Influence of Caffeine on Blood Pressure and Platelet Aggregation

José Wilson S. Cavalcante, Paulo Roberto M. Santos Jr., Marcus G. F. de Menezes, Hedylamar Oliveira Marques, Leonardo Pessoa Cavalcante, Walewska S. Pacheco

Manaus, AM - Brazil

Objective - *Studies have demonstrated that methylxanthines, such as caffeine, are A_1 and A_2 adenosine receptor antagonists found in the brain, heart, lungs, peripheral vessels, and platelets. Considering the high consumption of products with caffeine in their composition, in Brazil and throughout the rest of the world, the authors proposed to observe the effects of this substance on blood pressure and platelet aggregation.*

Methods - *Thirteen young adults, ranging from 21 to 27 years of age, participated in this study. Each individual took 750mg/day of caffeine (250mg tid), over a period of seven days. The effects on blood pressure were analyzed through the pressor test with handgrip, and platelet aggregation was analyzed using adenosine diphosphate, collagen, and adrenaline.*

Results - *Diastolic pressure showed a significant increase 24 hours after the first intake ($p<0.05$). This effect, however, disappeared in the subsequent days. The platelet aggregation tests did not reveal statistically significant alterations, at any time during the study.*

Conclusion - *The data suggest that caffeine increases diastolic blood pressure at the beginning of caffeine intake. This hypertensive effect disappears with chronic use. The absence of alterations in platelet aggregation indicates the need for larger randomized studies.*

Keywords: caffeine, adenosine, blood pressure

Universidade do Amazonas – CNPq
Adress: José Wilson S. Cavalcante - Av. Darcy Vargas, 378 - Parque 10 - 69050-020 - Manaus, AM - Brazil E mail: antenor@argo.com.br

Studies in vitro and in animals suggest that the methyxantines like caffeine are competitive antagonists of adenosine (ADO) receptors A_1 and A_2 [1]. A_1 receptors, at higher concentrations in the central nervous system (CNS), have high binding capability to ADO, which in the CNS has a neurodepressor action, through the inhibition of the release of norepinephrine, dopamine, gamma-aminobutyric acid (GABA), and glutamate. Through the inhibition of adenylate cyclase, and the subsequent decrease in intracellular cyclic adenosine monophosphate (AMPc), A_1 receptors also cause bronchoconstriction, reduce myocardial contractility, reduce A-V conduction, and cause constriction of the afferent renal arteriole. By binding to A_2 receptors, ADO causes activation of adenylate cyclase, leading to peripheral and cerebral vasodilation [1].

The effects of caffeine on arterial blood pressure (BP) are controversial [2]. Some studies suggest that its action on peripheral vascular resistance (PVR) is weaker than its effect on the CNS that leads to an increase in PVR [3]. On the other hand, studies in individuals with autonomous defects demonstrate that the peripheral effect plays an important role in the increase of PVR [4]. Caffeine causes this effect by blocking A_1 receptors (central), increasing the release of vasoconstrictive substances and by blocking A_2 receptors (peripheral), leading to vasoconstriction.

With regard to platelet aggregation (PA), studies in vitro point to caffeine as being a phosphodiesterase blocker, blocking the conversion of AMPc to 5-AMP, leading to an increase in AMPc and subsequent inhibition of PA [3]. However, controversy appears when it is demonstrated that caffeine, by blocking ADO A_2 receptors (on platelet surfaces), leads to PA [5] (fig. 1).

Because of the existing controversies and considering the usual habit in our country and all over the world of consumption of coffee and other caffeine-containing products, with a consumption of 15mg/kg/day in the United States and Canada [6], we decided to investigate the effects of caffeine on BP and PA behavior, as well as to observe the clinical effects of its use. The handgrip pressor test was chosen be-

cause it is a standard stimulus for the sympathetic system, and we sought to observe whether it is potentiated by caffeine.

Methods

Thirteen volunteers, aged 21 to 27, participated in the study. They were clinically healthy, with no addictions and did not use medications (table I). The Vanderbilt Clinical Research Center protocol (modified) [7] was used (fig. 2), and the guidelines of the National Council of Health [8] were observed for the execution of the research. The study consisted, initially, of 7 days of abstinence from caffeine-containing products, followed by 7 days of daily intake of 750mg of caffeine, divided into three doses of 250mg (capsules), and then followed by 7 days of abstinence. BP behavior was observed with the use of the handgrip pressor test (HPT), which consisted of maintaining 30% of maximum force for 2 minutes; the BP measurement was taken with the auscultatory method with a mercury column sphygmomanometer, before the test (basal measure), immediately after it, and every 2 minutes until the 8th minute after the stimulus, on the nondominant arm and with the participant in the supine position. Systolic and diastolic pressures were considered as the 1st and 5th Korotkoff phases, respectively.

For the study of PA, we used platelet rich plasma (PRP) obtained from venous blood samples collected in silicon test tubes, with sodium citrate at 3.8% and coagulant, avoiding both trauma and stasis during the puncture. The number of platelets in the PRP was standardized at 300,000/mm^3.

Table I – Sample distribution according to age, sex, weight, and caffeine dosage

Volunteer	Age/sex	Weight (kg)	Dose (mg/kg/dia)
1	23 M	76	9.3
2	27 F	53	14.1
3	24 M	63	11.0
4	24 M	93	8.0
5	24 F	56	13.4
6	24 M	86	8.7
7	24 M	58	12.9
8	26 F	54	13.9
9	27 M	60	12.5
10	25 M	53	14.1
11	24 M	58	12.9
Average	24.72	64.54	11.89
Standard deviation	1.35	14.0	2.26

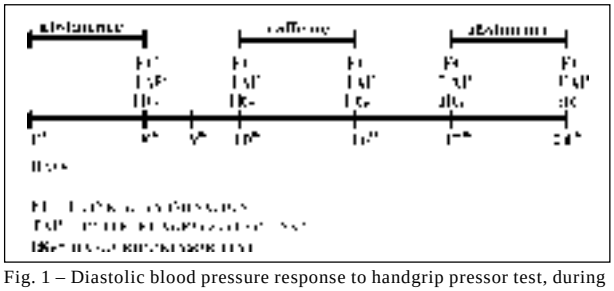

Fig. 1 – Diastolic blood pressure response to handgrip pressor test, during caffeine use

The aggregate agents used were adenosine diphosphate (ADP), adrenalin, and native collagen from equine tendon. The tests were done on the Chromo-log aggregometer, model 530, and on the model 705 register of the same brand.

The data were collected on the 8th day (basal), on the 10th and 16th days (acute phase and chronic phase of use, respectively), and on the 17th and 24th days (acute abstinence and chronic abstinence, respectively). The obtained results analyzed statistically with the analysis of variance (ANOVA) test, considered significant when $p<0.05$. The BP measurement and application of the handgrip pressor test were accomplished with the participation of all authors.

Results

Two of the 13 volunteers in the study dropped out. One of them because of an important side effect, and the other as a consequence of acute appendicitis.

During caffeine intake, the most common symptoms were insomnia (84.6%), tremors (46.1%), nausea (38.4%), polyuria (23%), diarrhea (15,4%), and polyphagia (15.4%); these symptoms were attenuated or disappeared with chronic caffeine use. After 24 hours of caffeine cessation, all volunteers experienced headaches and sleepiness, symptoms that disappeared after the 60th hour. Systolic BP was not significantly elevated in any phase of the study. Diastolic BP, however, was significantly elevated in the acute phase ($p<0.05$), a phenomenon that disappeared in the chronic phase (fig.1). Comparing diastolic BP basal values before caffeine intake and 24 hours after its withdrawal (acute abstinence), we observed a significant fall from 65 to 60.4mmHg ($p<0.05$) (fig. 3). Comparing BP values during the HPT applied in the acute phase of caffeine use with those obtained during the acute phase of caffeine abstinence, we verified a significant decline in diastolic BP from 69.5 to 62 mm Hg ($p<0.01$) (fig. 4). No significant alteration occurred in the PA during any phase of the study (fig. 5).

Discussion

Studies demonstrate that caffeine is a lipophilic component rapidly absorbed by the CNS [9]. Therefore, by caffeine induced inhibitory action on A_1 receptors of ADO, abundant in CNS, a neurostimulating effect occurs through the release of dopamine, adrenaline, GABA, and glutamate in many regions of the CNS. This finding was noted clinically in the present study by the appearance of insomnia, tremors, and irritability during caffeine intake, this effect being stronger in the acute phase. After 24 hours of caffeine interruption (acute abstinence), the volunteers experienced intense headache and sleepiness, probably because of cerebral vasodilatation and the neurodepressor effect, respectively. Those clinical manifestations are explained by the increase in ADO receptors A_1 and A_2 because of chronic caffeine use. These receptors, during acute abstinence, have a high affinity for ADO and interact more actively with G protein, through the adenylate cyclase system [10]. The cli-

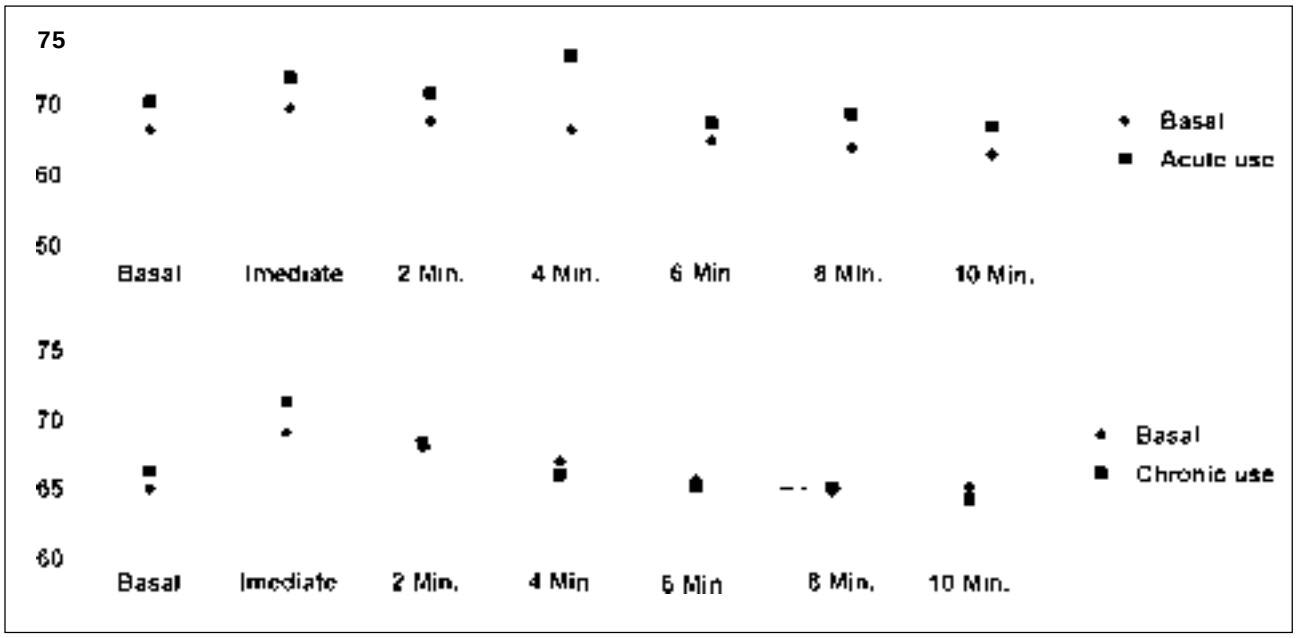

Fig. 2 – Vanderbilt Clinical Research Center modified protocol [7].

Fig. 3 – Diastolic blood pressor response to handgrip pressor test during acute caffeine abstinence (mmHg) ($p<0.05$*)

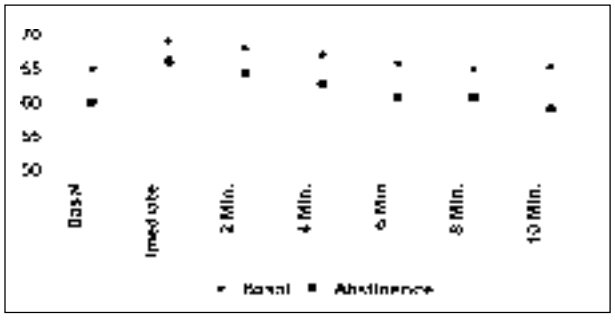

Fig. 4 – Comparison of diastolic blood pressure response to handgrip pressor test during acute caffeine use and acute caffeine abstinence (mmHg) ($p<0.01$*)

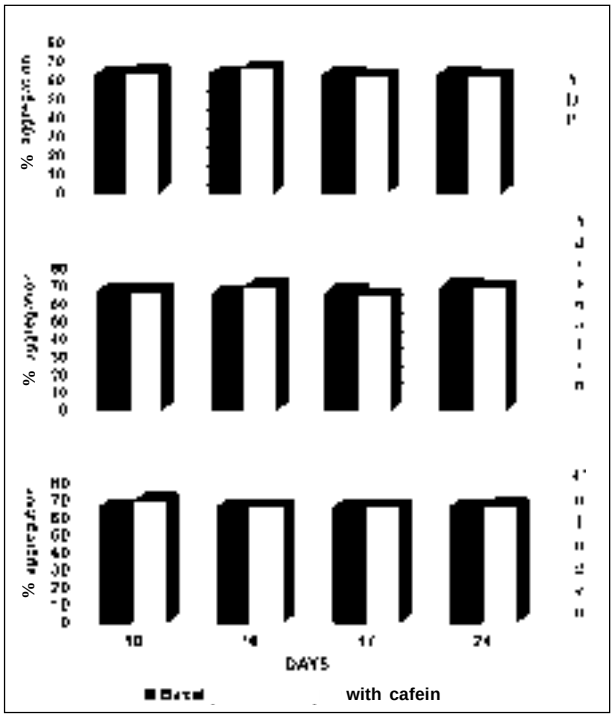

Fig. 5 – Platelet aggregation induced by ADP, adrenalin, and collagen.

nical manifestations corresponding to these caffeine effects disappeared within the 60th and the 72nd hour after the last caffeine dose.

The others clinical manifestations observed with acute caffeine use are related to its action on the phosphodiesterase receptors of smooth muscles, leading to an increase in AMPc levels and, consequently, to vasodilation of afferent renal arterioles, which explains the appearance of polyuria and decreased tonus of the lower esophageal sphincter, leading to gastroesophageal reflux, which manifests clinically as pyrosis, nausea, and anorexia. Besides that, high levels of AMPc on the smooth muscle of the gastrointestinal tract lead to an increase in motility, which manifested clinically as diarrhea and polyphagia in some of our volunteers, as reported by Benowitz [6]. With chronic caffeine use, a reduction or disappearance of symptoms was observed, a fact

that Brunus et al [11] attributed to the phenomenon of tolerance.

Mumford and Haltzman [12] demonstrated that caffeine effects are dose-dependent. In the present study, we used a dose that ranged from 8.7 to 14.1mg/kg, and the symptoms were more bothersome in those volunteers with higher doses.

Many researchers [13-15] have demonstrated that caffeine acts in smooth muscles, particularly the vascular smooth muscle, in three ways: 1) inhibitory action on phosphodiesterase, leading to an increase in AMPc and, consequently, avoiding calcium extrusion from the sarcoplasmic reticulum, leading, ultimately, to peripheral vasodilation; 2) activation of the sympathetic nervous system through the blockade of A_1 ADO receptors, at the central level, leading to an increase in PVR; 3) blockade of A_2 ADO receptors, which are both peripheral and central vasodilators, leading to vasoconstriction in both sites.

The present investigation found a significant rise in basal diastolic pressure after 24 hours of caffeine intake, which can be explained by either sympathetic nervous system activation or inhibition of A_2 ADO receptors, or both. The HPT did not demonstrate a significant rise in systolic pressure, although isotonic pressor tests have demonstrated otherwise [13]. In this case, comparative studies are needed of other forms of pressor stimulus. The lack of BP decline between chronic caffeine use and abstinence reinforces the belief in the existence of the tolerance phenomenon. This is more evident when one compares the BP values obtained during the acute phase of caffeine intake with those obtained 24 hours after caffeine interruption, when a significant decrease occurred.

Regarding the clinical manifestations during caffeine use, a reduction in symptoms occurred with its chronic use, which points to the phenomenon of tolerance. According to Grobbee et al [16], usual caffeine intake, in a dose of 250mg/day, would not lead to a higher risk of cardiovascular disease. It is important to observe that 150mL of homemade coffee contains 120mg of caffeine, 150mL of instant coffee contains 70mg of caffeine, 150mg of black tea contains 50mg of caffeine, 360mL of cola soft drink contains from 30 to 60mg of caffeine, 30mg of chocolate contains 7mg of caffeine, and some analgesic medications contain from 30 to 200mg of caffeine [11]. Considering that the recommended maximum daily caffeine intake according to Grobbee is 250mg/day [16] and that caffeine-containing products are used in our country with great frequency, it becomes important to make epidemiological surveys to check the real caffeine dose used by the Brazilian population, to define whether caffeine intake is or is not a risk factor for cardiovascular disease in our country.

Although the number of individuals studied is small and the dose of caffeine administered was unique, with different doses in relation to the corporal weight, the elevation of PD in the sharp phase indicates the need for caution in the use of this drug for hypertension, mainly for those who are not habitual consumers. The lack of platelet aggregation alteration, which is controversial in other studies, points to the need for randomized studies with a greater number of participants.

References

1. Schwabe UD, Ukena and Lohse MJ. Xanthine derivates as antagonists at A1 and A2 adenosine receptors. Arch Pharmacol 1985; 330: 212.
2. Kaplan NM. Systemic Hypertension: Therapy. In: Braunwald E. Heart Disease. 4th ed., vol I, cap 20. Baltimore: Williams & Wilkins, 1990: 852-74.
3. Giman AG, Rall TW, Nies AS, Tylor P. Drugs Used in the Treatament of Asthma. The Pharmacological Basis of Therapeutics. 8th ed. Baltimore: McGraw Hill, 1985: 618-30.
4. Onrot J, Goldeberg MR, Biaggioni J. Hemodynamic and humoral effects of caffeine in autonomic failures. N Engl J Med 1995; 313: 549-54.
5. Bak AA, Grobbee DE. Cofee, caffeine and hemostasis: a review. Neth J Med 1990; 37: 242-6.
6. Benowitz NL. Clinical pharmacology of caffeine. Annu Rev Med 1990; 41: 77-288.
7. Clinical Research Center, Pharmacology Infusion Studies. The Vanderbilt Hipertension Center. Specialized Center of Research. Vanderbilt University. School of Medicine, 1991. Nashiville – TN, USA.
8. Conselho Nacional de Saúde. Resolução 01/88: Normas de pesquisa em saúde. Diário Oficial da União 1993; 3: 197-207.
9. Dimpfel W, Shober F, Spüler M. The influence of caffeine on human EEG under resting condition and during mental loads. Clin Invest 1993; 3: 197-207.
10. Kaplan GB, Greenblatt DJ, Kent MA. Cotreau-Bibbo MM. Caffeine treatment and withdrawal in mice: Relationships between dosage, concentracions, locomotor activity and A1 adenosine receptor binding. J Pharmacol Exp Ther 1993; 3: 1563-72.
11. Bruns RF, Lug H, Pugsley TA. Adenosine Receptor Subtypes: Binding Studies. Topics and Perspectives in Adenosine Research. Berlim, Heidelberg, New York: Springer, 1987: 59-73.
12. Mumford GK, Haltzman SG. Methylxantines elevate reinforcement threshold for electrical brain stimulation: role of adenosine recptorsand phosphodiesterase inhibition. Brain Res 1990; 528: 32-8.
13. Sung BHS, Lovallo WR. Effects of caffeine on blood pressure response during exercise in normotensive healthy young men. Am J Cardiol 1990; 65: 909-13.
14. Robertson D, Hollister AS, Kincaid D. Caffeine and hypertension. Am J Med 1984, 77: 54-60.
15. Kaplan GB, Greenblatt DJ, Kent MA, Cotreau-Bibbo MM. Caffeine treatment and withdrawal mice: Relationships between dosage, concentracions, locomotor activity and A1 adenosine receptor binding. J Pharmacol Exp Ther 1993; 3: 1563-72.
16. Grobbee DE, Rimm EB, Giovannucci E, Colditz G, Stampfer M, Willett W. Cofee, caffeine, and cardiovascular disease in men. N Engl J Med 1991; 323: 1026-32.