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Body fluid homeostasis and cardiovascular adjustments during submaximal exercise: influence of chewing coca leaves

Abstract The present study was undertaken to determine the haematological and cardiovascular status, at rest and during prolonged (1 h) submaximal exercise (approximately 70% of peak oxygen uptake) in a group ($n = 12$) of chronic coca users after chewing approximately 50 g of coca leaves. The results were compared to those obtained in a group ($n = 12$) of nonchewers. At rest, coca chewing was accompanied by a significant increase in heart rate [from 60 (SEM 4) TO 76 (SEM 3) beats · min^{-1}], in haematocrit [from 53.2 (SEM 1.2) to 55.6 (SEM 1.1)%] in haemoglobin concentration, and plasma noradrenaline concentration [from 2.8 (SEM 0.4) to 5.0 (SEM 0.5) μmol · l^{-1}]. It was calculated that coca chewing for 1 h resulted in a significant decrease in blood [−4.3 (SEM 2.2)%] and plasma [−8.7 (SEM 1.2)%] volume. During submaximal exercise, coca chewers displayed a significantly higher heart rate and mean arterial blood pressure. The exercise-induced haemoconcentration was blunted in coca chewers compared to nonchewers. It was concluded that the coca-induced fluid shift observed at rest in these coca chewers was not cumulative with that of exercise, and that the hypovolaemia nduced by coca chewing at rest compromised circulatory adjustments during exercise.

Key words Plasma volume · Blood volume · Catecholamines · Erythropoietin

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Introduction

Leaves of the coca shrub (*Erythroxylum Coca*) have been chewed by the indigenous people of South America since pre-Inca times and the use of coca leaves has been reported to be widespread among Andean populations (Hanna 1970; Hanna and Hornick 1977); in 1970, it has been estimated that 6 million people chewed coca leaves in Bolivia and Peru alone (Zapata-Ortiz 1970). It has been said to be physiologically beneficial for Andean Indians in terms of adaptation to work, cold and hunger at high altitude (Hanna 1970; Hanna 1971; Hanna and Hornick 1977). The general effects of coca chewing have been equated by some authors with those produced by cocaine (Hanna and Hornick 1977; Zapata-Ortiz 1970).

During the last few years, most studies have investigated the combined effects of coca/cocaine and exercise and have focused on metabolic adaptations and adrenosympathetic system activation in relation to endurance performance (Bracken et al. 1988, 1989; Conlee et al. 1991; Favier et al. 1996; Spielvogel et al. 1996). On the other hand, various authors have shown that cocaine has profound effects at rest on the cardiovascular system (see review in Foltin et al. 1995). Thus, in subjects allowed to take cocaine repeatedly, it has generally been shown that both heart rate and blood pressure increase initially and return to near baseline levels between doses despite gradually increasing cocaine blood concentrations. By contrast, little work has been published on the cocaine-induced effects on cardiovascular function during exercise (McKeever et al. 1993). In that study, it has been shown that acute administration of cocaine (0.45 mg · kg^{-1}) in horses, resulted in a significant increase in maximal heart rate and blood pressure.

We are, however, unaware of any data describing the effects of prior coca chewing on cardiovascular adjustments during exercise. In our previous studies (Favier et al. 1996; Spielvogel et al. 1996), it did not appear that chewing approximately 15 g of coca leaves resulted in any significant alteration in heart rate or blood pressure

during submaximal (Favier et al. 1996) and maximal (Spielvogel et al. 1996) exercise. Nevertheless, the amount of coca leaves chewed by chronic coca users is highly variable, some subjects consuming up to 250 g of coca leaves per day (M. Sauvain, personal communication). During our screening of rural communities of the Altiplano for our experiments (Favier et al. 1996; Spielvogel et al. 1996), we encountered several subjects reporting a mean daily use of about 50 g coca leaves, and noted that, at rest, haematocrit (Hct) and haemoglobin concentration [Hb] were significantly increased after coca chewing. From these parameters, it can be calculated (see Greenleaf et al. 1979) that coca use induces a significant drop in plasma volume. Since alterations in body fluid volume before exercise have been shown to alter fluid-electrolyte homeostasis, cardiovascular function, and thermal regulation (Fortney et al. 1981a, b, 1984; Nose et al. 1988; Sawka and Pandolf 1990; Senay and Pivarnik 1985), we hypothesized that chewing coca in large amounts (approximately 50 g) should result in a significant alteration in body fluid homeostasis and cardiovascular adjustments during exercise.

To investigate the influence of coca chewing on body fluid and cardiovascular response to submaximal exercise, we recruited subjects from two rural communities of the Altiplano (mean altitude about 3800 m), in which we were able to find traditional heavy coca chewers (C) as well as non-chewers (NC). Given the fact that sociocultural 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. C after coca chewing and NC without chewing. Even though we realized that such an experimental design would not allow us to distinguish the acute from the chronic effects of coca chewing, we hypothesized that we should be able to determine whether coca chewing alters the haematological and cardiorespiratory responses during prolonged (1 h) submaximal exercise (approximately 70% of peak oxygen uptake, $\dot{V}O_{2peak}$).

Methods

Subjects

The subjects in this study were 24 men aged between 17 and 45 years. All were natives from the Altiplano (3800 m altitude-Bolivia) and all reported that their primary occupation was agriculture. Genetically, the subjects were Mestizos with a predominantly Aymara admixture. The experimental procedures and potential risks of the study were explained to each subject both verbally and in writing. All the subjects gave their informed consent and the experiment was approved by the local Ethics Committee (Universidad Major San Andres, La Paz, Bolivia). Before starting 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 group ($n = 12$) consisted of NC (i.e. subjects chewing less than three times a year), whereas the second group ($n = 12$) was composed of traditional C (i.e. subjects chewing more than three to four times a week while

working in the fields). 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 3600 m).

To minimize factors of learning that could affect exercise performance, each subject performed an incremental test on a cycle ergometer with a mechanical braking system. On the next day, the subject rested on a chair for 1 h. During this period, C were invited to chew their customary quantity of coca leaves.

Coca chewing

The leaves are in fact not chewed but sucked. The term chewing is not an appropriate one, but as it is commonly used, we use it throughout this paper. This is a technique developed over centuries. It consists in taking a mouthful of coca leaves without swallowing them. These are previously stripped of the veins to avoid traumatic action by these hard parts of the leaf on the mouth lining. Chewing is done softly, trying not to crush them totally, only enough to break the cell membranes and let the contents dissolve slowly in the saliva. The bolus thus formed (about 8–10 g), is left to repose between the gums and the cheek, just below the outlet of the excreting duct of the parotid salivary gland. When the half crushed leaves are sufficiently moistened, the chewer adds the *lejia* or any other alkaline agent (such as sodium bicarbonate). The *lejia* is a preparation made from several types of vegetables ashes, such as quiñoa and plantain. Its purpose is to provide an alkaline medium to maximize the extraction of the alkaloids from the leaf. Coca leaves contain a few alkaloids, among which cocaine is present in great quantities (about 0.5% dry mass). Extraction of this narcotic is most efficient and it is estimated that 80% of the cocaine in the leaves is removed by chewing. The amount of leaves chewed was determined by weighing the bag containing the coca leaves before and after 1 h of chewing.

$\dot{V}O_{2\ peak}$ determination

The $\dot{V}O_{2peak}$ was measured in the same way as on the day of familiarization using a continuous progressive protocol as has been described in detail elsewhere (Spielvogel et al. 1996). Briefly, the subjects completed an incremental exhausting cycling exercise protocol in which the subjects pedalled for 4 min at 60W and continued pedalling as the work load was increased by 30-W increments every 4 min until the subject was exhausted. The subjects cycled at 70 rpm on an ergometer (Ergomeca, France) and were paced using a metronome. The $\dot{V}O_{2peak}$ measured in these conditions was used to determine the exercise intensity used in the submaximal exercise test.

Submaximal exercise test

The subjects performed steady-state exercise 1 week after $\dot{V}O_{2peak}$ determination. A submaximal intensity was chosen individually to obtain an oxygen uptake ($\dot{V}O_2$) that was approximately 70% $\dot{V}O_{2peak}$. Before the test, the subjects refrained from vigorous exercise and C were requested to abstain from coca chewing until the next day. When the subjects reported to the laboratory after fasting overnight, they were provided, 3 h 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 wheat. They were prohibited from having tea or coffee.

Physiological measurements

Heart rate (HR) was monitored by bipolar electrocardiogram (ECG) telemetry (Sport tester). Arterial oxygen saturation (S_aO_2) was estimated using an ear oximeter (Ohmeda, Biox 3000, USA). The ear lobe was cleansed and massaged vigorously to increase perfusion before the ear clip was attached. Using a cuff around the

upper arm, systolic (BP_s), and diastolic (BP_d) blood pressures were measured using a manual sphygmomanometer and mean arterial blood pressure ($\overline{BP_a}$) was calculated as $BP_d + (BP_s-BP_d)/3$. A small catheter was inserted into an antecubital vein, and the subject rested on a chair for 1 h. During this period, the C 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 C. The same timing was used for NC and, in this case, the two resting samples were separated by 1 h during which the subjects only rested quietly in a chair. The subjects then sat on the cycle ergometer where they exercised for 60 min at an intensity chosen to elicit approximately 70% of $\dot{V}O_{2peak}$. Blood was withdrawn during the 60th min of exercise. 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 centrifugation and neutralized with KOH. A 2-ml sample of blood was collected in ethylene-diaminetetra-acetic acid for catecholamine determination.

Analytical methods

From each blood sample, Hct was determined with the micro-haematocrit technique, [Hb] was measured using a cyan-methaemoglogin kit (525-A, Sigma Chemical, L'Isle d'Abeau Chesnes, France), total protein concentration was measured spectrophotometrically and serum osmolality was measured using a freezing-point depression analyser (Fiske Osmometer, Model OS, Needham Heights, Massachusetts, USA). Relative changes in blood (LaForte et al. 1992; Lee 1994; Theodoridis and Lee 1995) and plasma (Greenleaf et al. 1979) volume with coca chewing and exercise were determined from Hct, [Hb], and protein concentration according to the equations published by Greenleaf et al. (1979) and Theodoridis and Lee (1995):

$$\%\Delta PV = \left[\frac{[Hb]_B}{[Hb]_A} \cdot \frac{(1 - Hct_A \cdot 10^{-2})}{(1 - Hct_B \cdot 10^{-2})} \right] - 100 \qquad (1)$$

where ΔPV is the change in plasma volume, A is after and B is before an interval of time; [Hb] is in $g \cdot 100 \text{ ml}^{-1}$ and Hct is a percentage.

$$\Delta V_b/V_b = (1 - F_{cell}H_B)(C_p - C_{p'})/(C_{p'} - C_f) \qquad (2)$$

$$\Delta V_{mic}/V_b = \{[F_{cell}(H_A - H_B)/H_A] + \Delta V_b/V_b\}/(1 - \alpha) \qquad (3)$$

Where V_b is the total blood volume in circulation, ΔV_b is equal to the volume of fluid restitution (or filtration, if negative), H_B is the initial systemic (macrovascular) Hct, H_{mic} the initial microvascular Hct, H_A the final systemic Hct, H_w the whole body or whole circulation Hct, F_{cell} equals the ratio $H_w:H_B$, α is the ratio $H_A:H_{mic}$, C_p the initial plasma protein concentration, and C_p' the final plasma protein concentration and C_f the plasma protein concentration is restituted fluid. In order to apply Eqs. 2 and 3, it is necessary to have the values of the ratios F_{cell}, α, and $C:C_p$. Arguments on what are reasonable values for these parameters have been presented in detail by Theodoridis and Lee (1995). In this paper, we took $F_{cell} = 0.87$, $\alpha = 0.64$, and $C_f:C_p = 1:3$.

Adrenaline (A) and noradrenaline (NA) concentrations were assayed by high-performance liquid chromatography with electrochemical detection as has been described previously (Koubi et al. 1991). Plasma erythropoietin (Epo) concentration was determined by radioimmunoassay (Epo, bioMérieux, Marcy l'Etoile, France).

Statistical analysis

For each dependent variable, data were analysed by two-way analysis of variance (ANOVA) corrected for repeated measures, with condition (coca chewing) as the 1st factor and sampling time as the 2nd factor. Fisher's protected least significant difference was used post-hoc when a significant F ratio was obtained. The level of significance was set at 5%.

Results

The amount of coca leaves used by C averaged approximately 47 g 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 given in Table 1. The anthropological characteristics and aerobic power ($\dot{W}$, $\dot{V}O_2$, HR, S_aO_2, and $\overline{BP_a}$ during maximal exercise were similar in the two groups.

At rest, HR was significantly higher in C after coca chewing than in NC (Table 2). In contrast, $\overline{BP_a}$ and S_aO_2 were similar in C and NC. The haematological status was significantly modified by coca chewing. Thus, Hct and [Hb] were significantly increased between R_1 and R_2 in C but remained unchanged in NC. From the Hct, [Hb] and protein changes, it can be calculated that coca chewing induced a significant decrease in blood and plasma volume (Fig. 1). Osmolality, plasma protein, Na^+ and K^+ concentrations were similar in C and NC and remained unaltered by coca chewing (Table 2). Plasma catecholamine and Epo concentrations were similar before chewing (R_1), and NA increased at R_2 in both groups. Nevertheless, at R_2 plasma NA was higher in C than in NC.

During prolonged submaximal exercise, HR, $\overline{BP_a}$, and the double product (HR × $\overline{BP_a}$), 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 compared to NC (Table 2). Otherwise, the catecholamine response during exercise was similar in C and NC whereas plasma Epo concentration remained unaffected by exercise in both groups.

Discussion

From the available literature, it would appear that the cardiovascular effects of coca chewing have scarcely been evaluated. In his pioneering studies, Hanna (Hanna

Table 1 Anthropometric characteristics and cardiorespiratory response to maximal exercise in coca chewers (C) and nonchewers (NC). $\dot{W}$ Power output, $\dot{V}O_2$ oxygen uptake, HR heart rate, S_aO_2 arterial oxygen saturation, $\overline{BP_a}$ mean arterial blood pressure

	NC		C	
	mean	SEM	mean	SEM
Age (year)	31.6	2.7	33.9	2.0
Body mass (kg)	61.8	3.2	64.0	2.7
Body height (cm)	162.1	1.1	161.8	0.9
$\dot{W}$ (W)	185	9	182	4
$\dot{V}O_2$ (ml $\cdot$ min^{-1} $\cdot$ kg^{-1})	42.4	1.6	40.5	1.4
HR (beats $\cdot$ min^{-1})	170	3	174	4
S_aO_2 (%)	90.8	1.3	90.2	0.7
$\overline{BP_a}$ (mm Hg)	96.4	3.2	101.2	2.6
Amount of coca leaves (g)	–	–	46.9	2.0

Table 2 Cardio-haematological parameters in coca chewers (C) and nonchewers (NC), at rest before (R_1) and after chewing (R_2) and during the 60th min of submaximal exercise (Ex 60). HR Heart rate, $\overline{BP_a}$ mean arterial blood pressure, S_aO_2 arterial oxygen saturation, Hct haematocrit, [Hb] haemoglobin concentration, Osm osmolality, Prot plasma protein concentration, A adrenaline, NA noradrenaline, EPO erythropoietin concentration

	NC						C					
	R_1		R_2		Ex60		R_1		R_2		Ex60	
	mean	SEM	mean	SEM	mean	SEM	mean	SEM	mean	SEM	mean	SEM
HR (beasts · min⁻¹)	60	2	65	3	143	5[b]	60	4	76.3	3[c]	156	6[b,c]
$\overline{BP_a}$ (mmHg)	90.9	2.8	90.7	2.7	92.2	1.9	88.2	1.9	91.3	2.1	97.9	2.7[c]
S_aO_2 (%)	91.7	0.7	94.3	0.9	89.3	1.0[b]	92.4	0.9	94.7	0.4	86.7	1.1[b]
Hct (%)	53.8	1.3	54.6	1.5	55.3	1.6	53.2	1.2	55.6	1.1[a]	55.8	1.1
[Hb] (g · dl⁻¹)	17.6	0.5	18.0	0.5	18.5	0.6	17.6	0.5	18.5	0.4[a]	18.9	0.5
Osm (mOsmol)	297	3	297	3	309	3[b]	296	3	303	3	307	3
Prot (g · l⁻¹)	78.4	1.8	80.0	1.6	84.2	1.6[b]	75.6	2.5	79.6	3.4	79.6	3.2
Na⁺ (mmol · l⁻¹)	134	1	132	1	139	4	133	1	140	6	139	6
K⁺ (mmol · l⁻¹)	4.0	0.2	4.1	0.1	4.9	0.1[b]	4.1	0.1	4.5	0.2[a]	4.8	0.2[b]
A (nmol · l⁻¹)	221	3	284	24	968	136[b]	267	33	328	39	1142	233[b]
NA (nmol · l⁻¹)	3097	449	3877	296[a]	8019	857[b]	2803	437	5018	491[a,c]	7363	971[b]
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

[a] Significantly different from R_1 ($P < 0.05$), [b] significantly different from R_2 ($P < 0.05$), [c] significantly different from NC at the same time ($P < 0.05$)
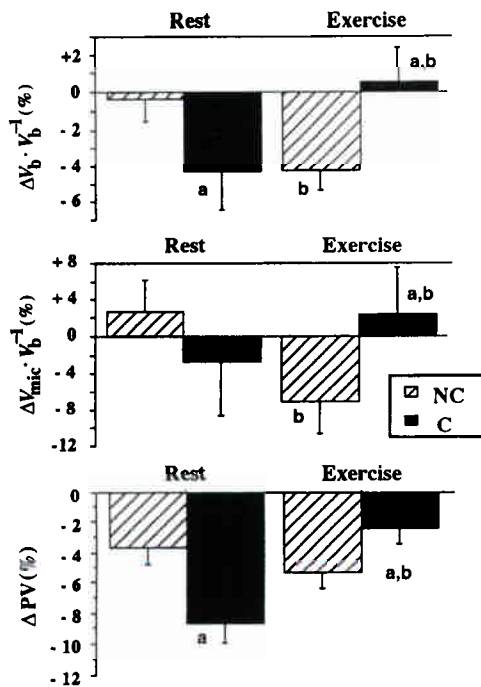

Fig. 1 Changes in blood($\Delta V_b \cdot V_b^{-1}$), micro-vascular ($\Delta V_{mic} \cdot V_{mic^{-1}}$) and plasma ($\Delta PV \cdot PV^{-1}$) volumes measured at rest (from R_1 to R_2) and during exercise (from R_2 to 60 min of exercise) in coca chewers C and nonchewers (NC). Values are means and SEM
[a] Significantly different from NC,
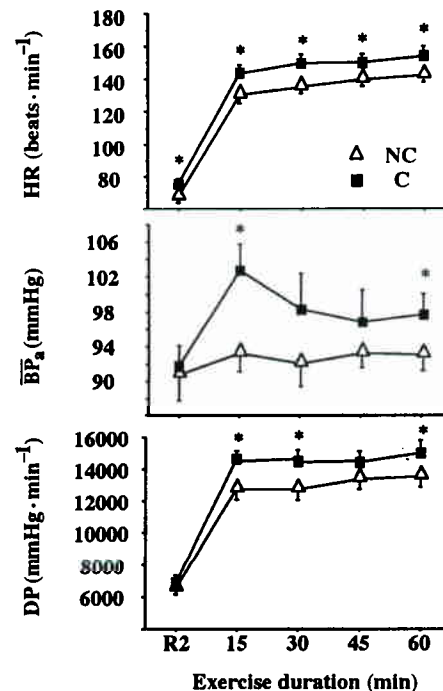[b] Significantly different from rest

Fig. 2 Heart rate (HR), mean arterial blood pressure ($\overline{BP_a}$), and double product (DP = HR × $\overline{BP_a}$), at rest (R_2) and during prolonged submaximal exercise, in coca chewers (C) and nonchewers (NC). Values are means and SEM
* Significantly different from NC at the same time

1970, 1971; Hanna and Hornick 1977) has reported a tendency toward a higher HR 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 acute cardiovascular effects of cocaine [i.e. increase in HR and blood pressure (Jaffe 1975; Ritchie and Greene 1985)]. However, studies with intranasal, intravenous, and smoked cocaine, all show that in cocaine addicts, HR returns to baseline levels between doses. Blood pressure has shown either the same pattern, or gradual increases with repeated dosing (Foltin et al. 1995).

The results provided by the present study are in keeping with these observations in that neither $\overline{BP_a}$, nor HR, nor double product were different in R_1 in chronic C and NC (Table 2). Nevertheless, in acute coca chewing R_2, C displayed a significantly higher HR, $\overline{BP_a}$ and plasma NA concentrations. In our previous studies (Favier et al. 1996; Spielvogel et al. 1996), we have not observed any significant effect of coca chewing for increasing resting HR and $\overline{BP_a}$. However, it has to be mentioned that in these latter studies, coca use was three times (about 15 g) lower than in the present experiment (about 47 g, Table 1). It is likely that in our findings the cardiovascular effects of coca were linked to a different amount of circulating cocaine compared to previous experiments. This hypothesis is partly supported by the data from McKeever et al. (1993) who have shown that $0.1 \text{ mg} \cdot \text{kg}^{-1}$ of cocaine was ineffective in modifying resting HR and blood pressure whereas $0.5 \text{ mg} \cdot \text{kg}^{-1}$ resulted in a significant increase in both HR and $\overline{BP_a}$. This would suggest that coca/cocaine alters total peripheral resistance, which could cause a significant increase in cardiac afterload.

There is some evidence for an involvement of the sympathoadrenergic system in mediating cardiovascular responses to cocaine. Indeed, cocaine has been shown to inhibit the neuronal uptake of NA at central and peripheral nerve terminals (Ritchie and Greene 1985). These effects of cocaine may cause synaptic accumulation of neurotransmitters, leading to an increased NA spillover into the blood stream. The present data extend these previous studies on the effects of cocaine to those observed following acute coca chewing. Indeed, NA was significantly higher in C at R_2 (Table 2), in agreement with our previous data (Favier et al. 1996).

Blood volume has been shown to play a critical role in the control of blood pressure (Braunwald and Ross 1979). 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. It is of interest that we found that, at rest, coca chewing was accompanied by a significant decrease in plasma volume (Fig. 1). Initially, ΔPV were calculated from Hct and [Hb] (Greenleaf et al. 1979). However, recent studies (LaForte et al. 1992; Lee 1994) have shown that a shift of blood volume from micro- to macro-circulations could be another factor in changing the systemic Hct. This results from the fact that Hct in the capillaries is lower than in larger blood vessels (Fahraeus effect).

To give a better insight into blood volume changes and fluid shifts induced by exercise, heat exposure or endotoxin injection, Theodoridis and Lee (1995) have introduced a set of equations, based on Hct and plasma protein concentration, to determine the redistribution of the blood volume between the micro- and macro-circulations. By using such a procedure, we found that, at rest, coca chewing induced a significant reduction in blood volume (Fig. 1) which could not be accounted for by a change in microvascular volume, but rather to a change in plasma volume. The mechanism(s) by which coca chewing altered plasma volume are not readily apparent. Firstly, it could be linked to a coca-induced shift of plasma water from the intra- to the extra-vascular fluid space, as has commonly been observed after dehydration (Nose et al. 1988). Secondly, it could be related to blood trapping in some large vascular territories (e.g. splanchnic area). Thus, it can be hypothesized that the higher NA plasma concentration observed at R_2 in C (Table 2) could have possibly induced greater splanchnic vasoconstriction than in NC. Thirdly, it is possible that coca chewing was accompanied by an increase in diuresis. This possibility is supported in part by our recent data (unpublished results) showing that, subsequent to chewing 30 g of coca leaves, diuresis was increased by approximately 70% in chronic coca users.

In addition, it appeared that superimposition of coca chewing with exercise resulted in a significant cardiovascular stimulation (Fig. 2) characterized by a higher HR, $\overline{BP_a}$, and double product in C than in NC. The present experiment is in agreement with recent data of McKeever et al. (1993) who have reported that, in exercising horses, cocaine administration caused an increase in BP_d, BP_s and $\overline{BP_a}$. Even though not directly addressed in that experiment (McKeever et al. 1993), it can be hypothesized that the reported cardiovascular effects were linked to a higher plasma catecholamine concentration after cocaine administration (see Conlee et al. 1991). However, during prolonged submaximal exercise, the plasma catecholamine concentration was similar in C and NC (Table 2), suggesting a similar sympathoadrenergic activation. Nevertheless, it has recently been shown that the cocaine cardiovascular effects are not only linked to inhibition of peripheral neuronal monoamine uptake but also that central stimulation of sympathoadrenal neural axis activity plays a key role in these effects (Tella et al. 1993).

It is possible that the plasma cocaine concentration was low in our C compared to those obtained after intravenous injection of cocaine. Even though we did not evaluate the plasma cocaine concentration in the present study, we have determined in a pilot experiment (M. Sauvain, unpublished results) that cocaine and benzoylecgonine (BE), a major metabolite of cocaine, reached 113 (SEM 22) $\text{ng} \cdot \text{ml}^{-1}$ and 320 (SEM 88) $\text{ng} \cdot \text{ml}^{-1}$, respectively, after chewing approximately 50 g of coca leaves. These levels are equivalent to the circulating concentrations that have been measured after 64 mg intranasal cocaine administration in humans (Javaid et al. 1978, 1983; Van Dyke et al. 1976). In addition, in our pilot experiment, we have found that plasma cocaine and BE concentrations remained elevated in coca chewers exercising for 30 min or longer [104 (SEM 22) $\text{ng} \cdot \text{ml}^{-1}$, and 508 (SEM 88) $\text{ng} \cdot \text{ml}^{-1}$, for cocaine and BE, respectively]. It could however be considered that the dose of cocaine absorbed by our C

was low compared with the quantities that have been used in topical anaesthesia (Ritchie and Greene 1985), or intravenously injected (Javaid et al. 1978, 1983). Much higher doses are known to be used illegally: cocaine addicts may use up to 10 g in a day (Jaffe 1975).

During submaximal exercise, NC displayed a significant reduction in blood and plasma volume (Fig. 1), in agreement with previous reported data (Fortney et al. 1981a, b; Sawka and Pandolf 1990; Senay and Pivarnik 1985). From the microvascular changes ($\Delta V_{mic} \cdot V_b^{-1}$, Fig. 1), it could be concluded that its negative value would suggest that many organs constrict to overcompensate for the exercise-induced dilatation of the microvessels in the skeletal muscle (see Lee 1994). In C, the shift in blood and plasma volume induced by exercise was blunted (Fig. 1) as has commonly been observed after hypohydration induced by withdrawal of blood (Fortney et al. 1981a), use of diuretics (Claremont et al. 1976) or thermal dehydration (Fortney et al. 1984). The mechanism(s) by which coca use prevents body fluid shift during exercise are not readily apparent but could be linked to a reduced sweating rate. Indeed, Hanna (Hanna 1970, 1971; Hanna and Hornick 1977) 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 the Andes, it is likely to be deleterious during exercise in a neutral or warm environment.

In conclusion, the present study provided evidence for a significant influence of chewing coca leaves on body fluid homeostasis and cardiovascular adjustments at rest as well as during submaximal exercise in chronic coca users. Even though the experimental design used in the present study did not allow us to delineate clearly the acute from the chronic effects of coca use, it would seem reasonable to suggest that the reported changes were in fact linked to the acute effects of coca chewing. Firstly, the cardiovascular (HR, $\overline{BP}_a$, BP_d), haematological (Hct, [Hb]) and hormonal (A, NA) status did not differ between NC and C at R$_1$ (Table 2), suggesting that body fluid volumes were probably similar in both groups of subjects before coca use. Secondly, in a subsequent experiment (Favier and Spielvogel, unpublished results), we have observed in nonhabitual coca users, that coca chewing prior to exercise reduced the body fluid shifts and enhanced the heart exercise response in a similar way to that observed in the present experiment dealing with chronic coca chewers.

It remains to determine, however, the mechanism(s) by which coca use alters the cardiovascular function and fluid homeostasis. In this respect, it is likely that, besides the adrenosympathetic system, other hormones (renin-angiotensin, vasopressin, aldosterone, atrial natriuretic factor) are involved in the disturbance of blood volume and pressure observed in chronic coca users.

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