UNIVERSIDADE FEDERAL DE MINAS GERAIS
Faculdade de Medicina
Programa de Pós-graduação em Ciências da Saúde:
Infectologia e Medicina Tropical

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TRATAMENTO DA TAQUICARDIA VENTRICULAR NA CARDIOPATIA CHAGÁSICA

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Tese apresentada ao Programa de Pós-Graduação em Ciências da Saúde: Infectologia e Medicina Tropical da Faculdade de Medicina da Universidade Federal de Minas Gerais como requisito parcial à obtenção do grau de Doutor.

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UFMG

FOLHA DE APROVAÇÃO

"Tratamento da Taquicardia Ventricular na Cardiopatia Chagásica"

ANDRÉ ASSIS LOPES DO CARMO

Tese submetida à Banca Examinadora designada pelo Colegiado, como requisito para obtenção do grau de Doutor em Ciências da Saúde pelo Programa de Pós-Graduação em CIÊNCIAS DA SAÚDE - INFECTOLOGIA E MEDICINA TROPICAL.

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Ao meu filho, Pedro.

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“Podemos estar cegos para o óbvio e cegos também para nossa cegueira”.

Daniel Kahneman.

RESUMO

A cardiopatia chagásica é uma miocardite crônica fibrosante altamente arritmogênica e a taquicardia ventricular sustentada (TV) é a principal causa de morte súbita nessa população. O cardioversor-desfibrilador implantável (CDI) é a terapia classicamente utilizada para a prevenção de morte súbita e a ablação por cateter com abordagem dos circuitos epicárdicos está indicada nos casos de arritmia recorrente ou incessante. **Objetivos**: a) descrever a eficácia do CDI para prevenção secundária na redução da mortalidade total nos pacientes portadores de cardiopatia chagásica; b) relatar a efetividade e as taxas de complicações do acesso epicárdico guiado por laparoscopia, uma técnica desenvolvida em nosso serviço, na ablação da TV. **Métodos**: foram realizadas revisão sistemática e metanálise comparando-se as taxas de mortalidade total nos pacientes submetidos ao CDI para prevenção secundária com os pacientes tratados clinicamente com amiodarona. Procedeu-se à análise dos dados de efetividade e das taxas de complicações dos primeiros casos submetidos a acesso epicárdico guiado por laparoscopia no Hospital das Clínicas da Universidade Federal de Minas Gerais (HC-UFMG). **Resultados**: foram incluídos seis estudos observacionais com 115 pacientes no grupo amiodarona e 483 pacientes no grupo CDI. A mortalidade total ajustada foi 9,6 por 100 pacientes/ano no grupo amiodarona (95% CI 6,7-12,4) e 9,7 por 100 pacientes/ano (95% CI 5,7-13,7) no grupo CDI (p=0,95); 11 pacientes portadores de cardiopatia chagásica e TV refratária ao tratamento medicamentoso foram submetidos à ablação epicárdica guiada por laparoscopia de janeiro de 2015 a setembro de 2018. Acesso epicárdico foi obtido em todos os pacientes. As complicações foram: um choque cardiogênico grave durante o procedimento, com necessidade de suporte mecânico; uma paralisia de nervo frênico; e um pequeno fluxo epicárdico de sangue ao final do procedimento (deixado dreno por precaução com remoção em menos de 24 horas). Não houve lesão de órgão intra-abdominal e ocorreu uma morte mais de 30 dias após o procedimento de insuficiência cardíaca refratária (paciente previamente inscrito na fila de transplante cardíaco). **Conclusão**: a) a melhor evidência disponível derivada de pequenos estudos observacionais sugere que o CDI para prevenção secundária não está associado a baixas taxas de mortalidade total na cardiopatia chagásica; b) o acesso epicárdico guiado por laparoscopia é uma alternativa efetiva e segura para abordagem das arritmias epicárdicas e pode ser empregado em pacientes com taquicardia ventricular e dilatação de órgãos intra-abdominais.

Palavras-chave: Cardiopatia chagásica. Cardioversor-desfibrilador implantável. Taquicardia ventricular sustentada.

ABSTRACT

Chagas cardiomyopathy is a chronic fibrosing myocarditis and sustained ventricular tachycardia (VT) is the main cause of sudden death in this population. Implantable cardioverter-defibrillator (ICD) is a well-established therapy for secondary prevention in patients with structural heart disease and catheter ablation approaching epicardial circuits is the main therapy for recurrent or incessant VT. **Objectives**: a) to assess the efficacy of the ICD for secondary prevention in patients with Chagas cardiomyopathy; b) to examine feasibility and complication rates for ventricular tachycardia ablation performed with laparoscopic guided epicardial access, a technique first described in our Service. **Methods**: we systematically searched five databases for studies assessing mortality outcomes in patients with Chagas cardiomyopathy and VT treated with ICD implantation or with amiodarone. We examined complication rates of the first eleven cases of VT ablation in patients with Chagas cardiomyopathy using laparoscopic guidance to access epicardial space. **Results**: six observational studies were included for qualitative and quantitative analysis, totalizing 115 patients in amiodarone group and 483 patients in ICD group. The mortality outcome in ICD population was 9.7 per 100 patient-years of follow-up (95% CI 5.7-13.7) and 9.6 per 100 patient-years in amiodarone group (95% CI 6.7-12.4) (p=0.95). All patients were sent to ventricular tachycardia ablation due to failure of medical therapy and reasons for laparoscopy were megacolon in 10 patient and massive liver enlargement in 1 patient. Epicardial access was achieved in all patients. Complications were 1 severe cardiogenic shock during ablation, requiring mechanical assistance, 1 phrenic nerve paralysis and in one patient, due to a low blood flow at the end of the procedure, for safety reasons, we left a drainage catheter that was removed on the next day. There was no intra-abdominal organ injury and only one death of progressive heart failure, more than one month after procedure, while waiting for heart transplantation. **Conclusions**: a) the best available evidence derived from small observational studies suggests that ICD therapy in secondary prevention of sudden cardiac death is not associated with a lower rate of all-cause mortality in patients with Chagas cardiomyopathy; b) laparoscopic guided epicardial access in the setting of ventricular tachycardia ablation and enlarged intra-abdominal organ is a simple alternative to more complex surgical access and can be performed with low complication rates.

Keywords: Chagas cardiomyopathy. Implantable cardioverter-defibrillator. Sustained ventricular tachycardia.

LISTA DE ABREVIATURAS E SIGLAS

AHA	*American Heart Association*
ATP	Estimulação antitaquicardia
AVID	*Antiarrhythmics Versus Implantable Defibrillators*
BAV	Bloqueio atrioventricular
BAVT	Bloqueio atrioventricular total
BDAS	Bloqueio divisional anterossuperior esquerdo
BRD	Bloqueio de ramo direito
BRE	Bloqueio de ramo esquerdo
CASH	*Cardiac Arrest Study Hamburg*
CCC	Cardiopatia chagásica crônica
CDI	Cardioversor-desfibrilador implantável
CENTRAL	*Cochrane review of systematic interventions* e *Cochrane central Register of controlled trials*
CI	Intervalo de confiança
CIDS	*Canadian Implantable Defibrillator Study*
CNPq	Conselho Nacional de Desenvolvimento Científico e tecnológico
CO_2	Dióxido de carbono
ECG	Eletrocardiograma
EPI	Epicárdio
et al.	*et alteri* ou *et alii* (e outros)
FEVE	Fração de ejeção do ventrículo esquerdo
FV	Fibrilação ventricular
HC	Hospital das Clínicas
HR	*Hazard ratio*
IC	Insuficiência cardíaca
IECA	Inibidores da enzima conversora de angiotensina
I_{Kr}	Corrente lenta de potássio
I_{Ks}	Corrente rápida de potássio
LILACS	*Latin American and Caribbean Health Science Literature*
MEDLINE	*Medical Literature Analysis and Retrieval System On-line*
MeSH	*Medical Subject Headings*
NYHA	*New York Heart Association*

PCR	Reação em cadeia da polimerase
PRISMA	*Preferred Reporting Items for Systematic Review and Meta-Analyses*
RX	Raios-X
SC3	Seio coronário médio
SCd	Seio coronário distal
SCp	Seio coronário proximal
SUS	Sistema Único de Saúde
T. cruzi	*Trypanosoma cruzi*
TCA	Tempo de coagulação total
TV	Taquicardia ventricular sustentada
UFMG	Universidade Federal de Minas Gerais
VD	Ventrículo direito

SUMÁRIO[1]

[1] Este trabalho foi revisado com base nas novas regras ortográficas aprovadas pelo Acordo Ortográfico assinado entre os países que integram a Comunidade de Países de Língua Portuguesa (CPLP), em vigor no Brasil desde 2009. E foi formatado de acordo com a ABNT NBR 14724 de 17.04.2017. As referências seguiram as normas de Vancouver.

1 INTRODUÇÃO

A doença de Chagas, causada pelo protozoário flagelado *Trypanosoma cruzi* e descrita pelo médico brasileiro Carlos Chagas[1], persiste como grave problema de saúde pública na América Latina, acometendo aproximadamente 6 milhões de indivíduos[2-4]. Recentemente, com o aumento dos fluxos migratórios, mesmo países desenvolvidos vêm apresentando notável aumento no número de indivíduos cronicamente infectados[5]. O curso da doença é extremamente variável e, apesar de muitos indivíduos permanecerem assintomáticos por longos períodos, um terço dos infectados desenvolve doença cardíaca grave, incluindo arritmias ventriculares malignas e insuficiência cardíaca[6].

A morte súbita é considerada umas das características mais marcantes da doença de Chagas desde sua descrição inicial[6] e, em pacientes com cardiopatia chagásica crônica, mais de 50% dos óbitos são devidos à morte súbita cardíaca[7]. Além disso, a taquicardia ventricular sustentada (TV) é a causa mais frequente de morte súbita nessa população e sua perpetuação depende de reentrada anatômica no músculo cardíaco. Os substratos anatômicos que compõem os istmos protegidos, parte fundamental do circuito da TV, são gerados por lesões miocárdicas inflamatórias necróticas e fibróticas[8].

O cardioversor-desfibrilador implantável (CDI), por sua vez, é considerado o tratamento de escolha para a prevenção secundária de morte súbita nos pacientes portadores de cardiopatia estrutural[9-11]. Entretanto, não há estudos randomizados específicos para cardiopatia chagásica, reconhecida como uma cardiopatia altamente arritmogênica. Nos estudos que tradicionalmente avaliaram o benefício do CDI na prevenção secundária de morte súbita[12-14], essa população de pacientes não foi avaliada.

Embora a indicação de CDI na prevenção secundária de morte súbita cardíaca seja usualmente considerada inequívoca em pacientes com cardiopatia estrutural[9,10], restrições econômicas nas áreas endêmicas[15] e opiniões divergentes de especialistas têm colocado em dúvida a eficácia do CDI nos pacientes portadores de cardiopatia chagásica[16-18].

Adicionalmente, outro desafio no manejo da cardiopatia chagásica é o tratamento das arritmias ventriculares recorrentes e refratárias ao tratamento medicamentoso, cenário muito frequente nessa população e que se expressa pela

elevada densidade de terapias apropriadas disparadas pelos dispositivos eletrônicos cardíacos ou pela taquicardia ventricular incessante[18,19].

Os pacientes portadores de cardiopatia chagásica com TV refratária e megacólon associado, por sua vez, representam um subgrupo especialmente complexo, pois a dilatação do cólon transverso ou sigmoide pode inviabilizar a punção epicárdica subxifoide tradicional, como descrito por Scanavacca *et al.*[20], e a alternativa tradicional – janela cirúrgica subxifoide – parece estar associada a alto índice de complicações (dados não publicados), já que esses indivíduos muitas vezes têm desnutrição grave[21].

Em 2015, descrevemos o primeiro caso de acesso epicárdico guiado por laparoscopia[22], uma técnica simples que permite a punção subxifoide percutânea em pacientes portadores de dilatação de estruturas intra-abdominais com menos estresse cirúrgico. Entretanto, não há, até o presente momento, a descrição inicial da série de casos em relação à sua efetividade e segurança.

Esta tese foi dividida em duas etapas: inicialmente, realizou-se metanálise de estudos não randomizados para avaliar o impacto do CDI para prevenção secundária na mortalidade dos pacientes com cardiopatia chagásica; posteriormente, foram avaliadas a eficácia e segurança do acesso epicárdico guiado por laparoscopia nos primeiros casos realizados no Hospital das Clínicas da Universidade Federal de Minas Gerais (HC-UFMG).

2 REVISÃO DA LITERATURA

2.1 Doença de Chagas

Em 1909, o médico brasileiro Carlos Chagas descreveu pela primeira vez o agente etiológico, o vetor, os reservatórios naturais e muitas das manifestações clínicas da doença de Chagas[1]. A transmissão da infecção para seres humanos pode ser feita por vetores hematófagos (triatomíneos) contaminados com *T. cruzi*, transmissão vertical[23], hemotransfusão[24], transplante de órgãos contaminados[25], via oral[26] ou por meio de acidentes biológicos[27].

Após período de incubação de uma a duas semanas, desenvolve-se a fase aguda, com duração de oito a 12 semanas, caracterizada por abundantes tripomastigotas circulantes detectáveis por microscopia direta. Geralmente manifesta-se com sintomas inespecíficos, tal como febre, ou pode ser assintomática.

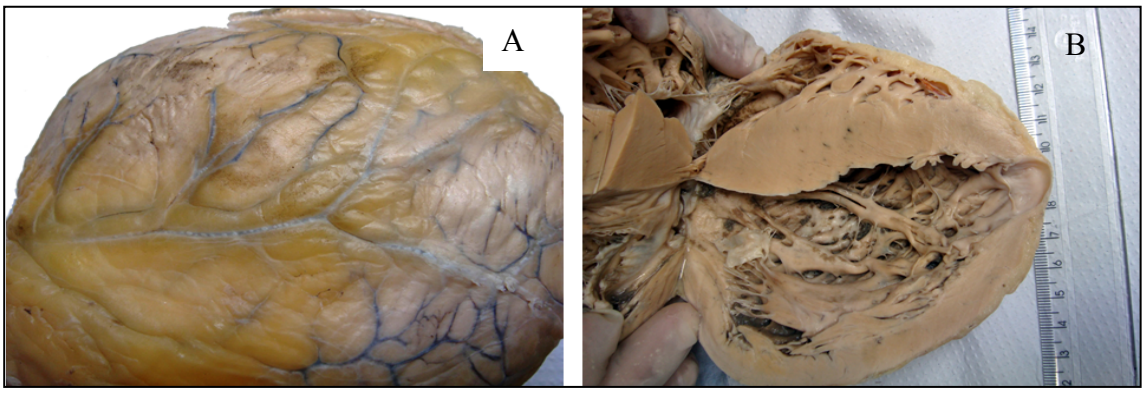
A fase crônica inicia-se quando a parasitemia decresce e torna-se indetectável por microscopia, o que, na ausência de tratamento específico, ocorre oito a 12 semanas após a infecção. Aproximadamente 60 a 70% dos pacientes infectados permanecem sem sinais ou sintomas de acometimento cardíaco ou gastrointestinal, caracterizando a forma crônica indeterminada. Cerca de 30% evoluem num período de anos a décadas com acometimento cardíaco ou intestinal clinicamente evidente.

A cardiopatia chagásica crônica acomete 30% dos indivíduos infectados e um terço destes desenvolve doença grave, incluindo insuficiência cardíaca e arritmias ventriculares malignas[28,29].

2.2 Cardiopatia chagásica crônica

A cardiomiopatia chagásica crônica é uma miocardite fibrosante (FIG. 1) e representa a principal causa de morte nos indivíduos com doença de Chagas[30]. Caracteriza-se por inflamação focal de intensidade variável composta de células linfomononucleares, desarranjo estrutural, hipertrofia, dilatação e intensa fibrose reativa e reparativa[31].

FIGURA 1 – Cardiopatia chagásica crônica



A) Espessamento nodular do pericárdio ao longo das artérias coronárias (epicardite rosariforme) em explante cardíaco de paciente com cardiomiopatia chagásica; B) aneurisma de ponta do ventrículo esquerdo em explante cardíaco de paciente com cardiopatia chagásica crônica.
Fonte: cedido pela Drª. Paula Carmo e Dr. Stanley Araújo.

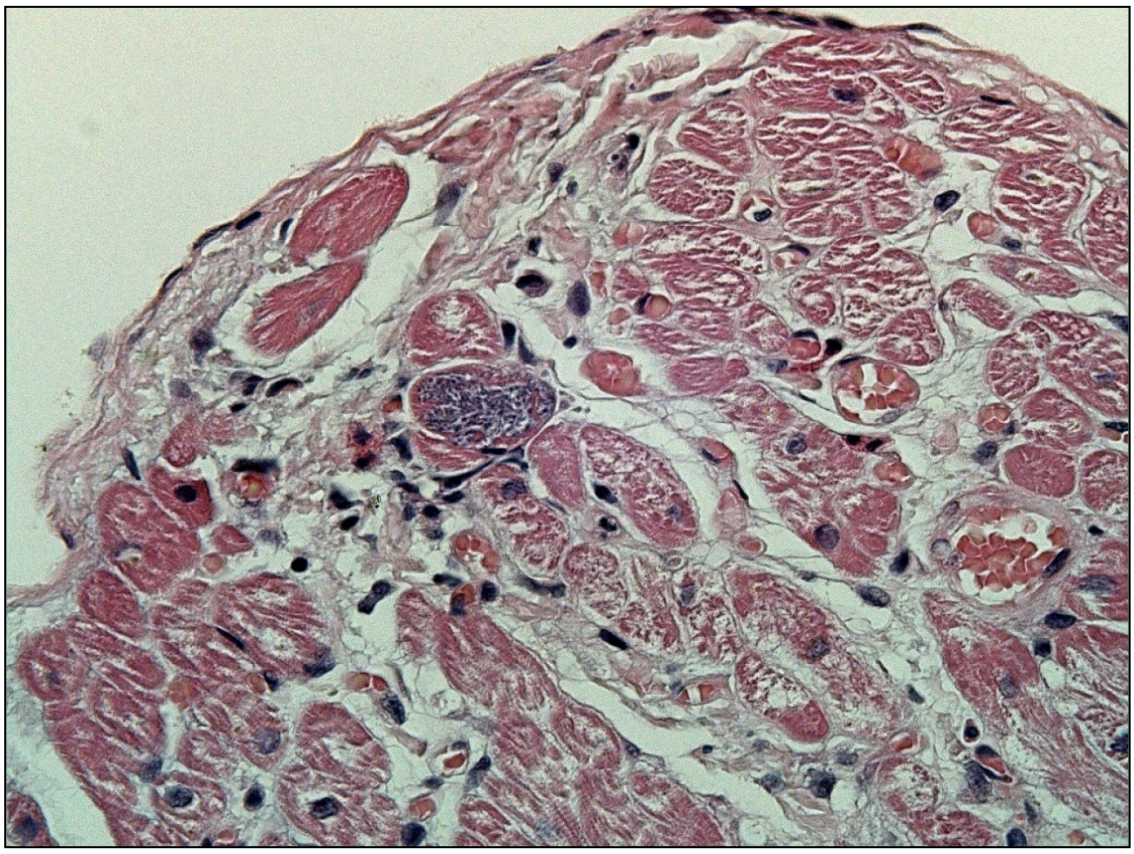
Os mecanismos patogênicos responsáveis pelo acometimento cardíaco incluem lesão miocárdica causada diretamente pelo *T. cruzi* e pela resposta imunológica à presença do microrganismo[32]. Entretanto, do ponto de vista patogenético, não se compreende ainda completamente a contribuição relativa da persistência do parasita *versus* o mecanismo imunológico.

O fato de o parasita ser raramente encontrado no tecido miocárdico por microscopia convencional, na fase crônica da doença (FIG. 2), levou diversos pesquisadores a sugerir que o processo inflamatório, nessa condição, seria essencialmente uma consequência da reação imunológica desencadeada pelo protozoário. Em modelos animais, evidências a favor do mecanismo imunológico incluem o desenvolvimento de distúrbios da condução cardíaca após imunização com antígenos de *T. cruzi* ou com base na transferência de linfócitos de animais infectados e pela melhora na miocardite crônica em animais infectados que se tornaram tolerantes a antígenos miocárdicos[33].

Por outro lado, pequenos estudos clínicos e alguns estudos experimentais sugerem que a persistência do parasita é importante para a patogênese da miocardite na doença de Chagas[34]. Estudo em seres humanos demonstrou associação entre a inflamação miocárdica e a carga parasitária detectada por reação em cadeia da polimerase (PCR) no coração[35]. Em modelo murino de infecção por *T. cruzi,* utilizando-se técnica de PCR *in situ*, observou-se correlação entre a persistência do parasita e a doença cardíaca[36]. Além disso, em estudo clínico não *randomizado* observou-se redução na progressão da cardiopatia chagásica nos pacientes tratados

com benzonidazol, corroborando a hipótese de que a persistência do parasita seja um elemento fundamental na patogênese da cardiopatia chagásica[37].

FIGURA 2 - Ninho de formas amastigotas de *T. cruzi* em biópsia endomiocárdica de paciente imunossuprimido pós-transplante cardíaco



H&E, 40x.
Fonte: cedida pela Drª Paula Carmo e Dr. Stanley Araújo.

Como, na maioria das vezes, a progressão da cardiopatia chagásica é lenta, os sinais e sintomas associados dependem do momento em que é feito o diagnóstico. Classificações da cardiopatia chagásica descritas por Rocha *et al.* em 2003 e 2007 levam em conta o grau de morbidade, a possibilidade evolutiva e o prognóstico da doença (QUADRO 1)[38,39].

Classicamente, essa forma clínica pode manifestar-se com sinais clínicos de insuficiência cardíaca, taqui ou bradiarritmia, tromboembolismo ou mesmo com morte súbita[6,40].

QUADRO 1 - Classificação clínica da cardiopatia chagásica crônica segundo Rocha *et al.* (2003, 2007), modificado

Grupo clínico	Características do Paciente
CCC 1	Assintomático e sem alteração ao exame físico, ECG, radiografias de tórax, esofagograma e enema opaco. Exames mais sensíveis podem detectar alterações de variável gravidade. Cardiopatia subclínica.
CCC 2	Assintomático ou em classe funcional NYHA I, sem cardiomegalia, mas alterações menores ao ECG, tais como baixa voltagem, bloqueio divisional do ramo esquerdo, alterações inespecíficas no ST e onda T.
CCC 3	Pacientes assintomáticos ou em classe funcional NYHA I ou NYHA II. Sem cardiomegalia, mas apresentando alterações avançadas da condução do estímulo ao ECG, tais como BRD, associado ou não a BDAS, BRE, BAV 2° grau ou BAVT. Pode haver arritmias ventriculares monomórficas, pouco frequentes.
CCC 4	Pacientes geralmente em NYHA I ou NYHA II, frequentemente com palpitações, sem cardiomegalia. Predominam as alterações do ritmo cardíaco, com extrassistolia frequente e complexa, associadas ou não a transtornos da condução do estímulo.
CCC 5	Pacientes com evidências clínicas, radiológicas e especialmente ecocardiográficas de dilatação cardíaca, podendo estar assintomáticos ou com manifestações clínicas de insuficiência cardíaca.

CCC: cardiopatia chagásica crônica; ECG: eletrocardiograma. Rx: Raios-X; NYHA: *New York Heart Association*; BRD: bloqueio de ramo direito; BDAS: bloqueio divisional anterossuperior esquerdo; BRE: bloqueio de ramo esquerdo; BAV: bloqueio atrioventricular; BAVT: bloqueio atrioventricular total: IC: insuficiência cardíaca.
Fonte: adaptado de Rocha *et al.*[38,39]

Uma nova classificação para a cardiopatia chagásica crônica foi adotada pelo Consenso Brasileiro e Latino-Americano de Insuficiência Cardíaca, considerando-se também a função ventricular esquerda sistólica obtida pela ecocardiografia (QUADRO 2). Essa classificação foi recentemente adotada pelo painel da *American Heart Association* (AHA), que publicou um *scientific statement* para a cardiopatia chagásica[2].

QUADRO 2 - Classificação da CCC segundo o Consenso Latino-Americano para o Diagnóstico e Tratamento da Cardiopatia Chagásica

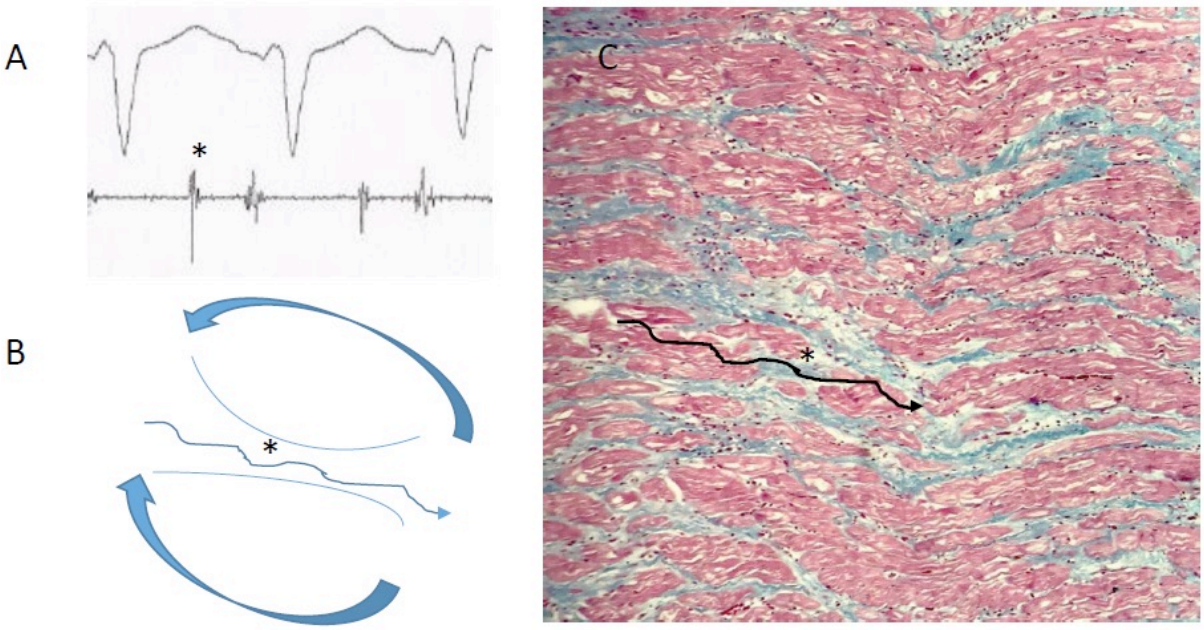
Estádios	Eletrocardiograma	Ecocardiograma	Insuficiência cardíaca
A	Alterado	Normal	Ausente
B1	Alterado	Alterado, função ventricular global preservada	Ausente
B2	Alterado	Alterado, disfunção ventricular global	Ausente
C	Alterado	Alterado	Compensável
D	Alterado	Alterado	Refratária

FEVE: fração de ejeção do ventrículo esquerdo.
Fonte: adaptado de Andrade *et al*.[41].

2.3 Taquicardia ventricular

As lesões necróticas e fibróticas causadas pela inflamação miocárdica, seja pela resposta imune ou pelo dano direto do parasita, são os principais substratos arritmogênicos na cardiopatia chagásica[42,43]. Além do mais, essas lesões também estão associadas à obstrução do fluxo sanguíneo, gerado pelo dano microvascular e por mudanças autonômicas na regulação do fluxo sanguíneo[44]. As injúrias inflamatórias e isquêmicas levam a acometimento das junções intercelulares que, em associação às mudanças do potencial elétrico transmembrana, comprometem a condução do estímulo elétrico entre as células. Essas alterações estruturais geram desacoplamento elétrico, que resulta em condução lenta do estímulo e bloqueio unidirecional. Todo esse processo forma os istmos protegidos (FIG. 3), que são os substratos para o circuito reentrante, mecanismo eletrofisiológico que perpetua as arritmias ventriculares[45,46].

FIGURA 3 – Representação do mecanismo de reentrada



A) traçado de estudo eletrofisiológico com o cateter posicionado no istmo protegido (*). B) representação esquemática do istmo protegido com a propagação lenta do estímulo elétrico no interior do istmo (*). C) corte histológico 40x com coloração tricômico de Masson demonstrando áreas e fibrose e possível istmo protegido (*).
Fonte: corte histológico gentilmente cedido pela Dr[a]. Paula Alves.

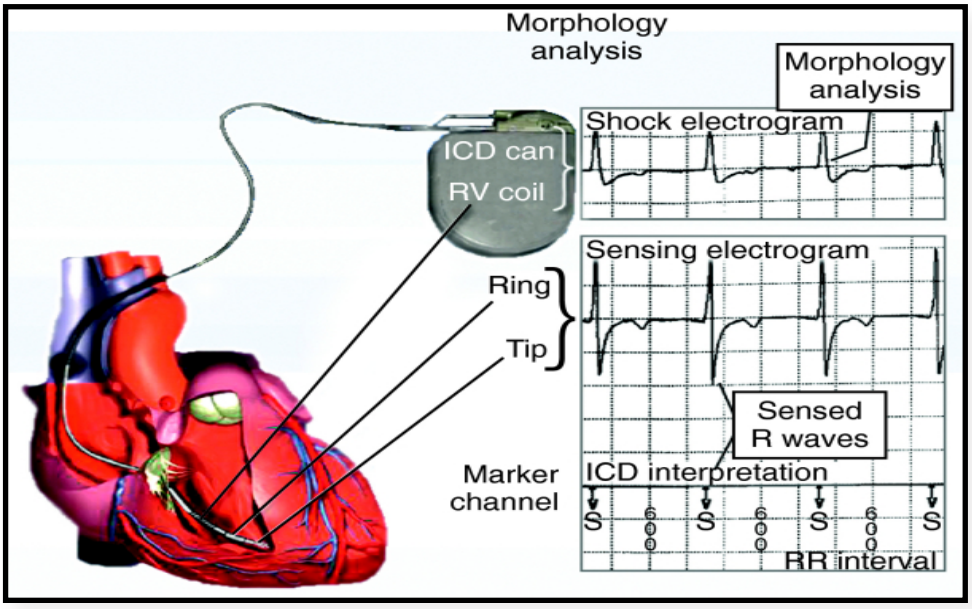
Além dos processos estruturais que ocorrem no músculo cardíaco, a disautonomia, um achado típico na doença de Chagas[47], parece estar relacionada à patogênese e ao risco aumentado de arritmias ventriculares[48-50]. Em modelos experimentais, demonstrou-se que, após denervação na fase aguda, ocorre a reinervação parcial ou total, seja por brotamento axonal de neurônios vagais intactos ou por crescimento axonal de terminações simpáticas[51]. A coexistência de áreas desnervadas e hiperinervadas no miocárdio doente pode levar ao aumento da heterogeneidade eletrofisiológica durante a ativação simpática, com potencial para indução de arritmias ventriculares e morte súbita[52]. Essa conexão é reforçada por achados recentes da associação de defeitos da inervação simpática (detectados pela cintilografia com 123-iodina metaiodobenzilguanidina) com a ocorrência de taquicardia ventricular e pelo efeito terapêutico da simpatectomia cardíaca no controle das arritmias ventriculares refratárias[50].

2.4 Cardioversor-desfibrilador implantável

Em 1980, Mirowski *et al.* descreveram os primeiros casos de interrupção de arritmias ventriculares malignas por CDI em seres humanos[53]. Desde então, esses dispositivos evoluíram de maneira muito rápida, incorporando novas ferramentas para a detecção apropriada e tratamento das arritmias ventriculares malignas, graças aos avanços significativos nas tecnologias dos microprocessadores e nas baterias. Inicialmente os CDIs foram utilizados para os pacientes com antecedente de morte súbita recuperada, entretanto, atualmente, são utilizados em larga escala para prevenção primária de morte súbita cardíaca[9,10].

Os CDIs modernos identificam as taquiarritmias acima de um limiar programável no dispositivo e, a partir de algoritmos também programáveis, classificam a taquicardia como ventricular ou supraventricular. Uma vez classificada como ventricular, dois tipos de terapias são possíveis: a estimulação antitaquicardia (ATP) ou o choque (FIG. 4).

FIGURA 4 – Ilustração esquemática do funcionamento básico de um cardioversor-desfibrilador implantável (CDI) com gerador, eletrodo e eletrogramas



Morphology analysis = análise morfológica; ICD *can* = gerador do desfibrilador; RV *coil* = *coil* do ventrículo direito; *shock electrogram* = eletrograma de choque*; sensing electrogram* = eletrograma de sensibilidade; *sensed R waves* = ondas R sentidas; ICD *interpretation* = interpretação do CDI; RR *interval* = intervalo RR; *ring* = anel; tip = ponta; *marker channel* = canal de marcas.
Fonte: Swerdlow *et al.*[54].

Os principais estudos que corroboraram a indicação de CDI para os pacientes sobreviventes de morte súbita cardíaca ou com TV sustentada associada à cardiopatia estrutural foram publicados no final dos anos 1990 e início dos anos 2000[11-14].

O estudo *Antiarrhythmics Versus Implantable Defibrillators* (AVID) avaliou pacientes sobreviventes de fibrilação ventricular (FV) ou TV sustentada com FEVE≤40%. População de 1.013 pacientes foi *randomizada* para implante de CDI ou terapia antiarrítmica. Em três anos de seguimento, a sobrevida do grupo CDI foi de 75,4% e do grupo antiarrítmicos foi de 64,1% (p<0,02), demonstrando diminuição de 31% do risco relativo de morte no grupo CDI[11]. Durante esse período, dois estudos menores foram publicados: o *Canadian Implantable Defibrillator Study* (CIDS) e o *Cardiac Arrest Study Hamburg* (CASH)[13,14].

Os estudos CIDS e CASH não demonstraram benefício do CDI, porém esses ensaios possuíam quase a metade da população do AVID, o que levantou a hipótese de ambos os estudos não apresentarem poder estatístico adequado para demonstrar a diferença entre os tratamentos. Entretanto, metanálise subsequente que incluiu os

três estudos revelou redução de 50% no risco relativo de morte súbita no grupo CDI[55]. Análises *post hoc* evidenciaram que arritmias ventriculares frequentes foram mais frequentes em pacientes com FEVE reduzida, pacientes não revascularizados após o evento índice, aqueles que se apresentavam com TV em vez de FV ou que tinham história de doença cerebrovascular[12,56].

2.4.1 Cardioversor-desfibrilador implantável na cardiopatia chagásica

Como era de se esperar, nos estudos clássicos de CDI para prevenção secundária, a população de pacientes portadores de cardiopatia chagásica não foi representada. Posteriormente, alguns estudos não randomizados avaliaram a mortalidade nos pacientes chagásicos submetidos ao implante do CDI para prevenção secundária[18,57-60].

Em 2007, foi publicado estudo retrospectivo[57] para avaliação de mortalidade total com 90 pacientes portadores de cardiopatia chagásica e TV hemodinamicamente instável documentada por eletrocardiograma (ECG). Em seguimento médio de 25,2 ± 19,3 meses, houve 31 (34%) mortes. Arritmias malignas foram observadas em 71% dos pacientes e a mediana de choques foi de 4,5 por paciente. Na análise multivariada, realizada pelo modelo de regressão de Cox, o único preditor de mortalidade total foi o número de choques (>4 episódios) por paciente no 30º dia após implante com um *hazard ratio* (HR) de 1,86 e intervalo de confiança (CI) de 95% entre 1,21 e 2,86. A expectativa média de sobrevida nos pacientes com >4 choques no dia 30 foi de 2,1 meses e nos pacientes com menos de quatro choques foi de 46,5 meses (p=0,0005).

Um registro multicêntrico patrocinado pela indústria teve sua atualização publicada[58]. Inicialmente o registro incluiu 90 pacientes[15] e posteriormente foi atualizado com 148 pacientes seguidos por 12 ± 7 meses. Apesar de ter incluído reduzida proporção de pacientes com prevenção primária (8,1%), os dados de mortalidade total foram disponibilizados para cada tipo de indicação separadamente; 63 pacientes tiveram terapias apropriadas e 15 (10,2%) faleceram (um no grupo de prevenção primária e 14 no grupo de prevenção secundária). A análise multivariada identificou idade >65 anos (HR 2,85; 95% CI 1,77-3,92) e FEVE <30% (HR 2,68; 95% CI 1,57-3,79) como preditores independentes de mortalidade.

Em 2012, autores reportaram os resultados de uma coorte retrospectiva de pacientes portadores de cardiopatia chagásica e CDI para prevenção secundária[59]. O estudo avaliou a mortalidade total e as taxas de choques apropriados. Foram incluídos 116 pacientes; 82,7% em classe funcional, segundo a *New York Heart Association* (NYHA) I ou II e com FEVE média de 42,4%. Durante seguimento médio de 45 ± 32 meses, ocorreram 31 (26,7%) mortes, com mortalidade anual de 7,1%. A análise multivariada identificou como preditor independente de mortalidade a classe funcional III da NYHA (HR 3,09; 95% CI 1,37-6,96). Estimulação acumulada do ventrículo direito (VD) menor que 40% foi preditora de maior sobrevida (HR 0,23; 95% CI 0,11-0,49). Em 58 pacientes (50%) houve episódios de TV/FV, com proporção de 5,8 choques por pacientes.

Outro estudo retrospectivo que comparou desfechos clínicos após implante de CDI para prevenção secundária na doença de Chagas[18] utilizou uma população de outras cardiopatias para comparação. No acompanhamento de 266 dias (mediana), 135 pacientes foram avaliados, dos quais 65 (48%) com cardiopatia chagásica, 22 (16,3%) com cardiopatia isquêmica, 28 (20,7%) com cardiopatia dilatada não isquêmica e 20 (15%) com outras etiologias. A FEVE foi 37% no grupo Chagas *versus* 32,5% no grupo não Chagas (p=0,99). Houve oito mortes em cada grupo (12,3 *vs* 11,4%, respectivamente, para os grupos Chagas e não Chagas, p=0,82). À análise multivariada a cardiopatia chagásica relacionou-se a aumentada chance de terapia apropriada (HR 2,2; 95% CI 1,2-4,3, p=0,02).

Em 2014, foi publicado o único estudo observacional[60] para prevenção secundária que utilizou um grupo-controle histórico tratado com amiodarona para comparação com o grupo CDI. Foram incluídos 76 pacientes no grupo CDI e 28 pacientes no grupo amiodarona. Todos os pacientes no grupo CDI receberam amiodarona e ambos os grupos tiveram características clínicas similares, exceto por mais uso de betabloqueador no grupo CDI (90% *vs* 17%, p<0,0001). Durante seguimento médio de 33 ± 16 meses no grupo CDI e 35 ± 17 meses no grupo amiodarona, houve redução de 72% no risco relativo de morte nos pacientes submetidos a implante de CDI (HR 0,28; 95% CI 0,11-0,72; p=0,007). Análise de subgrupo demonstrou benefício somente naqueles pacientes com FEVE<40%. Houve alto índice de terapias apropriadas, ocorrendo em 72% dos pacientes.

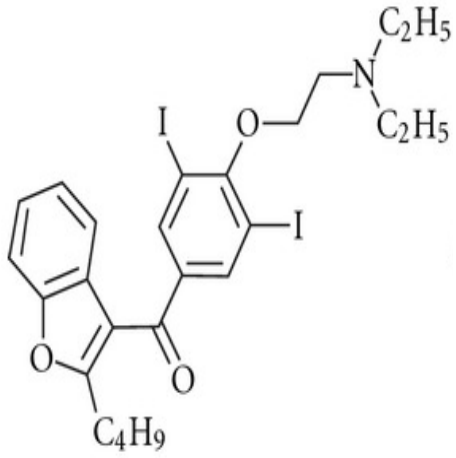
2.5 Amiodarona na cardiopatia chagásica

A grande quantidade de terapias apropriadas em pacientes com cardiomiopatia chagásica usando CDI, em comparação a outras cardiopatias[18], reforça a importância de grande esforço para a instituição de medidas que efetivamente previnam a recorrência das arritmias, seja por meio do tratamento medicamentoso, seja por técnicas de ablação[61,62].

É esse contexto altamente arritmogênico que justifica o uso tão disseminado da amiodarona – às vezes exagerado – na cardiopatia chagásica crônica. Além de ser uma droga com perfil de segurança cardíaco bem conhecido, a amiodarona é a droga antiarrítmica mais eficaz na cardiomiopatia chagásica, sendo geralmente bem tolerada[63-65].

A amiodarona, um benzofulran (FIG. 5) inicialmente desenvolvido como um antianginoso[66], é um antiarrítmico da classe III de Vaughan Williams (QUADRO 3), que interage com múltiplos canais iônicos e receptores da superfície celular. A droga é fortemente lipofílica, o que contribui para a sua eliminação lenta. O início de seu efeito varia de acordo com o mecanismo de ação envolvido: os efeitos antiadrenérgicos tendem a ser precoces, enquanto os efeitos dependentes de prolongamento do potencial de ação são mais tardios.

FIGURA 5 - Representação da estrutura química da amiodarona



Fonte: Rodrigues *et al.*[67].

A amiodarona prolonga a duração do potencial de ação miocárdico – que é o seu efeito predominante – de forma homogênea (reduzindo dispersão da

refratariedade, reentrada e pró-arritmia) a partir do bloqueio de canais de potássio (corrente lenta de potássio - I_{Kr} - e corrente rápida de potássio - I_{Ks}). Possui, ainda, diversos outros efeitos antiarrítmicos significativos: diminui a velocidade de condução pelo bloqueio dos canais de sódio (efeito classe I); bloqueio dos receptores beta-adrenérgicos (efeito classe II); redução da corrente interna tipo L dos canais de cálcio (efeito classe IV); além de inibir a conversão de tiroxina (T4) em tri-iodotironina (T3). Embora prolongue o intervalo QT, o risco de *torsades de pointes* é inferior a 1%, provavelmente pelo prolongamento homogêneo do potencial de ação[68].

QUADRO 3 - Classificação de Vaughan Williams dos antiarrítmicos

Classe IA - Diminui a velocidade de condução e prolonga o potencial de ação	Quinidina Procainamida Disopiramida
Classe IB - Sem efeito na velocidade de condução e pode encurtar o potencial de ação	Lidocaína Fenitoína Mexiletine
Classe IC - diminui a velocidade de condução e pode prolongar o potencial de ação (leve)	Propafenona Flecainida
Classe II - bloqueadores dos receptores beta-adrenérgicos	Betabloqueadores
Classe III - Prolonga o potencial de ação e sem efeito na velocidade de condução	Amiodarona Sotalol Dronedarona Dofetilida Ibutilida
Classe IV - Bloqueadores dos canais de cálcio	Bloqueadores dos canais de cálcio não di-idropiridínicos (verapamil e diltiazem)

Fonte: adaptado de Bashore TM *et al*.[69].

Os efeitos colaterais mais frequentes durante o tratamento crônico com amiodarona são extracardíacos[70]. A mais temida é a toxicidade pulmonar, com fibrose pulmonar ocorrendo em 1-17% dos casos, embora com observação menos frequente em nosso meio. Os demais efeitos adversos incluem: hipotireoidismo (6%); hipertireoidismo (0,9-2%); tremor e ataxia (3-35%); neuropatia periférica (0,3% ao ano), além de alterações na cor da pele. Microdepósitos corneanos estão presentes em praticamente todos os pacientes, mas raramente pode ocorrer neurite óptica. Alteração da função hepática não é incomum, mas é rara a progressão para cirrose.

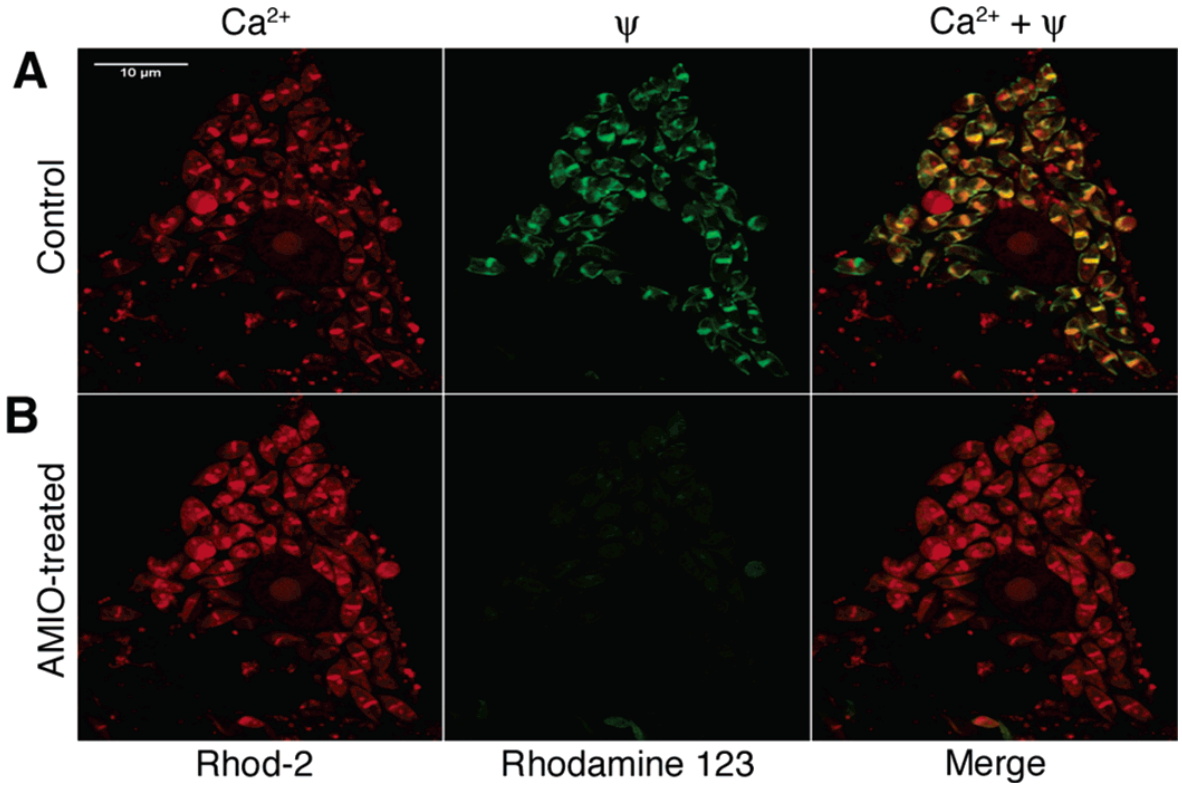
Em pacientes com cardiopatia estrutural, especialmente entre aqueles com depressão da função sistólica ventricular esquerda, a amiodarona, em associação com betabloqueadores, é o antiarrítmico de escolha para prevenção da recorrência

das taquicardias ventriculares. Sua eficácia, em dois anos de seguimento, para prevenção de TV sustentada, FV ou morte é de aproximadamente 60%[71-73], tem efeitos inotrópicos mínimos e baixo risco de pró-arritmia[74]. O uso empírico da amiodarona tem sido mais efetivo que o emprego de outros antiarrítmicos[72,75], e em pacientes com fração de ejeção acima de 35% parece ter eficácia semelhante à do CDI[12].

2.5.1 Efeito antiparasitário da amiodarona

Os efeitos antiarrítmicos da amiodarona são conhecidos e estudados há muito tempo, com diversas informações sobre sua segurança e eficácia. Somente em 2006 foi descrito, em modelos *in vitro* e em camundongos infectados, que a amiodarona possui efeito antiparasitário para o *T. cruzi*[76].

FIGURA 6 - Células vero infectadas com amastigotas de *T. cruzi* e incubadas simultaneamente com Rhd-2 AM e Rodamina 123

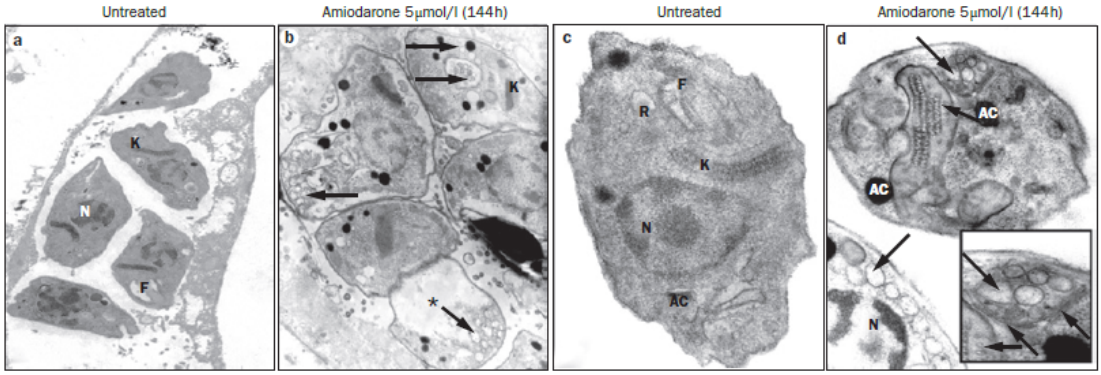


A Rhod-2 AM mostra a distribuição do Ca^{2+} em vermelho e a Rodamina 123, o potencial eletroquímico da membrana mitocondrial em verde. a) Na célula controle, a fluorescência vermelha da Rhod-2 AM vem dos compartimentos intracelulares ricos em Ca^{2+}, principalmente da mitocôndria (a baixa afinidade da Rhod-2 AM pelo Ca^{2+} limita a fluorescência do citoplasma dos amastigotas e da célula vero, que são pobres em Ca^{2+}); b) ainda em condições-controle, a fluorescência verde da Rodamina 123 na porção interna da membrana mitocondrial; c) a célula incubada com ambas as substâncias; d) a célula vero infectada foi tratada com amiodarona (12,5 µmol/L), com liberação e Ca^{2+} da mitocôndria dos parasitas e aumento do Ca^{2+} citoplasmático dos amastigotas; e) coloração com Rodamina 123 na presença de amiodarona, demonstrando perda do potencial da membrana mitocondrial.
Fonte: adaptado de Benaim *et al*.[76].

A amiodarona altera a homeostase do cálcio, induzindo a liberação do íon de seus estoques intracelulares (FIG. 6), especificamente de sua mitocôndria e das acidocalcisomas (organelas ácidas que contêm altas concentrações de pirofosfato e cálcio)[77,78]. Além disso, a droga bloqueia a biossíntese de esteróis no *T. cruzi* a partir da inibição da oxidosqualene cyclase, ação potencializada pelo posaconazol[76].

Análises por meio de microcopia eletrônica de cardiomiócitos infectados com *T. cruzi* e tratados com amiodarona também evidenciaram alterações estruturais nos amastigotas (FIG. 7)[79,80].

FIGURA 7 - Alterações estruturais do *T. cruzi* em cardiomiócitos tratados com amiodarona



a) Cardiomiócitos infectados com amastigotas de *T. cruzi*, demonstrando amastigotas intactos, com cinetoplasto em forma de bastão (K), núcleo (N) e flagelo (F); b) nas células tratadas com amiodarona 5 µmol/L, os amastigotas apresentam vacúolos na membrana (setas), perda de material intracelular (asterisco) e alterações no cinetoplasto; c) parasitas retirados de cultura de células exibem acidocalcisomas (AC), cinetoplasto em bastão, núcleo, reservosoma e flagelo sem alterações; d) quando retirados de culturas celulares tratadas com amiodarona, os parasitas demonstram alterações no cinetoplasto e no aparato de Golgi (seta).
Fonte: adaptado de Adesse *et al.*[79].

Além disso, há relato de paciente tratado com elevadas doses de amiodarona (1.600 mg/dia por cinco dias, seguido por 800 mg/dia) para controle de arritmia em que houve queda importante dos níveis de anti-rTc24 circulantes um mês após o início da medicação. Com a associação de itraconazol ao esquema terapêutico, os níveis de anti-rTc24 tornaram-se indetectáveis após seis meses[81]. A avaliação da carga parasitária a partir do anti-rTc24 constitui método indireto de avaliação da carga parasitária que, em pequenos estudos, parece se correlacionar com a persistência do parasita[82,83].

Contudo, estudos clínicos que avaliaram o efeito da amiodarona na carga parasitária falharam em identificar reduções significativas da parasitemia no contexto clínico do uso da medicação[84,85].

2.5.2 Amiodarona na prevenção secundária de morte súbita

Dois estudos avaliaram o efeito da amiodarona isoladamente na mortalidade total em pacientes com cardiopatia chagásica e TV sustentada[60,86]. Estudo avaliando o efeito do tratamento medicamentoso em 115 pacientes com TV (78 com TV espontânea e 37 com TV induzida ao estudo eletrofisiológico) apurou que todos os pacientes receberam amiodarona ou sotalol de acordo com a preferência do médico assistente[86]. No entanto, se o sotalol tivesse sido utilizado como primeira escolha e a TV continuasse indutível ao estudo eletrofisiológico, o estudo eletrofisiológico era

repetido após uma dose de impregnação da amiodarona. Ao final do estudo, 87 pacientes estavam em uso de amiodarona, 25 em uso de sotalol e três estavam em uso de amiodarona mais sotalol ou mexiletine. A mortalidade total não foi significativamente diferente: 40,2, 36 e 33,3%, respectivamente, para amiodarona, sotalol ou associação das drogas.

Como já mencionado na seção 2.4.1, autores[60] utilizaram um controle histórico, parcialmente publicado em manuscrito anterior[87], com 28 pacientes tratados com amiodarona. Durante seguimento médio de 35 ± 17 meses, houve nove mortes (11% ao ano), das quais sete (25%) foram classificadas como súbitas.

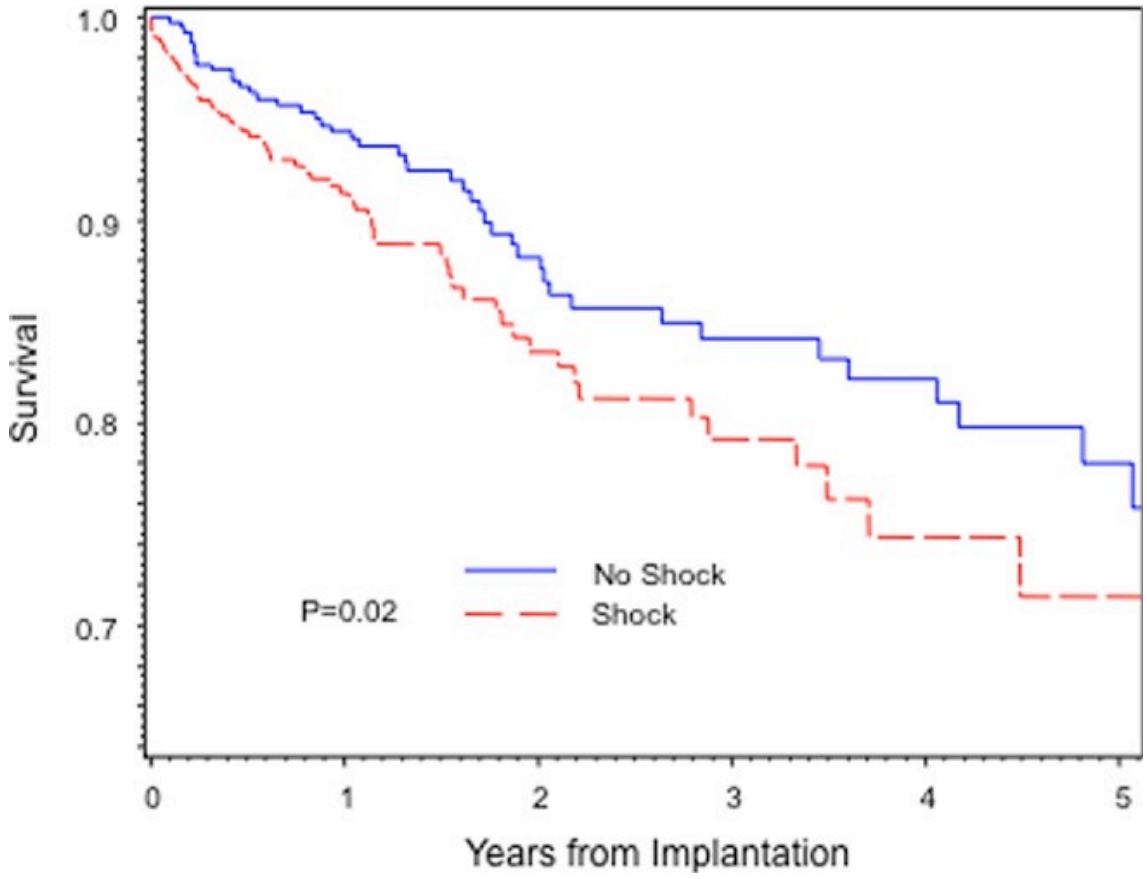
Em 1990, foi publicada pesquisa[88] sobre o uso empírico de amiodarona nos pacientes com cardiopatia chagásica e TV sustentada, entretanto, não foi possível obter os dados quanto à mortalidade total na população estudada.

2.6 Ablação por cateter

Nas últimas décadas, o CDI tornou-se a terapia de escolha para o tratamento das TVs sustentadas nos pacientes com cardiopatia estrutural[9,10]. Esses dispositivos revertem efetivamente as taquicardias ventriculares a partir dos ATPs ou dos choques (seção 2.4), prevenindo, na maioria das vezes, a morte súbita arrítmica.

Por outro lado, os choques administrados pelos CDIs ocasionam significativa piora na qualidade de vida[75,89] e podem, de fato, aumentar a mortalidade[90-92] (FIG. 8).

FIGURA 8 – Curva de sobrevida ajustada para os grupos choque e não choque em cinco anos de seguimento

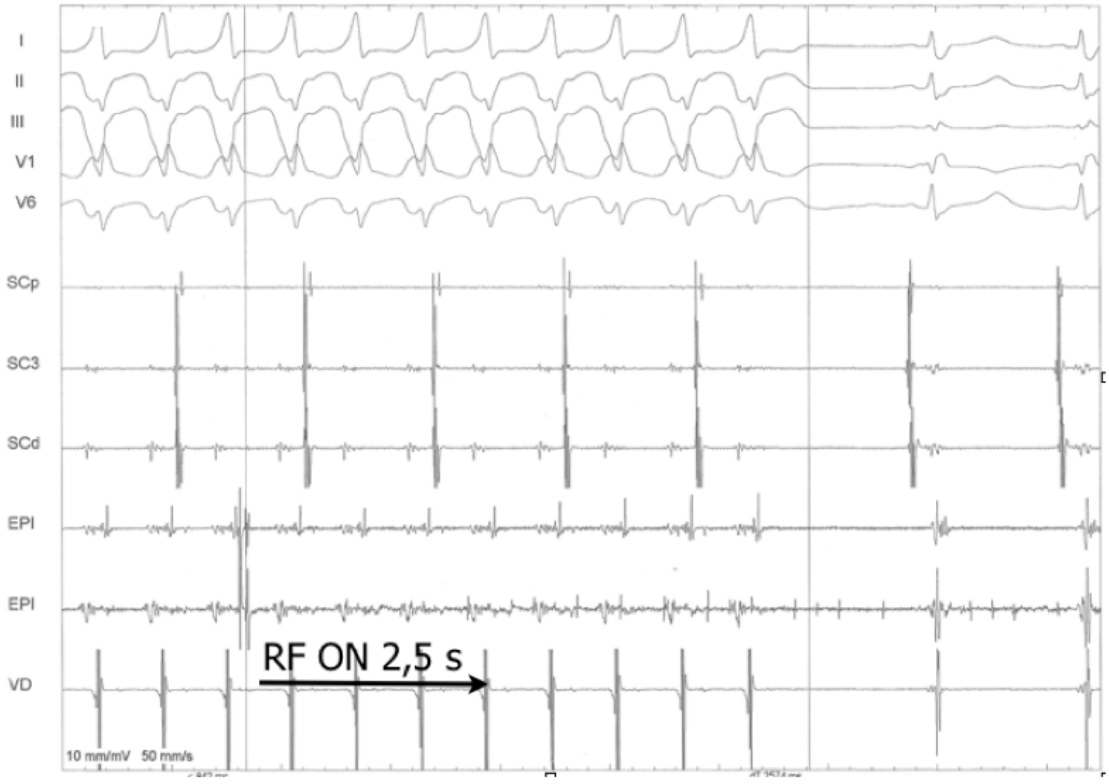


Fonte: Larsen *et al.*[90]

No caso específico da cardiopatia chagásica, o grande número de arritmias e a alta densidade de terapias administradas pelo CDI, mesmo nos pacientes em uso crônico de amiodarona[18,59,60], causam uma preocupação adicional no manejo clínico dos pacientes após implante. Nesse contexto, a ablação por cateter é uma ferramenta muito útil – às vezes a única – para o controle das arritmias ventriculares[93,94].

O princípio da ablação por cateter é identificar os istmos críticos para a perpetuação das reentradas (FIG. 3) e, através da aplicação de energia, destruir as células viáveis presentes no istmo. Quando a TV é hemodinamicamente tolerada, o mapeamento eletrofisiológico tradicional é possível e a aplicação de radiofrequência no istmo crítico durante a taquicardia resulta em sua interrupção (FIG. 9).

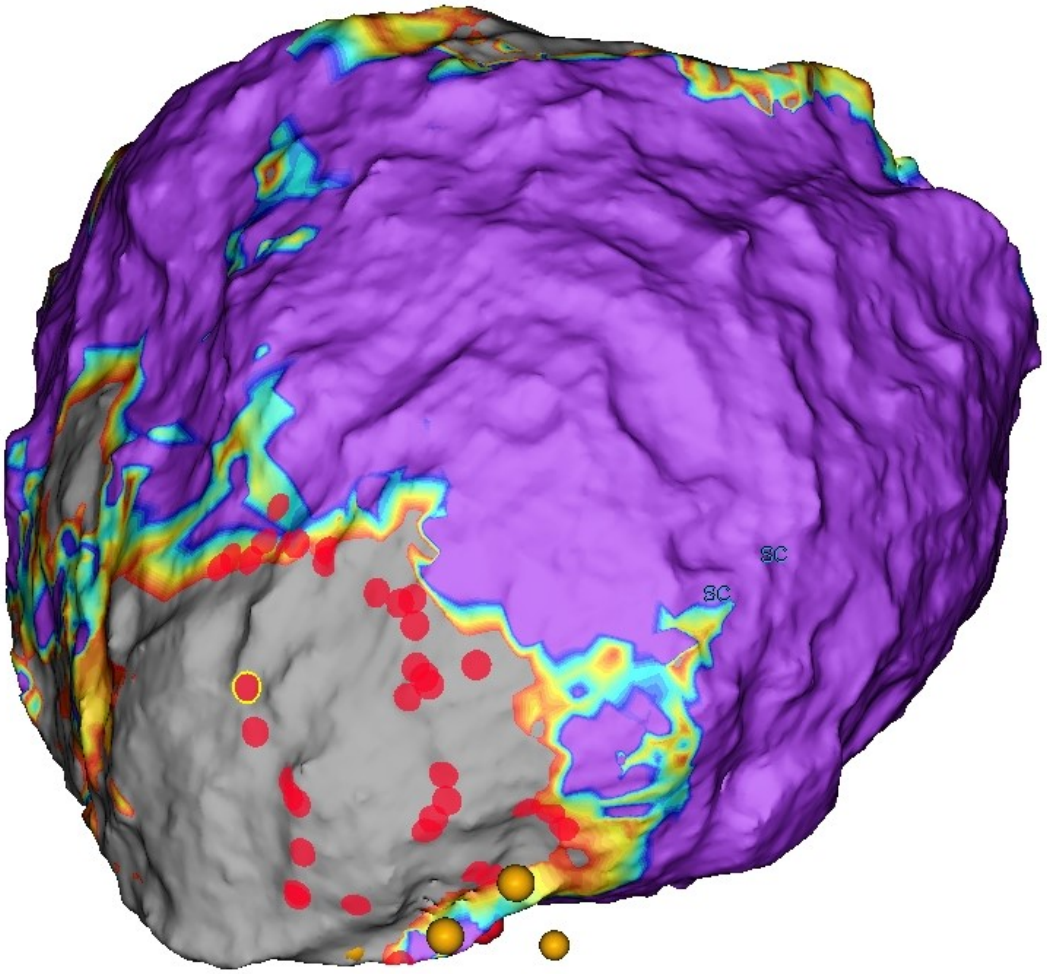
FIGURA 9 – Aplicação de radiofrequência no istmo crítico da taquicardia (epicárdico) com interrupção da arritmia em 2,5 s



SCp: seio coronário proximal; SC3: seio coronário médio; SCd: seio coronário distal; EPI: epicárdio; VD: ventrículo direito.
Fonte: do autor.

Quando a TV tem uma repercussão hemodinâmica considerável, além do suporte circulatório, a ferramenta mais utilizada é o mapeamento eletroanatômico. Essa ferramenta permite a identificação visual em três dimensões das áreas de fibrose, com o mapeamento dos potenciais tardios e fracionados em ritmo sinusal, que são potenciais alvos para a ablação por cateter (FIG. 10).

FIGURA 10 – Mapeamento eletroanatômico epicárdico com identificação de áreas sadias (roxo) e áreas doentes (a cor cinza denota cicatriz densa e as demais cores, áreas de transição)



Fonte: do autor.

Recentemente, demonstrou-se que a modificação estendida do substrato arritmogênico em pacientes com cardiomiopatia isquêmica (com abordagem endocárdica e epicárdica) foi mais efetiva que a abordagem tradicional para a prevenção de recorrência da taquicardia ventricular (19 *vs* 47%)[95].

Embora não haja estudos específicos para a população de chagásicos, os serviços com alto volume de ablação em Chagas têm concentrado esforços em realizar uma modificação mais ampliada do substrato arritmogênico, mesmo com as dificuldades de acesso às novas tecnologias no Serviço Único de Saúde (SUS).

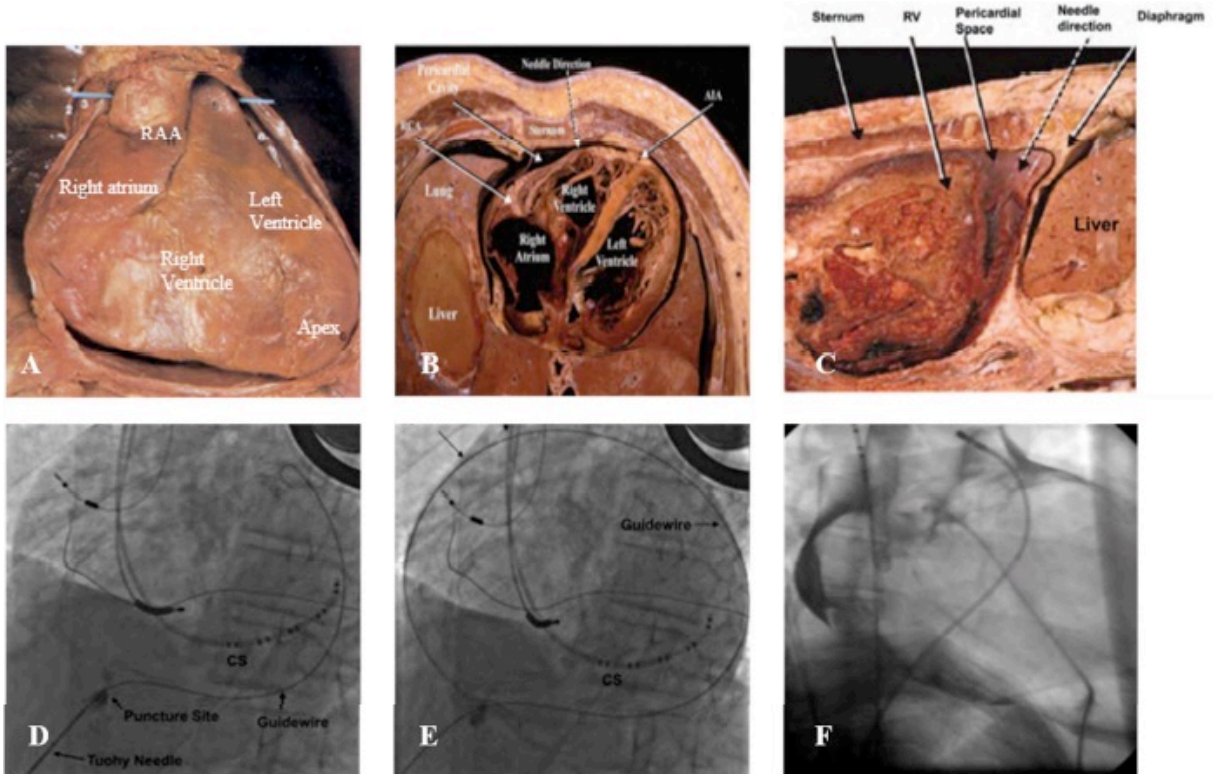
Desse modo, atenção especial deve ser dada à modificação do substrato epicárdico, superfície que concentra a maior parte dos circuitos arritmogênicos na cardiopatia chagásica[96].

2.6.1 Acesso epicárdico

O acesso epicárdico tem sido utilizado para mapeamento e ablação das TVs na cardiopatia chagásica desde 1995[20,93], com expansão de sua utilização para outras formas de cardiopatia[97-99]. A técnica do acesso epicárdico tornou-se indispensável no campo da eletrofisiologia devido à necessidade de abordagem dos substratos epicárdicos e manteve-se virtualmente inalterada até há bem pouco tempo, quando surgiram algumas pequenas modificações com o intuito de aumentar a segurança do procedimento[100-107].

A técnica original consiste na punção epicárdica por meio de uma agulha epidural que é introduzida 2 a 3 cm abaixo e pouco lateral ao processo xifoide, no espaço de Larrey. Posteriormente, a agulha é avançada sob visão fluoroscópica e, uma vez atingido o espaço epicárdico, um fio-guia é introduzido para passagem de uma bainha. Algumas variações quanto ao ângulo de entrada (anterior *vs* posterior) ou lateralidade são possíveis (FIG. 11).

FIGURA 11 – Acesso epicárdico



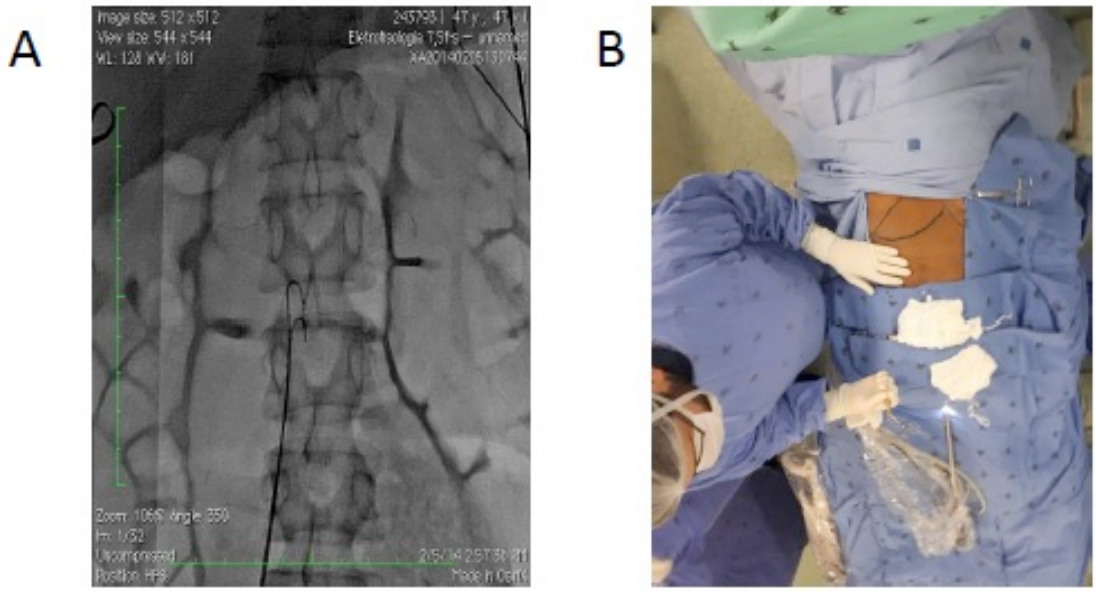
A-C) relações anatômicas do espaço pericárdico com as estruturas adjacentes. D-E) Imagens fluoroscópicas do acesso epicárdico
Fonte: Romero *et al.*[108]

As variações da técnica original que surgiram nos últimos anos incluem: insuflação de dióxido de carbono (CO_2) no apêndice atrial direito[103] ou seio coronário[104], agulha com sensor de pressão[102], tomografia computadorizada[107], ressonância magnética[106] e punção guiada por mapeamento eletroanatômico[105].

Ainda que tenha havido, nos últimos anos, algumas variações com vistas a aumentar a segurança da punção epicárdica, um cenário que permanece desafiador é a organomegalia intra-abdominal (FIG. 12). Nesse cenário, a alternativa mais utilizada é a janela cirúrgica subxifoide, no entanto, centros com experiência no acompanhamento a essa população relatam altos índices de morbidade (dados não publicados).

Para abordar esse problema, não infrequente na cardiopatia chagásica, descrevemos em 2015 o primeiro caso de acesso epicárdico guiado por laparoscopia[22], um método simples e rápido que pode ser realizado na maioria dos laboratórios de eletrofisiologia. Entretanto, faltam dados de eficácia e segurança em relação a esse procedimento.

FIGURA 12 – Acesso epicárdico guiado por laparoscopia



A) Imagem fluoroscópica de megacólon com ocupação completa da porção epigástrica pelo cólon sigmoide. B) Marcação cutânea de hepatomegalia em paciente com insuficiência cardíaca direita e congestão hepática.
Fonte: do autor.

3 OBJETIVOS

Considerando-se as lacunas no conhecimento científico identificadas na revisão da literatura médica, nesta tese realizamos dois estudos originais com objetivos distintos, que serão chamados, a partir deste momento, de estudo 1 e estudo 2.

3.1 Objetivo do estudo 1

O objetivo deste estudo foi realizar uma metanálise para avaliar a eficácia do CDI para prevenção secundária de morte súbita na cardiopatia chagásica, comparando a mortalidade total nos pacientes submetidos a implante de CDI com os pacientes tratados clinicamente com amiodarona.

3.2 Objetivo do estudo 2

Identificar a eficácia e as taxas de complicações do acesso epicárdico guiado por laparoscopia.

4 CASUÍSTICA E MÉTODOS

4.1 Estudo 1

4.1.1 Caracterização do estudo

Realizou-se revisão sistemática e metanálise para comparação do efeito do CDI na mortalidade total dos pacientes portadores de cardiopatia chagásica em comparação aos pacientes tratados clinicamente com amiodarona. Como não foram encontrados estudos *randomizados* para essa comparação, foram incluídos somente estudos observacionais nesta análise.

O estudo foi desenvolvido em parceria com a *Population Health Research Institute (McMaster University, Hamilton, Ontario, Canada)*, como parte do Programa de Doutorado-Sanduíche no Exterior, do Conselho Nacional de Desenvolvimento Científico e tecnológico (CNPq) – processo número: 200241/2015-0.

Este artigo foi publicado no periódico *International Journal of Cardiology* (APÊNDICE A)[109].

4.1.2 Registro e protocolo

Toda a metodologia desta revisão sistemática e metanálise foi previamente registrada no banco de dados PROSPERO (CRD42015027266) e o *checklist* da *Preferred Reporting Items for Systematic Review and Meta-Analyses* (PRISMA) foi utilizado para a realização deste trabalho.

4.1.3 Critérios de eleição

Buscas preliminares foram realizadas com o intuito de identificar publicações que incluíssem pacientes com cardiopatia chagásica e CDI implantado para prevenção secundária de morte súbita cardíaca e/ou cardiopatia chagásica e TV tratada clinicamente. Inicialmente, restringiram-se as buscas para ensaios clínicos aleatórios com pelo menos um ano de seguimento. Contudo, nenhum trabalho aleatório foi encontrado após três buscas preliminares. Por conseguinte, o protocolo de busca foi modificado e passou a incluir todos os registros clínicos e estudos

observacionais, independentemente do tempo de seguimento. A pesquisa final foi realizada em janeiro de 2017.

4.1.4 Fontes de informação e busca

Foram realizadas buscas abrangentes nas plataformas *Latin American and Caribbean Health Science Literature* (LILACS), *Medical Literature Analysis and Retrieval System On-line* (MEDLINE), EMBASE, *Cochrane review of systematic interventions* e *Cochrane central register of controlled trials* (CENTRAL). Os termos *Medical Subject Headings* (MeSH) empregados na busca foram: *"Chagas disease" AND "defibrillator" OR "ventricular tachycardia"*. Como grande parte da literatura médica referente à doença de Chagas é produzida em países de língua não inglesa, não restringimos as buscas de acordo com a língua de publicação.

Adicionalmente, foram realizadas buscas no *website* www.theheart.org para identificar apresentações em grandes eventos científicos internacionais. Especialistas em doença de Chagas foram contatados para identificar estudos não encontrados nas plataformas pesquisadas.

4.1.5 Seleção dos estudos

Devido à ausência de estudos *randomizados* que tenham avaliado o tratamento CDI *versus* tratamento clínico, foram utilizados os seguintes critérios de inclusão:

a) Estudos de pacientes com cardiopatia chagásica e CDI para prevenção secundária (caso o estudo houvesse incluído ambas as populações de prevenção primária e secundária, porém com dados relativos à mortalidade para cada grupo, esse estudo poderia ser incluído).
b) Estudo de pacientes chagásicos com TV tratada clinicamente.
c) Registros clínicos, desde que houvesse dados sobre mortalidade na prevenção secundária.

Após discussão entre os autores, decidiu-se excluir resumos apresentados exclusivamente em congressos, uma vez que foram considerados menos confiáveis

os dados relacionados a esse tipo de publicação. Não limitamos os estudos baseados no número de pacientes ou no tempo de seguimento.

As variáveis pré-selecionadas para extração dos estudos foram: mortalidade total; tempo de seguimento; idade média; FEVE; terapia medicamentosa e taxas de terapias apropriadas no grupo CDI.

A análise principal foi realizada utilizando-se como grupo-controle os pacientes com TV tratada com amiodarona, pois essa é a droga de escolha para prevenção da recorrência de TV em pacientes com cardiopatia estrutural[73,75], com evidências de benefícios mais pronunciados na cardiopatia chagásica[110]. A população inteira de tratamento medicamentoso foi utilizada em um segundo momento para análise de sensibilidade. Estudos sem dados separados de mortalidade para cada antiarrítmico foram excluídos.

4.1.6 Análise estatística

Toda a análise estatística foi realizada no *Comprehensive Meta-Analysis Software*, versão 2.22064. As taxas de eventos (porcentagem com intervalo de confiança de 95% nos grupos CDI ou drogas antiarrítmicas) foram agrupadas e comparadas indiretamente utilizando-se o modelo de efeitos aleatórios (*random-effects modeling*). Valor de $p < 0,05$ foi considerado estatisticamente significativo.

Uma questão central da análise estatística foi a grande variação do tempo de seguimento entre os diferentes estudos e entre as populações CDI e amiodarona. A primeira solução seria explorar o tempo de seguimento como fonte de heterogeneidade e a segunda opção seria ajustar a taxa de mortalidade por pacientes-ano. Após discussão exaustiva com os colaboradores, optou-se pelo ajuste da mortalidade geral, que fornece comparação mais real das taxas de eventos entre os grupos. Para utilizar as taxas ajustadas, teve-se que considerar que o risco de morte é constante durante o tempo[111].

A estatística I^2 foi utilizada para avaliar a heterogeneidade. A exploração das fontes de heterogeneidade foi realizada com base em metarregressão (*method of moments*) e as variáveis preestabelecidas foram a idade média, FEVE, uso de inibidores da enzima conversora de angiotensina (IECA) e de betabloqueadores. O teste de Egger foi empregado para avaliar vieses de publicação.

4.2 Estudo 2

4.2.1 Caracterização do estudo

Em 2015 publicamos o primeiro relato de punção epicárdica guiada por laparoscopia (APENDICE B)[22], técnica que visava estabelecer uma alternativa mais simples e menos agressiva que a janela subxifoide cirúrgica, para abordagem das arritmias ventriculares nos pacientes portadores de cardiopatia chagásica e organomegalia intra-abdominal (principalmente megacólon). Entretanto, não há, até o momento, descrição da eficácia e segurança da técnica em uma série de casos. Neste estudo, foram avaliadas a eficácia e as taxas de complicações dos primeiros casos (11, no total) de acesso epicárdico guiado por laparoscopia no HC-UFMG.

4.2.2 Seleção dos pacientes

Foram incluídos consecutivamente os pacientes submetidos a acesso epicárdico guiado por laparoscopia no HC-UFMG desde a sua descrição inicial até setembro de 2018. Todos os pacientes assinaram o termo de consentimento livre e esclarecido previamente ao procedimento. Os dados foram coletados e armazenados no banco de dados de TV da instituição.

A indicação da laparoscopia foi realizada pelo operador e baseou-se na dilatação de órgãos intra-abdominais (10 casos de megacólon e um caso de hepatomegalia), ocupando a região epigástrica com risco de perfuração de vísceras.

4.2.3 Procedimento de ablação

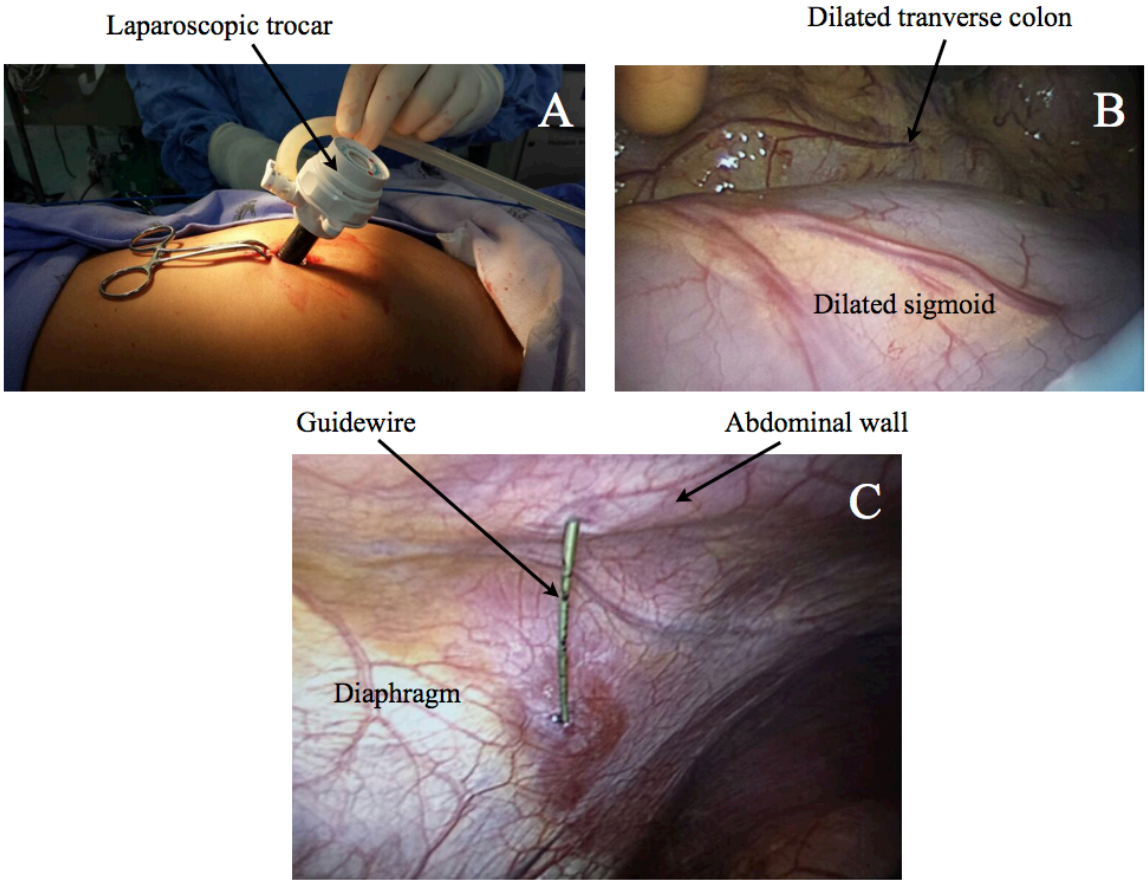
Todos os pacientes foram submetidos à ablação sob anestesia geral e com monitorização invasiva da pressão arterial. Foram utilizados cateteres terapêuticos irrigados e sistemas de mapeamento eletroanatômico comercialmente disponíveis.

Inicialmente foram obtidos acessos venosos femorais e cateteres diagnósticos inseridos no seio coronário e VD. Não foram realizadas tentativas de indução das arritmias nessa fase do procedimento.

Em sequência, um trocar era inserido na cicatriz umbilical através de incisão dos planos da parede abdominal (não foi realizada punção às cegas pelo risco de

lesão dos órgãos intra-abdominais). Através do trocar, uma ótica laparoscópica de 30º era inserida na cavidade peritoneal para permitir punção sob visão da superfície diafragmática e posteriormente do espaço pericárdico (FIG. 13). Durante toda a fase da laparoscopia, atenção especial era empregada para manutenção da pressão intra-abdominal inferior a 9 mmHg.

FIGURA 13 – Sequência da punção epicárdica guiada por laparoscopia

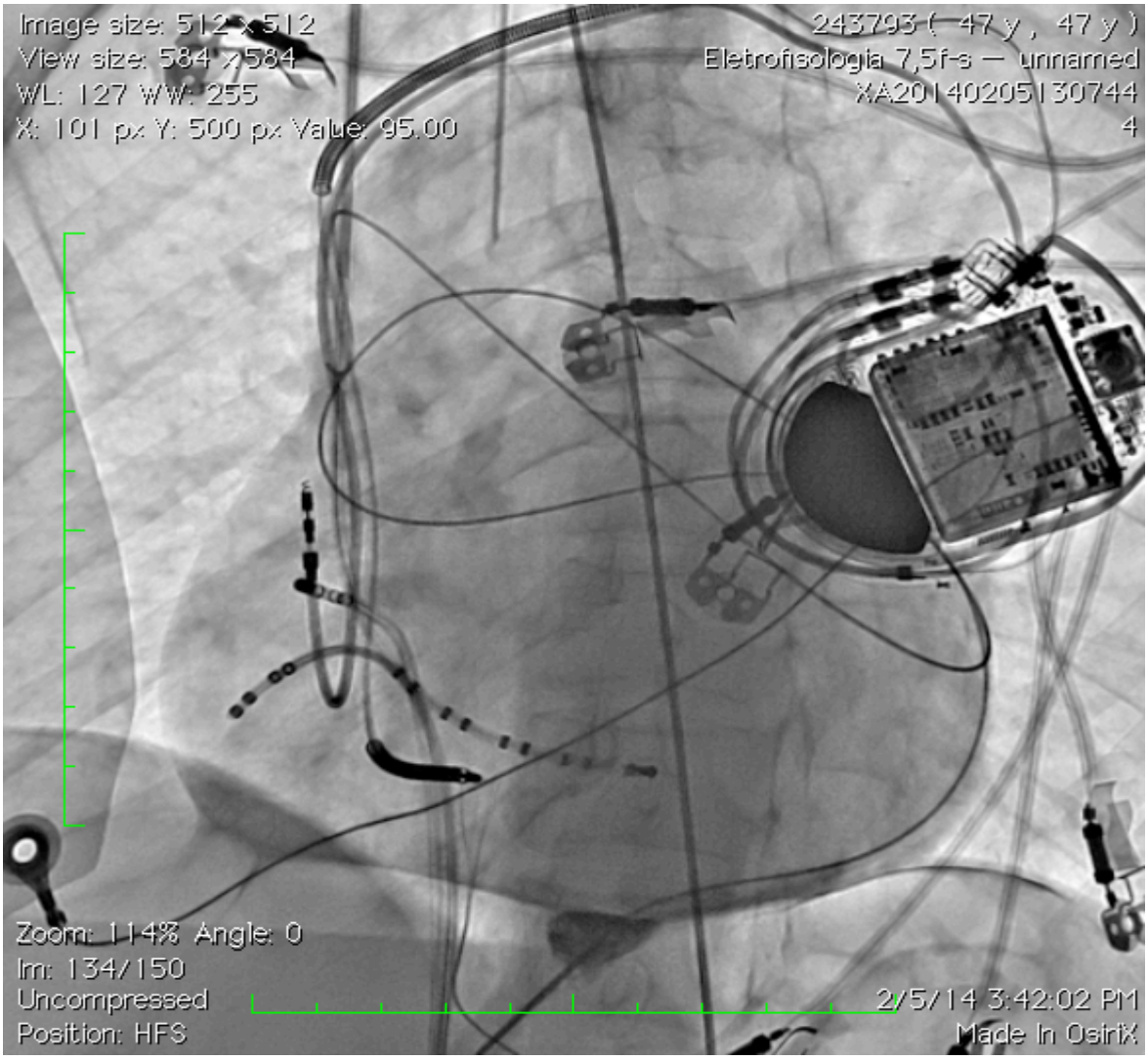


A) inserção do trocar. B) Imagem laparoscópica intra-abdominal com dilatação dos cólons transverso e sigmoide. C) fio guia metálico atravessando a parede abdominal e o diafragma.
Laparoscopic trocar = trocar laparoscópico; *dilated transverse colon* = cólon transverso dilatado; *dilated sigmoid* = sigmoide dilatado; *guidewire* = fio-guia; *abdominal wall* = parede abdominal; *diaphragm* = diafragma.
Fonte: Carmo *et al.*[22].

Após a inserção do fio-guia no espaço pericárdico (FIG. 14) e passagem de um introdutor vascular, o pneumoperitônio era desfeito e retirados a ótica e o trocar. Após o término da fase laparoscópica, a ablação propriamente dita era iniciada com o mapeamento eletroanatômico e ablação por radiofrequência (potência 40-50 W e temperatura de 43ºC), com o objetivo de eliminação mais ampla possível do substrato

arritmogênico e não indução de arritmias monomórficas ao final do procedimento. Ablações endocárdicas adicionais eram realizadas sempre que necessário ou tolerado, com atenção especial para o tempo total de procedimento, visando minimizar as complicações. Sempre que o acesso endocárdico era estabelecido (maioria por acesso transeptal), o tempo de coagulação total (TCA) era mantido >350 s.

FIGURA 14 – Imagem fluoroscópica de fio-guia longo no espaço pericárdico



Fonte: do autor.

4.2.4 Análise estatística

Como o presente estudo trata-se de uma série de casos, não foram feitas comparações estatísticas. Para caracterização da amostra, utilizou-se estatística

descritiva. As variáveis contínuas foram expressas como média ± desvio-padrão ou mediana e intervalo interquantil (Q1 e Q3).

5 RESULTADOS

5.1 Estudo 1: artigo publicado no periódico *International Journal of Cardiology* (APÊNDICE A)

Implantable Cardioverter-Defibrillator in Chagas Heart Disease: A systematic review and meta-analysis of observational studies

Carmo *et al*., ICD and Chagas cardiomyopathy

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Disclosure: Carlos A. Morillo: Grants CIHR, WHO-TDR, Boston Scientific, Merck. Consultant: Biotronik, Boston Scientific.

Keywords: Chagas heart failure; Implantable Cardioverter-defibrillator; ventricular tachycardia; amiodarone; antiarrhythmic drugs.

Structured abstract

Background: In patients with Chagas cardiomyopathy (ChCM), sudden cardiac death (SCD) is the leading cause of mortality. Implantable cardioverter-defibrillator (ICD) is a well-established therapy for secondary prevention in patients with structural heart disease, but there are conflicting opinions regarding its efficacy and safety in patients with ChCM. The aim of this meta-analysis was to assess the efficacy of the ICD for secondary prevention in patients with ChCM, comparing mortality as the primary outcome of patients treated with ICD with those treated with amiodarone. **Methods:** We systematically searched five databases for studies assessing mortality outcomes in patients with ChCM and sustained ventricular tachycardia (VT) treated with ICD implantation or with amiodarone. The results of studies were pooled using random-effects modeling. **Results:** There was no randomized clinical trial comparing efficacy of ICD versus medical treatment in patients with ChCM. Six observational studies were included for qualitative and quantitative analysis, totalizing 115 patients in amiodarone group and 483 patients in ICD group. The mortality outcome in the ICD population was 9.7 per 100 patient-years of follow-up (95% CI 5.7-13.7) and 9.6 per 100 patient-years in the amiodarone group (95% CI 6.7-12.4) (p=0.95). Meta-regression did not show any association with LV ejection fraction (p=0.32), age (p=0.44), beta-blocker (p=0.33) or angiotensin-converting enzyme inhibitors (p=0.096) usage. **Conclusion:** The best available evidence derived from small observational studies suggests that ICD therapy in secondary prevention of sudden death (VT or resuscitated SCD) is not associated with lower rate of all-cause mortality in patients with ChCM. Randomized controlled trials are direly needed to finally answer this question.

Introduction

The ICD is an accepted and effective therapy for prevention of sudden cardiac death (SCD) in patients with structural heart disease. Indications are derived from three sources of data: randomized clinical trials (RCTs), observational data from cohorts of high-risk patients with less common diseases and from guidelines and expert opinion on potential benefit for clinical conditions or specific circumstances in which data are limited or uncertain[1]. ICD benefit has been clearly established in patients with both ischemic and non-ischemic cardiomyopathies who have survived a cardiac arrest. Although primary prevention of SCD has also been supported by multiple large RCT's, notably in patients with ischemic cardiomyopathy, a recent study[2] did not show a mortality benefit of the ICD for primary prophylaxis in patients with nonischemic cardiomyopathy, raising some concerns about generalization of the results obtained for a specific cardiomyopathy.

In patients with ChCM, SCD is the leading mortality cause, accounting for nearly two-thirds of all deaths[3] and ICD implantation has emerged as a therapeutic strategy for both primary and secondary prevention of SCD. Some reports suggest similar

benefits compared to ischemic cardiomyopathy[4,5]. However, serious economic restrictions to a wider usage have been identified, limiting the population that can potentially benefit from ICDs[6]. Additionally, conflicting opinions regarding the efficacy of the ICD in ChCM have been reported[7-9].

The purpose of this systematic review was to assess the efficacy of the ICD for secondary prevention in patients with ChCM, comparing mortality as the primary outcome of patients treated with ICD with those treated medically.

Methods

Protocol and registration

The methodology of this review was previously registered in the PROSPERO database (CRD42015027266) and the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) checklist was used to perform this systematic review.

Eligibility criteria

All publications including patients with ChCM and an ICD implanted for secondary prevention of SCD or ChCM and ventricular tachycardia (VT) treated medically were included. Initially, we searched for RCTs with more than one year of follow up. No RCT was identified after three preliminary searches. Based on the above, the protocol was modified and all clinical registries and observational studies regardless of follow-up duration were included. The final search was performed on January 2017 and combined with the previous literature search.

Information sources and Search

A comprehensive literature search was conducted in LILACS (Latin American and Caribbean Health Science Literature), MEDLINE, EMBASE, Cochrane review of systematic interventions and the Cochrane central register of controlled trials (CENTRAL) using the following MeSH search terms: “Chagas disease” AND “defibrillator” OR “ventricular tachycardia”, until January 2017. No language restrictions were applied to the search. References of the retrieved articles were reviewed for other relevant studies. The website www.theheart.org was used to search for related presentations at any of the major scientific meetings. Experts were contacted to identify additional potential studies not identified by database searches.

Study Selection

All publications identified were independently reviewed for inclusion using predetermined criteria. The inclusion criteria were: 1 - studies of patients with ChCM and ICD implanted for secondary prevention (studies with both primary and secondary prevention strategies were allowed if mortality data were available for both groups). 2 - Studies of patients with ChCM and medically treated VT. 3 - Clinical registries. We excluded abstract presentations at national and international meetings. Taking into account the limited number of studies, there were no exclusions based on follow-up duration or number of patients included.

The following data were extracted from reports: all-cause mortality, follow-up, mean age, left ventricular ejection fraction (LVEF), medical therapy and appropriate therapy in patients with ICD.

For patients with ChCM and medically treated VT, as amiodarone is the drug of choice for prevention of recurrence of VT and structural heart disease[10,11], we used initially data from patients receiving only amiodarone and data from the entire population was used for sensitivity analysis. We excluded studies without data related with antiarrhythmic drugs.

Statistical Analysis

The event rates (percentages with 95% confidence intervals [CI]) in each group (ICD or antiarrhythmic drugs) were pooled and indirectly compared using random-effects modeling (Comprehensive Meta-Analysis Software, version 2.2.064). A P-value < 0.05 was statistically significant. Due to a wide range of follow-up among different studies, we adjusted the rate of event per patient-years, assuming a constant hazard of death during follow-up. In addition, sensitivity analysis was performed including patients treated with amiodarone and all other antiarrhythmic drugs compared to ICD treated patients, to explore robustness of the results in the presence of other antiarrhythmic drugs. Heterogeneity was assessed using I^2 statistic. Exploration of sources of heterogeneity was performed with meta-regression analysis (method of moments). Egger's test was used to evaluate publication bias[12].

Results

Literature search

The study selection process is shown in figure 1. We identified 285 eligible unique records. Two hundred and eight were excluded based on title and 19 were excluded based on the abstract, the remaining 58 articles underwent full-text analysis. After detailed analysis of the above, 52 studies were excluded, and the remaining six papers were included for qualitative and quantitative analysis. The present study included 143 patients treated medically (115 patients on amiodarone) and 483 patients with ICD implanted for secondary prevention of SCD.

Study quality

As previously stated, there was no RCT comparing efficacy of ICD versus medical treatment in patients with ChCM. In this setting, we used only non-randomized studies. Study quality was assessed using the Newcastle-Ottawa scale. The only study that included a population of Chagas disease patients treated medically in comparison to ICD patients was published by Gali et al, and was classified as good quality based on the Newcastle-Ottawa scale. Overall, the quality of studies was poor (table 1).

Study characteristics

Two studies evaluated the efficacy of antiarrhythmic drugs for treatment of sustained ventricular tachycardia in patients with ChCM[13,14]. Leite *et al.*[14] reported data on medical treatment of 115 patients with ChCM and VT (78 patients with sustained VT, 37 patients with symptomatic NSVT and sustained VT induced at baseline EPS). All patients received amiodarone or sotalol and the treating physician determined the choice between both drugs. However, when sotalol was used first and failed to render VT noninducible or was not tolerated, EPS was repeated after an amiodarone loading dose was administered. At discharge, 87 patients were taking amiodarone only, 25 sotalol only and 3 patients were taking a combination of amiodarone and sotalol or mexiletine. Total mortality was not significantly different: 40.2%, 36.0% and 33.3% respectively for amiodarone, sotalol or combination of amiodarone with sotalol or mexiletine (mean follow-up of 52 months). In this study, the population of patients only on amiodarone was used for the main analysis and the whole population was used for sensitivity analysis.

Cardinalli-Neto[15] reported data from a retrospective, single-center series of 90 patients with ChCM and ECG documented sustained and hemodynamically unstable VT. The aim was to determine predictors of all-cause mortality. Mean follow-up was

25.2 ± 19.3 months. Malignant arrhythmia (defined as ECG documented sustained VT with hemodynamic instability or VF;) was observed in 64 (71%) patients. There were 31 (34%) deaths during the study period. The median number of shocks per patient was 4.5. Multivariate analysis performed by Cox proportional hazards model, identified number of shocks (> 4 episodes) per patient by day 30 as the only independent predictor of all-cause mortality (HR 1.86, 95% CI 1.21 to 2.86). Mean life expectancy was 2.1 months (CI 0.79 to 3.4 months) in patients receiving > 4 shocks by day 30, and 46.5 months in patients receiving up to four shocks by day 30 (p = 0.0005).

Di Toro *et al.*[16] published an updated industry-sponsored multicenter registry. A previous report[17] of this registry included 89 patients followed for a mean of 12 ± 7 months (range 1 – 30). In this updated report, 148 patients followed for a mean of 12 ± 7 months were included (range 1 – 45). The aim was to determine mortality rate and risk factors of all-cause 1-year mortality in primary and secondary prevention patients with ChCM. Twelve patients (8.1%) had a primary prevention indication and 136 (91.9%) a secondary prevention indication; 13 (9.5%) resuscitated SCD; 87 (64%) spontaneous sustained VT and 36 (26.5%) syncope or near-syncope with inducible VT during EPS. Sixty-three patients (42.5%) had appropriate ICD therapies and 15 patients (10.2%) died (1 in primary prevention group and 14 in secondary prevention group). The multivariate Cox regression analysis identified age > 65 years (HR 2.85, 95% CI 1.77 – 3.92) and LVEF < 30% (HR 2.68, 95% CI 1.57 – 3.79) as strong independent predictors of mortality. Eight patients with LVEF < 30% and age > 65 died during follow-up (HR 7.34, 95% CI 5.82 – 8.82).

Martinelli and colleagues[18] reported data from a single-center retrospective cohort of patients with ChCM and ICD implanted for secondary prevention of SCD. This study reported all-cause mortality and appropriate ICD shock therapy rates and assessed the predictive value of a number of clinical variables. One hundred and sixteen patients were included; 82.7% in NYHA class I – II, and a mean LVEF of 42.4%. Indication for ICD was resuscitated VF or VT in 21 patients (18.1%) and symptomatic sustained VT in 95 patients (81.9%). Of these, 64 patients (55.2%) underwent an EPS and had hemodynamically unstable VT or VF induced by EPS. During a mean follow-up of 45 ± 32 months, 31 (26.7%) deaths occurred; annual mortality rate of 7.1%. Multivariate Cox proportional hazard model identified NYHA class III (HR 3.09, 95%CI 1.37 to 6.96) as a strong independent predictor. LVEF (HR 0.92 95% CI: 0.94 – 0.99) and a low rate of cumulative right ventricular pacing less than 40% of the time (HR

0.23, 95 CI 0.11 – 0.49) were predictors of better survival. Seven hundred and fifty VT/VF episodes in 58 patients (50% of the cohort) were recorded, and 339 appropriate shocks (5.8 shocks per patients) were reported. Inappropriate anti-tachycardia pacing or shocks were documented in only 4 and 18 patients (3.6 shocks/patient) respectively.

Barbosa *et al.*[4] retrospectively compared clinical outcomes in patients with and without ChCM after ICD implantation for secondary prevention of SCD. On hundred and thirty-five patients were followed for a median of 266 days. Of these, 65 (48%) patients had ChCM, 22 (16.3%) ischemic cardiomyopathy, 28 (20.7%) non-ischemic dilated cardiomyopathy, 20 (15%) other cardiomyopathies. Patients with ChCM were more likely to be using amiodarone (92% vs 61.2%, p = 0.01) and less likely to be on beta-blockers (54% vs 83.7%, p = 0.001). The median LVEF was 37% in the ChCM group and 32.5% in non-Chagas group (p = 0.99). Of the 65 patients with Chagas, 20 patients (30%) had LVEF ≥ 45%. There were 8 deaths in each group (12.3 vs 11.4%, respectively for ChCM and non-Chagas cardiomyopathy, p = 0.82). Appropriate ICD therapy occurred in 32 (49.2%) ChD and in 19 (27.1%) non-ChD patients (P = 0.005). ChCM had a 2-fold increase in the he risk of appropriate therapy (HR 2.2; 95% CI, 1.2–4.3, P = 0.02) and appropriate therapy or death (HR 2.2; 95% CI, 1.2–4.2, P = 0.01) in multivariate analysis.

Gali and colleagues[13] published the only observational study that compared efficacy of ICD on secondary prevention of mortality compared to medical therapy alone, using an historical control group treated with amiodarone and enrolled before ICD therapy was available at that Centre. There were 76 patients in the ICD group and 28 patients in the amiodarone group. All ICD group patients received amiodarone and both groups had similar baseline characteristics, except for higher use of beta-blockers in the ICD group (90% vs 17%) (p < 0.0001). During a mean follow-up of 33 ± 16 months in the ICD group and 35 ± 17 months for control group, there was a 72% relative risk reduction in all-cause mortality of (HR 0.28; 95% CI; 0.11-0.72; p = 0.007) among ICD-treated patients. Subgroup analysis identified patients with LVEF < 40% as those with the greatest survival benefit from the ICD (p = 0.01), not reaching a significant difference in those with a LVEF ≥ 40% (p = 0.15). Moreover, the number of appropriate therapy was very high, occurring in 72% of patients, with similar rates of interventions across patients with LVEF < 40% or ≥ 40%. In multivariate analysis, only LVEF < 40% was associated with increased risk of mortality (HR 6.63; 95% CI, 2.12-20.71; p = 0.001).

Main characteristics of each study's population and all-cause mortality for secondary prevention group are shown in table 2.

Mortality Outcomes

Mortality outcomes for each population are depicted in figure 2. Pooled data analysis did not show any difference in mortality outcomes between ICD and amiodarone treatment groups. The mortality outcome in ICD population was 9.7 per 100 patient-years of follow-up (95% CI 5.7-13.7) and 9.6 per 100 patient-years of follow-up in amiodarone group (95% CI 6.7-12.4) (p=0.95).

Sensitivity analysis including amiodarone plus other antiarrhythmic drugs, available in Leite *et al* study, showed a similar result in mortality rate for ICD group (9.7 per 100 patient-years; 95% CI 5.7-13.7) when compared to amiodarone plus other antiarrhythmic drugs group (9.3 per 100 patient-years; 95% CI 6.8-11.7, p=0.85). To determine heterogeneity in secondary prevention studies, meta-regression was performed and did not show any association with mean age (p=0.43), LV ejection fraction (p=0.32), ACEI (p=0.096) or beta-blocker therapy (p=0.33).

Publication bias was assessed by the Egger's test that yielded a negative result (p=0.11).

Discussion

The main finding of this meta-analysis was that ICD-based strategy was not associated with a lower mortality compared to amiodarone for treatment of ventricular arrhythmias in patients with ChCM. Even though lack of evidence from RCTs limited our ability to draw precise conclusions.

ICD adjusted mortality had marked variation among studies, ranging from 4.8 per 100 patient-years in Gali' study to 16.8 in Barbosa' study. The causes for this wide range of adjusted mortality cannot be fully explained, but they may include lack of ICD programing standardization, different population risk profile and supplementary therapy driven to suppress ventricular arrhythmia.

Although initial studies did not find an increased incidence of ICD therapies in Chagas disease[17], subsequent studies showed that a distinct characteristic of ChCM patients receiving an ICD for secondary prevention of sudden death is that VT/VF is earlier and more frequent in ChCM compared to patients with other cardiomyopathies particularly ischemic[4,18,19] and appropriate ICD therapies (shocks & ATP) delivered by

the ICD may impair quality of life[11,20] and, additionally, may increase mortality[21-23]. Therefore, a high burden of ICD therapies can offset the benefit of VT reversion, adding complexity to the management of ventricular arrhythmias in ChCM.

ICD programming is another factor closely related to the high burden of ventricular arrhythmias in ChCM. On one hand reports of SCD in patients with ChCM and preserved systolic left ventricular function[24] emphasize the importance of aggressive arrhythmia treatment, on the other hand, due to the high burden of ventricular arrhythmia, a high-rate zone or delayed therapy could potentially reduce the incidence of inappropriate therapies and all-cause mortality, as previously demonstrated for both ischemic and nonischemic cardiomyopathies[25]. We did not have information on ICD programming in our study and therefore cannot provide any further insight on this issue.

It is worth emphasizing that medical treatment based on Guidelines for heart failure in cardiomyopathies was suboptimal in the population included in this meta-analysis. Even though meta-regression did not show any significant findings, it may be due to lack of power. Interestingly, the lowest mortality was observed in ICD treated patients in Gali' study, the population with the highest usage of beta-blocker.

International Guidelines have limited discussion regarding ICD implantation in ChCM. The 2012 ACCF/AHA/HRS focused update incorporated into guidelines for device-based therapy of cardiac rhythm abnormalities[26] states that ICD implantation is reasonable for patients with Chagas disease (level of evidence C) with no comments on primary or secondary prevention strategies nor on disease severity. More recently, the 2015 Guidelines from European Society of Cardiology[27] recommend that ICD should be considered in patients with ChCM and LVEF < 40% (level of evidence C), primarily based on results from Gali *et al.*[13], but, as the American Guideline, there are no comments on primary *versus* secondary strategies. Our findings suggest that the recommendation of ICD implantation for secondary prevention of SCD in ChCM should be reassessed and RCTs are direly needed to provide high quality evidence.

Regarding amiodarone therapy, some investigators advocate the use of this drug because, in addition to its antiarrhythmic properties, there may be potential anti-*Trypanosoma cruzi* activity[28,29]. Notwithstanding, recent studies have not confirmed this potential trypanocidal effect of amiodarone assessed by *T.* cruzi DNA detection rates by PCR in spite of a potentially significant reduction in clinically relevant hard outcomes[30.31].

Based on our results and on ethical issues of withholding ICD implantation in patients presenting with sustained VT or SCD, efforts should be employed in evaluating the role of optimal ICD programming and suppression of ventricular arrhythmia, either by medical therapy or catheter ablation, aiming to reduce mortality in patients with ChCM and malignant ventricular arrhythmias.

The limitations of these analyses include lack of properly designed RCTs and the selection bias associated with observational studies. When we initiated the search process for the present meta-analysis we were unable to identify any RCTs comparing ICD to amiodarone treatment in patients with ChCM. This observation led us to include all observational studies that evaluated ICD therapy or amiodarone for secondary prevention or treatment of VT. Our meta-analysis is also limited to determine the role of ICD programming and additional therapies, such as catheter ablation, designed to reduce the recurrence of ventricular arrhythmias.

Conclusion

The best available evidence derived from small observational studies suggests that ICD therapy in secondary prevention of SCD (VT or resuscitated SCD) is not associated with a lower rate of all-cause mortality in patients with Chagas cardiomyopathy. Randomized controlled trials are direly needed to finally answer this question.

References

1. Myerburg RJ, Reddy V, Castellanos A. Indications for implantable cardioverter-defibrillators based on evidence and judgment. J Am Coll Cardiol. 2009; 54(9):747-63.

2. Køber L, Thune JJ, Nielsen JC, Haarbo J, Videbæk L, Korup E, *et al*. Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure. N Engl J Med. 2016; 375(13):1221-30.

3. Nunes MC, Carmo AA, Rocha MO, Ribeiro AL. Mortality prediction in Chagas heart disease. Expert Rev Cardiovasc Ther. 2012; 10(9):1173-84.

4. Barbosa MP, da Costa Rocha MO, de Oliveira AB, Lombardi F, Ribeiro AL. Efficacy and safety of implantable cardioverter-defibrillators in patients with Chagas disease. Europace. 2013; 15(7):957-62.

5. Dubner S, Valero E, Pesce R, Zuelgaray JG, Mateos JC, Galvão Filho S, *et al*. A Latin American registry of implantable cardioverter defibrillators: the ICD-LABOR study. Ann Noninvasive Electrocardiol. 2005; 10(4):420-8.

6. Muratore CA, Batista Sa LA, Chiale PA, Eloy R, Tentori MC, Escudero J, *et al*. Implantable cardioverter defibrillators and Chagas' disease: results of the ICD Registry Latin America. Europace. 2009; 11(2):164-8.

7. Rassi A, Jr. Implantable cardioverter-defibrillators in patients with Chagas heart disease: misperceptions, many questions and the urgent need for a randomized clinical trial. J Cardiovasc Electrophysiol. 18. United States. 2007, p. 1241-3.

8. Bestetti R, Cardinalli-Neto A. Implantable cardioverter defibrillator therapy for patients with chronic Chagas' disease: a randomized trial may not be necessary in high-risk patients. Europace. 11. England. 2009, p. 537.

9. Barbosa MP, Rocha MO, Lombardi F, Ribeiro AL. ICDs in Chagas heart disease: the standard treatment for secondary prevention of sudden death. Europace. 15. England. 2013, p. 1383-4.

10. Sim I, McDonald KM, Lavori PW, Norbutas CM, Hlatky MA. Quantitative overview of randomized trials of amiodarone to prevent sudden cardiac death. Circulation. 1997; 96(9):2823-9.

11. Connolly SJ, Dorian P, Roberts RS, Gent M, Bailin S, Fain ES, *et al*. Comparison of beta-blockers, amiodarone plus beta-blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators: the OPTIC Study: a randomized trial. JAMA. 2006; 295(2):165-71.

12. Egger M, Smith GD. Bias in location and selection of studies. BMJ. 1998; 316(7124):61-6.

13. Gali WL, Sarabanda AV, Baggio JM, Ferreira LG, Gomes GG, Marin-Neto JA, *et al*. Implantable cardioverter-defibrillators for treatment of sustained ventricular arrhythmias in patients with Chagas' heart disease: comparison with a control group treated with amiodarone alone. Europace. 16. England. 2014, p. 674-80.

14. Leite LR, Fenelon G, Simoes A, Jr., Silva GG, Friedman PA, de Paola AA. Clinical usefulness of electrophysiologic testing in patients with ventricular tachycardia and chronic chagasic cardiomyopathy treated with amiodarone or sotalol. J Cardiovasc Electrophysiol. 2003; 14(6):567-73.

15. Cardinalli-Neto A, Bestetti RB, Cordeiro JA, Rodrigues VC. Predictors of all-cause mortality for patients with chronic Chagas' heart disease receiving implantable cardioverter defibrillator therapy. J Cardiovasc Electrophysiol. 18. United States. 2007, p. 1236-40.

16. di Toro D, Muratore C, Aguinaga L, Batista L, Malan A, Greco O, *et al.* Predictors of all-cause 1-year mortality in implantable cardioverter defibrillator patients with chronic Chagas' cardiomyopathy. Pacing Clin Electrophysiol. 2011; 34(9):1063-9.

17. Muratore C, Rabinovich R, Iglesias R, González M, Darú V, Liprandi AS. Implantable cardioverter defibrillators in patients with Chagas' disease: are they

different from patients with coronary disease? Pacing Clin Electrophysiol. 1997; 20(1 Pt 2):194-7.

18. Martinelli M, de Siqueira SF, Sternick EB, Rassi A, Jr., Costa R, Ramires JA, *et al*. Long-term follow-up of implantable cardioverter-defibrillator for secondary prevention in chagas' heart disease. Am J Cardiol. 110. United States: 2012 Elsevier Inc; 2012. p. 1040-5.

19. Rabinovich R, Muratore C, Iglesias R, Gonzalez M, Daru V, Valentino M, *et al*. Time to first shock in implantable cardioverter defibrillator (ICD) patients with Chagas cardiomyopathy. Pacing Clin Electrophysiol. 1999; 22(1 Pt 2):202-5.

20. Schron EB, Exner DV, Yao Q, Jenkins LS, Steinberg JS, Cook JR, *et al*. Quality of life in the antiarrhythmics versus implantable defibrillators trial: impact of therapy and influence of adverse symptoms and defibrillator shocks. Circulation. 2002; 105(5):589-94.

21. Larsen GK, Evans J, Lambert WE, Chen Y, Raitt MH. Shocks burden and increased mortality in implantable cardioverter-defibrillator patients. Heart Rhythm. 2011; 8(12):1881-6.

22. Villacastín J, Almendral J, Arenal A, Albertos J, Ormaetxe J, Peinado R, *et al*. Incidence and clinical significance of multiple consecutive, appropriate, high-energy discharges in patients with implanted cardioverter-defibrillators. Circulation. 1996; 93(4):753-62.

23. Ha AH, Ham I, Nair GM, Connolly SJ, Dorian P, Morillo CA, *et al*. Implantable cardioverter-defibrillator shock prevention does not reduce mortality: a systemic review. Heart Rhythm. 2012; 9(12):2068-74.

24. Sternick EB, Martinelli M, Sampaio R, Sampaio RC, Gerken LM, Teixeira RA, *et al*. Sudden cardiac death in patients with chagas heart disease and preserved left ventricular function. J Cardiovasc Electrophysiol. 2006; 17(1):113-6.

25. Moss AJ, Schuger C, Beck CA, Brown MW, Cannom DS, Daubert JP, *et al*. Reduction in inappropriate therapy and mortality through ICD programming. N Engl J Med. 2012; 367(24):2275-83.

26. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA, Freedman RA, Gettes LS, *et al*. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2013 ;61(3):e6-75.

27. Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, *et al*. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC)Endorsed by:

Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J. 2015.

28. Benaim G, Paniz Mondolfi AE. The emerging role of amiodarone and dronedarone in Chagas disease. Nat Rev Cardiol. 2012; 9(10):605-9.

29. Benaim G, Sanders JM, Garcia-Marchán Y, Colina C, Lira R, Caldera AR, *et al*. Amiodarone has intrinsic anti-Trypanosoma cruzi activity and acts synergistically with posaconazole. J Med Chem. 2006; 49(3):892-9.

30. Carmo AA, Rocha MO, Silva JL, Ianni BM, Fernandes F, Sabino EC, *et al*. Amiodarone and Trypanosoma cruzi parasitemia in patients with Chagas disease. Int J Cardiol. 2015; 189:182-4.

31. Morillo CA, Marin-Neto JA, Avezum A, Sosa-Estani S, Rassi A, Rosas F, *et al*. Randomized Trial of Benznidazole for Chronic Chagas' Cardiomyopathy. N Engl J Med. 2015.

Table 1. Newcastle-Ottawa scale quality of studies assessing implantable cardioverter-defibrillator (ICD) treatment in patients with Chagas cardiomyopathy. In this scale, stars are awarded such that the highest quality studies are awarded up to nine stars

Study	Selection	Comparability	Outcome
Leite 2003	*	--	*
Cardinalli-Neto 2007	*	--	**
Di-Toro 2011	*	--	**
Martinelli Filho 2012	**	--	**
Barbosa 2013	**	--	**
Gali 2014	****	**	***

Table 2. Main baseline clinical characteristics and all-cause mortality of patients with sustained ventricular tachycardia (VT) treated medically or with ICD

	Leite 2003 (n = 115)	**Gali 2014 (n = 28)**	**Cardinalli-Neto 2007 (n = 90)**	**Di Toro 2011 (n = 148)**	**Martinelli 2012 (n = 116)**	**Barbosa 2013 (65)**	**Gali 2014 (n = 76)**
Treatment group	Medical	Medical	ICD	ICD	ICD	ICD	ICD
Secondary prevention (%)	115 (100)	28 (100)	90 (100)	136 (91.9)	116 (100)	65 (100)	76 (100)
Mean age	52 ± 10	54 ± 10	59 ±11	60 ± 9.4	54 ± 10	56.7†	57 ± 11
Amiodarone (%)	87 (75.7)	28 (100)	90 (100)	93 (63)	90 (78)	46 (92)	69 (90)
Beta-blocker (%)	ND	5 (17)	37 (40)	73 (49)	38 (33)	27 (54)	69 (90)
ACEI/ARB (%)	79 (68)	26 (92)	ND	65 (44)	95 (82)	ND	67 (88)
Mean LVEF	49 ± 14	41 ± 10	47 ± 13	40.1 ± 11.3	42.4 ± 15.7	38.8†	39 ± 12
Follow-up (months)	52 ± 32	35 ± 17	25 ± 20	12 ± 7	45 ± 32	8.8†	33 ± 16
VT/VF (%)	ND	ND	64 (71)	63 (42.5)	58 (50)	32 (49.2)	52 (72%)
All-cause Mortality‡ (95% CI)	9.3 (6.2–12.4)	11 (3.8–18.2)	16.5 (10.7–22.4)	10.3 (4.9–15.7)	7.1 (4.6–9.6)	16.8 (5.2–28.4)	4.8 (1.8–7.8)

†Standard Deviation (SD) not reported. ‡100 patient-years. CI: Confidence Interval. ICD: Implantable Cardioverter-defibrillator.

Figure 1. PRISMA diagram showing the search strategy results and exclusion steps and reasons for the search using the MESH terms “Chagas disease” AND “Cardioverter - defibrillator” OR “ventricular tachycardia”

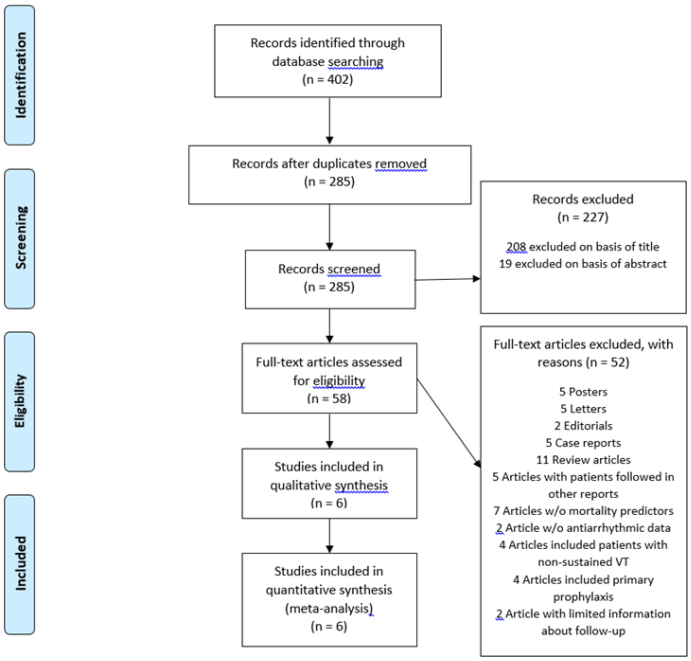
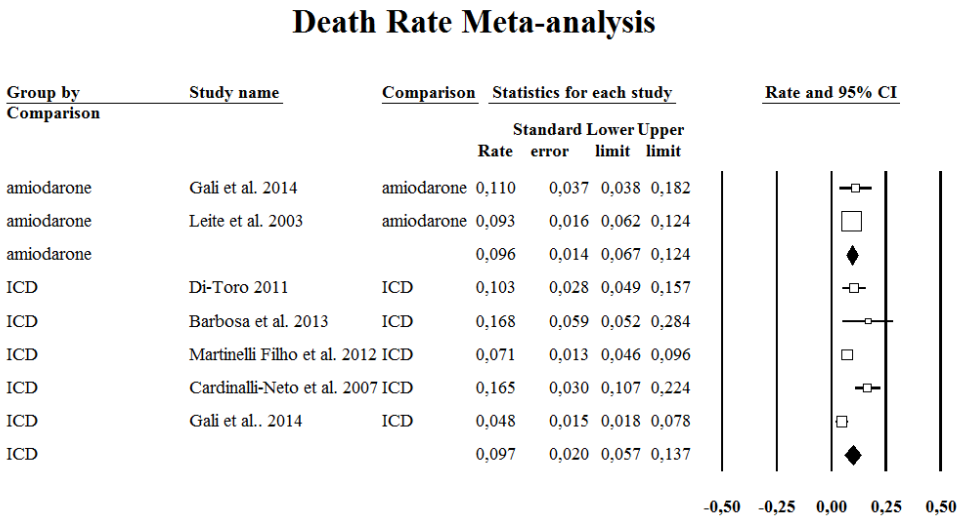


Figure 1

Figure 2. Forest plot showing event rate and 95% confidence interval for all-cause mortality for amiodarone and implantable cardioverter-defibrillator (ICD) therapies I^2 0% for amiodarone and 75% for ICD group (p=0.45 for difference between groups)



5.2 Estudo 2: artigo submetido ao periódico *Heart Rhythm*

Feasibility and safety of laparoscopic guided epicardial access for ventricular tachycardia ablation

Carmo - Laparoscopy and epicardial access

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Keywords: Ventricular tachycardia, epicardial ablation, laparoscopy

Abstract

Background: The usual approach to epicardial access in patients with Chagas cardiomyopathy and megacolon is surgical access to avoid bowel injury. However, there are concerns regarding patients safety in Chagas cardiomyopathy and expert opinions report prolonged mechanical ventilations and high mortality in patients with Chagas cardiomyopathy and megacolon. **Objective**: The aim of this study was to examine feasibility and complication rates for ventricular tachycardia ablation performed with laparoscopic guided epicardial access. **Methods**: This single-center study examined the complication rates of the first eleven cases of ventricular tachycardia (VT) ablation in patients with Chagas cardiomyopathy using laparoscopic guidance to access epicardial space. All eleven patients underwent epicardial VT ablation with laparoscopic guided epicardial access, and the resulting complications rates were compared with historical medical reports. **Results**: The main demographic features of this study's population were: mean age 63 ± 13 years, male 82% and median ejection fraction (EF) 31% (Q1=30% and Q3=46%). All patients were referred for ventricular tachycardia ablation due to failure in medical therapy. Laparoscopy was performed due to megacolon in ten patients and massive liver enlargement in one patient. Epicardial access was achieved in all patients. Complications included one severe cardiogenic shock during ablation, requiring mechanical assistance; one phrenic nerve paralysis; and, due to a low blood flow at the end of the procedure, for safety reasons, a drainage catheter was left in one patient and removed the following day. No intra-abdominal organ injury was observed and one only one death due to progressive heart failure was recorded, more than one month after the procedure while the patient was in the waiting line for a heart transplant. **Conclusion**: Laparoscopic guided epicardial access in the setting of ventricular tachycardia ablation and an enlarged intra-abdominal organ is a simple alternative to more complex surgical access and can be performed with low complication rates.

Introduction

Sudden death has been recognized as one of the most prominent features in Chagas disease since its initial description, and sustained ventricular tachycardia (VT) is the main cause of sudden death in this population[1,2]. Recently, with large-scale use of the implantable cardioverter-defibrillator (ICD) for prevention of sudden death in patients with chronic chagasic cardiomyopathy, recurrent VT has been increasingly observed, commonly appearing with electrical storms[3-5].

Ventricular tachycardia ablation is widely accepted as a first line therapy in patients with structural heart disease and ventricular tachycardia unresponsive to medical therapy[6]. Nevertheless, in Chagas cardiomyopathy, epicardial access is necessary in most cases due to a marked predominance of scar on epicardial surface[7], with intra-abdominal organ injury representing one of major issues when approaching the pericardial space[8], particularly in Chagas disease, because of its common association with megacolon.

One alternative to percutaneous subxiphoid approach, first described by Scanavacca et al.[9], is surgical pericardial window. However, there are concerns regarding patient safety in Chagas cardiomyopathy, a population subset with a high predisposition for malnutrition[10], and expert opinions report prolonged mechanical ventilations and high mortality in patients with Chagas cardiomyopathy and megacolon.

In 2015, we described the first case of laparoscopic guided percutaneous subxiphoid epicardial access[11] a simple alternative to surgical window, which can be performed in most Electrophysiology Laboratories. The present case series, examines the feasibility and safety of ventricular tachycardia ablation performed with laparoscopic guided epicardial access.

Methods

Patient population

The subjects included in this case series were consecutive patients with Chagas cardiomyopathy referred for ventricular tachycardia ablation and intra-abdominal organ enlargement (mostly megacolon) precluding the traditional percutaneous approach to epicardial access (Figure 1). All patients provided written informed consent for the ablation procedure. The patient data were prospectively collected in the VT database.

Ablation procedure

Ventricular tachycardia ablation was performed from January 2015 to September 2018. All patients underwent procedure under general anesthesia and with arterial line monitoring, using available commercial open-irrigated therapeutic catheters and tridimensional mapping systems. Initially, femoral vein access was obtained, and the catheters were placed in coronary sinus and right ventricle. After, a trocar was placed at umbilicus scar and a 30º optic laparoscope was inserted into the peritoneal cavity to allow direct puncture of the diaphragm surface and pericardial space (Video 1).

Once epicardial access has been obtained, both the optic laparoscope and trocar were withdrawn and programed ventricular stimulation was performed. If VT was hemodynamically stable, tachycardia was mapped and ablated. If VT was not stable, extensive substrate ablation was performed, as described elsewhere[12]. Additional endocardial ablation was performed when necessary or tolerated (attention was paid

to total procedure time, so as not to prolong it unnecessarily). When endocardial ablation was performed (always through transeptal access), total anticoagulation time was maintained >350 s. In all patients, a detailed epicardial voltage map was performed, using 3D mapping systems. Radiofrequency delivery was achieved with a commercial open irrigated-tip at a power of 40-50 W, seeking to achieve monomorphic VT non-inducibility at the end of the procedure.

Outcome assessments

All patients were followed up according to our standard of care after ventricular tachycardia ablation. After hospital discharge, all patients were seen in outpatient clinics, with defibrillator interrogations at least every 4 months.

Results

Demographic data are outlined in table 1. The mean age of our population was 63 ± 13 years, 82% were male and the median ejection fraction (EF) was 31% (Q1=30% and Q3=46%). Nine patients (82%) had New York Heart Association class III or IV heart-failure symptoms. Ten patients had an ICD previously implanted for secondary prevention of sudden death (the subject without ICD was referred for ablation of very frequent and symptomatic non-sustained ventricular tachycardia). Ten patients were referred for VT ablation due to electrical storm that proved to be refractory to drug therapy. In ten patients, laparoscopy was applied due to megacolon, while it was applied and in one patient due to hepatomegaly (Figure 2).

TABLE 1 DEMOGRAPHICS OF THE STUDY POPULATION

Age (Y)	63
Male gender (%)	82
NYHA	
I or II	2 (18)
III or IV	9 (82)
Ejection fraction (%)	
Median	31
First quartile	30
Third quartile	46
ICD	
Primary prevention	0
Secondary prevention	10 (91)
Chagas cardiomyopathy	11 (100)
Electrical storm	10 (91)
Megacolon	10 (91)
Hepatomegaly	1 (9)

Procedure data

Epicardial access guided by laparoscopy was achieved in all patients. Epicardial access was performed with large bore needle in eight patients[9] and using micropuncture technique in three patients[13]. Mean ablation procedural time was 279 ± 96 min. Seven patients (64%) received vasopressors during the procedure, with a mean infusion duration of 45 h (± 40 h).

One patient was receiving inotrope support even before procedure (waiting for heart transplantation). This patient underwent mechanical support with intra-aortic balloon counterpulsation (IAB) due to poor hemodynamic status.

In 9 patients extubation occurred at the end of procedure and in the remaining 2 patients on the next day.

Complications

Two periprocedure major complications were observed: one cardiogenic shock demanding mechanical support and one phrenic nerve paralysis, which was managed conservatively. In one patient, an epicardial drainage catheter was left due to a low flow of blood into the pericardium space at the end of the procedure. We considered that, due to megacolon, an urgent percutaneous pericardiocentesis would not be possible. The drainage catheter was removed 24 h after the procedure.

No in-hospital deaths were recorded, except for the patient waiting for a heart transplantation, who was transferred to another medical service and died of refractory heart failure.

Discussion

Recently, we performed a meta-analysis[14] to evaluate ICD implantation for secondary prevention of sudden death in Chagas cardiomyopathy. Although, there were no randomized studies for secondary prevention, pooled analysis of non-randomized studies showed no benefit of ICD in overall mortality in this population. This finding coupled with very high burden of ventricular arrhythmias[3-5] raises the hypothesis that arrhythmia control in Chagas disease is critical to improve survival, once shocks delivered by the ICDs may impair quality of life[15,16] and, additionally, may increase mortality[17-19]. Therefore, ablation strategies that actually prevent recurrence of VT or at least decrease the burden of ventricular arrhythmia are of utmost importance in Chagas cardiomyopathy.

Laparoscopic guided epicardial access was developed in our service, provided in 2015[11], to overcome the problem of megacolon and refractory VT in Chagas cardiomyopathy, most often requiring surgical window to access the epicardial surface.

As previously stated, this population often shows severe malnutrition[10] and serious concern regarding prolonged ventilation and high mortality in patients with Chagas cardiomyopathy and gastrointestinal injury (unpublished data). In addition, left lobe injury of the liver is a rare but well described complication of epicardial puncture[20].

Our initial experience in performing laparoscopy to avoid intra-abdominal organ injury shows that this procedure is safe and can be undertaken in most EP labs. In this small population with severe cardiomyopathy, the major complication rate was 18%, however, no complication was directly associated with laparoscopy in itself.

Large trials and registries[21,22] report major complication rates ranging from 8% to 10%. Nevertheless, in addition to known concerns when analyzing complication rates in small populations series, our population presented a severe cardiomyopathy with high mortality predicted by heart failure score models (Seattle Heart Failure model mortality of 31% in 1 year and 75.2 in 5 years) and complication rates are bigger when high risk patients undergo ablations for VT associated with structural heart disease[6].

Regarding laparoscopy procedure, low intra-abdominal pressure levels and removal of pneumoritoneum early in the procedure are likely key points to hemodynamic stability and attention to these steps must be paid. Moreover, careful placement of optical trocar must also be performed, due to the risk of organ injury caused by laparoscopy access.

Our case series cannot provide definitive information on whether laparoscopic guided epicardial access must replace the surgical subxiphoide window for patients with abdominal organ enlargement precluding traditional epicardial access. Nevertheless, our results encourage electrophysiologists to consider laparoscopic access, a simple technique that can be performed in many laboratories.

In conclusion, laparoscopic guided epicardial access for VT ablation is a feasible and safe alternative technique to reach the epicardial surface and can be easily employed in patients with VT and intra-abdominal organ enlargement.

References

1. Nunes MCP, Beaton A, Acquatella H, Bern C, Bolger AF, Echeverría LE, *et al.* Chagas Cardiomyopathy: An Update of Current Clinical Knowledge and Management: A Scientific Statement From the American Heart Association. Circulation. 2018; 138(12):e169-e209.

2. Benziger CP, do Carmo GAL, Ribeiro ALP. Chagas Cardiomyopathy: Clinical Presentation and Management in the Americas. Cardiol Clin. 2017; 35(1):31-47.

3. Barbosa MP, da Costa Rocha MO, de Oliveira AB, Lombardi F, Ribeiro AL. Efficacy and safety of implantable cardioverter-defibrillators in patients with Chagas disease. Europace. 2013; 15(7):957-962.

4. Martinelli M, de Siqueira SF, Sternick EB, Rassi A, Jr., Costa R, Ramires JA, *et al*. Long-term follow-up of implantable cardioverter-defibrillator for secondary prevention in chagas' heart disease. Am J Cardiol. 2012; 110:1040-1045. United States: Elsevier Inc.

5. Gali WL, Sarabanda AV, Baggio JM, Ferreira LG, Gomes GG, Marin-Neto JA, *et al*. Implantable cardioverter-defibrillators for treatment of sustained ventricular arrhythmias in patients with Chagas' heart disease: comparison with a control group treated with amiodarone alone. Europace. England. 2014; 16:674-680.

6. Cronin EM, Bogun FM, Maury P, Peichl P, Chen M, Namboodiri N, *et al.* 2019 HRS/EHRA/APHRS/LAHRS expert consensus statement on catheter ablation of ventricular arrhythmias. Heart Rhythm. 2019.

7. Soto-Becerra R, Bazan V, Bautista W, Malavassi F, Altamar J, Ramirez JD, *et al.* Ventricular Tachycardia in the Setting of Chagasic Cardiomyopathy: Use of Voltage Mapping to Characterize Endoepicardial Nonischemic Scar Distribution. Circ Arrhythm Electrophysiol. 2017; 10(11).

8. Killu AM, Friedman PA, Mulpuru SK, Munger TM, Packer DL, Asirvatham SJ. Atypical complications encountered with epicardial electrophysiological procedures. Heart Rhythm. 2013; 10(11):1613-1621.

9. Sosa E, Scanavacca M, d'Avila A, Pilleggi F. A new technique to perform epicardial mapping in the electrophysiology laboratory. J Cardiovasc Electrophysiol. 1996; 7(6):531-536.

10. Matsuda NM, Miller SM, Evora PR. The chronic gastrointestinal manifestations of Chagas disease. Clinics (Sao Paulo). 2009; 64(12):1219-1224.

11. Carmo AA, Miranda RC, Lacerda-Filho A, Ribeiro AL. Laparoscopic guided epicardial access. Heart Rhythm. 2015; 12(2):461-462.

12. Di Biase L, Santangeli P, Burkhardt DJ, Bai R, Mohanty P, Carbucicchio C, *et al*. Endo-epicardial homogenization of the scar versus limited substrate ablation for

the treatment of electrical storms in patients with ischemic cardiomyopathy. J Am Coll Cardiol. 2012; 60(2):132-141.

13. Gunda S, Reddy M, Pillarisetti J, Atoui M, Badhwar N, Swarup V, *et al.* Differences in complication rates between large bore needle and a long micropuncture needle during epicardial access: time to change clinical practice? Circ Arrhythm Electrophysiol. 2015; 8(4):890-895.

14. Carmo AAL, de Sousa MR, Agudelo JF, Ianni BM, Fernandes F, Sabino EC, *et al*. Implantable cardioverter-defibrillator in Chagas heart disease: A systematic review and meta-analysis of observational studies. Int J Cardiol. 2018; 267:88-93.

15. Connolly SJ, Dorian P, Roberts RS, Gent M, Bailin S, Fain ES, *et al*. Comparison of beta-blockers, amiodarone plus beta-blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators: the OPTIC Study: a randomized trial. JAMA. 2006; 295(2):165-171.

16. Schron EB, Exner DV, Yao Q, Jenkins LS, Steinberg JS, Cook JR, *et al.* Quality of life in the antiarrhythmics versus implantable defibrillators trial: impact of therapy and influence of adverse symptoms and defibrillator shocks. Circulation. 2002; 105(5):589-594.

17. Larsen GK, Evans J, Lambert WE, Chen Y, Raitt MH. Shocks burden and increased mortality in implantable cardioverter-defibrillator patients. Heart Rhythm. 2011; 8(12):1881-1886.

18. Villacastín J, Almendral J, Arenal A, Albertos J, Ormaetxe J, Peinado R, *et al*. Incidence and clinical significance of multiple consecutive, appropriate, high-energy discharges in patients with implanted cardioverter-defibrillators. Circulation. 1996; 93(4):753-762.

19. Ha AH, Ham I, Nair GM, Connolly SJ, Dorian P, Morillo CA, *et al.* Implantable cardioverter-defibrillator shock prevention does not reduce mortality: a systemic review. Heart Rhythm. 2012; 9(12):2068-2074.

20. Koruth JS, Aryana A, Dukkipati SR, Pak HN, Kim YH, Sosa EA, *et al.* Unusual complications of percutaneous epicardial access and epicardial mapping and ablation of cardiac arrhythmias. Circ Arrhythm Electrophysiol. 2011; 4(6):882-888.

21. Fox MC, Sircar M, Vaidya A, Katz JT, Lakdawala N. Interactive medical case. A patient with syncope. N Engl J Med. 2013; 369(7):e9.

22. Pothineni NV, Deshmukh A, Padmanabhan D, Kovelamudi S, Patel NJ, Badheka AO, *et al*. Complication rates of ventricular tachycardia ablation: Comparison of safety outcomes derived from administrative databases and clinical trials. Int J Cardiol. 2015; 201:529-531.

Figure 1: Radiographic appearance of the abdomen in a patient with megacolon at the beginning of the ablation procedure. Massive dilation of the sigmoid colon precludes safe traditional percutaneous approach to subxiphoid epicardial access

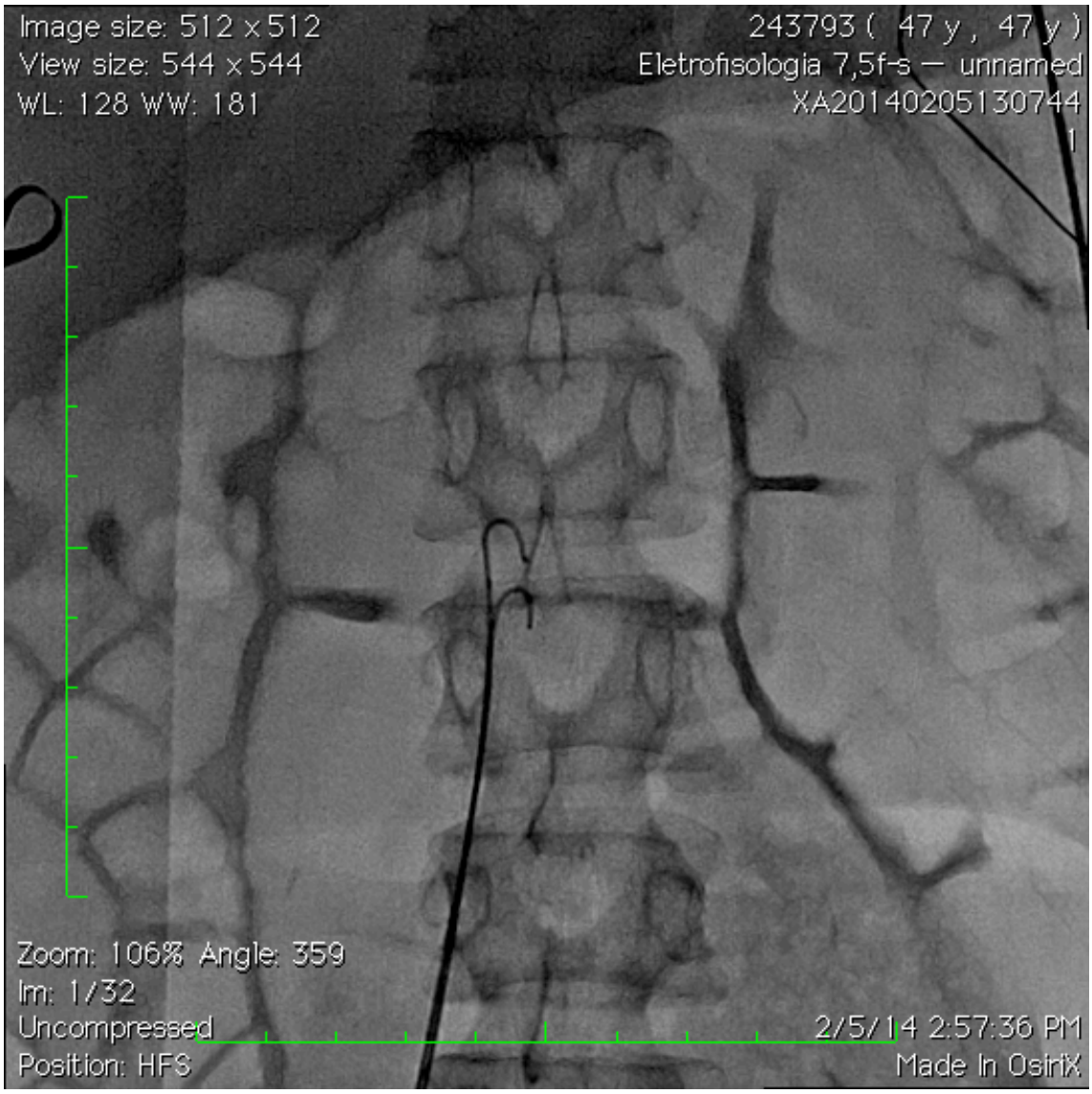
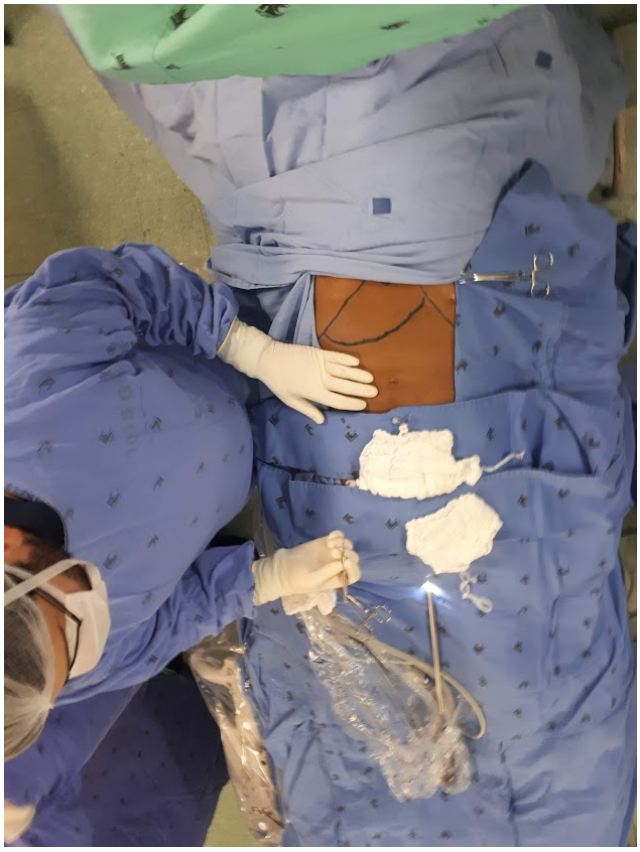


Figure 2: Pre-procedure image showing hepatomegaly (drawn line) with left lobe enlargement precluding traditional percutaneous subxiphoid epicardial access



6 LIMITAÇÕES DOS ESTUDOS

6.1 Limitações do estudo 1

A presente metanálise apresenta limitações inerentes à existência exclusiva de estudos observacionais, não randomizados, que podem levar a vieses de seleção das populações estudadas. Além disso, não há informações sobre a programação dos CDIs e as terapias adjuvantes para prevenção da recorrência das arritmias ventriculares, tal como ablação por cateter. Essas medidas podem ser importantes para o benefício do CDI na cardiopatia chagásica, doença altamente arritmogênica.

6.2 Limitações do estudo 2

Esta série de casos também é limitada pelo desenho do estudo. As taxas reais de complicações de novas terapias só podem ser avaliadas de maneira robusta com grandes registros e nossa análise em um pequeno grupo de pacientes não pode fornecer respostas definitivas.

7 IMPLICAÇÕES DOS ESTUDOS

7.1 Implicações do estudo 1

Esta metanálise proporciona uma nova perspectiva para a indicação do CDI na prevenção secundária no grupo de pacientes portadores de cardiopatia chagásica. As diretrizes internacionais[9,10] são unânimes na indicação de CDI para prevenção secundária em todos os pacientes portadores de cardiopatia estrutural. Entretanto, pode ser que, em algumas formas de cardiopatia, tal como a chagásica, o benefício da reversão das arritmias ventriculares possa ser ofuscado pelo alto número de terapias, sabidamente relacionado a um prognóstico adverso[90].

Uma questão que permanece aberta ao debate refere-se às questões éticas quanto à realização de um estudo prospectivo e randomizado sobre o implante de CDI na cardiopatia chagásica para prevenção secundária de morte súbita. De qualquer maneira, parece claro que todo o esforço deve ser empregado para prevenção da recorrência das arritmias ventriculares e para minimização das terapias eletrônicas desnecessárias.

7.2 Implicações do estudo 2

Nesta série de casos, o acesso epicárdico guiado por laparoscopia parece ser uma técnica associada a baixos níveis de complicações. A simplicidade da técnica e o baixo nível de tecnologia necessária são atrativos para a realização do procedimento. Os achados da metanálise no estudo 1 encorajam os especialistas a empreenderem esforços para o controle da recorrência da arritmia. E o acesso epicárdico guiado por laparoscopia pode tornar-se mais uma ferramenta para que se possa atingir esse objetivo.

8 CONCLUSÃO

A melhor evidência disponível derivada de pequenos estudos observacionais sugere que o CDI para prevenção secundária não está associado a baixas taxas de mortalidade total na cardiopatia chagásica.

O acesso epicárdico guiado por laparoscopia é uma alternativa efetiva e segura para abordagem das arritmias epicárdicas e pode ser empregado em pacientes com taquicardia ventricular e dilatação de órgãos intra-abdominais.

REFERÊNCIAS

1. Instituto Oswaldo Cruz. Nova tripanossomíase humana. Estudos sobre a morfologia e o ciclo evolutivo do *Schizotripanum cruzi* n.gen n. sp, agente etiológico de nova entidade mórbida do homem. Mem Inst. Oswaldo Cruz. 1909; 1:159-218.

2. Nunes MCP, Beaton A, Acquatella H, Bern C, Bolger AF, Echeverría LE, *et al.* Chagas Cardiomyopathy: An Update of Current Clinical Knowledge and Management: A Scientific Statement From the American Heart Association. Circulation. 2018; 138(12):e169-e209.

3. WHO. Chagas disease: control and elimination. In. Vol 17. http://apps.who.int/gb/ebwha/pdf files/WHA63/A6317-en.pdf: WHO; 2010:A63.

4. Ribeiro AL, Rocha MO. Indeterminate form of Chagas disease: considerations about diagnosis and prognosis]. Rev Soc Bras Med Trop. 1998; 31(3):301-314.

5. Schmunis GA, Yadon ZE. Chagas disease: a Latin American health problem becoming a world health problem. Acta Trop. 2010; 115(1-2):14-21.

6. Instituto Onwaldo Cruz. Cardiac form of American Trypanosomiasis. Mem.Inst.Oswaldo Cruz. 1922; 14:5-91.

7. Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, *et al*. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. N Engl J Med. 1986; 314(24):1547-1552.

8. Rochitte CE, Oliveira PF, Andrade JM, Ianni BM, Parga JR, Avila LF, *et al*. Myocardial delayed enhancement by magnetic resonance imaging in patients with Chagas' disease: a marker of disease severity. J Am Coll Cardiol. 2005; 46(8):1553-1558.

9. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, *et al*. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Heart Rhythm. 2018; 15(10):e73-e189.

10. Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, *et al*. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC)Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J. 2015.

11. Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med. 1997; 337(22):1576-1583.

12. Domanski MJ, Sakseena S, Epstein AE, Hallstrom AP, Brodsky MA, Kim S, *et al.* Relative effectiveness of the implantable cardioverter-defibrillator and antiarrhythmic drugs in patients with varying degrees of left ventricular dysfunction who have survived malignant ventricular arrhythmias. AVID Investigators. Antiarrhythmics Versus Implantable Defibrillators. J Am Coll Cardiol. 1999; 34(4):1090-1095.

13. Connolly SJ, Gent M, Roberts RS, Dorian P, Roy D, Sheldon RS, *et al.* Canadian implantable defibrillator study (CIDS) : a randomized trial of the implantable cardioverter defibrillator against amiodarone. Circulation. 2000; 101(11):1297-1302.

14. Kuck KH, Cappato R, Siebels J, Rüppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest : the Cardiac Arrest Study Hamburg (CASH). Circulation. 2000; 102(7):748-754.

15. Muratore CA, Batista Sa LA, Chiale PA, Eloy R, Tentori MC, Escudero J, *et al*. Implantable cardioverter defibrillators and Chagas' disease: results of the ICD Registry Latin America. Europace. 2009; 11(2):164-8.

16. Rassi A, Jr. Implantable cardioverter-defibrillators in patients with Chagas heart disease: misperceptions, many questions and the urgent need for a randomized clinical trial. United States, J Cardiovasc Electrophysiol. 2007; 18:1241-1243.

17. Bestetti R, Cardinalli-Neto A. Implantable cardioverter defibrillator therapy for patients with chronic Chagas' disease: a randomized trial may not be necessary in high-risk patients. England, Europace; 2009; 11:537.

18. Barbosa MP, da Costa Rocha MO, de Oliveira AB, Lombardi F, Ribeiro AL. Efficacy and safety of implantable cardioverter-defibrillators in patients with Chagas disease. Europace. 2013; 15(7):957-962.

19. Martinelli Filho M, De Siqueira SF, Moreira H, Fagundes A, Pedrosa A, Nishioka SD, *et al*. Probability of occurrence of life-threatening ventricular arrhythmias in Chagas' disease versus non-Chagas' disease. Pacing Clin Electrophysiol. 2000; 23(11 Pt 2):1944-6.

20. Sosa E, Scanavacca M, d'Avila A, Pilleggi F. A new technique to perform epicardial mapping in the electrophysiology laboratory. J Cardiovasc Electrophysiol. 1996; (6):531-536.

21. Matsuda NM, Miller SM, Evora PR. The chronic gastrointestinal manifestations of Chagas disease. Clinics, Sao Paulo. 2009; 64(12):1219-1224.

22. Carmo AA, Miranda RC, Lacerda-Filho A, Ribeiro AL. Laparoscopic guided epicardial access. Heart Rhythm. 2015; 12(2):461-462.

23. Azogue E, Darras C. Prospective study of Chagas disease in newborn children with placental infection caused by Trypanosoma cruzi (Santa Cruz-Bolivia)]. Rev Soc Bras Med Trop. 1991; 24(2):105-109.

24. Pedreira de Freitas JL, Amato Neto V, Sonntag R, Biancalana A, Nussenzveig V, Barreto JG. First tests on the accidental transmission of Chagas disease to man by blood transfusion. Rev Paul Med. 1952; 40(1):36-40.

25. Riarte A, Luna C, Sabatiello R, Sinagra A, Schiavelli R, De Rissio A, *et al*. Chagas' disease in patients with kidney transplants: 7 years of experience 1989-1996. Clin Infect Dis. 1999; 29(3):561-567.

26. Pereira KS, Schmidt FL, Guaraldo AM, Franco RM, Dias VL, Passos LA. Chagas' disease as a foodborne illness. J Food Prot. 2009; 72(2):441-446.

27. Herwaldt BL. Laboratory-acquired parasitic infections from accidental exposures. Clin Microbiol Rev. 2001; 14(4):659-688, table of contents.

28. Biolo A, Ribeiro AL, Clausell N. Chagas cardiomyopathy--where do we stand after a hundred years? Prog Cardiovasc Dis. 2010; 52(4):300-316.

29. Dias E, Laranja FS, Miranda A, Nobrega G. Chagas disease; a clinical, epidemiologic, and pathologic study. Circulation. 1956; 14(6):1035-1060.

30. Marin Neto JA, Simões MV, Sarabanda AV. Chagas' heart disease. Arq Bras Cardiol. 1999; 72(3):247-280.

31. Bogliolo L. Anatomie causes of cardiac insufficiency in chronic chagasic cardiopathy (myocarditis) studied in comparison to anatomic causes of cardiac insufficiency in other cardiopathies. Part I. Arq Bras Cardiol. 1976; 29(5):419-424.

32. Marin-Neto JA, Cunha-Neto E, Maciel BC, Simões MV. Pathogenesis of chronic Chagas heart disease. Circulation. 2007; 115(9):1109-1123.

33. Cunha-Neto E, Teixeira PC, Nogueira LG, Kalil J. Autoimmunity. Adv Parasitol. 2011; 76:129-152.

34. Machado CR, Ribeiro AL. Experimental American trypanomiasis in rats: sympathetic denervation, parasitism and inflammatory process. Mem Inst Oswaldo Cruz. 1989; 84(4):549-556.

35. Schijman AG, Vigliano CA, Viotti RJ, Burgos JM, Brandariz S, Lococo BE, *et al.* Trypanosoma cruzi DNA in cardiac lesions of Argentinean patients with end-stage chronic chagas heart disease. Am J Trop Med Hyg. 2004; 70(2):210-220.

36. Zhang L, Tarleton RL. Parasite persistence correlates with disease severity and localization in chronic Chagas' disease. J Infect Dis. 1999; 180(2):480-486.

37. Viotti R, Vigliano C, Lococo B, Bertocchi G, Petti M, Alvarez MG, *et al*. Long-term cardiac outcomes of treating chronic Chagas disease with benznidazole versus no treatment: a nonrandomized trial. Ann Intern Med. 2006; 144(10):724-734.

38. Rocha MO, Ribeiro AL, Teixeira MM. Clinical management of chronic Chagas cardiomyopathy. Front Biosci. 2003; 8:e44-54.

39. Rocha MO, Teixeira MM, Ribeiro AL. An update on the management of Chagas cardiomyopathy. Expert Rev Anti Infect Ther. 2007; 5(4):727-743.

40. Prata A, Lopes ER, Chapadeiro E. Characteristics of unexpected sudden death in Chagas disease. Rev Soc Bras Med Trop. 1986; 19(1):9-12.

41. Andrade JP, Marin-Neto JA, Paola AA, Vilas-Boas F, Oliveira GM, Bacal F, *et al.* I Latin American guidelines for the diagnosis and treatment of Chagas cardiomyopathy. Arq Bras Cardiol. 2011; 97(2 Suppl 3):1-48.

42. Milei J, Pesce R, Valero E, Muratore C, Beigelman R, Ferrans VJ. Electrophysiologic-structural correlations in chagasic aneurysms causing malignant arrhythmias. Int J Cardiol. 1991; 32(1):65-73.

43. Barbosa MP, Carmo AA, Rocha MO, Ribeiro AL. Ventricular arrhythmias in Chagas disease. Rev Soc Bras Med Trop. 2015; 48(1):4-10.

44. Rossi MA, Tanowitz HB, Malvestio LM, Celes MR, Campos EC, Blefari V, *et al.* Coronary microvascular disease in chronic Chagas cardiomyopathy including an overview on history, pathology, and other proposed pathogenic mechanisms. PLoS Negl Trop Dis. 2010;4(8).

45. Feldman AM, McNamara D. Myocarditis. N Engl J Med. 2000; 343(19):1388-1398.

46. de Carvalho AC, Tanowitz HB, Wittner M, Dermietzel R, Roy C, Hertzberg EL, *et al*. Gap junction distribution is altered between cardiac myocytes infected with Trypanosoma cruzi. Circ Res. 1992; 70(4):733-742.

47. Ribeiro AL, Moraes RS, Ribeiro JP, Ferlin EL, Torres RM, Oliveira E, *et al.* Parasympathetic dysautonomia precedes left ventricular systolic dysfunction in Chagas disease. Am Heart J. 2001;141(2):260-265.

48. Junqueira LF. Insights into the clinical and functional significance of cardiac autonomic dysfunction in Chagas disease. Rev Soc Bras Med Trop. 2012; 45(2):243-252.

49. Machado CR, Gomez MV, Machado AB. Changes in choline acetyltransferase activity of rat tissues during Chagas' disease. Braz J Med Biol Res. 1987; 20(6):697-702.

50. Saenz LC, Corrales FM, Bautista W, Traina M, Meymandi S, Rodriguez DA, *et al.* Cardiac sympathetic denervation for intractable ventricular arrhythmias in Chagas disease. Heart Rhythm. 2016; 13(7):1388-1394.

51. Machado CR, Machado AB, Chiari CA. Recovery from heart norepinephrine depletion in experimental Chagas' disease. Am J Trop Med Hyg. 1978 ;27(1 Pt 1):20-24.

52. Chen LS, Zhou S, Fishbein MC, Chen PS. New perspectives on the role of autonomic nervous system in the genesis of arrhythmias. J Cardiovasc Electrophysiol. 2007; 18(1):123-127.

53. Mirowski M, Reid PR, Mower MM, Watkins L, Gott VL, Schauble JF, *et al*. Termination of malignant ventricular arrhythmias with an implanted automatic defibrillator in human beings. N Engl J Med. 1980; 303(6):322-324.

54. Swerdlow C, Friedman P. Implantable cardioverter-defibrillator: Clinical Aspects. *In*: Zipes DP, Jalife J, (eds.). Cardiac Electrophysiology: From Cell to Bedside. 5. ed., Philadelphia, PA. USA: Saunders; 2009: 991-999.

55. Connolly SJ, Hallstrom AP, Cappato R, Schron EB, Kuck KH, Zipes DP, *et al*. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. Antiarrhythmics vs Implantable Defibrillator study. Cardiac Arrest Study Hamburg . Canadian Implantable Defibrillator Study. Eur Heart J. 2000; 21(24):2071-2078.

56. Hallstrom AP, McAnulty JH, Wilkoff BL, Follmann D, Raitt MH, Carlson MD, *et al*. Patients at lower risk of arrhythmia recurrence: a subgroup in whom implantable defibrillators may not offer benefit. Antiarrhythmics Versus Implantable Defibrillator (AVID) Trial Investigators. J Am Coll Cardiol. 2001; 37(4):1093-1099.

57. Cardinalli-Neto A, Bestetti RB, Cordeiro JA, Rodrigues VC. Predictors of all-cause mortality for patients with chronic Chagas' heart disease receiving implantable cardioverter defibrillator therapy. United States, J Cardiovasc Electrophysiol. 2007; 18:1236-1240.

58. di Toro D, Muratore C, Aguinaga L, Batista L, Malan A, Greco O, *et al.* Predictors of all-cause 1-year mortality in implantable cardioverter defibrillator patients with chronic Chagas' cardiomyopathy. Pacing Clin Electrophysiol. 2011; 34(9):1063-9.

59. Martinelli M, de Siqueira SF, Sternick EB, Rassi A, Jr., Costa R, Ramires JA, *et al*. Long-term follow-up of implantable cardioverter-defibrillator for secondary prevention in chagas' heart disease. Am J Cardiol. 110. United States: 2012 Elsevier Inc; 2012. p. 1040-5.

60. Gali WL, Sarabanda AV, Baggio JM, Ferreira LG, Gomes GG, Marin-Neto JA, *et al*. Implantable cardioverter-defibrillators for treatment of sustained ventricular arrhythmias in patients with Chagas' heart disease: comparison with a control group treated with amiodarone alone. Europace. England. 2014; 16:674-680.

61. Sosa E, Scanavacca M, D'Avila A, Bellotti G, Pilleggi F. Radiofrequency catheter ablation of ventricular tachycardia guided by nonsurgical epicardial mapping in chronic Chagasic heart disease. Pacing Clin Electrophysiol. 1999; 22(1 Pt 1):128-130.

62. Scanavacca M, Sosa E, d'Avila A, De Lourdes Higuchi M. Radiofrequency ablation of sustained ventricular tachycardia related to the mitral isthmus in Chagas' disease. Pacing Clin Electrophysiol. 2002; 25(3):368-371.

63. Haedo AH, Chiale PA, Bandieri JD, Lázzari JO, Elizari MV, Rosenbaum MB. Comparative antiarrhythmic efficacy of verapamil, 17-monochloracetylajmaline, mexiletine and amiodarone in patients with severe chagasic myocarditis: relation with the underlying arrhythmogenic mechanisms. J Am Coll Cardiol. 1986; 7(5):1114-1120.

64. Rosenbaum M, Posse R, Sgammini H, Núñez Burgos J, Chiale PA, Pastori JD, *et al.* Comparative multicenter clinical study of flecainide and amiodarone in the treatment of ventricular arrhythmias associated with chronic Chagas cardiopathy. Arch Inst Cardiol Mex. 1987; 57(4):325-330.

65. Rosenbaum MB, Chiale PA, Haedo A, Lázzari JO, Elizari MV. Ten years of experience with amiodarone. Am Heart J. 1983; 106(4 Pt 2):957-964.

66. Goldschlager N, Epstein AE, Naccarelli GV, Olshansky B, Singh B, Collard HR, *et al.* A practical guide for clinicians who treat patients with amiodarone: 2007. Heart Rhythm. 2007; 4(9):1250-1259.

67. Rodrigues M, Alves G, Lourenço N, Falcão A. Herb-Drug Interaction of Paullinia cupana (Guarana) Seed Extract on the pharmacokinetics of amiodarone in rats. Evid Based Complement Alternat Med. 2012; 2012:428560.

68. Darbar D. Standard Antiarrhythmic Drugs. *In*: Zipes DP, Jalife J, eds. Cardiac electrophysiology: From cell to bedside. 5 ed., Philadelphia, PA: Saunders Elsevier; 2009: 959-973.

69. Bashore T. Disorders of rate & rhythm. *In*: Papadakis MM, SJ. (ed.). Current medical diagnosis e treatment 2014. 53. ed., McGraw-Hill Education, 2014.

70. Vassallo P, Trohman RG. Prescribing amiodarone: an evidence-based review of clinical indications. JAMA. 2007; 298(11):1312-1322.

71. Heger JJ, Prystowsky EN, Jackman WM, Naccarelli GV, Warfel KA, Rinkenberger RL, *et al.* Clinical efficacy and electrophysiology during long-term therapy for recurrent ventricular tachycardia or ventricular fibrillation. N Engl J Med. 1981; 305(10):539-545.

72. Greene HL. The CASCADE Study: randomized antiarrhythmic drug therapy in survivors of cardiac arrest in Seattle. CASCADE Investigators. Am J Cardiol. 1993; 72(16):70F-74F.

73. Sim I, McDonald KM, Lavori PW, Norbutas CM, Hlatky MA. Quantitative overview of randomized trials of amiodarone to prevent sudden cardiac death. Circulation. 1997; 96(9):2823-2829.

74. [No authors listed]. Effect of prophylactic amiodarone on mortality after acute myocardial infarction and in congestive heart failure: meta-analysis of individual data from 6500 patients in randomised trials. Amiodarone Trials Meta-Analysis Investigators. Lancet. 1997; 350(9089):1417-1424.

75. Connolly SJ, Dorian P, Roberts RS, Gent M, Bailin S, Fain ES, *et al*. Comparison of beta-blockers, amiodarone plus beta-blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators: the OPTIC Study: a randomized trial. JAMA. 2006; 295(2):165-171.

76. Benaim G, Sanders JM, Garcia-Marchán Y, Colina C, Lira R, Caldera AR, *et al*. Amiodarone has intrinsic anti-Trypanosoma cruzi activity and acts synergistically with posaconazole. J Med Chem. 2006; 49(3):892-9.

77. Benaim G, Paniz Mondolfi AE. The emerging role of amiodarone and dronedarone in Chagas disease. Nat Rev Cardiol. 2012; 9(10):605-609.

78. Benaim B, Garcia CR. Targeting calcium homeostasis as the therapy of Chagas' disease and leishmaniasis - a review. Trop Biomed. 2011; 28(3):471-481.

79. Adesse D, Azzam EM, Meirelles MeN, Urbina JA, Garzoni LR. Amiodarone inhibits Trypanosoma cruzi infection and promotes cardiac cell recovery with gap junction and cytoskeleton reassembly in vitro. Antimicrob Agents Chemother. 2011; 55(1):203-210.

80. Veiga-Santos P, Barrias ES, Santos JF, de Barros Moreira TL, de Carvalho TM, Urbina JA, *et al*. Effects of amiodarone and posaconazole on the growth and ultrastructure of Trypanosoma cruzi. Int J Antimicrob Agents. 2012; 40(1):61-71.

81. Paniz-Mondolfi AE, Pérez-Alvarez AM, Lanza G, Márquez E, Concepción JL. Amiodarone and itraconazole: a rational therapeutic approach for the treatment of chronic Chagas' disease. Chemotherapy. 2009; 55(4):228-233.

82. Krettli AU. The utility of anti-trypomastigote lytic antibodies for determining cure of Trypanosoma cruzi infections in treated patients: an overview and perspectives. Mem Inst Oswaldo Cruz. 2009; 104 Suppl 1:142-151.

83. Krautz GM, Galvão LM, Cançado JR, Guevara-Espinoza A, Ouaissi A, Krettli AU. Use of a 24-kilodalton Trypanosoma cruzi recombinant protein to monitor cure of human Chagas' disease. J Clin Microbiol. 1995; 33(8):2086-2090.

84. Carmo AA, Rocha MO, Silva JL, Ianni BM, Fernandes F, Sabino EC, *et al*. Amiodarone and Trypanosoma cruzi parasitemia in patients with Chagas disease. Int J Cardiol. 2015; 189:182-4.

85. Morillo CA, Marin-Neto JA, Avezum A, Sosa-Estani S, Rassi A, Rosas F, *et al*. Randomized Trial of Benznidazole for Chronic Chagas' Cardiomyopathy. N Engl J Med. 2015.

86. Leite LR, Fenelon G, Simoes A, Jr., Silva GG, Friedman PA, de Paola AA. Clinical usefulness of electrophysiologic testing in patients with ventricular tachycardia and chronic chagasic cardiomyopathy treated with amiodarone or sotalol. J Cardiovasc Electrophysiol. 2003; 14(6):567-573.

87. Sarabanda AV, Marin-Neto JA. Predictors of mortality in patients with Chagas' cardiomyopathy and ventricular tachycardia not treated with implantable cardioverter-defibrillators. Pacing Clin Electrophysiol. 2011; 34(1):54-62.

88. Scanavacca MI, Sosa EA, Lee JH, Bellotti G, Pileggi F. Empiric therapy with amiodarone in patients with chronic Chagas cardiomyopathy and sustained ventricular tachycardia. Arq Bras Cardiol. 1990; 54(6):367-371.

89. Schron EB, Exner DV, Yao Q, Jenkins LS, Steinberg JS, Cook JR, *et al.* Quality of life in the antiarrhythmics versus implantable defibrillators trial: impact of therapy and influence of adverse symptoms and defibrillator shocks. Circulation. 2002; 105(5):589-594.

90. Larsen GK, Evans J, Lambert WE, Chen Y, Raitt MH. Shocks burden and increased mortality in implantable cardioverter-defibrillator patients. Heart Rhythm. 2011; 8(12):1881-1886.

91. Villacastín J, Almendral J, Arenal A, Albertos J, Ormaetxe J, Peinado R, *et al*. Incidence and clinical significance of multiple consecutive, appropriate, high-energy discharges in patients with implanted cardioverter-defibrillators. Circulation. 1996; 93(4):753-762.

92. Ha AH, Ham I, Nair GM, Connolly SJ, Dorian P, Morillo CA, *et al.* Implantable cardioverter-defibrillator shock prevention does not reduce mortality: a systemic review. Heart Rhythm. 2012; 9(12):2068-2074.

93. Scanavacca M, Sosa E. Epicardial ablation of ventricular tachycardia in Chagas heart disease. Card Electrophysiol Clin. 2010; 2(1):55-67.

94. Henz BD, do Nascimento TA, Dietrich Cde O, Dalegrave C, Hernandes V, Mesas CE, *et al*. Simultaneous epicardial and endocardial substrate mapping and radiofrequency catheter ablation as first-line treatment for ventricular tachycardia and frequent ICD shocks in chronic chagasic cardiomyopathy. J Interv Card Electrophysiol. 2009; 26(3):195-205.

95. Di Biase L, Santangeli P, Burkhardt DJ, Bai R, Mohanty P, Carbucicchio C, *et al*. Endo-epicardial homogenization of the scar versus limited substrate ablation for the treatment of electrical storms in patients with ischemic cardiomyopathy. J Am Coll Cardiol. 2012; 60(2):132-141.

96. Soto-Becerra R, Bazan V, Bautista W, Malavassi F, Altamar J, Ramirez JD, *et al.* Ventricular Tachycardia in the Setting of Chagasic Cardiomyopathy: Use of Voltage Mapping to Characterize Endoepicardial Nonischemic Scar Distribution. Circ Arrhythm Electrophysiol. 2017; 10(11).

97. Sosa E, Scanavacca M, d'Avila A, Oliveira F, Ramires JA. Nonsurgical transthoracic epicardial catheter ablation to treat recurrent ventricular tachycardia occurring late after myocardial infarction. J Am Coll Cardiol. 2000; 35(6):1442-1449.

98. Sacher F, Roberts-Thomson K, Maury P, Tedrow U, Nault I, Steven D, *et al.* Epicardial ventricular tachycardia ablation a multicenter safety study. J Am Coll Cardiol. 2010; 55(21):2366-2372.

99. Della Bella P, Brugada J, Zeppenfeld K, Merino J, Neuzil P, Maury P, *et al*. Epicardial ablation for ventricular tachycardia: a European multicenter study. Circ Arrhythm Electrophysiol. 2011; 4(5):653-659.

100. Gunda S, Reddy M, Pillarisetti J, Atoui M, Badhwar N, Swarup V, *et al.* Differences in complication rates between large bore needle and a long micropuncture needle during epicardial access: time to change clinical practice? Circ Arrhythm Electrophysiol. 2015; 8(4):890-895.

101. Kumar S, Bazaz R, Barbhaiya CR, Enriquez AD, Helmbold AF, Chinitz JS, *et al.* "Needle-in-needle" epicardial access: Preliminary observations with a modified technique for facilitating epicardial interventional procedures. Heart Rhythm. 2015; 12(7):1691-1697.

102. Di Biase L, Burkhardt JD, Reddy V, Romero J, Neuzil P, Petru J, *et al.* Initial international multicenter human experience with a novel epicardial access needle embedded with a real-time pressure/frequency monitoring to facilitate epicardial access: Feasibility and safety. Heart Rhythm. 2017; 14(7):981-988.

103. Rogers T, Ratnayaka K, Schenke WH, Faranesh AZ, Mazal JR, O'Neill WW, *et al.* Intentional right atrial exit for microcatheter infusion of pericardial carbon dioxide or iodinated contrast to facilitate sub-xiphoid access. Catheter Cardiovasc Interv. 2015; 86(2):E111-118.

104. Silberbauer J, Gomes J, O'Nunain S, Kirubakaran S, Hildick-Smith D, McCready J. Coronary Vein Exit and Carbon Dioxide Insufflation to Facilitate Subxiphoid Epicardial Access for Ventricular Mapping and Ablation: First Experience. JACC Clin Electrophysiol. 2017; 3(5):514-521.

105. Bradfield JS, Tung R, Boyle NG, Buch E, Shivkumar K. Our approach to minimize risk of epicardial access: standard techniques with the addition of electroanatomic mapping guidance. J Cardiovasc Electrophysiol. 2013; 24(6):723-727.

106. Halabi M, Faranesh AZ, Schenke WH, Wright VJ, Hansen MS, Saikus CE, *et al*. Real-time cardiovascular magnetic resonance subxiphoid pericardial access and pericardiocentesis using off-the-shelf devices in swine. J Cardiovasc Magn Reson. 2013; 15:61.

107. Ebrille E, Killu AM, Anavekar NS, Packer DL, Munger TM, McLeod CJ, *et al.* Successful percutaneous epicardial access in challenging scenarios. Pacing Clin Electrophysiol. 2015; 38(1):84-90.

108. Romero J, Shivkumar K, Di Biase L, Avendano R, Anderson RD, Natale A, *et al*. Mastering the art of epicardial access in cardiac electrophysiology. Heart Rhythm. 2019.

109. Carmo AAL, de Sousa MR, Agudelo JF, Ianni BM, Fernandes F, Sabino EC, *et al*. Implantable cardioverter-defibrillator in Chagas heart disease: A systematic review and meta-analysis of observational studies. Int J Cardiol. 2018; 267:88-93.

110. Doval HC, Nul DR, Grancelli HO, Perrone SV, Bortman GR, Curiel R. Randomised trial of low-dose amiodarone in severe congestive heart failure. Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA). Lancet. 1994; 344(8921):493-498.

111. Egger M, Smith GD. Bias in location and selection of studies. BMJ. 1998; 316(7124):61-66.

APÊNDICES

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Implantable cardioverter-defibrillator in Chagas heart disease: A systematic review and meta-analysis of observational studies

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ABSTRACT

Background: In patients with Chagas cardiomyopathy (ChCM), sudden cardiac death (SCD) is the leading cause of mortality. Implantable cardioverter-defibrillator (ICD) is a well-established therapy for secondary prevention in patients with structural heart disease, but there are conflicting opinions regarding its efficacy and safety in patients with ChCM. The aim of this meta-analysis was to assess the efficacy of the ICD for secondary prevention in patients with ChCM, comparing mortality as the primary outcome of patients treated with ICD with those treated with amiodarone.

Methods: We systematically searched five databases for studies assessing mortality outcomes in patients with ChCM and sustained ventricular tachycardia (VT) treated with ICD implantation or with amiodarone. The results of studies were pooled using random-effects modeling.

Results: There was no randomized clinical trial comparing efficacy of ICD versus medical treatment in patients with ChCM. Six observational studies were included, totalizing 115 patients in amiodarone group and 483 patients in ICD group. The mortality outcome in the ICD population was 9.7 per 100 patient-years of follow-up (95%CI 5.7–13.7) and 9.6 per 100 patient-years in the amiodarone group (95%CI 6.7–12.4) ($p = 0.95$). Meta-regression did not show any association with LV ejection fraction ($p = 0.32$), age ($p = 0.44$), beta-blocker ($p = 0.33$) or angiotensin-converting enzyme inhibitors ($p = 0.096$) usage.

Conclusion: The best available evidence derived from small observational studies suggests that ICD therapy in secondary prevention of sudden death (VT or resuscitated SCD) is not associated with lower rate of all-cause mortality in patients with ChCM. Randomized controlled trials are needed to answer this question.

1. Introduction

The ICD is an accepted and effective therapy for prevention of sudden cardiac death (SCD) in patients with structural heart disease. Indications are derived from three sources of data: randomized clinical trials (RCTs), observational data from cohorts of high-risk patients with less common diseases and from guidelines and expert opinion on potential benefit for clinical conditions or specific circumstances in which data are limited or uncertain [1]. ICD benefit has been clearly established in patients with both ischemic and non-ischemic cardiomyopathies who have survived a cardiac arrest. Although primary prevention of SCD has also been supported by multiple large RCT's, notably in patients with ischemic cardiomyopathy, a recent study [2] did not show a mortality benefit of the ICD for primary prophylaxis in patients with nonischemic cardiomyopathy, raising some concerns about generalization of the results obtained for a specific cardiomyopathy.

In patients with ChCM, SCD is the leading mortality cause, accounting for nearly two-thirds of all deaths [3] and ICD implantation has emerged as a therapeutic strategy for both primary and secondary prevention of SCD. Some reports suggest similar benefits compared to ischemic cardiomyopathy [4,5]. However, serious economic restrictions to a wider usage have been identified, limiting the population that can potentially benefit from ICDs [6]. Additionally, conflicting opinions regarding the efficacy of the ICD in ChCM have been reported [7–9].

Abbreviations: ICD, implantable cardioverter-defibrillator; ChCM, Chagas cardiomyopathy; RCT, randomized clinical trial.

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The purpose of this systematic review was to assess the efficacy of the ICD for secondary prevention in patients with ChCM, comparing mortality as the primary outcome of patients treated with ICD with those treated medically.

2. Methods

2.1. Protocol and registration

The methodology of this review was previously registered in the PROSPERO database (CRD42015027266) and the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) checklist was used to perform this systematic review.

2.2. Eligibility criteria

All publications including patients with ChCM and an ICD implanted for secondary prevention of SCD or ChCM and ventricular tachycardia (VT) treated medically were included. Initially, we searched for RCTs with more than one year of follow-up. No RCT was identified after three preliminary searches. Based on the above, the protocol was modified and all clinical registries and observational studies regardless of follow-up duration were included. The final search was performed on January 2017 and combined with the previous literature search.

2.3. Information sources and search

A comprehensive literature search was conducted in LILACS (Latin American and Caribbean Health Science Literature), MEDLINE, EMBASE, Cochrane review of systematic interventions and the Cochrane central register of controlled trials (CENTRAL) using the following MeSH search terms: "Chagas disease" AND "defibrillator" OR "ventricular tachycardia", until January 2017. No language restrictions were applied to the search. References of the retrieved articles were reviewed for other relevant studies. The website www.theheart.org was used to search for related presentations at any of the major scientific meetings. Experts were contacted to identify additional potential studies not identified by database searches.

2.4. Study selection

All publications identified were independently reviewed for inclusion using predetermined criteria. The inclusion criteria were: 1 - studies of patients with ChCM and ICD implanted for secondary prevention (studies with both primary and secondary prevention strategies were allowed if mortality data were available for both groups). 2 - Studies of patients with ChCM and medically treated VT. 3 - Clinical registries. We excluded abstract presentations at national and international meetings. Taking into account the limited number of studies, there were no exclusions based on follow-up duration or number of patients included.

The following data were extracted from reports: all-cause mortality, follow-up, mean age, left ventricular ejection fraction (LVEF), medical therapy and appropriate therapy in patients with ICD.

For patients with ChCM and medically treated VT, as amiodarone is the drug of choice for prevention of recurrence of VT and structural heart disease [10,11], we used initially data from patients receiving only amiodarone and data from the entire population was used for sensitivity analysis. We excluded studies without data related with antiarrhythmic drugs.

2.5. Statistical analysis

The event rates (percentages with 95% confidence intervals [CI]) in each group (ICD or antiarrhythmic drugs) were pooled and indirectly compared using random-effects modeling (Comprehensive Meta-Analysis Software, version 2.2.064). A p-value <0.05 was statistically significant. Due to a wide range of follow-up among different studies, we adjusted the rate of event per patient-years, assuming a constant hazard of death during follow-up. In addition, sensitivity analysis was performed including patients treated with amiodarone and all other antiarrhythmic drugs compared to ICD treated patients, to explore robustness of the results in the presence of other antiarrhythmic drugs. Heterogeneity was assessed using I^2 statistic. Exploration of sources of heterogeneity was performed with meta-regression analysis (method of moments). Egger's test was used to evaluate publication bias [12].

3. Results

3.1. Literature search

The study selection process is shown in Fig. 1. We identified 285 eligible unique records. Two hundred and eight were excluded based on title and 19 were excluded based on the abstract, the remaining 58 articles underwent full-text analysis. After detailed analysis of the above, 52 studies were excluded, and the remaining six papers were included for qualitative and quantitative analysis. The present study included 143 patients treated medically (115 patients on amiodarone) and 483 patients with ICD implanted for secondary prevention of SCD.

3.2. Study quality

As previously stated, there was no RCT comparing efficacy of ICD versus medical treatment in patients with ChCM. In this setting, we used only non-randomized studies. Study quality was assessed using the Newcastle-Ottawa scale. The only study that included a population of Chagas disease patients treated medically in comparison to ICD patients was published by Gali et al., and was classified as good quality based on the Newcastle-Ottawa scale. Overall, the quality of studies was poor (Table 1).

3.3. Study characteristics

Two studies evaluated the efficacy of antiarrhythmic drugs for treatment of sustained ventricular tachycardia in patients with ChCM [13,14]. Leite et al. [13] reported data on medical treatment of 115 patients with ChCM and VT (78 patients with sustained VT, 37 patients with symptomatic NSVT and sustained VT induced at baseline EPS). All patients received amiodarone or sotalol and the treating physician determined the choice between both drugs. However, when sotalol was used first and failed to render VT noninducible or was not tolerated, EPS was repeated after an amiodarone loading dose was administered. At discharge, 87 patients were taking amiodarone only, 25 sotalol only and 3 patients were taking a combination of amiodarone and sotalol or mexiletine. Total mortality was not significantly different: 40.2%, 36.0% and 33.3% respectively for amiodarone, sotalol or combination of amiodarone with sotalol or mexiletine (mean follow-up of 52 months). In this study, the population of patients only on amiodarone was used for the main analysis and the whole population was used for sensitivity analysis.

Cardinalli-Neto [15] reported data from a retrospective, single-center series of 90 patients with ChCM and ECG documented sustained and hemodynamically unstable VT. The aim was to determine predictors of all-cause mortality. Mean follow-up was 25.2 ± 19.3 months. Malignant arrhythmia (defined as ECG documented sustained VT with hemodynamic instability or VF;) was observed in 64 (71%) patients. There were 31 (34%) deaths during the study period. The median number of shocks per patient was 4.5. Multivariate analysis performed by Cox proportional hazards model, identified number of shocks (>4 episodes) per patient by day 30 as the only independent predictor of all-cause mortality (HR 1.86, 95% CI 1.21 to 2.86). Mean life expectancy was 2.1 months (CI 0.79 to 3.4 months) in patients receiving >4 shocks by day 30, and 46.5 months in patients receiving up to four shocks by day 30 ($p = 0.0005$).

Di Toro et al. [16] published an updated industry-sponsored multicenter registry. A previous report [6] of this registry included 89 patients followed for a mean of 12 ± 7 months (range 1–30). In this updated report, 148 patients followed for a mean of 12 ± 7 months were included (range 1–45). The aim was to determine mortality rate and risk factors of all-cause 1-year mortality in primary and secondary prevention patients with ChCM. Twelve patients (8.1%) had a primary prevention indication and 136 (91.9%) a secondary prevention indication; 13 (9.5%) resuscitated SCD; 87 (64%) spontaneous sustained VT and 36 (26.5%) syncope or near-syncope with inducible VT during EPS. Sixty-three patients (42.5%) had appropriate ICD therapies and 15 patients (10.2%) died (1 in primary prevention group and 14 in secondary prevention group). The multivariate Cox regression analysis identified age > 65 years (HR 2.85, 95% CI 1.77–3.92) and LVEF <30% (HR 2.68, 95% CI 1.57–3.79) as strong independent predictors of mortality. Eight patients with LVEF <30% and age > 65 died during follow-up (HR 7.34, 95% CI 5.82–8.82).

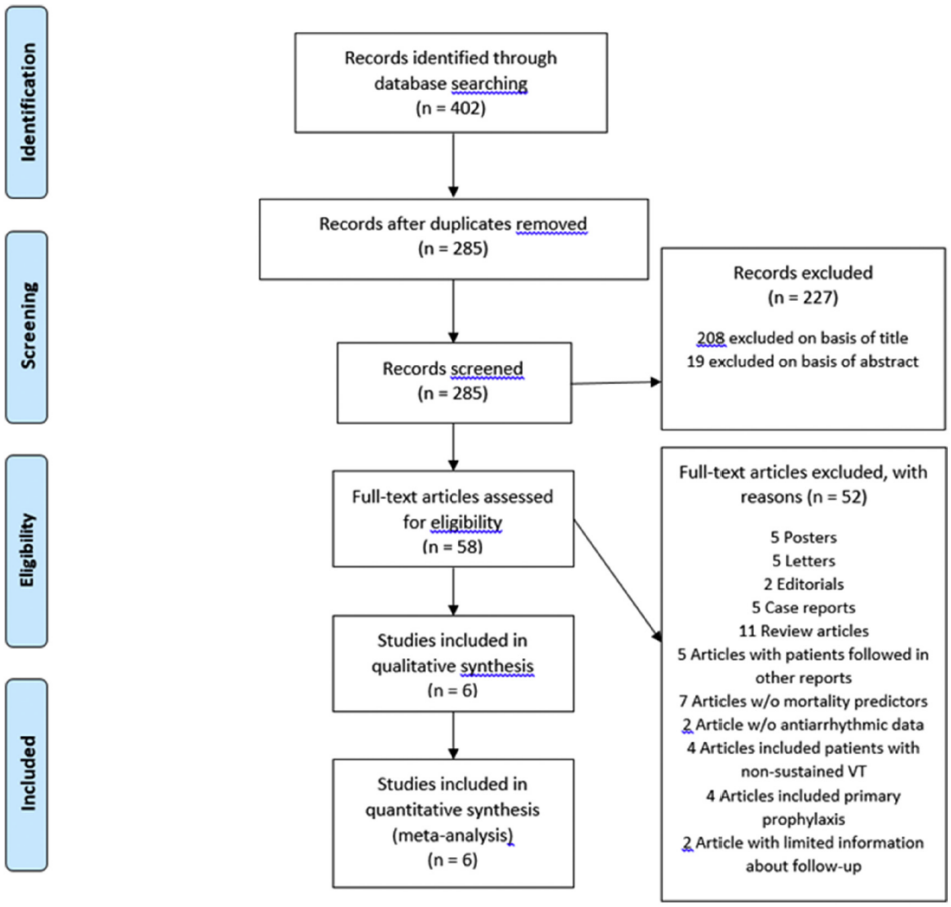

Fig. 1. PRISMA diagram showing the search strategy results and exclusion steps and reasons for the search using the MESH terms "Chagas disease" AND "Cardioverter - defibrillator" OR "ventricular tachycardia".

Martinelli and colleagues [17] reported data from a single-center retrospective cohort of patients with ChCM and ICD implanted for secondary prevention of SCD. This study reported all-cause mortality and appropriate ICD shock therapy rates and assessed the predictive value of a number of clinical variables. One hundred and sixteen patients were included; 82.7% in NYHA class I–II, and a mean LVEF of 42.4%. Indication for ICD was resuscitated VF or VT in 21 patients (18.1%) and symptomatic sustained VT in 95 patients (81.9%). Of these, 64 patients (55.2%) underwent an EPS and had hemodynamically unstable VT or VF induced by EPS. During a mean follow-up of 45 ± 32 months, 31 (26.7%) deaths occurred; annual mortality rate of 7.1%. Multivariate Cox proportional hazard model identified NYHA class III (HR 3.09, 95% CI 1.37 to 6.96) as a strong independent predictor. LVEF (HR 0.92 95% CI: 0.94–0.99) and a low rate of cumulative right ventricular pacing <40% of the time (HR 0.23, 95 CI 0.11–0.49) were predictors of better survival. Seven hundred and fifty VT/VF episodes in 58 patients (50% of the cohort) were recorded, and 339 appropriate shocks (5.8 shocks per patient) were reported. Inappropriate anti-tachycardia pacing or shocks were documented in only 4 and 18 patients (3.6 shocks/patient) respectively.

Table 1
Newcastle-Ottawa scale quality of studies assessing implantable cardioverter-defibrillator (ICD) treatment in patients with Chagas cardiomyopathy. In this scale, stars are awarded such that the highest quality studies are awarded up to nine stars.

Study	Selection	Comparability	Outcome
Leite 2003	*	–	*
Cardinalli-Neto 2007	*	–	**
Di-Toro 2011	*	–	**
Martinelli Filho 2012	**	–	**
Barbosa 2013	**	–	**
Gali 2014	****	**	***

Barbosa et al. [4] retrospectively compared clinical outcomes in patients with and without ChCM after ICD implantation for secondary prevention of SCD. On hundred and thirty-five patients were followed for a median of 266 days. Of these, 65 (48%) patients had ChCM, 22 (16.3%) ischemic cardiomyopathy, 28 (20.7%) non-ischemic dilated cardiomyopathy, 20 (15%) other cardiomyopathies. Patients with ChCM were more likely to be using amiodarone (92% vs 61.2%, $p = 0.01$) and less likely to be on beta-blockers (54% vs 83.7%, $p = 0.001$). The median LVEF was 37% in the ChCM group and 32.5% in non-Chagas group ($p = 0.99$). Of the 65 patients with Chagas, 20 patients (30%) had LVEF ≥45%. There were 8 deaths in each group (12.3 vs 11.4%, respectively for ChCM and non-Chagas cardiomyopathy, $p = 0.82$). Appropriate ICD therapy occurred in 32 (49.2%) ChD and in 19 (27.1%) non-ChD patients ($p = 0.005$). ChCM had a 2-fold increase in the he risk of appropriate therapy (HR 2.2; 95% CI, 1.2–4.3, $p = 0.02$) and appropriate therapy or death (HR 2.2; 95% CI, 1.2–4.2, $p = 0.01$) in multivariate analysis.

Gali and colleagues [14] published the only observational study that compared efficacy of ICD on secondary prevention of mortality compared to medical therapy alone, using a historical control group treated with amiodarone and enrolled before ICD therapy was available at that Centre. There were 76 patients in the ICD group and 28 patients in the amiodarone group. All ICD group patients received amiodarone and both groups had similar baseline characteristics, except for higher use of beta-blockers in the ICD group (90% vs 17%) ($p < 0.0001$). During a mean follow-up of 33 ± 16 months in the ICD group and 35 ± 17 months for control group, there was a 72% relative risk reduction in all-cause mortality of (HR 0.28; 95% CI; 0.11–0.72; $p = 0.007$) among ICD-treated patients. Subgroup analysis identified patients with LVEF <40% as those with the greatest survival benefit from the ICD ($p = 0.01$), not reaching a significant difference in those with a LVEF ≥40% ($p = 0.15$). Moreover, the number of appropriate therapy was very high, occurring in 72% of patients, with similar rates of interventions across patients with LVEF <40% or ≥40%. In multivariate analysis, only LVEF <40% was associated with increased risk of mortality (HR 6.63; 95% CI, 2.12–20.71; $p = 0.001$).

Main characteristics of each study's population and all-cause mortality for secondary prevention group are shown in Table 2.

3.4. Mortality outcomes

Mortality outcomes for each population are depicted in Fig. 2. Pooled data analysis did not show any difference in mortality outcomes between ICD and amiodarone treatment groups. The mortality outcome in ICD population was 9.7 per 100 patient-years of follow-up (95% CI 5.7–13.7) and 9.6 per 100 patient-years of follow-up in amiodarone group (95% CI 6.7–12.4) ($p = 0.95$).

Sensitivity analysis including amiodarone plus other antiarrhythmic drugs, available in Leite et al. study, showed a similar result in mortality rate for ICD group (9.7 per 100 patient-years; 95% CI 5.7–13.7) when compared to amiodarone plus other antiarrhythmic drugs group (9.3 per 100 patient-years; 95% CI 6.8–11.7, $p = 0.85$). To determine heterogeneity in secondary prevention studies, meta-regression was performed and did not show any association with mean age ($p = 0.43$), LV ejection fraction ($p = 0.32$), ACEI ($p = 0.096$) or beta-blocker therapy ($p = 0.33$).

Publication bias was assessed by the Egger's test that yielded a negative result ($p = 0.11$).

4. Discussion

The main finding of this meta-analysis was that ICD-based strategy was not associated with a lower mortality compared to amiodarone for treatment of ventricular arrhythmias in patients with ChCM. Even though lack of evidence from RCTs limited our ability to draw precise conclusions.

ICD adjusted mortality had marked variation among studies, ranging from 4.8 per 100 patient-years in Gali's study to 16.8 in Barbosa's study. The causes for this wide range of adjusted mortality cannot be fully explained, but they may include lack of ICD programing standardization, different population risk profile and supplementary therapy driven to suppress ventricular arrhythmia.

Although initial studies did not find an increased incidence of ICD therapies in Chagas disease [18], subsequent studies showed that a distinct characteristic of ChCM patients receiving an ICD for secondary prevention of sudden death is that VT/VF is earlier and more frequent in ChCM compared to patients with other cardiomyopathies particularly ischemic [4,19,20] and appropriate ICD therapies (shocks & ATP) delivered by the ICD may impair quality of life [11,21] and, additionally, may increase mortality [22–24]. Therefore, a high burden of ICD therapies can offset the benefit of VT reversion, adding complexity to the management of ventricular arrhythmias in ChCM.

ICD programming is another factor closely related to the high burden of ventricular arrhythmias in ChCM. On the one hand reports of SCD in patients with ChCM and preserved systolic left ventricular function [25] emphasize the importance of aggressive arrhythmia treatment, on the other hand, due to the high burden of ventricular arrhythmia, a high-rate zone or delayed therapy could potentially reduce the incidence of inappropriate therapies and all-cause mortality, as previously demonstrated for both ischemic and nonischemic cardiomyopathies [26]. We did not have information on ICD programming in our study and therefore cannot provide any further insight on this issue.

It is worth emphasizing that medical treatment based on Guidelines for heart failure in cardiomyopathies was suboptimal in the population included in this meta-analysis. Even though meta-regression did not show any significant findings, it may be due to lack of power. Interestingly, the lowest mortality was observed in ICD treated patients in Gali's study, the population with the highest usage of beta-blocker.

International Guidelines have limited discussion regarding ICD implantation in ChCM. The 2012 ACCF/AHA/HRS focused update incorporated into guidelines for device-based therapy of cardiac rhythm abnormalities [27] states that ICD implantation is reasonable for patients with Chagas disease (level of evidence C) with no comments on primary or secondary prevention strategies nor on disease severity. More recently, the 2015 Guidelines from European Society of Cardiology [28] recommend that ICD should be considered in patients with ChCM and LVEF <40% (level of evidence C), primarily based on results from Gali et al. [14], but, as the American Guideline, there are no comments on primary versus secondary strategies. Our findings suggest that the recommendation of ICD implantation for secondary prevention of SCD in ChCM should be reassessed and RCTs are direly needed to provide high quality evidence.

Regarding amiodarone therapy, some investigators advocate the use of this drug because, in addition to its antiarrhythmic properties, there may be potential anti-*Trypanosoma cruzi* activity [29,30]. Notwithstanding, recent studies have not confirmed this potential trypanocidal effect

Table 2
Main baseline clinical characteristics and all-cause mortality of patients with sustained ventricular tachycardia (VT) treated medically or with ICD.

	Leite 2003 (n = 115)	Gali 2014 (n = 28)	Cardinalli-Neto 2007 (n = 90)	Di Toro 2011 (n = 148)	Martinelli 2012 (n = 116)	Barbosa 2013 (65)	Gali 2014 (n = 76)
Treatment group	Medical	Medical	ICD	ICD	ICD	ICD	ICD
Secondary prevention (%)	115 (100)	28 (100)	90 (100)	136 (91.9)	116 (100)	65 (100)	76 (100)
Mean age	52 ± 10	54 ± 10	59 ± 11	60 ± 9.4	54 ± 10	56.7†	57 ± 11
Amiodarone (%)	87 (75.7)	28 (100)	90 (100)	93 (63)	90 (78)	46 (92)	69 (90)
Beta-blocker (%)	ND	5 (17)	37 (40)	73 (49)	38 (33)	27 (54)	69 (90)
ACEI/ARB (%)	79 (68)	26 (92)	ND	65 (44)	95 (82)	ND	67 (88)
Mean LVEF	49 ± 14	41 ± 10	47 ± 13	40.1 ± 11.3	42.4 ± 15.7	38.8†	39 ± 12
Follow-up (months)	52 ± 32	35 ± 17	25 ± 20	12 ± 7	45 ± 32	8.8†	33 ± 16
VT/VF (%)	ND	ND	64 (71)	63 (42.5)	58 (50)	32 (49.2)	52 (72%)
All-cause mortality‡ (95% CI)	9.3 (6.2–12.4)	11 (3.8–18.2)	16.5 (10.7–22.4)	10.3 (4.9–15.7)	7.1 (4.6–9.6)	16.8 (5.2–28.4)	4.8 (1.8–7.8)

†Standard Deviation (SD) not reported. ‡100 patient-years. CI: Confidence Interval. ICD: Implantable Cardioverter-defibrillator.

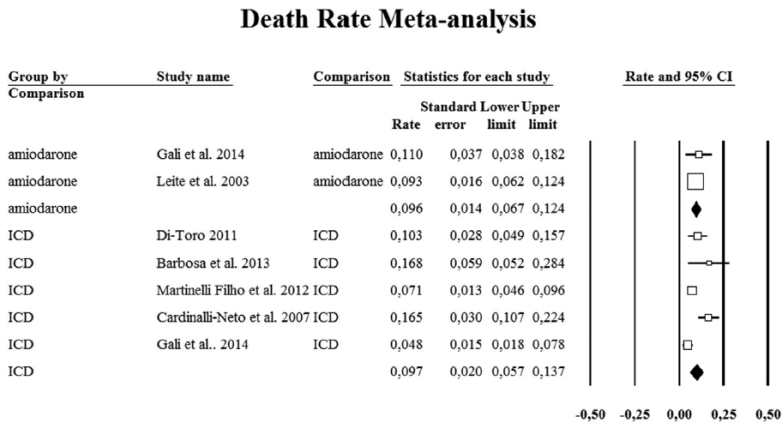

Fig. 2. Forest plot showing event rate and 95% confidence interval for all-cause mortality for amiodarone and implantable cardioverter-defibrillator (ICD) therapies. I^2 0% for amiodarone and 75% for ICD group ($p = 0.45$ for difference between groups).

of amiodarone assessed by *T. cruzi* DNA detection rates by PCR in spite of a potentially significant reduction in clinically relevant hard outcomes [31,32].

Based on our results and on ethical issues of withholding ICD implantation in patients presenting with sustained VT or SCD, efforts should be employed in evaluating the role of optimal ICD programming and suppression of ventricular arrhythmia, either by medical therapy or catheter ablation, aiming to reduce mortality in patients with ChCM and malignant ventricular arrhythmias.

The limitations of these analyses include lack of properly designed RCTs and the selection bias associated with observational studies. When we initiated the search process for the present meta-analysis we were unable to identify any RCTs comparing ICD to amiodarone treatment in patients with ChCM. This observation led us to include all observational studies that evaluated ICD therapy or amiodarone for secondary prevention or treatment of VT. Our meta-analysis is also limited to determine the role of ICD programming and additional therapies, such as catheter ablation, designed to reduce the recurrence of ventricular arrhythmias.

5. Conclusion

The best available evidence derived from small observational studies suggests that ICD therapy in secondary prevention of SCD (VT or resuscitated SCD) is not associated with a lower rate of all-cause mortality in patients with Chagas cardiomyopathy. Randomized controlled trials are direly needed to finally answer this question.

Disclosure

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References

[1] R.J. Myerburg, V. Reddy, A. Castellanos, Indications for implantable cardioverter-defibrillators based on evidence and judgment, J. Am. Coll. Cardiol. 54 (9) (2009) 747–763.
[2] L. Køber, J.J. Thune, J.C. Nielsen, J. Haarbo, L. Videbæk, E. Korup, et al., Defibrillator implantation in patients with nonischemic systolic heart failure, N. Engl. J. Med. 375 (13) (2016) 1221–1230.
[3] M.C. Nunes, A.A. Carmo, M.O. Rocha, A.L. Ribeiro, Mortality prediction in Chagas heart disease, Expert. Rev. Cardiovasc. Ther. 10 (9) (2012) 1173–1184.
[4] M.P. Barbosa, M.O. da Costa Rocha, A.B. de Oliveira, F. Lombardi, A.L. Ribeiro, Efficacy and safety of implantable cardioverter-defibrillators in patients with Chagas disease, Europace 15 (7) (2013) 957–962.
[5] S. Dubner, E. Valero, R. Pesce, J.G. Zuelgaray, J.C. Mateos, S.G. Filho, et al., A Latin American registry of implantable cardioverter defibrillators: the ICD-LABOR study, Ann Noninvasive Electrocardiol. 10 (4) (2005) 420–428.
[6] C.A. Muratore, L.A. Batista Sa, P.A. Chiale, R. Eloy, M.C. Tentori, J. Escudero, et al., Implantable cardioverter defibrillators and Chagas' disease: results of the ICD Registry Latin America, Europace 11 (2) (2009) 164–168.
[7] A. Rassi Jr., Implantable cardioverter-defibrillators in patients with Chagas heart disease: misperceptions, many questions and the urgent need for a randomized clinical trial, J. Cardiovasc. Electrophysiol. 18 (2007) 1241–1243.
[8] R. Bestetti, A. Cardinalli-Neto, Implantable cardioverter defibrillator therapy for patients with chronic Chagas' disease: a randomized trial may not be necessary in high-risk patients, Europace 11 (2009) 537.
[9] M.P. Barbosa, M.O. Rocha, F. Lombardi, A.L. Ribeiro, ICDs in Chagas heart disease: the standard treatment for secondary prevention of sudden death, Europace 15 (2013) 1383–1384.
[10] I. Sim, K.M. Mcdonald, P.W. Lavori, C.M. Norbutas, M.A. Hlatky, Quantitative overview of randomized trials of amiodarone to prevent sudden cardiac death, Circulation 96 (9) (1997) 2823–2829.
[11] S.J. Connolly, P. Dorian, R.S. Roberts, M. Gent, S. Bailin, E.S. Fain, et al., Comparison of beta-blockers, amiodarone plus beta-blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators: the OPTIC study: a randomized trial, JAMA 295 (2) (2006) 165–171.
[12] M. Egger, G.D. Smith, Bias in location and selection of studies, BMJ 316 (7124) (1998) 61–66.
[13] Leite LR, Fenelon G, Simoes A, Jr., Silva GG, Friedman PA, de Paola AA. Clinical usefulness of electrophysiologic testing in patients with ventricular tachycardia and chronic chagasic cardiomyopathy treated with amiodarone or sotalol. J. Cardiovasc. Electrophysiol. 2003;14(6):567–73.
[14] W.L. Gali, A.V. Sarabanda, J.M. Baggio, L.G. Ferreira, G.G. Gomes, J.A. Marin-Neto, et al., Implantable cardioverter-defibrillators for treatment of sustained ventricular arrhythmias in patients with Chagas' heart disease: comparison with a control group treated with amiodarone alone, Europace 16 (2014) 674–680.
[15] A. Cardinalli-Neto, R.B. Bestetti, J.A. Cordeiro, V.C. Rodrigues, Predictors of all-cause mortality for patients with chronic Chagas' heart disease receiving implantable cardioverter defibrillator therapy, J. Cardiovasc. Electrophysiol. 18 (2007) 1236–1240.
[16] D. di Toro, C. Muratore, L. Aguinaga, L. Batista, A. Malan, O. Greco, et al., Predictors of all-cause 1-year mortality in implantable cardioverter defibrillator patients with chronic Chagas' cardiomyopathy, Pacing Clin. Electrophysiol. 34 (9) (2011) 1063–1069.
[17] M. Martinelli, S.F. de Siqueira, E.B. Sternick, A. Rassi Jr., R. Costa, J.A. Ramires, et al., Long-term follow-up of implantable cardioverter-defibrillator for secondary prevention in Chagas' heart disease, Am. J. Cardiol. 110 (2012) 1040–1045.
[18] C. Muratore, R. Rabinovich, R. Iglesias, M. González, V. Darú, A.S. Liprandi, Implantable cardioverter defibrillators in patients with Chagas' disease: are they different from patients with coronary disease? Pacing Clin. Electrophysiol. 20 (1 Pt 2) (1997) 194–197.
[19] M. Martinelli Filho, S.F. De Siqueira, H. Moreira, A. Fagundes, A. Pedrosa, S.D. Nishioka, et al., Probability of occurrence of life-threatening ventricular arrhythmias in Chagas' disease versus non-Chagas' disease, Pacing Clin. Electrophysiol. 23 (11 Pt 2) (2000) 1944–1946.
[20] R. Rabinovich, C. Muratore, R. Iglesias, M. Gonzalez, V. Daru, M. Valentino, et al., Time to first shock in implantable cardioverter defibrillator (ICD) patients with Chagas cardiomyopathy, Pacing Clin. Electrophysiol. 22 (1 Pt 2) (1999) 202–205.
[21] E.B. Schron, D.V. Exner, Q. Yao, L.S. Jenkins, J.S. Steinberg, J.R. Cook, et al., Quality of life in the antiarrhythmics versus implantable defibrillators trial: impact of therapy and influence of adverse symptoms and defibrillator shocks, Circulation 105 (5) (2002) 589–594.

[22] G.K. Larsen, J. Evans, W.E. Lambert, Y. Chen, M.H. Raitt, Shocks burden and increased mortality in implantable cardioverter-defibrillator patients, Heart Rhythm. 8 (12) (2011) 1881–1886.
[23] J. Villacastín, J. Almendral, A. Arenal, J. Albertos, J. Ormaetxe, R. Peinado, et al., Incidence and clinical significance of multiple consecutive, appropriate, high-energy discharges in patients with implanted cardioverter-defibrillators, Circulation 93 (4) (1996) 753–762.
[24] A.H. Ha, I. Ham, G.M. Nair, S.J. Connolly, P. Dorian, C.A. Morillo, et al., Implantable cardioverter-defibrillator shock prevention does not reduce mortality: a systemic review, Heart Rhythm. 9 (12) (2012) 2068–2074.
[25] E.B. Sternick, M. Martinelli, R. Sampaio, R.C. Sampaio, L.M. Gerken, R.A. Teixeira, et al., Sudden cardiac death in patients with Chagas heart disease and preserved left ventricular function, J. Cardiovasc. Electrophysiol. 17 (1) (2006) 113–116.
[26] A.J. Moss, C. Schuger, C.A. Beck, M.W. Brown, D.S. Cannom, J.P. Daubert, et al., Reduction in inappropriate therapy and mortality through ICD programming, N. Engl. J. Med. 367 (24) (2012) 2275–2283.
[27] A.E. Epstein, J.P. Dimarco, K.A. Ellenbogen, N.A. Estes, R.A. Freedman, L.S. Gettes, et al., 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society, J Am Coll Cardiol. 61 (3) (2013) e6–e75.
[28] S.G. Priori, C. Blomström-Lundqvist, A. Mazzanti, N. Blom, M. Borggrefe, J. Camm, et al., 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC) endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), Eur. Heart J. 36 (41) (2015) 2793–2867.
[29] G. Benaim, A.E. Paniz Mondolfi, The emerging role of amiodarone and dronedarone in Chagas disease, Nat. Rev. Cardiol. 9 (10) (2012) 605–609.
[30] G. Benaim, J.M. Sanders, Y. Garcia-Marchán, C. Colina, R. Lira, A.R. Caldera, et al., Amiodarone has intrinsic anti-*Trypanosoma cruzi* activity and acts synergistically with posaconazole, J. Med. Chem. 49 (3) (2006) 892–899.
[31] A.A. Carmo, M.O. Rocha, J.L. Silva, B.M. Ianni, F. Fernandes, E.C. Sabino, et al., Amiodarone and *Trypanosoma cruzi* parasitemia in patients with Chagas disease, Int. J. Cardiol. 189 (2015) 182–184.
[32] C.A. Morillo, J.A. Marin-Neto, A. Avezum, S. Sosa-Estani, A. Rassi, F. Rosas, et al., Randomized trial of Benznidazole for chronic Chagas' cardiomyopathy, N. Engl. J. Med. 373 (14) (2015) 1295–1306.

Apêndice B – Artigo original publicado no periódico *Heart Rhythm*

IMAGE

Laparoscopic guided epicardial access

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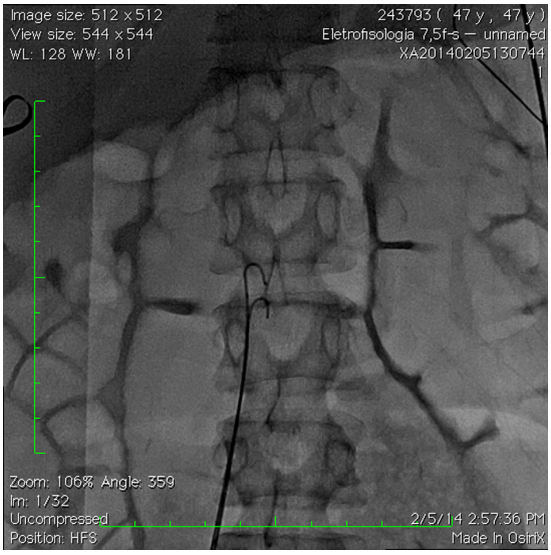

Figure 1

A 47-year-old female patient with chagasic cardiomyopathy and ejection fraction 32% who had a cardioverter-defibrillator implanted 1 year before because of syncope and inducible ventricular tachycardia (VT) during programmed stimulation presented to the emergency department complaining of worsening dyspnea and near syncope. The initial evaluation showed incessant VT with a rate (126 bpm) below the detection of the device. She was managed with intravenous amiodarone and was referred for ablation of VT.

KEYWORDS Ventricular tachycardia; Epicardial ablation; Laparoscopy
ABBREVIATIONS **VT** = ventricular tachycardia (Heart Rhythm 2015;12:461–462)

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During evaluation for VT ablation, a massive megacolon and severe malnutrition were detected. Figure 1 shows the radiographic appearance of the abdomen at the beginning of the ablation procedure.

Owing to concerns about colon injury during percutaneous subxiphoid epicardial approach[1,2] and complications related to surgical subxiphoid pericardial window, we decided to perform epicardial access with visualization of the abdominal cavity guided by laparoscopy. As shown in Figure 2, the low-pressure pneumoperitoneum (9 mm Hg) moved away the abdominal wall from the dilated colon, allowing free access to the diaphragm and epicardial surface. In addition, the trocar placed at the umbilicus level allowed direct visualization and placement of the needle and guidewire (Figures 2A and 2B). Thereafter, we performed endocardial and epicardial ablation and there were no further inducible VT. The patient was discharged 48 hours after the procedure.

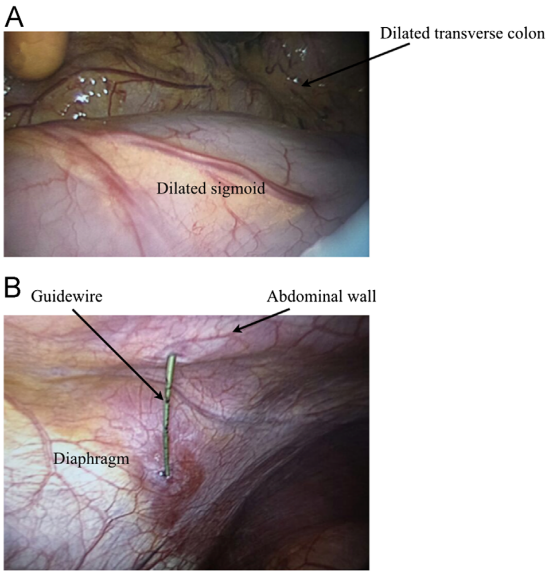

Figure 2

 http://dx.doi.org/10.1016/j.hrthm.2014.11.039

Figure 2B clearly shows that in the subxiphoid percutaneous approach, passing through the diaphragm muscle or its fibrous insertions is mandatory to reach the pericardial space, either in the anterior or the posterior approach. In addition, there are vessels in the abdominal aspect of the muscle running across the anterior and posterior regions, where they can be damaged and lead to intra-abdominal bleeding.

Intra-abdominal organ injury is one of main issues when approaching the pericardial space,[3] particularly in Chagas disease, because of its common association with megacolon. In this particular patient, the massive dilatation of the transverse colon raised serious concerns about organ injury even in the anterior approach.

To our knowledge, this is the first report of laparoscopic guided percutaneous subxiphoid epicardial access. It was an extremely well-tolerated and safe procedure and can be an alternative not only for patients with megacolon but also for patients with enlarged liver and increased risk of intra-abdominal organ injury.

References

1. Sosa E, Scanavacca M, d'Avila A, Pilleggi F. A new technique to perform epicardial mapping in the electrophysiology laboratory. J Cardiovasc Electrophysiol 1996;7:531–536.
2. Sosa E, Scanavacca M. Epicardial mapping and ablation techniques to control ventricular tachycardia. J Cardiovasc Electrophysiol 2005;16:449–452.
3. Killu AM, Friedman PA, Mulpuru SK, Munger TM, Packer DL, Asirvatham SJ. Atypical complications encountered with epicardial electrophysiological procedures. Heart Rhythm 2013;10:1613–1621.