metabolic factors related to exercise intolerance in HF patients, authors suggest the occurrence of mitochondrial changes in the activity of Cytochrome C-oxidase, creatine kinase and other oxidative enzymes, as well as the remodeling of fibers of fast contraction (anaerobic) to the detriment of the slow contraction fibers. These functional and metabolic changes in HFpEF lead to the early onset of anaerobic metabolism during exercise, increased metabolic acidosis and early central stimulation of respiratory control, increasing minute ventilation, inducing early fatigue at low loads of continuous exercise (44).

In this study, PImax increased in the Y and BT groups. In group Y, respiratory muscle strength (Pth) showed significant gain in incremental load with increasing intensity, according to the mean time interval test - predominance of glycolytic metabolism. However, the resistance characteristics of this same musculature, ventilating with constant load and temporal measure of oxidative metabolic predominance, did not obtain significant differences between the intervention group and C group. Nevertheless,

a study showing acute effect of a 30-minute single session in 17 patients with HFpEF and IMW (60% of the sample), ventilating against a constant load (80% of the PImax), evaluated hemodynamic rates of the LV filling derived from the Doppler echocardiogram and concluded that immediate IMT appeared to promote significant changes in these patients' heart rates(45).

Other relevant findings in HF and IMT refer to some RCTs, all with HFrEF patients, and detail improvements on inspiratory muscle strength and endurance, VO_{2peak}, QoL and dyspnea over a minimum period of 12 weeks and in IMW patients only (4, 11, 19, 29, 46), which contributes to the deficit of exercise capacity in HF (47). In another study, IMT also appeared to significantly reduce sympathetic flow in HF patients; it was reported a reduction (15%) in the resting sympathetic muscle activity of these patients when compared to other individuals with similar systolic dysfunction, but with no training nor pharmacological treatment (48). However, IMT has not yet been widely used as a non-pharmacological treatment option in HF, perhaps because of the lack of information and scope of effects on functional capacity. The sample size of those studies, comparing these benefits to those obtained with control groups, has also been small (49). The chronic modulations to continuous or interval IMT are still unknown in HFpEF.

A study with yoga and HF, which described a significant increase in VO_2, was completed after 8 weeks of intervention with 17 HFrEF patients (33-76 years, mean age 55.8 ± 7.5 and 52.5 ± 12) and 1 HFpEF patient randomized to yoga group (YG); in the control group (CG), of the 16 patients randomized, 3 had HFpEF (EF> 45%) (50). YG performed 2 supervised one-hour sessions/week, and were recommended to perform a third session at home. All patients, intervention and controls, were instructed to keep an unsupervised walking routine and maintain standard medication treatment. In this study, there was a functional improvement; however, the sample of HFpEF patients was very small and it was not possible to evaluate the response in this subgroup. In the present study with HFpEF patients, no significant changes were observed in the ability to perform maximum effort after training with yoga and BT. In the new guidelines and statements for older adults with CVD (AHA), measures obtained from exercise testing of VO_{2peak} (or METs) have modest correlations with health-related QoL. The capacity to generate work decreases 8-10% every decade, and the generation of muscle strength declines in the face of diminished oxidative and mitochondrial action. These complex associations between

function and activity lead to high inter-patient variability and may trigger different responses in functional capacity among elderly people with CVD (23).

Regarding the findings of this study on autonomic modulation and BT, it seems that the slower respiratory frequency (RF), performed by alternate nasal block and having inspiratory and expiratory restraints, increases HRV in HFpEF patients. Similarly, beta blockers and ACEI/ARA decrease neurohormonal activation and reduce morbidity and mortality in HF(51, 52). A study with BT similar to that used in this RCT showed that yoga breathing through the right nostril (RNYB) increases SBP, DBP and BP, whereas left nostril breathing (LNYB) decreases SBP, DBP and MBP, suggesting that Yoga seems to influence BP in healthy subjects (53). Other authors corroborate this finding, describing a decrease in BP in a group of hypertensives that performed a slower BT for 3 months (54). Another recent study associating yoga and breathing techniques in the same exercise session concluded that this practice improves symptoms and arrhythmia burden, reduces anxiety and depression, and improves QoL in patients with Atrial Fibrillation (AF) (55). Interestingly, a meta-analysis on yoga showed no cardiovascular effects in studies with physical postures, but there were significant increases in vagal autonomic activity with BT and meditation (32).

Limitations of the study

Some limitations of the study need to be considered. The ergospirometric variables were limited by the gas analysis record that was not considered due to the imprecise extraction of these volumes. Thus, incline and velocity increase estimated the metabolic equivalent and VO_2 using the standardized formulas for maximal exercise stress test (ACMS).

In addition, longer intervention time and/or greater number of sessions per week might have been important to obtain significant results of functional capacity.

Despite the reasoned difficulty in performing RCTs with a greater number of patients, especially HFpEF patients, and the statistical support in methods that provide power to the sample calculation, a greater number of patients per group could confer

greater significance and reproducibility to functional and subjective outcomes, such as T6min, Borg and QoL questionnaires.

Further studies on yoga and breathing might focus on biochemical changes, central vagal stimulation, and changes in HR induced by respiratory rate, and these might clarify parameters of exercise intolerance and contribute to the reduction of morbidity and mortality in HFpEF.

CONCLUSIONS

In HFpEF patients, with and without IMW, yogic training with physical postures and faster conducted breathing promoted as much increased respiratory muscle strength as in conventional IMT with equipment. Yoga BT training with slower-conducted ventilation showed increased clinically relevant vagal activity. No improvement in the functional capacity of these patients was observed.

List of abbreviations

HFrEF = Heart Failure with Reduced Ejection Fraction

CPET =Cardiopulmonary Exercise Testing

IMT =Inspiratory Muscle Training

IMW = Inspiratory Muscle Weakness

RMW = Respiratory Muscle Weakness

VO_{2peak} = consumption of oxygen

PImax =Maximal static Inspiratory Pressure

Pthmax =Maximal Inspiratory Pressure sustained for 1 min during incremental test

R = Respiratory Exchange Ratio

RT = Respiratory Training

HRV= Heart Rate Variability

RF = Respiratory Frequency

RR = Respiratory Rate

BP = Blood Pressure

SBP = Systolic Blood Pressure

DBP = Diastolic Blood Pressure

MBP = Mean Blood Pressure

SAH = Systemic Arterial Hypertension

DM = Diabetes Mellitus

COPD = Chronic Obstructive Pulmonary Disease

YG = Yoga Group

RT = Respiratory Techniques

CG = Control Group

AF = Atrial Fibrillation

ETT= Exercise Tolerance Test

FC= Functional Capacity

CVD= Cardiovascular disease

RCT = Randomized Clinical Trial

QoL = Quality of Life

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Conclusões

No presente estudo, avaliamos os efeitos das posturas físicas do yôga somado ao respiratório (yôga ativo: posturas acompanhadas da respiração intensa e conduzida) e somente respiratório (yôga passivo: técnicas respiratórias com menor frequência respiratória (FR), sem mobilidade corporal significativa) sobre avaliações de força muscular inspiratória, capacidade funcional, aptidão cardiorrespiratória e variabilidade cardíaca, além da qualidade de vida após 8 semanas de treinamento (16 sessões) com pacientes com IC-FEP. Aos pacientes do grupo controle foi solicitado manter rotina de atividades diárias e tratamento farmacológico padrão do início até o fim deste ensaio clínico.

Ambos os treinamentos resultaram em aumento da Pressão inspiratória máxima entre o tempo basal e pós intervenção, melhorando a função pulmonar destes pacientes. Nas medidas específicas de força da musculatura envolvida na ventilação, o treinamento com yôga apresentou importante incremento na capacidade de realizar esforço respiratório, aumentando cargas de trabalho intervaladas e demonstrando efeito benéfico das posturas físicas e da respiração intensa com FR em torno de 18 ciclos por minuto.

Na modulação autonômica, o treinamento de técnica respiratória específica do yôga, sem movimentos corporais e com menor FR (aproximadamente 9 ciclos respiratórios por minuto), aumentou a variabilidade da frequência cardíaca (VFC) melhorando a função vagal, mesmo em pacientes diabéticos que apresentam redução do reflexo vagal cardíaco e menor resposta ao exercício.

Neste estudo, não foram observados efeitos dos treinamentos sobre a capacidade funcional, nem sobre parâmetros de disfunção diastólica como E/e´ e peptídeo natriurético (Pro- BNP).

A qualidade de vida (QdV) apresentou queda dos escores do questionário Minnesota em todos os grupos. No entanto, o treinamento com yôga pareceu ter maior relevância clínica no domínio emocional e geral, onde foi evidenciado melhor impacto do pós-treinamento sobre as respostas na QdV dos pacientes com IC-FEP.

Os benefícios encontrados no presente estudo devem ser confirmados em estudos maiores e com avaliação de desfechos clínicos para que se possa considerar a indicação destas intervenções em pacientes com IC-FEP.

APÊNDICES

Protocolo 1: Yôga (*Àsanas*) para Pacientes com IC

Posição Inicial (PI)   1 – Inspira (I)   2- Inspira (I) ↔   3 – Exala (E)

↑

4- (I)   5- (I)   ↔   6- (E)   →   (PI):(I)→ 7(E) + 5 Resp.

↑   ↑
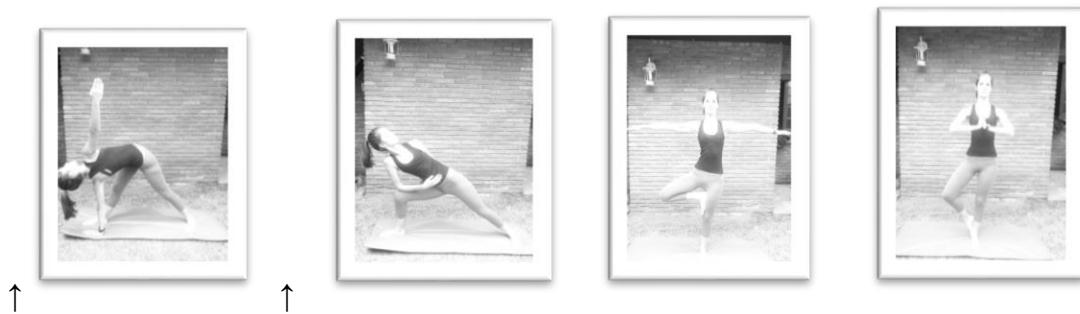
(PI): (I) → 8 (E)   (PI):(I)→ 9 (E)   10 -(I)   ↔   11- (E)

+ 5 Resp.Dir(D)/Esq(E)   + 5 Resp.D/E

- *** Série adaptada do *Ashtanga Vinyasa Yôga:* àsanas e *respiração alinhados* em condução contínua.**
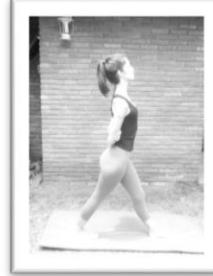
12- (I) ↔ **13-(E)** **14 -(I)** → **16- (E) : mantém 5 R**

(3x)

17- (5 R) **18- (5 R)** **19- (5 R)** **20- (E)** ↔

21- (I) : (3x) **22- (5 R)** **23- (5 R)** **24- (5 R)**

↔
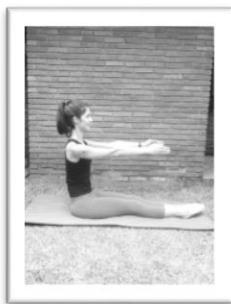
25- (I) → **26 -(I)** → **27- (E) : (5R)** **28- (I)**
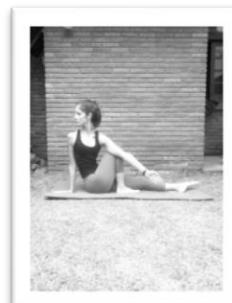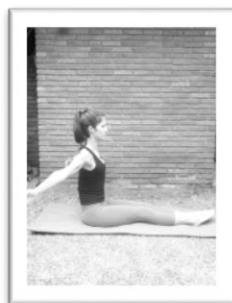
29- (I) → **30-(E) : (5 R)** **31- (I)** **32- (E): (5R)**

(D/E) **(D/E)**

32- (I) ↔ **33- (E) : (3x)** **34- (I)** ↔ **35- (E) : (3x)**

36- (I) ↔ **37- (E) : (3x)** **38- I ↑ (5 R)** **39- (5 R)**

Legendas • (I): Inspiração;

40- Final da Sessão • (E): Expiração;

• (PI): Posição Inicial: Fig. 1;

• (nX): Nº de vezes de execução ;

• (R):Respirações na postura;

• (D/E): Direita/ Esquerda.

Instruções:

(1) **Os Pacientes serão orientados previamente sobre a execução combinada entre movimentos físicos e respiratórios;**

(2) **A série será conduzida pelo supervisor do Grupo de Yôga (GrY), através dos comandos "inspira" e "exala" enquanto demonstra os movimentos a serem realizados com a respiração;**

(3)   **Nas posturas em que o paciente permanece por 5 respirações, naquelas de execução bilateral como também nas que apresentam movimentos seriados, o supervisor facilita a aprendizagem através de ajustes posturais (correções) aos pacientes do grupo.**

Protocolo 2: Técnicas Respiratórias do Yôga (*Pranayàmas*) para pacientes com IC

a)Posição Inicial - *Pranayàma* I**: Respiração Abdominal (a_1); e** *Pranayàma* II**: Respiração Completa (a_2) :**

Prática de Técnicas Respiratórias e posturas adaptadas para fins terapêuticos (***Pranayàma* I:** postura 1 *ou* 3: Respiração Diafragmática; **e *Pranayàma* II:** postura 2 *ou* 4**:** Respiração em 3 estágios (Abdome/intercostal/clavicular);

1-   2-
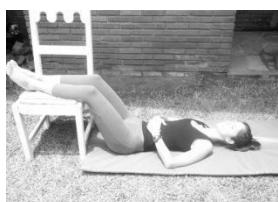
3-   4-

- **** Série adaptada para fins terapêuticos: Técnicas de Respiração do Yôga* (pranayàmas)**[42-44]

b)Posições Preparatórias para *pranayàmas* (técnica respiratória III) em manutenção de postura sentada:

1-Inspira (I)   2- (I)   3-Exala (E)   4-(E)

5- Inspira (I)   2- Exala (E)   3- (I)   4- (E)

d) Anuloma Viloma Pranayama (Samavrtti ou Visamavrtti Pranànayàma*):
Técnica de Respiração Nasal Alternada

1.   **Inala/Exala/   2- Exala Narina   3- Inspira Narina   4- Exala Narina**

Inala   Esquerda: (N/E)   Esquerda: (N/E)   Direita

5- Inala (N/D)   6- Exala (N/E)   7- Inala (N/E)   8- Exala (N/D)

Instruções:

1. **As Respirações (inalações/exalações e ciclos completos) serão realizadas em 4 tempos iguais, contados pelo supervisor da atividade enquanto os pacientes realizam asessão;**

* pranayàma relacionado ao trabalho de recuperação dos sistemas cardíaco, pulmonar e autonômico[42]

2. **Após 2 séries completas** *pranayàma* **III** (*Viloma*: respiração alternada: Figuras 1- 8) **serão incuídas** *retenções* **de ar (após a Inspiração) com duração de 2 tempos, configurando a série na seguinte sequência: "inspira": 1- 2- 3 – 4** (em quatro tempos); *"retém":* **1-2** (2 tempos);**"exala": !-2-3-4** (em quatro tempos) **e "exala": 1-2 ... (total: 2 séries completas)**

3. **Nas séries posteriores (5 e 6) serão incluídas as** *suspensões* **de ar (após a exalação) em 2 tempos. O supervisor orientará os pacientes em comandos de "inspira": 1-2-3-4; "exala" :1-2-3-4 e** *"suspende"* **(1-2); "inspira": 1-2-3 ...**

4. **Na série 7,** *retenções* **e** *suspensões* **de dois tempos serão combinadas, respectivamente, entre cada** *inspiração* **e** *expiração* **da série: "inspira": 1-2-3-4; retém: 1-2; "exala: 1-2-3-4 e "suspende" 1,2.**

5. **A série 8 será igual a série de número 1, finalizando os ciclos d respiração alternada (***viloma***:** *pranayâma* **III)**

e) Respiração Completa: repete *Pranayàma* **II (a$_2$);**

d) Respiração Abdominal: repete *Pranayáma* **I (a$_1$);**

f) Respiração Natural (não dirigida): Encerramento da Sessão.

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Título do Projeto: **YÔGA E O TREINAMENTO DE TÉCNICAS RESPIRATÓRIAS NO MANEJO DE PACIENTES COM INSUFICIÊNCIA CARDÍACA**

O objetivo desta pesquisa é verificar os efeitos da terapia do Yôga e de Técnicas respiratórias sobre a musculatura respiratória em pacientes com Insuficiência Cardíaca Crônica (ICC). Poderão participar do estudo aproximadamente 48 indivíduos atendidos no Ambulatório de Insuficiência Cardíaca do Hospital de Clinicas de Porto Alegre – HCPA, R. Ramiro Barcelos, 2350 - Santa Cecília, Porto Alegre - RS e Ambulatório de Insuficiência Cardíaca do Hospital Universitário Mãe de Deus/ HU - ULBRA Av. Farroupilha, 8001 – Prédio 21, São José - Canoas/RS. Serão incluídos no estudo os indivíduos que aceitarem participar voluntariamente do projeto e que assinarem este Termo de Consentimento Livre e Esclarecido.

Este estudo se justifica por identificar os efeitos de um programa de exercícios de Yôga e Técnicas de Respiração para a musculatura inspiratória, que é composta pelos músculos que o(a) Sr.(ª) utiliza quando puxa o ar para seus pulmões. Dentre os benefícios que o(a) Sr.(ª) poderá obter está a oportunidade de atendimento individualizado e gratuito de reabilitação da força muscular respiratória, a possibilidade da melhora da qualidade de vida, de fortalecimento dos músculos respiratórios, da melhora do seu estado geral de saúde, da sua flexibilidade e da capacidade em realizar exercícios em sua vida diária. Também gostaríamos de salientar que este treinamento não acarretará riscos à sua saúde, sendo que o(a) Sr.(ª) foi indicado pelo seu médico responsável para participar deste projeto. Os procedimentos de avaliação, no entanto, podem causar certo desconforto e/ou mal estar, como cansaço e dificuldades respiratórias durante a execução dos testes propostos.

Para a avaliação inicial iremos utilizar três equipamentos diferentes. Serão realizados dois exames com o aparelho manovacuômetro, no qual o(a) Sr.(ª) precisará primeiramente puxar a maior quantidade de ar que puder, dentro do aparelho manovacuômetro, repetindo este movimento de três a seis vezes, e, após, soltar a maior quantidade de ar possível, também de três a seis vezes. A resistência dos seus músculos respiratórios será testada com um equipamento chamado powerbreathe ou Threshold no qual o(a) Sr. (ª) deverá respirar pelo tempo máximo que conseguir, conectado ao bocal do equipamento.

Para verificar a variabilidade de seus batimentos cardíacos durante suas atividades diárias (o) Sr. (ª) usará por período de 24h um equipamento chamado holter que será colocado em seu tórax conectado a eletrodos em seu peito que registrará sua frequência cardíaca e não poderá ter contato com água enquanto estiver sendo usado.

Será realizado um teste de caminhada, que terá a duração de seis minutos, no qual o(a) Sr.(ª) deverá caminhar o máximo que conseguir, sem correr. Ainda para avaliar sua capacidade de exercício, o(a) Sr.(ª) será submetido a um teste em uma esteira elétrica, devendo caminhar pelo maior tempo que se achar capaz, respirando dentro de um bocal, e ao seu pedido a esteira será parada.

Para avaliar sua qualidade de vida, iremos aplicar um questionário com perguntas sobre o que o (a) Sr.(ª) pensa sobre a sua saúde.

Coleta de amostra sanguínea será realizada para avaliar e caracterizar níveis do marcador BNP para classificação das condições cardíacas do(a) Sr (ª).

Ao final das avaliações iniciais o(a) Sr.(ª) será orientado sobre como proceder com os exercícios, que serão orientados e realizados duas (2) vezes por semana, durante 45 minutos a 1h, em um período inicial de 8 semanas (2 meses). Lembramos que após 8 semanas (16 sessões) repetiremos todos os testes citados para verificar os efeitos do exercício realizado.

Desde já, lhe informamos que serão formados três grupos de estudo sendo que dois deles terão exercícios, submetidos a cargas e treinamento diferentes e em um dos grupo o(a) Sr(ª) permanecerá sem fazer atividade, apenas repetindo os testes ao final de 2 meses. O (a) Sr(ª) tem a mesma chance de ser colocado em qualquer um dos três grupos, pois essa distribuição será feita por um programa de computador, independente da vontade dos pesquisadores.

Portando, o(a) Sr.(ª) participante tem total garantia de esclarecimentos, antes, durante e após a pesquisa, a qualquer dúvida acerca dos procedimentos, riscos, benefícios e outros assuntos relacionados com a pesquisa e o tratamento do indivíduo. Assumimos o compromisso de lhe proporcionar informação atualizada sobre o andamento do projeto, ainda que esta possa afetar a sua vontade de continuar participando. Também asseguramos que lhe serão disponibilizadas, gratuitamente, passagens de ônibus para que o(a) Sr.(ª) possa cobrir os gastos com transporte devido aos testes e medidas do referido projeto. Se possuir novas perguntas sobre este estudo, sobre os seus direitos como participante ou se acredita que a sua participação pode lhe prejudicar, o(a) Sr.(ª) poderá entrar em contato com a pesquisadora Carla Pinheiro Lopes pelo telefone (51) 8195 8810 no horário que julgar necessário e com o Comitê de Ética em Pesquisa do Hospital de Clínicas de Porto Alegre pelo telefone (51) 3359 8304 ou (51) 3359 8000 em horário comercial.

O(a) Sr.(ª) participante tem a liberdade de se recusar a participar ou de retirar o seu consentimento, em qualquer fase da pesquisa, sem penalização alguma e sem prejuízo à continuidade de seu tratamento.

As informações coletadas servirão para o entendimento dos efeitos deste treinamento e serão compartilhadas através de publicação de um ou mais artigos e/ou trabalho na área, preservando em sigilo a identidade de todos os participantes.

Desta forma salienta-se que: sua participação em qualquer tipo de pesquisa, inclusive nesta, é voluntária. Este documento é elaborado e assinado em duas (2) vias, sendo que uma delas ficará em posse do (a) Sr.(ª) e a outra com o pesquisador responsável pela pesquisa. Em caso de dúvida quanto aos seus direitos, o (a) Sr(ª) também pode escrever para o Comitê de Ética em Pesquisa da ULBRA (Rua Farroupilha, 8001; Prédio 14 – Sala 224 - São José, *Canoas* - RS, CEP 92.425-900) ou para o Comitê de Ética do Hospital de Clínicas de Porto Alegre, Rua Ramiro Barcellos, 2350 - Bairro Rio Branco - Porto Alegre – RS CEP 90035-903.   ,

Pelo presente instrumento que atende às exigências legais, o(a) Sr. (a) _____ portador(a)da cédula de identidade _____, após leitura minuciosa do TERMOS DE CONSENTIMENTO LIVRE E ESCLARECIDO, devidamente explicada pelos profissionais em seus mínimos detalhes, declara estar ciente dos serviços e procedimentos aos quais será submetido, não restando quaisquer dúvidas a respeito dos

procedimentos que envolvem esta pesquisa, firmando assim, seu CONSENTIMENTO LIVRE E ESCLARECIDO concordando em participar deste estudo.

Fica claro que o participante da pesquisa e/ou seu representante legal pode a qualquer momento retirar seu CONSENTIMENTO LIVRE E ESCLARECIDO e deixar de participar da pesquisa, estando ciente de que todas as informações prestadas tornaram-se confidenciais e guardadas por força de sigilo profissional.

E, por estarem de acordo, assinam o presente termo.

_____ de _____ de _____.

_____
Assinatura do Paciente

_____
Carla Pinheiro Lopes (Pesquisadora)

ORIENTAÇÕES PARA O TESTE DE CAMINHADA DE SEIS MINUTOS (TC6min)

Explicação padrão: "Faremos agora o teste de caminhada de seis minutos (TC6 min). Este teste consiste em caminhar a máxima distância possível (não correr) durante o tempo cronometrado de 6 minutos. O objetivo do teste será avaliar sua capacidade funcional, para isso precisamos que o senhor (a) caminhe então, a maior distância que puder nestes seis minutos de teste. O senhor(a) deverá encontrar a velocidade do seu próprio passo para percorrer a maior distância. Devo salientar que é permitido interromper o teste quantas vezes for necessário, caso sinta qualquer tipo de desconforto, como por exemplo: dor no peito, dor de cabeça, tontura, fraqueza ou falta de ar insuportável. Caso algum destes desconfortos ocorrer, o(a) senhor(a) deverá interromper a caminhada e imediatamente me comunicar. Caso precise escorar-se na parede, sentar-se na cadeira, isto lhe é permitido. Eu lhe acompanharei e informarei o tempo de prova a cada minuto, eu também o (a) monitorarei durante os seis minutos da prova e após três minutos do final do teste, que é o tempo para recuperação."

Avaliação das orientações:

a) "O (a) senhor(a) entendeu que deverá caminhar a maior distância possível, que deverá achar o seu próprio passo, que poderá interromper o teste a qualquer momento e que estaremos lhe monitorando antes, durante e após o teste?" ( )sim ( ) não. Se o (a) paciente respondeu não, pergunta-se qual a dúvida? _____.

Explica-se novamente procurando esclarecer a dúvida, e assim sucessivamente até que o (a) paciente responda sim ao questionamento sobre a metodologia e o objetivo do teste.

b) "O (a) senhor (a) está suficientemente orientado e consente em realizar o teste? *( ) sim ( )não.

*O (a) paciente precisará dizer "sim" para o teste ser executado.

ESCALA DE BORG MODIFICADA PARA SENSAÇÃO DE CANSAÇO (BORG)

0   Nenhuma..

1   Muito leve.

2   Leve.

3   Moderada.

4   Levemente Cansativo.

5   Cansativo.

6

7   Muito Cansativo.

8

9   Muito, muito Cansativo.

10

* Máximo

UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL – UFRGS

YÔGA E O TREINAMENTO DE TÉCNICAS RESPIRATÓRIAS NO MANEJO DE PACIENTES COM INSUFICIÊNCIA CARDÍACA

DATA início:

1- IDENTIFICAÇÃO

NOME _____

DN ____/____/____   IDADE ____ anos   SEXO 1- M / 2 – F

OCUPAÇÃO 1 – aposentado / 2 - _____ TELEFONE _____

CIDADE 1 – / 2 –   MÉDICO 1-   Drª / 2 - _____

Ambulatório: ( ) HCPA

            ( ) ULBRA

2 – FATORES DE RISCO / HÁBITOS DE VIDA

SEDENTARISMO:

 1 – SEDENTÁRIO / 2 – NÃO SEDENTÁRIO

DIABETES: 1 – TIPO 1 / 2 – TIPO 2 / 3 - NÃO

TABAGISMO: 1 – NÃO / 2 – EX TABAGISMO

ÁLCOOL: 1 – SOCIAL / 2 – NÃO / 3 – Já teve USO ABUSIVO

3 – HISTÓRICO

a) CLASSE IC

b) MEDICAMENTOS EM USO

NOME	DOSE	FREQUÊNCIA	OBSERVAÇÃO

TOTAL: _____ medicamentos

4 – INÍCIO/ FIM DA ATIVIDADE (intervenção)

Data Ínicio:

 Data FIM da Atividade:

5– SINAIS DE SINTOMAS

PRÉ ( ) - PÓS ( )

 DISPNÉIA – Classificação da New York Heart Association

1 – Nenhum sintoma em atividade normal. Dispnéia somente com grande esforço (subir morro, corrida).

2 – Sintomas em atividades normais (subir escada, arrumar a cama, carregar uma quantidade maior de compras).

3 – Sintoma com médio esforço (tomar banho, vestir-se).

4 – Sintoma no repouso.

Avaliador:

Data (s):

Local:

Minnesota Living with Heart Failure Questionnaire

Durante o último mês seu problema cardíaco o impediu de viver como você queria por quê?

		Pré	6m	12m	18m	24m	36m	48m
		_/_/_	_/_/_	_/_/_	_/_/_	_/_/_	_/_/_	_/_/_
1.	Causou inchaço em seus tornozelos e pernas	( )	( )	( )	( )	( )	( )	( )
2.	Obrigando você a sentar ou deitar para descansar durante o dia	( )	( )	( )	( )	( )	( )	( )
3.	Tornando sua caminhada e subida de escadas difícil	( )	( )	( )	( )	( )	( )	( )
4.	Tornando seu trabalho doméstico difícil	( )	( )	( )	( )	( )	( )	( )
5.	Tornando suas saídas de casa difícil	( )	( )	( )	( )	( )	( )	( )
6.	Tornando difícil dormir bem a noite	( )	( )	( )	( )	( )	( )	( )
7.	Tornando seus relacionamentos ou atividades com familiares e amigos difícil	( )	( )	( )	( )	( )	( )	( )
8.	Tornando seu trabalho para ganhar a vida difícil	( )	( )	( )	( )	( )	( )	( )
9.	Tornando seus passatempos, esportes e diversão difícil	( )	( )	( )	( )	( )	( )	( )
10.	Tornando sua atividade sexual difícil	( )	( )	( )	( )	( )	( )	( )
11.	Fazendo você comer menos as comidas que você gosta	( )	( )	( )	( )	( )	( )	( )
12.	Causando falta de ar	( )	( )	( )	( )	( )	( )	( )
13.	Deixando você cansado, fatigado ou com pouca energia	( )	( )	( )	( )	( )	( )	( )
14.	Obrigando você a ficar hospitalizado	( )	( )	( )	( )	( )	( )	( )
15.	Fazendo você gastar dinheiro com cuidados médicos	( )	( )	( )	( )	( )	( )	( )
16.	Causando a você efeitos colaterais das medicações	( )	( )	( )	( )	( )	( )	( )
17.	Fazendo você sentir-se um peso para familiares e amigos	( )	( )	( )	( )	( )	( )	( )
18.	Fazendo você sentir uma falta de auto controle na sua vida	( )	( )	( )	( )	( )	( )	( )
19.	Fazendo você se preocupar	( )	( )	( )	( )	( )	( )	( )
20.	Tornando difícil você concentrar-se ou lembrar-se das coisas	( )	( )	( )	( )	( )	( )	( )
21.	Fazendo você sentir-se deprimido	( )	( )	( )	( )	( )	( )	( )

NÃO	MUITO POUCO				DEMAIS
0	1	2	3	4	5

TC6M

TC 6 min	Pré		Pós	
	Inicial	Final	Inicial	Final
PAS				
PAD				
FC				
Sp02				
Dispnéia S/N				
BORG				

PRÉ	MIN	FC	Sp02	BORG Inic	BORG Fim	Pas	Pad
Voltas	1						
	6						

Avaliador:

PÓS Int	MIN	FC	Sp02	BORG d.	BORG p.	Pas	Pad
Voltas	1						
	6						

Avaliador:

Homens (7,57x __cm) – (1,76x __kg) – (5,02x __anos) – 309 = ____m Dist. Prev.   **PRÉ**

Homens (7,57x __cm) – (1,76x __kg) – (5,02x __anos) – 309 = ____m Dist. Prev.   PÓS

Mulheres (2,11x __cm) – (2,29x __kg) – (5,78x __anos) – 667 = ____m Dist. Prev.   PRÉ

Mulheres (2,11x __cm) – (2,29x __kg) – (5,78x __anos) – 667 = ____m Dist. Prev.   PÓS

Observações no TC 6 _____

Avaliador:

MEDIDA DA PRESSÃO ARTERIAL (extras)- anotar motivos de medidas extraordinárias

	Inicial	2ª	3ª	4ª	5ª	6ª	7ª	8ª	Final
PAS									
PAD									
Data(s)									

Motivos:

Avaliador:

MANOVACUOMETRIA-(Pré)

PIMAX Repouso	Data	1ª	2ª	3ª	4ª	5ª	6ª	7ª	8ª	9ª	Pimax	50% PImax	CProgr: 1Pw;2TR
Av (1)													
Final PImaxS=													

PEMAX Repouso	Data	1ª	2ª	3ª	4ª	5ª	6ª	7ª	8ª	9ª	PEmax
Av (1)											
Final PImaxS=											

PIMAX 5' ergo	Data		
Final PImaxS=			

PEMAX 5' ergo	Data		
Final PImaxS=			

PIMAX 10' ergo	Data		
Final PImaxS=			

PEMAX 10' ergo	Data		
Final PImaxS=			

PImax prevista: Se homem (-0,8x ___anos) + 155,3 = _____

                            Se mulher   (-0,49x ___anos) + 110,4 = _____

Teste de Carga Progressiva: (Pré)

PImáx: 50% PImax:

Estágios(m)	FC	PAS	PAD	PAM	SO2	BorG	Carga
3							
6							
9							
12							
15							

PImaxS=

80% PImaxS=

Teste de Carga Constante: (Pré)

Estágios(m)	FC	PAS	PAD	PAM	SO2	BorG	Carga
3							
6							
9							
12							
15							

RMR(segundos)=

Avaliador:

MANOVACUOMETRIA-(Pós)

PIMAX Repouso	Data	1ª	2ª	3ª	4ª	5ª	6ª	7ª	8ª	9ª	Pimax	50% PImax	CProgr: 1Pw;2TR
Av (1)													
Final PImaxS=													

PEMAX Repouso	Data	1ª	2ª	3ª	4ª	5ª	6ª	7ª	8ª	9ª	PEmax
Av (1)											
Final PImaxS=											

PIMAX 5' ergo	Data		
Final PImaxS=			

PEMAX 5' ergo	Data		
Final PImaxS=			

PIMAX 10' ergo	Data		
Final PImaxS=			

PEMAX 10' ergo	Data		
Final PImaxS=			

PImax prevista: Se homem (-0,8x ___anos) + 155,3 = _____

                    Se mulher   (-0,49x ___anos) + 110,4 = _____

Teste de Carga Progressiva: (Pós)

PImáx: 50% PImax:

Estágios(m)	FC	PAS	PAD	PAM	SO2	BorG	Carga
3							
6							
9							
12							
15							

PImaxS=

80% PImaxS=

Teste de Carga Constante: (Pós)

Estágios(m)	FC	PAS	PAD	PAM	SO2	BorG	Carga
3							
6							
9							
12							
15							

RMR(segundos)=

Avaliador:

FÍSICO

	FR	MASSA	ALTURA	IMC	OBESIDADE S/N
PRÉ					
PÓS					

1- Abaixo do peso (< 18,5)
2- Normal (18,5 – 24,9)
3- Sobrepeso (25 – 29,9)
4- Obeso grau I (30 – 34,9)
5- Obeso grau II (35 – 39,9)
6- Obesidade mórbida (> 40)
   Ass. Bras. Estudo da Obesidade

BNP

PRÉ		PÓS	
Data		**Data**	
Valor		**Valor**	

Check-in Paciente Yôga

NOME:_____ DATA NASC:___/___/___   IDADE: ____

PRONTUÁRIO: _____ ID: _____

PRÉ		PÓS	
	Entrevista		Entrevista
	Minessota		Minessota
	Ergoespirometria		Ergoespirometria
	Manovacuometria 5´ e 10´		Manovacuometria 5´ e 10´
	Manovacuometria		Manovacuometria
	PowerBreathe		PowerBreathe
	TC6´		TC6´
	Holter 24h		Holter 24h
	BNP		BNP