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Short-term Effects of High-Dose Caffeine on Cardiac Arrhythmias in Patients With Heart Failure
A Randomized Clinical Trial

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IMPORTANCE The presumed proarrhythmic 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, SETTING, AND PARTICIPANTS Double-blinded randomized clinical trial with a crossover design conducted at the heart failure and cardiac transplant clinic of a tertiary-care university hospital. The trial included patients with chronic heart failure with moderate-to-severe systolic dysfunction (left ventricular ejection fraction <45%) and New York Heart Association functional class I to III between March 5, 2013, and October 2, 2015.

INTERVENTIONS Caffeine (100 mg) or lactose capsules, in addition to 5 doses of 100 mL decaffeinated coffee at 1-hour intervals, for a total of 500 mg of caffeine or placebo during a 5-hour protocol. After a 1-week washout period, the protocol was repeated.

MAIN OUTCOMES AND MEASURES Number and percentage of ventricular and supraventricular premature beats assessed by continuous electrocardiographic monitoring.

RESULTS We enrolled 51 patients (37 [74%] male; mean [SD] age, 60.6 [10.9] years) with predominantly moderate-to-severe left ventricular systolic dysfunction (mean [SD] left ventricular ejection fraction, 29% [7%]); 31 [61%] had an implantable cardioverter-defibrillator device. No significant differences between the caffeine and placebo groups were observed in the number of ventricular (185 vs 239 beats, respectively; $P = .47$) and supraventricular premature beats (6 vs 6 beats, respectively; $P = .44$), as well as in couplets, bigeminal cycles, or nonsustained tachycardia during continuous electrocardiographic monitoring. 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. We observed no increases in ventricular premature beats (91 vs 223 vs 207 beats, respectively) in patients with higher levels of plasma caffeine concentration compared with lower plasma levels ($P = .91$) or with the placebo group ($P = .74$).

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.

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Invited Commentary

Supplemental content

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The relationship between caffeine consumption and the triggering of arrhythmias has been explored for decades but remains controversial.[1-3] Early experimental studies indicated that caffeine appeared to cause severe ventricular arrhythmias.[4] Evidence from human studies, however, suggests 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 consumption 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, presumably mediated by arrhythmias, remains a major cause of mortality and morbidity in patients with heart failure (HF), particularly in those with moderate-to-severe left ventricular 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 present study was to compare the effect of high-dose caffeine intake or placebo on the rate of supraventricular and ventricular ectopies at rest and during a symptom-limited exercise test in a double-blinded randomized clinical trial of patients with HF at high risk for ventricular arrhythmias, using baseline standard-of-care therapy.

Key Points

Question Is there a proarrhythmic action of caffeine in patients with heart failure?

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

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

Methods

Study Design and Randomization

We conducted a randomized double-blinded clinical trial with a crossover design to evaluate the short-term 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. Trial participants, research personnel, outcomes adjudicators, and statisticians were blinded to group 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 at Hospital de Clínicas de Porto Alegre. The trial was designed, conducted, and reported according to the Consolidated Standards of Reporting Trials recommendations.[14] The protocol is available in the Supplement).

Patients

The study was performed from March 5, 2013, to October 2, 2015, and the participants were recruited from the heart failure and cardiac transplant clinic of a tertiary-care university hospital in Porto Alegre, Brazil. Patients were eligible if they had a previous diagnosis of HF, left ventricular ejection fraction less than 45% assessed by 2-dimensional echocardiography within 3 months of enrollment, and New York Heart Association (NYHA) functional class I to III. A prerequisite for enrollment during the initial phase of the protocol (first 25 participants) 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 inability to ingest caffeine or lactose (placebo), any major physical limitation on performing a treadmill stress test, the use of antiarrhythmic drugs (except for β-blockers and amiodarone hydrochloride), an HF-related hospitalization within 2 months of randomization, and documented episodes of unstable ventricular arrhythmias (with shock or antitachycardia 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 with major sources of caffeine and a 24-hour recall record to verify washout adherence. Patients were then monitored by continuous electrocardiographic (ECG) monitoring (GE Mars 8000 analyzer, GE Seer Light recorder, GE Medical Systems). Participants with an ICD were interrogated prior to enrollment and after the conclusion of the protocol. The 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 5 doses of 100 mL decaffeinated coffee, mixed with 100 mg of either caffeine or lactose powder. Doses were consumed at 1-hour intervals. Patients arrived at 8:00 AM at the research clinic; continuous ECG monitoring began at 9:00 AM simultaneously with the first coffee ingestion;

the last administration was at 1:00 PM; and the treadmill test was performed at approximately 2:00 PM. The mean (SD) duration of ECG monitoring was 6.7 (0.7) hours.

Blood samples were collected before and after the first and last dose to measure levels of brain natriuretic peptide (n = 25). At the end of each day, plasma was collected and stored to measure plasma caffeine level. Caffeine plasma concentration was measured by high-performance liquid chromatography (using a Nexera XR Shimadzu system) as previously described by Alvi and Hammami.[15] One hour after the last ingestion, patients underwent a treadmill test (Naughton protocol) conducted by a trained and blinded cardiologist. Our goal was to test the potential proarrhythmic effect of caffeine use during exercise at the highest caffeine plasma concentration.[16] Monitoring during exercise recovery, a particularly vulnerable period for arrhythmias, lasted a mean (SD) of 5.9 (0.4) minutes.

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 nonsustained ventricular and supraventricular tachycardia, appropriate or inappropriate ICD therapies, functional capacity, and number of VPBs and SVPBs during the exercise treadmill test.

Statistical Analysis

Baseline clinical characteristics were expressed as mean with SD or median and interquartile range (IQR) for continuous variables, and absolute numbers and percentage for categorical variables. Continuous variables were compared using the *t* test for paired samples or Wilcoxon test as appropriate, whereas categorical variables were compared using the χ^2 test or Fisher exact test. The primary outcome was also analyzed using a generalized estimating equation model. A 2-tailed $P < .05$ was considered statistically significant. Sample size (n = 49) was estimated considering a difference of 100 VPBs between groups (considering a standard deviation of 414 and 350 VPBs and an expected correlation of 0.8 between the 2 periods),[6] with a statistical power of 80% and significance level of 5%. Statistical analyses were performed using PASW Statistics for Windows, version 18.0 (SPSS Inc).

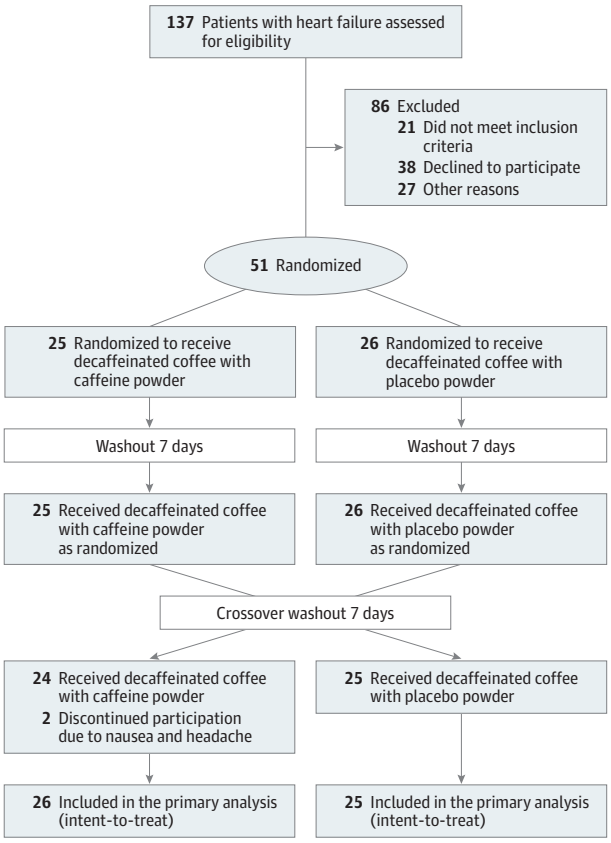
Results

Between March 5, 2013, and October 2, 2015, a total of 137 patients with HF were assessed for eligibility. Up to October 31, 2014, only patients with HF with an ICD were screened for eligibility. Major reasons for noninclusion are described in the **Figure**; 2 patients discontinued participation 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 patients with HF enrolled are described in **Table 1**. The predominant HF etiology was nonischemic (35 [67%]), the most common comorbid condition was hypertension (22 [45%]), and left ventricular systolic dysfunction was predominantly moderate to severe. Most patients were in NYHA functional class I to II and receiving standard pharmacological HF treatment (>95% of patients were taking an angiotensin converting enzyme inhibitor or angiotensin II receptor antagonist and a β-blocker). The ICD implants were for primary prevention in 23 (45%) patients and for secondary prevention in 8 (16%) patients. Seven of these patients had at least 1 previous documented ICD therapy.

Figure. Consolidated Standards of Reporting Trials Flow Diagram



Caffeine and Brain Natriuretic Peptide Plasma Concentrations

As expected, the median plasma caffeine concentration was 0 (IQR, 0-800) µg/L in the placebo group and 9480 (IQR, 5250-19 000) µg/L in the caffeine group ($P < .001$) (to convert to micromoles per liter, multiply by 0.515). Baseline, final, and variation of brain natriuretic peptide levels during each phase of the crossover protocol were not statistically different between groups (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, or nonsustained tachycardia) were observed between groups. Interestingly, mean heart rate was also indistinguishable. Sixteen participants in the caffeine group and 19 in the placebo

Table 1. Baseline Clinical Characteristics

Variable	Value (N = 51)
Age, mean (SD), y	60.6 (10.9)
Male sex, No. (%)	37 (74)
White race, No. (%)	40 (80)
Heart failure etiology, No. (%)	
Ischemic	16 (33)
Hypertensive	6 (12)
Idiopathic	5 (10)
Other	29 (45)
New York Heart Association functional class I-II, No. (%)	39 (78)
Implantable cardioverter-defibrillator, No. (%)	31 (61)
Primary prevention	23 (45)
Secondary prevention	8 (16)
Clinical comorbidities, No. (%)	
Previous myocardial infarction	12 (25)
Hypertension	22 (45)
Chronic atrial fibrillation	6 (13)
Chronic renal failure	5 (10)
Diabetes	16 (33)
Left ventricular ejection fraction, mean (SD), %	29 (7)
Mild systolic dysfunction,[a] No. (%)	4 (8)
Moderate to severe systolic dysfunction,[b] No. (%)	47 (92)
Left ventricular diastolic diameter, mean (SD), mm	6.6 (0.8)
Medication use, No. (%)	
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker	48 (97)
β-Blocker	49 (98)
Amiodarone	10 (20)
Digoxin	26 (53)
Spironolactone	31 (63)
Diuretics	43 (86)

[a] Left ventricular ejection fraction of 40% to 45%.

[b] Left ventricular ejection fraction of less than 40%.

group had at least 1 nonsustained ventricular tachycardia episode (odds ratio [OR], 0.76; 95% CI, 0.31-1.80) (Table 2), with no difference between the median number of episodes between groups. The same behavior was observed for nonsustained supraventricular tachycardia: 7 and 9 participants recorded episodes on the caffeine and placebo days of the protocol, respectively (OR, 0.69; 95% CI, 0.30-1.61). 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 end points stratified by plasma caffeine concentrations (above and below the median). We did not observe increased arrhythmias in patients with higher plasma levels of caffeine compared with lower levels or with the placebo group (**Table 3**). Eight participants in the caffeine group with higher plasma levels and 7 with lower plasma levels had at least 1 nonsustained ventricular tachycardia episode (OR, 1.22; 95% CI, 0.35-4.25), while 4 and 3 participants recorded episodes of nonsustained supraventricular tachycardia in the higher and lower level of caffeine subgroups, respectively (OR, 1.41; 95% CI, 0.28-7.18).

Other subgroups of interest were also analyzed (habitual coffee drinkers, use of amiodarone and digoxin, ischemic etiology). No significant differences were observed for major arrhythmic outcomes in this analysis (data not shown).

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 were similar between groups (**Table 4**). The only significant differences were higher values of peak systolic and diastolic blood pressure in the caffeine group.

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. Subgroup analysis stratified by patients with the ICD for primary or for secondary prevention, or those with previous ICD therapy did not demonstrate any effect of caffeine ingestion on arrhythmic outcomes.

Discussion

Caffeine, a methylxanthine compound related to theophylline, is the most widely consumed vasoactive substance in the world.[17] 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.[18,19] The presumed proarrhythmic action of caffeine has been the focus of debate in recent years. In this double-blind randomized crossover clinical trial, we evaluated the acute effects of high-dose caffeine consumption in an HF population at increased risk for arrhythmic events. After 500 mg 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 indication of a potential increased risk of ventricular or supraventricular premature beats, couplets, or nonsustained 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 concerns about the risks associated with caffeine ingestion. Ishida et al[20] have shown that continuous infusions of caffeine were associated with VPBs in rabbits, while Mehta

Table 2. Comparison of Total Ventricular Premature Beats (VPBs) and Supraventricular Premature Beats (SVPBs) on Continuous Electrocardiographic Monitoring Between Groups

	Caffeine	Placebo	OR (95% CI)[a]	*P* Value[a]
VPBs				
Median (IQR)	185 (44-603)	239 (37-1045)	NA	.47
Time, %, median (IQR)	0.8 (0.2-2.3)	0.9 (0.15-3.7)	NA	.60
Isolated, median (IQR)	196 (44-629)	206 (33-881)	NA	.68
Couplets, median (IQR)	1 (0-16)	2 (0-25)	NA	.88
Couplets, No. (%)	30 (64)	28 (60)	1.20 (0.50-2.80)	NA
NSVT				
Median (IQR)	0 (0-2)	0 (0-1.5)	NA	.48
No. (%)	16 (34)	19 (40)	0.76 (0.31-1.80)	NA
SVPBs				
Median (IQR)	6 (0-48)	6 (0-50)	NA	.44
Time, %, median (IQR)	0.02 (0-0.21)	0.02 (0-0.22)	NA	.33
Isolated, median (IQR)	6 (0-42)	3 (0-27)	NA	.14
Couplets, median (IQR)	0 (0-0)	0 (0-0.5)	NA	>.99
Couplets, No. (%)	9 (19)	12 (26)	0.69 (0.26-1.84)	NA
NSSVT				
Median (IQR)	0 (0-0)	0 (0-0)	NA	.29
No. (%)	7 (15)	9 (19)	0.69 (0.30-1.61)	NA
Mean heart rate, median (IQR)	70 (62-77)	70 (63-76)	NA	.40

Abbreviations: IQR, interquartile range; NA, not applicable; NSSVT, nonsustained supraventricular tachycardia; NSVT, nonsustained ventricular tachycardia; OR, odds ratio.

[a] *P* values were calculated for continuous variables and odds ratios were calculated for categorical variables.

Table 3. Arrhythmic End Points According to Plasma Caffeine Concentration[a]

	Caffeine Group Plasma Caffeine Level, Median (IQR)				
End Point	Above Median[b]	Below Median[b]	*P* Value[c]	Placebo Group	*P* Value[d]
Plasma caffeine concentration, µg/L	18 500 (15 400-24 800)	52 500 (4400-7200)	<.001	0 (0-700)	<.001
No. of ventricular premature beats	91 (39-600)	223 (87-388)	.91	207 (36-970)	.74
Nonsustained ventricular tachycardia	0 (0-1)	0 (0-1)	.61	0 (0-0.1)	.94
No. of supraventricular premature beats	7 (0-36)	4 (1-70)	.85	6 (0-50)	.91
Nonsustained supraventricular tachycardia	0 (0-0)	0 (0-0)	.74	0 (0-0)	.93

Abbreviation: IQR, interquartile range.

SI conversion factor: To convert plasma caffeine concentration to micromoles per liter, multiply by 0.515.

[a] No plasma caffeine data for 4 participants.

[b] Median plasma caffeine concentration was 9500 µg/L.

[c] For comparisons within caffeine groups.

[d] For comparisons between caffeine (above median) and placebo groups.

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 of developing 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,[10,21] 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 in different populations, mostly between 1980 and 1990. Most reports failed to suggest a caffeine-related increase in arrhythmic risk.[7,8] Myers et al[22] tested 300 mg 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[23] 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 VPB frequency. In an attempt to find a more robust answer to this question, we recently conducted a systematic review with meta-analysis of experimental and intervention studies of caffeine in both healthy and unhealthy individuals.[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 2 animal studies were probably the result of very high caffeine doses that are not regularly consumed by humans. Nevertheless, we observed that most reports included in this systematic review had poor methodological quality in both 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 participants.

Reports evaluating caffeine ingestion in patients with HF are also scarce. Mostofsky et al[24] performed a dose-response

Table 4. Comparison of Treadmill Test Variables Between Groups

Variable	Caffeine	Placebo	*P* Value
Before exercise, mean (SD)			
Resting heart rate, bpm	74 (13.5)	76.7 (14.6)	.48
Resting systolic BP, mm Hg	117 (24)	110 (14)	.10
Resting diastolic BP, mm Hg	75 (11)	71 (11)	.048
During exercise, mean (SD)			
Exercise duration, min	10 (4.6)	9.4 (4.7)	.56
Peak heart rate, bpm	121 (22.6)	114.6 (18.4)	.07
Peak systolic BP, mm Hg	147 (25)	136 (21)	.004
Peak diastolic BP, mm Hg	78.2 (12.3)	72 (10.8)	.001
Ventricular premature beats, median (IQR)	19 (5-72)	11 (4-66)	.57
Isolated	24 (2.5-75)	9 (1.5-50)	.56
Couplets	0 (0-2.8)	0 (0-1)	.58
Nonsustained ventricular tachycardia, median (IQR)	0 (0-0)	0 (0-0)	.69
Supraventricular premature beats, median (IQR)	3 (0.7-17)	1 (0-8.5)	.39
Isolated	0 (0-2.8)	0 (0-1)	.24
Couplets	0 (0-0)	N	NA
Nonsustained supraventricular tachycardia, median (IQR)	N	0 (0-0)	NA
Estimated peak oxygen consumption, mean (SD), mL/kg/min	19.5 (7.1)	18.4 (6.9)	.53

Abbreviations: BP, blood pressure; IQR, interquartile range; N, no episode of arrhythmia was observed, preventing calculation of *P* value; NA, not applicable.

meta-analysis of prospective studies and suggested that moderate coffee consumption (4 cups/d) 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 duration of 10% ($P = .004$) in 10 stable patients with HF, without any evidence of arrhythmias.[25] 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 in 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.[26,27] The effect of caffeine also leads to a temporary blood pressure increase, which does not result in long-term hypertension.[28] In our study, this acute and expected increase in blood pressure was observed during the Naughton protocol on the caffeine day. Although we used high doses of caffeine, the final net effect on heart rate was neutral during the exercise protocol. This could be attributed to the interaction of elevated plasma caffeine levels in a background of 98% use of β-blockade. Notarius et al[25] have reported similar results previously, observing no effect of caffeine infusion on the resting and peak exercise heart rate in patients with HF, but significant changes in healthy individuals.

Our protocol and study design have several unique characteristics. We initially recruited patients with HF with an ICD device for 2 reasons: first, to guarantee that patients would not be exposed to the risk of potentially life-threatening events without an adequate protective device, and second, to ensure that the studied sample would represent a group of patients at moderate to high risk for major ventricular arrhythmias. Stratified analysis based on plasma caffeine levels also added important information, as absorption of caffeine ingested orally might be variable depending on individual metabolism.[29] Concentrations observed in our study are in agreement with the few previous reports that describe caffeine plasma levels,[22,30] and reinforce that even in those with high blood concentrations (above the median), arrhythmias were not induced. Finally, patients evaluated in the present 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.

Limitations

Some limitations of the present 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 unlikely, we cannot ensure that long-term and high-dose use of caffeine is not associated with a proarrhythmic effect in patients with HF. In this sense, our findings should be interpreted with caution because of the small number of patients included and the relatively low prevalence of arrhythmias that was observed. We also acknowledge that our subgroup analyses are underpowered for definitive conclusions.

Conclusions

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. To date, there is no solid evidence to support the common recommendation to limit moderate caffeine consumption in patients at risk for arrhythmias.

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