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SERVANDO AE GRIS MEDEBOR
Escola Bahiana de
Medicina e Saúde Pública

INCIDÊNCIA E PREDITORES DE INSUFICIÊNCIA RENAL AGUDA RELACIONADA AO TRATAMENTO DE INSUFICIÊNCIA CARDÍACA CONGESTIVA COM INIBIDORES DA ENZIMA CONVERSORA DA ANGIOTENSINA

Tese de Doutorado

Constança Margarida Sampaio Cruz

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Tese apresentada ao curso de Pós-Graduação em medicina e saúde humana da Escola Bahiana de Medicina e Saúde Pública para obtenção do título de doutor em medicina.

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DEDICATÓRIA

Dedico este trabalho a:

Meus pais Álvaro Augusto Souza da Cruz, *in memoriam*, e Dilma Sampaio Cruz que me ofereceram toda a infra-estrutura educacional e afetiva tão necessária por toda a minha vida.

Meus irmãos Álvaro Augusto Souza da Cruz Filho e Luzia Arlinda Sampaio Cruz, companheiros de sempre.

Meus filhos Rafael e Luisa, razões maiores da minha existência.

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"O segredo dos que triunfam é começar sempre de novo"

Autor desconhecido

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Resumo

Introdução. Estudos recentes têm mostrado aumento nas taxas de morbimortalidade relacionada à hiperpotassemia em portadores de insuficiência cardíaca congestiva tratados com a associação de inibidor da ECA com espironolactona e também que o mais importante preditor deste distúrbio eletrolítico foi a piora da função renal nestes pacientes. Nosso objetivo é determinar os principais preditores de insuficiência renal aguda (IRA) em portadores de insuficiência cardíaca tratados com inibidor da ECA com ou sem espironolactona e também estimar a sua incidência.

Métodos. Nós conduzimos um estudo de coorte prospectivo acompanhando 114 casos consecutivos de portadores de insuficiência cardíaca descompensada em uso de inibidor da ECA desde a admissão em hospital universitário por um período de 30 dias, realizando dosagens séricas de creatinina e potássio três vezes por semana e medindo a pressão arterial de 8/8h, diariamente. O desfecho primário foi o desenvolvimento de insuficência renal aguda e, os secundários foram ocorrência de hiperpotassemia e hiperpotassemia severa. SPSS 11.0 foi utilizado para realização de análises estatísticas e análise de regressão logística multivariada para identificar preditores independentes de IRA.

Resultados. Dentre 114 pacientes, 25% desenvolveram IRA, 15% hiperpotassemia e 3% hiperpotassemia severa. O melhor ponto de corte identificado pela curva ROC de queda da PAM após tratamento com inibidor da ECA relacionado com desenvolvimento de IRA foi 25mmHg. Os fatores preditores de IRA encontrados na análise de regressão logística univariada foram: queda da PAM $\geq$ 25mmHg pós-inibidor da ECA(OR = 18.2; 95%CI: 2.6, 42.4); diagnóstico de ICC classe IV (OR = 4.7; 95%CI: 1.7 a 2.7); diabetes (OR = 2.6; 95%CI: 1.1, 6.4) e hipertensão (OR = 3.0; 95%CI: 1.2, 7.4).

Conclusões: A incidência de Insuficiência Renal Aguda durante os primeiros 30 dias de tratamento com inibidor da ECA em portadores de Insuficiência Cardíaca Congestiva descompensada foi estimada em 25%, sendo que queda da PAM $\geq$ 25mmHg pós-inibidor da ECA e diagnóstico de ICC classe IV foram os fatores preditores independentes encontrados na análise de regressão logística multivariada.

Abstract

Background. Recent studies have shown an increase in rates of morbimortality associated with hyperkalaemia in congestive heart failure (CHF) patients treated with ACE inhibitors (ACEI) plus spironolactone. Those studies have also demonstrated that the best independent predictor of this electrolytic disorder was a decrease in renal function. We aimed to find the independent predictors and incidence of development of acute renal failure (ARF) in CHF patients treated with ACEI.

Methods. We conducted a prospective cohort study and followed for 30 days 114 consecutive cases of CHF patients treated with ACEI since admission to a University Hospital in Brasil, from November 2003 to September 2005. We performed measurements of serum creatinine and potassium levels three times a week and systolic and diastolic blood pressures every 8hs, daily. The primary end-point was established to find the independent predictors of development of ARF and its incidence. We used SPSS® 11.0 to perform all statistical analysis with an alpha set at 0.05.

Results. Among 114 patients, 25% developed ARF, 15% developed hyperkalaemia and 3% developed severe hyperkalaemia. The better cut off point identified by ROC curve regarding the decrease in mean blood pressure (MBP) after ACEI was 25mmHg. Predictors of development of ARF were a decrease in mean blood pressure (Δ MBP) $\geq$ 25mmHg after initiation of treatment with ACEI (OR = 18.2; 95%CI: 2.6, 42.4); the occurrence of NYHA class IV CHF (OR = 4.7; 95%CI: 1.7 a 2.7); diabetes (OR = 2.6; 95%CI: 1.1, 6.4) and hypertension (OR = 3.0; 95%CI: 1.2, 7.4).

Conclusions. The incidence of development of ARF during the first 30 days of treatment with ACEI was estimated in 25% and the predictors of a decrease in renal function were Δ MBP $\geq$ 25mmHg after initiation of treatment with ACEI; the occurrence of NYHA class IV CHF, diabetes and hypertension.

INTRODUÇÃO

Nas últimas décadas, os inibidores da enzima de conversão da angiotensina (IECA) têm sido drogas muito importantes no tratamento da insuficiência cardíaca. Os inibidores dos receptores da aldosterona também têm sido utilizados para o tratamento da síndrome, muitas vezes de maneira associada aos IECA. Ensaios Clínicos Randomizados: RALES[1] – (*The Randomized Aldactone Evaluation Study*) e CONSENSUS[2] – (*The Cooperative North Scandinavian Enalapril Survival Study*) demonstraram uma queda importante na morbimortalidade associada ao tratamento com inibidores da enzima de conversão da angiotensina e inibidores da aldosterona em portadores de insuficiência cardíaca.

.

Apesar do estudo RALES ter demonstrado uma taxa baixa de hiperpotassemia (2%) em portadores de insuficiência cardíaca que faziam uso associado de inibidor da ECA e espironolactona, posteriormente foram relatadas taxas bem mais altas relacionadas ao uso combinado destas drogas para tratamento de insuficiência cardíaca.

O mais importante fator preditor de hiperpotassemia nestes estudos[3 - 10] foi a ocorrência simultânea de insuficiência renal durante o uso associado de inibidores da enzima de conversão da angiotensina e espironolactona para tratamento de insuficiência cardíaca descompensada. Por esta razão, dando continuidade a pesquisa anterior, decidimos estudar de maneira prospectiva a incidência e os fatores preditores de desenvolvimento de insuficiência renal aguda em portadores de insuficiência cardíaca congestiva descompensada tratados com inibidor da ECA associado ou não a espironolactona.

Os três trabalhos desenvolvidos no Curso de Pós-graduação em Medicina e Saúde Humana da Fundação Bahiana para o Desenvolvimento das Ciências – Fundação Instituto Oswaldo Cruz no período de março de 2003 a agôsto de 2006 descritos a seguir estão anexados a este manuscrito:

1) Incidência e preditores de insuficiencia renal aguda relacionada ao tratamento de insuficiência cardíaca com inibidores de enzima de conversão da angiotensina – trabalho original a ser apresentado como pré-requisito para a obtenção do titulo de Doutor (a) em Medicina Interna (manuscrito em inglês e comprovação de aceitação para publicação em revista internacional em anexo).
2) Novas estratégias para o tratamento de Insuficiência Cardíaca com antagonistas da aldosterona e risco de hiperpotassemia – artigo de revisão publicado no periódico *Expert Opinion on Drugs Safety* em 2005, durante o período do doutorado (manuscrito publicado em anexo).
3) Ocorrência de hiperpotassemia em portadores de insuficiência cardíaca em uso da associação de inibidor da enzima de conversão da angiotensina e espironolactona – Dissertação de Mestrado defendida em outubro de 2002, artigo original publicado no periódico *Nephrology Dialysis and Transplantation* em 2003 (manuscrito publicado em anexo).

REVISÃO DA LITERATURA

Nas últimas décadas, os inibidores de conversão da angiotensina (IECAs) têm sido drogas importantes para o tratamento da insuficiência cardíaca congestiva. A adição de espironolactona (SLN) como droga coadjuvante tem sido fortemente recomendada após publicação do RALES[1] em setembro de 1999, demonstrando uma queda importante na mortalidade no grupo de pacientes que associou espironolactona a IECAs quando comparado com o grupo que usou IECA sem espironolactona, independentemente do uso de outras drogas convencionais para o tramento da síndrome. Por outro lado, a adição de espironolactona, um diurético poupador de potássio, poderia resultar em aumento do risco de desenvolvimento de hiperpotassemia, principalmente em pacientes com reduzida taxa de filtração glomerular.

O estudo CONSENSUS[2] recomenda monitoração da creatinina e potássio séricos após início da terapia com IECA ou quando sua dosagem é aumentada. Este estudo demonstra que existe uma redução da taxa de filtração glomerular (TFG) após introdução de enalapril da ordem de 20 a 30% que tende a normalização após um período de 20 a 30 dias, porém novos estudos têm demonstrado redução bem maior da TFG após introdução de IECAs principalmente em certos grupos de risco.

Bridoux & Vanhille[3] estudaram 27 casos de insuficiência renal aguda após introdução de IECAs sem estenose de artéria renal em pacientes portadores de insuficiência cardíaca e/ ou hipertensão arterial sistêmica. Os autores realizaram biópsia renal em 13 pacientes sendo que em 8 casos foi detectada a presença de severa microangiopatia e em

5 casos a presença de necrose tubular aguda. Os achados clínicos mais relevantes foram: depleção de volume em 21 pacientes, hipotensão em 12 pacientes, também sendo fatores facilitadores de IRA a presença de diabetes como co-morbidade, a associação de IECAs com antiinflamatórios não hormonais e insuficiência cardíaca descompensada. A maior parte dos pacientes (22) recuperou a função renal após expansão de volume, suspensão de IECA e diminuição da dose de diurético, 2 pacientes morreram e quatro não recuperaram a função renal necessitando de tratamento dialítico de manutenção. Os autores concluem que a depleção de volume e de sal têm um importante papel na IRA induzida por IECAs e que a combinação de tal droga com diuréticos requer cuidado especialmente em idosos e portadores de doença da microvasculatura renal, tanto quanto indivíduos com doença da macrovasculatura renal.

Ahmed[4] em revisão sistemática de 12 ensaios clínicos randomizados, demonstrou que pacientes com reserva funcional renal diminuída e insuficiência cardíaca podem apresentar taxas de elevação de creatinina sérica bem maiores do que Ljungman, Kjekshun & Swedberg[2] descreveram anteriormente. Em certos grupos de risco como insuficiência cardíaca descompensada, depleção de volume ou estenose bilateral de artéria renal houve elevação de creatinina sérica tão importante quanto 75% a 150% em relação à creatinina basal nas quatro primeiras semanas de introdução de IECAs. O autor alerta também para o fato de que os dados são muito limitados quando se trata de paciente com insuficiência renal severa (TFG < 30ml/min) e conclui que o uso de IECAs tem uma forte associação com perda de função renal durante os primeiros dois meses de introdução que usualmente não excede a taxa de 30% e que tende a estabilização, por esta razão, recomendam que a terapia com tal droga não seja

descontinuada a menos que a taxa de elevação na creatinina sérica seja maior que 30% em relação à creatinina basal ou ocorra hiperpotassemia.

As diretrizes do American Heart Association[5] (AHA) publicadas em 2001 recomendam a suspensão de IECAs para tratamento de insuficiência cardíaca caso haja elevação da creatinina sérica em mais de 50% em relação a creatinina basal ou hiperpotassemia após introdução da referida droga.

Shlipak[6] em publicação recente argumenta que os ensaios clínicos que demonstram a melhora na sobrevida em pacientes com insuficiência cardíaca (IC) com o uso de inibidores da enzima de conversão da angiotensina e espironolactona não contemplam aqueles pacientes que são portadores de insuficiência renal e insuficiência cardíaca ao mesmo tempo. O autor acrescenta que cerca de um terço dos pacientes com insuficiência cardíaca têm também insuficiência renal (TFG< 60ml/min) e que a presença de insuficiência renal associada está entre os mais fortes preditores de mortalidade na IC. Em conclusão, o autor afirma que as evidências são insuficientes no que diz respeito aos benefícios dos IECAs e da espironolactona em portadores de IC associada a disfunção renal avançada e sugere que os novos ensaios clínicos sejam mais representativos deste grupo de pacientes que apresentam ao mesmo tempo IC e disfunção renal.

Sica[7] pontua a importância do bloqueio do sistema renina-angiotensina-aldosterona na insuficiência cardíaca grave e naqueles pacientes que sofreram infarto agudo do miocárdio, mas alerta para a freqüente associação de insuficiência renal à insuficiência

cardíaca, seja pelo déficit efetivo da volemia a nível de artérias renais, ou seja pela própria patologia de base, como por exemplo, diabetes mellitus e hipertensão que levam a longo prazo à deterioração tanto da função renal quanto da função cardíaca.

Svensson & Gustafsson[8] concluíram que o uso de espironolactona associada a inibidor da enzima de conversão de angiotensina para tratamento de insuficiência cardíaca têm se associado a bem mais efeitos colaterais do que se havia pensado (33% de IRA com elevação de níveis de creatinina sérica maior que 50% em relação à creatinina sérica basal e 36% de hiperpotasssemia). Os autores encontraram que os fatores preditores independentes de insuficiência renal e hiperpotassemia nestes pacientes foram pertencer a pior classe funcional segundo os critérios do NYHA (*New York Heart Association*), baixa fração de ejeção de ventrículo esquerdo ao ecodopplercardiograma e idade avançada.

Bozkurt & Ildiko[9] em estudo de coorte retrospectivo envolvendo pacientes que iniciaram simultaneamente o uso de IECAs e espironolactona para tratamento de insuficiência cardíaca após a pré-divulgação do RALES, encontraram 25% de insuficiência renal, 21% de hiponatremia, 24% de hiperpotassemia e 12% de hiperpotassemia severa, contra apenas 2% de hiperpotassemia severa reportado pelo RALES, sendo que dos 104 pacientes estudados, 21 tiveram que interromper o uso de espironolactona.

Cruz & Marcílio de Souza[10] encontraram 33% de hiperpotassemia e 14% de hiperpotassemia severa em pacientes portadores de insuficiência cardíaca classes III e

IV (NYHA) em uso de terapia combinada com IECA/SLN. Os principais preditores de hiperpotassemia encontrados foram: pertencer à classe funcional IV segundo o NYHA e principalmente a piora da função renal refletida no aumento da creatinina sérica após introdução de IECA/SLN. Por esta razão, os autores hipotetizaram que a introdução simultânea das duas drogas possa ter aumentado o risco de hiperpotassemia nestes pacientes, uma vez que Ljungman, Kjekshun & Swedberg[2] bem descreveram o efeito na queda da taxa de filtração glomerular após introdução de enalapril em portadores de insuficiência cardíaca com tendência a estabilização após 30 dias.

Considerando que a espironolactona quando associada à IECA promoveria um total bloqueio do sistema renina-angiotensina-aldosterona (SRAA), aventamos também a possibilidade da queda da taxa de filtração glomerular ser mais acentuada ainda com o uso simultâneo das duas drogas, uma vez que estamos falando de pacientes recém descompensados de insuficiência cardíaca e, portanto, com fluxo sanguíneo efetivo renal reduzido e altamente dependente do SRAA para sua autoregulação. Os autores encontraram que todos os casos de hiperpotassemia severa estiveram associados à perda importante da função renal após uso de IECA/SLN, com retorno ao padrão anterior tanto da função renal (creatinina sérica) quanto do potássio sérico após suspensão das duas drogas, o que reforça a relação de causalidade entre a ocorrência de IRA e hiperpotassemia e o uso simultâneo de IECAs e SLN para tratar insuficiência cardíaca recém-descompensada.

OBJETIVOS

1) Determinar a incidência de insuficiência renal aguda em portadores de insuficiência cardíaca congestiva descompensada tratados com inibidor da enzima de conversão da angiotensina durante os primeiros 30 dias de internamento.

2) Estabelecer fatores preditores de desenvolvimento de insuficiência renal aguda em portadores de insuficiência cardíaca congestiva descompensada tratados com inibidor da enzima de conversão da angiotensina nos primeiros 30 dias de internamento.

3) Estabelecer a incidência de hiperpotassemia e hiperpotassemia severa em portadores de insuficiência cardíaca descompensada tratados com inibidor da enzima de conversão da angiotensina durante os primeiros 30 dias de internamento.

CASUÍSTICA, MATERIAIS E MÉTODOS

Para determinar a incidência de IRA em portadores de insuficiência cardíaca em uso de IECA associado ou não a SLN nos 30 dias de observação e também determinar seus principais fatores preditores, foi conduzido um estudo observacional de coorte prospectivo.

A hipótese alternativa original (H_1) do estudo foi de que a incidência de IRA nos pacientes que associaram IECA/SLN (grupo teste ou GT) fosse diferente da incidência de IRA naqueles pacientes que usaram IECA (grupo controle ou GC); tal que:

H_1: GT $\neq$ GC

H_0 (hipótese nula): GT = GC

O cálculo do N amostral foi feito a partir da fórmula de Halperin, apropriada para estudo de coorte e variável dependente dicotômica a seguir:

$$N = [Za\sqrt{2GMx(1-GM)} + Zb\sqrt{GCx(1-GC) + GTx(1-GT)}]^2 \div (GC-GT)^2$$

Onde GM = média aritmética de GT e GC; Za para $\alpha = 0,05$ é de 1.960 (teste bicaudal) e Zb para $\beta = 0,10$ é de 1.282 (teste bicaudal). Encontramos um N = 56 para cada grupo e, portanto um N amostral total de 112 pacientes.

Foram incluídos no estudo 167 pacientes portadores de ICC classes III e IV internados consecutivamente nas enfermarias de Clínica Médica do Hospital Santo Antônio no período de primeiro de novembro de 2003 a 15 de setembro de 2005 tratados com IECA (específicamente captopril). Um total de 53 foram excluídos: 18 por apresentarem creatinina sérica maior que 1,2mg/dl na admissão, 11 por terem seus dados incompletos, 7 por estarem usando concomitantemente aminoglicosídeos, 5 que fizeram uso de antiinflamatórios não esteróides (AINES) e 12 por não consentirem participar do estudo. Permaneceram 114 pacientes para análise final.

Protocolo do estudo

Os pacientes foram acompanhados por um período de 30 dias após internamento até o desenvolvimento de IRA, alta, óbito, ou término do período estipulado para observação. Dosagens séricas de creatinina e potássio foram feitas através do método de Jaffe modificado[11] e fotometria de chama[12] respectivamente pelo menos três vezes por semana. Caso houvesse elevação da creatinina ou do potássio séricos, uma amostra de sangue independente era colhida para confirmação do resultado. As medidas de pressão arterial eram verificadas no mínimo 3 vezes ao dia através de método auscultatório com estetoscópio, sendo que o aparelho utilizado para verificar a pressão arterial foi o manômetro de coluna de mercúrio. A determinação da pressão arterial sistólica (PAS) era feita ao desaparecimento do primeiro ruído e da pressão arterial diastólica (PAD) ao desaparecimento dos sons. A pressão arterial média (PAM) foi calculada segundo a fórmula a seguir: [PAM = (PAS + 2PAD): 3].

O desfecho principal foi o desenvolvimento de IRA (definida como elevação da creatinina sérica > 0,5mg/dl em relação à creatinina basal. Hiperpotassemia e hiperpotassemia severa foram consideradas como desfechos secundários e definidos como potássio serico $\geq$ 5,5 mEq/l e > 6,0mEq/l, respectivamente As variáveis independentes foram: idade, gênero, raça, etiologia da insuficiência cardíaca, classe funcional da IC, presença ou não de diabetes, PAS da admissão, PAD da admissão, PAM da admissão, queda de PAS (Δ PAS) após o uso de IECA, a queda de PAD (Δ PAD) após o uso de IECA, a queda da PAM (Δ PAM) após o uso de IECA, a dose de IECA, dose de espironolactona, dose de furosemida , dose de digitálico, tipo de alta e causa do óbito, quando apropriado.

Análise estatística

Utilizamos o SPSS versão 11.0 para análise dos dados. Estatística descritiva foi utilizada para estimar a incidência de IRA, hiperpotassemia e hiperpotassemia severa nestes pacientes. Os níveis séricos de creatinina e potássio, assim como as cifras pressóricas foram representados por médias. A análise de regressão logística univariada foi realizada para determinar fatores preditores de insuficiência renal aguda nestes pacientes, permanecendo para análise de regressão logística multivariada aquelas variáveis que apresentaram um $p < 0,10$, sendo que todos os testes estatísticos foram bicaudais com erro tipo α de 0,05 e erro tipo β de 0,10.

Os 114 pacientes foram divididos em dois grupos assim definidos: Grupo 1 (25 pacientes que apresentaram uma queda da PAM $\geq$ 25mmHg pós-IECA e Grupo 0 (89 pacientes que apresentaram uma queda < 25 mmHg pós-IECA.

Para comparação de risco cumulativo de IRA, foram confeccionadas curvas de Kaplan-Meier (Figura 2) de acordo com o grau de queda da PAM pós-IECA. O teste de log rank foi utilizado para comparar os riscos cumulativos de IRA nos diferentes grupos em um período de 30 dias de acompanhamento. A curva ROC (*Receiver Operating Characteristics*) foi realizada para determinação do mais acurado ponto de corte de queda da PAM associada a desenvolvimento de IRA (Figura 3).

Nosso projeto de pesquisa foi aprovado pelo Comitê de Ética da Fundação Bahiana para o Desenvolvimento das Ciências (FBDC)/Escola Bahiana de Medicina e Saúde Pública (EBMSP). Apesar de o estudo ser observacional, os pesquisadores aconselharam os médicos a descontinuar a terapia com IECA em caso de densenvolvimento de IRA e/ ou hiperpotassemia, segundo recomendação do *American Heart Association*[5] *(AHA)*.

Resultados:

As características clínicas, laboratoriais e demográficas dos pacientes estudados encontram-se expostas na Tabela 1. A média de idade foi de 59 anos, 62% destes eram do gênero masculino, e 87% eram não brancos.

As principais causas de insuficiência cardíaca foram: miocardiopatia chagásica crônica (34%), seguida de cardiopatia hipertensiva (26%) e cardiopatia isquêmica (18%). Diabetes Mellitus (29%) e hipertensão arterial sistêmica (49%) foram co-morbidades freqüentes. O uso simultâneo de inibidor da ECA e espironolactona ocorreu em 67% dos casos e as demais medicações usadas e respectivas doses estão expressas também na Tabela 1.

A incidência de insuficiência renal aguda em um período de 30 dias de observação foi de 25%. Hiperpotassemia ocorreu em 15% dos pacientes e hiperpotassemia severa ocorreu em apenas 3% dos pacientes em questão.

Sete pacientes tiveram que descontinuar o uso de captopril devido à tosse, tais pacientes tiveram o IECA substituído por um bloqueador do receptor da angiotensina (losartan). Dezesseis pacientes tiveram que suspender o captopril devido a queda severa da PAM, a maioria destes pacientes desenvolveu concomitantemente insuficiência renal aguda.

Cinco pacientes foram a óbito, 2 deles faleceram devido a choque cardiogênico, 2 outros devido a choque séptico e um devido a acidente vascular cerebral isquêmico. Entre os pacientes que foram a óbito, 3 desenvolveram insuficiência renal aguda e hiperpotassemia – Tabelas 4 e 5.

Os preditores de desenvolvimento de insuficiência renal aguda encontrados através de regressão logística univariada foram: queda da pressão arterial média (PAM) maior ou igual a 25mmHg após início de terapia com inibidor da ECA (*odds ratio* = 18,2; I.C. a

95%: 6,2 a 53,5); diagnóstico de insuficiência cardíaca congestiva classe IV segundo os critérios do NYHA (*odds ratio* = 4,7; I.C. a 95%: 1,7 a 12,7); diagnóstico de hipertensão arterial sistêmica (*odds ratio* = 3,0; I.C. a 95%: 1,2 a 7,4) e diagnóstico de diabetes mellitus (odds ratio = 2,6; I.C. a 95%: 1,1 a 6,4) - Tabela 2. Os preditores independentes de desenvolvimento de insuficiência renal aguda identificados através de análise de regressão logística multivariada foram: uma queda maior ou igual a 25 mmHg na pressão arterial média (PAM) após uso de inibidor da ECA (*odds ratio* = 13,8; I. C. a 95%: 5,1 a 38,5) e diagnóstico de insuficiência cardíaca classe funcional IV segundo os critérios do NYHA (odds ratio = 3,5; I. C a 95%: 1,3 a 9,4) – Tabela 3.

O uso concomitante de IECA/ espironolactona não esteve relacionado com maior chance de desenvolvimento de IRA (Tabela 2).

Apesar da média da dose de captopril ter sido maior no grupo IRA (74.1 ± 31.9) *versus* não IRA (62.5 ± 29.14), não houve diferença significativa entre os 2 grupos (p = 0.08).

A média da dose de furosemida também foi maior no grupo IRA (61.4 ± 12.8) *versus* não IRA (57.44 ± 9.1), sem diferença estatísticamente significativa entre os 2 grupos (p = 0.07). A dose da espironolactona foi menor no grupo IRA (27.1 ± 7.1) *versus* não IRA (32.6 ± 25.4); p = 0.29.

Os vinte e nove casos de insuficiência renal aguda estão apresentados na Tabela 4. Dentre estes pacientes, apenas quatro tiveram sintomas relacionados com hipotensão e três foram a óbito (1 choque cardiogênico; 1 choque séptico e 1 acidente vascular isquêmico – Tabela 4). A Tabela 5 mostra em detalhes as dosagens dos diversos diuréticos utilizados em associação com o captopril para tratamento de insuficiência cardíaca nos 29 casos de insuficiência renal aguda, bem como chama atenção para as dosagens prévias ao internamento e como elas foram modificadas após a internação neste grupo de pacientes.

A Figura 1 mostra os dois grupos em diferentes *boxplots*, onde podem ser observadas as diferentes medianas da creatinina sérica após tratamento com captopril segundo o grau de queda de PAM.

A Figura 2 apresenta curvas de Kaplan-Meier mostrando o risco cumulativo para desenvolvimento de insuficiência renal aguda durante um período de 30 dias de observação após introdução de captopril para tratamento de insuficiência cardíaca descompensada. O Grupo I está representado em violeta e o Grupo 0 em verde.

A curva ROC (R*eceiver Operating Characteristics*) identifica o melhor ponto de corte de queda da PAM relacionada ao desenvolvimento de IRA em portadores de insuficiência cardíaca descompensada após introdução de inibidor da ECA: 25mmHg - Figura 3.

DISCUSSÃO

A incidência de insuficiência renal aguda em portadores de insuficiência cardíaca classe III e IV segundo os critérios do NYHA submetidos a tratamento farmacológico com captopril foi de 25%, taxa esta que está de acordo com diversos trabalhos recentemente publicados[8-10]. Os preditores de desenvolvimento de insuficiência renal aguda em portadores de insuficiência cardíaca tratados com inibidor da ECA já descritos na literatura são: idade avançada; diagnóstico de insuficiência cardíaca classe IV segundo os critérios do NYHA; baixa fração de ejeção de ventrículo esquerdo; insuficiência renal crônica prévia e hipotensão.

O estudo CONSENSUS[2] foi o que melhor correlacionou os baixos níveis pressóricos com o desenvolvimento de IRA nestes pacientes, porém não estabeleceu um ponto de corte abaixo do qual, mesmo que não ocorra hipotensão sintomática, uma perda importante de função renal possa acontecer.

No presente estudo, identificamos um ponto de corte de queda da PAM, abaixo da qual o risco de desenvolvimento de IRA aumenta consideravelmente. Encontramos que uma queda maior ou igual a 25mmHg na pressão arterial média (PAM) após tratamento de insuficiência cardíaca classes III e IV segundo os critérios do NYHA com inibidor da ECA, mesmo sem hipotensão sintomática, está associada à perda importante de função renal – Figura 3. Entre os 29 pacientes que desenvolveram insuficiência renal aguda, apenas quatro pacientes apresentaram hipotensão sintomática – Tabela 4.

Não encontramos associação estatisticamente significativa entre desenvolvimento de IRA com diferentes doses de captopril, apesar das médias terem sido maiores no grupo IRA *versus* não IRA; o mesmo ocorreu com as doses de furosemida endovenosa. É muito provável que o grau de contração volêmica resultante da associação desta droga

com os diversos diuréticos utilizados por via venosa e oral (Tabela 5), tenha tido um importante papel no efeito hipotensor do captopril em tais pacientes. É possível também que o nosso N amostral não tenha sido suficientemente grande para demonstrar uma relação entre doses mais elevadas de Captopril e furosemida endovenosa com desenvolvimento de IRA. O uso da associação inibidor da ECA com espironolactona não representou maior chance de desenvolvimento de IRA quando comparado ao uso isolado de inibidor da ECA. As doses de espironolactona, ao contrário do esperado, foram mais elevadas no grupo não IRA *versus* IRA, sem significância estatística. A interpretação que aventamos é a de que os médicos-assistentes, mais atentos a elevações séricas de creatinina e potássio pós-IECA, tenham reduzido a dose de espironolactona caso houvesse qualquer alteração dos últimos. Idade avançada não esteve associada a maior chance de desenvolvimento de IRA, porém a média de idade da nossa amostra é inferior às descritas em estudos americanos e europeus[2, 13]. Isto se deve ao fato de que na nossa população a principal causa de insuficiência cardíaca foi miocardiopatia crônica chagásica.

A Tabela 3 mostra os preditores independentes para desenvolvimento de IRA identificado através de regressão logística multivariada. Pertencer à classe funcional IV de insuficiência cardíaca congestiva (*odds ratio* = 3,5; I. C a 95%: 1,3 a 9,4) e uma queda na pressão arterial média maior ou igual a 25mmHg após tratamento com inibidor da ECA (*odds ratio* = 13,8; I. C. a 95%: 5,1 a 38,5) foram os dois preditores independentes para desenvolvimento de IRA na amostra estudada. Ser portador de diabetes mellitus e hipertensão arterial sistêmica foram encontrados como preditores apenas na análise de regressão logística univariada – Tabela 2.

Uma queda maior ou igual a 25mmHg em portadores de insuficiência cardíaca congestiva submetidos a tratamento com inibidor da ECA certamente leva a uma

redução importante na perfusão renal. Em tais circunstâncias, três fatores se somariam e desempenhariam um papel determinante no desenvolvimento de disfunção renal aguda: a) baixo débito cardíaco; b) queda maior ou igual a 25mmHg na PAM e c) efeito supressor da auto-regulação da perfusão renal dos inibidores da ECA, culminando em maior chance de desenvolvimento de IRA. Além disso, a presença de co-morbidades como diabetes mellitus e hipertensão arterial sistêmica poderiam tornar estes pacientes ainda mais susceptíveis a desenvolver IRA, por causa de uma possível microangiopatia pré-existente. Esta hipótese se torna mais provável devido ao baixo nível educacional e sócio-econômico dos pacientes estudados, pouco acesso a serviços de saúde e conseqüentemente incapacidade de aderência aos tratamentos antihipertensivos e antidiabéticos, fato este corroborado pelas sucessivas reinternações devido a não utilização das medicações prescritas pelo médico assistente na ocasião da alta hospitalar. Apesar disso, temos que reconhecer como uma limitação do estudo o fato de não ter sido possível a realização de microlbuminúria nestes pacientes, o que não nos permite tirar conclusões a respeito da existência ou não de microangiopatia relacionada à hipertensão e diabetes.

Comparando os resultados de estudo anterior por Cruz & Marcílio de Souza[10] com o presente estudo, observamos que a incidência de IRA foi similar em ambos os estudos (27% *versus* 25% no atual estudo). Entretanto, no atual estudo houve uma importante queda nas taxas de hiperpotassemia (15% neste *versus* 33% naquele), o mesmo acontecendo com as taxas de hiperpotassemia severa (apenas 3% no estudo atual *versus* 14% em estudo anterior). Acreditamos que esta importante redução nas taxas de hiperpotassemia ocorreu como conseqüência de uma série de publicações recentes que, ao contrário do RALES, revelaram risco mais alto de desenvolvimento de

hiperpotassemia em portadores de insuficiência cardíaca em tratamento com a associação inibidor da ECA e espironolactona[8-10, 13]. O *American Heart Asociation*[5] (AHA) publicou um documento que teve como tema central as considerações renais sobre o tratamento da insuficiência cardíaca congestiva com antagonistas da aldosterona, recomendando a monitoração da função renal e do potássio sérico após introdução da associação inibidor da ECA/espironolactona, sugerindo que naqueles pacientes onde houvesse uma elevação sustentada da creatinina sérica em mais do que 50% quando comparados aos valores basais ou então hiperpotassemia (potássio sérico maior que 5,5mEq/l), o tratamento fosse descontinuado e fossem tratadas as prováveis condições preditoras de insuficiência renal aguda nestes pacientes tais como: excesso de diuréticoterapia, diarréia, desidratação e uso concomitante de antiinflamatórios não esteróides.

O estudo ATLAS[14] demonstrou que a proteção cardiovascular é maior com o aumento das doses de inibidor da ECA para tratamento de insuficiência cardíaca congestiva. Há que se convir que as doses devam ser aumentadas sim, mas antes disso deve ser verificada a tolerância e segurança da droga em cada paciente em relação à perda relevante de função renal e ocorrência de hiperpotassemia.

Os cinco óbitos que ocorreram durante o período de observação não estiveram relacionados diretamente com insuficiência renal aguda ou hiperpotassemia, entretanto, três destes pacientes apresentaram IRA e hiperpotassemia. Muitos estudos apontam para um prognóstico ruim em portadores de insuficiência cardíaca que desenvolvem concomitante insuficiência renal[15].

CONCLUSÕES

1) A incidência de insuficiência renal aguda, hiperpotassemia e hiperpotassemia severa em pacientes com insuficiência cardíaca congestiva descompensada que foram tratados com inibidor da ECA em 30 dias de observação foram de 25%; 15% e 3% respectivamente.
2) Os fatores preditores independentes de desenvolvimento de IRA encontrados foram: uma queda maior ou igual a 25mmHg na PAM após introdução do captopril e diagnóstico de insuficiência cardíaca classe IV segundo os critérios do NYHA.
3) Uma queda da pressão arterial média (PAM) $\geq$ 25mmHg em portadores de insuficiência cardíaca congestiva descompensada tratados com IECA deve ser interpretada como um sinal de alerta para descontinuar terapia com esta classe de drogas visando evitar desenvolvimento de IRA e subseqüente hiperpotassemia.

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Tabela 1. Características clínicas e demográficas de portadores de Insuficiência Cardíaca descompensada que foram tratados com inibidor da ECA (IECA) à admissão (N = 114)

*Variável	Pacientes que iniciaram uso de IECA†
Idade	59 ± 14
Gênero masculino	62%
Raça não branca	87%
Classe funcional da insuficiência cardíaca	classe IV(52%)
	classe III (48%)
Etiologia da insuficiência cardíaca	Miocardiopatia crônica chagásica (34%)
	Cardiopatia hipertensiva (26%)
	Cardiopatia isquêmica (18%)
	Miocardiopatia dilatada de origem desconhecida (12%)
	Valvulopatias (8%)
	Outros (2%)
Creatinina sérica em mg/dl	1.0 ± 0.2
Potássio sérico em mEq/l	4.2 ± 0.6
Pressão arterial sistólica em mmHg (PAS)	144 ± 25
Presão arterial diastólica em mmHg (PAD)	83 ± 15
Diabetes mellitus	75% não
	25% sim
Hipertensão arterial sistêmica	54% não
	46% sim
Dose de IECA em mg/dia	60 ± 34
Dose de digoxina em mg/dia	0.23 ± 0.05
Dose de furosemida endovenosa em mg/dia	56 ± 23
Associação de IECA com espironolactona	Sim (67%)
	Não (33%)
Dose de espironolactona em mg/dia	27 ± 12

*As varáveis contínuas estão expressas em média ± desvio padrão e as categóricas em percentagem válida; † inibidor da enzima de conversão da angiotensina

Tabela 2. Associações univariadas entre variáveis clínico-demográficas e desenvolvimento de Insuficiência Renal Aguda (IRA) em portadores de insuficiência cardíaca congestiva tratados com inibidor da ECA (N = 114)

Variável	*Odds ratio*	I. C. a 95%
Idade	1.0	0.95 a 1.0
Inibidor da ECA (mg/dia)	1.0	0.3 a 3.3
Inibidor da ECA/espironolactona	1.0	0.3 a 2.9
NYHA Class IV	4.7	1.7 a 12.7
† Δ PAM	18.2	6.2 a 53.5
Diabetes Mellitus	2.6	1.1 a 6.4
Hipertensão arterial sistêmica	3.0	1.2 a 7.4

† Δ PAM = queda da pressão arterial média (PAM) $\geq$ 25mmHg após início do tratamento com inibidor da ECA

Tabela 3. Associações multivariadas entre variáveis clínicas e desenvolvimento de Insuficiência Renal Aguda (IRA) em portadores de insuficiência cardíaca congestiva descompensada tratados com inibidor da ECA (N = 114).

Variável	*Odds ratio*	I.C. a 95%
Pertencer a classe funcional IV de IC	3.5	1.3 a 9.4
† Δ PAM ≥ 25mmHg	13.8	5.1 a 38.5
Diagnóstico de Diabetes Mellitus	1.7	0.5 a 6.1
Diagnóstico de Hipertensão arterial	1.2	0.3 a 4.2

† Δ PAM = queda da pressão arterial média (PAM) ≥ 25mmHg após início do tratamento com inibidor da ECA

Tabela 4. Características clínicas e laboratoriais de 29 casos de Insuficiência Renal Aguda (IRA) após introdução de inibidor da ECA (IECA) para tratamento de Insuficiência Cardíaca (IC) descompensada.

Casos de IRA	Etiologia da IC	NYHA classe IV	Dose de IECA* mg/dia	Dias de uso de IECA para tratamento IC descompensada	Creat 1¶	Creat 2 Ŧ	Creat 3 §	PAM 1†	PAM 2 ‡	Hipertensão	Diabetes	Hipotensão sintomática	Tipo de alta hospitalar
1	Isquêmica	Sim	50	20	1.01	1.6	1.0	97	70	Não	Não	Não	Melhor
2	Doença de Chagas	Não	100	26	0.61	1.3	0.83	73	70	Não	Sim	Não	Melhor
3	Hipertensão	Sim	100	04	1.0	2.12	1.5	127	80	Sim	Sim	Não	Óbito
4	Isquêmica	Sim	75	09	0.8	1.58	1.2	107	83	Sim	Sim	Não	Melhor
5	Outras	Sim	100	08	0.92	1.5	1.1	122	70	Sim	Sim	Sim	Melhor
6	Doença de Chagas	Sim	37.5	30	0.72	1.3	0.9	97	70	Sim	Não	Não	Melhor
7	Desconhecida	Sim	25	26	0.8	1.4	1.1	103	70	Não	Não	Não	Melhor
8	Outras	Não	75	12	0.75	1.4	1.32	93	83	Não	Não	Não	Melhor
9	Doença de Chagas	Não	75	17	0.62	1.3	1.0	96	70	Não	Sim	Não	Melhor
10	Hipertensão	Não	100	17	0.81	1.4	1.3	127	93	Sim	Sim	Não	Melhor
11	Outras	Sim	75	15	1.0	1.76	1.22	90	77	Não	Não	Não	Melhor
12	Desconhecida	Sim	50	30	0.8	1.49	1.07	73	70	Não	Não	Não	Melhor
13	Desconhecida	Sim	50	30	0.81	2.3	1.59	93	70	Sim	Sim	Não	Melhor
14	Doença de Chagas	Sim	37.5	21	1.11	2.85	2.0	117	97	Sim	Não	Não	Melhor
15	Desconhecida	Sim	50	18	0.82	1.76	1.2	93	73	Não	Não	Não	Melhor
16	Hipertensão	Sim	100	07	1.15	2.44	1.7	123	87	Sim	Sim	Não	Melhor
17	Doença valvular	Sim	50	21	1.0	1.51	1.0	120	90	Sim	Sim	Não	Melhor
18	Hipertensão	Sim	150	30	1.05	2.42	1.45	140	83	Sim	Não	Não	Melhor
19	Doença de Chagas	Sim	75	08	1.0	1.9	1.5	107	80	Sim	Não	Não	Melhor
20	Isquêmica	Sim	50	28	1.01	2.03	1.14	123	87	Sim	Sim	Sim	Óbito
21	Doença valvular	Não	75	19	0.43	1.21	0.85	97	93	Sim	Não	Não	Melhor
22	Hipertensão	Sim	75	10	1.11	2.55	1.65	123	77	Sim	Sim	Não	Melhor
23	Doença de Chagas	Sim	75	11	1.02	1.75	1.1	120	93	Sim	Não	Não	Melhor
24	Hipertensão	Não	75	11	0.46	1.33	0.9	122	87	Sim	Sim	Não	Melhor
25	Hipertensão	Não	150	14	0.43	1.26	0.75	147	83	Sim	Não	Sim	Óbito
26	Hipertensão	Sim	100	05	1.04	2.00	1.3	133	77	Sim	Não	Não	Melhor
27	Desconhecido	Sim	37.5	08	1.02	1.52	1.18	70	70	Não	Não	Não	Melhor
28	Isquêmica	Sim	100	13	1.02	2.0	1.37	133	77	Sim	Sim	Sim	Melhor
29	Desconhecida	Sim	37.5	05	1.13	1.75	1.34	100	70	Sim	Não	Não	Melhor

*Dose de Captopril ao desenvolvimento de IRA; ¶ Creat 1 = creatinina basal sérica (mg/dl); Ŧ Creat 2 = creatinina sérica após uso de Captopril (mg/dl);

§ Creat 3 = creatinina sérica após suspensão de Captopril (mg/dl); † PAM 1 = pressão arterial média; ‡ PAM 2 = pressão arterial média após uso de Captopril

Tabela 5. Doses de diuréticos e captopril usadas para tratamento de Insuficiência Cardíaca Congestiva (ICC) antes e ao desenvolvimento de 29 casos de Insuficiência Renal Aguda (IRA)

29 casos de IRA	Dose de captopril (mg/dia) 1*	Dose of captopril (mg/dia) 2§	Dias de uso de captopril após descompensação da IC	Dose de furosemida na admissão†	Dose de furosemida (mg/dia) iv‡	Dose de espironolactona (mg/dia)Σ	Creat 1¶	Creat 2 ₸	Creat 3 ¥	PAM 1Ψ	PAM 2 £
1	50	50	20	40	60	25	1.01	1.6	1.0	97	70
2	75	100	26	80	40	—	0.61	1.3	0.83	73	70
3	50	100	04	80	80	25	1.0	2.12	1.5	127	80
4	50	75	09	40	60	25	0.8	1.58	1.2	107	83
5	75	100	08	40	80	25	0.92	1.5	1.1	122	70
6	25	37.5	30	40	60	25	0.72	1.3	0.9	97	70
7	25	25	26	40	60	25	0.8	1.4	1.1	103	70
8	50	75	12	60	40	25	0.75	1.4	1.32	93	83
9	50	75	17	40	60	25	0.62	1.3	1.0	96	70
10	75	100	17	60	80	25	0.81	1.4	1.3	127	93
11	50	75	15	40	60	25	1.0	1.76	1.22	90	77
12	25	50	30	40	40	—	0.8	1.49	1.07	73	70
13	25	50	30	40	60	25	0.81	2.3	1.59	93	70
14	25	37.5	21	40	60	25	1.11	2.85	2.0	117	97
15	25	50	18	40	40	25	0.82	1.76	1.2	93	73
16	50	100	07	40	60	25	1.15	2.44	1.7	123	87
17	37.5	50	21	40	60	25	1.0	1.51	1.0	120	90
18	100	150	30	40	80	50	1.05	2.42	1.45	140	83
19	50	75	08	80	60	25	1.0	1.9	1.5	107	80
20	25	50	28	80	60	25	1.01	2.03	1.14	123	87
21	50	75	19	60	40	25	0.43	1.21	0.85	97	93
22	50	75	10	60	80	25	1.11	2.55	1.65	123	77
23	50	75	11	40	60	25	1.02	1.75	1.1	120	93
24	50	75	11	40	60	25	0.46	1.33	0.9	122	87
25	100	150	14	40	80	50	0.43	1.26	0.75	147	83
26	75	100	05	40	80	25	1.04	2.00	1.3	133	77
27	25	37.5	08	40	40	—	1.02	1.52	1.18	70	70
28	75	100	13	40	80		1.02	2.0	1.37	133	77
29	25	37.5	05	40	60	25	1.13	1.75	1.34	100	70

*

Dose de captopril antes da admissão; §dose de captopril ao desenvolvimento de IRA; † dose de furosemida (mg/dia) antes da admissão; ‡dose de furosemida (intra-venosa) ao desenvolvimento de IRA; Σ dose de espironolactona (mg/dia) ao desenvolvimento de IRA; ¶ creatinina basal sérica (mg/dl); ₸ creatinina sérica após uso de Captopril (mg/dl); ¥ creatinina sérica após suspensão de Captopril; Ψ PAM 1 = pressão arterial média basal; £ PAM 2 = pressão arterial média após uso de Captopril

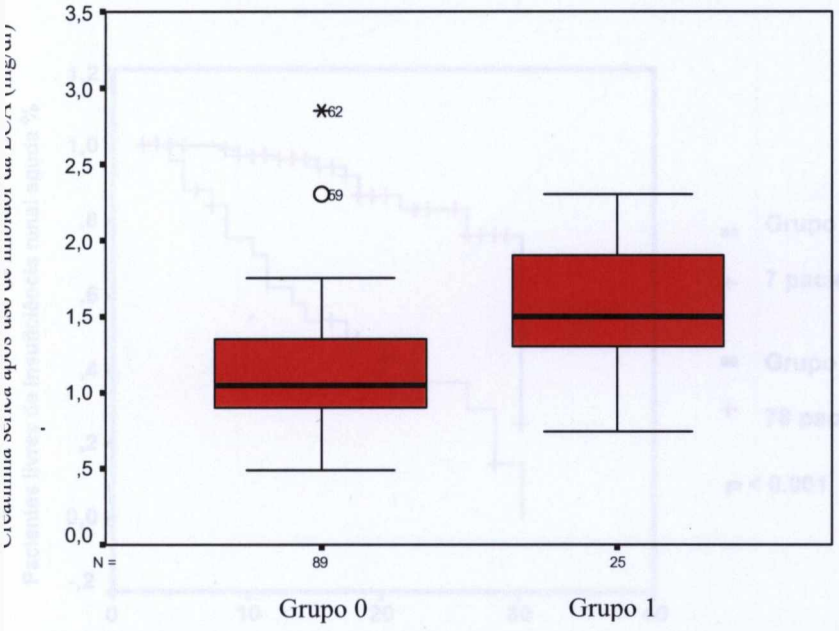


Figura 1. *Boxplots* representando os níveis séricos de creatinina após uso de inibidor da ECA para tratamento de Insuficiência Cardíaca descompensada em 2 grupos diferentes: Grupo 1 (25 pacientes cuja queda da pressão arterial média ≥25mmHg após introdução de inibidor da ECA) e Grupo 0 (89 pacientes cuja queda da presão arterial média < 25mmHg após introdução do inibidor da ECA)

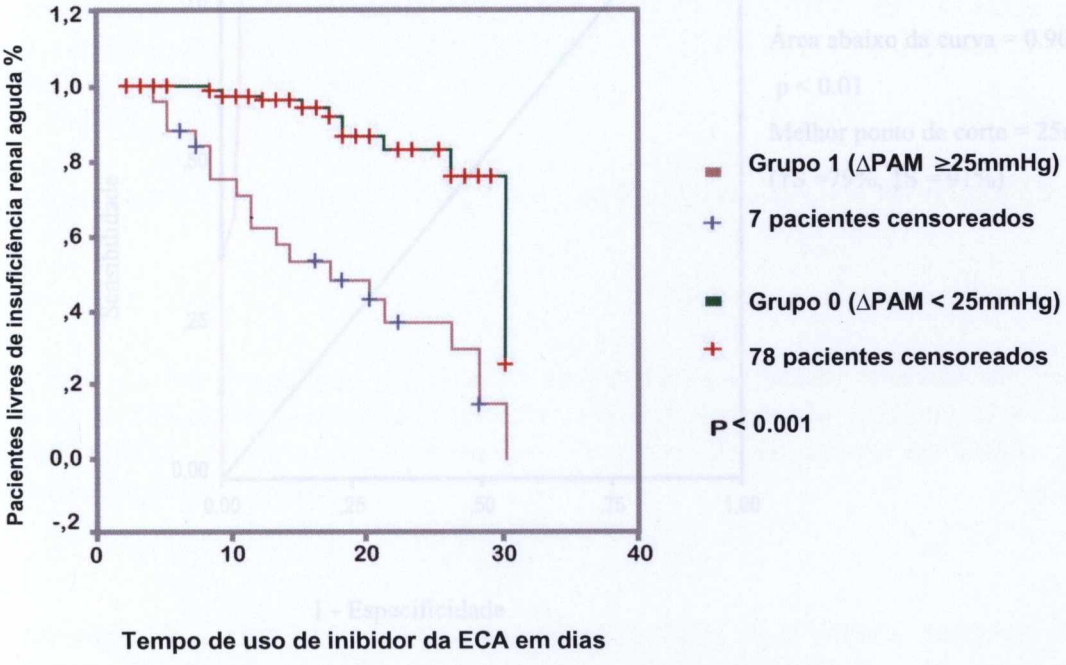
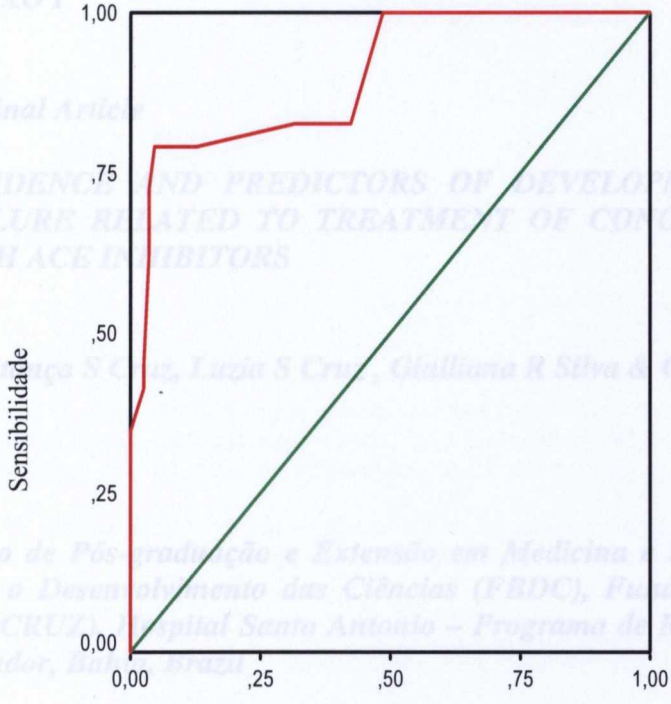


Figura 2. Curvas de Kaplan-Meier demonstrando o risco cumulativo de desenvolvimento de Insuficiência Renal Aguda (IRA) durante os 30 primeiros dias de observação. O Grupo 1 está representado em violeta (25 pacientes cuja queda da PAM ≥25 mmHg pós-IECA) e o Grupo 0 em verde (89 pacientes cuja queda da PAM < 25mmHg pós-IECA)



Área abaixo da curva = 0.90

$p < 0.01$

Melhor ponto de corte = 25mmHg;

(†S =79%, ‡S = 91%)

Figura 3. Curva ROC identifica o melhor ponto de corte de queda da pressão arterial media (PAM) associada com desenvolvimento de Insuficiência Renal Aguda (IRA) após uso de inibidor da ECA em portadores de Insuficiência Cardíaca descompensada: 25mmHg [†Sensibilidade = 79%, ‡Especificidade = 91%]

ANEXO I

Original Article

INCIDENCE AND PREDICTORS OF DEVELOPMENT OF ACUTE RENAL FAILURE RELATED TO TREATMENT OF CONGESTIVE HEART FAILURE WITH ACE INHIBITORS

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Dear Prof. Dr. Sampaio,

Thank you for submitting your manuscript to Nephron Clinical Practice. I am pleased to inform you that it has now been accepted for publication and passed on to the publishers from whom you will hear shortly.

I wish you every success with your future research studies and hope that you will consider submitting future manuscripts for consideration by Nephron Clinical Practice.

With kind regards

Prof Steve Powis
Editor, Nephron Clinical Practice.
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INCIDENCE AND PREDICTORS OF DEVELOPMENT OF ACUTE RENAL FAILURE RELATED TO TREATMENT OF CONGESTIVE HEART FAILURE WITH ACE INHIBITORS

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Running head: Acute renal failure due to treatment with ACE inhibitors

Keywords: acute renal failure; ACE inhibitors; heart failure; predictors of acute renal failure due to ACE inhibitors

Introduction

In recent years, Angiotensin-Converting Enzyme Inhibitors (ACEI) have been important drugs for treatment of Congestive Heart Failure (CHF). The "CONSENSUS" (Cooperative North Scandinavian Enalapril Survival Study)[1] recommends close monitoring of serum creatinine and potassium levels after introduction of ACEI therapy and after an increase in its dosage. This study shows a 20-30% reduction of Glomerular Filtration Rate (GFR) after introduction of Enalapril that trends toward stabilization following a 20 to 30 day period; however, other studies have demonstrated a higher reduction in GFR after introduction of ACEI, especially in certain risk group of patients[2-6].

Bridoux & Vanhille[2] studied 27 cases of Acute Renal Failure (ARF) after introduction of ACEI for treatment of CHF and/or Systemic Arterial Hypertension in patients without Renal Artery Stenosis. The most relevant clinical findings were: volume depletion in 21 patients and hypotension in 12 patients. The presence of Diabetes Mellitus, association of ACEI with non steroid anti-inflammatory drugs and decompensated heart failure were also predictive factors for development of ARF .The majority of patients recovered renal function after volume expansion, suspension of ACEI and a decrease in diuretic doses; 2 patients died and 4 patients did not recover renal function requiring dialysis therapy. The authors concluded that volume and salt depletion have an important role in ARF caused by ACEI therapy and that the association of these drugs with diuretics requires an extra caution, especially in elderly and patients with macro/micro vascular renal disease.

Ahmed[3] in a systemic review of 12 randomized clinical trials showed that patients with decreased functional renal reserve and CHF may present higher rates of serum creatinine levels than those previously showed by Ljungman, Kjekshun & Swedberg. In certain risk group of patients, such as those with decompensated CHF, volume depletion and bilateral renal artery stenosis, there was an increase in serum creatinine levels as high as 75% to 150% compared to basal levels during the first four weeks of ACEI therapy.

The American Heart Association guidelines[7], published in 2001, recommends suspension of ACEI for treatment of CHF if there is an increase in serum creatinine levels of 50% compared to basal creatinine levels or if hyperkalaemia occurs. Correction of predictive factors of decreased renal function such as hypotension, high doses of diuretic drugs and micro/macrovasular renal disease is also recommended. In a recent study, Schlipak[8] verified that CHF patients who experienced intolerance to ACEI therapy were those with end stage CHF, a condition that he entitles: "Cardio-renal Syndrome". Caramelo & Gil[9] also recognized the "Cardio-renal Syndrome" as a therapeutic challenge, stating the existence of two different subgroups of patients: a) those who need high concentrations of Angiotensin II to preserve their GFR and experience worsening of renal function with ACEI treatment; b) those who have their GFR worsened by the decompensated CHF and experience a improvement of renal function with ACEI treatment.

We aimed to observe the behavior of renal function in CHF patients treated with ACEI in order to answer the following questions: 1) What is the incidence of Acute Renal Failure in these patients? 2) What predictive factors are related to an important decrease in renal function (increase in serum creatinine levels higher than 50%–100% compared to basal creatinine levels) in certain groups of patients in the first days of ACEI therapy?

Subjects and Methods

We performed a prospective cohort study of New York Heart Association (NYHA) class III or IV CHF patients treated with ACE inhibitors (ACEI), associated or not with spironolactone, and admitted to Santo Antonio University Hospital (Salvador, Brasil) from November 1st 2003 through September 15th 2005 . A total of 167 patients fulfilled the inclusion criteria. We excluded 53 patients from the study because 18 had a serum creatinine level > 1,2mg/dl at admission; 11 because we lacked follow-up information on serum creatinine levels; 7 were excluded because of treatment with amino glycoside; 5 because of treatment with non-steroid anti-inflammatory drugs and 12 patients did not agree to participate in the study.

After admission, we followed these patients for a period of 30 days or until the development of acute renal failure (ARF); hyperkalaemia; discharge or death. ARF was defined by an increase in levels of serum creatinine of 0,5mg/dl from basal values; hyperkalaemia was defined by serum potassium levels ≥ 5,5mEq/l and severe hyperkalaemia by serum potassium levels > 6,0mEq/l. The Average blood pressure was estimated through the formula: [Systolic Blood Pressure-SBP + (2xDiastolic blood pressure-DBP) ÷ 3. Monitoring of serum creatinine and potassium levels were performed at least three times a week and blood pressure measurements were performed every 8 hours, daily. If high levels of serum creatinine or potassium levels were detected, a second blood sample was collected for confirmation. The Jafee modified method[10] was used for measurement of serum creatinine levels and measurement of serum potassium levels was performed using flame photometry[11].

The 114 patients were split into two groups: Group 1 [25 patients who experienced a decrease in average blood pressure (ABP) > 25mmHg after treatment with ACEI] and Group 0 [89 patients who experienced a decrease in average blood pressure (ABP) ≤ 25mmHg after treatment with ACEI].

Statistical analysis

We used descriptive statistics to estimate the incidence of development of ARF, hyperkalaemia and severe hyperkalaemia. Serum creatinine levels, potassium levels and blood pressure were represented by means, before and after use of Captopril. For comparisons of numeric data between two groups, unpaired t test was used. Frequencies were compared using Chi-square and Fisher's exact test. Univariate logistic regression was performed to determine the association of development of ARF with the observed clinical and laboratory findings. Multivariate regression analysis was performed to identify independent predictors for development of acute renal failure. The cumulative risk of ARF during the observation period was determined using Kaplan-Meier curves and the log rank test was used for comparisons between the two groups. All analysis was performed using the SPSS® version 11.0. Two-tailed statistical tests were used with an alpha level set at 0.05.

This study was approved by the Ethical Committee of Fundação para o Desenvolvimento das Ciências (FBDC)/ Escola Bahiana de Medicina e Saúde Publica (EBMSP).

Results

All demographic and clinical features upon admission are shown on Table 1. Mean age of patients studied was 59 years old, 62% were men, and 87% were non-white. The leading causes of CHF were: cardiomyopathy secondary to Chagas' disease (trypanosomiasis) – 34%, followed by hypertension (26%) and ischemia (18%). Diabetes (29%) and hypertension (49%) were frequent co-morbidities. The simultaneous use of ACE inhibitor and spironolactone occurred in 67% of CHF patients and doses of all medications are shown on Table 1.

The incidence of development of ARF after thirty days of treatment with ACE inhibitors associated or not with spironolactone, was estimated in 25%. Hyperkalaemia occurred in 15% of CHF patients treated with ACEI and severe hyperkalaemia occurred in only 3% of them.

Seven patients had cough related to ACEI and this drug had to be switched to an AT1-receptor antagonist. Sixteen patients had a severe drop in arterial blood pressure after use of ACE inhibitors and the majority of these patients developed concomitant ARF; captopril was discontinued in all of these patients.

Five patients died and of those, 2 developed cardiogenic shocks; 2 septic shocks and 1 developed an isquemic stroke. Among patients that died, 3 developed acute renal failure and Hyperkalaemia. The following were predictors for development of ARF: a decrease in ABP (average blood pressure) $\geq$ 25mmHg after initiation of treatment with ACE inhibitor (*OR*= 18. 2; 95%CI: 6.2, 53. 5); a diagnosis of NYHA class IV CHF (OR = 4. 7; 95%CI: 1. 7, 12. 7); hypertension (*OR* = 3.0; 95%CI: 1.2, 7.4) and diabetes (*OR*= 2.6; 95%CI: 1.1, 6.4) Table 2. The independent predictors for ARF were identified by a

multivariate logistic regression analysis (Table 3). A decrease in average blood pressure ≥ 25mmHg and a diagnosis of NYHA Class IV congestive heart failure were both independent predictors of ARF.

The twenty nine cases of ARF are presented in Table 4. Death occurred in three patients, 1 patient had a cardiogenic shock, 1 had a septic shock and the last one had a stroke. Only four patients had symptomatic hypotension after using captopril (Table 4). The three cases of severe Hyperkalaemia had an increase in serum creatinine > 100% from the basal levels and all of them have used ACE inhibitors plus spironolactone. After suspending these drugs, potassium levels returned to normal levels. Doses of furosemide, captopril and spironolactone used in all cases of ARF are presented in Table 5.

Among the 114 patients treated with Captopril, 25 developed an important decrease in ABP ≥ 25mmHg (Group 1) and 89 had a decrease in ABP < 25mmHg (Group 0). Figure 1 show in box plots, the serum creatinine levels of each group, after treatment with ACEI. Figure 2 presents Kaplan-Meier curves showing the cumulative risk for development of ARF during a 30 days period. The Group1 was represented in violet and Group 0 in green.

Discussion

We have estimated the incidence of development of ARF in NYHA class III and IV CHF patients treated with ACEI in 25%, in accordance with other recent studies[2-6]. The predictors of development of ARF among decompensated CHF patients treated with ACEI, already described are: advanced age; a diagnosis of NYHA class IV CHF; low ejection fraction of left ventricle; concurrent renal insufficiency and average blood pressure < 65mmHg. There is no data regarding the association of treatment of CHF patients with ACEI and a concurrent decrease in systolic, diastolic or average blood pressures, with development of acute renal failure.

In the present study, we found that a decrease ≥ 25mmHg in ABP after initiation of treatment of decompensated CHF patients with ACE inhibitors (ACEI) is a predictor of development of ARF. Among 29 patients who developed ARF, only four patients had symptomatic hypotension (Table 4).The occurrence of NYHA class IV CHF, diabetes and hypertension were also predictors of development of acute renal failure in these patients as shown in Table 2. We did not find association statistically significant of development of ARF with different doses of captopril, probably the degree of volume contraction had an important role in the hypotensive effect of ACEI in such patients – Table 4 and 5. Advanced age was not associated with ARF, but the mean age of our sample is lower than those described in the American and European studies[1, 12]. This fact is probably due to our leading cause of heart failure, Chagas' disease. Table 3 shows the independent predictors for development of ARF, identified by multivariate logistic

regression. NYHA class IV (*OR* = 3.5), p value = 0.04, and a decrease in average blood pressure ≥ 25mmHg (*OR* = 13.8), p value < 0.01, were the 2 independent predictors of acute renal failure.

A decrease in average blood pressure (ABP) ≥ 25 mmHg in decompensated congestive heart failure patients after treatment with ACE inhibitors certainly leads to a reduction in renal blood perfusion. Under these circumstances, three major factors would play an important role in the development of acute renal failure: a) insufficient cardiac output; b) a decrease > 25mmHg in ABP and c) ACE inhibitor suppressing effect on auto regulation of renal perfusion, culminating in higher risk of development of ARF. Also, Hypertensive and diabetic patients could be more susceptible to ARF because of pre-existing microangiopathy[2, 7].

Comparing the results of a retrospective cohort study conducted by Cruz & Marcílio de Souza[6] with the present study, we observed that the incidence of development of ARF was similar in both studies (27% in the retrospective study *versus* 25% in this prospective cohort), but in the present study, there was an important decrease in rates of hyperkalaemia and severe hyperkalaemia (15% in the present study *versus* 33% in the retrospective study and only 3% of severe hyperkalaemia in the present study *versus* 14% in the retrospective cohort). We believe that this important reduction in rates of hyperkalaemia occurred as a consequence of publication of studies[4-6] that showed higher risk of development of hyperkalaemia in comparison with the results reported on RALES. As a result, the primary care physicians possibly became more aware of the

importance of monitoring renal function and serum potassium levels after the introduction of an ACE inhibitor, with or without spironolactone, for treatment of heart failure. We also believe that the decrease in rates of hyperkalaemia observed in this prospective study, when compared to the retrospective cohort, was due to a strict observation of the AHA[7] recommendations, that these drugs should be suspended if hyperkalemia occurs and also if an increase in levels of serum creatinine > 0,5mg/dl is observed, when compared with baseline levels.

In spite of the fact that the five deaths observed in this study were not associated with the development of acute renal failure and neither of them was caused by hyperkalaemia, three of these patients developed ARF and hyperkalaemia. It is well known that a bad prognosis is reserved for congestive heart failure patients if acute renal failure develops concurrently[13-15].

Conclusion

We have studied and followed prospectively 114 hospitalized decompensated NYHA class III and IV congestive heart failure patients during the first 30 days of treatment with ACE inhibitors, associated or not with spironolactone. We estimated in 25%, 15%, and 3% the incidence of occurrence of ARF, hyperkalaemia and severe hyperkalaemia, respectively.

The observed predictors of development of acute renal failure were the occurrence of NYHA class IV congestive heart failure, a decrease ≥ 25mmHg in average blood pressure

(ABP) after initiation of treatment with an ACE inhibitor, associated or not with spironolactone; diabetes and hypertension.

A fall in average blood pressure (ABP) $\geq$ 25mmHg in severe congestive heart failure patients treated with ACE inhibitors should be a sign to discontinue therapy with this class of drugs in order to avoid development of Acute Renal Failure and subsequent hyperkalaemia in these patients.

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Table 1. Clinical and demographic characteristics of Congestive heart failure (CHF) patients treated with ACE inhibitors upon admission

*Variable	CHF patients treated with ACE inhibitors
Age	59 ± 14
Men	71 (62%)
Non-white	99 (87%)
NYHA class of CHF	
Class IV	59 (52%)
Class III	55 (48%)
CHF aetiology	
Chagas' disease	39 (34%)
Hypertension	29 (25, 5%)
Ischemic	21 (18, 5%)
Valvular disease	14 (12%)
Unknown	9 (8%)
Others	2 (2%)
Baseline creatinine (mg/dl)	1,0 ± 0,2
Baseline potassium (mEq/l)	4,2 ± 0,6
Systolic blood pressure (mmHg)	144 ± 25
Diastolic blood pressure (mmHg)	83 ± 15
Diabetic patients	33 (29%)
Hypertensive patients	56 (49%)
ACE inhibitor (mg/day)	60 ± 34
Digoxin (mg/day)	0,23 ± 0,05
‡Furosemide (mg/day)	56 ± 23
ACE inhibitor plus spironolactone	76 (67%)
Spironolactone (mg/day)	27 ± 12

*Data are presented as means ± SD for quantitative variables or absolute number (valid percentage) for categorical variables; †CHF = congestive heart failure; ‡intravenous furosemide

Table 2. Univariate associations of clinical variables with Acute Renal Failure (ARF) in congestive heart failure patients treated with ACE inhibitors (N = 114).

Variable	*Odds ratio*	95%CI
Age	1.0	0.95 - 1.03
ACE inhibitor (mg/day)	1.0	0.3 - 3.3
NYHA Class IV	4.7	1.7 – 12.7
† Δ ABP	18.2	6.2 - 53.5
Diabetic patients	2.6	1.1 - 6.4
Hypertensive patients	3.0	1.2 - 7.4

† Δ ABP = decrease in average blood pressure > 25mmHg after initiation of treatment with ACE inhibitor

Table 3. Multivariate associations of clinical variables with Acute Renal Failure (ARF) in congestive heart failure patients treated with ACE inhibitors (N = 114).

Variable	*Odds ratio*	p value
NYHA class IV	3.5	0.04
† Δ ABP	13.8	0.01
Diabetic patients	1.7	0.4
Hypertensive patients	1.2	0.8

† Δ ABP = decrease in average blood pressure > 25mmHg after initiation of treatment with ACE inhibitor.

Table 4. Clinical and laboratorial characteristics of twenty-nine cases of Acute Renal Failure (ARF) related to treatment of Congestive Herat Failure patients with ACE inhibitors (ACEI)

29 cases of ARF	Heart failure etiology	NYHA class IV	Dose of captopril* mg/day	Days of exposure to captopril	Creat 1¶	Creat 2 Ŧ	Creat 3 §	ABP 1†	ABP 2 ‡	Hypertension	Diabetes	Symptomatic Hipotension	Discharge
1	Ischemic	Yes	50	20	1.01	1.6	1.0	97	70	No	No	No	Better
2	Chagas' disease	No	100	26	0.61	1.3	0.83	73	70	No	Yes	No	Better
3	Hypertension	Yes	100	04	1.0	2.12	1.5	127	80	Yes	Yes	No	Death
4	Ischemic	Yes	75	09	0.8	1.58	1.2	107	83	Yes	Yes	No	Better
5	Others	Yes	100	08	0.92	1.5	1.1	122	70	Yes	Yes	Yes	Better
6	Chagas' disease	Yes	37.5	30	0.72	1.3	0.9	97	70	Yes	No	No	Better
7	Unknown	Yes	25	26	0.8	1.4	1.1	103	70	No	No	No	Better
8	Others	No	75	12	0.75	1.4	1.32	93	83	No	No	No	Better
9	Chaga's disease	No	75	17	0.62	1.3	1.0	96	70	No	Yes	No	Better
10	Hypertension	No	100	17	0.81	1.4	1.3	127	93	Yes	Yes	No	Better
11	Others	Yes	75	15	1.0	1.76	1.22	90	77	No	No	No	Better
12	Unknown	Yes	50	30	0.8	1.49	1.07	73	70	No	No	No	Better
13	Unknown	Yes	50	30	0.81	2.3	1.59	93	70	Yes	Yes	No	Better
14	Chagas' disease	Yes	37.5	21	1.11	2.85	2.0	117	97	Yes	No	No	Better
15	Unknown	Yes	50	18	0.82	1.76	1.2	93	73	No	No	No	Better
16	Hypertension	Yes	100	07	1.15	2.44	1.7	123	87	Yes	Yes	No	Better
17	Valvular disease	Yes	50	21	1.0	1.51	1.0	120	90	Yes	Yes	No	Better
18	Hypertension	Yes	150	30	1.05	2.42	1.45	140	83	Yes	No	No	Better
19	Chagas' disease	Yes	75	08	1.0	1.9	1.5	107	80	Yes	No	No	Better
20	Ischemic	Yes	50	28	1.01	2.03	1.14	123	87	Yes	Yes	Yes	Death
21	Valvular disease	No	75	19	0.43	1.21	0.85	97	93	Yes	No	No	Better
22	Hypertension	Yes	75	10	1.11	2.55	1.65	123	77	Yes	Yes	No	Better
23	Chagas' disease	Yes	75	11	1.02	1.75	1.1	120	93	Yes	No	No	Better
24	Hypertension	No	75	11	0.46	1.33	0.9	122	87	Yes	Yes	No	Better
25	Hypertension	No	150	14	0.43	1.26	0.75	147	83	Yes	No	Yes	Death
26	Hypertension	Yes	100	05	1.04	2.00	1.3	133	77	Yes	No	No	Better
27	Unknown	Yes	37.5	08	1.02	1.52	1.18	70	70	No	No	No	Better
28	Ischemic	Yes	100	13	1.02	2.0	1.37	133	77	Yes	Yes	Yes	Better
29	Unknown	Yes	37,5	05	1.13	1.75	1.34	100	70	Yes	No	No	Better

*Dose of captopril at the development of ARF; ¶ Creat 1 = Basal serum cratinine (mg/dl); Ŧ Creat 2 = serum creatinine after use of ACE inhibitor (mg/dl);

§ Creat 3 = serum creatinine after suspending ACE inhibitors (mg/dl); † ABP 1 = basal average blood pressure; ‡ ABP 2 = average blood pressure after use of ACE inhibitor

Table 5. Doses of diuretics and captopril used for treatment of Congestive Heart Failure patients before and at the development of the twenty-nine cases of Acute Renal Failure (ARF)

29 cases of ARF	Dose of captopril mg/day 1*	Dose of captopril (mg/day) 2§	Exposure to captopril before ARF (days)	Dose of furosemide before admission†	Dose of furosemide (mg/day) iv‡	Dose of spironolactone (mg/day)∑	Creat 1¶	Creat 2 ₮	Creat 3 ¥	ABP 1Ψ	ABP 2 £
1	50	50	20	40	60	25	1.01	1.6	1.0	97	70
2	75	100	26	80	40	—	0.61	1.3	0.83	73	70
3	50	100	04	80	80	25	1.0	2.12	1.5	127	80
4	50	75	09	40	60	25	0.8	1.58	1.2	107	83
5	75	100	08	40	80	25	0.92	1.5	1.1	122	70
6	25	37.5	30	40	60	25	0.72	1.3	0.9	97	70
7	25	25	26	40	60	25	0.8	1.4	1.1	103	70
8	50	75	12	60	40	25	0.75	1.4	1.32	93	83
9	50	75	17	40	60	25	0.62	1.3	1.0	96	70
10	75	100	17	60	80	25	0.81	1.4	1.3	127	93
11	50	75	15	40	60	25	1.0	1.76	1.22	90	77
12	25	50	30	40	40	—	0.8	1.49	1.07	73	70
13	25	50	30	40	60	25	0.81	2.3	1.59	93	70
14	25	37.5	21	40	60	25	1.11	2.85	2.0	117	97
15	25	50	18	40	40	25	0.82	1.76	1.2	93	73
16	50	100	07	40	60	25	1.15	2.44	1.7	123	87
17	37.5	50	21	40	60	25	1.0	1.51	1.0	120	90
18	100	150	30	40	80	50	1.05	2.42	1.45	140	83
19	50	75	08	80	60	25	1.0	1.9	1.5	107	80
20	25	50	28	80	60	25	1.01	2.03	1.14	123	87
21	50	75	19	60	40	25	0.43	1.21	0.85	97	93
22	50	75	10	60	80	25	1.11	2.55	1.65	123	77
23	50	75	11	40	60	25	1.02	1.75	1.1	120	93
24	50	75	11	40	60	25	0.46	1.33	0.9	122	87
25	100	150	14	40	80	50	0.43	1.26	0.75	147	83
26	75	100	05	40	80	25	1.04	2.00	1.3	133	77
27	25	37.5	08	40	40	—	1.02	1.52	1.18	70	70
28	75	100	13	40	80		1.02	2.0	1.37	133	77
29	25	37.5	05	40	60	25	1.13	1.75	1.34	100	70

*Doses of captopril before admission; §dose of captopril at the development of ARF; † dose of furosemide (mg/day, orally) before admission; ‡dose of furosemide (intra-venous) at the development of ARF; ∑dose of spironolactone (mg/day) at the development of ARF; ¶basal serum creatinine (mg/dl); ₮serum creatinine after use of ACE inhibitor (mg/dl); ¥serum creatinine after suspending ACE inhibitors; ΨABP 1 = basal average blood pressure; £ABP 2 = average blood pressure after use of ACE inhibitor

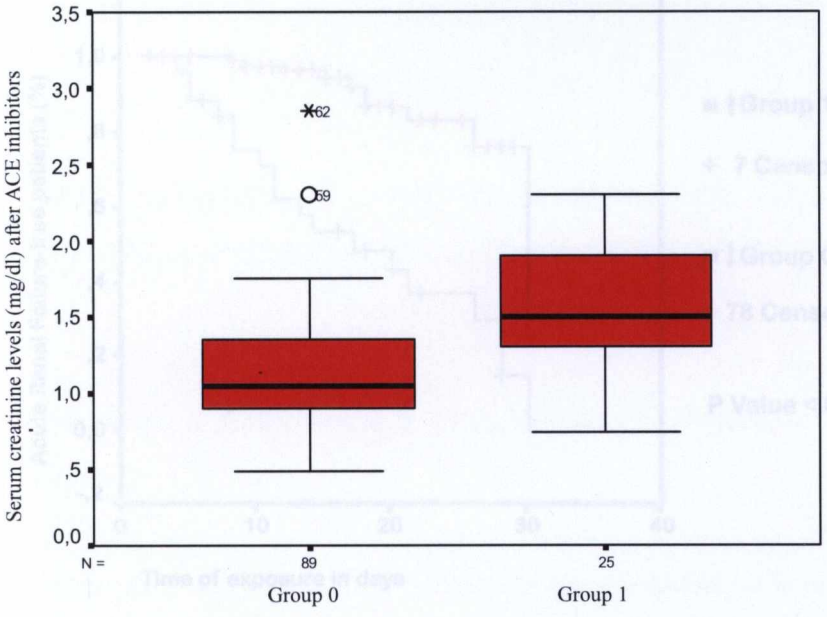

Figure 1. Serum creatinine levels after initiation of therapy with an ACE inhibitor for treatment of heart failure in two different groups: Group 1 (25 patients who experienced a decrease ≥25 mmHg in average blood pressure after introduction of an ACE inhibitor) and Group 0 (89 patients who experienced a decrease < 25mmHg in average bood pressure after introduction of an ACE inhibitor)

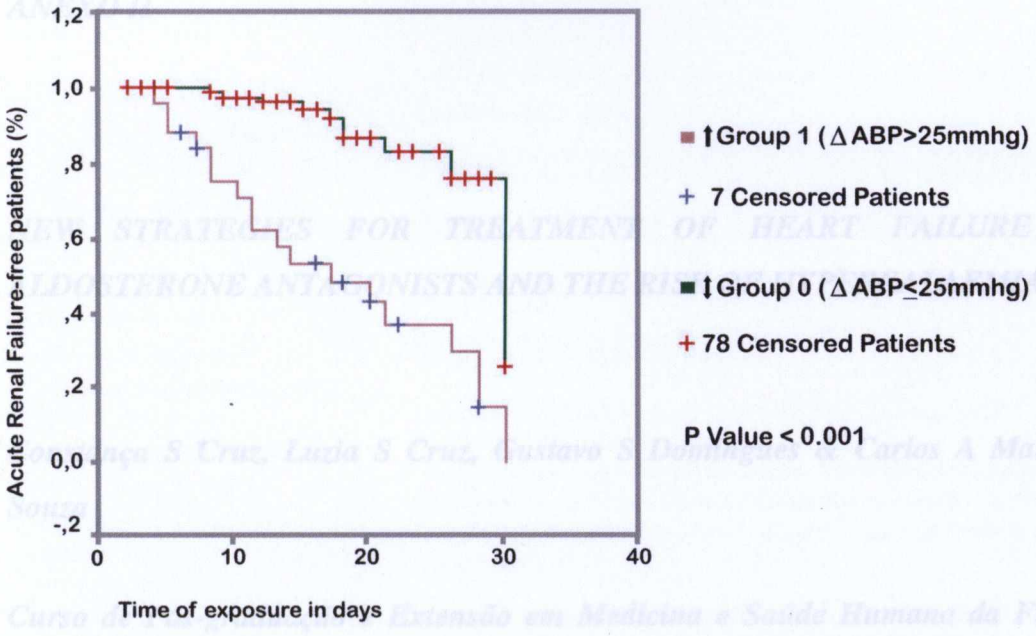

Figure 2. Kaplan- Meier curves showing cumulative risk for development of Acute Renal Failure during 30 days of exposition to ACE inhibitors (ACEI). Group 1 = 25 patients who experienced a decrease in average blood pressure ≥ 25 mmhg after treatment with ACEI; Group 0 = 89 patients who experienced a decrease < 25mmhg after ACEI.

ANEXO II

NEW STRATEGIES FOR TREATMENT OF HEART FAILURE WITH ALDOSTERONE ANTAGONISTS AND THE RISK OF HYPERKALAEMIA

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Keywords: angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor bockers, eplerenone, heart failure, hyperkalaemia, spironolactone

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Expert Opinion

1. Introduction
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4. Predictive factors for the occurrence of hyperkalaemia in CHF patients treated concurrently with spironolactone and ACEI
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New strategies for treatment of heart failure with aldosterone antagonists and the risk of hyperkalaemia

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Since the publication of The Randomized Aldactone Study (RALES) in 1999, the association of angiotensin-converting enzyme (ACE) inhibitors and spironolactone has been largely used for the treatment of congestive heart failure (CHF). Although this study had shown a diminished morbimortality in patients with CHF that are treated with spironolactone and ACE inhibitors and a low risk (2%) of development of severe hyperkalaemia, other clinical studies have shown higher rates of hyperkalaemia and serious adverse clinical events culminating in death. Therefore, the identification of risk factors for the development of hyperkalaemia in CHF patients, close monitoring of serum potassium and determination of renal function before and after the initiation of combined therapy or after a dose increment, should be routinely performed. It is strongly recommended that these drugs be initiated in low doses and that the increment in dose should only occur after considering all safety issues.

Keywords: angiotensin-converting enzyme (ACE) inhibitor, angiotensin-receptor blockers, eplerenone, heart failure, hyperkalaemia, spironolactone

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1. Introduction

After the publication of the results of The Randomized Aldactone Evaluation Study (RALES) in September, 1999, there was a rapid increase in the number of prescriptions of spironolactone for the treatment of congestive heart failure (CHF) associated with the standard therapy (angiotensin-converting enzyme [ACE] inhibitors, digitalis, loop diuretics and β-blockers). Although the RALES study had not shown a high risk for the development of hyperkalaemia (2%), other clinical studies revealed higher rates of hyperkalaemia and an increase in morbimortality [1,2].

Georges *et al.* in a letter published in April 2000, had emphasised that the hospitalisation rates caused by hyperkalaemia had not increased when spironolactone was prescribed to patients with cirrhosis. However, after the publication of the preliminary results of the RALES study in 1995, there was a rapid increase in the number of hospital admissions caused by hyperkalaemia in patients being treated for edematous syndromes of cardiac origin [3].

CHF patients are more susceptible to develop hyperkalaemia for a variety of reasons. First, ACE inhibitors have become the cornerstone in the treatment of these patients even in the early stages of CHF [4-8], β-blockers are also prescribed in CHF

class II/III and treatment with both drugs can result in hyperkalaemia, regardless of its association with spironolactone [9].

Second, patients with advanced CHF may exhibit renal dysfunction caused by a reduction in renal blood flow with glomerular hypoperfusion.

Third, the majority are elderly patients and have other associated co-morbidities such as diabetes mellitus. This later condition has been associated with hyporeninemic hypoaldosteronism and hyperkalaemia [10].

This review article aims to present current evidences of risk factors for the development of hyperkalaemia in patients treated with aldosterone antagonists as well as introduce measures to prevent and manage this electrolytic abnormality in CHF patients, so that there is less risk and more benefits associated to the therapy with this class of drugs.

2. The role of the renin angiotensin aldosterone system in CHF pathogenesis

The renin angiotensin aldosterone system (RAAS) plays a major role in the regulation of blood pressure and electrolytic homeostasis. This is rather a complex system and involves endocrine, paracrine and autocrine functions. Besides the plasma and endocrine RAAS, there is a local activity of the RAAS in the myocardia [11]. The plasma system is dependent upon the production of renin in the kidneys and the release of aldosterone by the adrenals that is triggered by the plasma levels of angiotensin II.

A reduction in renal blood flow with glomerular hypoperfusion, as a result of a decrease in the ejection fraction that occurs in CHF, is detected by the sensorial receptors in renal arterioles. The activation of these receptors results in the production of renin by the kidneys initiating the activation of the RAAS system [12,13].

The kidney arteriole's exposure to shear stress and stretch, a reduction in the content of sodium in fluid entering distal tubules and an increase in the kidney sympathetic nerve activity also stimulate renin release.

Renin is produced by the juxtaglomerular apparatus in the distal nephron and catalyses cleavage of angiotensinogen to angiotensin I, an inactive decapeptide. Angiotensinogen is released into the circulation by the liver, heart, kidneys, vascular wall and the CNS. Angiotensin I is in turn cleaved by a kininase, the ACE, to produce angiotensin II, an oligopeptide of 8 amino acids [11-14].

There are two well-described subtypes of angiotensin II receptors, designated AT1 and AT2, both of which have a high affinity for angiotensin II. The AT1 subtype mediates the powerful vasoconstrictor effect of angiotensin II that will promote important cardiovascular effects and changes in renal function. Besides its important effects in blood pressure and direct constrictor action in the vascular smooth muscle, angiotensin II promotes augmentation of peripheral noradrenergic activity and increases vasopressin and adrenocorticotropic hormone secretion. The vasoconstrictor action of angiotensin II is potentiated by vasopressin and noradrenalin, resulting in an increase in peripheral vascular resistance and oxygen consumption by the myocardium. Angiotensin II has been shown to mediate cell growth and proliferation of vascular smooth cells, cardiomyocytes and coronary endothelial cells, extracellular matrix formation, apoptosis and myocardium fibrosis [11-16]. Aldosterone, produced by the adrenal cortex through the stimulatory effect of angiotensin II, exerts mineralocorticoid actions and has been implicated in the pathogenesis of CHF [17]. Recent studies have shown that aldosterone secretion can also occur in myocardium and vascular walls [17,18]. Aldosterone receptors have also been identified in myocardia and vascular media of large vessels and tissue release of aldosterone does not depend on the stimulatory effect of angiotensin II. Aldosterone has been implicated in the pathogenesis of myocardium and vascular fibrosis, ventricular arrythmias and sudden death. Some studies have shown clear correlation of high levels of plasma aldosterone and an increase in mortality [19]. In CHF, chronic neurohumoral stimulation leads to vascular and cardiac remodelling, therefore, accelerating the syndrome progression. The neurohormones, angiotensin II and noradrenalin, promotes cell growth, leading to hypertrophy of cardiomyocytes, augmentation of cardiac extracellular matrix, fibroblast proliferation and collagen synthesis. Taking into consideration the multiple molecular and cell mediators involved in the pathogenesis of ventricular remodelling in CHF, it is important to emphasise that apoptosis represents a final common pathway as a result of a cascade of injury mechanisms precipitated by endothelial cell exposure to shear stress and stretch, cytokine production, activation of RAAS and sympathetic nervous system [20].

3. RAAS blockade and its role in the treatment of CHF

3.1 Angiotensin-converting enzyme inhibitors (ACEI)

The angiotensin-converting enzyme inhibitors (ACEI), are inactive drugs, developed by the addition of an ester group, turning its molecules into lipophilic compounds and promoting better absorbability by the gastrointestinal tract. After its absorption and metabolism by the liver, plasma and kidneys, the inactive drugs are converted into active and hydrophilic compounds able to inhibit the ACE. The speed of metabolism and bioavailability of the active compounds determine the time required for its beginning and peak of action. The time required for its maximum concentration (C_{max}) is 30 minutes to 6 hours, and it is variable among various compounds. After oral absorption, the bioavailability and protein binding of active molecules are 25 – 75% and 10 – 95%, respectively. The drugs are mainly eliminated by the kidneys, however, some of the compounds are removed from circulation by the liver.

In experimental models of hypertension with low levels of renin, the observed vasodilator properties of those compounds possibly result from inhibition of RAAS in the vascular wall,

thus suppressing the local, autocrine and paracrine actions of angiotensin II. Other mechanisms are thought to induce arterial vasodilatation such as inhibition of breakdown of kinins, especially bradykinin, which may induce the release of vasodilator factors by endothelial cells, prostacyclins and may also exert inhibitory effects in the sympathetic nervous system [21].

The importance of activation of RAAS in the pathogenesis of CHF was definitely elucidated with the demonstration of the beneficial effects of the use of ACEI in CHF patients and a significant reduction in morbimortality rates and in the progression of the disease. Important clinical studies, Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) [4] and Studies of Left Ventricular Dysfunction (SOLVD) [5,6], have clearly shown that there is an increase in survival rates in CHF patients treated with ACEI and also a prevention of progressive left ventricular dilatation and systolic dysfunction [4-6].

Through the blockade of the ACE, the ACEI exerts haemodynamic, neurohumoral and tropic effects. Besides its haemodynamic effects, there are strong evidences supporting that the benefits achieved with the use of ACEI in CHF patients are the result of a direct action in cardiomyocytes. The ACEI may reverse the process of remodelling and inhibit cell growth. Because remodelling has been implicated in myocardia vascular injury, it is possible that ACEIs could play a major role also in preventing ischaemic events. Enalapril, captopril, ramipril and lisinopril, the most commonly prescribed ACEI, reduce the systemic vascular resistance without promoting an increase in heart rate, as observed with the use of other vasodilators. There is an improvement in the patient's well being, an important decrease in hospital admissions for CHF and a reduction in reinfarction and unstable angina rates [4-8,22].

Although the efficacy of ACEI is very high as shown in controlled studies, those results are not completely reproduced in daily practice because of the usual prescription of low doses. The Assessment of Treatment Study with Lisinopril and Survival (ATLAS), published in 1999, evaluated 3164 patients comparing the effect of high and low doses of lisinopril and its impact in morbimortality related to CHF. There was an 8% decrease in global mortality rates and a 10% decrease in cardiac mortality in patients treated with high doses of lisinopril in comparison to the rates obtained in patients treated with low doses. They conclude that CHF patients should not be treated with very low doses of an ACEI, unless higher doses are not tolerated [22].

The Veteran Administration Heart Failure Trial II (V-HeFT II) has shown that treatment with ACEI was associated with a better prognosis when compared to a combination of vasodilators such as nitrates and hydralazin [23]. On the other hand, the use of ACEI has been associated with a decline in renal function in some patients with advanced stages of CHF. This effect is attributed to the blockade of the vasoconstrictor action at the glomerular efferent arteriole level, which will in turn result in a decrease in intraglomerular hydraulic pressure and the glomerular filtration rate. The CONSENSUS study has shown that 35% of patients treated with enalapril had a 10 – 30% increase in serum creatinine levels after the first three weeks of treatment. However, the survival rates were similar in groups that had a substantial increase in serum creatinine when compared to those patients that did not present this abnormality [24].

More often, the use of ACEI promotes a slight increase in serum creatinine levels followed by a trend towards normalisation. However, serum creatinine levels should be monitored and if there is a steady increment, the drug should be suspended. According to AHA Scientific Statement, treatment with ACEI may be associated with prerenal azotemia and/or hyperkalaemia. The acute renal failure related to treatment with ACEI usually occurs in the beginning of therapy, however, there are cases reported after months or years of initiation of drugs. The risk of developing hypotension and renal insufficiency is higher in the elderly and in patients treated for advanced stages of CHF, particularly those who receive high doses of diuretics or present hyponatremia. The occurrence of acute renal failure may also be precipitated by a decrease in intravascular volume, bilateral renovascular disease and coexisting treatment with nephrotoxins. The AHA Scientific Statement also recommends the immediate interruption of ACEI and adequate treatment of precipitating events if there is an increase of 50% in basal levels of serum creatinine or if serum potassium is equal or higher than 5.5 mEq/l. After normalisation of renal function and correction of the electrolyte abnormality, the ACEI then could be carefully reintroduced under close supervision [12].

Hyperkalaemia may also occur during treatment with ACEI, especially in patients with diabetes mellitus, the elderly and in cases of coexisting renal insufficiency. Recent studies have shown that the association of ACEI with spironolactone increases the risk of hyperkalaemia. As a result, a judicious approach is recommended when there is concurrent treatment with these drugs and close monitoring of serum electrolytes is required [9].

A significant adverse effect observed with treatment of CHF with ACEI is symptomatic arterial hypotension, however, the most frequent side effect observed in clinical practice with the treatment with ACEI is a dry and irritative cough that requires suspension of the drug in 10 – 20% of cases. It is important to mention that it is difficult to differentiate the cough associated with the use of ACEI, from cough related to pulmonary congestion [21].

3.2 Angiotensin II receptor antagonists

The recent findings of angiotensin II production within tissue, through ACE-independent alternative enzymatic pathways and characterisation of angiotensin II receptors, culminated in the development of specific AT1 receptor blockers and their therapeutic use.

Since the determination of the amino acid sequence of the angiotensin II octapeptide chain almost 40 years ago, peptides that competitively inhibit angiotensin II action have been

eveloped. However, those drugs have not been shown to be dequate for clinical use. The angiotensin II receptor antagoists, losartan and other nonpeptide similar drugs, are active /hen orally administered. Losartan interacts with transmemrane domains of AT1 receptors, preventing the attachment f angiotensin II without binding to AT2 receptors [24]. Losatan is metabolised into a powerful compound that has a onger half-life than its precursor. Its antihypertensive actions re better correlated with plasma concentrations of the netabolite than with the original drug [25].

The angiotensin II receptor antagonists (ARA) are vasodilaors that promote a decrease in the peripheral arterial resistnce, in final diastolic pressure of left ventricle and an increase n the ejection fraction. ARA provides modulation of neuroumoral activity and may interfere with ventricle remodelling rocesses, thus reducing the ventricular dilatation postmyoardial infarction. The blockade of angiotensin II receptors nay represent an appealing therapeutic strategy because it hould produce more complete blockade of RAAS, and preerve the beneficial effects mediated by AT2 stimulation. Iowever, ACEI treatment results in elevated bradykinin evels, an effect not seen with ARA [21,25,26].

Similar efficacies have been shown in clinical studies that ompared treatment with losartan or ACEI in patients with ssential hypertension. However, a more gradual antihypertenive effect of losartan was observed in comparison to ACEI. he fastest actions of ACEI in regard to the antihypertensive ffects have been attributable to increased kinin levels [27-29].

The Evaluation of Losartan in the Elderly Study (ELITE) nrolled 722 patients < 65 years of age who were randomised o receive either captopril 50 mg three-times a day or losartan 0 mg once a day, during a 48 week trial. The study showed ower mortality rates in the losartan group. However, ELITE I studied a cohort of 3152 patients and did not show any diference among groups treated with losartan versus captopril egarding mortality rates and occurrence of sudden death or ardiopulmonary resuscitation. The incidence of cough was lbeit lower in the group receiving losartan [30,31].

In 2003, a clinical study evaluated a group of patients at igh risk for cardiac events post acute myocardial infarction nd compared treatment with valsartan versus captopril versus combination of these two drugs. Treatment with valsartan vas shown to be as effective as with captopril regarding reduction of cardiac death rates and an association of the two drugs ncreased the occurrence of adverse effects with no impact on urvival [32]. ARA should be used in cases of development of ough associated with ACEI. Unfortunately, hyperkalaemia nd/or renal insufficiency may occur with both classes of rugs [29,30]. Further clinical studies are required to justify the herapeutic use of an association of ARA and ACEI [32].

.3 Aldosterone receptor blockers

.3.1 *Spironolactone*

pironolactone belongs to the group of synthetic steroids, esembles aldosterone structurally, and acts on the type A intercalated cells in the distal tubule, by competitive inhibition of aldosterone and binds to mineralocorticoid receptors at the cortical and medullar collecting duct. After oral administration, spironolactone is partially absorbed by the gastrointestinal tract (60 – 70%) and strongly binds to plasma proteins. It is metabolised in the liver and originates compounds that exert oestrogenic and progestogenic actions. The active metabolite of spironolactone is canrenon, which is responsible for threequarters of the pharmacological actions of the primary compound after continuous use. The half-life of canrenon is ~ 16.5 hours, which promotes a prolongation of the action of spironolactone [33,34].

The observation of the extra adrenal production of aldosterone and its deleterious actions in the cardiovascular system allowed testing the hypothesis that the blockade of aldosterone receptors could have a beneficial effect in CHF patients [2,34]. There are strong evidences that ACEIs only exert a transient suppression in aldosterone production, therefore, the chronic treatment with these drugs will not prevent an increase in plasma concentrations of aldosterone with time, originating the well-described escape phenomenon [17,18]. Spironolactone has been considered a sparing potassium diuretic and it is an aldosterone antagonist that has proven efficacy in controlling the escape of aldosterone phenomenon [2,18]. Aldosterone is associated with an increase in fibroblast proliferation and with perivascular and myocardial fibrosis. Its blockade reduces collagen synthesis, ameliorates cardiac function and prevents remodelling [17,18].

RALES, which enrolled 1663 patients for a two-year trial, has shown the importance of treatment with spironolactone as a strategy known to avoid the escape phenomenon. There was a decrease in morbimortality in patients with advanced stages of CHF and a 30% reduction in risk of death in the group treated with 25 – 50 mg of spironolactone, when compared with placebo [2].

After the publication of RALES, various clinical studies have demonstrated the occurrence of hyperkalaemia associated with the combination of ACEI and spironolactone for treatment of CHF and serious consequences were related to the increase in plasma levels of this electrolyte, including death [1,36-41] (**Tables 1 and 2**). In the majority of these studies, there was at least one more risk factor for the development of hyperkalaemia in CHF patients treated with the combination spironolactone/ACEI. The major risk factors for development of hyperkalaemia described in those studies were advanced age, renal insufficiency, stage IV of CHF according to the New York Heart Association (NYHA), reduced left ventricle ejection fraction, concomitant diabetes mellitus, co-treatment with β-blockers, potassium supplements and anti-inflammatory agents [36-44].

3.3.2 *Eplerenone*

Eplerenone is the first of a new class of drugs known as selective aldosterone receptor blocker, which selectively block the

Table 1. Studies published after the results of The Randomized Aldactone Evaluation Study (RALES).

Reference	Year	N*	$K^+ \geq 6.0$mEq/l‡	Number of deaths	Risk factors
Schepkens & Vanholder [36]	2001	262	25	02	Age, renal insufficiency, diabetes, NSAID§
Berry & McMurray [37]	2001	04	04	03	Diarrhoea, Prerenal azotemia
Svensson & Gustafsson [38]	2003	108	13	None	Age, renal insufficiency, low ejection fraction of left ventricle
Wrenger & Müller [41]	2003	44	44	02	Advanced age, renal insufficiency and diabetes
Bozkurt & Ildiko [39]	2003	104	12	None	Renal insufficiency, diabetes, potassium supplements
Cruz & Marcílio de Souza [40]	2003	49	07	None	Renal insufficiency, diabetes and congestive heart failure stage IV¶

Cases of severe hyperkalaemia, death and risk factors for development of severe hyperkalaemia ($K \geq$ to 6.0 mEq/l) are described in congestive heart failure patients treated with ACE inhibitors and spironolactone.

* Number of patients treated with ACE inhibitors associated with spironolactone

‡ Severe hyperkalemia (serum potassium ≥ 6.0 mEq/l)

§ Non-steroidal anti-inflammatory drugs

¶ Congestive Heart Failure stage IV according to NYHA classification.

NSAID: Non-steroidal anti-inflammatory drug.

Table 2. Prescription rates of spironolactone hospital admissions and cases of death associated with hyperkalaemia in congestive heart failure patients treated with ACEI in Ontario before and after publication of RALES†.

Spironolactone prescription and posterior events related to hyperkalaemia	Before RALES†	After RALES†	Increase factor
Spironolactone prescription rates	30/1000	149/1000	5X
Hospitalisation rates secondary to hyperkalaemia	4/1000	11/1000	3X
Death rates associated with hyperkalaemia	0.17/1000	0.38/1000	2X
Excess of hospital admissions per hyperkalaemia/ year after publication of RALES†		37000	
Excess of deaths per hyperkalaemia/year after publication of RALES†		4200	

Data taken from Juurlink *et al.* [1].

RALES: The Randomized Aldactone Evaluation Study.

aldosterone receptor with a minimal effect at other steroid receptors, thereby minimising many of the hormonal side effects seen with spironolactone such as gynecomastia. This drug derives from spironolactone, through a replacement of a 17-α-thioacetyl by a carboxymethyl group and the addition of a 9-α, 11-α-epoxy bridge in its molecule [45-47].

Eplerenone is administered orally and its absorption and bioavailability have still not been completely elucidated. The plasma concentration peak of eplerenone occurs ~ 1.5 hours after oral administration and 49% of the drug binds to plasma proteins, mainly an α-1-glycoprotein. Its half-life of elimination is 4 – 6 hours and plasma clearance is ~ 10 hours. Nearly 32% of the drug is eliminated in the faeces and 67% in urine. Eplerenone is inactivated by the P450 cytocrome 3A4 (CYP3A4) in the liver. There are described interactions of eplerenone with drugs that block CYP3A4. The use of ketoconazole twice a day promoted a 1.7 increase in C_{max} of eplerenone. Other inhibitors of CYP3A4 were tested – erythromycin 500 mg twice/day, verapamil 240 mg/day, saquinavir 1.2 grams three-times/day and fluconazole 200 mg/day – resulting in a 1.4 – 1.6 increase in C_{max} of eplerenone [47].

Wewinberger *et al.* designed a multi-centre, double-blind and placebo-controlled study to establish the efficacy, safety and tolerability of eplerenone in patients with moderate essential hypertension. In this study, 417 patients were randomised in 4 groups to receive: 1) eplerenone 50, 100 or 400 mg/day; 2) eplerenone 25, 50 or 200 mg twice/day; 3) spironolactone 50 mg twice/day; 4) placebo. The results have demonstrated a statistically significant reduction in

blood pressure in all groups compared with placebo. When eplerenone and spironolactone groups were compared, there was a trend towards lower blood pressure levels in the group treated with spironolactone, although it was not statistically significant. The incidence of adverse events including gynecomastia was similar in eplerenone and placebo groups [48].

Krum *et al.* tested the efficacy and tolerability of eplerenone associated with ACEI and ARA for treatment of hypertension in a double-blind and placebo-controlled study for 8 weeks. The results showed a significant reduction in systolic blood pressure in both the eplerenone/ACEI and eplerenone/ARA groups when compared with placebo; however, significant reduction in diastolic blood pressure was observed only in the group treated with eplerenone/ARA when compared to placebo. Gynecomastia and hyperkalaemia were not observed in any of the studied groups [49].

Levy *et al.* in a randomised, multi-centre, double-blind and placebo-controlled study tested the hypothesis that the reduction in blood pressure observed with the use of eplerenone might be associated with an increase in serum potassium levels. The increase in serum potassium levels observed in three different analyses performed were compatible with the expected increase associated with the use of eplerenone as previously described [50,51], but the association of an increase in serum potassium levels with response to treatment was not validated [52].

Epstein *et al.* tried to determine if treatment with eplerenone reduced proteinuria in patients with diabetes mellitus Type II and essential hypertension. A total of 215 patients were randomised in three groups to receive treatment with eplerenone, enalapril, or eplerenone and enalapril for 24 weeks. The results have shown that the combined therapy reduced proteinuria by 74% versus 62% in the eplerenone group although hyperkalaemia was observed in patients treated with the association of eplerenone and enalapril, especially when higher doses were used. The occurrence of gynecomastia was not observed in any groups [53].

Eplerenone has been approved for the treatment of hypertension and later on, for the treatment of CHF and acute myocardial infarction. Pitt *et al.* tested the safety and efficacy of treatment with eplerenone for CHF patients classified in stages II – IV of NYHA. The study was conducted for 12 weeks and besides the standard therapy with ACEI, patients were randomised to receive eplerenone or spironolactone. The results have shown a statistically significant decrease in brain natriuretic peptide and an increase in urinary levels of renin and aldosterone in patients treated with eplerenone and spironolactone when compared with patients treated with placebo; however, no changes in classification of CHF according to NYHA criteria was observed in any group. Hyperkalaemia, defined as serum potassium levels > 6.0 mEq/l, occurred in 12% of patients treated with 100 mg/day of eplerenone and in 8% of patients treated with spironolactone. On the other hand, plasma testosterone levels were significantly higher in patients treated with spironolactone [54]. The Eplerenone PostAcute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) was a randomised, double-blind and placebo-controlled study also conducted by Pitt *et al.* to determine the effect of eplerenone in mortality of patients with simultaneous myocardial infarction and heart failure. The results have shown a significant reduction in cardiovascular morbimortality and sudden death rates related to the use of eplerenone. There was a significant increase in the occurrence of severe hyperkalaemia (K > or equal to 6 mmol/l) and a decrease in the occurrence of hypokalaemia (K < 3.5 mmol/l) in the group treated with eplerenone [55].

4. Predictive factors for the occurrence of hyperkalaemia in CHF patients treated concurrently with spironolactone and ACEI

4.1 Renal insufficiency

CHF is commonly associated with renal insufficiency, especially in advanced stages of the disease. Low renal perfusion is a consequence of the syndrome per se, or may be secondary to concurrent conditions such as advanced age, diabetes mellitus and essential hypertension.

In all studies published after RALES, renal insufficiency has been associated with hyperkalaemia and also with the severity of the electrolyte abnormality. All described cases of severe hyperkalaemia with serious clinical consequences such as death, necessity of cardiopulmonary resuscitation measures or emergency haemodialysis were associated with moderate-to-severe loss of renal function [36-41] (**Table 1**).

CONSENSUS evaluated the most representative number of patients with renal insufficiency among other clinical studies that showed an increase in survival rates in CHF patients treated with ACEI as compared with placebo. Patients with serum creatinine levels > 3.4 mg/dl were excluded, however, only 26 patients out of 253 that had serum creatinine levels > 2.0 mg/dl were included and none of patients in the study had serum creatinine levels > 2.8 mg/dl. The average serum creatinine and glomerular filtration rate (GFR) in the study mentioned above was 1.4 mg/dl and 45 ml/min per 1.73 m^2, respectively, characterising an average stage of moderate renal insufficiency [4]. Other studies excluded patients with serum creatinine > 2.0 mg/dl, 2.5 mg/dl and 2.3 mg/dl and, therefore, were not representative regarding the simultaneous occurrence of CHF and renal insufficiency [5-7,56].

The CONSENSUS results have provided important clues regarding efficacy of treatment with ACEI of patients with the simultaneous diagnosis of CHF and renal insufficiency, however, the efficacy and safety of treatment with these drugs in cases of CHF and severe stages of renal insufficiency (GFR < 30 ml/min per 1.73 m^2) are still unknown. The use of ACEI in patients in advanced stages of renal insufficiency should be considered with caution because the potential

benefits of treatment with these agents could be overwhelmed by an important risk of developing hyperkalaemia and also a decrease in renal function [24,43,44].

Regarding the association of spironolactone and ACEI, an extra caution should be observed. In RALES, the patients studied had average serum creatinine levels of 1.2 mg/dl and those with serum creatinine levels above 2.5 mg/dl were excluded from the study. In this trial, the number of patients with GFR < 30 ml/min per 1.73 m^2 and between 30 – 60 ml/min per 1.73 m^2 has not been published. Therefore, it is recommended that the association of spironolactone with ACEI or ARA should be avoided in patients with GFR < 30/ml/min per 1.73 m^2. In moderate stages of renal insufficiency (GFR between 30 and 60 ml/min per 1.73 m^2) the use of spironolactone should be considered with caution and the maximum dose employed should not surpass 25 mg/day [2,43,44].

4.2 Advanced age

Ageing is associated with a variety of changes in renal and extrarenal regulatory mechanisms of potassium homeostasis. A significant number of nephrons are lost, progressively, with advanced ageing. An important reduction in renal blood flow, in GFR, and also in renin and aldosterone secretion has been described [57].

CHF represents the most important cause related to cardiovascular morbimortality and the most common disease that occurs in hospitalised patients > 65 years of age. Scientific and technological advances have increased longevity of the general population and also of patients suffering from cardiac diseases. An increase in the global occurrence of CHF has also been described [11].

The prevalence of renovascular diseases and diabetes is higher among the elderly [58]. All of those age-related events that promote impairment of renal function above mentioned predispose the elderly to the development of hyperkalaemia and to an increase in their susceptibility to hyperkalaemia pharmacologically induced. Under such circumstances, a judicious approach is recommended when a combination of multiple drugs are prescribed [59].

4.3 Diabetes mellitus

In patients with CHF and concurrent diabetes mellitus, there is an increase in susceptibility to development of hyperkalaemia drug-induced. The higher predisposition to the development of hyperkalaemia in diabetic patients occurs with co-existing renal insufficiency and is related, at least partially, to an abnormality known as hyporeninemic hypoaldosteronism. In this condition, there is a distal renal tubular impairment in the reabsorption rates of sodium and potassium secretion. Moreover, the higher risk for development of hyperkalaemia in patients with diabetes is related to a decrease in insulin production, therefore limiting the intracellular movement of potassium from extra cellular fluid [10,44].

Ahuja *et al.* showed that the co-existence of renal insufficiency and diabetes mellitus might increase the risk for development of hyperkalaemia in patients treated with ACEI. One hundred and nineteen patients were studied and 38.6% developed hyperkalaemia. Among those, 96% had renal insufficiency and 84% had diabetes mellitus. The above-mentioned study considered diabetes mellitus and abnormal levels of serum creatinine as predictive factors for the development of hyperkalaemia [60].

Albareda *et al.*, in 1998, described a case of a patient with the diagnosis of Type I diabetes mellitus that developed hyperkalaemia after 2 years of treatment with enalapril [61].

Odawara *et al.* described a case of a 43 year-old patient with Type II diabetes mellitus who developed severe hyperkalaemia 18 days after initiation of treatment with a combination of a standard dose of spironolactone (25 mg/day) and lisinopril. The patient was then hospitalised with severe bradycardia, unconscious, with serum potassium and creatinine levels of 8.9 mmol/l and 194 mmol/l, respectively. After suspension of both ACEI and spironolactone and correction of patient's volemia, renal function and serum potassium levels returned to normal [62].

4.4 Hypovolaemia associated with vomiting and diarrhoea

Schepkens & Vanholder related a series of 25 cases of severe life-threatening episodes of hyperkalaemia in patients treated with an association of spironolactone and ACEI for heart failure and/or hypertension. Twelve of those cases showed signs of volume depletion, related to vomiting and diarrhoea, infection, fever or a recent increment in prescription dose of a loop diuretic [36].

The clinical study published by Berry and McMurray describes 4 cases of hyperkalaemia induced by the association of spironolactone with ACEI precipitated by episodes of diarrhoea. One death was described in an out-patient that did not receive medical assistance [37].

The above authors call the attention for the fact that ambulatory patients treated with the combination ACEI plus spironolactone for CHF and, especially the elderly, should immediately seek medical assistance in case of development of vomiting and diarrhoea. In this situation, there is an imminent risk of deterioration of renal function and development of life-threatening hyperkalaemia [36,37].

4.5 Reduced left ventricle ejection fraction and class IV CHF according to NYHA

Svensson and Gustafsson followed 125 patients with CHF who received spironolactone plus ACEI or ARA for 370 days. The authors found a 33% incidence of acute renal failure and 36% incidence of hyperkalaemia. In a multivariate analysis the authors found that low left ventricle ejection fraction and advanced stages of congestive heart failure according to NYHA were independent predicting factors for hyperkalaemia [38].

Bozkurt and Ildiko studied patients, the majority in stage IV of CHF according to NYHA, and found a 25% incidence of acute renal failure and 24% of hyperkalaemia. In an editorial comment, Tang and Francis call the attention for the fact that much higher doses of spironolactone have been prescribed to patients than the dose recommended by RALES. Besides that, in RALES there was a predominance of patients in stage III of CHF as determined by NYHA. Other studies, however, enrolled more patients in stage IV [39,42].

Cruz and Marcílio de Souza found a 33% incidence of hyperkalaemia in patients with CHF treated with spironolactone and ACEI. All of the cases of severe hyperkalaemia were included in stage IV of CHF according to NYHA classification. The following were described as risk factors for development of hyperkalaemia: co-existence of diabetes mellitus, development of acute renal failure after the initiation of treatment and the occurrence of stage IV of CHF according to NYHA classification [40].

4.6 Drugs

NSAIDS inhibit prostaglandin synthesis. Prostaglandins stimulate renin release and, therefore, there is an exacerbation of hypoaldosteronism when these agents are combined to ACEI. The COX-2 selective inhibitors may also cause hyperkalaemia and should be cautiously prescribed when associated with an ACEI [9].

Cyclosporin suppresses renin release and directly interferes with potassium secretion by the collecting ducts. Patients that received a transplant and are treated with cyclosporin, may be predisposed to develop hyperkalaemia. β-blockers also favour the increase in serum potassium levels through two distinct mechanisms: blockade of the stimulatory action of the sympathetic nervous system on renin release and inhibition of sodium-potassium ATPase pump, therefore, reducing the cellular uptake of potassium. Heparin may cause hyperkalaemia by a blockade in aldosterone synthesis by adrenals. Ketoconazole interferes with steroids synthesis by adrenal glands and may contribute to aldosterone deficiency [9] (**Figure 1**).

5. Prevention of hyperkalaemia in patients treated with RAAS blockers alone or combined

The fundamental strategies that aim to decrease the risk of development of hyperkalaemia and, simultaneously, enable patients to obtain the benefits of this class of drugs for the treatment of CHF or myocardial infarction complicated by left ventricle dysfunction are described below.

5.1 Identification of risk factors and correction if possible

- Determination of renal function and serum electrolytes before the initiation of treatment with RAAS blockers, such as, serum creatinine, serum potassium and creatinine clearance. Patients with creatinine clearance < 30 ml/min or serum potassium levels > 5.0 mmol/l should not receive treatment with spironolactone or with the combination of spironolactone plus ACEI or ARA [12,43,44].
- Regular blood pressure measurement avoiding average levels < 65 mmHg [12,24].
- Watch for potential causes of hypovolemia such as abuse of diuretics, states of diarrhoea and vomiting that can lead to dehydration [36,37].
- Cautious use of drugs such as NSAIDs, potassium supplements, cyclosporin, ketoconazole, heparin and trimethoprim [9].

5.2 Careful monitoring of renal function and serum potassium levels after initiation of therapy with ACEI or ARA.

Ljungman and Kjekshus have found a 10 – 30% increase in basal serum creatinine values in patients with CHF stage IV after treatment for 3 weeks with 2.5 to 40 mg/day of enalapril. However, 13 patients out of 123 that were treated with enalapril, showed an increase of ≥ 100% in basal serum creatinine values. The maximum increase in serum creatinine was inversely correlated with basal blood pressure levels and with systolic and diastolic levels [24]. Cruz and Marcílio de Souza have found that the average time of occurrence of hyperkalaemia after simultaneous treatment with spironolactone and ACEI for congestive heart failure was 15 days. This study has also shown that the majority of cases of severe hyperkalaemia had been associated with an increase of 50% in basal serum creatinine levels. The authors hypothesised that simultaneous treatment with spironolactone and ACEI might increase the risk of development of hyperkalaemia because the renal function abnormalities have been well-described after the first weeks of therapy with an ACEI [24,40]. The following procedures are recommended for renal function and serum potassium monitoring in patients treated with RAAS blockers.

- ACEI and spironolactone should not be introduced simultaneously. It is well-known that there is a decrease in renal function in the first 3 weeks of therapy with ACEI in CHF patients and that the loss of renal function is the main predictor of hyperkalaemia in these patients [24,36-41].
- Start with low doses followed by serum creatinine and potassium monitoring after 7, 14 and 21 days of the initiation of therapy with ACEI. Only after checking tolerance to the initial dose, further gradual increments in dose should be prescribed [24].
- After each increase in dose, one should proceed a re-evaluation of renal function and serum potassium levels, with the periodicity described above.
- If there is good tolerance to the use of ACEI or ARA, spironolactone may be added to the therapeutic regimen and a dose of 25 mg/day should not be surpassed. Serum potassium and renal function monitoring should be

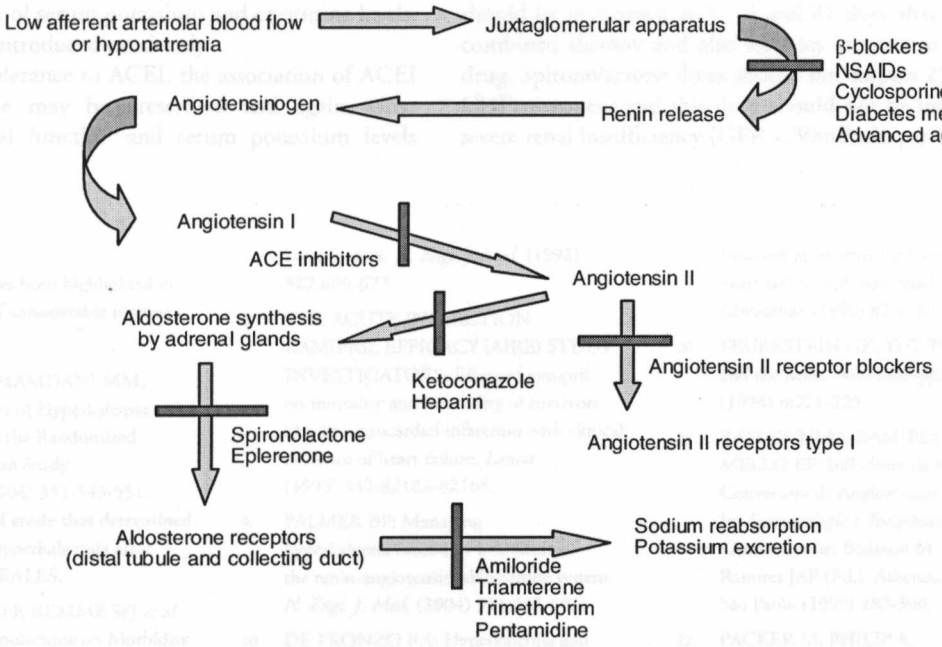

Figure 1. Schematic model of drugs or conditions that affect the renin angiotensin aldosterone system.
ACE: Angiotensin-converting enzyme; NSAID: Non-steroidal anti-inflammatory drug

performed after introduction of combined therapy [2,24,43,44] and also if there is any condition that determines sudden decrease in renal perfusion such as dehydration, vomiting, diarrhoea, concomitant increase of diuretic dose or worsening of heart failure [36,37].

- Cautious and judicious approaches are required when the conditions mentioned above occur during treatment and a deterioration of renal function or hyperkalaemia should be promptly identified. In this case, doses should be reduced or suspended and the immediate correction of hypovolemia, treatment of concomitant metabolic acidosis with sodium bicarbonate, use of cationic exchange resins such as sodium polystyrene sulfonate and eletrocardiographic monitoring should be performed [36-39,62].

6. Conclusion

Unfortunately, in current daily practice, the occurrence of hyperkalaemia in CHF patients, related to combined therapy with ACEI/spironolactone, has been more frequently observed than what has been reported in RALES. CHF patients are older, have multiple associated co-morbidities such as diabetes mellitus, and often have an important decrease in renal function as compared with patients studied in RALES. There may also be concurrently exposed to other drugs such as NSAIDs and potassium supplement agents. As a consequence, one cannot extrapolate the results obtained in RALES to daily clinical practice, regarding the risk of development of hyperkalaemia.

Therefore, it is necessary that population-based studies such as the Ontario's study, be performed to evaluate the safety of new drugs on the market and also to re-evaluate drugs in current use, such as spironolactone, that has been employed for the treatment of oedema secondary to liver diseases and that after the publication of RALES, became an important therapeutic agent used in combination with other RAAS blockers for CHF treatment.

7. Expert opinion

A reasonable strategy to achieve the benefits of RAAS inhibition in reducing morbi-mortality of patients with CHF and acute myocardial infarction, and simultaneously, to obtain a decrease in the risk for development of hyperkalaemia, is to introduce each drug separately and in low doses, while closely monitoring serum creatinine and potassium levels before and after the initiation of therapy.

According to current evidences, the ACEI are still the cornerstone of CHF therapy and may be substituted by ARA in case of cough. If there is an increase of $\geq 50\%$ in basal serum creatinine values or if there is development of hyperkalaemia, ACEI should be suspended and concurrent risk factors corrected, such as abuse of diuretic therapy, dehydration, hypotension, concomitant use of nephrotoxic agents and renovascular disease. After correction of those abnormalities

and a normalisation of serum potassium and creatinine levels, the drug may be reintroduced cautiously.

After checking tolerance to ACEI, the association of ACEI with spironolactone may be prescribed and again, close monitoring of renal function and serum potassium levels should be performed at 7, 14 and 21 days after initiation of combined therapy and also after an increase in dose of any drug. Spironolactone doses should not surpass 25 mg/day for CHF treatment and this drug should not be used in case of severe renal insufficiency (GFR < 30ml/min per 1.73m^2).

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ANEXO III

Original Article

HYPERKALEMIA IN CONGESTIVE HEART FAILURE PATIENTS USING ACE INHIBITORS AND SPIRONOLACTONE

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Original Article

Hyperkalaemia in congestive heart failure patients using ACE inhibitors and spironolactone

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Abstract

Background. Recent studies have shown a fall in global mortality with minimal side effects in severe congestive heart failure (CHF) patients receiving angiotensin-converting enzyme inhibitors (ACEI) plus spironolactone (SLN). However, the risk of hyperkalaemia due to ACEI may be increased by the concomitant use of SLN.

Methods. We conducted a retrospective cohort study by examining consecutive cases of severe decompensated CHF admitted to a university hospital in Brazil from March 1999 to March 2000, which had used ACEI with or without SLN. We reviewed charts for the 30 days following admission and assessed various therapeutic regimens used for heart failure as well as serum potassium and creatinine, before and after drug exposure. The primary end-point was the development of hyperkalaemia (K $\geq$5.5 mEq/l). For analysis, the subjects were split into patients treated with ACEI/SLN ($n=49$) and patients treated with ACEI ($n=51$) by itself.

Results. Although demographical and clinical features were comparable between the two groups, ACEI/SLN patients had a higher proportion of class IV CHF. We found 16 cases of hyperkalaemia in ACE/SLN patients, but only one case in ACEI subjects. The odds ratio for developing hyperkalaemia in ACEI/SLN patients was 24. When class III CHF subjects were excluded, the odds ratio was 14.6 (95% confidence interval: 1.8–119.6). The best predictors of hyperkalaemia were class IV CHF, increases in creatinine following treatment and diabetes.

Conclusions. Patients with severe decompensated CHF using ACEI with SLN are at major risk for developing hyperkalaemia.

Keywords: angiotensin-converting enzyme inhibitors; drug-induced hyperkalaemia; heart failure; hyperkalaemia; spironolactone

Introduction

In recent years, angiotensin-converting enzyme inhibitors (ACEI) have emerged as key drugs for the management of congestive heart failure (CHF). The addition of spironolactone (SLN) as an adjuvant has been advocated following publication of the Randomized Aldactone Evaluation Study (RALES) [1], which found that subjects using ACEI/SLN had lower mortality rates than those using ACEI without SLN. Combination therapy also resulted in rare adverse events. Elderly patients, CHF patients, subjects with renal disfunction, renovascular diseases and diabetes are all more susceptible to ACEI-induced hyperkalaemia [2–8]. In the present work, we compared the incidence of hyperkalaemia in CHF inpatients using ACEI/SLN with those receiving ACEI without SLN.

Subjects and methods

We performed a retrospective cohort study of decompensated New York Heart Association (NYHA) class III or IV CHF patients admitted to internal medicine wards of Santo Antônio University Hospital (Salvador, Brazil) from 1 March 1999 to 31 March 2000, which were treated with ACEI with or without SLN. A total of 139 patients fulfilled the inclusion criteria. We excluded 39 of these because four

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had documented hyperkalaemia at admission, nine were using concomitant potassium replacement therapy, eight were using other drugs known to induce hyperkalaemia (e.g. potassium penicillin, trimetropim, β-blockers and non-steroidal anti-inflammatory drugs) and one presented end-stage renal failure. Seventeen additional patients were excluded because we lacked follow-up information on potassium and creatinine levels. After admission, charts were reviewed for 30 days or until hyperkalaemia (≥5.5 mEq/l), death or hospital discharge had occurred. We obtained all records of blood potassium and creatinine before and after treatment with ACEI/SLN or ACEI and registered the time of drug exposure preceding all observed cases of hyperkalaemia. All data were collected from printed charts archived at the hospital. Blood levels of creatinine and potassium were measured in all patients at admission and twice a week during the 30 day observation period. If high levels of potassium were detected, an independent blood sample was collected for confirmation and drug treatment was withdrawn. New blood samples were later taken to assure that blood potassium had returned to normal. Potassium was measured using flame photometry [9] and the Jaffé modified method [10] was used for measuring creatinine. At the day of admission, drug treatment was started immediately and patients were classified into the ACEI/SLN and ACEI groups, which were independent of other drugs used for CHF.

The cumulative risk for hyperkalaemia during the observation period was determined using Kaplan–Meier survival curves. Means and proportions were compared using Student's *t*-tests, χ^2 and Fisher's exact tests. Odds ratios were used to compare the risk for developing hyperkalaemia associated with ACEI/SLN *vs* ACEI. Univariate logistic regression was used to determine the association between development of hyperkalaemia and the observed clinical and laboratory characteristics. All analyses were performed using the SPSS[®] version 9.0. Two-tailed statistical tests were used with an alpha level set at 0.05.

Results

All demographic and clinical features were comparable between the two groups (Table 1), except for higher numbers of class IV CHF in the ACEI/SLN group ($P < 0.005$). The leading causes of CHF were cardiomyopathy secondary to Chagas' disease (trypanosomiasis), followed by ischaemia and hypertension. Baseline potassium and creatinine did not differ between the groups.

Hyperkalaemia was observed in 16 individuals receiving ACEI/SLN, but in only one individual receiving ACEI (Table 2). The odds ratio for development of hyperkalaemia in the ACEI/SLN group was 24.24 [95% confidence interval (CI): 3.07–191.65]. We found seven cases of severe hyperkalaemia (K > 6.0 mEq/l) and all of these occurred in class IV CHF patients (Table 3). When class III CHF subjects were excluded from the analysis, the odds ratio for developing hyperkalaemia among class IV CHF patients using ACEI/SLN compared with those using ACEI without SLN was 14.6 (95% CI: 1.8–119.6; Table 3). The 17 cases of hyperkalaemia are presented in Tables 4 and 5 and univariate associations between clinical/laboratory characteristics and hyperkalaemia are shown in Table 6.

The average duration of treatment with ACEI/SLN was 13 ± 8 days and the average time before onset of

Table 1. Clinical and demographic characteristics of CHF patients upon admission, according to use of ACEI and SLN

Variable[a]	ACEI plus SLN ($n=49$)	ACEI without SLN ($n=51$)	*P*-value
Age (years)	54 ± 13	56 ± 17	0.3
Men	31 (63%)	33 (65%)	0.9
Non-white	15 (83%)	23 (85%)	0.7
Baseline creatinine (mg/dl)	1.3 ± 0.5	1.1 ± 0.4	0.07
Baseline potassium (mEq/l)	4.2 ± 0.5	4.1 ± 0.6	0.4
NYHA class of CHF[b]			0.005[b]
III	11 (22%)	25 (49%)	–
IV	38 (78%)	26 (51%)	–
Diabetic patients	5 (10%)	5 (10%)	0.9
CHF actiology[c]			0.9[c]
Chagas' disease	18 (37%)	16 (31%)	–
Ischaemic	4 (8%)	3 (6%)	–
Hypertension	4 (8%)	3 (6%)	–
Valvular disease	2 (4%)	3 (6%)	–
Unknown	19 (39%)	23 (45%)	–
Others	2 (4%)	3 (6%)	–
Medications			
Captopril (mg/day)	46 ± 32	48 ± 23	0.7
Enalapril (mg/day)	15 ± 7	14 ± 5	0.8
Digoxin (mg/day)	0.22 ± 0.005	0.23 ± 0.004	0.15
Furosemide (mg/day)	69 ± 33	62 ± 28	0.27
SLN (mg/day)	37 ± 32	–	–

[a]Data are presented as means ± SD for quantitative variables or absolute number (valid percentage) for categorical variables.
[b]$P=0.005$ (χ^2 test) for comparison between groups.
[c]$P=0.9$ (χ^2 test) for comparison between groups.

Table 2. Incidence of hyperkalaemia (K ≥5.5 mEq/l) and severe hyperkalaemia (K >6.0 mEq/l) in the two groups

Group	Cases of hyperkalaemia	Cases of severe hyperkalaemia	Odds ratio for hyperkalaemia[a]	CI (95%)
ACEI plus SLN ($n=49$)	16 (33%)	7 (14%)	24.2[b]	3.1–191.6
ACEI without SLN ($n=51$)	1 (2%)	0	–	–

[a]Odds ratio for development of hyperkalaemia (K ≥5.5 mEq/l) in ACEI plus SLN group *vs* ACEI without SLN group.
[b]95% CI.

Table 3. Incidence of hyperkalaemia (K ≥5.5 mEq/l) and severe hyperkalaemia (K >6.0 mEq/l) in the two groups after excluding CHF class III patients

Groups	Cases of hyperkalaemia	Cases of severe hyperkalaemia	Odds ratio for hyperkalaemia[a]	CI (95%)
ACEI plus SLN ($n=38$)	14 (37%)	7 (18%)	14.6	1.8–119.6
ACEI without SLN ($n=26$)	1 (4%)	0	–	–

[a]Odds ratio for development of hyperkalaemia (K ≥5.5 mEq/l) among subjects using ACEI plus SLN *vs* those using ACEI without SLN after excluding CHF class III patients.

hyperkalaemia was 15 ± 9 days (all subjects initiated treatment with ACEI/SLN simultaneously). In contrast, the average duration of treatment with ACEI was 11 ± 6 days and the only patient that developed hyperkalaemia showed a potassium level of 5.5 mEq/l on day 15 of treatment. A list of other medications and their respective doses is presented in Table 1.

Kaplan–Meier curves for hyperkalaemia are shown in Figure 1. There were no deaths during the 30 day observation period. Importantly, only 10 (20%) of 49 individuals treated with ACEI/SLN over the 30 day observation period, excluding subjects discharged before day 30, were free of hyperkalaemia.

Figure 2 illustrates blood potassium levels in the two groups following initiation of treatment.

Discussion

The risk for hyperkalaemia was 24.2 times greater in patients using ACEI/SLN. However, the ACEI/SLN group had a greater proportion of class IV CHF patients that are at major risk for hyperkalaemia because worsening CHF stimulates the renin–angiotensin system [8,11]. We reanalysed the data after excluding class III CHF patients to minimize this potential confounding variable and found that the odds ratio for hyperkalaemia in class IV CHF patients was 14.6 (95% CI: 1.8–119.6). Although the ACEI/SLN group had higher baseline creatinine than the ACEI group ($P=0.07$), exclusion of class III CHF patients resulted in a smaller difference (1.3 ± 0.6 mg/dl for ACEI/SLN patients *vs* 1.2 ± 0.4 mg/dl for ACEI patients; $P=0.2$), suggesting that renal function deterioration and subsequent hyperkalaemia was more related to the functional class of CHF than to baseline creatinine levels. The higher post-treatment serum creatinine in the ACEI/SLN patients was probably due to more severe CHF in this group.

We found that rising creatinine after treatment with ACEI (with or without SLN), class IV CHF and diabetes were all significant predictors for the development of hyperkalaemia (Table 6). We hypothesize that the simultaneous introduction of ACEI and SLN increases the risk of hyperkalaemia because of the reduced glomerular filtration rate associated with initiation of ACEI treatment [8]. One-third (33%) of the 49 CHF patients using ACEI/SLN developed hyperkalaemia and this was severe in seven patients. Although these patients with hyperkalaemia were unskilled and socially disadvantaged, which are factors associated with trypanosomiasis, there was no evidence that hyperkalaemia occurred more frequently in CHF patients with Chagas' disease than in patients with other conditions.

Controlled clinical trials have reported a lower incidence of hyperkalaemia in heart failure patients using ACEI/SLN [1,12,13], but these studies excluded patients with serum creatinine >2.5 mg/dl and with serum potassium >5.0 mEq/l. Moreover, these studies recruited outpatients and included a smaller proportion of subjects with class IV CHF [1]. Following a preliminary report from the RALES study [12,13], a letter by Georges *et al.* [14] emphasized the rising risk of hyperkalaemia in patients using ACEI/SLN for cardiologic conditions and highlighted the important difference between well-conducted clinical trials with close follow-up compared with cursory monitoring by busy clinicians. Schepkens *et al.* [15] reported that 25 hyperkalaemic patients using ACEI/SLN mainly for cardiologic reasons also experienced severe adverse events.

In the present retrospective study, there was potential for selection and measurement bias and the possibility for confounding variables. However, the potential for

Table 4. Characteristics of severe hyperkalaemic (serum potassium >6.0 mEq/l) patients before and after exposure and after suspension of ACEI plus SLN

ACEI[a] dose (mg/day)	SLN dose (mg/day)	Time (days) of exposure	K[b] before exposure	K[b] after exposure	K[b] after suspending treatment	Creat[c] before exposure	Creat[c] after exposure	Creat[c] after suspending treatment	Heart failure aetiology	Presence of diabetes
25	25	30	4.6	6.6	3.8 (5[d])	1.1	3.2	1.1 (5[d])	Chagas' disease	No
75	100	2	4.3	6.4	4.6 (8[d])	1.8	2.4	1.8 (8[d])	Unknown	Yes
75	25	18	3.4	6.2	4.4 (3[d])	1.2	2.1	1.3 (3[d])	Unknown	No
37.5	25	4	4.3	7.0	4.3 (3[d])	2.1	2.4	2.1 (3[d])	Unknown	No
75	25	4	5.0	6.4	4.8 (6[d])	3.3	4.2	3.0 (6[d])	Unknown	No
37.5	25	9	3.2	7.9	3.5 (5[d])	1.3	2.5	1.4 (5[d])	Unknown	No
37.5	25	30	4.3	6.2	4.7 (4[d])	1.8	3.4	2.0 (4[d])	Ischaemic	Yes

[a]Captopril.
[b]K, serum potassium (mEq/l).
[c]Creat, serum creatinine (mg/dl).
[d]Days after suspension of ACEI and SLN.

Table 5. Characteristics of hyperkalaemic patients without severe hyperkalaemia (5.5 mEq/l ≤ serum potassium ≤ 6.0 mEq/l) before and after exposure and after suspension of ACEI and/or SLN

ACEI[a] dose (mg/day)	SLN dose (mg/day)	Time (days) of exposure	K[b] before exposure	K[b] after exposure	K[b] after suspending treatment	Creat[c] before exposure	Creat[c] after exposure	Creat[c] after suspending treatment	Heart failure aetiology	Presence of diabetes
12.5	25	19	3.5	5.7	4.8 (3[d])	1.0	1.5	0.4 (3[d])	Chagas' disease	No
37.5	0	15	5.3	5.5	3.5 (3[d])	1.0	0.8	1.0 (3[d])	Unknown	Yes
37.5	25	15	4.6	5.6	–	0.9	1.0	–	Unknown	No
37.5	25	7	4.7	5.9	5.3 (5[d])	1.0	1.2	1.3 (5[d])	Chagas' disease	No
25	100	13	4.5	5.6	4.6 (6[d])	0.9	1.4	1.2 (6[d])	Unknown	No
37.5	50	7	4.7	5.5	3.8 (3[d])	0.9	0.9	1.1 (3[d])	Chagas' disease	No
150	50	22	4.2	5.8	–	1.0	0.9	–	Unknown	Yes
75	25	15	3.8	5.6	5.2 (3[d])	0.9	1.9	1.4 (3[d])	Hypertension	No
50	25	10	4.6	6.0	5.4 (3[d])	1.1	2.5	1.2 (3[d])	Unknown	No
25	25	28	4.7	5.5	4.9 (6[d])	2.0	2.4	2.5 (6[d])	Unknown	No

[a]Captopril.
[b]K, serum potassium (mEq/l).
[c]Creat, serum creatinine (mg/dl).
[d]Days after suspension of ACEI and/or SLN.

Table 6. Univariate associations between clinical or laboratory variables and hyperkalaemia in all patients ($n = 100$)

Factor[a]	Odds ratio (95% CI)	*P*-value
Age >60 years	1.5 (0.5–4.1)	0.5
Serum creatinine at admission (mg/dl)	1.7 (0.7–4.4)	0.3
Serum creatinine after exposure to ACEI with or without SLN (mg/dl)	7.9 (2.7–23)	0.0001
Diabetic patients	3.9 (1.0–16)	0.05
Heart failure (functional class IV)	5.2 (1.1–24)	0.04

[a]For development of hyperkalaemia (K ≥5.5 mEq/l).

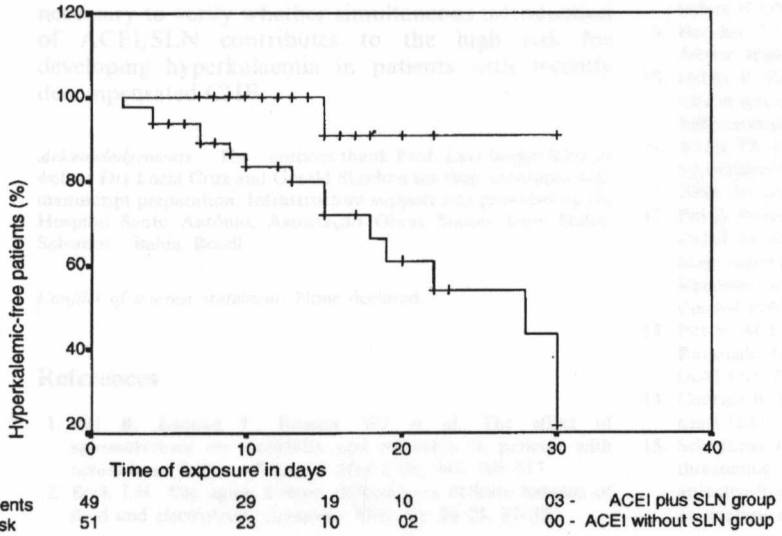

Fig. 1. Kaplan–Meier curves showing cumulative risk for development of hyperkalaemia (serum potassium ≥5.5 mEq/l) during 30 days of drug exposure. Patients given ACEI plus SLN are shown by the lower line and patients given ACEI without SLN are shown by the upper line.

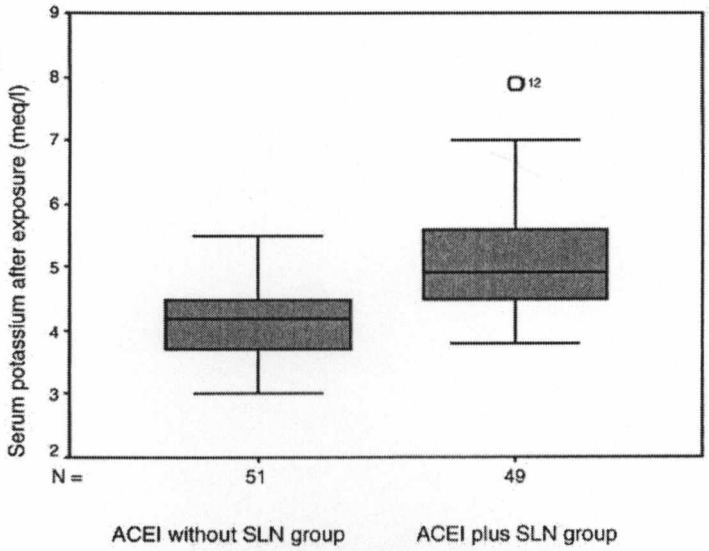

Fig. 2. Serum potassium (mEq/l) after exposure to ACEI plus SLN and to ACEI without SLN. Shown are the final potassium measurements prior to hospital discharge or to suspension of medications. This box-plot represents the distribution by median, by 25 and 75% percentiles and extreme values.

bias was reduced by consecutively including patients in the study as they had been admitted to the hospital and by verification of hyperkalaemia using two independent blood samples. Moreover, our statistical analysis has taken into consideration the most likely confounding variables.

In conclusion, treatment of decompensated severe heart failure with ACEI plus SLN was associated with frequent and severe hyperkalaemia. The major predictors of hyperkalaemia in these patients were decreased renal function, as reflected by rising serum creatinine following treatment, and the functional class of CHF. New and larger prospective studies will be necessary to verify whether simultaneous introduction of ACEI/SLN contributes to the high risk for developing hyperkalaemia in patients with recently decompensated CHF.

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