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[1]*Instituto Boliviano de Biologia de Altura, Casilla 717, La Paz, Bolivia; and* [2]*Laboratoire de Physiologie, Unité Mixte de Recherche 5578, Centre National de la Recherche Scientifique and* [3]*Laboratoire de Physiologie de l'Environnement, Université Claude Bernard, 69373 Lyon cedex 08, France*

Favier, R., E. Caceres, B. Sempore, J. M. Cottet-Emard, G. Gauquelin, C. Gharib, and H. Spielvogel. Fluid regulatory hormone response to exercise after coca-induced body fluid shifts. *J. Appl. Physiol.* 83(2): 376–382, 1997.—To determine the effect of coca chewing on heart rate (HR), mean arterial blood pressure (MAP), and plasma volume and their relationship with the hormones regulating cardiovascular and body fluid homeostasis, 16 male volunteers were examined at rest and during 1 h of cycle exercise at ~75% of their peak oxygen uptake in two trials separated by 1 mo. One trial was performed after the subjects chewed a sugar-free chewing gum ($Coca^-$ trial), whereas the other was done after the subjects chewed 15 g of coca leaves ($Coca^+$), with the order of the $Coca^-$ and $Coca^+$ trials being randomized. Blood samples were taken at rest, before (R_1) and after 1-h chewing (R_2), and during the 5th, 15th, 30th, and 60th min of exercise. They were analyzed for hematocrit, hemoglobin concentration, red blood cell count, plasma proteins, and for the fluid regulatory hormones, including plasma catecholamines [norepinephrine (NE) and epinephrine], renin, arginine vasopressin, and the atrial natriuretic peptide (ANP). During the control trial ($Coca^-$), from R_1 to R_2, there was no significant change in hematologic, hormonal, and cardiovascular status except for a small increase in plasma NE. In contrast, it can be calculated that coca chewing at rest induced a significant hemoconcentration ($-3.8 \pm 1.3\%$ in blood and $-7.0 \pm 0.7\%$ in plasma volume), increased NE and MAP, and reduced plasma ANP. Chewing coca before exercise reduced the body fluid shifts but enhanced HR response during exercise. These effects were not accompanied by changes in NE, epinephrine, renin, and arginine vasopressin plasma levels. In contrast, plasma ANP response to exercise was lower during the $Coca^+$ trial, suggesting that central cardiac filling was reduced by coca use. It is likely that the reduction in body fluid volumes is a major contributing factor to the higher HR at any given time of exercise after coca chewing.

arginine vasopressin; atrial natriuretic peptide; catecholamines; hypovolemia; renin

THE LEAVES OF SEVERAL SPECIES of the shrub *Erythroxylum*, popularly known as coca and the natural source of cocaine, have played an important role in Andean daily life for perhaps 5,000 years (2, 13). They are chewed throughout the Andean highlands, chiefly by Aymara and Quechua Indians, and scientific interest in coca chewing derives from the self-reports of coca users, who claim that coca enhances tolerance for work at altitude (see Refs. 2 and 13 for reviews). Recently, we have provided evidence that coca chewing does not increase work capacity (29) but could possibly delay the appearance of fatigue during prolonged exercise (6). Nevertheless, in a subsequent study (29), we noted that coca chewing resulted, at rest, in a significant decrease in blood and plasma volume. Furthermore, during submaximal exercise, we observed a significantly higher heart rate (HR) and mean arterial blood pressure (MAP) after coca chewing, and the exercise-induced hemoconcentration was blunted by coca use (29). In this latter study (29), physiological data were obtained in traditional coca users after acute coca chewing, and the results were compared with those of nonchewers. However, because of the experimental protocol design, we felt in retrospect that the observations could be linked either to acute effects of coca chewing or to some physiological adaptations consequent to chronic coca use. To clarify this issue, in the present study, we examined plasma and blood volume changes in response to coca and exercise in a group of subjects submitted to a prolonged (1-h) submaximal [~75% peak oxygen uptake ($\dot{V}O_{2peak}$)] exercise after they chewed 15 g of coca leaves ($Coca^+$). The results were compared with those obtained in the same subjects in a control trial, during which the subjects chewed a sugar-free gum before exercise ($Coca^-$), with the order of the trials being randomized.

Additionally, we evaluated the coca-induced changes in the level of hormones involved in the conservation of body fluids and cardiovascular adjustments. Indeed, it has been reported (10) that when human volunteers were hypohydrated by ~5%, some stress hormones (cortisol) and body fluid regulatory hormones (renin, aldosterone) increased more during exercise following dehydration. Because the variability in coca use duration between chronic chewers could possibly confound the responses to the two independent variables (coca chewing, exercise) and to increase the homogeneity of the response to the exercise and coca challenge, we used young, physically active, nonhabitual coca chewers.

MATERIALS AND METHODS

Subjects. Sixteen male students [age 27.7 ± 1.7 (SE) yr, weight 66.8 ± 1.6 kg, height 169.1 ± 1.6 cm] who had lived at high altitude for several years volunteered to participate in the study. Genetically, the subjects ranged from Amerindian to European, with most being mestizo of predominantly Amerindian ancestry. The experimental procedures and potential risks of the study were explained to each subject both verbally and in writing. Before participation, each volunteer was screened by a physician; this procedure included medical

history, physical examination, and hematocrit (Hct) measurement. Bases for exclusion from participation included evidence of anemia (Hct <42%), excessive polycythemia (Hct >65%), or any condition or illness that contraindicated performance of heavy work. All subjects gave informed consent, and the experiment was approved by the local Ethics Committee (Universidad Major San Andres, La Paz, Bolivia). On the basis of a questionnaire, all of these subjects were considered nonchewers (chewing less than once a year). All subjects were physically active, but none was involved in a training program. They were asked to maintain their usual activity throughout the study. All measurements were performed at the Instituto Boliviano de Biología de Altura (La Paz, Bolivia, mean altitude 3,600 m).

Procedure. Before the experimental trials, all subjects were subjected to an incremental exercise test on a mechanical bike, allowing $\dot{V}O_{2peak}$ determination as previously described (29). The mean $\dot{V}O_{2peak}$ of the subjects averaged 38.6 ± 0.8 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$. This test was conducted to select an appropriate work rate for the subsequent trials.

The subjects were asked to maintain their eating and drinking habits constant throughout the study and to abstain from vigorous exercise for 24 h before the tests. They reported to the laboratory after fasting overnight, and a catheter was inserted into an antecubital vein for blood withdrawal. After a 15-min supine rest (group R_1), the subjects remained seated on a chair for a 60-min period during which they were asked to participate in $Coca^-$ trial or in $Coca^+$ trial. The order of trials was randomized, and one-half of the subjects began first with the $Coca^+$ trial, whereas the other half were examined initially without chewing coca ($Coca^-$).

Thereafter, the subjects sat on the bicycle while resting gas exchanges were determined and blood was withdrawn (group R_2). The exercise was then started and lasted 60 min at a power output designed to elicit ~75% $\dot{V}O_{2peak}$. Identical weights were placed on the pan balance of the bicycle in each trial, and revolutions per minute were closely monitored to ensure identical power outputs in both trials.

At R_2 and at 5, 15, 30, 45, and 60 min of the submaximal exercise, HR was monitored continuously by electrocardiographic telemetry (Sport tester). Using a cuff around the upper arm, systolic and diastolic pressures were measured by using a manual sphygmomanometer, and MAP was calculated as diastolic pressure + (systolic − diastolic pressure)/3.

All subjects performed both trials 1 mo apart. Fluid intake was not allowed during chewing or during exercise.

Body fluid volume measurements. Body fluids were estimated only at R_2 for both trials ($Coca^-$ and $Coca^+$). Total body water (TBW), extracellular and intracellular fluid volumes were determined by bioelectrical impedance (14). The impedance meter measures the impedance of a conductor to an injection of an alternating current at 50 μA at two frequencies: 1 MHz and 5 KHz. A microprocessor automatically and instantaneously checked the analyzer, counterbalanced deflection errors, and calculated impedance (14). A microcomputer (Casio, model FX-795P) worked out further calculations immediately afterward.

Blood sampling: analytical methods. Blood samples (10 ml) were collected without stasis before exercise (R_1, R_2) and during the 5th, 15th, 30th, and 60th min of cycling. Hct was immediately determined in duplicate by using heparinized microhematocrit tubes spun for 10 min at 11,500 revolutions/min. Hemoglobin concentration ([Hb]) was quantified by use of a commercially available test kit (Sigma Chemical). The red blood cell (RBC) count was measured by using standard Thoma pipettes and Hayem solution as the diluting fluid. The remainder of the blood was transferred to iced heparinized tubes and centrifuged, after which the plasma was carefully removed, frozen, and stored (−80°C) for subsequent assays. Total protein concentration was measured spectrophotometrically, and serum osmolality was measured by using the freezing-point depression method. Plasma Na^+ and K^+ were measured by flame photometry.

Relative changes in plasma volume with coca chewing and exercise were determined from Hct and [Hb] (12). Blood volume change was evaluated from Hct and plasma protein concentration, as described by Theodoridis and Lee (30).

Epinephrine (Epi) and norepinephrine (NE) were assayed by high-performance liquid chromatography with electrochemical detection (15). Plasma renin was quantified by using a commercially available kit (Renin III generation, ERIA Diagnostics Pasteur, France). In this immunoradiometric method, the first monoclonal antibody recognizes both the active and inactive form of renin, whereas the second monoclonal antibody, labeled with ^{125}I, specifically recognizes the active form of renin. The intra- and interassay variability averaged 4.5 and 14.5% for samples containing <10 pg/ml of renin and 1 and 4.5% for samples exceeding 250 pg/ml. Arginine vasopressin (AVP) and atrial natriuretic peptide (ANP) were determined as described previously (18).

Statistical analysis. For each dependent variable, data were analyzed by two-way analysis of variance (STATVIEW 4.02, Abacus Concepts, Berkeley, CA) 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 test was used post hoc when significant F ratios were obtained. The level of significance was set at 5%. Data are presented as means ± SE.

RESULTS

Effects of coca chewing on the hematologic and hormonal status at rest (Table 1). The hematologic and hormonal characteristics before chewing at R_1 were identical in both the $Coca^-$ and $Coca^+$ trials. From R_1 to R_2 in the $Coca^-$ trial, there was a significant increase in plasma NE, whereas the other hematologic and hormonal parameters remained unchanged (Table 1). During the $Coca^+$ trial, Hct, [Hb], RBC, K^+, proteins, and NE were higher and ANP was lower at R_2 than at R_1. In addition, plasma volume decreased from R_1 to R_2 after coca chewing, a change that was accompanied by a significant increase in MAP (from 90.3 ± 2.7 to 96.2 ± 2.6 mmHg, $P < 0.01$) without significant changes in HR (80 ± 3 and 78 ± 4 beats/min, at R_1 and R_2, respectively).

Effects of prior coca chewing on the hormonal and cardiovascular response to submaximal exercise. Work intensity during exercise was identical in both trials (119.6 ± 6.6 and 119.8 ± 6.5 W for $Coca^-$ and $Coca^+$, respectively). Exercise was characterized by significant increases in Hct, [Hb], osmolality, protein concentration, and K^+, irrespective of coca chewing (Table 2). The exercise-induced changes in blood and plasma volumes were attenuated in the $Coca^+$ trial (Fig. 1), whereas the increase of HR with exercise was significantly higher during the $Coca^+$ than in the $Coca^-$ trial (Fig. 2). With respect to MAP, we found that the exercise-induced response was similar in both trials.

Neither plasma catecholamines (Fig. 2), renin, nor AVP (Fig. 3) was different between the $Coca^-$ and the $Coca^+$ trials. With respect to ANP, it appeared that its

Table 1. *Hematologic and hormonal parameters in subjects at rest before and after chewing either chewing gum or 15 g of coca leaves*

	Coca$^-$		Coca$^+$	
	R_1	R_2	R_1	R_2
Hct, %	49.8±0.6	49.4±0.6	49.4±0.7	51.5±0.7*†
[Hb], g/dl	16.4±0.2	16.6±0.2	16.5±0.2	17.1±0.2*†
RBC, $\times 10^{-6}$	5.666±0.130	5.825±0.164	5.572±0.105	5.924±0.149†
ΔPV, %		−2.6±0.6		−7.0±0.7†
ΔVb, %		−1.9±0.9		−3.8±1.3†
TBW, liters		31.85±1.42		31.29±1.07
EFV, liters		15.47±0.64		15.22±0.55
IFV, liters		16.38±0.82		16.07±0.54
Osmolality, mosmol/ kgH_2O	283±3	281±2	282±2	283±2
Na^+, meq/l	137±1	138±1	140±1	139±1
K^+, meq/l	3.9±0.1	4.0±0.1	3.9±0.1	4.2±0.1*†
Urea, mM	5.6±0.1	5.7±0.2	5.7±0.3	5.6±0.3
Creatinine, μM	98.0±3.5	97.2±3.7	101.6±2.9	104.9±2.9*
Proteins, g/l	82.1±2.0	84.2±2.4	84.1±1.9	88.5±2.3†
NE, pg/ml	325±44	454±37*	269±31	485±64*
Epi, pg/ml	153±12	156±14	162±23	167±12
AVP, μU/ml	2.4±0.4	2.5±0.3	2.3±0.3	2.1±0.3
Renin, pg/ml	17.5±2.5	15.9±2.3	15.9±2.3	15.4±2.5
ANP, pg/ml	23.6±2.0	23.4±1.7	24.0±1.6	20.3±1.1*†

Values are means ± SE. R_1 and R_2, subjects at rest before and after, respectively, chewing either chewing gum (Coca$^-$) or 15 g of coca leaves (Coca$^+$); Hct, hematocrit; [Hb], hemoglobin concentration; RBC, red blood cell count; ΔPV, changes in plasma volume from R_1 to R_2; ΔVb, changes in blood volume from R_1 to R_2; TBW, total body water; EFV, extracellular fluid volume; IFV, intracellular fluid volume; NE, plasma norepinephrine; Epi, plasma epinephrine; AVP, plasma arginine vasopressin; ANP, plasma atrial natriuretic peptide. *Significantly different from R_1; †significantly different from Coca$^-$ at the same time.

plasma level was lower during the first 30 min of exercise of the Coca$^+$ trial (Fig. 3).

DISCUSSION

The Coca shrub *Erythroxylum Coca* is a plant originating in the Andean mountain range; its historical significance dates back to before the conquest of the Incas. It was, and continues to be, chewed by the Aymaras and Quechuas of Bolivia, Peru, and other Andean countries. Although coca chewing could potentially enhance tolerance for work (6), we recently found (29) that coca chewing in traditional users is accompanied, at rest, by a significant decrease in blood and plasma volume. These fluid shifts were accompanied by an exaggerated HR and blood pressure response to exercise, as commonly observed after hypovolemia induced by blood withdrawal (7), diuretic use (3), or thermal dehydration (9). The present study provides evidence that in nonhabitual users coca chewing resulted at rest in a significant hypovolemia. During prolonged submaximal exercise, the exercise-induced hemoconcentration was blunted by prior coca chewing, and this effect was not linked to an alteration in catecholamine, renin, or AVP response (Figs. 2 and 3). Nevertheless, plasma ANP was significantly reduced during exercise after coca chewing (Fig. 3).

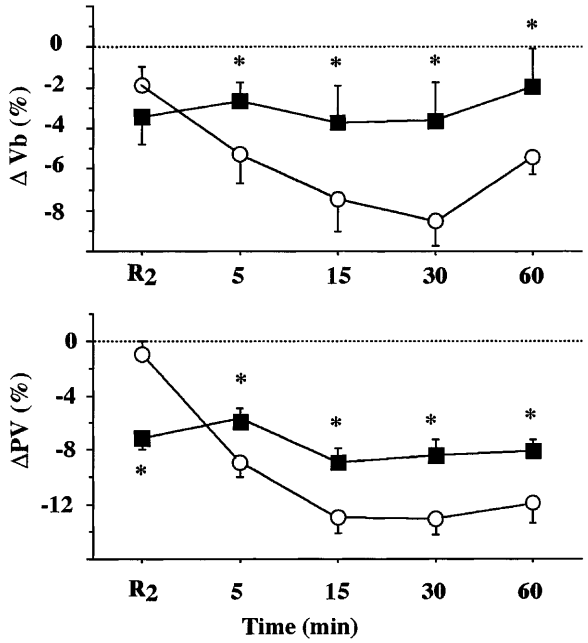

Fig. 1. Exercise-induced changes in plasma (ΔPV) and blood volumes (ΔVb) during prolonged submaximal exercise in subjects cycling after 1 h of chewing either a sugar-free chewing gum (Coca$^-$; ○) or 15 g of coca leaves (Coca$^+$; ■). R_2, rest after 1-h chewing. Values are means ± SE. *Significantly different from Coca$^-$ at same time point.

Effects of coca chewing at rest. Before examining the effects of coca, it must be kept in mind that the present experiments were performed on high-altitude residents and that fluid balance and hormonal status are clearly affected by a hypoxic environment (4). Our

Table 2. *Hematologic parameters during submaximal exercise for either Coca$^-$ or Coca$^+$ subjects*

	5 min		15 min		30 min		60 min	
	Coca$^-$	Coca$^+$	Coca$^-$	Coca$^+$	Coca$^-$	Coca$^+$	Coca$^-$	Coca$^+$
Hct, %	52.4±0.7*	52.8±0.6	53.2±0.8*	53.6±0.7*	53.1±0.8*	53.2±0.7*	52.4±0.7*	52.8±0.7
[Hb], g/dl	17.4±0.1*	17.6±0.2*	18.0±0.2*	18.0±0.2*	18.0±0.2*	18.0±0.2*	18.0±0.3*	18.1±0.2*
Osmolality, mosmol/ kgH_2O	285±1	287±2	289±2*	290±2	289±2*	292±2*	289±2*	295±2*
Na^+, meq/l	141±2	142±2	141±1	139±1	141±1	140±1	140±1	142±1
K^+, meq/l	4.4±0.1*	4.5±0.1*	4.8±0.1*	4.7±0.1*	4.9±0.1*	4.9±0.1*	5.1±0.1*	5.2±0.1*
Urea, mM	5.6±0.3	5.6±0.2	5.6±0.2	5.5±0.3	5.8±0.2	5.5±0.3	6.1±0.2	6.0±0.4
Creatinine, μM	96.7±4.2	104.9±2.3	99.9±4.1	104.9±3.5	101.1±4.5	106.3±3.2	106.8±5.5	114.3±4.6
Proteins, g/l	90.7±2.0	91.4±2.6	94.2±3.1*	95.9±3.1*	95.5±3.0*	94.1±2.5	90.2±2.4	91.5±2.7

Values are means ± SE given for varying-length exercise duration. *Significantly different from R_2.

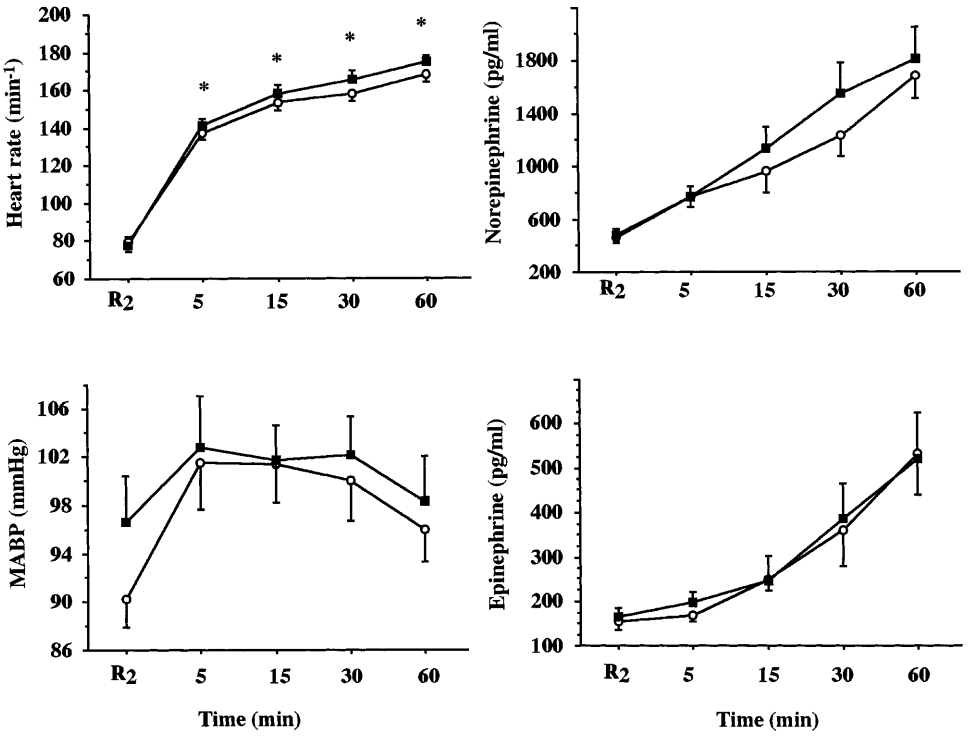

Fig. 2. Cardiovascular and catecholamine response during prolonged submaximal exercise in Coca$^-$ (○) or in Coca$^+$ subjects (■). MABP, mean arterial blood pressure. Values are means ± SE. * Significantly different from Coca$^-$ at same time point.

estimates of TBW by bioelectrical impedance (31.85 ± 1.42 liters; Table 2) are similar to those measured with antipyrine by Picon-Reategui (24) in Andean natives (31.0 ± 0.77 liters). It must be noted, however, that our TBW values and those of Picon-Reategui appeared to be lower than those reported in sea-level natives exposed to acute high-altitude exposure (16, 25). This suggests that high-altitude residents might display some signs of chronic hypohydration. This hypothesis is somewhat supported by the lower ANP levels reported in the present (Table 1) and previous (1) studies in Andean natives, compared with those measured in Caucasians in the same posture (1, 11). Because the hematologic and hormonal parameters were similar before chewing (R_1) in both conditions (Table 1), it can be considered that the status of the subjects was stable over the experimental period (1 mo), that their absolute body fluid volumes were likely identical initially for both trials, and that body fluid shifts can be accurately estimated from Hct, [Hb], and protein (12, 30) changes.

The amount of coca leaves (15 g) that the subjects had to chew was chosen on the basis of our previous experiments (6, 28) in which we found that the mean quantity of leaves used freely by chronic coca users averaged ~16 g. On the other hand, it has been shown that plasma cocaine level increases sharply after coca chewing, reaches a plateau at ~1 h, and persists in the plasma for several hours (22).

It can be calculated that during the control trial (Coca$^-$) plasma and blood volume were not significantly affected between R_1 and R_2 (Table 1). In contrast, during the Coca$^+$ trial, there was a significant decrease in plasma and blood volumes, but the distribution between intra- and extracellular volume remained the same (Table 1). The reported changes in body fluid homeostasis after coca chewing are reminiscent of those observed after hypohydration (3, 7, 9). The mechanism of the plasma volume decrease after coca chewing is difficult to assess, because we have no data on the main forces involved in fluid movement through the capillary membrane (Starling forces). First, such mechanism could be linked to a modification in fluid movement between the intra- and the extravascular fluid (21), and it is likely that the increase in MAP following coca chewing has facilitated the movement of fluid into the extravascular space. Second, it could be due to blood trapping in some large vascular territories (e.g., splanchnic area). Third, it can be hypothesized that coca chewing increased diuresis. Indeed, we recently noted in a group (n = 10) of chronic coca users that, subsequent to 1 h of coca chewing, urine production increased significantly from 276 ± 76 to 359 ± 55 ml/h (unpublished observations). Nevertheless, assuming a blood volume of 5 liters, a 3.8% reduction in blood volume would represent ~190 ml, and the increase in urine flow rate (83 ml/h) would account for <50% of blood volume decrease. Fourth, it is possible that coca chewing affected body sweating rate. Unfortunately, we did not monitor sweat production in the present study, but it has been reported (13) that coca use produces peripheral vasoconstriction and reduces heat loss during cold exposure. The coca-induced vasoconstriction would result in a greater heat storage and thus a greater drive for evaporative heat loss. This cannot be excluded as a possibility if coca has a direct action on sweat glands, which is presently unknown.

In addition, during the Coca$^+$ trial, ANP decreased from R_1 to R_2. To our knowledge, there are no data in the literature on ANP levels after coca chewing. An explanation for the decrease in ANP we observed after

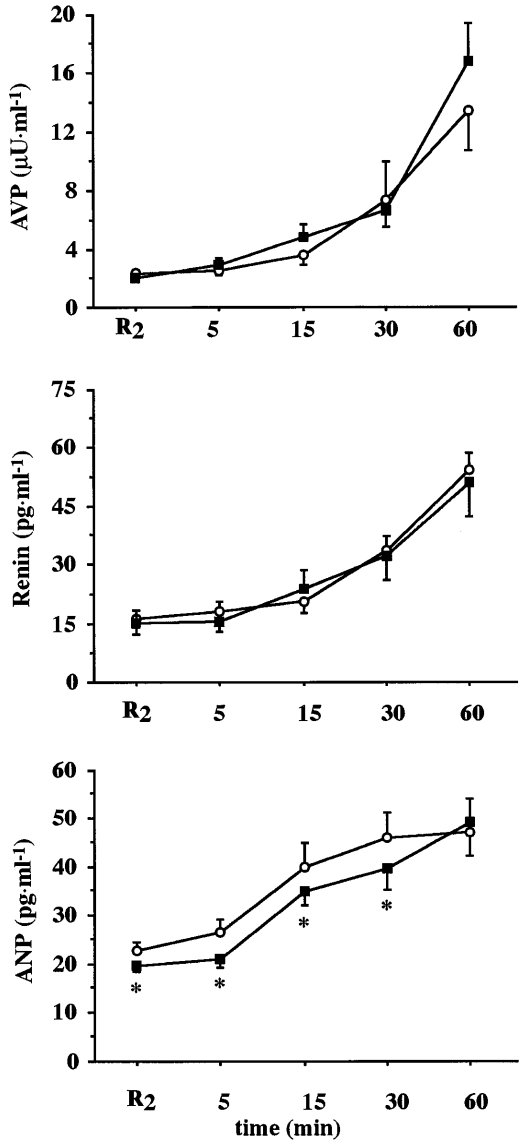

Fig. 3. Plasma hormonal response to exercise in Coca$^-$ (○) or in Coca$^+$ subjects (■). AVP, arginine vasopressin; ANP, atrial natriuretic peptide. Values are means ± SE. *Significantly different from Coca$^-$ at same time point.

coca chewing is not readily apparent. Because plasma levels of ANP are a function of relative rates of synthesis, release, and clearance of the hormone, the levels we measured probably reflect alterations in the balance of these rates. Because ANP secretion is stimulated by right atrial distension (see, e.g., the rapid increase in ANP in response to head-down tilt; Ref. 18), it can be assumed that the coca-induced reduction in fluid volume could be expected to cause a decrease in right atrial stretching and to reduce plasma ANP level.

On the basis of acute alterations of blood and plasma volume changes induced by coca chewing at rest, we hypothesized that coca use before exercise should alter the fluid shifts and cardiovascular response to exercise.

Effects of prior coca chewing on the hormonal and cardiovascular response to submaximal exercise. Body fluid homeostasis during prolonged submaximal exercise (including bicycle ergometry) at low altitudes has been reported in the past (27, 33). The general pattern is that plasma volume decreases progressively with increasing exercise duration and intensity (27, 33), in conjunction with an increase of the fluid regulatory hormones such as NE, Epi, AVP, renin, ANP, and aldosterone (33) to ensure an adequate cardiovascular function during exercise.

During the Coca$^-$ trial, the exercise-induced increases in plasma AVP, renin, and catecholamines (Figs. 2 and 3) were in keeping with those previously reported for a similar exercise test in terms of intensity or duration (20, 23). With respect to ANP, it was recently reported that chronic hypoxia resulted in a blunted ANP response to exercise (25). These data contrast with the present study in which we found a progressive increase in plasma ANP level with exercise duration (Fig. 3). One of the reasons evoked by Rock et al. (25) to explain the apparent lack of ANP response to exercise during altitude acclimatization was a reduced cardiac output and, consequently, lack of the mechanical stretch of cardiomyocytes during exercise after ~15 days at 4,300 m altitude. Although decreased cardiac output during chronic but short-lasting hypoxic exposure (≤2 wk; Ref. 32) may be a possible explanation for the results of Rock et al. (25), it is possible that the normal ANP response observed in Andean dwellers in the present paper (Fig. 2) and in another study (1) was linked to a better maintenance of cardiac function during exercise in high-altitude residents. Indeed, it was shown by Vogel et al. (31) that high-altitude residents are able to exercise up to the maximum level without any reduction in cardiac output.

When exercise was preceded by coca chewing, it appeared that the exercise-related plasma and blood volume shifts were reduced, whereas HR was higher throughout the exercise test (Fig. 2). This is the second study that we are aware of to report body fluid balance and cardiovascular response during exercise in humans after coca chewing. Indeed, Spielvogel et al. (29) recently observed that the exercise-induced body fluid changes were reduced while HR and MAP responses were enhanced in chronic coca users after chewing, in agreement with data reported in horses after cocaine administration (19). It thus seems that the influence of coca chewing on HR response is rather similar after acute (this study) and chronic (29) coca use, whereas the blood pressure response to exercise differs strikingly between habitual and nonhabitual coca users. Indeed, the exercise-induced changes in MAP are enhanced in chronic coca chewers (29) but unchanged in nonhabitual users (Fig. 2). These differences could be linked to a differential sympathetic activation by coca chewing in these populations. Thus, during submaximal prolonged exercise, we observed a significantly higher Epi level after chewing coca in chronic users (6), but not in nonhabitual coca chewers (Ref. 5; Fig. 2). In fact, the observed changes in the present study were rather comparable to those reported after hypohydration (8). In that study, a significantly smaller decrease in blood volume during exercise when the subjects were

hypohydrated was shown, in conjunction with a reduction in sweating rate. Even though we did not measure whole body sweating rate in the present experiment, it was previously shown that coca chewing induced peripheral vasoconstriction (13), which likely reduced the ability to dissipate heat during exercise. This assumption is supported by the results obtained in exercising rats that displayed a higher core temperature after cocaine administration (17). Clearly, more data are needed to determine whether coca chewing affects thermal regulation during exercise.

The coca-induced hematologic and cardiovascular alterations were not accompanied by changes in fluid regulatory hormones during exercise (Figs. 2 and 3). These data contrast with those obtained with graded levels of hypohydration, which elicited incremental levels of hormones regulating body fluid homeostasis (10). The reasons for the lack of dependence of fluid shift to hormonal status after coca-induced hypovolemia are not obvious but could be related to some of the following factors. First, it might be that the changes in plasma and blood volumes were associated with alterations of other hormonal systems, not examined in the present study but involved in body fluid maintenance (e.g., aldosterone, cortisol, prostaglandins). This possibility is, however, unlikely because most of these latter hormones display an exercise kinetics similar to that observed with NE, Epi, renin, AVP, and ANP (33). To clearly refute this hypothesis, we should have screened all the hormones susceptible to influence body fluid homeostasis. Unfortunately, such determinations would have increased substantially the necessary amount of blood, and it is possible that larger blood withdrawal could have invalidated the study. Alternatively, it is possible that coca chewing affected renal sympathetic activity without resulting in a higher level of plasma catecholamines. During exercise, the loss of fluid and electrolytes via the kidneys is significantly reduced in relation to a catecholamine-related decrease in renal blood flow (35). Even though the plasma level of free NE and Epi during exercise was similar in the $Coca^-$ and $Coca^+$ trials (Fig. 2), we found during a 24-h urine collection after exercise (unpublished observation) that dopamine was significantly higher (by ~60% for both conjuguated and total dopamine) during the $Coca^+$ than during the $Coca^-$ trial. Given the influence of dopamine in renal blood flow (34), it can be hypothesized that, at least partly, body fluid preservation during exercise after coca chewing was linked to a greater decrease in renal blood flow. Furthermore, it has been suggested that the reduced sweating rate following hypohydration (8) might involve the atrial stretch receptors and thus likely affects the plasma ANP level. This suggestion is somewhat supported by the present data (Fig. 3) showing that up to 30 min of exercise plasma ANP was reduced after coca chewing.

Conclusions. The findings of the present study provide evidence that chewing 15 g of coca leaves during 1 h before exercise results in a significant modification in hematologic parameters, leading to a substantial decrease in blood and plasma volumes. These body fluid shifts are accompanied by a significantly higher MAP. The coca-induced hemoconcentration attenuates the exercise-related shift of body fluids, which cannot be accounted for by changes in the major hormones involved in fluid homeostasis. Further work is needed to determine the mechanisms that limit hemoconcentration during exercise when it is preceded by prior coca chewing. There is, however, some reason to believe that the ability to retain fluid during exercise after coca chewing is linked to a reduced heat transfer from the contracting muscles to the skin and from the skin to the environment. Whereas this increased heat retention after coca chewing could be beneficial for exercise in a cold environment like that encountered in the Altiplano of South America, it is probably undesirable for exercise in a neutral or warm environment. This would readily explain the reason why coca is mainly chewed by high-altitude natives daily exposed to cold during work (see Ref. 13).

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