INFLUENCE OF COCA CHEWING ON HEMATOLOGICAL AND CARDIORESPIRATORY RESPONSES TO SUBMAXIMAL EXERCISE

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Summary

The cardiovascular effects of cocaine are relatively well known but little information is available concerning those of coca chewing. The present study was undertaken to determine the hematological and cardiovascular status, at rest and during prolonged (1hr) submaximal exercise in a group (n=12) of chronic coca users after chewing 50 grams of coca leaves. The results were compared to those obtained in a group (n=12) of non chewers. At rest, coca chewing was accompanied by a significant increase in heart rate, hematocrit, hemoglobin concentration, and plasma norepinephrine level. In addition, we found that coca chewing for 1hr resulted in a significant decrease in blood and plasma volume. During submaximal exercise, coca chewers displayed a significantly higher heart rate and mean arterial blood pressure. The exercise-induced hemoconcentration was similar in coca chewers and non-chewers. It is concluded that 1/ the coca-induced fluid shift observed in resting conditions in coca chewers are cumulative to that of exercise, and 2/ coca chewing prior to exercise increases heart rate and blood pressure. These changes in normal hematological and cardiovascular functions could not only impair exercise tolerance, but more important, could be potentially dangerous.

Coca chewing has been an integral part of the cultural life in South America since pre-Incaic times and the use of coca leaves is widespread among Andean populations (1); in 1970, it was estimated that 6 million people chewed coca leaves in Bolivia and Peru alone (2). It has been said to be physiologically beneficial for Andean Indians in terms of adaptation to work, cold and hunger at high altitude (1). The general effects of coca chewing have been equated by some authors with those produced by cocaine (1).

Various authors have shown that cocaine has profound effects at rest on the cardiovascular system (3), but little work has been published on the cocaine-induced effects on cardiovascular function during exercise (4). Indeed, most of the studies have investigated the combined effects of acute cocaine administration and exercise and have focused on metabolic adaptations and adrenosympathetic activation in relation to endurance performance (4-9). We are however unaware of any data describing the effects of prior coca chewing on hematological and cardiovascular adjustments during exercise.It has to be mentioned however that some author (10) has suggested some possible effects of coca use on erythropoiesis. Thus, on the basis of previous investigation

adjustments during exercise. It has to be mentioned however that some author (10) has suggested some possible effects of coca use on erythropoiesis. Thus, on the basis of previous investigation (11), it was claimed that coca chewers have lower hemoglobin concentration [Hb] and hematocrit (Ht) values than non chewers.

It seems thus necessary to provide data to determine whether the combination of coca use and exercise alters the hematological status and cardiovascular function, and to know, if coca leaf chewing and cocaine abuse can be regarded as one and the same problem.

For this purpose, we recruited subjects from two rural communities of the Altiplano (mean altitude ~ 3800m), in which we were able to find traditional coca chewers (C) as well as non-chewers (NC). Given the fact that socio-cultural reasons restrict blood withdrawal in these subjects (agriculturalists who think that blood is part of the soul), each group was only examined according to its customary conditions, i.e. chewers after coca chewing and non-chewers without chewing. Even though we realize that such an experimental design does not allow us to distinguish the acute from the chronic effects of coca chewing, we hypothesized that we should be able to determine if, whether or not, coca chewing alters the hematological and cardiorespiratory responses during prolonged (1hour) submaximal exercise (~70% of peak oxygen uptake). .

Methods

Subjects.

The subjects in this study were 24 males between the ages of 17 and 45 years. All were natives from the Altiplano (3,800m altitude-Bolivia) and all reported that their primary occupation was agriculture. Genetically, the subjects were Mestizos with a predominantly Aymara admixture. The subjects were instructed about the protocol before they gave their informed consent for participation. Before initiation of the experiment, each volunteer was examined by a physician, and was deemed free of any cardiovascular, or pulmonary disease. The subjects were divided into two groups : the first (NC, n = 12) consisted of non-chewers (i.e. subjects chewing less than 3 times a year), whereas the second group (C, n = 12) was composed of traditional coca users (i.e. subjects chewing more than 3-4 times a week during work in the field). Body mass and height were measured with a standard scale, and with an anthropometer. All measurements were performed at the Instituto Boliviano de Biologia de Altura (La Paz- Bolivia - mean altitude = 3600m).

In order to minimize factors of learning that could affect exercise performance, each subject performed an incremental test on a bicycle ergometer with a mechanical braking system. On the next day, the subject rested on a chair for one hour. During this period, the coca users were invited to chew their customary quantity of coca leaves. Thereafter, peak oxygen uptake (VO_{2peak}) was measured in the same way as on the day of familiarization using a continuous progressive protocol as described in detail elsewhere (9). Briefly, the subjects completed an incremental exhaustive cycling exercise protocol in which the work load was increased by $30W.min^{-1}$. Subjects cycled at 70 revolutions per min on a cycle ergometer (Ergomeca, France) and were paced with a metronome. Initially, subjects pedaled for 4 min with 60W and continued pedaling as the work load was increased by 30W increments each 4 minutes until exhaustion. VO_{2peak} measured in these conditions was used to determine the workload used for the submaximal exercise test.

Submaximal exercise test

One week after VO_{2peak} determination, the subjects were submitted to a steady state exercise. A submaximal work load was chosen individually to obtain a VO_2 that was ~70% VO_{2peak}. Before the test, the subjects abstained from vigourous exercise and the chewers were asked to abstain from coca chewing until the next day. When all the subjects reported to the laboratory after fasting overnight, they were provided, 3 hours before the exercise trial, with a light standardized breakfast (mainly bread without fats). They were allowed to drink Cañawa juice. Cañawa is an Andean grain like Quinua. They were prohibited to have tea or coffee.

Heart rate (HR) was monitored by bipolar ECG telemetry (Sport tester). Arterial oxygen saturation (SaO_2) was estimated using an ear oximeter (Ohmeda, Biox 3000). The ear lobe was cleansed and massaged vigourously to increase perfusion before ear clip attachment. Using a cuff around an

upper arm, systolic (SP), diastolic (DP) were measured using a manual sphygmomanometer and mean arterial (MABP) blood pressure was calculated as DP + (SP-DP)/3.

A small catheter was inserted into an antecubital vein, and the subject rested on a chair during one hour. During this period, the coca users were invited to chew their customary quantity of coca leaves.

Respiratory gas exchanges and blood samples were obtained twice at rest, before (R_1) and after (R_2) coca chewing in coca users. The same timing protocol was used for non-chewers and, in this case, the two resting samples were separated by one hour during which the subjects only rested quietly in a chair. Subjects were then seated on the cycle ergometer where they exercised for 60 min at a work rate chosen to elicit ~ 70% of VO_{2peak}. Blood was withdrawn during exercise at 60 min. From each blood sample, a 0.5 ml aliquot was deproteinized by adding 1.0 ml of ice-cold 10% $HClO_4$. The acid extract was separated by centrifugation and neutralized with KOH. Two ml of blood were collected in EDTA for catecholamine determination.

Analytical methods.
From each blood sample, hematocrit was determined with the microhematocrit technique, hemoglogin concentration [Hb] was measured by using a cyanmethemoglogin solution (Sigma Chemical), total protein concentration was measured spectrophotometrically, and serum osmolality was measured by using the freezing-point depression method. Relative changes in blood and plasma volume with coca chewing and exercise were determined from Ht and protein concentration (12).

Epinephrine (Epi), and Norepinephrine (Norepi) were assayed by high-pressure liquid chromatography with electrochemical detection as described previously (13). Plasma erythropoietin (EPO) was determined by radioimmunoassay.

Statistical analysis.
For each dependent variable, data were analyzed by two-way analysis of variance (ANOVA) corrected for repeated measures, with condition (coca chewing) as the first factor and sampling time as the second factor. Fisher's Protected Least Significant Difference was used post-hoc when significant F ratios were obtained. The level of significance was set at 5%. Data are presented as means ± SE

	NC	C
Age (year)	31.6 ± 2.7	33.9 ± 2.0
Body Weight (kg)	61.8 ± 3.2	64.0 ± 2.7
Body Height (m)	162.1 ± 1.1	161.8 ± 0.9
POmax (watts)	185 ± 9	182 ± 4
VO_{2peak} (ml.min^{-1};kg^{-1})	42.4 ± 1.6	40.5 ± 1.4
HR_{max} (beats.min^{-1})	170 ± 3	174 ± 4
SaO_{2peak} (%)	90.8 ± 1.3	90.2 ± 0.7
$MABP_{peak}$ (torr)	96.4 ± 3.2	101.2 ± 2.6
Amount of Coca leaves (g)		46.9 ± 2.0

Table I:

Anthropometric characteristics and peak oxygen uptake (VO_{2peak}) of the subjects. Values are means ±SE.

Results

The amount of coca leaves uséd by the chewers averaged ~47 grams in addition to alkaline ashes *(Lejia)* used to increase the extraction of the alkaloids.

The anthropometric data and cardiorespiratory variables during maximal exercise of NC and C groups are reported in Table 1. The anthropological characteristics and aerobic power (PO), VO_2 , HR, SaO_2, and MABP during maximal exercise were similar in the two groups.

	NC			C		
	R_1	R_2	Ex60	R_1	R_2	Ex60
HR(beats.min^{-1})	-	65 ± 3	143 ± 5†	-	76.3 ± 3§	156 ±6 †§
MABP(torr)	-	90.7 ± 2.7	92.2 ± 1.9	-	91.3 ± 2.1	97.9 ± 2.7§
SaO2 (%)	-	94.3 ± 0.9	89.3 ± 1.0†	-	94.7 ± 0.4	86.7 ± 1.1†
Ht (%)	53.8 ± 1.3	54.6 ± 1.5	55.3 ± 1.6	53.2 ± 1.2	55.6 ± 1.1*	55.8 ± 1.1
[Hb] (g/dl)	17.6 ± 0.5	18.0 ± 0.5	18.5 ± 0.6	17.6 ± 0.5	18.5 ± 0.4*	18.9 ± 0.5
RBC (x10^6)	6.13 ± 0.38	6.48 ± 0.32	6.67 ± 0.29	6.55 ± 0.36	6.76 ± 0.30	6.94 ± 0.28
Osm (mOsm)	297 ± 3	297 ± 3	309 ± 3†	296 ± 3	303 ± 3	307 ± 3
Prot (g.L^{-1})	78.4 ± 1.8	80.0 ± 1.6	84.2 ± 1.6†	75.6 ± 2.5	79.6 ± 3.4	79.6 ± 3.2
Na$^+$ (meq.L^{-1})	134 ± 1	132 ± 1	139 ± 4	133 ± 1	140 ± 6	139 ± 6
K$^+$ (meq.L^{-1})	4.0 ± 0.2	4.1 ± 0.1	4.9 ± 0.1†	4.1 ± 0.1	4.5 ± 0.2*	4.8 ± 0.2†
Epi (nM)	221 ± 3	284 ± 24	968 ± 136†	267 ± 33	328 ± 39	1142 ± 233†
Norepi (nM)	3097 ± 449	3877 ± 296*	8019 ± 857†	2803 ± 437	5018 ± 491*§	7363 ± 971†
EPO (mU.ml^{-1})	4.9 ± 0.4	5.2 ± 0.6	5.0 ± 0.4	4.7 ± 0.4	4.9 ± 0.4	5.1 ± 0.7

Table II:
Cardio-hematological parameters in Coca chewers (C) and non-chewers (NC), at rest before (R_1) and after chewing (R_2) and during the 60th minute of submaximal exercise. Results are means ± SE. HR: heart rate; MABP: mean arterial blood pressure; SaO_2: arteriel oxygen saturation; Ht: hematocrit; [Hb]: hemoglobin concentration; Osm: Osmalality; Prot: plasma proteins concentration; Epi: epinephrine; Norepi: norepinephrine; EPO: plasma erythropoietin concentration.
*: Significantly different from R_1 (p<0.05)- †: Significantly different from R_2 (p<0.05)
§: Significantly different from NC at the same time (p<0.05)

At rest, HR was significantly higher in C after coca chewing than in NC (Table 2). In contrast, MABP and SaO_2 were similar in C and NC. The hematological status was significantly modified by coca chewing. Thus, Ht and [Hb] were significantly increased between R_1 and R_2 in C but remained unchanged in NC. From the Ht and protein changes, it can be calculated that coca chewing induced a significant decrease in blood and plasma volume (Fig 1). Osmolality, plasma proteins, Na$^+$ and K$^+$ concentrations were similar in C and NC and remained unaltered by coca chewing (Table 2). Plasma

catecholamines and EPO were similar before chewing (R_1), and Norepi increased at R_2 in both groups. Nevertheless, at R_2, plasma Norepi was higher in C as compared to NC.
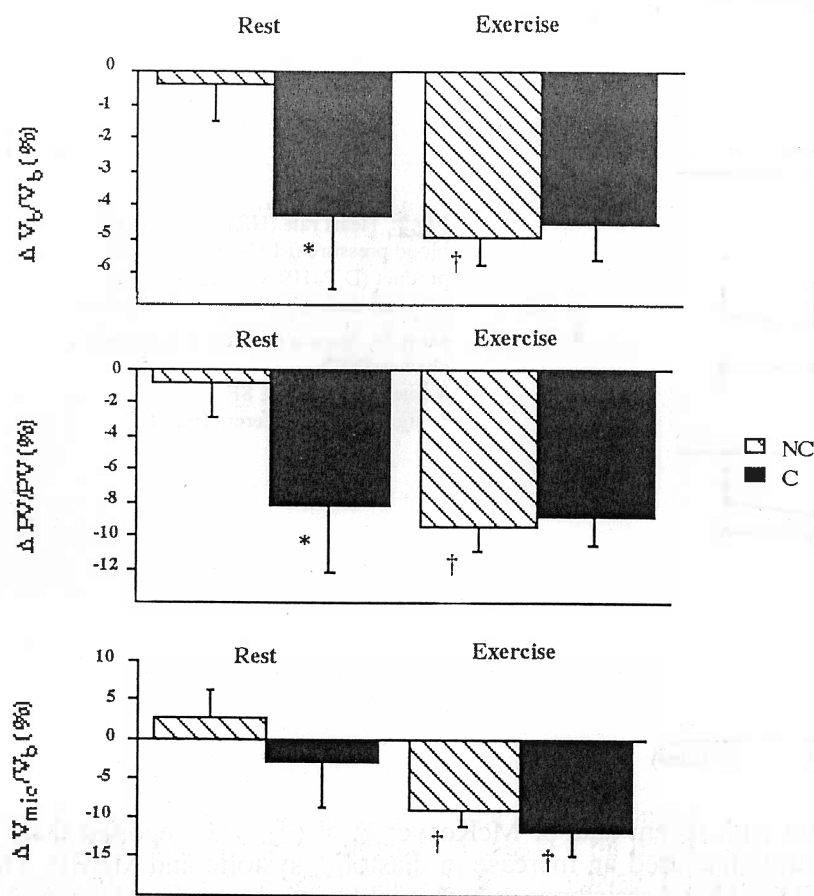

Fig.1: Changes in blood ($\Delta Vb/Vb$), plasma ($\Delta PV/PV$), and micro-vascular ($\Delta Vmic/Vmic$) volumes measured at rest (from R_1 to R_2) and during exercise (from R_2 to 60 mi of exercise) in coca chewers (C) and non chewers (NC). Values are means ±SE.
*: significantly different from NC †: significantly different from rest

During prolonged submaximal exercise, HR, MABP, and double product (HR x MABP), an indirect estimate of cardiac output, were significantly higher in C than in NC (Fig 2, Table 2). In addition, the exercise-induced changes in osmolality, proteins, and K^+ were blunted in C as compared to NC (Table 2). Otherwise, the catecholamine response during exercise was similar in C and NC whereas plasma EPO remained unaffected by exercise in both groups.

Discussion

From the available litterature, it appears that the cardiovascular effects of coca chewing have been scarcely evaluated. In his pioneer'study, Hanna (14, 15) reported a tendency toward a higher heart rate during exercise with coca chewing but concluded that the « stimulatory effect of coca seems to have little influence on the performance of work ». These data contrast with the well known cardiovascular effects of cocaine (3). Studies with intranasal, intravenous, and smoked cocaine, all show that under conditions in which subjects are allowed to take cocaine repeatedly, heart generally returns to near baseline levels between doses despite gradually increasing cocaine blood levels. Blood pressure either shows the same pattern, or gradual increases with repeated dosing (16). The results provided by the present study are in keeping with these observations in that neither MABP, nor HR, nor double product, an indirect estimate of cardiac output were different, before chewing, in chronic coca users and non users (Table 2). Nevertheless, following acute coca chewing, C displayed a significantly higher HR. In addition, it appeared that superimposition of coca chewing with exercise resulted in a significant cardiovascular stimulation (Fig 2) characterized by a higher HR, MABP, and DP in C than in NC.
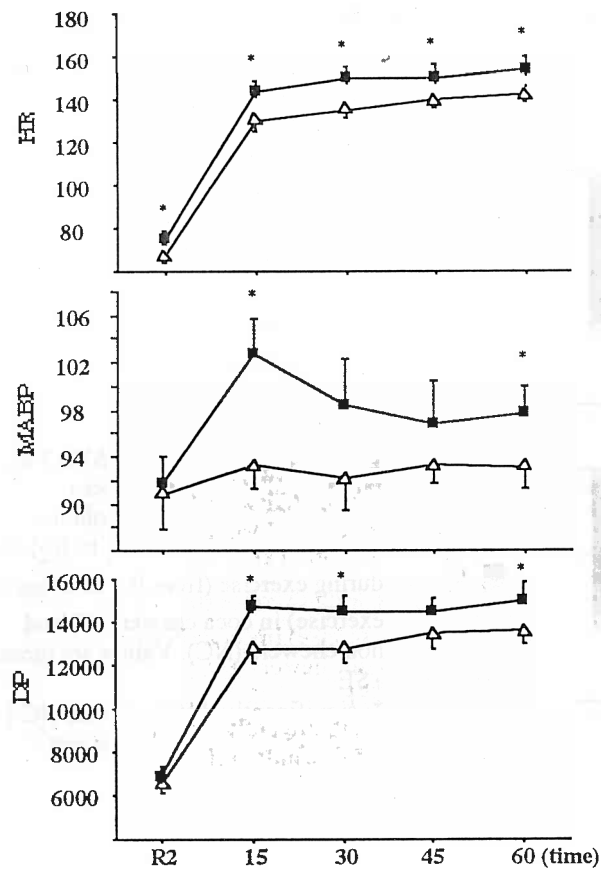
Fig.2: Heart rate (HR), mean arterial blood pressure (MABP), and double product (D P=HR x MABP), at rest (R_2) and during prolonged submaximal exercise, in coca chewers (C) and non-chewers(NC).
Values are means ± SE
*: significantly different from NC

△ NC
■ C

These latter results are in agreement with recent data of McKeever et al (4) who reported that, in exercising horses, cocaine administration caused an increase in diastolic, systolic and MABP. This suggest that coca/cocaine alters total peripheral resistance, which could cause a significant increase in cardiac afterload. There is some evidence for an involvment of the sympathoadrenergic system in mediating cardiovascular responses to cocaine. Indeed, cocaine inhibits the neuronal uptake of NE at central and peripheral nerves terminals (3). Based upon findings of in vivo and in vitro studies, cocaine has been suggested to cause the release of NE from sympathetic nerve terminals in a manner similar to that of indirect acting sympathomimetic agents (3). These effects of cocaine may cause synaptic accumulation of neurotransmitters, leading to an increased NE spillover into the blood stream. The present data extend these previous studies on cocaine's effects to those observed following acute coca chewing. Indeed, NE was significantly higher in C at R_2 (Table 2), in agreement with our previous data (8). During prolonged submaximal exercise however, the plasma catecholamine level was similar in C and NC, suggesting a similar sympathoadrenergic activation. Nevertheless, it was recently shown (17) that the cocaine's cardiovascular effects was not only linked to inhibition of peripheral neuronal monoamine uptake but also that central stimulation of sympathadrenal neural axis activity plays a key role in these effects. It is possible that plasma cocaine level was low in our chronic coca users as compared to those obtained after intravenous injection of cocaine. Even though we did not evaluate plasma cocaine level in the present study, we determined in a pilot experiment (M. Sauvain, unpublished results) that cocaine (Co) and benzoylecgonine (BE), a major metabolite of cocaine, reached 113 ± 22 ng/ml and 320 ± 88 ng/ml, respectively after chewing ~ 50 grams of coca leaves. These levels are equivalent to the circulating level measured after 64mg intranasal cocaine administration in humans (18). In addition, in our pilot experiment, we found that plasma Co and BE remained elevated in coca chewers exercising for ≥ 30min (104 ± 22 ng/ml, and 508 ± 88ng/ml, for Co and BE, respectively). It can be however considered that the dose of cocaine absorbed by our C was low as compared with the quantities used in topical anesthesia (19), or intravenously injected (20). Much higher doses are known to be illegally used: cocaine addicts may use up to 10g in a day (21).

The blood volume plays a critical role in the control of blood pressure (22). Likewise, the capacity of the peripheral circulation returning to the heart is a factor in the regulation of stroke volume. Therefore, the dependence of cardiac output on both blood pressure and stroke volume underlines the importance of blood volume maintenance for cardiovascular efficiency. Interestingly, we found that , in resting conditions, coca chewing was accompanied by plasma volume changes (Fig 1). Initially, plasma volume changes were calculated from Ht and [Hb]. However, recent studies (23, 24) have shown that a shift of blood volume from micro- to macro-circulation could be another factor in changing the systemic hematocrit. This results from the fact that the hematocrit in the capillaries is smaller than in larger blood vessels (Fahraeus effect). To give a better insight on blood volume changes and fluid shifts induced by exercise, heat exposure or endotoxin injection, Lee and his colleagues (12, 23, 24) have developed a set of equations, based on hematocrit and plasma protein concentration, to determine the redistribution of the blood volume between micro- and macro-circulation. By using such a procedure, we found that, in resting conditions, coca chewing induced a significant reduction in blood volume (Fig 1) which cannot be accounted for by a change in microvascular volume changes, but rather to changes in plasma volume. The mechanism(s) by which coca chewing altered plasma volume are not readily apparent. First; it could be linked to a coca-induced shift of plasma water from the intra- to the extra-vascular fluid space, as commonly observed after dehydration (25). Second, it could be related to blood trapping in some large vascular territories (e.g. splanchnic area). Thus, it can be hypothesized that the higher Norepi plasma level observed at R_2 in C (Table 2) would have possibly induced greater splanchnic vasoconstriction than in NC. Third, it is possible that coca chewing was accompanied by an increase in diuresis. This possibility is somewhat supported by our recent data (unpublished results) showing that, subsequent to chewing 30 grams of coca leaves, diuresis was increased by ~70% in chronic coca users.

During submaximal exercise, NC displayed a significant reduction in blood and plasma volume (Fig 1), in agreement with previous reported data (26). From the microvascular changes ($\Delta V_{mic}/Vb$, Fig 1), it can be concluded that its negative value suggests that many organs constricte to overcompensate for the exercise-induced dilation of the microvessels in the skeletal muscle (24). In C, the shift in blood and plasma volume induced by exercise was similar to those observed in NC (Fig.1). This would mean that the coca-induced fluid shift did not prevent those linked to exercise, and as a consequence, it is likely that exercise in chronic coca users will result in an enhanced hypohydration state which is known to impair exercise tolerance (27). It can be hypothesized that this hypohydration was related to an a reduced sweating rate after coca chewing. Indeed, Hanna (14, 15) has provided evidence that coca chewing is accompanied by a reduced peripheral temperature but an elevated central temperature during a cold challenge. Whereas, this increased heat storage capacity of C could be beneficial in a cold environment like that encountered in Andes, it is likely deleterious for exercise in neutral or warm environment.

In conclusion, the present study provides evidence for a significant alteration in cardiovascular and hematological status following coca chewing at rest as well during submaximal exercise. Nevertheless, it remains to determine the mechanism(s) by which coca use alters the cardiovascular function. In this respect, it is likely that, besides the adrenosympathetic system, other hormones (renine-angiotensin, vasopressin, aldosterone, atrial natriuretic factor) are involved in the disturbance of blood volume and pressure observed in chronic coca users.

Acknowledgments:

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