TESE DE DOUTORADO

EFEITOS ARRÍTMICOS DA CAFEÍNA:

METANÁLISE E ENSAIO CLÍNICO RANDOMIZADO

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PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA SAÚDE: CARDIOLOGIA E CIÊNCIAS CARDIOVASCULARES

EFEITOS ARRÍTMICOS DA CAFEÍNA:
METANÁLISE E ENSAIO CLÍNICO RANDOMIZADO

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DEDICATÓRIA

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Esta tese de doutorado segue o formato proposto pelo Programa de Pós-Graduação em Ciências da Saúde: Cardiologia e Ciências Cardiovasculares da UFRGS, sendo apresentada na forma de revisão da literatura e de um manuscrito sobre o tema da tese:

1. Revisão da literatura;

2. Artigo original em inglês referente ao trabalho de pesquisa propriamente dito que deverá ser submetido para publicação em periódico científico de circulação internacional, conforme as normas do mesmo**.**

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CDI – Cardiodesfibrilador implantável

DCV – Doença Cardiovascular

FA – Fibrilação atrial

IC – Insuficiência cardíaca

LISTA DE ABREVIATURAS DOS ARTIGOS EM INGLÊS

AF – Atrial Fibrilation

ACE – Angiotensin converting enzyme

ARA II – Angiotensin receptor II antagonist

BNP – Brain natriuretic peptide

CTL – Control

CF – Caffeine

CI – Confidence Interval

CNPq - Conselho Nacional de Desenvolvimento Científico e Tecnológico

FFQ – Food frequency questionnaire

HF – Heart failure

IR – Interquartile range

LV – Left ventricular

LVEF – Left ventricular ejection fraction

NSSVT - Non-sustained supraventricular tachycardia

NSVT - Non-sustained ventricular tachycardia

NYHA – New York Heart Association

RCT – Randomized Clinical Trial

SCD – Sudden cardiac death

SVPB – Supraventricular premature beat

VPB – Ventricular premature beat

VFT - Ventricular fibrillation threshold

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RESUMO

A relação entre o consumo de cafeína e a ocorrência de arritmias permanece controverso. Apesar desta falta de evidência científica, a redução do consumo de cafeína ainda é amplamente recomendada. No intuito de elucidar esta questão, foram desenvolvidos I) revisão sistemática com metanálise e II) ensaio clínico randomizado. **I) Métodos e resultados**: A pesquisa foi realizada no Pubmed, Embase e Cochrane, e termos relacionados ao café, a cafeína, e arritmia cardíaca foram utilizados. Após avaliação de texto completo, sete estudos em humanos e dois estudos em animais foram incluídos na metanálise. Em estudos com animais, o principal resultado relatado foi uma redução significativa no limiar para fibrilação ventricular, no qual foi observada uma diferença média de 22,15 mA. O principal resultado avaliado em estudos com humanos foi o risco para batimentos prematuros ventriculares (BPV) em 24h (RR 1,00 (95% IC 0,94-1,06). **II) Métodos e resultados:** Em um estudo duplo-cego randomizado cruzado, comparou-se o efeito da cafeína e placebo sobre a frequência de BPV e batimentos prematuros supraventriculares (BPS), em repouso e durante um teste ergométrico, em 51 pacientes (60,6 ± 7 anos) com insuficiência cardíaca. Após a ingestão de 5 doses de 100ml de café descafeinado com um total de 500mg de cafeína ou placebo, não foram observadas diferenças significativas entre os grupos no número de BPV ou BPS (150 vs. 212 BPV, p = 0,39; 6 SVPBs vs. 7 SVPBs, p = 0,83). Além disso, variáveis derivadas de testes de esforço também não foram influenciadas pela ingestão de cafeína.

Conclusão: Não há nenhuma evidência para apoiar a recomendação comum para limitar o consumo moderado de cafeína em pacientes cardiopatas.

1. MARCO TEÓRICO

1.1 Arritmias cardíacas

O sinal elétrico para a contração do coração origina-se no nodo sinoatrial, a partir do qual ele percorre os átrios até atingir o nodo atrioventricular. A ativação, em seguida, se espalha ao longo dos ventrículos para completar um ciclo de contração. Em situações de arritmia, a coordenação da contração está perdida. A causa subjacente da arritmia é geralmente um fenômeno de reentrada em que o estímulo elétrico circula em torno de um núcleo de tecido inexcitável.

Taquiarritmias cardíacas são divididas em arritmias dos ventrículos e arritmias do átrio e do nodo atrioventricular. As arritmias são muitas vezes devido a doença cardíaca estrutural causada pela aterosclerose, hipertensão, doença valvular ou cardiomiopatia, e raramente ocorrem em pessoas com corações estruturalmente normal. Arritmias ventriculares sustentadas são uma complicação freqüente e potencialmente fatais de infarto do miocárdio, porque a falta de oxigênio resultante da estenose coronariana pode danificar o tecido do músculo e impedir a difusão de correntes elétricas. Isso pode levar à arritmia ventricular fatal, na qual o coração não contrai corretamente, os tecidos não recebem o sangue, resultando em morte.

Este tipo de taquiarritmia é a causa mais freqüente de morte súbita, e qualquer componente da dieta que seja suspeito de promover arritmia deve ser analisado com seriedade. (Katan, 2005).

1.2 Insuficiência Cardíaca

A insuficiência cardíaca (IC) é a via final comum da maioria das doenças que acometem o coração. É uma síndrome clínica complexa que se manifesta com disfunção do músculo cardíaco, hipertrofia ventricular e alterações hemodinâmicas causadas pela interação de fatores circulatórios, neuro-hormonais e metabólicos. Visando a aumentar a força contrátil do miocárdio e a preservar a função cardíaca e a perda de células miocárdicas, mecanismos hemodinâmicos e neuro-humorais são ativados (Kenchaiah, 2002).

1.3 **Insuficiência Cardíaca e Arritmias**

A IC congestiva continua a ser uma das principais causas de mortalidade e morbidade no mundo inteiro. Em aproximadamente 50% destes doentes, o modo de morte é súbita. A taquicardia ventricular e fibrilação representam a maioria das arritmias; os mecanismos responsáveis são heterogêneos e complexos (Ebinger, 2004). Em alguns casos específicos, essas arritmias são causadas por alterações de canais iônicos cardíacos, tais como sódio, cálcio, potássio e canais, que transportam correntes iónicas e são determinantes fundamentais da excitabilidade cardíaca. Anormalidades desses canais iônicos são atribuídas a mutações em genes que codificam as proteínas de canal e causam função alterada de canais que podem predispor ao aparecimento de arritmias (Ji, 2004). Além disso, os mecanismos compensatórios podem se tornar nocivos e potencialmente arritmogênios através de uma variedade de mecanismos.

Em relação à fibrilação atrial (FA), o estudo SOLVD nos demonstrou que, em indivíduos em classe funcional II e III de ICC, cerca de 10% já a apresentaram ou a apresentam atualmente (Francis, 1990); já um trabalho do grupo CONSENSUS, com

pacientes com ICC clsse IV, apresenta um percentual muito mais considerável, de 50% (CONSENSUS Group, 1987). Um fato que deve ser lembrado é que, devido a melhoras no tratamento, com consequente aumento da sobrevida, cresce o número de pessoas com ICC, e o percentual daqueles afetados em algum momento pela FA tende a crescer concomitantemente.

Devido ao alto risco de morte súbita associado à insuficiência cardíaca, em determinados grupos de pacientes, especialmente naqueles com disfunção sistólica grave (fração de ejeção < 30-35%), há indicação de implante de cárdio-desfibrilador implantável (CDI). Além de essencial no caso de parada cardíaca, o CDI também é importante para quantificação e avaliação das arritmias, já que o aparelho é capaz de registrar eventos.

1.4 Cafeína

A cafeína (1,3,7-trimetilxantina) é uma purina que ocorre naturalmente nos grãos de café (figura 1). Em níveis de ingestão associados ao consumo de café, a cafeína parece exercer seus efeitos biológicos através do antagonismo dos subtipos A1 e A2 do receptor de adenosina. A adenosina é um neuromodulador endógeno com efeitos inibitórios na maior parte, e antagonismo de adenosina pela cafeína resulta em efeitos que geralmente são estimulantes. Alguns efeitos fisiológicos associados com a administração de cafeína incluem estimulação do sistema nervoso central, elevação aguda da pressão arterial, aumento da taxa metabólica e diurese. A cafeína é rápida e quase completamente absorvida no estômago e no intestino delgado, e distribuída a todos os tecidos, incluindo o cérebro (Higdon, 2006).

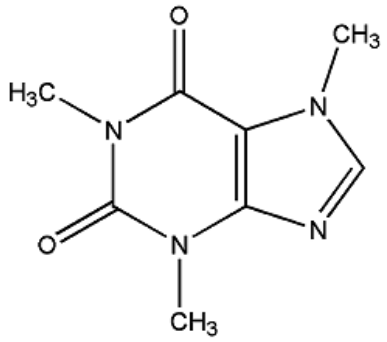

Figura 1. Estrutura da cafeína

As concentrações de cafeína em bebidas de café podem ser muito variáveis. Estudos de análise dos cafés brasileiros encontraram uma média de 0,55mg/ml de cafeína no “café passado” e 0,24mg/ml no chimarrão, bebida vastamente consumida no Rio Grande do Sul. Em estudo de base populacional realizado no Brasil observou-se uma média de consumo de aproximadamente 140ml/dia, sendo este consumo ainda maior na região sul do país, com uma média de 160ml/dia de café passado, além do consumo do chimarrão, que alcança uma média de consumo de ~1300ml/dia, demonstrando a presença desta substância no consumo diário dos brasileiros (Canela, 2009).

1.5 **Cafeína e o coração**

Há muito tempo, suspeita-se que exista uma associação entre ingestão de café e doença cardiovascular, em particular a doença coronariana. Os estudos existentes são inconsitentes, no entanto, alimentam o debate a respeito do risco do consumo de café (Grobbee, 1990). Em metanálises relizadas a respeito dessa relação, observou-se uma indicação não clara de que consumo de café determina

risco aumentado para doença coronariana em estudos caso-controle; já em estudos de coorte prospectiva essa associação não foi observada (Cornelis, 2007 e Sofi, 2009). Em 2014, uma metanálise de estudos de coorte avaliou a relação entre consumo de café e risco de desenvolvimento de doença cardiovascular e encontrou uma associação não-linear entre o consumo de café e o risco de doença cardiovascular (DCV), onde o consumo moderado de café foi inversamente associado com o risco de DCV, com o menor risco encontrado em 3 a 5 xícaras por dia e o consumo pesado de café não foi associado com o risco elevado (Ding, 2014).

Freedman et al (2012), examinaram a associação entre o consumo de café com mortalidade total e por causas específicas entre 229.119 homens e 173.141 mulheres do National Institutes of Health–AARP Diet e Health Study com idade de 50 a 71 anos de idade. Os resultados demonstraram associações inversas significativas do consumo de café com as mortes por todas as causas e, especificamente, com mortes devido à doença cardíaca.

Além disso, outra relação que vem sendo explorada diz respeito à possível associação entre consumo de cafeína e arritmias cardíacas. Um estudo com 697 médicos demonstrou que 80-90% recomendam redução do consumo de cafeína para pacientes com arritmia, taquicardia e palpitações, embora esse aparente "consenso" não apresente fundamento teórico (Hughes, 1988).

Em sua maioria, os estudos com humanos que exploram esta relação são estudos de coorte, com pacientes saudáveis e avaliam somente a incidência de fibrilação atrial (FA) (Wilhelmsen, 2001; Frost, 2005; Mukamal 2009). A exemplo disso, um estudo foi realizado com a coorte de Framingham, onde avaliou-se aproximadamente 4.500 pacientes durante 4 anos de tempo de seguimento e não foi encontrada relação entre consumo de cafeína e incidência de FA (Shen, 2010). Mais

recentemente, uma metanálise de estudos observacionais confirmou este achado em análise incluindo 7 artigos e 115.993 indivíduos. Além de observar a falta de associação entre cafeína e FA, ainda sugeriu-se um possível efeito protetor em consumo baixo (OR 0.85; IC 95%:0.78 – 0.92) (Caldeira, 2013).

Uma revisão da literatura avaliando a relação entre consumo de cafeína e arritmias cardíacas observou resultados semelhantes, de que o consumo moderado de cafeína não se associa a risco de arritmias; essa relação só foi encontrada em padrões de consumo muito elevados, acima de 9 copos de café por dia. Em um dos estudos, intervenções que atingiram até 450mg/dia de cafeína em pacientes pós-infarto foram testadas e não foi encontrado risco para arritmias (Pelchovitz, 2011).

Em se tratando de doses moderadas, um trabalho em que 50 pacientes com arritmias graves (taquicardia ou fibrilação ventricular) e frequentes ingeriam 200mg de cafeína e eram submetidos a esforço físico demonstrou não haver relação aparente entre café e surgimento de arritmias (Graboys, 1989). Dois estudos epidemiológicos recentes, um com 33.638 mulheres e outro com 47.949 indivíduos, sugeriram não só que não havia relação direta entre cafeína e arritmias, mas que poderia haver relação inversa, embora esta segunda evidência não tenha tido significância estatística (Conen, 2010 e Frost, 2005).

Em relação a doses suprafisiológicas, há alguns estudos em animais que devem ser levados em conta. Um trabalho demonstrou que a cafeína em altas doses (12,5mg/kg) diminui o limiar para fibrilação ventricular em cachorros (Bellet, 1972). Em outro, em que foram dados até 5mg/kg de cafeína para cachorros, é apontado

que a incidência e a gravidade das arritmias dependem da dose oferecida, sendo estas diretamente proporcionais (Metha, 1997).

Até o presente momento, não foram realizados estudos em pacientes com IC, que representam uma população de risco para desenvolvimento de arritmias devido à própria patologia. Além disso, os estudos de intervenção são muito distintos no que diz respeito à metodologia aplicada e à dose de cafeína administrada.

2. JUSTIFICATIVA

Existe uma suspeita de que o consumo de cafeína na dieta possa representar um acréscimo no risco para arritmias, porém, até o presente momento não existe um consenso a respeito deste assunto.

Alguns estudos realizados em animais sugerem uma possível associação com doses suprafisiológicas, porém esse achado não aparece em estudos com humanos. Em especial, na população de pacientes com IC, pouco se sabe a respeito da associação entre consumo de cafeína e arritmias, em especial em doses mais altas.

Na presença da necessidade de orientações mais específicas e seguras a respeito do consumo de cafeína, torna-se importante a realização de estudos que sumarizem os achados de estudos anteriores na intenção de responder a esta questão.

3. HIPÓTESE

O consumo de cafeína não está associado a aumento de ocorrência de arritmias, mesmo em pacientes com IC.

4. OBJETIVOS

- Avaliar o efeito do consumo de cafeína sobre o risco de ocorrência de arritmias cardíacas em estudos de intervenção em animais e humanos (metanálise);
- Avaliar o efeito de uma alta dose de cafeína sobre parâmetros eletrofisiológicos em repouso e durante teste de esforço em pacientes com IC portadores de cardio-desfibrilador implantado ou não (ensaio clínico randomizado).

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6. Artigo 1. Efeito de consumo de cafeína sobre arritmias cardíacas – revisão sistemática e metanálise

Effect of caffeine on ventricular arrhythmia: a systematic review and meta-analysis of experimental and clinical studies

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Aims The relationship between caffeine consumption and the occurrence of arrhythmias remains controversial. Despite this lack of scientific evidence, counselling to reduce caffeine consumption is still widely advised in clinical practice. We conducted a systematical review and meta-analysis of interventional studies of the caffeine effects on ventricular arrhythmias.

Methods and results The search was performed on Pubmed, Embase, and Cochrane database, and terms related to coffee, caffeine, and cardiac arrhythmias were used. Methodological quality was assessed based on The Cochrane Collaboration recommendations and the ARRIVE guidelines. There were 2016 citations retrieved on the initial research. After full-text assessment, seven human and two animal studies were included in the meta-analysis. In animal studies, the main outcome reported was the ventricular fibrillation threshold. We observed a significant mean difference of −2.15 mA (95% CI −3.43 to −0.87; I^2 0.0%, P for heterogeneity ¼ 0.37). The main outcome evaluated in human studies was the rate of ventricular premature beats (VPBs). The overall relative risk for occurrence of VPBs in 24 h attributed to caffeine exposure was 1.00 (95% CI 0.94–1.06; I^2 13.5%, P for heterogeneity ¼ 0.32). Sensitivity analysis for caffeine dose, different designs, and subject profile was performed and no major differences were observed.

Conclusion Our meta-analysis demonstrates that data from human interventional studies do not show a significant effect of caffeine consumption on the occurrence of VBPs. The effects observed in animal studies are most probably the result of very high caffeine doses that are not regularly consumed in a daily basis by humans.

Keywords Caffeine † Coffee † Arrhythmias

Introduction

Caffeine is the major component of coffee, tea, and some of the most consumed beverages worldwide. Caffeine (1,3,7-trimethylxanthine) is a naturally occurring purine that exert its biological effect through the antagonism of adenosine receptors (subtypes A1 and A2), resulting in a stimulatory property.[1,2] The relationship between caffeine consumption and the occurrence of arrhythmias has been explored for many decades, but remains controversial.[3,4]

Early experimental studies indicated that caffeine appeared to cause severe ventricular arrhythmias.[5] This pro-arrhythmic effect, however, has not been consistent in all animal studies, including reports that assessed dose-dependent protocols.[6,7] Similarly, human studies have also been conflicting. Isolated case reports have suggested a direct association between caffeine consumption and sudden death, presumably mediated by severe ventricular arrhythmias.[8] On the other hand, recent dose–response meta-analysis of cohort studies resulted in a counterintuitive protective effect of caffeine exposure on the risk of atrial fibrillation (AF).[9]

Small prospective clinical trials did not demonstrate an increase in clinically significant ventricular or supraventricular arrhythmias, even after exposure to high doses of caffeine.[4] Moreover, studies in patients at risk of arrhythmia showed that moderate caffeine consumption apparently did not induce arrhythmic events.[10] However,

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What's new?

- † Based on a meta-analysis of data from seven human interventional studies, we did not observe a significant effect of caffeine consumption on the occurrence of VPBs.
- † Caffeine doses associated with increased risk of arrhythmia in animal studies are not regularly consumed in a daily basis by humans.
- † As such, there is no scientific reasoning that supports a clinical recommendation to decrease or avoid caffeine consumption in patients at risk or with suspicious symptoms of arrhythmias.

there is no large-scale prospective randomized controlled trial that convincingly evaluate the effect of caffeine on the risk of arrhythmias.

Despite this lack of strong scientific evidence, counselling to reduce caffeine consumption is still very tempting and widely used in clinical practice. In particular, drinking caffeine-rich beverages is often discouraged by physicians to patients presenting with a wide range of unspecific symptoms, such as palpitations, tachycardia, or irregular heartbeats, even in the absence of structural heart disease. Thus, the aim of this study was to systematically review the literature of animal and human interventional studies, and conduct a meta-analysis of the caffeine effects on ventricular arrhythmias, in healthy and unhealthy subjects.

Methods

For this systematic review and meta-analysis, we followed the Cochrane Collaboration[11] methods and PRISMA statement.[12]

Search strategy and study selection

Studies were identified through electronic database searches on Medline (accessed by Pubmed), Embase, and Cochrane Central Register of Controlled Trials database up to 05/2014, without update limits. In order to obtain a high-sensitivity strategy, the following search terms were used, both as free-text and subject headings: coffee, caffeine, arrhythmias, cardiac. Only eligible full texts in English, Portuguese, or Spanish were considered for review. The complete search strategy used for the PubMed database was ('Arrhythmias, Cardiac'[Mesh] OR arrhythmia) AND ((coffee OR caffeine) OR ('coffee'[Mesh] OR 'caffeine'[Mesh])).

Eligibility criteria

To comprehensively assess the association between arrhythmia and caffeine, were included interventional studies that evaluated caffeine alone and its effects on arrhythmia outcomes. Studies should show comparison data of groups of patients that did not receive caffeine or has received a matching placebo. Both animal and human reports, including healthy and unhealthy subjects were included. There was no restriction to study design, except for ex vivo models.

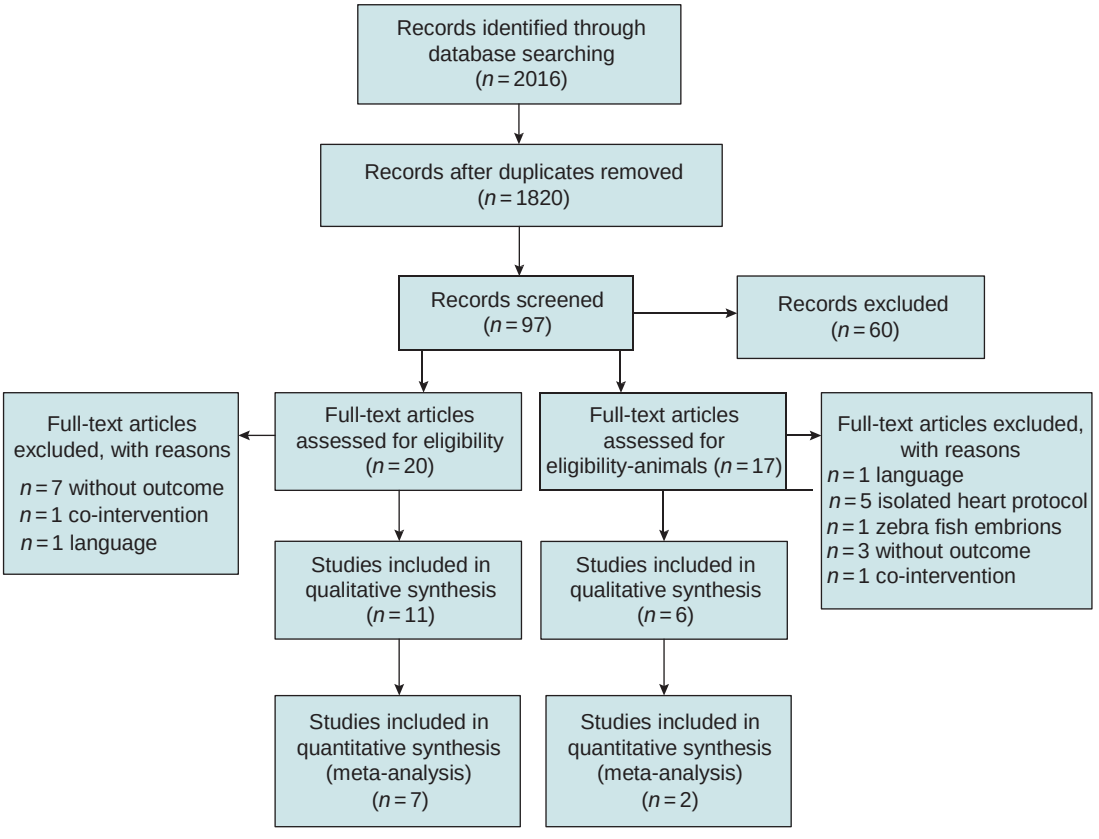

Figure 1 Flow diagram showing the number of records identified, screened, extracted, and included in the final analysis.

Table 1 Characteristics of the animal studies

Study	Study design	Animal model	n	Age	Weight	Dose (mg)	Duration of intervention	Outcome	Results
Bellet et al. 1972[15]	Experimental Trial	Dogs	Implanted electrodes: 10 CF 10 CTL	NR	25–30 pounds	 25 mg/kg	Single administration	VFT	 CF ¼ 9.6 + 6.0 mA‡ CTL ¼ 14 + 0.72 mA
Fusilli et al.[16]	Experimental Trial	Dogs	7 CF 8 CTL	2 years	CF:10.4 + 0.33 kg CTL:9.9 + 0.27 kg	35 mg	30 min infusion	VFT	 CF ¼ 41.9 + 1.3 mA CTL ¼ 43.9 + 1.3 mA
Ilback et al.[6]	Experimental Trial	Rats	1 CTL 1 CF low dose 1 CF mod. Dose 1 CF high dose	NR	300 g	 5 mg/kg 15 mg/kg 45 mg/kg	Single administration	Arrhythmias	No effect associated to high dose of caffeine
Ishida et al.[7]	Experimental Trial	Rabbits	5 CTL 5 CF low dose 24 CF high dose	NR	2.5–3.3 kg	 0.3 mg/kg/min 1.0 mg/kg/min	Continuous infusion until outcome	Time to VPBs	CTL ¼ No VPBs CF low dose ¼ No VPBs CF high dose ¼ 35 min
Mehta et al.[5]	Experimental Trial	Dogs	13 animals that underwent: 10 low CF[a] 16 mod. CF[a] 25 high CF[a]	NR	NR	 1.0 mg/kg 2.5 mg/kg 5.0 mg/kg	Single administration	VPBs	 n ¼ 5‡ n ¼ 20‡ n ¼ 50‡
Rashid et al.[17]	Experimental Trial	Dogs	7 CTL 10 CF 8 CF 7 CF 4 CF	NR	20–24 kg	CTL[b] 2–4 mg/mL[b] 5–7 mg/mL[b] 8–10 mg/mL[b] 11–20 mg/mL[b]	3 subsequent doses with 2 min of interval	WOV for AF	271 + 85 ms‡ 154 + 114 ms‡ 167 + 55 ms‡ 126 + 32 ms‡ 115 + 84 ms‡

CTL, control; CF, caffeine; VTF, ventricular fibrillation threshold; Mod., moderate; VPBs, ventricular premature beats; WOV, window of vulnerability.
[a]Number of experiments.
[b]Seric dosage of caffeine.
‡P , 0.05 compared with control group.

Data extraction

Titles and abstracts were evaluated by two independent reviewers (P.Z. and P.A.B.R.) and any discrepancy was solved by consensus or by a third reviewer (L.E.R.). Reviewers were not blinded to author, institutions, or manuscripts journals. Abstracts that did not provide enough information were accepted for subsequent evaluation. The full-text analysis and data extraction were performed by the same two reviewers. For each study, we extracted information about publication data, population characteristics, intervention and comparison group, study protocol, outcomes, and limitations.

Assessment of bias risk and study quality

Methodological quality was explored using an approach similar to that recommended by The Cochrane Collaboration in assessing risk. Quality assessment and risk of bias for human studies included specific questions for clinical trials and cross-over designs. The following dimensions were considered: study design, sequence generation, allocation concealment, blinding, losses and exclusions, randomization, and carry-over effects. For animal studies, data selected for extraction were related to experimental procedures, animal characteristics, facilities and animal conditions, sample numbers, as described in Kilkenny et al.[13] and the ARRIVE Guidelines.[14]

Risk judgement was assessed using pre-specified criteria about the adequacy of the study and expressed as 'low risk', 'high risk', or 'unclear risk'. It was considered high risk of bias when the information was not provided at all. For animal studies, the bias and quality assessment was expressed as 'Yes', 'No', and 'Unclear' answers.

Data analyses

For each study, we looked for arrhythmic outcomes reported after caffeine intervention and control. Analyses were performed using a random-effects model. Statistical heterogeneity among studies was assessed using the I^2 statistic in which values $\geq 50\%$ were considered indicative of high heterogeneity. Possible publication bias was evaluated with the Egger's regression asymmetry test. We performed subgroup analysis for potential confounding factors. All statistical analyses were conducted using the Stata software version 11.0 (Stata Inc., College Station, TX, USA) with two-tailed α set at $P \leq 0.05$ for statistical significance.

Results

There were 2016 citations retrieved on the initial assessment. After full-text evaluation, 11 human and 6 animal studies were selected for the systematic review, and 7 human and 2 animal studies were selected for the meta-analysis. A flow diagram of the search and selection protocol is shown in Figure 1.

Animal studies

Description of studies

After full-text analysis, most of the excluded reports were due to the use of isolated hearts in the protocol. The number of animals in each experiment group varied from 1 to 24, including rats, dogs, and rabbits. Information extracted from included studies in qualitative and quantitative analysis is shown in Table 1. Five different arrhythmic-related outcomes were reported. In general, research protocols had an additional stimulatory phase and different doses of caffeine were compared. Overall, animal studies demonstrated a significant increase in arrhythmic outcomes after exposure to caffeine (Table 1).

Table 2 Quality assessment of animal studies

Study	SD	A	W	G	Temperature control setting	Description of losses and exclusions	Blinding of outcome	Randomization	Are unbiased data available?	Numbers of animals stratified by report section where information is reported		
										Methods	Results	Matched[a]
Bellet et al.[15]	Experimental Trial	No	Yes	No	No	Unclear	No	No	No	Yes	Yes	No
Fusilli et al.[16]	Experimental Tria	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No
Ilback et al.[6]	Experimental Tria	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Ishida et al.[7]	Experimental Tria	No	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes
Mehta et al.[5]	Experimental Trial	No	No	No	No	Unclear	No	No	No	Yes	No	No
Rashid et al.[17]	Experimental Trial	No	Yes	No	Yes	Unclear	No	No	No	Yes	No	No

SD, study design; A, age; W, weight; G, gender.
[a]Numbers in 'Methods' and 'Results' sections are consistent; if inconsistent, authors provide reasons (e.g. animal death).

Ilback et al.[6], however, did not observe an association of high-dose caffeine (45 mg/kg) with the prevalence of arrhythmias in a rat model.

Quality and publication bias assessment

Description and methodology of animal protocols did not achieve high-quality standards in many important aspects. No animal study was blinded or randomized. Characteristics of the animals used in the protocols, such as age, weight, and gender, were not presented in many of the studies (Table 2). Two studies reported unbiased data, i.e. without possible carry-over effect. Only 50% of the studies had description of losses and exclusions and most of them did not report the number of animals in each part of the protocol.

Meta-analysis of animal studies

Only two experimental studies were included in the meta-analysis, both conducted in dogs (n ¼ 35 animals). The outcome reported in both reports was the ventricular fibrillation threshold (VFT). Bellet et al.[15] have reported results from different groups of animals; we have chosen the group that uses a comparable measure of VFT. Ventricular fibrillation threshold was expressed as mean of milliamps, measured 60 min after the acute intervention (Figure 2). The mean difference in VFT over the two studies was 2.15 mA (95% confidence interval [CI] 3.43 to 0.87; I^2 0.0%, P for heterogeneity ¼ 0.37). The lack of a common arrhythmic-related outcome was the major reason that did not allow other studies to be included in the meta-analysis.

Human studies

Description of studies

A total of 11 human studies (n ¼ 434 subjects) fulfilled the inclusion criteria for the systematic review and 7 were included in the meta-analysis (n ¼ 290 subjects). Prakash and Kaushik[18] was excluded from the final analysis because no patient had arrhythmia at the end of protocol. Characteristics of the 11 studies are summarized in Table 3. Four of these had a randomized cross-over design, three were double-blinded randomized clinical trials (RCTs), and four were classified as quasi-experiment trials, i.e. studies that had a comparison group or control period but did not fit the RCT design. Most of the studies included patients with some previous risk condition for arrhythmia, two included only healthy subjects and one report included both healthy and unhealthy populations. The study protocols were predominantly short-term interventions with a single dose of caffeine or matching control, although one study had a 2-week interventional period. Subjects were monitored by Holter or continuous electrocardiogram to evaluate arrhythmic-related outcomes.

The 11 studies included in the systematic review reported 4 different arrhythmic-related outcomes. For the meta-analysis, we restricted to the most commonly reported event: the number of ventricular premature beats (VPBs), also referred as ventricular ectopic beats, extrasystoles, and/or premature contractions. Because of the differences in temporal presentation, we standardized the measure as number of VPBs in 24 h after the experimental and control protocols. Importantly, none of the studies reported major adverse events.

Quality and publication bias assessment

None of the studies had a clear description of sequence generation, allocation concealment, and description of losses and exclusions. The studies with a cross-over design appropriately reported that the interventions were randomized. Only one cross-over study had unbiased data available, i.e. it reported the data from the first period of the protocol (Table 4).

Meta-analysis of human studies

The overall relative risk for occurrence of VPBs in 24 h after caffeine exposure was 1.00 (95% CI 0.94–1.06; I^2 13.5%, P for heterogeneity ¼ 0.32). Sutherland et al. provided more than one interventional group and both were included and analysed separately. We performed sensitivity analysis for study design, caffeine dose (and ≥300 mg) and subject condition (healthy and unhealthy status) (Figures 3–5). Overall, none of these analyses provided different results, although we observed increased heterogeneity in

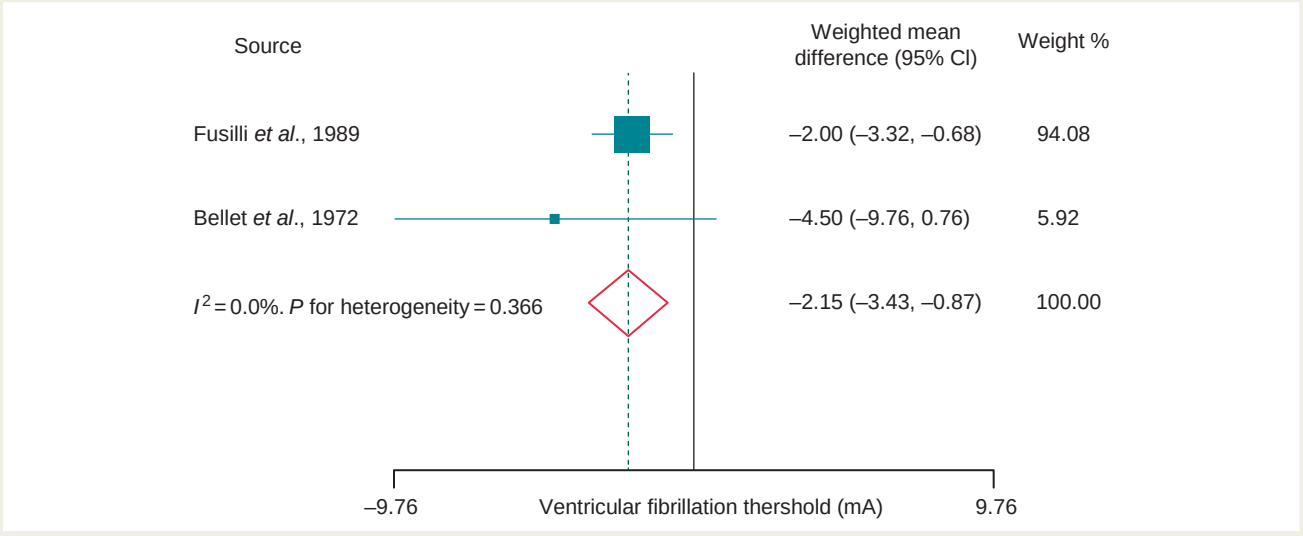

Figure 2 Absolute changes in the VFT of animal studies comparing caffeine vs. control.

Table 3 Characteristics of the human studies

Study	SD	Condition	n	Age	Intervention	Control	Duration of intervention	Outcome	Other relevant outcomes
Cheslky et al.[19]	1 day/1 group Trial[a]	Symptomatic VT or VF	22	60 ± 10	275 mg + electrical stimulation	Control period without caffeine	Single dose	Inducibility and severity scores	–
Graboys et al.[20]	1 day/2 groups Trial[a]	Malignant VA	50	NR	200 mg	Decaffeinated coffee	Single dose	VPBs	VT CF: 6 ± 24 CTL: 6 ± 24
Lemery et al.[21]	RCT	Symptomatic SVT	80	49 ± 14	5 mg/kg + electrical stimulation	Placebo	Single dose	VT	SVT cycle length CF: 314 (286–382) CTL: 314 (280–360) No VT
Myers and Harris[22]	Cross-over	Previous AMI	70	64 ± 2	300 mg	Placebo lactose powder	2 doses with 4 h of interval	VPBs	Patients with VT CF: 1 CTL: 0
Myers et al.[23]	Cross-over	Previous AMI	35	58 ± 2	450 mg	Placebo lactose powder	Single dose	VPBs	Patients with VT CF: 1 CTL: 0
Newby et al.[24]	Cross-over	Symptomatic palpitations and frequent VPBs	13	NR	Minimum 3 cups/day	Decaffeinated coffee	1 week for each protocol	VPBs	–
Newcombe et al.[25]	2 days/1 group Trial[a]	Healthy	34	31 (21–49)	1 mg/kg/ half life	Control period without caffeine	24 h	VPBs	SVPBs CF: 3 ± 4 CTL: 5 ± 11
Prakash and Kaushik[18]	Cross-over	Healthy	12	25–39	175 mg	Decaffeinated coffee	Single dose	Arrhythmia	–
Richardson et al.[26]	RCT	Type 1 diabetic patients and healthy controls	30	NR	250 mg	Matched placebo	2 weeks for each protocol	VPBs	No effect associated to VT SVPB or SVT
Richardson et al.[27]	RCT	Previous STEMI	52	CTL: 67.4 ± 12.1 CF: 67.8 ± 10.6	353 ± 90[b]	Decaffeinated coffee	5 days	VPBs	VT CF: 5.3% CTL: 2.9% SVT CF: 2.6% CTL: 2.9%
Sutherland et al.[28]	2 days/1 group Trial[a]	Healthy subjects and subjects with VPBs	36	Healthy: 32 ± 7 VPBs: 39 ± 11	1 mg/kg/ half life	Control period without caffeine	24 h	VPBs	Patients with VT CF: 1 CTL: 0

SD, study design; CTL, control group; CF, caffeine group; NR, not reported; VT, ventricular tachycardia; VF, ventricular fibrillation; VA, ventricular arrhythmia; SVT, supraventricular tachycardia; SVPBs, supraventricular ectopic beats; AMI, acute myocardial infarction; STEMI, ST-segment elevation myocardial infarction; VPBs, ventricular premature beats.

[a]Not randomized intervention.

[b]Consumption average.

Table 4 Quality assessment of human studies

Study	SD	RSG	AC	Blinding of OA	Blinding of PP	Description of LE	C-O design appropriate?	The order of treatments was randomized?	No carry-over bias effects?	Are unbiased data available?
Chesley et al.[19]	Trial[a]	NA	NA	High risk	NA	High risk	NA	NA	NA	NA
Graboys et al.[20]	Trial[a]	NA	Unclear risk	High risk	Low risk	Unclear risk	NA	NA	NA	NA
Lemery et al.[21]	RCT	Low risk	Unclear risk	Unclear risk	Low risk	Unclear risk	NA	NA	NA	NA
Myers and Harris[22]	C-O	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	High risk
Myers et al.[23]	C-O	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	High risk
Newby et al.[24]	C-O	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	High risk	Low risk
Newcombe et al.[25]	Trial[a]	NA	NA	Low risk	NA	Unclear risk	NA	NA	NA	NA
Prakash and Kaushik[18]	C-O	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
Richardson et al.[26]	RCT	High risk	High risk	Low risk	Low risk	Unclear risk	NA	NA	NA	NA
Richardson et al.[27]	RCT	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	NA	NA	NA	NA
Sutherland et al.[28]	Trial[a]	NA	NA	Low risk	NA	Unclear risk	NA	NA	NA	NA

SD, study design; RSG, random sequence generation; AC, allocation concealment; OA, outcome assessment; PP, participants and personnel; LE, losses and exclusions; C-O, cross-over.
[a]Not randomized intervention.

subgroups. The highest caffeine dose was 450 mg (roughly equivalent to four to five cups of regular coffee) and the lowest dose was 175 mg (roughly equivalent to a single dose). Sensitivity analysis was also performed excluding a study that involved an exercise phase as a second intervention and one study evaluating a chronic intervention of caffeine. Again, no major differences in the main results were observed.

Discussion

Caffeine-rich beverages have been traditionally considered the main culprit environmental factor implicated in a variety of ordinary but unspecific complaints (like palpitations and heartbeat irregularities) in clinical practice. Physicians are particularly worried that these symptoms might be mediated by potentially dangerous arrhythmic events. In this scenario, case reports have linked caffeine overdose to ventricular and supraventricular arrhythmias. In addition, fatal ingestion of the substance has been described (usually with doses over 5 g),[8,29] which reinforced the hypothesis of a positive cause and effect relationship between caffeine intake and arrhythmias. The present systematic review and meta-analysis was specifically designed to address the impact of prospective interventions using coffee or caffeine supplements compared with a matching control on the incidence of ventricular arrhythmias. We have demonstrated that although animal studies suggest that high-dose caffeine might reduce the threshold for several types of arrhythmias, human studies consistently failed to show and increased risk for ventricular arrhythmias.

Initial experimental studies in dogs in the early 1970s and 1980s have raised the concern about the association of caffeine use and the risk of severe ventricular arrhythmic events. Two of these studies were meta-analysed in the present report, demonstrating an increased risk to develop ventricular fibrillation in animals that received very high doses of caffeine (up to 35 mg/kg). Similarly, Ishida et al. have shown that a high-dose continuous infusion of caffeine (1 mg/kg/min) was associated with the appearance of ventricular ectopic beats in rabbits, while Mehta et al. demonstrated a dose–response effect on the occurrence of VPBs after a single dose of caffeine in dogs. Except for Ilback et al., all animal models were consistent to demonstrate a positive and significant association with arrhythmic outcomes, including vulnerability to AF.[5,17] The results in animal studies that could not be meta-analysed showed a possible dose–effect relationship, as we observe in the experiments performed by Rashid et al.,[17] in which the time to the arrhythmic outcome decreased with increasing blood concentration of caffeine. However, human studies analysing coffee intake, the most common source of ingestion of caffeine, did not confirm this behaviour. In a recent meta-analysis of prospective studies that examined dose–response effect of usual intake of coffee, it has been shown that the risk of developing AF decreases by 6% for each increase of habitual intake of 300 mg of coffee,[9] leading us to consider that usual intake of caffeine may even be protective against arrhythmic outcomes. On the other hand, fatal doses of caffeine have been reported in the literature. New prospective well-designed animal studies that evaluate progressive doses of caffeine (from very low to very high) in different scenarios (healthy and post-myocardial infarction) are needed to elucidate this hypothesis.

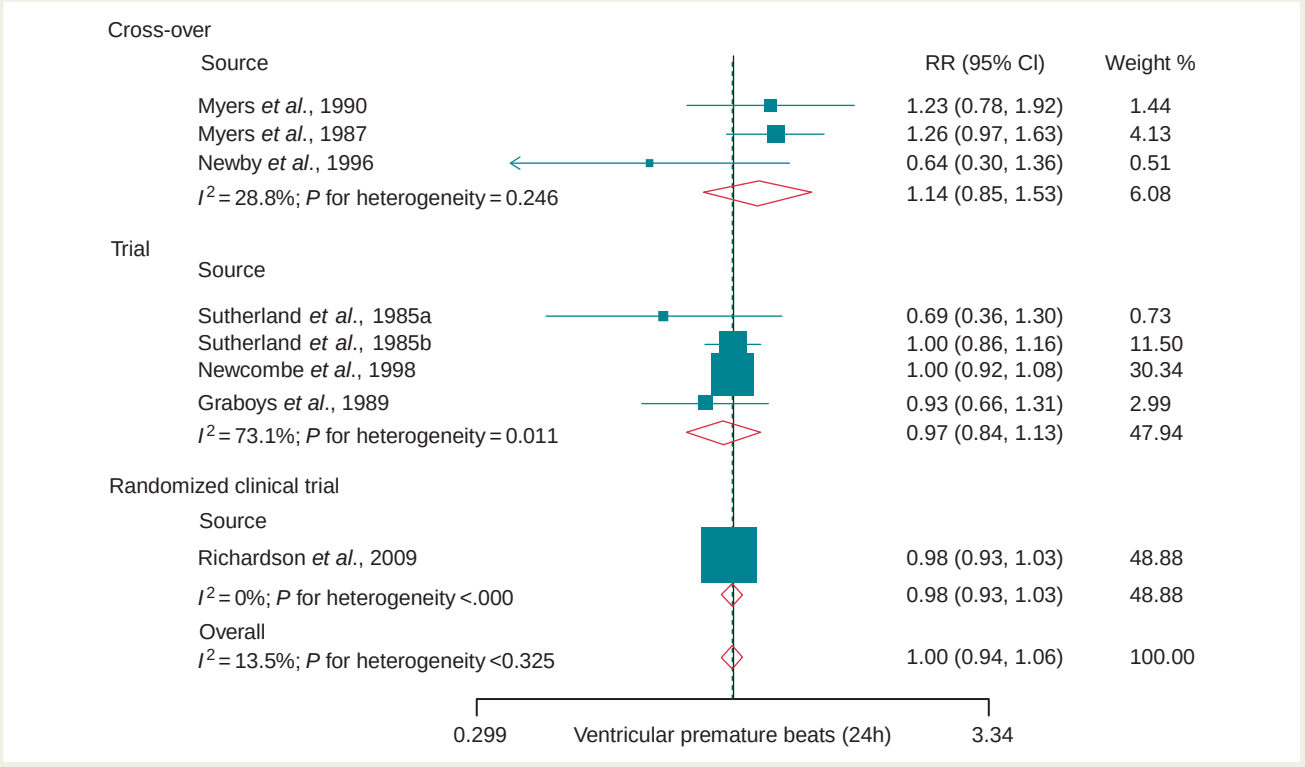

Figure 3 Relative risk for VPBs in 24 h of human studies comparing caffeine vs. control by study design.

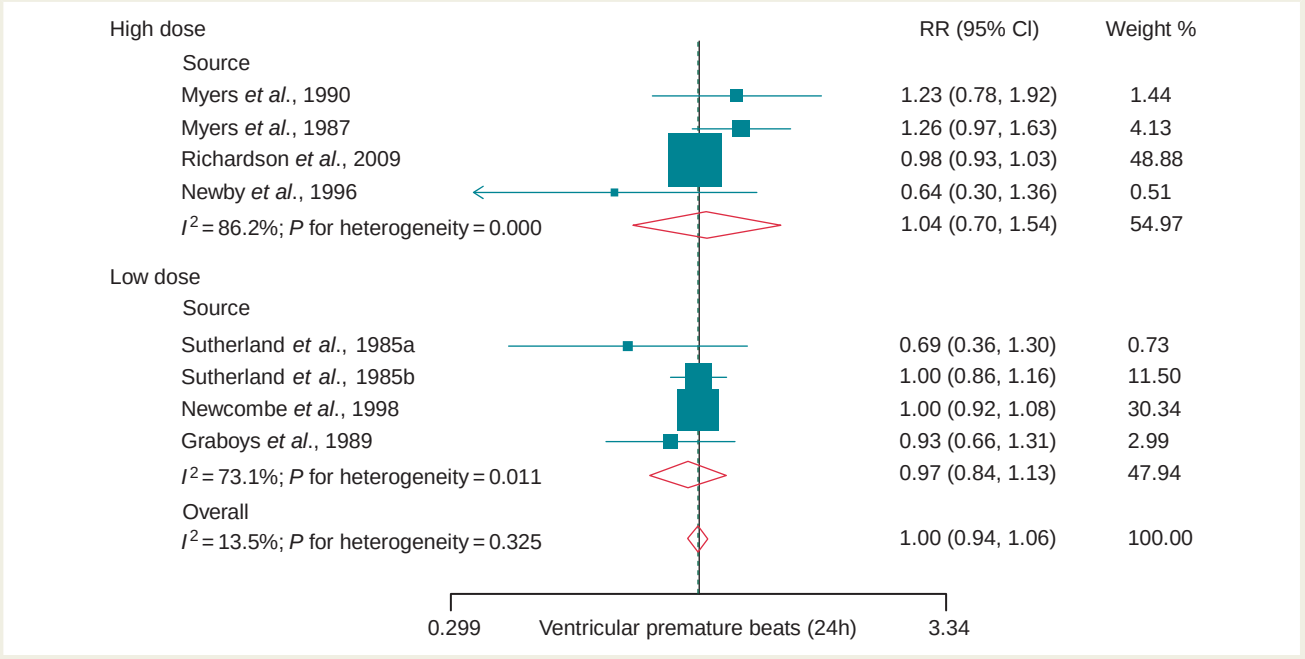

Figure 4 Relative risk for VPBs in 24 h of human studies comparing caffeine vs. control by dose of caffeine.

In addition, large epidemiologic studies did not demonstrate a significant association of caffeine intake with increased rates of arrhythmias.[30,31] Similarly, a recent meta-analysis of seven observational studies evaluated the association between chronic exposure to caffeine and AF in more than 100 000 individuals. Overall, caffeine exposure was not associated with an increased risk of AF. Interestingly, pooled results from high-quality studies showed a 13% odds reduction in AF risk, particularly after low-dose caffeine exposure

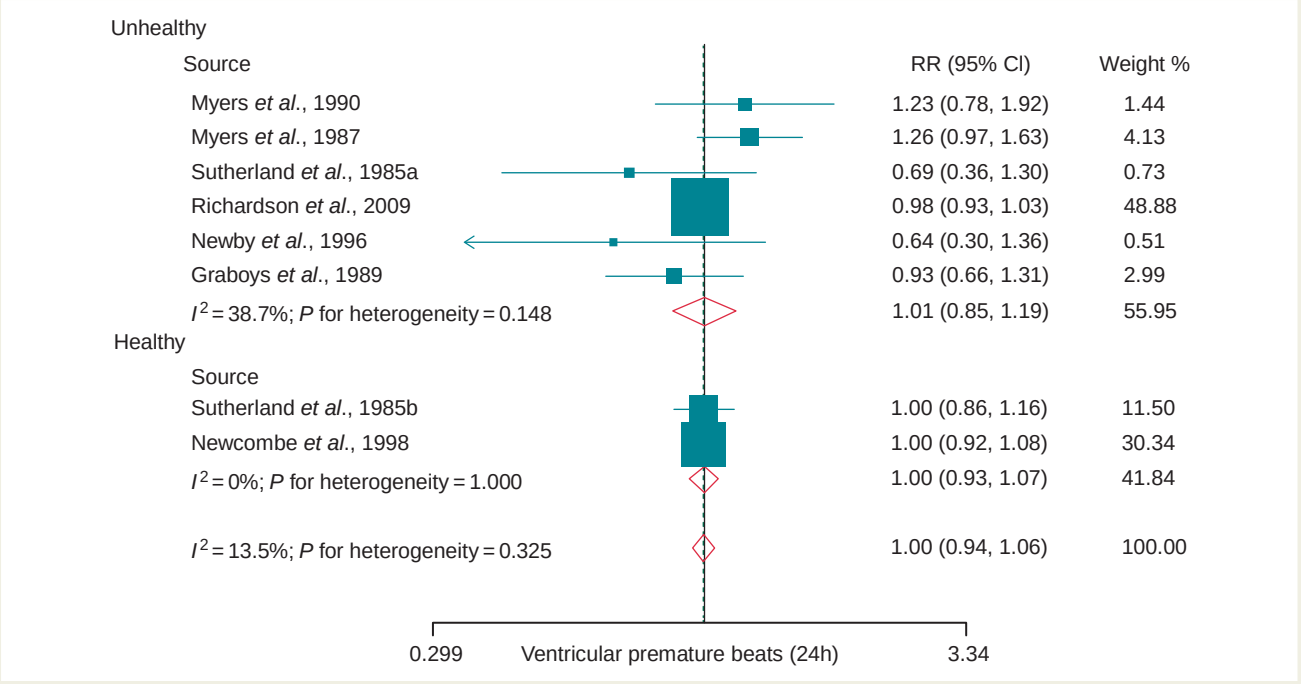

Figure 5 Relative risk for VPBs in 24 h of human studies comparing caffeine vs. control by subject condition.

(odds ratio 0.85, 95% CI 0.78–92, I^2 ¼ 0%).[32] This counterintuitive protective effect was attributed to a J-shaped curve, a phenomenon that has been previously described between coffee consumption and risk of heart failure.[33] O'Keefe et al. recently reviewed the effects of coffee consumption on overall cardiovascular health. They concluded that there is a growing body of observational evidence suggesting that habitual coffee consumption is neutral to beneficial regarding the risks of a variety of cardiovascular outcomes. Furthermore, population-based studies indicate that a daily intake of """2–3 cups of coffee appears to be safe and does not increase the risk of arrhythmias.[4]

Human studies included in this systematic review and meta-analysis used either coffee or caffeine supplements as the main intervention, in doses consistent with real life use, although most reports assessed acute or short-term protocols. It is important to point out that most studies had small samples (n ➢ 40 subjects) and could not provide a definitive answer, making useful and necessary the compilation of these data. The final result of our meta-analysis did not reveal any significant overall effect of coffee or caffeine supplements on the rates of VPBs in humans. The differences in protocols, populations (healthy or at risk for arrhythmias), dose of caffeine, and study design were analysed separately and the main results were not changed.

Few studies have evaluated the effects of different ways of preparing coffee (filtered or not) or intravenous administration of caffeine on cardiovascular outcomes.[34] Instead, most reports have demonstrated that caffeine can impair the absorption of several nutrients. A pharmacological study compared different ways of caffeine ingestion (capsule, coffee, and cola). Peak caffeine absorption, time to peak absorption, and subjective effects did not appear to be substantially influenced by the type of vehicle.[35]

Limitations

Some limitations of the current analysis deserve consideration. We acknowledge that data relating caffeine consumption and risk of arrhythmias are still incomplete. Individual studies are small-sized with poor methodological quality. Internationally accepted quality parameters of the included studies were consistently faulty for both animal and human reports, with omission of important information regarding protocol description, allocation of interventions, and baseline characteristics of research subjects. A recent meta-analysis that evaluated the effect of caffeine on intraocular pressure also reported methodological limitations.[36] In the current analysis, we observed increased heterogeneity in most subgroup analysis (Figures 3–5).

Furthermore, studies evaluating the effect of energy drinks on arrhythmia could not be included in the current protocol, since it would not be possible to isolate the effect of caffeine. This type of beverage usually contains high concentrations of taurine, vitamins, herbal supplements, and sugar or sweeteners.[37] High doses of taurine have been associated with an increased risk of atrial and ventricular arrhythmias or cardiac arrest,[38] which could be an important confounder factor.

Conclusion

Our systematic review and meta-analysis demonstrates that compilation of data from human interventional studies does not identity any meaningful interaction between caffeine consumption in different doses and VPBs. The effects found in animal studies are most probably the result of caffeine doses that are not consumed in regular daily basis in humans. Despite these evidences, a survey of

medical personnel indicate that more than 75% of the specialists recommended reduction in caffeine in patients with anxiety, arrhythmias, palpitations, and tachycardia.[39] Our data reinforce the concept that there is no scientific reasoning that supports a clinical recommendation to decrease or avoid caffeine consumption in patients at risk or with suspicious symptoms of arrhythmias. However, further high-quality prospective studies are warranted to clearly address the impact of coffee consumption on the risk of arrhythmias.

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Conflict of interest: none declared.

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7. Artigo 2. Efeito de alta dose de cafeína sobre arritmias cardíacas em pacientes com insuficiência cardíaca – ensaio clínico randomizado

Effect of high-dose caffeine on cardiac arrhythmias in patients with heart failure: A double-blinded randomized crossover trial.

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KEY POINTS

Question: Is there a pro-arrhythmic action of caffeine in heart failure patients?

Findings: In this double-blind randomized crossover clinical trial, we evaluated the acute effects of high-dose caffeine in heart failure patients at increased risk for arrhythmic events. After 500mg of caffeine administered over a 5-hour period, we found no statistically significant effect of caffeine ingestion on the number of ventricular or supraventricular arrhythmias, even during the physical stress of a treadmill test.

Meaning: Our results challenge the intuitive perception that caffeine intake should be limited in patients with heart disease and at risk for arrhythmia.

ABSTRACT (327 words)

Importance: The presumed pro-arrhythmic action of caffeine is controversial. Few studies have assessed the effect of high doses of caffeine in patients with heart failure due to left ventricular systolic dysfunction at high risk for ventricular arrhythmias.

Objective: To compare the effect of high-dose caffeine or placebo on the frequency of supraventricular and ventricular arrhythmias,both at rest and during a symptom-limited exercise test.

Design: Double-blinded randomized crossover study.

Setting: Heart Failure and Cardiac Transplant clinic of a tertiary university-care hospital.

Participants: Chronic heart failure patients with moderate-to-severe systolic dysfunction (left ventricular ejection fraction below 45%) and New York Heart Association functional class I-III.

Intervention: Caffeine (100 mg) or lactose capsules, in addition to 5 doses of 100 ml decaffeinated coffee at 1-hour intervals. After a one-week washout period, the protocol was repeated.

Main Outcomes: Number and percentage of ventricular and supraventricular premature beats assessed by continuous ECG monitoring.

Results: We enrolled 51 middle-aged patients (60.6 ± 7 years) with moderate-to-severe left ventricular systolic dysfunction (left ventricular ejection fraction = 29 ± 7%); 61% had an implantable cardioverter-defibrillator device. No significant differences between the caffeine and placebo groups were observed in the number of ventricular (150 vs. 212 beats, respectively; p=0.39) and supraventricular

premature beats (6 vs. 7 beats, respectively;p=0.83), as well as in couplets, bigeminal cycles or non-sustained tachycardia during continuous ECG monitoring (all p values > 0.10). Moreover, exercise test derived variables, such as ventricular and supraventricular premature beats, duration of exercise, estimated peak oxygen consumption and heart rate, were not influenced by caffeine ingestion. Finally, we did not observe increases in ventricular or supraventricular arrhythmias in patients with higher levels of plasmatic caffeine (> 9.5 mg/L) compared with lower plasmatic levels or with the placebo group (all p values > 0.60).

Conclusions and Relevance: Acute ingestion of high doses of caffeine did not induce arrhythmias in patients with systolic heart failure and at high risk for ventricular arrhythmias.

Trial Registration: NCT-02045992 at www.clinicaltrials.gov

Keywords:caffeine, hear failure, arrhythmias

INTRODUCTION

The relationship between caffeine consumption and the triggering of arrhythmias has been explored for many decades, but remains controversial[1-3].Early experimental studies indicated that caffeine appeared to cause severe ventricular arrhythmias[4]. Evidence from human studies, however, suggest that caffeine might not be arrhythmogenic in most scenarios[5-8], except in extraordinary circumstances and at very high doses[2,9,10]. A recent systematic review and meta-analysis of interventional studies in humans that assessed the effects of caffeine on ventricular arrhythmias performed by our group did not demonstrate a significant association between caffeine consumption and ventricular premature beats (VPBs)[11]. Several studies that were incorporated in this meta-analysis, however, were performed more than 3 decades ago, were not randomized, used single doses of caffeine, and had low methodological quality, limiting its applicability in current practice.

Sudden cardiac death (SCD), presumably mediated by arrhythmias, remains a major cause of mortality and morbidity in heart failure (HF) patients, particularly in those with moderate-to-severe left ventricular (LV) dysfunction. Ventricular tachycardia and fibrillation represent most events, but the responsible mechanisms are heterogeneous and complex[12]. Despite the lack of evidence of an arrhythmogenic effect of caffeine on these high-risk patients,counseling to reduce caffeine consumption is intuitive and widely recommended in clinical practice[13].

The aim of the current study was to compare the effect of high-dose caffeine intake or placebo on the rate of supraventricular and ventricular arrhythmias at rest and during a symptom-limited exercise test in a double-blinded randomized clinical

trial of HF patients at high risk for ventricular arrhythmias, using baseline standard-of-care therapy.

METHODS

Study Design and Randomization

We conducted a randomized double-blinded clinical trial with a crossover design to evaluate the acute effects of a high-dose caffeine powder, resembling real life doses of coffee intake. An allocation and randomization list was generated by a computer program and controlled by an investigator who was not involved in the study protocol. Randomization determined the order in which patients were allocated to intervention or placebo, and both patient and investigator were blinded to allocation.

Ethics

All patients signed an informed consent prior to enrollment and the research protocol was approved by the institutional review Committee on Ethics and Research.The trial was designed, conducted and reported according to the CONSORT recommendations[14].The protocol was registered on www.clinicaltrials.gov (NCT02045992).

Patients

The study was performed from March 2013 to September 2015 and the participants were recruited from the Heart Failure and Cardiac Transplant clinic of a tertiary university-care hospital in Porto Alegre, Brazil. Patients were eligible if they had a previous diagnosis of HF, moderate-to-severe systolic dysfunction (left

ventricular ejection fraction [LVEF] below 45% assessed by two-dimensional echocardiography within 3 months of enrollment) and New York Heart Association (NYHA) functional class I-III. A pre-requisite for enrollment during the initial phase of the protocol (first 25 subjects) was the presence of an implantable cardioverter-defibrillator (ICD), for safety purposes. As no clinically significant events were observed, a research protocol addendum was approved to include patients without an ICD. For those with an ICD, it must have been implanted successfully and be normally functioning for at least 30 days. Exclusion criteria were impossibility to ingest caffeine or lactose (placebo), any major physical limitation to perform a treadmill stress test, the use of amiodarone or other anti-arrhythmic drugs (except for beta-blockers), a HF hospitalization within 2 months of randomization and documented episodes of unstable ventricular arrhythmias (with shock or anti-tachycardia pacing) within 2 months of randomization for those with an ICD.

Intervention and Protocol

Patients were instructed not to consume food and beverage sources of caffeine during a 7-day washout period. After the washout period, patients came to the hospital and remained at the clinical research center during the 6 hours of the protocol. First, all participants answered a 15-item food frequency questionnaire (FFQ) with major sources of caffeine and a 24-hour recall record to verify washout compliance. Patients were then monitored by continuous ECG monitoring (GE Mars 8000 analyzer, GE Seer Light recorder, GE Medical Systems, Milwaukee, WI, USA).Subjects with an ICD were interrogated prior to enrollment and after the conclusion of the protocol. ICDs had their monitoring zone programmed to detect heart rates greater than 140 beats per minute prior to initiation, and event analysis

was performed by a blinded electrophysiologist by the end of the protocol. After randomization, participants ingested five doses of 100ml decaffeinated coffee, mixed with 100mg of either caffeine or lactose powder. Doses were consumed at 1-hour intervals. Blood samples were collected before and after the first and last dose to measure levels of brain natriuretic peptide (BNP) (n = 25). At the end of each day, plasma was collected and stored to measure plasmatic caffeine. Caffeine plasma concentration was measured by high-performance liquid cromatography (HPLC; using a Nexxera XR Shimadzu system,Kyoto, Japan) as previously described by Alvi *et al.*[15]. One hour after the last ingestion, patients underwent a treadmill test (Naughton protocol) conducted by a trained and blinded cardiologist.

Arrhythmic Outcomes

The primary outcome was the number and percentage of VPBs and supraventricular premature beats (SVPBs) measured by continuous ECG monitoring during each phase of the protocol. Other outcomes of interest were episodes of non-sustained ventricular and supraventricular tachycardia, appropriate or inappropriate ICD therapies, functional capacity and number of VPBs and SVPBs during the exercise treadmill test.

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Statistical analysis

Baseline clinical characteristics were expressed as mean ± SD or median and interquartile range (IQR) for continuous variables, and absolute numbersa nd percentage for categorical variables. Continuous variables were compared using the Student's t-test for paired samples or Wilcoxon test as appropriate, whereas categorical variables were compared using the chi-square test or Fisher's exact test. The primary outcome was also analyzed using a generalized estimating equation model. A two-tailed p value less than0.05 was considered statistically significant. Statistical analyses were performed using PASW Statistics for Windows, Version 18.0 (Chicago: SPSS Inc.)

RESULTS

Between March 2013 and September 2015, a total of 137 HF patients were assessed for eligibility. Up to October 2014, only HF patients with an ICD were screened for eligibility. Major reasons for non-inclusion are described in Figure 1 (CONSORT flow diagram); 2 patients were discontinued before finishing the second phase of the protocol because of nausea and headache (both were receiving caffeine).

Baseline characteristics

The baseline clinical characteristics of the 51 HF patients enrolled are described in Table 1. The predominant HF etiology was non-ischemic (67%), the most common comorbid condition was hypertension (45%), and LV systolic dysfunction was moderate to severe. Most patients were in NYHA functional class I-II and receiving standard pharmacological HF treatment (more than 95% of patients

were on an angiotensin converting enzyme (ACE) inhibitor or angiotensin II receptor antagonist and on a beta-blocker).

Caffeine and BNP plasmatic concentrations

Plasmatic caffeine concentrations at the end of each protocol are displayed in Figure 2. As expected, the median of plasmatic caffeine concentration was 0 (IQR: 0-0.8) in the placebo group and 9.48 mg/L (IQR: 5.25-19) in the caffeine group ($p < 0.001$). Baseline, final and variation of BNP levels during each phase of the crossover protocol were not statistically different between groups (all p values > 0.50;data not shown; n = 25).

Arrhythmic Outcomes

The rate of arrhythmias is described in Table 2. Overall, no significant differences in VPBs or SVPBs (isolated, couplets, bigeminal cycles or non-sustained tachycardia) were observed between groups. Interestingly, mean heart rate was also indistinguishable. Seventeen participants on the caffeine group and 20 on the placebo group had at least one NSVT episode, with no difference between the median number of episodes between groups ($p = 0.48$). The same behavior was observed for NSSVT: 7 and 9 subjects recorded episodes on the caffeine and placebo days of the protocol, respectively. We also analyzed the percentage of VPBs and SVPBs relative to the overall duration of continuous ECG monitoring according to group allocation (Table 2). The period in which patients were performing the treadmill test was included in this analysis. No significant effect of caffeine administration was observed on these parameters. Time analysis results showed no

effect of sequence order of crossover on our findings, confirming the effectiveness of the randomization and washout procedures.

An additional analysis compared rates of arrhythmic endpoints stratified by plasmatic caffeine concentrations (above and below the median). We did not observe increased arrhythmias in patients with higher levels of caffeine compared with lower levels or with the placebo group (Table 3).

Treadmill Test Variables

During the treadmill test, there were also no differences in VPBs or SVPBs between both days of the protocol. Likewise, duration of exercise and estimated peak oxygen consumption (peak VO_2) was similar between groups (Table 4). The only significant differences were higher values of peak systolic and diastolic blood pressure in the caffeine group (both p values < 0.05).

ICD Analysis

Analysis of arrhythmic events was conducted in the 31 enrolled patients that had an ICD. The final reading of ICD parameters was conducted after the last dose of caffeine or placebo, and no therapies (shocks or pacing) or other major arrhythmic events were identified during each protocol.

DISCUSSION

Caffeine, a methylxanthine compound related to theophylline, is the most widely consumed vasoactive substance in the world[16]. Its primary action is to stimulate the sympathetic nervous system through different mechanisms, but mainly by antagonizing adenosine receptors. Coffee is a major source of caffeine, with varying amounts and concentrations of caffeine according to different types and

brands of coffee[17,18]. The presumed pro-arrhythmic action of caffeine has been the focus of intense debate in recent years. In this double-blind randomized crossover clinical trial, we evaluated the acute effects of high-dose caffeine in a HF population at increased risk for arrhythmic events. After 500mg of caffeine administered over a 5-hour period, we found no association between caffeine ingestion and arrhythmic episodes, even during the physical stress of a treadmill test. In fact, we did not observe any trend indicating a potential increased risk of ventricular or supraventricular premature beats, couplets or non-sustained tachycardia. Our results challenge the intuitive notion that caffeine intake should be limited or prohibited in patients with heart disease and at risk for arrhythmia.

Early experimental studies and human case reports have raised strong concerns about the risks associated with caffeine ingestion. Ishida *et al*.[19] have shown that continuous infusions of caffeine were associated with VPBs in rabbits, while Mehta *et al*.[4] demonstrated a dose-response effect on ventricular arrhythmias after a single dose of caffeine in dogs. Meta-analysis from animal studies also suggests an increased risk to develop ventricular fibrillation in animals that received very high doses (up to 35 mg/kg) of caffeine. In this scenario, blood caffeine concentrations seem to influence the predisposition to arrhythmia in experimental models[11]. Furthermore, fatal ingestion of caffeine has been described in at least 2 reports[10,20], reinforcing the potential cause and effect relationship between this substance and presumably severe and complex arrhythmias.

Human intervention studies that assessed the arrhythmogenic actions of caffeine have been conducted with different populations, mostly between 1980 and 1990. Most reports failed to suggest a caffeine-related increase in arrhythmic risk[7,8]. Myers *et al*.[21] tested 300mg of caffeine against placebo in patients with a previous

myocardial infarction. Although they observed a 26% increased risk of VPBs, this finding was not statistically significant. They demonstrated that neither the frequency nor the severity of ventricular arrhythmias was increased with caffeine. In 1996, Newby *et al.*[22] tested whether caffeine restriction in patients with frequent VPBs could reduce symptomatic palpitations; after 6 weeks of intervention there were no significant changes in palpitation scores or VPBs frequency. In an attempt to find a more robust answer to this question, we have recently conducted a systematic review with meta-analysis of experimental and intervention studies of caffeine in both healthy and unhealthy subjects[11]. Our findings suggest that there is no significant effect of caffeine consumption on VBPs in human interventional studies. The positive associations observed and meta-analyzed in animal studies were most probably the result of very high caffeine doses that are not regularly consumed in a daily basis by humans. Nevertheless, we observed that most reports included in this systematic review had poor methodological quality both in animal and human protocols. Internationally accepted quality parameters of the included studies were consistently faulty, with omission of important information regarding protocol description, allocation of interventions, and baseline clinical characteristics of research subjects.

Reports evaluating caffeine ingestion in HF patients are also scarce. Mostofsky *et al.*[23] have performed a dose-response meta-analysis of prospective studies and suggested that moderate coffee consumption (4 cups/day) could even be protective against HF development. In patients with established HF, a protocol of intravenous infusion of 4 mg/kg (roughly equivalent to 2 cups of coffee) led to an increase in mean exercise time of 10% ($p = 0.004$) in 10 stable HF patients, without any evidence of arrhythmias[24]. Our results are in agreement with these findings. Despite the speculation that caffeine might be a possible trigger for arrhythmias

during exercise, our study showed no difference in VPBs and SVPBs during a symptom-limited treadmill protocol. Although we did not observe an improvement on exercise performance, it has been suggested that caffeine in doses from 4 to 9 mg/kg can also induce analgesia, reduce fatigue sensations and improve neuromuscular function, all of which could prolong time to fatigue during muscular exercise[25,26]. The effect of caffeine also leads to a temporary blood pressure increase, which does not result in long-term hypertension[27]. In our study, this acute and expected increase in blood pressure was observed during the Naughton protocol on the caffeine day.

Our protocol and study design has several unique characteristics. We initially recruited HF patients with an ICD device for two reasons. First, to guarantee that patients would not be exposed to the risk of potentially life-threatening events without an adequate protective device. Second, to assure that the studied sample would represent a moderate to high-risk group of patients for major ventricular arrhythmias. During the protocol we did not observe any detectable events using a monitoring zone programmed to identify heart rates greater than 140 beats per minute. Stratified analysis based on plasmatic caffeine levels also added important information, as oral absorption of caffeine might be variable depending on individual metabolism[28]. Concentrations observed in our study are in agreement with the few previous reports that describe caffeine plasmatic levels[21,29], and reinforce that even in those with high blood concentrations (above the median), arrhythmias were not induced. Finally, patients evaluated in the current protocol were also receiving standard of care HF drug therapy, indicating that our sample resembles real-world contemporary HF cohorts and that our results could be applicable in most clinical scenarios.

Some limitations of the current analysis deserve consideration.Our results demonstrate no effect of acute (1-day) use of caffeine on ventricular and supraventricular arrhythmias. Also, some of our patients (approximately 50%) were habitual coffee drinkers and this may potentially exert an influence on our results, as routine consumers might be less prone to the modulatory effects of the substance. Although we believe this to be highly unlikely, we cannot assure that chronic and high-dose use of caffeine is not associated witha pro-arrhythmic effect in HFpatients. Moreover, not all patients included in our analysis had a preemptive ICD implantation. As the primary outcome was measured by continuous ECG monitoring, we do not believe that this has affected our findings.

In conclusion, the acute ingestion of high doses of caffeine did not induce arrhythmias in patients with chronic systolic HF at rest and during a symptom-limited physical exercise. There is no evidence to support the common recommendation to limit moderate caffeine consumption in patients at risk for arrhythmias.

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Table 1. Basal clinical characteristics

Variables	Total (n = 51)
Age, years	60.6 ± 10.9
Males	37 (74%)
Caucasians	40 (80%)
HF Etiology	
Ischemic	16 (33%)
Hypertensive	6 (12%)
Idiopathic	5 (10%)
Others	29 (45%)
NYHA functional class I-II	39 (78%)
ICD	31 (61%)
Clinical comorbidities	
Previous myocardial infarction	12 (25%)
Hypertension	22 (45%)
Chronic atrial fibrillation	6 (13%)
Chronic renal failure	5 (10%)
Diabetes	16 (33%)
LVEF (%)	29.5 ± 7.5
LVDD (mm)	6.6 ± 0.8
Medication	
ACEi/ARAII	48 (97%)
Beta-blocker	49 (98%)
Amiodarone	10 (20%)
Digoxin	26 (53%)
Spironolactone	31 (63%)
Diuretics	43 (86%)

HF – heart failure; NYHA – New York Heart Association; ICD – implantable cardio-defibrillator; LVEF – left ventricular ejection fraction; LVDD – left ventricular diastolic diameter; ACEi/ARAII – angiotensin converting enzyme inhibitor or angiotensin II receptor antagonist.

Table 2. Comparison of total VPBs and SVPBs on continuous ECG monitoring between groups.

	Caffeine	**Placebo**	**p**
Number of VPBs	185 (44-603)	239 (37-1045)	0.47
VPBs (% of time)	0.8 (0.2-2.3)	0.9 (0.15-3.7)	0.60
Isolated	196 (44-629)	206 (33-881)	0.68
Couplets	1 (0-16)	2 (0-25)	0.88
Bigeminal cycles	0 (0-6)	0 (0-0.5)	0.69
NSVT	0 (0-2)	0 (0-1.5)	0.48
Number of SVPBs	6 (0-48)	6 (0-50)	0.44
SVPBs (% of time)	0.02 (0-0.21)	0.02 (0-0.22)	0.33
Isolated	6 (0-42)	3 (0-27)	0.14
Couplets	0 (0-0)	0 (0-0.5)	1.00
Bigeminal cycles	0 (0-0)	0 (0-0)	0.70
NSSVT	0 (0-0)	0 (0-0)	0.29
Mean Heart Rate	70 (62-77)	70 (63-76)	0.40

Data expressed as median (interquartile range)

VPBs – ventricular premature beats; NSVT – non-sustained ventricular tachycardia; VPBs – supraventricular premature beats; NSSVT – non-sustained supraventricular tachycardia

Table 3. Arrhythmic endpoints according to plasmatic caffeine concentration

	Plasmatic Caffeine Levels			Placebo	
	Above Median (>9.5 mg/L)	**Below Median (<9.5 mg/L)**	**P value***		**P value†**
Plasmatic caffeine (mg/L)	18.5 (15.3-24.7)	5.25 (4.2-7.2)	<0.01	0 (0-0.7)	<0.01
Number of VPBs	91 (37-649)	223 (51-395)	0.91	207 (36-970)	0.74
NSVT	0 (0-1.2)	0 (0-1)	0.61	0 (0-0.1)	0.94
Number of SVPBs	7 (0-40)	4 (1-96)	0.85	6 (0-50)	0.91
NSSVT	0 (0-0)	0 (0-0)	0.74	0 (0-0)	0.93

Data expressed as median (interquartile range)

VPBs – ventricular premature beats; NSVT – non-sustained ventricular tachycardia; VPBs – supraventricular premature beats; NSSVT – non-sustained supraventricular tachycardia.

* P<0.05 for difference within caffeine groups

† P<0.05 for difference between caffeine (above median) and placebo groups

Table 4. Comparison of treadmill test variables between groups.

	Caffeine	**Placebo**	**p**
Exercise duration (min)	10 ± 4.6	9.4 ± 4.7	0.56
Peak Heart Rate (bpm)	121 ± 22.6	114.6 ± 18.4	0.07
Peak Systolic Blood Pressure (mmHg)	147 ± 25	136 ± 21	0.004
Peak Diastolic Blood Pressure (mmHg)	78.2 ± 12.3	72 ± 10.8	0.001
VPBs	19 (5-72)	11 (4-66)	0.57
SVPBs	3 (0.7-17)	1 (0-8.5)	0.39
Estimated peak VO_2 (ml/kg/min)	19.5 ± 7.1	18.4 ± 6.9	0.53

Data expressed as median (interquartile range) or mean ± standard deviation

VPBs – ventricular premature beats; SVPBs – supraventricular premature beats.

FIGURE LEGENDS

Figure 1. CONSORT flow diagram.

Figure 2. Box plots of plasmatic caffeine concentration at the end of each protocol according to group allocation. Box plots represent medians (line), interquartile ranges (box) and standard deviations.

Figure 1.

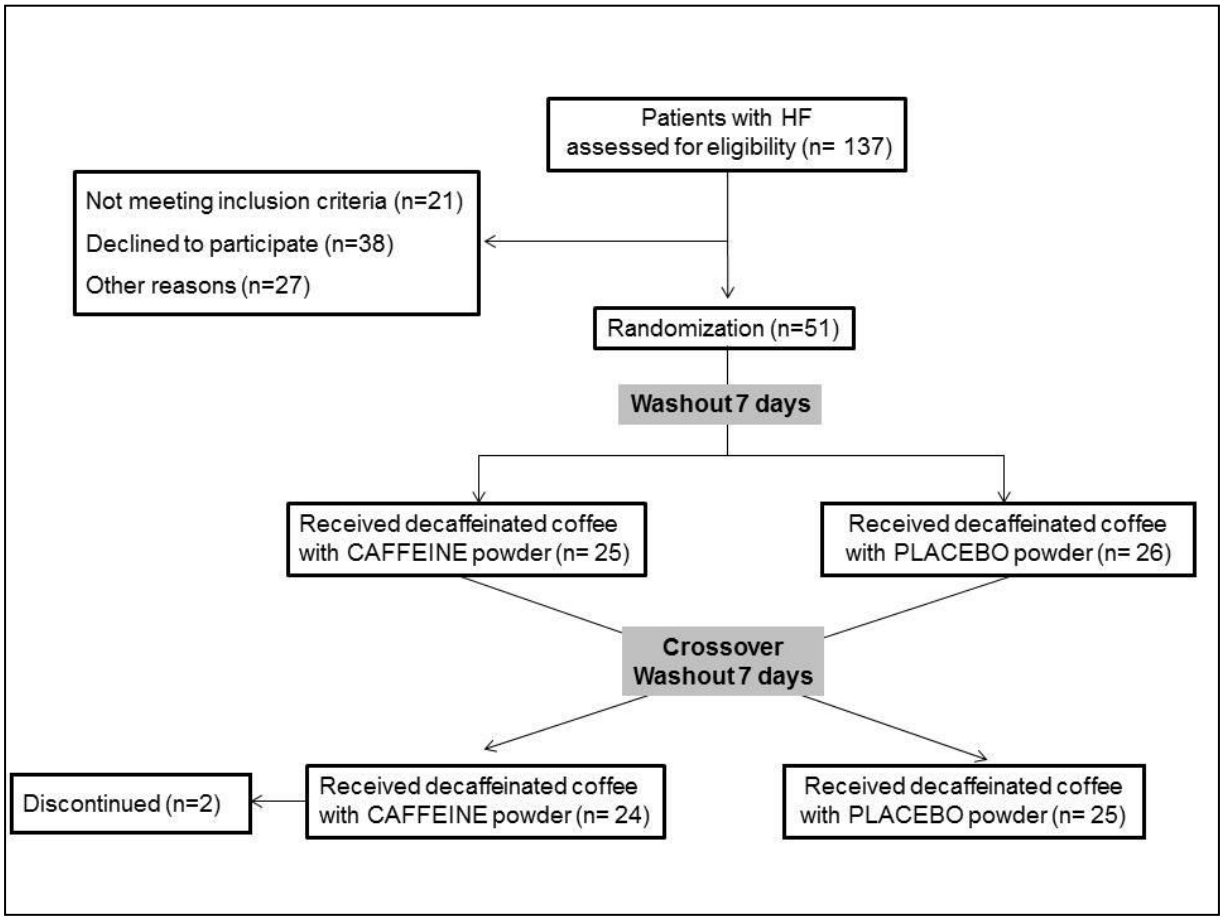
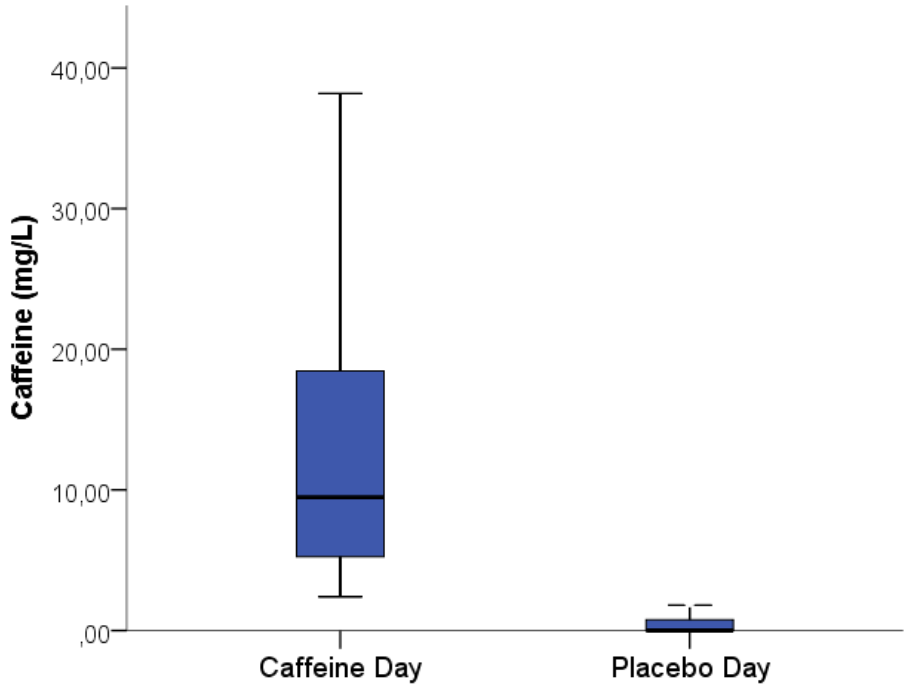

Patients with HF assessed for eligibility (n= 137)
Not meeting inclusion criteria (n=21)
Declined to participate (n=38)
Other reasons (n=27)
Randomization (n=51)
Washout 7 days
Received decaffeinated coffee with CAFFEINE powder (n= 25)
Received decaffeinated coffee with PLACEBO powder (n= 26)
Crossover Washout 7 days
Discontinued (n=2)
Received decaffeinated coffee with CAFFEINE powder (n= 24)
Received decaffeinated coffee with PLACEBO powder (n= 25)

Figure 2.


40,00
30,00
20,00
10,00
,00
Caffeine (mg/L)
Caffeine Day
Placebo Day

8. CONCLUSÕES E CONSIDERAÇÕES FINAIS

A realização dos projetos descritos nesta tese agrega resultados de grande importância para o conhecimento da relação entre consumo de café e fontes de cafeína e ocorrência de eventos arrítmicos, considerando que tratamos de uma bebida vastamente consumida mundialmente. Nossa meta-análise demonstra que os dados de estudos de intervenção em humanos não encontram um efeito significativo do consumo de cafeína e batimentos ventriculares prematuros. Os efeitos observados em estudos em animais são, muito provavelmente, o resultado de doses muito elevadas de cafeína que não são regularmente consumidos no cotidiano.

Focando em uma população de alto risco de ocorrência de arritmias como são os pacientes com IC e disfunção sistólica, nosso ECR encontrou que a ingestão aguda de doses elevadas de cafeína não induziram arritmias ventriculares ou supraventriculares.

Sendo assim, as orientações atuais relacionadas à cafeína devem ser revistas à luz das novas evidências.