筑　波　大　学

博 士 （医 学） 学 位 論 文

Oral caffeine intake amplifies the effect of isoproterenol in patients with frequent premature ventricular contractions.

（カフェインの経口摂取は心室期外収縮頻発患者におけるイソプロテレノールの効果を増強する）

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筑波大学大学院博士課程人間総合科学研究科

長谷部　秀幸

CONTENTS

ABSTRACT

Aims Infrequent appearance and failed induction of premature ventricular contractions (PVCs) at catheter ablation make their localization difficult and are associated with a poor procedural outcome. This study aimed to assess the effect of preprocedural oral caffeine intake on induction of PVCs during catheter ablation.

Methods Seventy patients (age: 54 ± 14 years, 37 men) undergoing catheter ablation for monofocal PVCs were randomized to receive oral caffeine (5 mg/kg) or placebo. Before ablation, PVC counts for 5 min were performed at baseline and during isoproterenol infusion and the isoproterenol washout period. PVC count fluctuation was defined as the difference between the highest and lowest 5-min count among the three time periods.

Results The 5-min PVC counts during baseline and isoproterenol infusion were equivalent between the groups. However, those during the isoproterenol washout period and PVC count fluctuation were significantly higher in the caffeine group than the control group (73.1 ± 73.2 vs. 38.9 ± 28.9 beats/5 min, P = .012 and 69.3 ± 61.3 vs. 37.7 ± 30.9 beats/5 min, P = .008, respectively). The procedure and ablation times were significantly shorter in the caffeine group than the control group (105.0 ± 23.4 vs. 136.9 ± 43.2 min, P < .01 and 219.1 ± 104.7 vs. 283.5 ± 136.0 sec, P < .01, respectively).

Conclusions Oral caffeine intake amplified the effect of isoproterenol infusion on PVC induction during catheter ablation. The combined use of oral caffeine intake and isoproterenol infusion can be an option to increase intraprocedural PVCs.

KEYWORDS Premature ventricular contractions; Catheter ablation; Caffeine; Isoproterenol

Introduction

Premature ventricular contractions (PVCs) may impair the quality of life due to associated symptoms such as palpitations and dyspnea and can potentially lead to a reversible form of cardiomyopathy.[1] Although radiofrequency catheter ablation (RFCA) has been established as a curative therapy, the inability of creating an activation map in the case of infrequent PVCs during RFCA makes their localization difficult and is associated with a poor procedural outcome.[2] Isoproterenol, a non-selective β-adrenoreceptor agonist can increase intraprocedural PVCs, but its effect varies among patients.[3] A more reliable method of inducing PVCs during catheter ablation is needed.

In the daily clinical situation, some patients show a temporal association between arrhythmia episodes and caffeine intake.[4] We have noted clinically that preprocedural coffee intake successfully induced the target arrhythmia during catheter ablation in such patients, implying that preprocedural caffeine intake may increase the occurrence of PVCs. Caffeine is the major component of some of the most consumed beverages, such as tea and coffee.[5] Pharmacologically, caffeine is a methylxanthine alkaloid that stimulates the central nervous system and has effects on intracellular calcium trafficking and sympathetic activation.[6–8] Some effects of caffeine are common with those of isoproterenol.[6] Based on these facts and our clinical experience, we hypothesized that oral caffeine intake could also increase the occurrence of PVCs or augment the effects of isoproterenol during an ablation procedure. As a method of caffeine intake, ingesting a caffeine-containing drink is not favorable because catheter ablation should be performed under the fasting condition. However, caffeine is commercially available in a powdered form, thus allowing the administration of caffeine with a small amount of water before an ablation procedure. So, we conducted this study using powdered caffeine to assess the effect of

preprocedural oral caffeine intake at a moderate amount of 5 mg/kg (corresponding to 2 or 3 cups of coffee) on intraprocedural PVC frequency and the response to isoproterenol infusion for the induction of PVCs at RFCA.

Methods

Study Population and Design

This study included 70 consecutive patients with frequent monofocal PVCs who were scheduled to undergo initial catheter ablation from April 2013 to December 2018. The indications for catheter ablation were PVC-associated symptoms in 34 (49%) patients and PVC-induced cardiomyopathy (left ventricular ejection fraction [LVEF] ≤ 50%) in 25 (36%) patients. The remaining 11 (16%) patients also underwent catheter ablation because of high PVC burdens (≥ 20%) even though they only had mildly decreased LVEF (50–60%). In all enrolled patients, medical therapy was ineffective or patients preferred catheter ablation to medical therapy. An electrocardiogram, 24-h Holter electrocardiogram, and transthoracic echocardiogram were obtained in all patients. Patients with atrial fibrillation or structural heart disease other than PVC-induced cardiomyopathy, or patients who were on medications that may react with caffeine through the cytochrome P450 1A2 pathway (CYP1A2) were excluded from the study. Patients who were on α-blockers and antiarrhythmic medications including β-blockers, and L-type calcium blockers were also excluded.

Enrolled patients were assigned to the caffeine group or the control group before the ablation based on a computer-generated randomization. The study protocol was approved by the local institutional review board (approval no. 27-12-01), and all patients provided informed written consent.

Caffeine Administration

The taking of caffeine-containing beverages was not allowed for 48 h prior to catheter ablation based on its half-life of 5.7 hours. Patients ingested powders of oral caffeine of 5 mg/kg or placebo (lactose) immediately prior to entering the catheterization room according to random assignment.

PVC Count

Electrophysiological study and catheter ablation proceeded under conscious mild sedation with midazolam of 0.3 mcg/kg/min in all patients. Surface electrocardiograms and intracardiac electrograms were continuously monitored and stored on a LabSystem Pro digital recording system (Bard Electrophysiology, Lowell, MA). A 5F 10-pole unidirectional catheter (EPstar, Japan Lifeline Co. Ltd., Tokyo, Japan) was advanced to the His bundle position, and a 3F 8-pole mapping catheter (INC Monorail I, Inter Nova Inc., Tokyo, Japan) was advanced into the great cardiac vein or anterior interventricular cardiac vein through the right femoral vein for reference at ablation. Isoproterenol was infused intravenously at a dose up to 0.03 mcg/kg/min to increase the sinus rate by 30% or higher than that at the baseline measurement.

Only the clinical PVC was studied. The PVC counts for 5 min were performed at baseline, during continuous isoproterenol infusion, and during the isoproterenol washout period, which was defined as the time period between isoproterenol cessation until the sinus rate returned to baseline conditions. The PVC count during isoproterenol infusion started when the sinus rate reached a 30% increase from baseline, and that during the isoproterenol washout period started when the sinus rate began to decrease. PVC count fluctuation was defined as the difference between the highest and lowest 5-min PVC counts among the three time periods. The study

protocol is summarized in Figure 1.

Catheter Ablation

After the PVC counts were completed, catheter ablation proceeded in all patients using a CARTO 3-dimensional mapping system (Biosense Webster, Diamond Bar, CA). Mapping and RFCA were performed with a 3.5-mm open irrigation-tip catheter (ThermoCool, Biosense Webster). In the cases in which the target PVC was infrequent, continuous infusion of isoproterenol and its cessation were repeated to increase PVC frequency. The site of PVC origin was identified by activation mapping or pace mapping. Radiofrequency (RF) energy with power up to 35 W was delivered for 30–120 sec at the site of origin. Acute success was considered when the clinical PVC was eliminated and not inducible even with isoproterenol infusion.

Follow-Up

Patients were seen in follow-up at 1, 3, and 12 months after ablation. A 24-h Holter electrocardiogram was performed at 12 months after ablation. Ablation success was defined as > 80% decrease in PVC burden without antiarrhythmic drugs.[1–3]

Statistical Analysis

Continuous variables are expressed as mean ± SD, and categorical variables are reported as number and percentage. Differences between groups were tested using an unpaired Student *t*-test or χ^2 test, as appropriate. Statistical significance was considered when the P value was $< .05$. Statistical tests were performed using SPSS version 24 (SPSS, Inc., Chicago, IL).

Results

The baseline characteristics of the enrolled patients are summarized in Table 1. There were no significant differences in baseline characteristics between the groups. The right ventricular outflow tract (46% in the caffeine group, 40% in the control group) was the most common location of PVC origin. The study protocol was performed safely in all patients. The time interval from caffeine or placebo intake to the start of the PVC count was 44.4 ± 8.5 min in the caffeine group and 47.1 ± 9.2 min in the control group (P = .90). The duration to completion of the PVC count protocol was 17.5 ± 0.5 min in the caffeine group and 17.5 ± 0.5 min in the control group (P = .64). No patients in the caffeine group developed caffeine-related symptoms such as tremor, dizziness, or emotional confusion. None of the enrolled patients experienced ventricular fibrillation (VF) or tachycardia (VT) during the procedure. RFCA was performed without any procedure-related complications.

PVC Counts and Response to Isoproterenol Infusion

Individual 5-min PVC counts during baseline, isoproterenol infusion, and the isoproterenol washout period in all patients and 3 subgroups based on the time period during which the PVCs were most frequently observed are shown in Figure 2. PVCs disappeared (i.e., no PVCs were observed) throughout the measurement period in two (6%) and four patients (11%) in the caffeine and control groups, respectively (P = .39). The distributions of subgroups based on the 5-min PVC count (0-9, 10-99, ≥ 100 beats/5 min) in each time period are shown in Figure 3.

The 5-min PVC counts during baseline and isoproterenol infusion were equivalent between the two groups (baseline: 47.5 ± 51.1 vs. 34.9 ± 41.1 beats/5 min, P = .26; during isoproterenol: 56.4 ± 75.5 vs. 36.1 ± 40.0 beats/5 min, P = .17; Figure 4A, B). However, the 5-min PVC count

during the isoproterenol washout period was significantly higher in the caffeine group than the control group (73.1 ± 73.2 vs. 38.9 ± 28.9 beats/5 min, P = .012; Figure 4C). The PVC count fluctuation was significantly higher in the caffeine group than the control group (69.3 ± 61.3 vs. 37.7 ± 30.9 beats/5 min, P = .008; Figure 4D).

Blood Pressure, Sinus Rate, and Response to Isoproterenol Infusion

The systolic and diastolic blood pressures at baseline, during isoproterenol infusion, and during the isoproterenol washout period were significantly higher in the caffeine group than the control group. However, the sinus rates were not significantly different between the two groups at any time period (Table 2).

Impact on Catheter Ablation Procedure and Outcome

In all patients, RFCA was performed with the references of activation and pace mapping. Although PVCs disappeared (i.e., no PVCs were observed) during the PVC count in two and four patients in the caffeine and control groups, respectively, PVCs were successfully induced by repeating the administration and cessation of isoproterenol, thus allowing activation mapping. Acute success was achieved in 29 patients (83%) in the caffeine group and in 27 patients (77%) in the control group (P = .55). The procedure time and total duration of RF applications were significantly shorter in the caffeine group than the control group (procedure time: 105.0 ± 23.4 vs. 136.9 ± 43.2 min, P < .01; RF duration: 219.1 ± 104.7 vs. 283.5 ± 136.0 sec, P = .030). At 12 months after the ablation, ablation success was achieved in 31 patients (89%) in the caffeine group and in 28 patients (80%) in the control group (P = .32), and the mean PVC burden measured by 24-h Holter electrocardiogram was 2.4 ± 6.8% in the caffeine group and 4.6 ± 9.4%

in the control group (P = .25). In the caffeine group, the PVC origin of all four patients with ablation failure was the left ventricular summit. In the control group, the PVC origins of the seven patients with ablation failure were the left ventricular summit in four patients (57%) and the para-Hisian tricuspid annulus in three patients (43%).

Discussion

Main Findings

The key observations of the present study are as follows. Oral caffeine intake amplified the effect of isoproterenol: caffeine increased both the number of PVCs during the isoproterenol washout period and the isoproterenol-induced fluctuation in PVC frequency. The RFCA procedure time and total duration of RF applications in the caffeine group were significantly shorter than those in the control group.

Effect of Caffeine on PVC Frequency and Response to Isoproterenol Infusion

The caffeine concentration reached its maximum level within 1 h of consumption, and the half-life of caffeine is 5.7 h with nearly 100% bioavailability.[6] In a previous study, caffeine given at the moderate amount of 5 mg/kg increased caffeine blood levels to 7.45 (interquartile range: 4.8–8.8) μg/mL about 1 h after caffeine intake.[9] In the present study, the time interval from caffeine intake to the start of PVC counts was 44.2 ± 8.6 min in the caffeine group and 47.5 ± 9.3 min in the control group, suggesting that the PVC count was performed under conditions in which the blood level of caffeine was nearly at its highest. In fact, the blood pressure in the caffeine group was significantly higher than that in the control group. The sinus rate was equivocal between the two groups, which is consistent with prior studies. It is estimated that

activation of a vagal baroreflex induced by a rise in blood pressure counteracts the positive chronotropic effects of caffeine.[9,16]

Caffeine increases plasma norepinephrine and epinephrine levels and intracellular calcium and stimulates sympathetic activity via various mechanisms: mainly inhibition of type A1 and A2 adenosine receptors and phosphodiesterase.[6–8,10–12] Caffeine intake has various effects on cardiac electrophysiology and autonomic activity, and some are common with those of isoproterenol. The PVC frequency is complicatedly modulated by multiple factors including autonomic activity and intracellular calcium trafficking.[2,3,13] Whether PVCs are sympathetically or parasympathetically mediated is case dependent; therefore, there was considerable interindividual variation in the response to isoproterenol as shown in Figure 2. Among all subgroups based on the time period during which the PVCs were most frequently observed, patients in the caffeine group showed larger isoproterenol-induced fluctuation in PVC frequency when compared with the control group (Figure 2). We used PVC count fluctuation to express the magnitude of the response to isoproterenol regardless of its response pattern. The PVC fluctuation was larger than that in the control group, implying that there might be an incremental effect between oral caffeine intake and isoproterenol infusion. This speculation is supported by an animal experimental study in which propranolol and verapamil were effective in suppressing cardiac arrhythmias induced by caffeine at a toxic level.[13]

Although the PVC counts at baseline and during isoproterenol infusion were equivalent between the two groups, that during isoproterenol washout was significantly higher in the caffeine group. As in an exercise recovery period, the isoproterenol washout period induces complex fluctuation in autonomic activity: parasympathetic activity is progressively increasing while sympathetic activity is decreasing.[14] Previous studies showed that caffeine affected

parasympathetic activity assessed by heart rate variability (HRV) although its effects were inconsistent across the studies and its mechanism is unclear.[15–17] da Silva Rolim et al. reported that a moderate amount (~3 mg/kg) of caffeine intake increased parasympathetic reactivation after exercise on a treadmill, whereas caffeine did not alter parasympathetic activation at rest or during exercise.[17] Our result that caffeine increased PVC frequencies only during the washout period seems to be related with the study by da Silva Rolim et al. As in an exercise recovery period, caffeine intake might increase parasympathetic reactivation during the washout period. Such fluctuation in autonomic activity might have increased the PVC frequency during the washout period.

Prior Studies

Previous animal experimental studies showed that caffeine at a toxic level induced ventricular arrhythmias, whereas caffeine intake at a moderate or high dose did not.[13,18] Chelsky et al. reported that a moderate amount of oral caffeine intake (275 mg) did not change the inducibility of ventricular arrhythmia in patients with VT or VF.[19] A study by Zuchinali et al. showed that high-dose oral caffeine intake (500 mg) did not induce arrhythmias in patients with systolic heart failure.[20] Dobmeyer et al. reported that intravenous caffeine administration did not induce ventricular arrhythmia but slightly shortened the refractory period (~10 ms) in the right ventricle in healthy volunteers and patients with heart disease.[12] Based on these previous studies, there seems to be either no or little effect of a moderate amount of oral caffeine intake alone on ventricular arrhythmias. However, these studies lack data concerning the response to isoproterenol. Our results indicated that the combined use of caffeine intake and isoproterenol infusion has synergistic effects on PVC induction.

Clinical Implications

Although an inability to reach the site of origin for anatomical or technical reasons is a common cause of the failure of ablation for PVCs, infrequent intraprocedural PVCs are also an important cause. At catheter ablation for PVCs, frequent intraprocedural PVCs are preferable as they enable quick and accurate creation of an activation map. The total duration of RF applications was significantly shorter in the caffeine group than that in the control group. In the case of infrequent PVCs, operators might create larger lesions due to difficulty in PVC localization. Such excessive lesion formation can potentially lead to complications such as cardiac tamponade and other collateral damage. The increased frequency of PVCs might have contributed to the shorter procedural time and shorter duration of RF applications in the caffeine group.

Oral caffeine intake before PVC ablation is safe, and the combined use of caffeine intake and isoproterenol infusion can be a useful option to increase intraprocedural PVCs. In daily clinical practice, there are some individual patients in whom a clear temporal association between caffeine intake and increased PVC burden is observed. Oral caffeine intake prior to ablation may be recommended especially for such patients.

Limitations

First, this study assessed a small cohort of patients. The ablation outcome was equivocal between the two groups, which might be attributable to the small cohort size of this study. In catheter ablation for PVCs, PVC disappearance during the procedure is a critical issue because it would disable any mapping. Although there was no significant difference in the prevalence of the disappearance of PVCs in the present study, this result also might be attributable to the small cohort size. Further study with a larger cohort is needed to evaluate the effect of caffeine intake

on ablation outcome and prevention for complete disappearance of targeted PVCs. Second, most of our patients were habitual drinkers of caffeine-containing drinks, and this might have potentially influenced our results. However, the taking of caffeine-containing beverages was not allowed for 48 h prior to catheter ablation. Third, this study lacks data regarding the dose dependency of isoproterenol and caffeine. Further studies with different doses of isoproterenol and caffeine are needed to clarify the dose dependency of these two drugs on PVC frequency. Fourth, mild sedation using midazolam might have influenced our results. However, the dosage of midazolam was unified across all of the enrolled patients. Finally, we excluded patients with structural heart disease from the study. This may preclude application of the present results to ventricular arrhythmias with reentrant mechanisms.

Conclusion

Oral caffeine intake amplified the effect of isoproterenol infusion on PVC induction in patients with frequent PVCs. The combined use of oral caffeine intake and isoproterenol infusion can be a helpful option to increase intraprocedural PVCs at catheter ablation.

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Table Captions

Table 1. Baseline Patient Characteristics

Table 2. Measurements of Blood Pressure and Sinus Rates

Figure Legends

FIGURE 1 Study protocol. ISP = isoproterenol; PVC = premature ventricular contraction.

FIGURE 2 Response of PVCs to ISP infusion. Individual 5-min PVC counts during baseline, ISP infusion, and ISP washout period in all patients and 3 subgroups based on the time period during which the PVCs were most frequently observed. ISP = isoproterenol; PVC = premature ventricular contraction.

FIGURE 3 Stacked bar graphs illustrating the distribution of subgroups based on 5-min premature ventricular complex (PVC) count (0–9, 10–99, or ≥ 100 beats/5 min) in each time period. ISP = isoproterenol.

FIGURE 4 Differences in the 5-min PVC counts at baseline (A), during ISP infusion (B), during the ISP washout period (C), and PVC count fluctuation (difference between the highest and lowest 5-min PVC count) (D). N.S. = not significant; ISP = isoproterenol; PVC = premature ventricular contraction.

TABLE 1 Baseline Patient Characteristics

Characteristic	Caffeine group (n = 35)	Control group (n = 35)
Male sex (N)	19 (54%)	18 (51%)
Age (yrs)	55.8 ± 14.8	52.8 ± 12.2
BMI (kg/m^2)	23.1 ± 4.0	23.1 ± 2.9
Hypertension (N)	6 (17%)	7 (20%)
Symptomatic (N)	16 (46%)	18 (51%)
Daily caffeine consumption (cups)	3.2 ± 1.5	3.1 ± 1.7
Holter PVC number (/day)	23390 ± 12130	22860 ± 12890
Holter PVC burden (%)	21.3 ± 10.9	20.3 ± 10.4
LVEF (%)	58.9 ± 15.2	57.9 ± 10.8
PVC-induced cardiomyopathy (N)	12 (34%)	13 (37%)
PVC origin		
RVOT	16 (46%)	14 (40%)
Tricuspid annulus	3 (9%)	3 (9%)
LVOT	6 (17%)	5 (14%)
Mitral annulus	5 (14%)	7 (20%)
Sinus of Valsalva	1 (3%)	2 (6%)
LV summit	4 (11%)	4 (11%)

BMI = body mass index; LV = left ventricle; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; PVC = premature ventricular contraction; RVOT = right ventricular outflow tract.

TABLE 2 Measurements of Blood Pressure and Sinus Rate

Parameter	Caffeine group (n = 35)	Control group (n= 35)
Systolic blood pressure (mmHg)		
Baseline	151.0 ± 18.4	137.8 ± 17.2*
During ISP infusion	146.1 ± 21.4	130.8 ± 17.3*
ISP washout period	148.7 ± 19.1	137.3 ± 17.8†
Diastolic blood pressure (mmHg)		
Baseline	81.9 ± 9.1	74.2 ± 9.6*
During ISP infusion	72.3 ± 11.1	65.9 ± 9.4†
ISP washout period	77.2 ± 10.4	70.9 ± 10.1†
Sinus rate (bpm)		
Baseline	70.7 ± 10.3	72.1 ± 9.5
During ISP infusion	112.6 ± 17.8	114.2 ± 20.6
ISP washout period	90.3 ± 13.2	91.6 ± 15.9

*P < .01 vs. caffeine group, †P < .05 vs. caffeine group
ISP = isoproterenol.

Figure 1

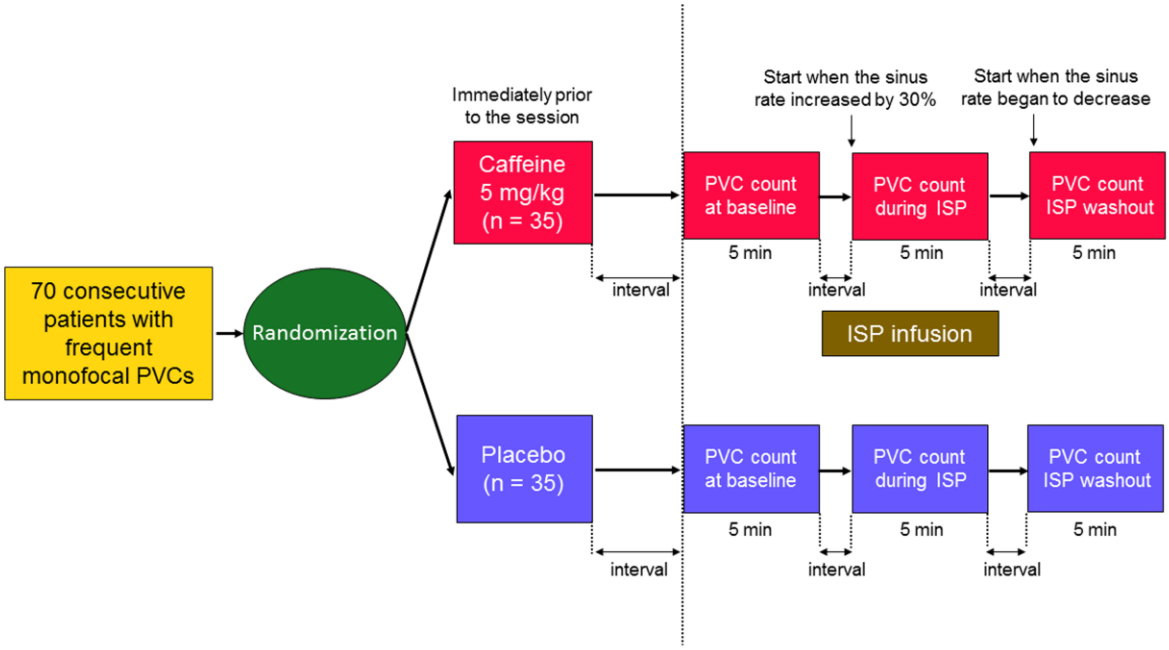

70 consecutive patients with frequent monofocal PVCs
Randomization
Immediately prior to the session
Caffeine 5 mg/kg (n = 35)
Placebo (n = 35)
interval
PVC count at baseline
5 min
Start when the sinus rate increased by 30%
PVC count during ISP
5 min
Start when the sinus rate began to decrease
PVC count ISP washout
5 min
ISP infusion

Figure 2

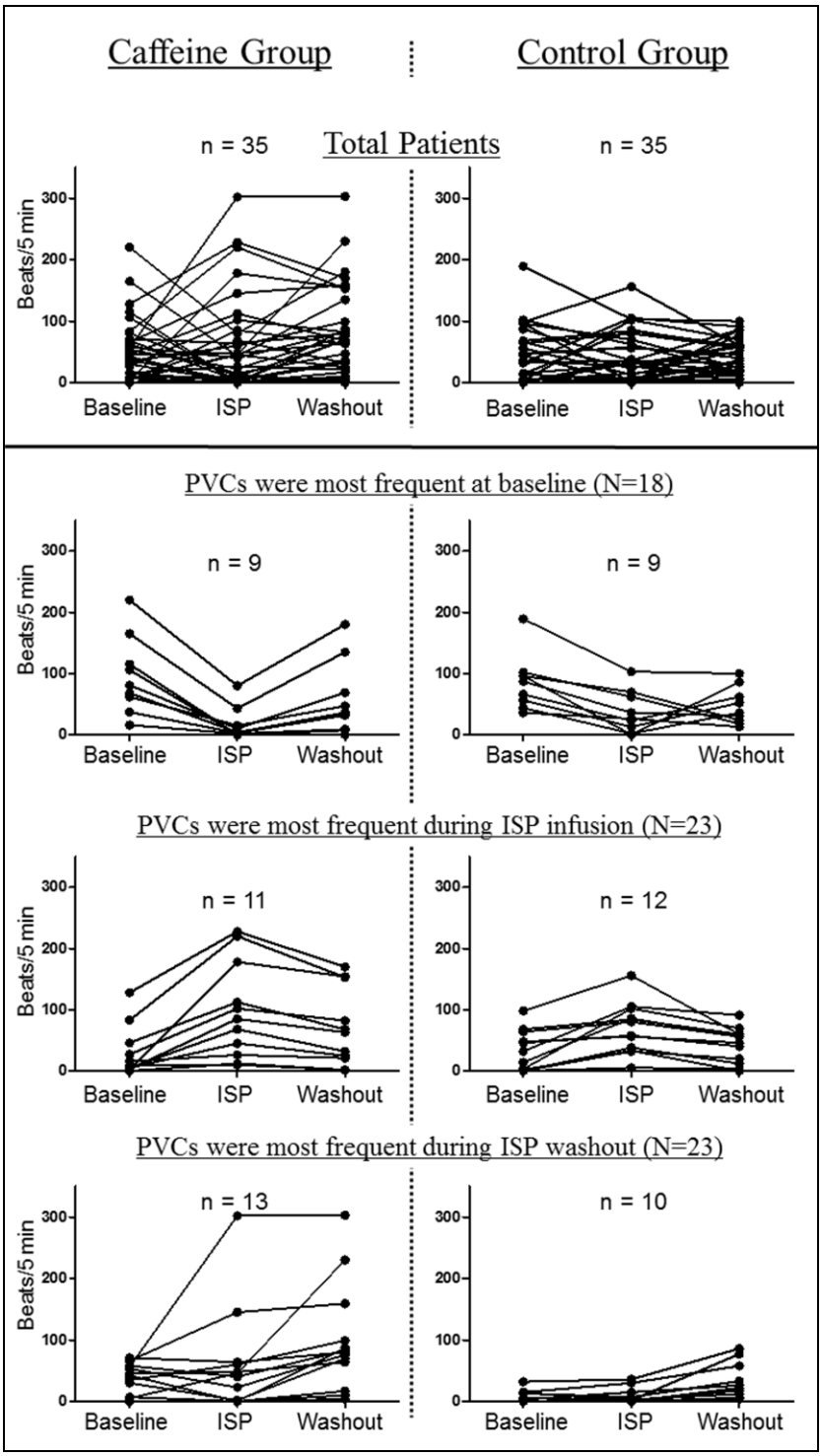

Caffeine Group
Control Group
n = 35
Total Patients
n = 35
Beats/5 min
300
200
100
0
Baseline
ISP
Washout
PVCs were most frequent at baseline (N=18)
n = 9
n = 9
PVCs were most frequent during ISP infusion (N=23)
n = 11
n = 12
PVCs were most frequent during ISP washout (N=23)
n = 13
n = 10

Figure 3

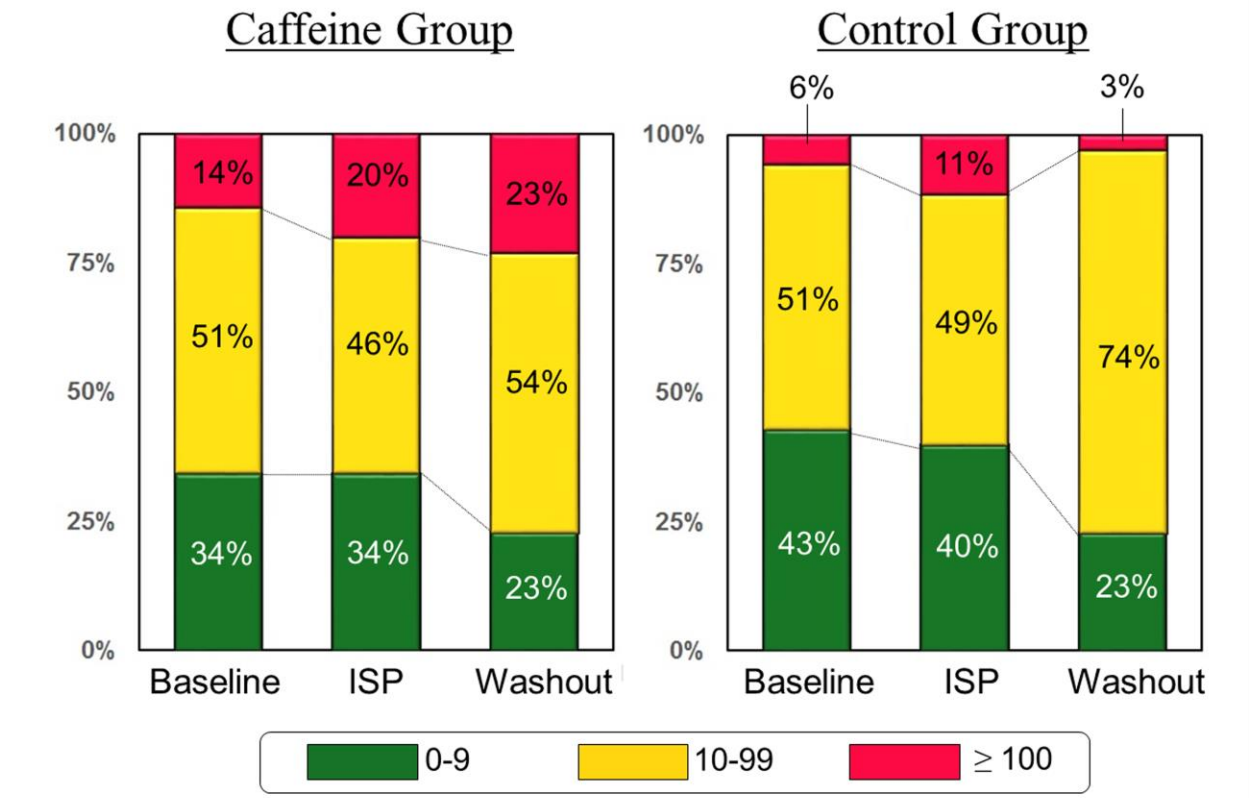
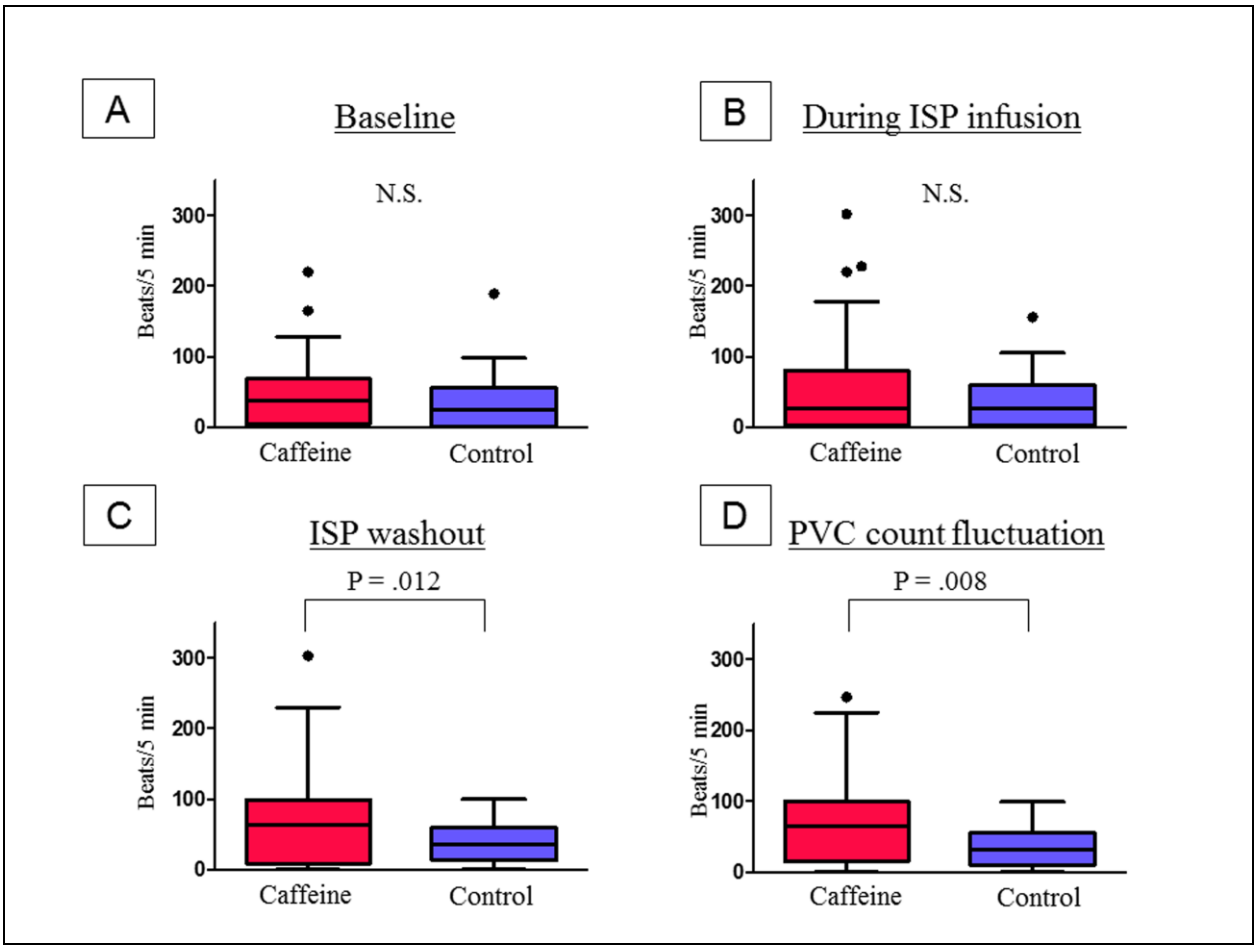

Caffeine Group
Control Group
100%
75%
50%
25%
0%
14%
20%
23%
51%
46%
54%
34%
34%
23%
6%
3%
11%
51%
49%
74%
43%
40%
23%
Baseline
ISP
Washout
0-9
10-99
≥ 100

Figure 4


A
Baseline
N.S.
Beats/5 min
300
200
100
0
Caffeine
Control
B
During ISP infusion
N.S.
Beats/5 min
300
200
100
0
Caffeine
Control
C
ISP washout
P = .012
Beats/5 min
300
200
100
0
Caffeine
Control
D
PVC count fluctuation
P = .008
Beats/5 min
300
200
100
0
Caffeine
Control