Caffeine and Ventricular Arrhythmias

An Electrophysiological Approach

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Little information is known regarding caffeine's effect on the substrate supporting sustained ventricular arrhythmias. This prospective study evaluated the effect of coffee (275 mg of caffeine) on this substrate with programmed ventricular stimulation in 22 patients with a history of symptomatic nonsustained ventricular tachycardia, ventricular tachycardia, or ventricular fibrillation. Patients underwent electrophysiological testing before and 1 hour after coffee ingestion. Mean (± SEM) plasma caffeine level achieved after coffee consumption was 6.2 ± 0.5 mg/L. Mean plasma catecholamine and potassium values were not altered significantly 1 hour following caffeine ingestion. The number of extrastimuli required to induce an arrhythmia was unchanged in 10 patients (46%), increased in six (27%), and decreased in six (27%). Rhythm severity was unchanged in 17 patients (77%), more severe in two (9%), and less severe in three (14%). In those patients with clinical ventricular arrhythmias, caffeine did not significantly alter inducibility or severity of arrhythmias, suggesting little effect on the substrate supporting ventricular arrhythmias.

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AMERICANS love caffeine. Eighty percent of adults consume an average of 3.5 cups of coffee per day.[1] While caffeine has many cardiovascular effects, medical care providers have worried about its potential adverse effect on ventricular arrhythmias. The concern is greatest when considering survivors of ventricular tachycardia and fibrillation and those known to be at high risk for recurrent arrhythmias and early sudden death. It is unknown if caffeine ingestion is safe for these patients.

Previous investigators have measured the effect of caffeine on premature ventricular beats, considering these as the potential "initiators" of more severe ventricular arrhythmias. Their results have varied, with some showing an increase in the frequency or severity of ventricular arrhythmias[2-4] and others showing no change.[5-10] These discrepancies may be a result of the different methods used for measuring arrhythmias, the amount of caffeine that was administered, or the subject sample studied.

An alternate approach to evaluating the initiator of severe arrhythmias is to study the effect of caffeine on the underlying "substrate" that makes maintenance of ventricular rhythms possible. Using programmed electrical stimulation as the initiator of the rhythms, the induced rhythms can be a measure of caffeine's effect on the substrate.

The purpose of our study was to use programmed electrical stimulation to evaluate the effect of caffeine on inducibility and severity of ventricular arrhythmias in patients with a history of severe symptomatic ventricular arrhythmias. The aim was to test the characteristics of the substrate using programmed extrastimuli as the initiator. Since the effect of caffeine on this substrate could be indirect and mediated through catecholamine or potassium changes, these changes were also evaluated.

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METHODS

Protocol

Patients with documented clinical ventricular tachycardia and fibrillation who were undergoing electrophysiological testing were invited to participate in this study. Informed written consent, in agreement with the Human Research Committee of the Oregon Health Sciences University, was obtained from each subject prior to beginning the protocol. A baseline electrophysiological test that included programmed ventricular stimulation was conducted at least five half-lives after all antiarrhythmic medications (excluding digoxin and calcium channel blockers) were discontinued. This was the caffeine-free test. Caffeine consumption was terminated 24 hours prior to this. Patients were excluded from participation if they required cardioversion to terminate a ventricular arrhythmia during the caffeine-free electrophysiological test. Other exclusion criteria included abnormal serum electrolytes, hemodynamic instability, pregnancy or lactation, renal or hepatic failure, psychological disorders, and use of drugs that alter caffeine metabolism or action, including β-blockers, oral contraceptives, cimeti-

dine, theophylline products, and quinolone antibiotics.

Immediately prior to the caffeine-free test, baseline plasma catecholamine and potassium levels were obtained. These samples, along with plasma caffeine levels, were collected again before the caffeine electrophysiological test.

Thirty minutes after the caffeine-free test was completed, the fasting subject consumed 500 mL of coffee over a 15-minute period. This coffee contained 275 mg of caffeine, a combination of arabica and robusta coffee beans. The caffeine content was established by multiple laboratory measures using high-performance liquid chromatography. A caffeine electrophysiological test using programmed ventricular stimulation was performed 60 minutes after initiation of coffee ingestion.

Electrophysiological Protocol

Electrophysiological testing was performed following a standard protocol established by this institution.[11] A hexapolar pacing catheter was positioned in the right ventricular apex by a subclavian approach. Programmed ventricular stimulation was completed using up to four extrastimuli at fixed cycle lengths of 600 and 400 milliseconds until an end point was reached. An *end point* was defined as induction of a sustained ventricular arrhythmia or completion of the protocol. *Sustained ventricular arrhythmias* were defined as those requiring intervention for termination. *Nonsustained ventricular tachycardia* was defined as four or more induced beats with the rhythm terminating spontaneously within 30 seconds. A *noninducible rhythm* was defined as three or fewer induced repetitive ventricular beats.

Plasma Samples

Plasma caffeine concentrations were measured by high-performance liquid chromatography. Each sample was standardized with a quality control sample containing 5 mg/L. A venous blood specimen was obtained and centrifuged at 25 000 rpm for 5 minutes and stored at less than −20°C for later analysis.

High-performance liquid chromatography was also used to measure plasma catecholamine levels. Venous blood was transported to the laboratory in an ice bath within 15 minutes after obtaining the specimen. The sample was placed in a refrigeration centrifuge for 10 minutes at 10 000 rpm. The separated plasma was stored at −80°C until analysis.

Plasma potassium levels were measured by flame emission photometry. The venous blood sample was centrifuged at room temperature for 10 minutes at 10 000 rpm. The plasma was frozen at −80°C until later assay. Venipuncture was required in six of the subjects (27%) when blood samples could not be obtained from an indwelling catheter.

Table 1.—Arrhythmia Inducibility Scoring Method

Inducibility Score*	Type of Stimulation
1	Four extrastimuli required to induce an arrhythmia†
2	Three extrastimuli required to induce an arrhythmia
3	Two extrastimuli required to induce an arrhythmia
4	One extrastimulus required to induce an arrhythmia

*The score increases as the ease of inducing an arrhythmia increases.
†If no arrhythmia was induced, a score of 1 was assigned.

Table 2.—Arrhythmia Severity Scoring Method

Severity Score	Arrhythmia Induced
1	0-3 beats of repetitive ventricular response
2	4 beats to less than 30 s of nonsustained ventricular tachycardia
3	Ventricular tachycardia at rate of 100-200 beats/min
4	Ventricular tachycardia at rate of 201-300 beats/min
5	Ventricular tachycardia at rate of >300 beats/min or ventricular fibrillation

Data Analysis

To evaluate inducibility of arrhythmias with caffeine, each electrophysiological test was assigned an *inducibility score* (Table 1) based on the number of extrastimuli needed to induce an arrhythmia. While it was not assumed that this scoring system was linear, for the purpose of this study it was assumed that a higher score represented greater ease in arrhythmia inducibility and a lower score represented a lower ease of inducibility. Wilcoxon's rank sum test was used to determine whether there was a statistical difference between the groups before and after caffeine ingestion.

To evaluate the severity of arrhythmias before and after caffeine ingestion, each electrophysiological test was also assigned a *severity score* (Table 2). Again not presuming linearity, it was still assumed that a higher score reflected a greater arrhythmia severity and a lower score reflected lower severity. Wilcoxon's rank sum test was used to determine whether there was a statistical difference between the groups before and after caffeine ingestion.

Table 3.—Patient Characteristics

	n (%)
Gender	
M	20 (91)
F	2 (9)
Heart disease	
Coronary artery disease	19 (86)
Previous myocardial infarction	14 (74)
Left ventricular aneurysm	4 (21)
Other	3 (14)
Clinical arrhythmia	
Nonsustained VT*	5 (23)
Sustained VT	12 (54)
Ventricular fibrillation	5 (23)
Cardiac medications at time of testing	
Calcium channel blockers	8 (36)
Digoxin	5 (23)
Nitrates	2 (9)
Diuretics	5 (23)
ACE† inhibitor	4 (18)

*VT indicates ventricular tachycardia.
†ACE indicates angiotensin-converting enzyme.

The caffeine-induced changes in plasma catecholamine and potassium levels were evaluated in relation to changes in severity and inducibility scores. The statistical significance of these changes was determined by Spearman's rank correlation coefficient. The *t* test was used to evaluate the differences between the mean plasma catecholamine and potassium levels before and after caffeine consumption.

RESULTS

Subjects

Twenty-two adult volunteers who were undergoing electrophysiological evaluation of ventricular arrhythmias agreed to participate in this study. They ranged from 39 to 72 years of age with a mean (SD) age of 60 ± 10 years. All patients were habitual coffee drinkers. All had clinically documented ventricular arrhythmias; five had presented with symptomatic nonsustained ventricular tachycardia, 12 with sustained ventricular tachycardia, and five with ventricular fibrillation (Table 3).

Electrophysiological Data

Inducibility and severity scores were assigned to the caffeine-free and caffeine electrophysiological test results. The individual electrophysiological results and scores are shown in Table 4. The changes in both the inducibility and the severity scores after caffeine ingestion were not significant ($P>.05$). These changes did not exceed those that have been observed to occur randomly when serial electrophysiological testing is performed with no intertest intervention.[11]

Effect of Caffeine on Rhythm Inducibility.—The frequency of changes in inducibility scores are displayed in Fig 1. Ten subjects (46%) showed no

change in inducibility of ventricular arrhythmias after caffeine. Six subjects (27%) had a negative change in their inducibility score. These subjects had a decrease in ease of rhythm induction after caffeine consumption. Six subjects (27%) had a positive change in their scores with easier induction of ventricular arrhythmias after caffeine ingestion. Two patients who had sustained ventricular tachycardia induced in the caffeine-free test had a decrease in the number of extrastimuli required to induce ventricular tachycardia after caffeine ingestion. Two other patients with sustained ventricular tachycardia induced in the caffeine-free test had no change in their inducibility score after ingesting caffeine.

Effect of Caffeine on Rhythm Severity.—The frequency of changes in severity scores are presented in Fig 1. Seventeen subjects (77%) showed no change in their arrhythmia score. Three subjects (14%) had a negative change in their arrhythmia score. Their ventricular arrhythmias became less severe after drinking coffee. Two subjects (9%) had a positive change in their scores after caffeine consumption. These two subjects had no inducible rhythms before caffeine and nonsustained ventricular tachycardia after caffeine consumption (Fig 2).

Three of the five subjects who had sustained ventricular tachycardia induced in the caffeine-free test had a faster ventricular tachycardia rate induced after caffeine ingestion. The rate of ventricular tachycardia increased 20 to 30 beats per minute from the baseline ventricular tachycardia rate in these subjects. None of the patients had a slower rate of inducible ventricular tachycardia following caffeine ingestion. One subject with sustained ventricular tachycardia during the caffeine-free test had no inducible arrhythmias after caffeine ingestion.

Effect of Caffeine on Effective Refractory Period.—The mean (±SD) right ventricular effective refractory period for the first extrastimulus at cycle length 600 milliseconds (500) was 259±20 milliseconds before caffeine and 260±23 milliseconds after caffeine consumption (*P* not significant). At cycle length 400 milliseconds before caffeine ingestion, the mean (SD) effective refractory period was 238±21 milliseconds and 237±19 milliseconds after caffeine consumption (*P* not significant).

Plasma Caffeine Levels

Caffeine plasma levels ranged from 2.7 to 12.4 mg/L. The mean (±SEM) caffeine level was 6.2±0.5 mg/L. The interassay mean value was 5.49±0.43 mg/L with a coefficient of variation of 8%. The intra-assay variation of five samples was 6.5%.

Plasma Catecholamine Levels

The mean (±SEM) plasma epinephrine level before caffeine consumption was 2190±592 pmol/L (SEM) and ranged from 260 to 10 455 pmol/L (17 samples). The mean plasma epinephrine level after caffeine ingestion was 2154±451 pmol/L and ranged from 553 to 6931 pmol/L. The intra-assay variation for epinephrine values was 12.4%

Table 4.—Electrophysiological Testing Before and After Caffeine*

	Caffeine-Free Test		Caffeine Test		Change in Score With Caffeine‡	
Subject	Rhythm†	Extrastimuli	Rhythm†	Extrastimuli	Inducibility	Severity
1	R1	2	None	4	−2	0
2	R2	2	N11 beats	2	0	1
3	N4 beats	2	R3	2	0	−1
4	R2	1	None	4	−3	0
5	VT, rate 250	4	VT, rate 280	3	1	0
6	N4 beats	4	R2	3	1	−1
7	R2	1	R2	1	0	0
8	R2	3	R2	3	0	0
9	R1	1	R2	2	−1	0
10	VT, rate 230	2	VT, rate 250	2	0	0
11	R2	1	R1	2	−1	0
12	N9 beats	3	N4 beats	2	1	0
13	VT, rate 220	2	VT, rate 220	2	0	0
14	VT 200	4	R2	1	3	−3
15	R2	1	R2	1	0	0
16	N27 seconds	2	N25 beats	2	0	0
17	R1	3	R1	3	0	0
18	R1	1	N4 beats	4	−3	1
19	N7 beats	4	N8 beats	3	1	0
20	R3	3	R2	3	0	0
21	VT, rate 210	4	VT, rate 240	2	2	0
22	R2	1	R1	2	−1	0

*R indicates induced repetitive ventricular beats when three or less are induced (R1=one repetitive beat, R2=two repetitive beats, and R3=three repetitive beats); N, induced nonsustained ventricular tachycardia (four beats to 30 seconds); and VT, sustained ventricular tachycardia.
†Most severe arrhythmia induced.
‡See Tables 1 and 2.

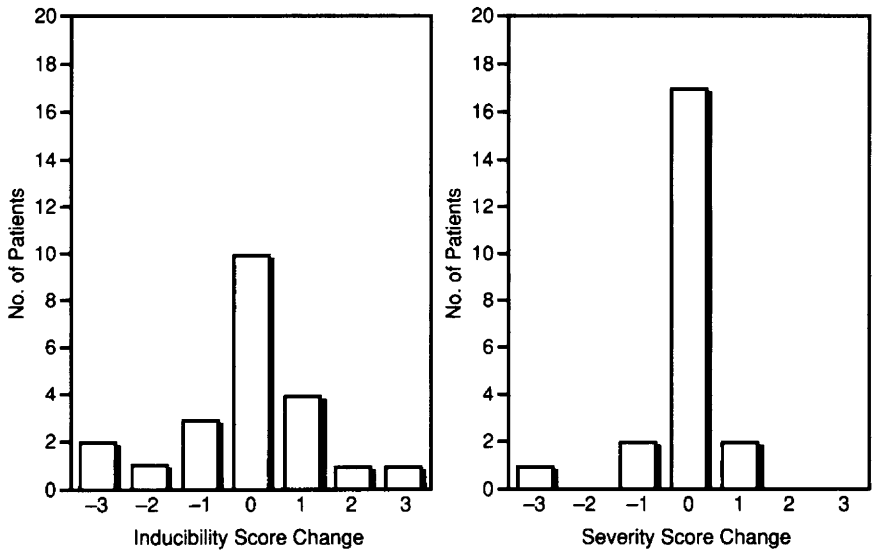

Fig 1.—Caffeine tended to be associated with less easily induced and less severe rhythms (negative scores) as often as it was associated with more easily induced or more severe rhythms (positive scores). Most patients had no change in inducibility or severity scores.

(six samples). A one-tailed paired t test showed no statistical difference in the mean epinephrine values.

The mean (±SEM) plasma norepinephrine level before caffeine ingestion was 3.30±0.38 nmol/L for 17 samples and the values ranged from 1.43 to 7.64 nmol/L. After caffeine consumption, the mean (±SEM) norepinephrine value increased to 3.70±0.41 nmol/L (SEM) with the values ranging from 1.46 to 7.30 nmol/L. The intra-assay variation for norepinephrine was 6.5% for six samples. A one-tailed t test showed no statistical difference in the mean norepinephrine values ($P=.053$).

The coefficients of variation for the assay setup of epinephrine and norepinephrine were 7.1% and 4.1%, respectively. These coefficient variabilities were calculated using repeated assays from three normal plasma samples.

Plasma Potassium Levels

The mean (±SEM) plasma potassium level prior to caffeine intake was 4.10±0.1 mmol/L with a range from 3.3 to 4.8 mmol/L for 18 samples (intra-assay variability was 2.2% for 16 samples). After caffeine, the mean (±SEM) level was 4.13±0.1 mmol/L with a range of 3.7 to 4.5 mmol/L (intra-assay variability was 2.5% for 15 samples). The coefficient of variation for this analysis was 3.1%. There was no significant change in the mean plasma potassium value by t test analysis.

Relationship Between Arrhythmias, Catecholamine, and Potassium Values

There was no significant correlation between increased catecholamines and severity or inducibility of ventricular arrhythmias ($P>.05$). The individual correlation values are as follows: epinephrine and severity, $r_s=.49$; norepinephrine and inducibility, $r_s=-.22$; norepinephrine and severity, $r_s=.49$; and norepinephrine and inducibility, $r_s=.41$. Among those patients who demonstrated a decline in potassium levels following caffeine ingestion, no significant relationship between this decline and ventricular arrhythmias (severity or inducibility) could be demonstrated. The correlation values are $r_s=.51$ for potassium and severity and $r_s=.23$ for potassium and inducibility.

The two patients who had increased arrhythmia severity after caffeine ingestion had elevations in plasma epinephrine levels and reductions in plasma potassium levels. The plasma norepinephrine levels varied, with a decline in one patient and an increase in the other. Caffeine concentrations for these patients were 3.0 and 6.3 mg/L, respectively. These two male patients with increased arrhythmia severity were 69 and 70 years of age and had coronary artery disease with ejection fractions of 0.22 and 0.15, respectively.

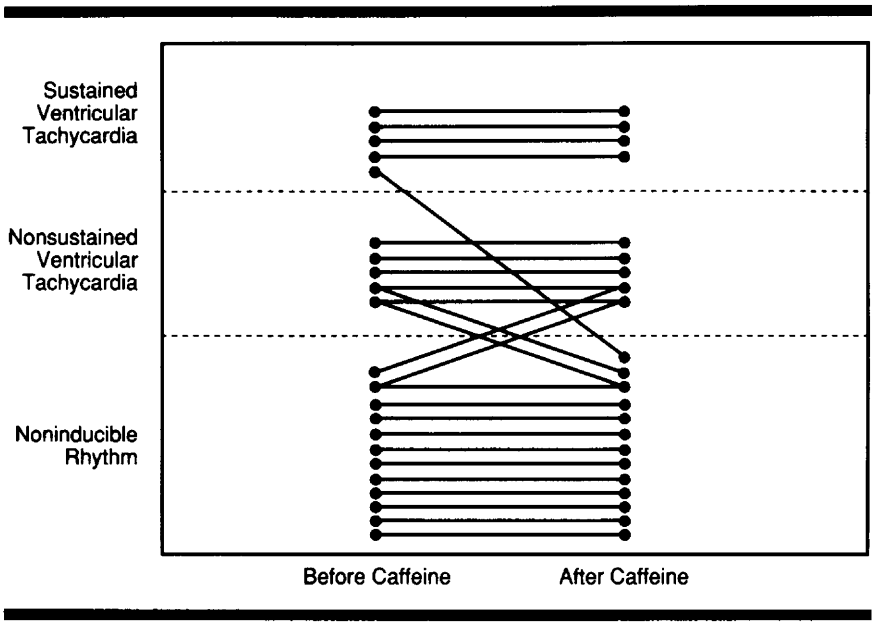

Fig 2.—In most patients, the results of electrophysiological testing were the same before and after caffeine consumption. In those patients in whom there was a change, no consistent pattern was demonstrated.

COMMENT

A serving of coffee with 275 mg of caffeine did not alter the inducibility or severity of ventricular arrhythmias in these survivors of clinical ventricular tachycardia and fibrillation. This serving of coffee is the amount of caffeine ingested in two to three cups of typical automatic drip American coffee or in four to eight 12-oz cans of many soft drinks.[1,12] Assuming the timed extrastimuli delivered during the electrophysiological testing act as the initiator of ventricular arrhythmias, caffeine did not clearly alter the maintenance substrate in these patients.

If caffeine does promote sustained or nonsustained ventricular tachycardia in some patients, then the results of this study suggest that it is not due to their effect on the maintenance substrate. This substrate is ill defined. In patients with ventricular tachycardia, it is thought to be a section of myocardial tissue with abnormal automaticity or uneven refractoriness or conduction properties. Part of the substrate, however, could be chemical or electrical abnormalities.

Electrophysiological testing cannot be easily used to evaluate the presumed initiator of severe ventricular arrhythmias, the premature ventricular beat (PVB). Electrocardiographic monitoring has been used to evaluate frequency and severity of PVBs after caffeine ingestion. Using a random 2-minute electrocardiogram, Prineas et al[2] demonstrated an increase in frequency of PVBs when normal subjects consumed up to nine cups of coffee. When a group of patients with a history of frequent PVBs were given coffee (1 mg/kg of body weight), they also had increased ventricular ectopy during 24 hours of Holter monitoring.[3] Harris et al[4] stated that caffeine was proarrhythmic in patients with organic heart disease and low ejection fractions based on an increased frequency and severity of PVBs after caffeine ingestion (using doses of up to 900 mg/d) measured by 24 to 48 hours of Holter monitoring.

Others have demonstrated that the frequency of PVBs did not increase significantly in normal subjects after caffeine ingestion.[3,9] Furthermore, increased PVB frequency was not shown with Holter monitoring measurements in patients 7 to 10 days after acute myocardial infarction following caffeine ingestion (up to 450 mg).[6-8] In patients with a history of malignant ventricular arrhythmias, Graboys et al[10] demonstrated no change in frequency and severity of ventricular arrhythmias after consumption of 200 mg of caffeine with continuous electrocardiographic recording.

The only study evaluating caffeine's effect with electrophysiological testing was performed by Dobmeyer et al.[5] In 12 patients, no ventricular arrhythmias were induced during baseline testing and nonsustained ventricular tachycardia was induced in two of these patients

after ingesting 200 mg of caffeine. They also demonstrated that right ventricular effective refractory periods shortened after caffeine ingestion. This did not occur in our study.

Non–coffee drinkers were excluded from our study because it is unknown whether the effect of caffeine on ventricular arrhythmias is different in this group in comparison with long-term coffee drinkers. Prior investigations have indicated that hemodynamic responses to caffeine do differ in these two groups.[13,14]

While prior investigations have demonstrated significant increases in plasma catecholamine levels after drinking coffee,[13-15] our present study does not support this finding. It is possible that the small sample size limited our ability to demonstrate small changes in catecholamines. Furthermore, plasma catecholamine concentrations have been demonstrated to be significantly higher after acute caffeine ingestion rather than after long-term caffeine ingestion.[13] The lack of significant catecholamine changes may be because all of the subjects were long-term caffeine users.

Plasma potassium levels are known to decrease as a result of β-adrenergic receptor stimulation secondary to elevated plasma epinephrine levels.[16-18] Evaluation of plasma potassium concentrations following coffee ingestion has not been assessed by previous investigators. This study does not support an early decline in potassium values after coffee consumption.

CONCLUSION

The results of this study suggest that caffeine does not alter the substrate maintaining ventricular arrhythmias. No clear relationship between caffeine, catecholamine, or potassium levels and rhythm induction or maintenance was demonstrated, although some changes in rhythm severity or inducibility did occur with individual patients.

Despite the results and because of the small number of patients evaluated, this study does not justify the recommendation of unrestricted caffeine ingestion in patients with clinical ventricular tachycardia or ventricular fibrillation. A few patients demonstrated more easily induced and more severe ventricular arrhythmias with the amount of caffeine used in this study. It is unknown if these patients represent a select population of "caffeine-sensitive" individuals, and what characteristics, if any, would define such a group. Since survivors of ventricular tachycardia or fibrillation are often burdened with other restrictions, we are reluctant to emphasize caffeine restrictions as well. However, when advising these patients, it is our approach to limit coffee consumption to two cups per day or approximately 150 to 200 mg of caffeine per day.

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