TESE

EFEITO DA RESTRIÇÃO AGRESSIVA DE SÓDIO E LÍQUIDOS NO MANEJO DE PACIENTES COM INSUFICIÊNCIA CARDÍACA COM FRAÇÃO DE EJEÇÃO PRESERVADA: UM ENSAIO CLÍNICO RANDOMIZADO

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Efeito da restrição agressiva de sódio e líquidos no manejo de pacientes com insuficiência cardíaca com fração de ejeção preservada: um ensaio clínico randomizado

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LISTA DE ABREVIATURAS

ACC/AHA – American College of Cardiology/American Heart Association

DMV – Densidade microvascular

ESC – European Society of Cardiology

EUA – Estados Unidos da América

FEVE – Fração de ejeção do ventrículo esquerdo

IC – Insuficiência cardíaca

IC-FEP – Insuficiência cardíaca com fração de ejeção preservada

SBC – Sociedade Brasileira de Cardiologia

SRAA – Sistema renina-angiotensina-aldosterona

VE – Ventrículo esquerdo

RESUMO

Objetivos: Comparar o efeito de uma dieta com restrição hidrossalina com uma dieta livre, na redução do peso, estabilidade clínica, sede e ativação neuro-hormonal em pacientes internados por IC e fração de ejeção preservada (IC-FEP). **Métodos:** Ensaio Clinico Randomizado. Grupo intervenção (GI) recebeu dieta com 0,8g/sódio e 800ml/dia ou dieta livre, grupo controle (GC). O desfecho primário foi perda de peso; secundários: estabilidade clínica, sede, ingestão calórica, ativação neuro-hormonal, readmissões e mortalidade. **Resultados:** Foram incluídos 30 pacientes GI e 23 GC; a perda de peso durante a internação, redução da congestão, ativação neuro-hormonal e readmissões e mortalidade foram semelhantes entre os grupos; a percepção de sede foi maior ($p=0,033$) e a ingestão calórica menor no GI ($p<0,001$). **Conclusão:** A estratégia testada não proporcionou benefício clínico sintomático ou prognóstico, produziu mais percepção de sede, menor ingestão calórica e não parece ter efeito neuro-hormonal relevante em pacientes com tratamento hospitalar da IC-FEP.

1. REVISÃO DA LITERATURA

Insuficiência cardíaca – definição e epidemiologia

A insuficiência cardíaca (IC) é uma síndrome clínica complexa de caráter sistêmico, que acarreta inadequado e insuficiente suprimento sanguíneo para atender às demandas metabólicas dos tecidos em situações de repouso e exercício. Suas manifestações clínicas incluem dispneia, fadiga, função cardíaca anormal e retenção hídrica[1, 2].

Apesar de grandes avanços na terapêutica ocorridos nas últimas décadas, a IC continua sendo responsável por significativa morbidade e mortalidade, sendo considerado um dos mais importantes desafios clínicos atuais na área da saúde[2-4].

Os casos prevalentes de IC já ultrapassam 5,8 milhões nos Estados Unidos da América (EUA) e, a cada ano, mais de 550.000 novos casos são diagnosticados[5]. No ano de 2010, segundo dados da *American Heart Association*, a IC foi a principal causa de hospitalização e morte nos EUA e na Europa. Além disso, os custos diretos e indiretos com a IC nos EUA neste mesmo ano foram de 39 bilhões de dólares[6].

No Brasil, estudos epidemiológicos estimam que cerca de 6,4 milhões de brasileiros sofram de IC[7]. Segundo dados do DATASUS, no período de 2011 a 2016, a IC foi responsável por 1.234.279 internações e 136.660 óbitos, com um custo de 1,6 bilhões de reais em internações para o Sistema Único de Saúde[8].

Insuficiência cardíaca com fração de ejeção preservada

A insuficiência cardíaca com fração de ejeção preservada (IC-FEP), historicamente conhecida como IC diastólica, refere-se à síndrome clínica de IC

com função sistólica normal ou quase normal[9]. A divisão clássica da IC em sistólica e diastólica tem sido questionada por diversos autores, que argumentam que se trata de uma mesma doença com diferentes fenótipos de apresentação[10, 11]. Contudo, fatores epidemiológicos, estruturais, cardíacos e, baseados no tipo de resposta terapêutica corroboram com a hipótese de que sejam duas entidades distintas[10, 11].

A principal terminologia usada para descrever a IC é baseada nos valores de fração de ejeção do ventrículo esquerdo (FEVE). Recentemente, as diretrizes europeias de IC definem IC-FEP como aqueles pacientes que apresentam FEVE ≥50%[12]. O diagnóstico da IC-FEP é mais desafiador do que aqueles com disfunção sistólica, e geralmente acontece quando a síndrome clínica de IC (sobrecarga de volume, dispneia, intolerância ao esforço) é associada com função sistólica preservada e alguma evidência de disfunção diastólica (por avaliação hemodinâmica invasiva, ecocardiográfica ou através de biomarcadores cardíacos)[13]. Pacientes com IC-FEP apresentam remodelamento concêntrico do ventrículo esquerdo (VE), com um volume diastólico final do VE normal, anormalidades de relaxamento ativo, e aumento da rigidez passiva ventricular[14-17].

Estudos epidemiológicos relatam que, entre os pacientes com IC, a prevalência de IC-FEP varia de 40% a 71% (média ~ 50%)[18]. Além disso, estima-se que até 2020, mais de 8% da população com idade superior a 65 anos terá IC-FEP, com prevalência geral estimada em 69% nesta faixa etária, tornando a IC-FEP o fenótipo mais comum entre os pacientes com IC[17].

A crescente epidemia da IC-FEP parece estar relacionada com o aumento das taxas de comorbidades associadas, decorrente principalmente do

aumento da expectativa de vida e envelhecimento da população; e está associada à significativa morbidade e mortalidade[19]. Mulheres e idosos com comorbidades como hipertensão, diabetes, obesidade, síndrome metabólica e doença arterial coronariana são mais frequentemente afetados[20]. Em uma amostra de pacientes brasileiros que procuraram o serviço de emergência por descompensação da IC, observou-se que a fração de ejeção preservada (>50%) esteve associada com idade avançada (>70 anos de idade), sexo feminino, etiologia não isquêmica, fibrilação ou flutter atrial, anemia, pressão de pulso ampla (>45 mmHg) e sem alterações de condução no eletrocardiograma[21].

Além disso, estudos têm demonstrado que, uma vez hospitalizados por descompensação aguda da IC, as taxas de readmissão são de aproximadamente 30% a 35% no prazo de um ano e as taxas de mortalidade são de 22% a 30% em um ano e de 65% em 5 anos[22, 23].

Apesar da importância da IC-FEP, a fisiopatologia e tratamento deste fenótipo continuam mal compreendidos. Até o momento, os grandes ensaios clínicos (I-Preserve, PEP-CHF, CHARM-Preserved, DIG, TOPCAT)[24-28] falharam em demonstrar a eficácia de qualquer tratamento específico sobre a mortalidade desses pacientes.

Atualmente, a base do tratamento da IC-FEP envolve o controle de sintomas e o manejo de comorbidades que predispõem os indivíduos à condição, incluindo hipertensão, diabetes, isquemia e arritmias[1, 29]. Dentre esses fatores de risco, a hipertensão e, consequente, hipertrofia ventricular esquerda são os mais prevalentes e altamente associados à IC-FEP. A contribuição significativa da hipertensão para a disfunção diastólica indica que

o controle da hipertensão pode ser benéfico não só para o tratamento, mas também para a prevenção da própria síndrome[30]. O controle adequado da hipertensão pode promover benefícios em curto prazo por favoravelmente alterar condições de carga, e em longo prazo, levando à regressão da hipertrofia ventricular esquerda[30].

Recentemente, contudo, uma nova hipótese sobre o curso fisiopatológico da IC-FEP tem sido estudada. Mohammed e col. analisaram os dados de densidade microvascular (DMV) e fibrose miocárdica em pacientes com IC-FEP, obtidos a partir dos relatórios de autópsia[31]. Nesse estudo, a redução da DMV observada foi independente da gravidade da estenose da artéria coronária epicárdica ou de história de hipertensão. Além disso, a fibrose miocárdica foi inversamente associada com a DMV, mas não foi associada com a gravidade da doença arterial coronariana[31]. Ou seja, a redução da DMV e o aumento de fibrose miocárdica podem explicar, pelo menos em parte, o aumento da rigidez passiva ventricular.

Os autores sugerem que os achados encontrados podem elucidar a patogênese da IC-FEP como resultado do envelhecimento, múltiplas comorbidades e, provavelmente, fatores ainda não identificados. Há um estado pró-inflamatório sistêmico que resulta em disfunção arterial sistêmica e microvascular e aumento da rigidez ventricular[31, 32].

Sódio e líquidos na IC: recomendações

Por ser eficaz na redução do estado congestivo, a restrição de sódio e líquidos é a medida de autocuidado mais frequentemente orientada aos pacientes com IC. Contudo, os dados disponíveis na literatura sobre os quais

essa recomendação é baseada são escassos e os poucos estudos conduzidos tem demonstrado resultados inconsistentes[33].

A falta de consenso sobre essa orientação pode ser observada nas atuais diretrizes de manejo da IC, que falham em ter uma orientação única[1, 2, 12]. As diretrizes da American College of Cardiology/American Heart Association (ACC/AHA)[1] recomendam a restrição de líquidos em pacientes sintomáticos para manejo de sintomas congestivos, sem determinar um volume específico de restrição, assim como as diretrizes da Sociedade Brasileira de Cardiologia (SBC)[2]; enquanto a European Society of Cardiology (ESC) indica restrição de 1,5 a 2 litros/dia[12]. Com relação ao consumo de sódio dietético, as diretrizes da ESC e SBC recomendam um consumo de até 2,4g de sódio/dia, enquanto as diretrizes americanas (ACC/AHA) fazem orientações conforme o estágio da IC, indicando consumo de até 1,5g de sódio/dia para pacientes nos estágios A e B e menor que 3g para os estágios C e D.

Sódio e líquidos na IC: impacto clínico e mecanismos envolvidos

Um consumo excessivo de sódio pode aumentar o risco de desenvolvimento de IC, uma vez que está diretamente relacionado com o aumento da pressão arterial e, consequentemente, ao risco de desenvolvimento de hipertrofia e disfunção do ventrículo esquerdo[34].

De maneira geral, a manutenção do volume extracelular é regulada pelo balanço entre o consumo dietético e a excreção urinária de sódio. Quando esse consumo é aumentado, ocorre retenção de sódio e de água, expandindo esse volume. O aumento de volume leva, consequentemente, a ativação de

mecanismos compensatórios para promover a excreção urinária de sódio, porém com continuada retenção deste íon e água[34].

No cenário da IC, a função cardíaca reduzida e a pressão venosa sistêmica elevada podem levar a uma perfusão renal diminuída e, por sua vez, à ativação excessiva do sistema renina-angiotensina-aldosterona (SRAA). Além disso, observa-se um aumento do apetite ao sódio como um sintoma da doença, mediado em grande parte por hormônios efetores do SRAA[35, 36].

Essas alterações acarretam um ciclo vicioso de retenção de sódio e água apesar da sobrecarga do fluido, estando, dessa maneira, relacionado com a fisiopatologia da descompensação e o aparecimento da IC congestiva[35, 37].

Estudos têm demonstrado, contudo, que a restrição de sódio pode, também, estar relacionada a uma maior ativação neuro-hormonal em pacientes com IC[38-42]. Além disso, em estudos experimentais, tem sido demonstrado que uma dieta restrita em sódio pode levar a uma diminuição no débito cardíaco e um aumento da resistência vascular devido à ativação do SRAA[33]. A relação entre o consumo de sódio e as alterações neuro-hormonais na IC estão esquematicamente descritos na Figura 1.

As manifestações da descompensação da IC podem também influenciar negativamente diversos fatores relacionados com a ingestão de alimentos. Alterações morfológicas e funcionais significativas no intestino desses pacientes já foram descritas. Dentre essas alterações, destacam-se o espessamento da parede intestinal, sugestivo de edema, e disfunções da barreira intestinal, que podem estar envolvidos na má absorção de nutrientes e presença de náuseas e sensação de plenitude[43, 44].

Ao investigar os fatores que afetam o consumo alimentar em pacientes com IC, Lennie e col. destacam as restrições alimentares, a saciedade precoce e a fadiga como principais fatores. Além disso, destacam que um dos maiores impedimentos para aumentar com sucesso a palatabilidade da dieta relacionou-se com as restrições dietéticas, principalmente a restrição de sódio[45].

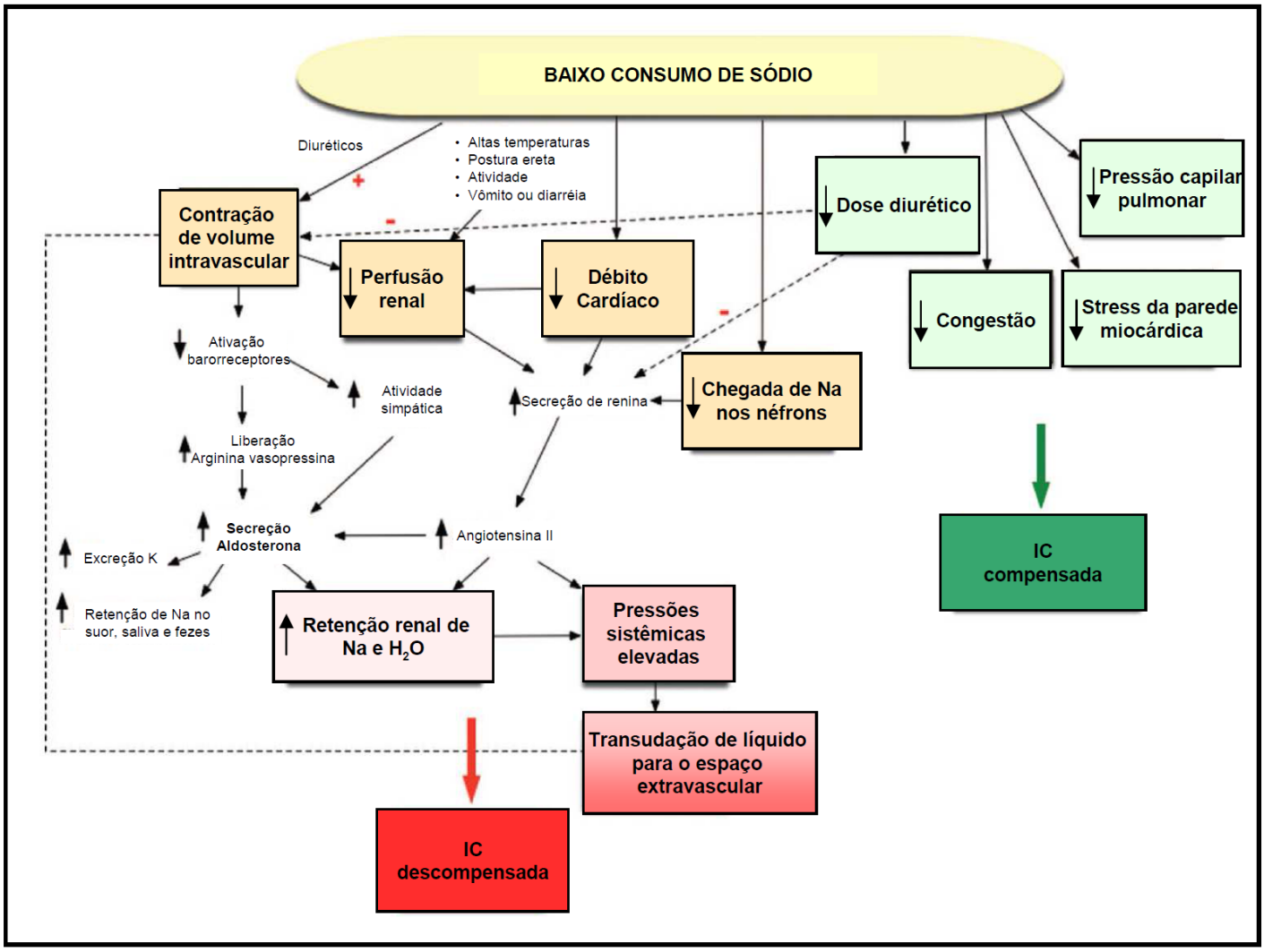

Figura 1 – Consumo de sódio e IC (adaptado de Gupta et al., 2012)[33].

Sódio e líquidos na IC: evidências

Diversos estudos têm investigado os efeitos do consumo de sódio e líquidos em pacientes com IC (Tabela 1). Com relação à investigação da fisiopatologia, Damgaard e col.[41] observaram uma diminuição do índice cardíaco e do volume sistólico, além de aumento na resistência vascular quando os pacientes consumiam uma dieta com restrição de sódio (1,6g sódio). Mais recentemente, no entanto, Hummel e col. observaram redução na pressão arterial e melhora na função ventricular e elasticidade arterial em pacientes estáveis com IC-FEP que seguiram uma dieta com restrição de 1,2g sódio/dia[46]. Estudos conduzidos por Volpe e col.[47, 48] concluíram que o consumo de 5,75g de sódio não apresentou efeitos hemodinâmicos, contudo, houve diminuição na capacidade de excreção de sódio em pacientes com IC.

Sobre as respostas neuro-hormonais (renina e aldosterona), observou-se maior ativação no grupo restrição na maioria dos estudos[38-42, 47, 49]. Além disso, os níveis de peptídeo natriurético tipo-B (BNP) foram afetados de forma inconsistente entre os estudos[38-42, 48-51].

Na investigação de desfechos de readmissões e morte, observou-se, no grupo restrição, maior número de internações em três estudos[38, 39, 52] e menor em dois estudos[53, 54]. Ao comparar as readmissões por categorias de classe funcional, Lennie e col. evidenciaram que um consumo menor de sódio (<3g/dia) foi associado com piores desfechos para pacientes em classe funcional I e II e que esse resultado foi inverso quando eram avaliados os pacientes com classe funcional III e IV[55]. Resultados semelhantes foram relatados por Song e col., em que um consumo menor (<2g/dia) foi associado a um maior número de eventos em pacientes em classe funcional I e II[56].

Portanto, estes dois estudos levantam a possibilidade de que a restrição de sódio e líquidos, pelo menos em pacientes menos graves, pode ser inclusive deletéria.

Além da avaliação dos efeitos da restrição de sódio na ativação neuro-hormonal e hospitalizações, seu impacto no consumo alimentar de pacientes com IC também tem sido alvo de estudos[42, 57]. Jefferson col., ao comparar o consumo alimentar de pacientes com IC com e sem restrição, observaram um menor consumo de energia, quando os pacientes consumiram a dieta restrita em sódio[57].

O impacto de restrição hídrica no tratamento da IC também foi recentemente avaliado em duas metanálises[58, 59]. Não foram observadas diferenças significativas entre os grupos em relação às hospitalizações (RR=1,32 [0,86-2,01]; p=0,2), mortalidade (RR=1,50 [0,87-2,57]; p=0,14) e sensação de sede (p=0,46), além do tempo de terapia intravenosa com diuréticos (p=0,81) e sódio sérico (p=0.06). Contudo, os níveis séricos de creatinina e BNP aumentaram no grupo com ingestão mais liberal de líquidos (p<0,001)[58]. Os autores concluem que um consumo hídrico mais liberal não parece ter um efeito desfavorável em relação a hospitalizações por descompensação da IC e morte por todas as causas[58]. Além disso, considerando o fato de que não foi encontrada superioridade da restrição hídrica nos desfechos avaliados, desaconselham a implementação sistemática da restrição de líquidos no manejo dos pacientes[59]. Contudo, apontam limitações como a heterogeneidade das intervenções e o pequeno tamanho amostral, destacando a necessidade de mais estudos controlados para confirmar estes achados[58, 59].

Ainda que diversos estudos tenham avaliado os efeitos da restrição de sódio e líquidos na IC; a busca por evidências de ensaios clínicos randomizados revela as lacunas ainda existentes, principalmente no que diz respeito ao cenário da descompensação, sendo avaliado em apenas um estudo[50]. Além disso, a comparação entre esses estudos é dificultada pela variação no tamanho amostral, desenho do estudo, além do grau de restrição de sódio e líquidos e avaliação da ingestão destes. Com exceção de alguns estudos observacionais e três estudos de intervenção que incluíram em sua amostra pacientes com IC-FEP, os efeitos da restrição de sódio e líquidos na ativação neuro-hormonal e estabilidade clínica nesse fenótipo da IC ainda é pouco explorado e, portanto, o papel da restrição nesses pacientes permanece incerto.

Tabela1. Revisão de estudos sobre restrição de sódio e líquidos na Insuficiência Cardíaca

Autor	N	Pacientes	Desenho do estudo	Variáveis	Principais resultados	Relevância Clínica
Volpe et al[47]	24	12 IC estáveis + 12 controles FE <50% NYHA I e II	Drogas descontinuadas por 2 semanas 5 dias – 2,3g sódio 6 dias – 5,75g sódio Líquidos 1500 a 1800ml	Renina, Aldosterona, ECO, Sódio 24hs	Sem alterações hemodinâmicas, mas redução na habilidade de excreção de sódio	Neutro
Volpe et al[48]	20	10 IC estáveis+ 10 controles) FE <50% NYHA I e II	Drogas descontinuadas por 3 semanas 6 dias – 2,3g sódio 8 dias – 5,75g sódio Líquidos 1500 a 1800ml	BNP, ANP, Sódio 24hs	Sem alterações hemodinâmicas, mas redução na habilidade de excreção de sódio	Neutro
Alvelos et al[49]	24	Pacientes estáveis FE<40%	ECR 12pcts – 2,3g sódio 12pcts – dieta normal 15 dias	L-DOPA, BNP, Aldosterona, Creatinina, Na e Cr 24hs	Dieta 2,3g sódio: ↑ativação SRAA ↓L-DOPA, BNP, Peso	Não restringir
Damgaard et al[41]	24	12 IC estáveis + 12 controles FE<40% NYHA II-III	1,6g sódio – 7dias 5,75g sódio – 7 dias Líquidos livres	IC, PP, Resistência, periférica Norepinefrina, BNP, Angiotensina II, Sódio 24hs	Dieta 5,75g: ↑ performance cardíaca Induz vasodilatação periférica ↓ angiotensina II e norepinefrina	Não restringir
Paterna et al[38]	232	Pacientes estáveis FE <35% NYHA II – IV	ECR 118pcts – 2,8g sódio 114pcts – 1,8g sódio + Furosemida 250 -500 BID Líquidos 1000ml 30 e 180 dias	Sinais de descompensação, Peso, pressão arterial, ECO BNP, Aldosterona, Renina, Readmissões	Dieta 2,8g sódio: ↓ readmissão e BNP Dieta 1,8g sódio: ↑ Renina e Aldosterona	Não restringir

Paterna et al[39]	410	Pacientes estáveis FE <35% NYHA II – IV	ECR 8 grupos: 1,8g ou 2,8g sódio + Diferentes doses furosemida 1000 ou 2000 ml líquidos 30 e 180 dias	Sinais de descompensação, Peso, pressão arterial, ECO BNP, Aldosterona, Renina, Readmissões	Grupo A (2,8g sódio/ 1000ml / 250mg BID furo): ↓ readmissões ↓ BNP, renina, aldosterona	Não restringir
Parrinelo et al[40]	173	Pacientes estáveis FE <35% NYHA II – IV	ECR 86pcts – 2,8g sódio 87pcts – 1,8g sódio + Furosemida 125-250 BID Líquidos 1000ml 12 meses	BNP, Renina, Aldosterona, TNF-α, Interleucina 6 e 10	Dieta 2,8g sódio: ↑ Interleucina 10 ↓ TNF-α, int. 6 ↓ BNP, renina e aldosterona	Não restringir
Nakasato et al[42]	50	Pacientes estáveis FE ≤40% NYHA I – III	ECR Fase 1 (todos): 0,8g sódio – 7 dias Fase 2 (randomizados): 0,8g sódio ou 2,4g – 7 dias Líquidos 1000 ml	Aldosterona, renina, norepinefrina, BNP, consumo alimentar, qualidade de vida	Dieta 0,8g sódio: ↑ norepinefrina ↑ aldosterona ↓ consumo	Não restringir
Arcand et al[54]	123	Pacientes estáveis FE <35%	COORTE Tercis de consumo: ≤1,9g sódio 2,0-2,7g sódio ≥2,8g sódio 36 meses	Sinais descompensação, Readmissões e morte	Tercil ≥ 2,8g sódio: ↑ admissões e mortalidade	Restringir
Lennie et al[55]	302	Pacientes estáveis IC sistólica e diastólica NYHA I-IV	COORTE Consumo sódio: <3g ou ≥3g 12 meses	Sobrevida livre de eventos (hospitalizações e/ou morte)	Grupo <3g sódio I-II: ↑eventos III-IV: ↓eventos	I-II: Não restringir III-IV: Restringir

Aliti et al[50]	75	Pacientes descompensados FE ≤45%	ECR 38pcts – 0,8g sódio + 800ml líquidos 37pcts – dieta normal 7dias	Peso, Estabilidade clínica, Sede, BNP, Readmissões	Grupo 0,8g: Maior sensação de sede, sem efeitos nas demais variáveis	Neutro
Philipson et al[53]	97	Pacientes estáveis IC sistólica ou diastólica NYHA II-IV	ECR 49pcts – 2g sódio + 1500ml 48pcts – orientações alimentação saudável 12 semanas	Desfecho combinado: Classe funcional, edema, peso, sede, qualidade de vida, readmissões	Grupo 2g + 1,5l: Maior % de melhora dos desfechos	Restringir
Hummel et al[46]	13	Pacientes estáveis FE≥ 50% NYHA I-III	Dieta DASH (1,2g sódio) 21 dias	Pressão arterial, Função ventricular, Elasticidade arterial	Dieta DASH: ↓ pressão arterial ↑ função ventricular e elasticidade arterial	Restringir
Song et al[56]	244	Pacientes estáveis IC sistólica e diastólica NYHA I-IV	COORTE Tercis de consumo: <2g sódio 2-3g sódio >3g sódio 12 meses	Sobrevida livre de eventos (hospitalizações e/ou morte)	Tercil <2g sódio: I-II: ↑ eventos Tercil >3g sódio: III-IV: ↑ eventos	I-II: Não restringir III-IV: Restringir
Colin-Ramirez et al[51]	38	Pacientes estáveis IC sistólica e diastólica NYHA II-III	ECR 19pcts – <1,5 sódio 19pcts – <2,3g sódio 6 meses	BNP, Qualidade de vida	Grupo <1,5g sódio: ↓ BNP ↑ qualidade de vida	Restringir
Doukky et al[52]	260	Pacientes estáveis IC sistólica e diastólica NYHA II-III	COORTE Consumo sódio: <2,5g ou ≥2,5g 36 meses	Hospitalizações e morte por IC	Grupo <2,5g sódio: ↑ desfecho combinado de morte e/ou hospitalizações	Não restringir

2. JUSTIFICATIVA DO ESTUDO E OBJETIVOS

Justificativa

Ainda que metade dos pacientes com IC apresente IC-FEP, e que o prognóstico pouco difira daqueles com fração de ejeção reduzida, a fisiopatologia e tratamento deste fenótipo continuam mal compreendidos. Até o momento, os grandes ensaios clínicos falharam em demonstrar a eficácia de qualquer tratamento específico sobre a mortalidade desses pacientes. Atualmente, a base do tratamento envolve o controle de sintomas e o manejo de comorbidades que predispõem os indivíduos a esta condição.

A prescrição da restrição de sódio e líquidos é a mais frequente medida de autocuidado orientada para pacientes com IC para manejo de episódios congestivos. Seu papel no tratamento de pacientes com fração de ejeção preservada, contudo, ainda é incerto. A avaliação dos efeitos dessa restrição sobre a ativação neuro-hormonal e episódios de descompensação na IC-FEP pode promover aprofundamento do conhecimento fisiopatológico e da progressão dessa complexa síndrome e beneficiar pacientes.

Hipótese

A restrição agressiva de sódio e líquidos tem efeito sobre a perda de peso corporal, tempo para estabilidade clínica e ativação neuro-hormonal em pacientes com IC-FEP hospitalizados por descompensação IC.

Objetivo geral

Comparar o efeito de uma dieta com restrição agressiva de sódio (0,8g) e líquidos (800ml) com uma dieta sem restrição em pacientes com IC-FEP na redução do peso corporal, estabilidade clínica e ativação neuro-hormonal.

Objetivos específicos

Comparar o efeito de uma dieta com restrição agressiva de sódio e líquidos com uma dieta sem restrição:

- Na percepção de sede;
- Em variáveis laboratoriais (creatinina, ureia, sódio e potássio);
- No consumo alimentar;
  - Macronutrientes;
  - Micronutrientes;
  - Líquidos
- Em readmissões hospitalares e óbitos 30 dias após a alta;

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ARTIGOS

4. ARTIGO 1

STUDY PROTOCOL Open Access

Effect of fluid and dietary sodium restriction in the management of patients with heart failure and preserved ejection fraction: study protocol for a randomized controlled trial

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Abstract

Background: Although half of all patients with heart failure (HF) have a normal or near-normal ejection fraction and their prognosis differs little from that of patients with a reduced ejection fraction, the pathophysiology of HF with preserved ejection fraction (HF-PEF) is still poorly understood, and its management poorly supported by clinical trials. Sodium and fluid restriction is the most common self-care measure prescribed to HF patients for management of congestive episodes. However, its role in the treatment of HF-PEF remains unclear. This trial seeks to compare the effects of a sodium- and fluid-restricted diet versus an unrestricted diet on weight loss, neurohormonal activation, and clinical stability in patients admitted for decompensated HF-PEF.

Methods/Design: This is a randomized, parallel trial with blinded outcome assessment. The sample will include adult patients (aged ≥18 years) with a diagnosis of HF-PEF admitted for HF decompensation. The patients will be randomized to receive a diet with sodium and fluid intake restricted to 0.8 g/day and 800 mL/day respectively (intervention group) or an unrestricted diet, with 4 g/day sodium and unlimited fluid intake (control group), and followed for 7 days or until hospital discharge. The primary outcome shall consist of weight loss at 7 days or discharge. The secondary outcome includes assessment of clinical stability, neurohormonal activation, daily perception of thirst and readmission rate at 30 days.

Discussion: Assessment of the effects of sodium and fluid restriction on neurohormonal activation and clinical course of HF-PEF can promote a deeper understanding of the pathophysiology and progression of this complex syndrome.

Trial registration number: ClinicalTrials.gov identifier: NCT01896908 (date of registration: 8 August 2013).

Keywords: Heart failure, Dietary sodium, Preserved ejection fraction, Randomized clinical trial

Background

Heart failure (HF) with preserved ejection fraction (HF-PEF), historically known as diastolic HF, is the clinical syndrome characterized by HF with normal or near-normal systolic function [1]. More recent epidemiological studies and registries have suggested that HF with reduced ejection fraction and HF-PEF are equally prevalent, with the latter accounting for 40 to 71% (mean approximately 50%) of cases [2,3].

The etiology and epidemiology of HF-PEF appear to be distinct from those of HF with reduced ejection fraction. Women and older adults with comorbidities such as hypertension, diabetes, obesity, and coronary artery disease are more commonly affected [4-8].

Despite the importance of HF-PEF, the pathophysiology and treatment of this phenotype of HF are still poorly understood. Thus far, the major clinical trials (I-Preserve,

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PEP-CHF, CHARM-Preserved, DIG-CHF and TOPCAT trial) [9-13] have failed to demonstrate the efficacy of any specific treatment on mortality in these patients.

Currently, the mainstay of HF-PEF treatment is symptomatic care and management of comorbidities that predispose patients to this condition, including hypertension, diabetes, ischemia, and arrhythmias [14,15], and include guidance on lifestyle modifications, such as restricted sodium and fluid intake [14,15]. Sodium restriction is the self-care measure most commonly prescribed to patients with HF, as it appears to be effective in reducing congestion. However, the evidence base for this recommendation is scarce, and the few studies that have been conducted have yielded inconsistent findings [16-25]. Research has focused on the physiological effects of intake of different amounts of sodium, and few have assessed morbidity and mortality outcomes [17-25]. Except for an observational study by Lennie and colleagues [24] that compared number of hospital admissions and emergency department visits between patients with a sodium intake of >3 g/day versus <3 g/day, no studies have evaluated the effects of sodium restriction in patients with HF-PEF; therefore, its role in these patients remains unknown. Recently, however, Hummel and colleagues [26], investigating the effects of the sodium restricted DASH diet, showed an increased urinary aldosterone excretion during low-sodium diet in patients with HF-PEF.

In an attempt to bridge the knowledge gap in patients with decompensated HF-PEF, this trial seeks to compare the effect of a sodium- and fluid-restricted diet versus an unrestricted diet on weight loss, neurohormonal activation, and clinical stability at 7 days or at hospital discharge in patients admitted for decompensation of HF-PEF.

Methods/Design

Study design and centers

This is a randomized, parallel trial with blinded outcome assessment. The study population will comprise patients with a diagnosis of HF-PEF who have presented to hospital with HF decompensation. The study will be carried out at Hospital de Clínicas de Porto Alegre (HCPA), Brazil, and take place at the Emergency Department or other inpatient units.

Inclusion and exclusion criteria

The sample will include adult patients with a diagnosis of HF (and left ventricular ejection fraction >50%) within 36 hours of hospital admission for decompensation of HF – defined as clinical signs of congestion, history of dyspnea and orthopnea in the week before hospitalization, and B-type natriuretic peptide (BNP) levels >100 pg/mL – who agree to take part in the study and provide written informed consent. Patients with an estimated glomerular filtration rate (Modification of Diet in Renal Disease formula) ≤30 mL/minute, those with cardiogenic shock, HF due to valvular disease and those whose survival is jeopardized by another ongoing condition and/or by difficulty adhering to treatment (for example, due to dementia or cognitive deficits) will be excluded.

Ethical considerations

All procedures were conducted in accordance with the ethical standards for human subject research set forth in the Declaration of Helsinki. Written informed consent shall be obtained from all patients included in the trial. The project was approved by the Research Ethics Committee of Hospital de Clínicas de Porto Alegre (registration number 12–0437) and is registered in the ClinicalTrials.gov database under identification number NCT01896908.

Sample size

Sample size calculations were carried out in WINPEPI 11.20 (Brixton Health, Israel). We used the weight loss values reported in the studies of Aliti and colleagues [25] and Cardoso and colleagues [27], which assessed weight loss in patients with HF and systolic dysfunction admitted for HF decompensation and congestion. For a significance level of $\alpha = 0.05$ and a statistical power of 80%, with a standard deviation of 3 kg and a between-group difference in weight corresponding to a weight loss of 2 kg in 7 days, the minimum sample size will be 74 patients (37 randomized to each group).

Interventions

The control group (CG) will receive the standard hospital diet, which provides approximately 4 g sodium (10 g salt)/day and unlimited fluid intake. The intervention group (IG) will receive an otherwise identical diet restricted to 0.8 g sodium (2 g salt)/day and 800 mL fluids/day until the 7th day of admission or hospital discharge, whichever comes first.

Study protocol

Patients who meet the inclusion criteria and are eligible will be invited to take part in this trial during their hospitalization. Data will be collected on sociodemographic parameters, clinical variables, results of laboratory tests performed as part of routine patient care (creatinine, urea, potassium, sodium, complete blood count, and BNP on admission), current medications, body weight, and clinical congestion score, and blood will be collected for assessment of neurohormonal activation. Patients will then be randomized to IG or CG.

Once allocation has been completed, the on-call dietitian will be notified so as to change the participants' meal plan as appropriate. The same dietary prescription will be used for participants in both the IG and CG: *DIET AS PER RESEARCH PROTOCOL. PATIENT WILL RECEIVE*

DIET UNTIL __/__ OR DISCHARGE. PLEASE DO NOT ALTER DIET. This practice will be implemented in agreement with the medical staff and with the hospital Department of Nutrition and Dietetics.

A daily check of medical records will be performed to identify modification of any drug prescription. The search for hypotensive episodes will be performed by checking blood pressure every 6 hours and by questioning patients about symptoms of hypotension (dizziness, fainting or lightheadedness) on a daily basis.

Outcomes assessment 30 days after discharge will be carried out at the study facility by means of a face-to-face encounter between the investigators and each participant, at which time a clinical assessment will be performed and blood will be collected for analysis of neurohormonal activation (Figure 1).

Randomization

The randomization will be performed through a simple sequential randomization plan generated online, using the www.randomization.com website.

Blinding

During hospitalization, the medical staff involved in patient care will be blind to group allocation. All clinical assessments during hospitalization and at 30-day follow-up will be conducted by a nurse also blinded to group allocation.

Variables in the study

Clinical variables

Clinical congestion score The clinical congestion score is an instrument composed of seven questions designed to assess signs and symptoms of congestion, including presence of pulmonary crackles, third heart sound, jugular venous distension, peripheral edema, hepatojugular reflux, orthopnea, paroxysmal nocturnal dyspnea, and New York Heart Association functional class. This score ranges from 1 to 22 points, with higher scores being directly indicative of worse congestion [28].

Blood pressure and heart rate Blood pressure and heart rate will be measured by the trial investigators shortly after randomization.

Estimation of glomerular filtration rate The Modification of Diet in Renal Disease formula will be used for estimation of the glomerular filtration rate [29].

Left ventricular ejection fraction The left ventricular ejection fraction will be assessed by means of echocardiography, using the Teichholz method or, if available, the Simpson method.

Body weight Weight will be measured with participants barefoot, wearing minimal clothing, and standing on the center of a digital platform scale, and recorded in a spreadsheet.

Medical history Data on the etiology of HF, history of present illness, past medical history, comorbidities, and current medications will be collected from patient records and checked during the patient interview.

Demographic variables

A structured questionnaire will be administered to all participants for collection of demographic parameters (age, sex, ethnicity), socioeconomic, and educational data.

Laboratory variables

Blood samples will be collected by a trained professional at the time of study enrollment, at hospital discharge, and 30 days after discharge. Samples will be centrifuged at 4°C, 3,670 rpm, for 10 minutes and stored in Eppendorf tubes at −80°C for later analysis of neurohormonal activation (renin and aldosterone).

General blood work General blood work will comprise of complete blood count, urea (ultraviolet kinetic assay), serum creatinine (Jaffé method), plasma sodium and potassium (ion selective electrode).

B-type (brain) natriuretic peptide Immunofluorescence methods will be used for quantitation of BNP in plasma.

Renin A radioimmunoassay for measurement of angiotensin I generated by the action of renin on its substrate, angiotensinogen, will be used for quantitation of plasma renin activity.

Aldosterone A solid phase radioimmunoassay based on aldosterone-specific antibodies will be used for quantitation of serum aldosterone levels.

Primary outcome

The primary outcome measure shall consist of weight loss at 7 days or discharge.

Secondary outcomes

The secondary outcome measures shall consist of:

a) Clinical stability, defined as improvement in symptoms with no evidence of congestion (assessed by congestion score); weight stable for 2 days, with no loss or gain greater than 1 kg (daily weight check); no intravenous HF drugs for 48 hours (daily medication record: diuretics, vasodilators); no

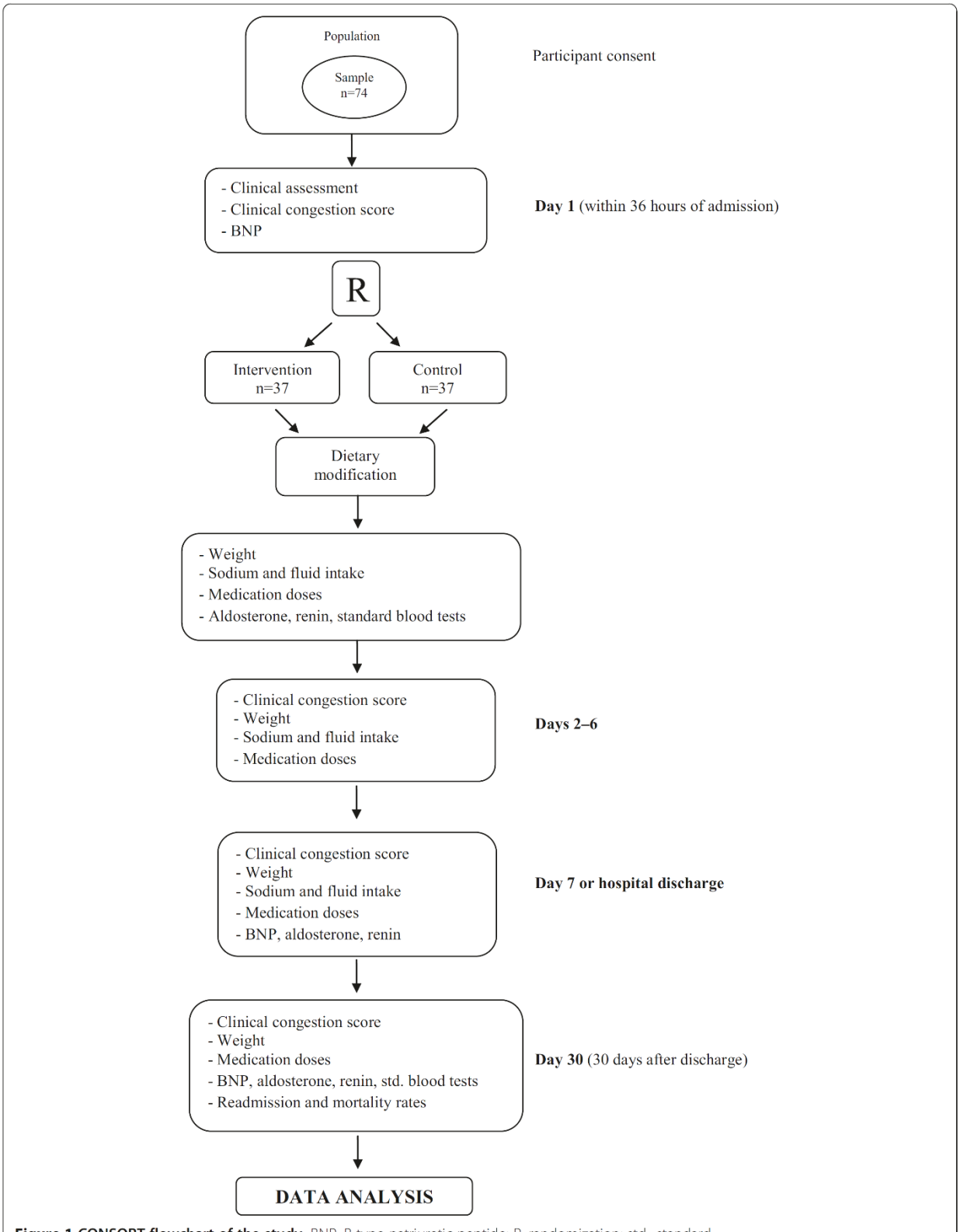

Figure 1 CONSORT flowchart of the study. BNP, B-type natriuretic peptide; R, randomization; std., standard.

increase in diuretics dose for 48 hours (daily medication record).

b) Neurohormonal activation: assessment of neurohormonal activation shall include measurement of serum renin, aldosterone, and BNP levels on admission, at discharge, and at 30 days.

c) Daily perception of thirst: a visual scale (with values ranging from 0 to 10) will be used daily to verify the degree of thirst.

d) Hospital readmission rate for all-causes. Patients shall be followed for 30 days after discharge.

Statistical analyses

Continuous variables following a normal distribution will be expressed as mean ± standard deviation; asymmetrically distributed continuous variables will be expressed as median and interquartile range; and categorical variables will be expressed as absolute and relative frequencies. For between-group comparisons, Student's *t*-test will be used for normally distributed variables, and the Mann–Whitney *U* test for asymmetrically distributed variables. A paired *t*-test will be used for within-group analysis of body weight and congestion score. The chi-square or Fisher's exact tests will be used to evaluate associations between categorical variables. The generalized estimating equations test with Bonferroni adjustment will be used for comparison between variables during the study period. The significance level will be set at 5%, and all data will be analyzed in SPSS 18.0 (SPSS Inc., Chicago, IL, USA).

For assessment of clinical stability, in accordance with pre-established criteria, two blinded examiners (physician HF specialists not involved in the care of the study participants) will analyze the outcome variables in both groups.

Discussion

During protocol, patients will receive the standard hospital diet for both the control (normal diet) and intervention group (low-sodium diet), modified only in the amount of fluid offered to the intervention group. During the study, patients will be instructed to consume only foods and beverages offered by the hospital. The plate-waste method shall be used to measure sodium intake for 7 days or until hospital discharge, whichever comes first. A trained investigator will assess dietary intake twice daily: after lunch, for collection of information on intake during breakfast, morning snack, and lunch; and after dinner, for collection of information on intake during the afternoon snack, dinner, and supper. In addition, a visual scale (with values ranging from 0 to 10) will be used to verify the degree of thirst.

Trial status

The trial is ongoing. Thirteen patients have completed the study protocol and additional patients are being recruited.

Abbreviations

BNP: B-type natriuretic peptide; CG: control group; HF: heart failure; HF-PEF: heart failure with preserved ejection fraction; IG: intervention group.

Competing interests

The authors declare that they do not have any competing interests.

Authors' contributions

KSMD, MMT, SLSB and JVM will conduct the data collection. KSMD, ERRS, GCS, AB, LEPR, NC and LBS conceived the study and drafted this manuscript. ERRS will be responsible for the randomization. KSMD, ERRS, GCS and LBS will participate in the data analysis. All authors read and approved the final manuscript.

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5. ARTIGO 2

AGGRESSIVE FLUID AND SODIUM RESTRICTION IN HEART FAILURE WITH PRESERVED EJECTION FRACTION DO NOT CHANGE CLINICAL OUTCOMES: RESULTS FROM A RANDOMIZED CLINICAL TRIAL

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ABSTRACT

Importance: Sodium and fluid restriction is commonly prescribed for heart failure patients for the management of congestive episodes. However, its role in the treatment of heart failure with preserved ejection fraction (HFpEF) remains unclear.

Objective: To compare the effect of a diet with sodium and fluid restriction with an unrestricted diet, on weight loss, clinical stability, daily perception of thirst, neurohormonal activation, nutrient intake and readmission and mortality rate in patients admitted for decompensated HFpEF.

Design, Setting and Participants: Randomized Clinical Trial. Adult patients with decompensated HFpEF were included.

Methods: Patients were randomized to receive a diet with sodium (0.8g/day) and fluid (800mL/day) restriction in the intervention group (IG) or an unrestricted diet and unlimited fluid intake in the control group (CG) and followed for 7 days or until hospital discharge.

Main outcomes and measures: The primary outcome was weight loss. Secondary outcomes include clinical stability (Clinical Congestion Score), perception of thirst, neurohormonal activation, nutrient intake, and readmission and mortality rate after 30 days.

Results: Fifty-three patients were included (30, IG; 23, CG). Predominately female (68%), with a mean age of 72±12 years. The mean ejection fraction was 62±8% for IG and 60±7% for CG (P=.44). The median length of stay was 6 (1-17) days for IG and 4 (2-8) for CG (P=.52). Weight loss was similar in both groups, being 1.6±2.2kg in the IG and 1.8±2.1kg in CG (P=.49) as well as the reduction in the congestion score (IG= 3.4±3.5; CG= 3.8±3.4, P=.70). The daily

perception of thirst was higher in the IG (P=.03). There were no significant differences in the between-group variation for serum sodium, potassium, creatinine and urea values at baseline, as well as in neurohormonal activation. There was a lower energy consumption in the IG (P<.001). No significant between-group differences regarding readmissions and mortality at 30 days were found.

Conclusions and relevance: Aggressive sodium and water restriction do not provide symptomatic or prognosis benefits; produces greater perception of thirst; may impair the patients´ food intake and does not seem to have an important neurohormonal effect in patients admitted for decompensated HFpEF.

Trial Registration: clinicaltrial.gov Identifier: NCT01896908.

Keywords: Heart Failure, preserved ejection fraction, Heart failure, diastolic, Sodium restriction, Fluid restriction

INTRODUCTION

Heart failure (HF) with preserved ejection fraction (HFpEF) is a complex and heterogeneous clinical syndrome characterized by HF with normal or near-normal systolic function[1,2]. Among patients with HF, the prevalence of HFpEF is approximately 50%[1,3]. In addition, it is estimated that by 2020, HFpEF will exceed 8% of the population aged over 65 years and its relative prevalence is predicted to be 69%, becoming HFpEF, the most common phenotype among patients with HF[1]. The growing epidemic of HFpEF seems to be related to the increasing rates of associated comorbidities, due to increased life expectancy and an aging population; it is associated with poor outcomes[4].

In contrast to HF with reduced ejection fraction, current HF pharmacotherapy did not improve outcomes in HFpEF[5-9]. This lack of efficacy underscores the pathophysiological differences between these syndromes.

The mainstay of treatment is, to date, symptomatic care and management of comorbidities that predispose patients to this condition[1,4]. Sodium and fluid restriction are frequently prescribed to patients with HF, as it appears to be effective in reducing congestion[10], despite a lack of clear evidence on their therapeutic effects. The lack of agreement in this orientation can be seen in current HF management guidelines, which fail to have consistent recommendations [11-13].

Although several studies have evaluated the effects of sodium and fluid restriction in patients with HF[14-21], the search for evidence from randomized trials reveals the remaining gaps, particularly in the setting of HF decompensation, evaluated in only one trial[17]. Therefore, doubts remain about the potential benefit or harm of sodium and fluid restriction in patients with

clinical congestion. Moreover, with the exception of some observational studies and interventional studies that included patients with HFpEF in their samples [15,18,21-24]; the effects of sodium and fluid restriction in HFpPEF is poorly documented and therefore, its role in these patients remains unknown.

This trial seeks to compare the effect of an aggressive fluid and sodium restricted diet versus an unrestricted diet on weight loss, clinical stability, daily perception of thirst, neurohormonal activation, nutrient intake and readmission and mortality rate at 30 days in patients admitted for decompensated HFpEF.

METHODS

Study design

This was a randomized, parallel trial with blinded outcome assessment. We evaluated patients with a diagnosis of HFpEF who were admitted to hospital due to HF decompensation between March 2013 and July 2016, at a public teaching hospital. The trial was approved by the local Research Ethics Committee and is registered in the ClinicalTrials.gov database under identification number NCT01896908.

Inclusion and exclusion criteria

Adult patients with a diagnosis of HF and left ventricular ejection fraction (EF) ≥50% admitted to hospital for decompensation of HF – defined as overt clinical signs of congestion, history of dyspnea and orthopnea in the week before hospitalization, and B-type natriuretic peptide (BNP) levels >100 pg/mL – were included. Patients with an estimated glomerular filtration rate ≤30 mL/minute, with cardiogenic shock, HF due to severe valvular disease and

those whose survival is jeopardized by another ongoing condition and/or by difficulty in adhering to treatment (for example, due to dementia or cognitive deficits) were excluded.

Intervention

The study intervention consisted of a sodium-restricted diet of 0.8g sodium (2g salt)/day and 800mL fluids/day (IG). Patients in the control group (CG) received the standard hospital diet, which provides approximately 4g sodium (10g salt)/day and unlimited fluid intake. Patients were evaluated until the 7th day of admission or hospital discharge, whichever came first.

Study protocol

This study protocol has been described elsewhere in detail[25]. After screening, potentially eligible patients were invited to participate in this trial during their hospitalization. Data were then collected on sociodemographic parameters, clinical variables, results of laboratory tests performed as part of routine patient care (creatinine, urea, potassium, sodium, complete blood count), current medications, body weight, and clinical congestion score, and blood samples were collected for assessment of neurohormonal activation. Patients were then randomly allotted to IG or CG groups.

Once allocation was completed, the on-call dietitian was notified to modify the participants' meal plans as appropriate and so that the randomized diet would be delivered at the next meal. The same dietary prescriptions were used for both groups: "*DIET AS PER RESEARCH PROTOCOL. PATIENT WILL*

RECEIVE DIET UNTIL __/__ OR DISCHARGE. PLEASE DO NOT ALTER DIET".

Study outcomes

Primary end-point

The primary end-point consisted of the evaluation of weight loss at 7 days or discharge. Body weight was measured by the investigators using digital scales. Patients were weighed every morning, wearing as little clothing as possible, while barefoot, standing at the center of the scale´s platform.

Secondary end-points

Clinical stability

Clinical stability was defined as improvement in symptoms with no evidence of congestion (assessed by congestion score) and cessation of all intravenous pharmacotherapy for HF.

The clinical congestion score (CCS) is an instrument composed of seven questions designed to assess signs and symptoms of congestion, including the presence of pulmonary crackles, third heart sound, jugular venous distension, peripheral edema, hepatojugular reflux, orthopnea, paroxysmal nocturnal dyspnea, and New York Heart Association functional class. This score ranges from 1 to 22 points, with higher scores being directly indicative of worsening congestion[26].

Daily perception of thirst

A visual scale (with values ranging from 0 to 10) was used daily to verify the degree of thirst.

Neurohormonal activation

The assessment of neurohormonal activation included measurements of serum aldosterone, plasma renin activity (PRA) and brain-type natriuretic peptide (BNP) levels on admission, and at discharge.

Nutrient intake

During the study, patients were instructed to consume only foods and beverages offered by the hospital. For the investigation of nutrient intake, a trained investigator assessed dietary intake twice daily: after lunch, for collection of information on intake during breakfast, morning snack, and lunch; and after dinner, for the collection of information pertaining to intake during the afternoon snack, dinner, and supper.

Hospital readmission and mortality for all-causes

Patients were followed for 30 days after discharge and these event rates were recorded.

Sample size

Sample size calculations were carried out in WINPEPI 11.43 (Brixton Health, Jerusalem, Israel). As an effect of size measurement, we used the weight loss values reported by Aliti et al.[17], which were assessed in patients with HF and systolic dysfunction admitted for HF decompensation as well as the

weight loss values obtained from the first ten patients allocated in this study. The mean values of these two sources were then used for sample size calculation. For a significance level of α=0.05 and a statistical power of 80%, with a standard deviation of 2.5kg and a between-group difference in weight corresponding to a weight loss of 2kg in 7 days, the minimum sample size would be 52 patients (26 randomly allocated to each group).

Randomization

Randomization was performed through a simple sequential randomization plan generated online, using the website www.randomization.com.

Blinding

During hospitalization, the medical staff involved with patient care were blinded to the group allocations. All clinical assessments during hospitalization and at the 30-day follow-up were conducted by a nurse, also blinded to group allocation.

Statistical analyses

Continuous variables following a normal distribution were expressed as mean ± standard deviation; asymmetrically distributed continuous variables were expressed as median and interquartile range; and categorical variables were expressed as absolute and relative frequencies. The statistical analysis aimed to compare intra-patient changes between treatment groups. Therefore, mixed effects models were conducted to measure such changes. For between-

group comparisons, Student's t-test was used for normally distributed variables, and the Mann–Whitney U test was performed for asymmetrically distributed variables. The chi-square or Fisher's exact test was used to evaluate associations between categorical variables. All analyses were performed by intention to treat. PRA and aldosterone data were log-transformed for analyses. The significance level was set at P<.05 and all data were analyzed in SPSS 20.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 308 patients with preserved EF were admitted for HF decompensation during the study period and were assessed for eligibility. Fifty-three patients were randomized (30 allocated to the IG and 23 to the CG). During the 30 day follow-up, five patients were lost from the study (IG, 4; CG, 1) due to being unavailable for contact to schedule the final evaluation visit. Four patients (IG, 2; CG, 2) died in this period. A Consolidated Standards for Reporting of Trials flow diagram of patient progress through the trial is shown in Figure 1.

Sociodemographic and clinical characteristics

Table 1 describes sample characteristics at baseline. In both groups, patients were predominately female with a mean age of 73.7 (11.1) years in the IG and 70.4 (12.6) years in the CG. The most commonly associated condition was hypertension (71.7%), followed by atrial fibrillation (49.1%) and diabetes mellitus (49.1%). The mean left ventricular ejection fraction was 61.6 (8.1%) in the IG and 60.0 (6.7%) in the CG and hypertension was the most prevalent

cause of HF in both groups (IG, 73.3% CG, 69.6%). There were no significant between group differences in the baseline characteristics. The overall median length of stay was 5 days (2-13), being 6 days (1-17) in the IG, and 4 days (2-8) in the CG (P=.52).

Weight loss

Figure 2 indicates weight variation during the intervention in both groups. Mean baseline body weight was 80.5 (17.8) kg in the IG and 77.6 (16.1) kg in the CG (P=.58). Weight loss was similar in both groups when evaluated at the third day of intervention (P>.99) and from baseline to the end of the study period (IG, -1.6 [2.2] kg vs GC, -1.8 [2.1] kg; P=.49).

Clinical stability

The mean CCS at baseline was 12.2 (3.2) points in the IG and 11.4 (2.7) points in the CG (P=.36). There were no significant between-group differences in the change of CCS at the third day of intervention (P=.10), and from baseline to the end of the study period (IG, -3.4 [3.5] points vs CG, -3.8 [3.4] points; P=.70). Both groups exhibited similar improvements in the CCS score (Figure 3).

Perceived thirst

The variation between groups in perceived thirst from baseline to the end of the study period is shown in Figure 4. There were no significant between-group differences in perceived thirst at baseline (IG, 4.2 [3.6] points vs CG, 5.8 [2.6] points; P=.14).

During the days of intervention, there was a statistically significant difference between groups regarding their perceived thirst (Figure 4). The IG had a significantly greater perception of thirst at days 3, 4 and 5 than the control group (time, P=.001; group, P=.02; time x group, P=.03).

Neurohormonal activation

The effects of the intervention on neurohormonal activation are described in Table 2. During intervention, both groups experienced similar variations in BNP (P=.85), PRA (P=.42) and aldosterone (P=.85) levels.

There was a consistent increase in PRA and aldosterone and a decrease in BNP levels, but no significant differences between groups.

Nutrient intake

Table 3 describes nutrient intake in both groups during the days of intervention. There was a lower energy consumption in the IG when compared to the CG (P<.001) with no effect on macronutrient consumption (all P>.05). As expected, a higher intake of sodium and fluids in the CG (P<.001) was observed.

Laboratory monitoring

There were no significant difference in variation between groups during the study period regarding levels of creatinine, urea, sodium and potassium (Table 2).

A significant intra-group increase in creatinine (P=.01) and urea (P=.02) levels in the IG was observed. There was no statistically significant differences in renal function in the inter-group comparisons (P=NS).

Intravenous medications

The median time to transition from intravenous to oral diuretic therapy was similar in both groups, being 3.0 days (2.3) in the IG, and 2.7 days (2.0) in the CG (P=.63).

The mean dose of loop diuretics administered were similar in both groups at baseline (IG, 72.7 [29.0] mg/d; CG, 69.0 [26.9] mg/d; P=.64); at the third day of intervention (IG, 74.7 [34.8] mg/d; CG, 66.1 [31.0] mg/d; P=.36) and at the end of the study (IG, 68.0 34.3] mg/d; CG, 60.0 [29.5] mg/d; P=.38).

Follow-up

Twenty-four patients from the IG and 20 from the CG returned for a 30-day follow-up (Table 4). There were no significant between-group differences in any clinical or laboratory data (all P>.05). When evaluated the change in the CCS between 30-day follow-up and the end of the study, patients in both groups experienced similar variations (IG, -3.2 [4.5]; CG, -1.7 [4.6], P=.24).

Readmissions and mortality

All visits to the emergency department or hospital admission were computed within a 30-day period after hospital discharge. There were no significant between-group differences in the number of readmissions (IG, 12

patients [41.4%]; CG, 10 patients [43.5%], P>.99) nor in the mortality rate (IG, 2 patients [6.9%]; CG, 2 patients [8.7%], P>.99).

DISCUSSION

To the best of our knowledge, this is the first clinical trial to address the effects of an aggressive restrictive diet regarding salt and water in patients admitted due to decompensated HFpEF. The population included in this study reflects the available data describing the profiles of patients with HFpEF[4]. The sample was predominantly elderly, female patients, who presented with hypertension and atrial fibrillation along with others comorbidities.

The findings of this study are consistent with a number of other trials that have in some way addressed this issue in HF with reduced EF. We have demonstrated that salt and water restriction, a time-honored recommendation in patients with HF, may offer no clinical benefit for these patients; may worsen quality of life and may impair the patients´ food intake.

The intervention performed in this study had no significant effect on weight loss or time to clinical stability when compared to an unrestricted diet. Aliti et al. showed similar results in which weight loss and reduction in CCS (clinical stability) did not differ between groups at 3 days and at the end of the study[17]. Travers et al.[27], who investigated the effect of fluid restriction on weight loss and time to clinical stability also found similar results for both groups.

These findings indicate that restricting sodium and fluids appears to be neutral in terms of the relief of clinical congestion during hospitalization. Regarding patient therapy, one could argue that the absence of differences between groups would be compensated due to differences in the treatment of

these patients regarding diuretics. However, we have documented that patients have received the same amount and the same duration of intravenous diuretics.

In the setting of HF, sodium and water restriction, associated with impairment of cardiac function may lead to excessive activation of the renin-angiotensin-aldosterone system (RAAS) and promote stimulation of the thirst center in the hypothalamus and could be worsened by xerostomia due to the use of diuretic treatment[28-30]. In our study, there were greater perceptions of thirst in the IG during intervention and these results were similar to those found in previous studies, which assessed thirst sensation in patients with decompensated and stable HF[17,31]. These findings suggest that this intervention can promote a negative effect on these patients, who are already experiencing discomfort related to the symptoms of HF.

The sodium and fluid restriction applied in this study did not cause significant between-group differences in neurohormonal activation. These results differ from those found in previous sodium restriction studies in HF[14,16]. In studies conducted by a group of Italian researchers, who evaluated the combined effects of sodium and water restriction associated with high doses of diuretics, there was greater neurohormonal activation in the restriction group[32-34]. These studies, however, were performed in stable patients with reduced EF. As described in the literature, sodium restriction can signal our body to retain sodium through neurohormonal activation[35]. We hypothesize that the conflicting results found in this study may be caused by the fact that, in the hospital setting, possibly both our groups of patients can be considered as patients treated with the contemporary armamentarium for treatment of HF. These treatments, or at

least ACEIs, ARBs and spironolactone, are inhibitors of the RAAS and therefore may be buffering or aborting any additional effects of the diet.

We observed a statistically significant lower nutrient intake in the IG. The reduction in nutrient intake in patients with HF has already been described. Nakasato el al.[36] and Jefferson et al.[19] found a significant reduction in energy consumption in patients in a sodium-restricted diet. The objective in our study was to ascertain if a sodium-restricted diet could have a negative impact on food intake. Patients with HF often have poor absorption and a lack of appetite due to edema, gastric and bowel hypomotility, besides changes in taste as a consequence of the disease [37,38]. Making the diet more palatable in this scenario is, therefore, extremely important. Aquilani et al.[39] recommended an intake of at least 28.1 kcal/kg for HF patients to preserve body composition or to limit the effects of hypercatabolism. In our study, both groups did not achieve this recommendation (17.2 kcal/kg) and consumption was even lower in the IG (15.1 kcal/kg). These results indicate that sodium restriction may have a negative impact on the food intake of patients with decompensated HFpEF.

There were no significant differences between groups in changes of serum sodium, potassium, creatinine and urea. There was a significant intra-group increase in creatinine and urea levels in the IG. These changes have been described previously by Alvelos et al.[16], who identified a significant reduction in creatinine clearance in patients with HF that received a sodium restricted diet. Moreover, in a recent meta-analysis[40] that evaluated the association between creatinine and mortality in patients with stable and decompensated HF, the worsening of renal function was associated with unfavorable outcomes (OR 1.81, 95% CI 1:55 to 2:12, P<.001). Our results

somewhat reinforce these findings, indicating that during hospitalization aggressive sodium and water restriction may have a deleterious effect on renal function.

Hypertension and ventricular hypertrophy has often been associated with HFpEF. However, recent studies suggest that the impairment of cardiac function seen in HFpEF may be related to factors such as systemic inflammation and fibrosis, regardless of having a history of hypertension[41]. These findings suggest that HFpEF may have other pathophysiological courses and that sodium restriction, for the treatment of HFpEF, may not be required for all patients.

Finally, regarding patient follow-up, there were no significant between-group differences in clinical stability, readmissions and mortality rate at 30 days.

Our data should be viewed with some limitations. First, the intervention time was relatively short. However, despite the short duration, it was sufficient to demonstrate similar between-group weight loss and a reduction in CCS; and increased perception of thirst in the IG. Second, due to the logistics in the emergency room, it was not possible to assess the diuresis and natriuresis of patients. However, to confirm compliance with the study protocol, a trained researcher systematically verified the food intake to confirm that all patients followed the assigned diets. Third, these results deserve exploration in other ethnic groups because 81% of the studied population was white.

Conclusions

Taken together, our findings demonstrate that, in the setting of HFpEF, an aggressive restriction of sodium and water does not provide symptomatic or

prognostic benefits; may impair quality of life due to an increased perception of thirst, may decrease patient´s energy intake and does not seems to have an important neurohormonal effect in patients with in-hospital treatment for heart failure.

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Author Contributions: d'Almeida, Rabelo-Silva, and Beck-da-Silva had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* d'Almeida, Souza, Rabelo-Silva, Biolo and Beck-da-Silva. *Acquisition of data:* d'Almeida, Trojahn, Barilli. *Analysis and interpretation of data:* d'Almeida, Rabelo-Silva, and Beck-da-Silva. *Drafting of the manuscript:* d'Almeida, Rabelo-Silva and Beck-da-Silva.

Conflict of Interest Disclosures: None.

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Table 1. Sociodemographic and clinical profile.

	Overall (n=53)	IG (n=30)	CG (n=23)	p
Sociodemographic data				
Age, years, mean (SD)	72.3 (11.7)	73.7 (11.1)	70.4 (12.6)	.31 [a]
Female sex, n(%)	36 (67.9)	22 (73.3)	14 (60.9)	.38 [b]
White ethnicity, n(%)	43 (81.1)	22 (73.3)	21 (91.3)	.16 [b]
Clinical data				
Etiology, n(%)				.76 [b]
Hypertensive	38 (71.1)	22 (73.3)	16 (69.6)	
Non-hypertensive	15 (28.3)	8 (26.7)	7 (30.4)	
Left Ventricular Ejection Fraction, mean (SD)	60.9 (7.5)	61.6 (8.1)	60.0 (6.7)	.44 [a]
SBP, mmHg, mean (SD)	127.0 (25.9)	128.4 (26.1)	125.3 (26.0)	.68 [a]
DBP, mmHg, mean (SD)	70.5 (12.9)	73.2 (13.9)	67.1 (11.0)	.10 [a]
Endogenous creatinine clearance, median (IQR)	60.0 (45.5 – 60.0)	60.0 (46.8 – 60.0)	57.0 (44.0 – 60.0)	.48 [c]
Functional class, n(%)				.67 [d]
NYHA II	5 (9.5)	2 (6.7)	3 (13.0)	
NYHA III	27 (50.9)	15 (50.0)	12 (52.2)	
NYHA IV	21 (39.6)	13 (43.3)	8 (34.8)	
Associated conditions, n(%)				
Hypertension	38 (71.7)	22 (73.3)	16 (69.6)	.76 [b]
Atrial fibrillation	26 (49.1)	15 (50.0)	11 (47.8)	>.99 [b]
Diabetes mellitus	26 (49.1)	14 (46.7)	12 (52.2)	.79 [b]
Dyslipidemia	15 (28.3)	9 (30.0)	6 (26.1)	>.99 [b]
Chronic obstructive pulmonary disease	5 (9.4)	4 (13.3)	1 (4.3)	.37 [b]
Current medications, n(%)				
B-blockers	40 (75.5)	22 (73.3)	18 (78,3)	.76 [b]
Angiotensin-converting enzyme inhibitors	34 (64.2)	18 (60.0)	16 (69.6)	.57 [b]
Angiotensin receptor blockers	9 (17.0)	5 (16.7)	4 (17.4)	>.99 [b]
Spironolactone	14 (26.4)	10 (33.3)	4 (17.4)	.23 [b]
Hydralazine	10 (18.9)	8 (26.7)	2 (8.7)	.16 [b]
Furosemide	44 (83.0)	26 (86.7)	18 (78.3)	.48 [b]
Hydrochlorothiazide	6 (11.3)	5 (16.7)	1 (4.3)	.22 [b]

Abbreviations: IG, intervention group; CG, control group; SD standard deviation; IQR, interquartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure; NYHA, New York Heart Association.

[a] Determined by Student´s T test

[b] Determined by Fischer exact test

[c] Determined by Mann-Whitney test

[d] Determined by Pearson Chi-square test

Table 2. Progression of laboratory variables during the study period in the intervention and control groups.

	IG (n=30)		p[a]	CG (n=23)		p[a]	p[b]
	Baseline	Study end		Baseline	Study end		
Creatinine, mg/dL, mean (SD)	1.0 (0.3)	1.2 (0.7)	.01	1.2 (0.4)	1.3 (0.5)	.09	.32
Urea, mg/dL, mean (SD)	51 (19)	60 (33)	.02	54 (21)	55 (21)	.72	.11
Sodium, mEq/L, mean (SD)	140 (4)	140 (4)	.33	141 (3)	140 (3)	.09	.64
Potassium, mEq/L, mean (SD)	4.2 (0.6)	4.4 (0.5)	.29	4.4 (0.5)	4.6 (0.5)	.17	.89
BNP, pg/mL, median (IQR)	301 (215–524)	286 (161–368)	.40	186 (100–325)	184 (113–286)	.12	.85
PRA, ng/mL/h, median (IQR)	2.4 (0.6–9.1)	4.5 (2.3–22.1)	.02	2.8 (0.4–6.4)	5.8 (1.5–21.3)	.003	.42
Aldosterone, pg/mL, median (IQR)	65 (44–159)	81 (58–164)	.07	61 (35–126)	66 (36–129)	.28	.85

Abbreviations: IG, intervention group; CG, control group; SD standard deviation; IQR, interquartile range; BNP, brain-type natriuretic peptide; PRA, plasma renin activity.

[a] Multiple comparisons with Bonferroni adjustment;

[b] Repeated-measures analysis (generalized estimating equations method) for comparison of variation between groups from baseline to the end of study.

Table 3. Nutrient intake during the study period in the intervention and control groups.

	IG (n=30)	CG (n=23)	p
Energy, Kcal, mean (SD)	1159.4 (238.5)	1471.6 (265.8)	<.001 [a]
Kcal/kg, mean (SD)	15.1 (5.1)	19.5 (5.4)	.01[a]
Carbohydrate, %Kcal, mean (SD)	55.4 (3.1)	56.1 (4.0)	.48 [a]
Protein, %Kcal, median (IQR)	18.3 (15.4 – 19.2)	17.3 (1.4 – 18.3)	.17 [b]
Lipids, %Kcal, mean (SD)	27.5 (3.1)	27.1 (3.0)	.69 [a]
Sodium, g, median (IQR)	1.2 (1.1 – 1.3)	2.5 (2.4 – 2.8)	<.001 [b]
Fluid, ml, median (IQR)	582.7 (496.9 – 662.4)	895.4 (751.2 – 1121.8)	<.001 [b]

Abbreviations: IG, intervention group; CG, control group; SD standard deviation; IQR, interquartile range;
[a] Determined by Student´s T test
[b] Determined by Mann-Whitney test

Table 4. Clinical and laboratory variables at the 30-Day follow-up.

	IG (n=24)	CG (n=20)	p
Clinical data			
Weight, kg, mean (SD)	75.8 (22.8)	78.4 (17.2)	.75[a]
Clinical congestion Score, mean (SD)	5.6 (4.3)	6.0 (3.6)	.74 [a]
SBP, mmHg, mean (SD)	123.6 (25.9)	129.8 (31.6)	.50 [a]
DBP, mmHg, mean (SD)	72.9 (16.1)	74.1 (15.3)	.81 [a]
Functional class, n(%)			.06 [b]
NYHA I	0	1 (5.0)	
NYHA II	5 (21.7)	10 (50.0)	
NYHA III	13 (56.5)	4 (20.0)	
NYHA IV	5 (21.7)	5 (25.0)	
Laboratory data			
Creatinine, mg/dL, median (IQR)	1.0 (0.8 –1.5)	1.1 (1.0 –1.4)	.73 [c]
Urea, mg/dL, median (IQR)	52 (39 – 66)	56 (43 – 63)	.73 [c]
Sodium, mEq/L, mean (SD)	140 (6)	141 (3)	.64 [a]
Potassium, mEq/L, mean (SD)	4.5 (0.7)	4.5 (0.5)	.73 [a]

Abbreviations: IG, intervention group; CG, control group; SD standard deviation; IQR, interquartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure; NYHA, New York Heart Association.

[a] Determined by Student´s T test

[b] Determined by Pearson Chi-square test

[c] Determined by Mann-Whitney test

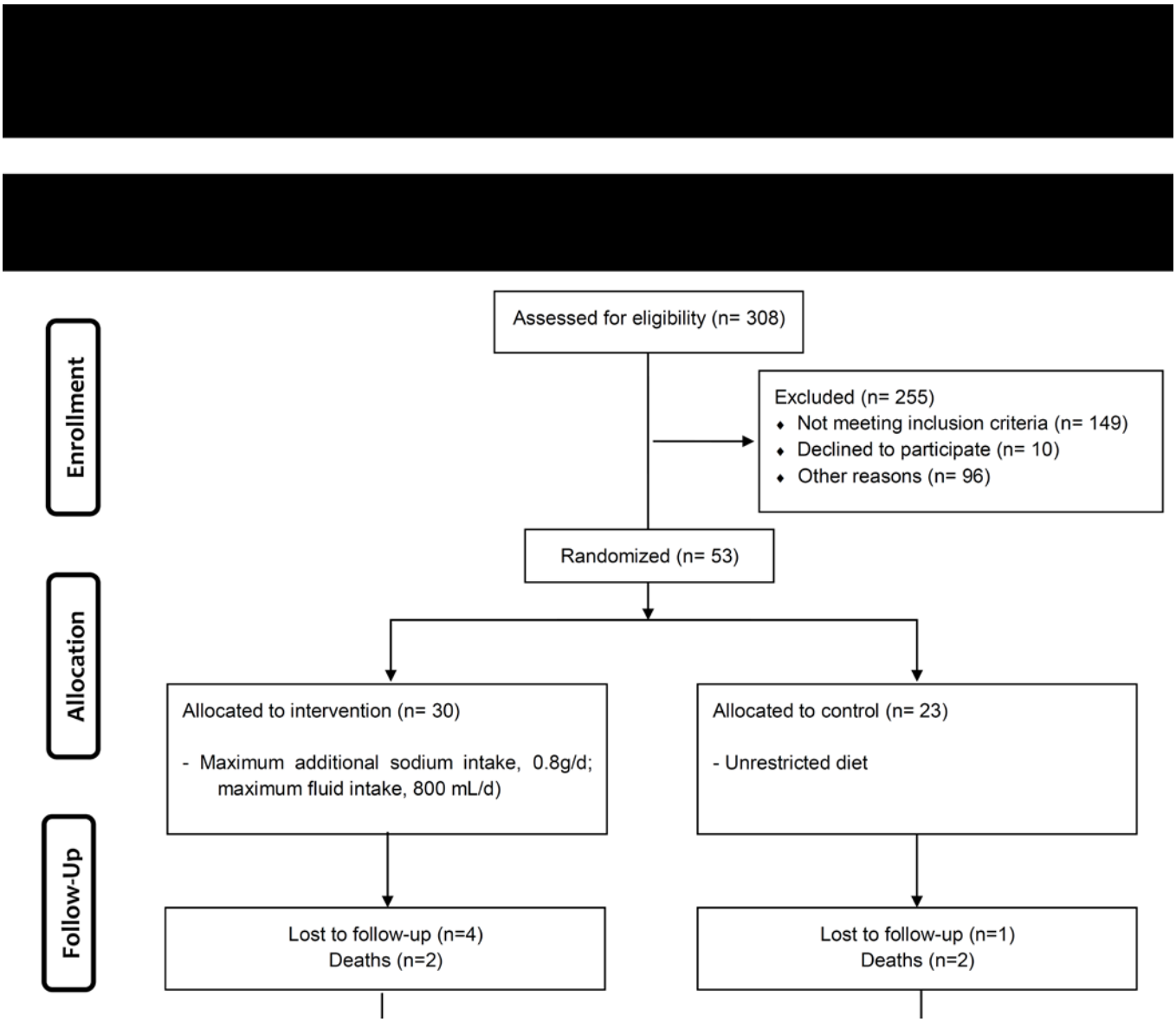

Figure 1. Consolidated Standards for Reporting of Trials flowchart.

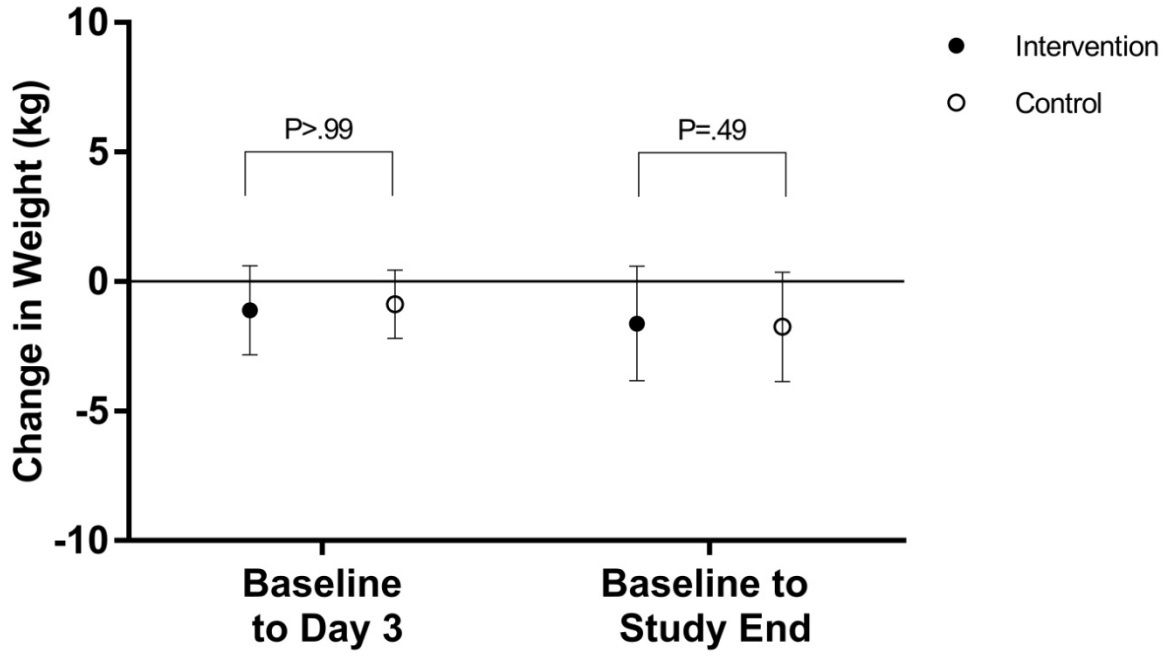

Figure 2. Change in body weight from baseline to day-3 reassessment and from baseline to the end of the study period in the intervention and control groups.

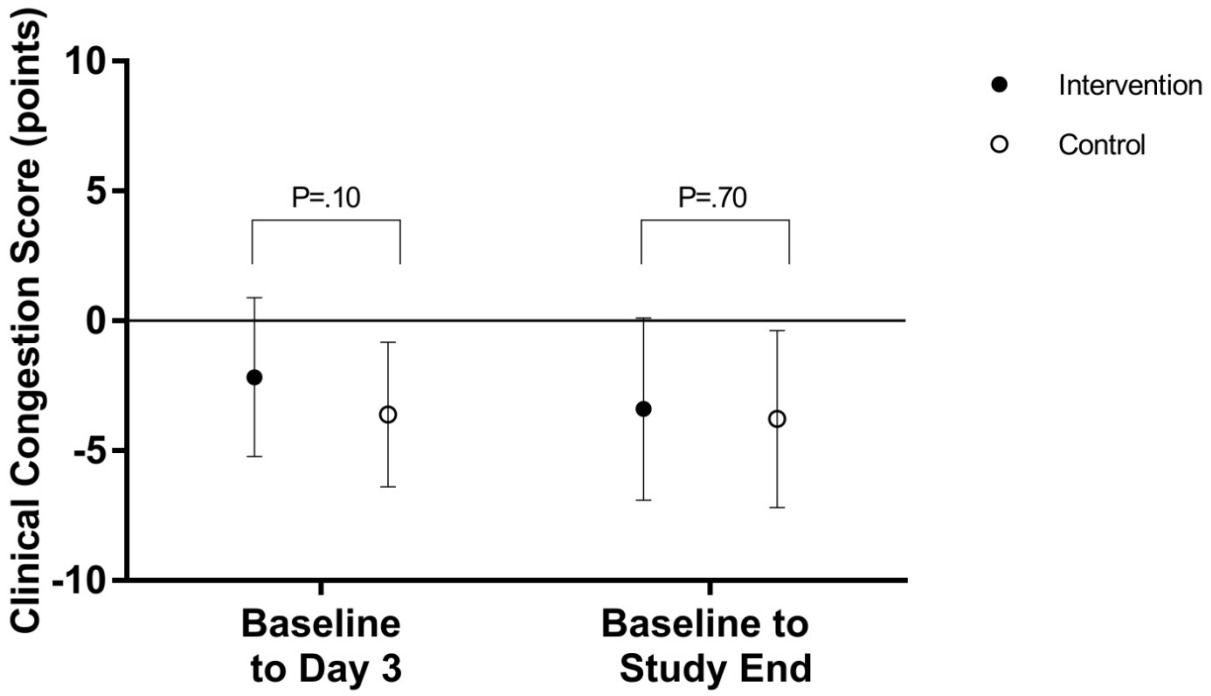

Figure 3. Change in clinical congestion score from baseline to day-3 reassessment and from baseline to the end of the study period in the intervention and control groups.

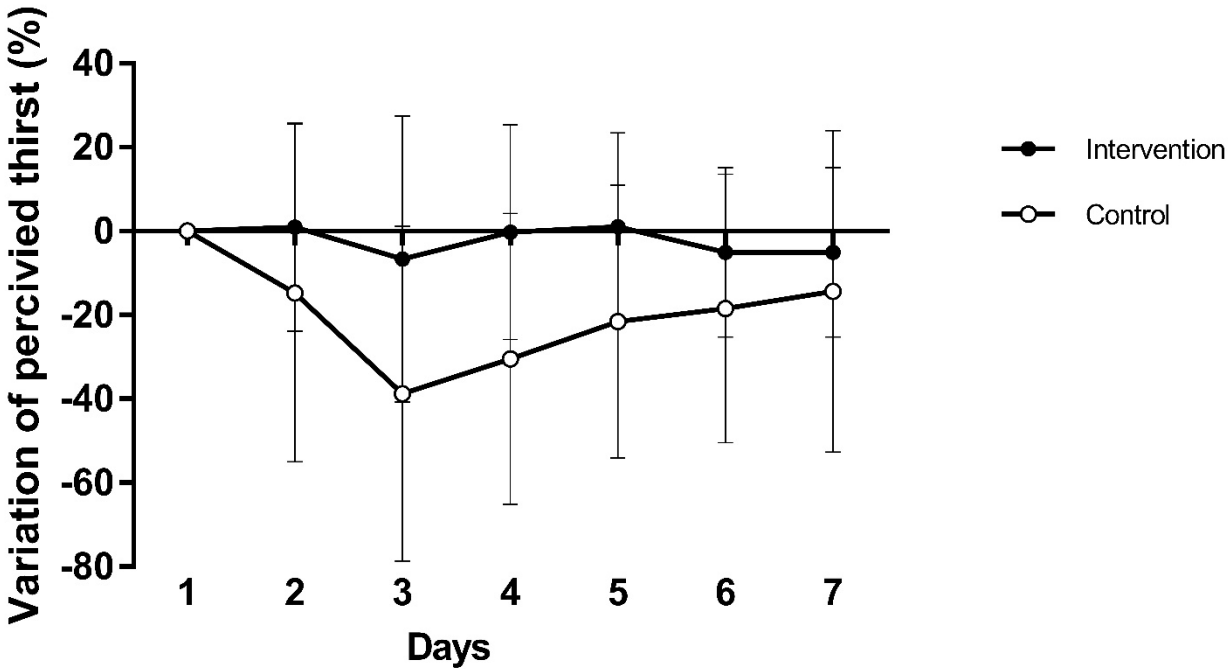

Figure 4. Variation of perceived thirst during the study period (time, p=.001; group, p=.02; time x group, p=0.03).

6. CONCLUSÕES E CONSIDERAÇÕES FINAIS

Conclusões

A estratégia de restrição agressiva de sódio e líquidos testada neste estudo não proporcionou benefício clínico sintomático em desfechos como a redução do peso corporal e tempo para estabilidade clínica nos pacientes avaliados. Além disso, produziu maior percepção de sede, não parece ter efeito neuro-hormonal relevante em pacientes com tratamento hospitalar da IC-FEP, apresentou um efeito negativo no consumo alimentar e não apresentou impacto na taxa de hospitalizações e mortalidade 30 dias após a alta.

Considerações finais

Os resultados demonstrados com este estudo são consistentes com os dados recentes da literatura produzidos nesse cenário clinico. Foi observado que a restrição de sódio e líquidos, uma recomendação consagrada na literatura mundial, não oferece benefício clínico para pacientes admitidos por descompensação da IC e fração de ejeção preservada, semelhante ao que já foi testado para pacientes com IC e disfunção sistólica.

De fato, as evidências produzidas por este estudo refletem as recomendações atuais de diretrizes internacionais quanto a oferecer uma dieta saudável, sem necessidade de restrição agressiva para todos os pacientes.

Esses achados indicam a necessidade de personalizar as decisões, levando em consideração o estágio da doença, história clínica e otimização terapêutica dos pacientes.

ANEXOS

ANEXO 1

CARTA DE APROVAÇÃO DO PROJETO

HCPA - HOSPITAL DE CLÍNICAS DE PORTO ALEGRE
GRUPO DE PESQUISA E PÓS-GRADUAÇÃO

COMISSÃO CIENTÍFICA

A Comissão Científica do Hospital de Clínicas de Porto Alegre analisou o projeto:

Projeto: 120437
Data da Versão do Projeto:

Pesquisadores:
ENEIDA REJANE RABELO DA SILVA
ANDREIA BIOLO
GABRIELA CORREA SOUZA
KARINA SANCHES MACHADO D ALMEIDA

Título:
EFEITO DA RESTRIÇÃO DE SÓDIO DIETÉTICO NO MANEJO DE PACIENTES COM INSUFICIÊNCIA CARDÍACA E FRAÇÃO DE EJEÇÃO PRESERVADA: UM ENSAIO CLÍNICO RANDOMIZADO

Este projeto foi APROVADO em seus aspectos éticos, metodológicos, logísticos e financeiros para ser realizado no Hospital de Clínicas de Porto Alegre.
Esta aprovação está baseada nos pareceres dos respectivos Comitês de Ética e do Serviço de Gestão em Pesquisa.

- Os pesquisadores vinculados ao projeto não participaram de qualquer etapa do processo de avalição de seus projetos.

- O pesquisador deverá apresentar relatórios semestrais de acompanhamento e relatório final ao Grupo de Pesquisa e Pós-Graduação (GPPG)

Porto Alegre, 03 de janeiro de 2013.

Prof. Flávio Kapczinski
Coordenador GPPG/HCPA

ANEXO 2

ESCORE CLÍNICO DE CONGESTÃO

Nome:_____Data:

_____Hora:_____Avaliador:_____

Estertores crepitantes ou abolição dos murmúrios
[ ] 0= não está presente [ ] 1= < ¼ campos do pulmão (bases) [ ] 2= ¼ a ½ dos campos pulmonares [ ] 3= = > ½ dos campos pulmonares [ ] 4= todo campo pulmonar
Terceira Bulha Cardíaca (B3), som de galope. Identificar ictus em decúbito lateral esquerdo e auscultar com o estetoscópio. [ ]0=Ausente [ ] 1=Presente **Distensão Jugular.** Considerar quantos centímetros a partir do angulo retroesternal [ ] 0= sem distensão jugular acima das clavículas (jugular interna e externa) [ ] 1= ¼ ou 25% da altura da jugular (pescoço) [ ] 2= ½ ou 50% da altura da jugular (pescoço) Distância:clavícula-lóbulo:_____ [ ] 3= ¾ ou 75% da altura da jugular (pescoço) [ ] 4= distensão jugular próximo ao lobo da orelha **Edema periférico** [ ] 0= Sem edema [ ] 1= Edema apenas nos tornozelos [ ] 2= edema nas pernas [ ] 3= Edema que alcança os joelhos [ ] 4= Edema que alcança as coxas **História de ortopnéia (se 1ª vez: na última semana; se no leito: na última noite; se sentado: no exame físico)** [ ] 0= 1 travesseiro em cama plana.

[ ] 1= É necessário mais de um travesseiro par dormir.

[ ] 2= pelo menos um episódio de DPN (dispnéia paroxística noturna).

[ ] 3= múltiplos episódios de DPN.

[ ] 4= Pelo menos 1 noite dormiu sentado com respiração curta.

Refluxo hepatojugular. Comprimir o fígado firmemente e continuamente por 1 minuto enquanto se observa as veias do pescoço.

[ ] 0= Ausente. [ ] 1= Presente.

Classe Funcional- De acordo com NYHA (na entrado e na alta do estudo)

[ ] 1 = classe I [ ] 2 = classe II

[ ] 3 = classe III [ ] 4 = classe IV

SOMA TOTAL:_____**/**_____

Hepatomegalia

[ ] presente [ ] ausente Cm do rebordo costal:_____PVC:_____

Pressão Arterial:_____/_____(mmHg)

Freqüência Cardíaca:_____ ( ) RR ( ) RI

PPP:_____

APÊNDICES

APÊNDICE 1

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Projeto: Efeito da restrição hídrica e de sódio dietético no manejo de pacientes com insuficiência cardíaca e fração de ejeção preservada: um ensaio clínico randomizado

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O(a) sr(a) está sendo convidado(a) a participar de uma pesquisa científica que tem por objetivo avaliar o efeito da restrição da ingestão de sódio e líquidos na estabilidade clínica, ativação neuro-hormonal e peso corporal de pacientes com insuficiência cardíaca e fração de ejeção preservada. No nosso meio ainda não está claramente estabelecido se a restrição de sódio e líquidos auxilia na perda de peso e na melhora dos sintomas da sua doença. Portanto a avaliação desta intervenção poderá promover um aprofundamento do conhecimento da fisiopatologia e progressão desta complexa síndrome.

Esta pesquisa tem um caráter científico. Trata-se de um estudo clínico randomizado, ou seja, os pacientes poderão ser sorteados para um dos seguintes grupos: no grupo intervenção os pacientes poderão consumir 1,6g de sódio (4g de sal) e 800ml de líquidos ao dia; enquanto que no grupo controle não haverá restrição de sódio e líquidos. Fica claro que o(a) sr(a) tem as mesmas chances de outros pacientes do estudo em participar de um ou de outro grupo e isso se dará através de um sorteio. Ao aceitar participar da pesquisa, o(a) sr(a) responderá algumas questões importantes para a sua inclusão no estudo. Durante o período de sete dias, ou até a sua alta hospitalar, o pesquisador deste estudo irá lhe orientar sobre os cuidados necessários realizar, como por exemplo, o de só consumir alimentos e líquidos enviados pelo serviço de nutrição e dietética do hospital. Serão realizados neste período, exames clínicos para avaliação de seus sintomas e o(a) sr(a) deverá pesar-se diariamente. Durante sua internação, será realizada uma coleta de sangue, onde serão coletados 10 mL de sangue para exames laboratoriais. O(a) sr(a) poderá sentir um desconforto, e, além disso, hematomas (manchas roxas) poderão ocorrer no local da coleta.

Após sua alta hospitalar, será realizado contato telefônico para avaliação de seus sintomas e necessidade de internação no período de 30 dias, quando deverá

retornar ao hospital para nova avaliação. Neste dia, será realizada nova coleta de sangue. Em um segundo momento, será realizado um exame clínico para avaliação de seus sintomas.

O Sr (a) poderá ter todas as informações que quiser e poderá não participar da pesquisa ou retirar seu consentimento a qualquer momento, sem prejuízo no seu atendimento. Pela sua participação no estudo, você não receberá qualquer valor em dinheiro, mas terá a garantia de que todas as despesas necessárias para a realização da pesquisa não serão de sua responsabilidade. Seu nome não será divulgado para outras pessoas, pois você será identificado com um número ou com uma letra. As informações serão utilizadas somente para fins de pesquisa. Este termo de consentimento é elaborado em duas vias de igual valor.

Eu, _____, li e/ou ouvi o esclarecimento acima e compreendi para que serve o estudo e qual procedimento a que serei submetido. A explicação que recebi esclarece os riscos e benefícios do estudo. Eu entendi que sou livre para interromper minha participação a qualquer momento, sem justificar minha decisão e que isso não afetará meu tratamento. Sei que meu nome não será divulgado, que não terei despesas e não receberei dinheiro por participar do estudo. Eu concordo em participar desta pesquisa.

Os pesquisadores envolvidos neste projeto são as professoras Eneida Rabelo, Gabriela Souza e Luiz Beck da Silva e a nutricionista Karina d'Almeida. Em caso de dúvidas, você poderá entrar em contato com os pesquisadores pelos telefones: (51) 9561-8545 ou 3359-8843 ou com o CEP pelo telefone: 3359-7604.

_____ _____

Assinatura paciente ou responsável Assinatura Pesquisador

Porto Alegre, ____ de _____ de _____.

APÊNDICE 2

FICHA CLÍNICA PARA COLETA DE DADOS

Data do Screening:				**Hora:**					
Data da Randomização: **Grupo RND:**				**Data do início da intervenção:**					
IDENTIFICAÇÃO									
Nome - Iniciais:				Prontuário:					
Data de Nascimento:		Idade:		Sexo:			Vínculo marital:		
Cor:		Anos de estudo:		Atividade profissional:					
EXAME FÍSICO / LABORATORIAIS									
	D1	D2	D3	D4	D5	D6	D7	D30	Observações
Peso									
ECC									
Creatinina									
DCE									
Uréia									
Sódio									
Potássio									
BNP									
Aldosterona									
Renina									
PAS/PAD									
FC:									
Medicações dose + via adm.									
Furosemida									
HCTZ									
Betabloq									
IECA									

ARA II									
Digoxina									
Espironolactona									
Hidralazina									
Isossorbida									
AAS									
Estatina									
NPS									
Milrinona									
( ) Diabetes Mellitus ( ) Hipertensão Arterial ( ) Cardiopatia isquêmica			( ) Doença cerebrovascular ( ) Infarto Agudo do miocárdio prévio ( ) Fibrilação atrial				( ) Tabagismo ( ) Etilismo		
IC etiologia:									
Tempo de diag. da IC – em anos:									
Ano da 1ª internação por IC:									
Internações prévias por IC - nº:									