The nature of opioid involvement in the 
hemodynamic respiratory and humoral responses 
to exercise

J. Staessen, M.D., R. Fiocchi, M.D., R. Bouillon, M.D., R. Fagard, M.D., P. Liinen, Ph.D., E. Moerman, M.D., A. De Schaepdryver, M.D., and A. Amery, M.D.

ABSTRACT After 30 min rest in the lying position, 12 healthy male volunteers (average age 22 years) received, in a randomized double-blind cross-over protocol, either saline or naloxone (10 mg iv followed by a continuous infusion of 10 mg/hr). Thereafter they rested for a further 30 min in the recumbent position and for 15 min sitting on a bicycle ergometer; they then exercised to exhaustion. At rest plasma levels of adrenocorticotropin (ACTH), cortisol, and aldosterone increased during infusion of naloxone, while body temperature decreased. During exercise the difference in plasma ACTH between naltroxone and saline periods was abolished, while the differences in plasma cortisol and aldosterone lost statistical significance. Intra-arterial pressure, heart rate, ventilation, O2 uptake, and CO2 output were continuously monitored throughout the experiment and were not affected by naloxone. This was also the case for several hormonal and biochemical measurements, including those of plasma renin, angiotensin II, norepinephrine, 13,14-dihydro-15-keto-prostaglandin F2α, glucose and lactate, and serum insulin and growth hormone. Exercise performance was not changed by naloxone. In conclusion (1) during exhaustive graded exercise of short duration opioidergic inhibition of the pituitary-adrenocortical axis is probably not sustained, (2) apart from the latter mechanism, the present study does not support the hypothesis that endogenous opioids are involved in various hemodynamic, respiratory, and hormonal responses to this type of exercise.


THE SENSITIVITY of the human cardiovascular and endocrine systems to exogenous opiates has been recognized for a long time. More recently, the interest in opioid-mediated mechanisms in cardiovascular and neuroendocrine physiology has been revived by the discovery of an endogenous opiate system. Opioid peptides and receptors have been shown to be densely distributed not only in nociceptive anatomic sites, but also in autonomic centers closely involved in cardiopulmonary and peripheral neuroendocrine regulation. These localizations include the brainstem, the hypothalamopituitary axis, the sympathetic ganglia, and the adrenal medulla. In addition, since the discovery of immunoreactive \(\beta\)-endorphin in normal human plasma, several investigators have demonstrated that the levels of circulating \(\beta\)-endorphin\(^1\) and its precursor \(\beta\)-lipotropin\(^6\) are stimulated by both maximal and submaximal exercise and that this increase is related to the intensity of effort\(^6\) and is augmented by training.\(^8\)

In view of these findings, the present study aimed to investigate in healthy human volunteers the role of opioid mechanisms in various hemodynamic, respiratory, and humoral responses to exercise with the use of naloxone as a pharmacologic probe. Accordingly, throughout this article the term opioid refers to any directly acting endogenous compound, the actions of which are stereospecifically antagonized by naloxone.

**Methods**

**Subjects.** Twelve normal male volunteers from 21.7 ± 0.4 (SE) years old and weighing at initial examination 69.5 ± 1.9 kg gave their informed written consent and participated in the present study. Their mean height was 180 ± 2 cm. They remained on a liberal diet. Their 24 hr urinary sodium and potassium excretion averaged 142 ± 16 and 72 ± 7 mmol, respectively, and remained constant throughout the study.

**Experimental protocol.** All experiments were performed in an air-conditioned laboratory, where room temperature was sta-
proven between 18° and 22° C. The protocol, which was approved by the Ethical Committee of the Faculty of Medicine (K. U. Leuven), is summarized in figure 1. The subjects, sitting on a bicycle ergometer, performed graded and uninterrupted exercise tests until exhaustion. A pretest, meant to assess the subjects’ maximal exercise capacity, antedated the subsequent experiments on average by 1 month. For this pretest the initial external workload of 10 W was increased by 10 W every minute. Oxygen uptake, carbon dioxide output, and ventilation at the maximal workload were determined and the external workloads, corresponding to incremental steps of 10% of the maximal exercise capacity, were computed.

On the morning of the two subsequent “experimental” tests, which were on average 2 months apart, the subjects had a light breakfast without caffeine-containing beverages. Thereafter they came to the laboratory. First a small catheter (Vygon 115.09) was inserted into the brachial artery for continuous registration of arterial pressure and for sampling of blood. For drug administration a cannula (Abbocath-T, 18G) was inserted in an antecubital vein and kept patent with a 0.9% sodium chloride solution. Throughout the experiments the intravenous infusion rate was kept constant at a speed of 0.33 ml/min with a Harvard pump, model 906.

After the aforementioned manipulations, the subjects were allowed to rest in the recumbent position for 30 min (RR control period). Then, according to a double-blind cross-over design with balanced randomization, either 10 mg naloxone (Endo Laboratories Inc., New York, USA) dissolved in 25 ml 0.9% sodium chloride or a dose of volume-matched saline were injected intravenously over 5 min. Throughout the remaining part of the experiments the intravenous infusion was continued, delivering 10 mg naloxone in a 0.9% sodium chloride solution or volume-matched dose of saline per hour. Apart from the two physicians supervising each experiment neither the subjects nor any of the other investigators who contributed to the acquisition and processing of the data were aware of the nature of the infusion administered.

After the start of the experimental intervention, the subjects remained recumbent for a further 30 min (RR experimental period). The subjects then assumed the sitting position on the bicycle ergometer for 15 min (RS period). Finally, the exercise test was started at an external workload corresponding to 10% of the maximal exercise capacity determined on the occasion of the pretest. Every 3 min the external workload was augmented by a further 10% of the pretest maximum. The volunteers were asked to continue cycling up to 3 min at 100% of their previously determined maximal exercise capacity, but could stop the two exercise tests earlier if they reached complete exhaustion. The subjects were not informed about the maximal exercise level they attained during any of the tests.

Hemodynamic and respiratory measurements and body temperature. Systolic and diastolic intra-arterial pressure were measured directly through the indwelling catheter in the brachial artery with an electronic transducer (Elema Schönander EMT 34) and recorded continuously on a Mingograph 81 ink-jet recorder. The zero reference point for arterial pressure was kept constant at the midchest level independent of the position of the body. Mean arterial pressure was obtained by electrical damping every 5 min during the RR control and experimental periods and every minute during RS and cycling. Heart rate was determined from the electrocardiogram, which was continuously registered throughout each experiment.

Expired gas was collected in a mixing box by an open-circuit method. Oxygen uptake and carbon dioxide output were continuously calculated from the volume of the expired gas and its O2 and CO2 concentrations, determined by electronic gas analyzers that were calibrated before each experiment with test gases of known composition (Siregnost FD, Siemens). The

![Study protocol](http://circ.ahajournals.org/)

FIGURE 1. Study protocol. See Methods for further explanation.
respiratory gas exchange ratio was calculated as carbon dioxide output divided by oxygen uptake.

Body temperature was measured sublingually at the end of the RR control and RR experimental periods. The same regular mercury thermometer was used for all experiments and read to the nearest 0.05°C after having been applied for exactly 5 min. The subjects were dressed in sportswear, consisting of a sleeveless shirt and shorts, and remained covered by a blanket throughout both the RR control and RR experimental periods.

Biochemical measurements. On both experimental days arterial blood (160 to 180 ml per experiment) was sampled for the following determinations: hemoglobin; plasma renin activity; plasma angiotensin II, aldosterone, norepinephrine, adrenocorticotropic, cortisol, glucose, lactate, and immunoreactive 13, 14-dihydr-o-15-keto-prostaglandin F₂α; and serum insulin, growth hormone, electrolytes, bicarbonate, and protein. Arterial blood samples were obtained at the end of the RR control and RR experimental periods, at 10 min of RS, at 30% and 60% of the previously determined maximal exercise capacity, and immediately after the interruption of peak exercise. Arterial blood for hormonal measurements was collected in chilled test tubes and immediately spun at 4°C, the supernatant being instantly frozen and stored at −20°C until assay.

Electrolytes were measured by flame photometry and plasma lactate was determined by an enzymatic method. The plasma concentration of cortisol was determined by a kit based on competitive binding and displacement of radiolabeled cortisol from transcortin. Plasma norepinephrine was assayed by high-performance liquid chromatography with electrochemical detection and the other plasma hormones were assayed by standard radioimmunoassays, with the use of a double antibody technique for serum insulin and growth hormone.

Statistical analyses. Blood pressure, heart rate, and the respiratory measurements were analyzed by three-way analysis of variance, taking into account as main sources of variation (1) subjects, (2) experimental days or treatments (saline vs naloxone), and (3) time or levels of physical activity. For all other variables comparisons between RR control and RR experimental periods and between experimental days or treatments were performed by Student’s two-tailed t test for paired observations.

The distributions of several hormonal measurements were positively skewed. These distributions were linearized by a logarithmic transformation before parametric statistical tests were computed. For these distributions geometric means and ranges are reported, while for other items arithmetic means ± SE are given.

Results

Pretest. At the pretest the volunteers attained a maximal workload of 298 ± 11 W (mean ± SE). At maximal exercise, peak ventilation, oxygen uptake, and carbon dioxide output averaged 114 ± 5, 3.54 ± 0.10, and 3.82 liters/min, respectively.

Measurements obtained before the injection of saline or naloxone. In the comparison of the two experimental days before the injection of saline or naloxone, no differences were found in body weight (69.6 ± 2.1 vs 69.7 ± 1.9 kg, respectively), temperature (36.64 ± 0.08°C vs 36.62 ± 0.10°C), blood pressure (figure 2), heart rate (table 1), or any respiratory (table 1), hormonal (figure 3 and table 2), or biochemical measurements (table 3).

Influence of opioid antagonism at recumbent rest (RR experimental). Compared with the administration of saline, opioid antagonism by naloxone did not influence systolic, diastolic, or mean intra-arterial pressure (figure 2), or heart rate (table 1) and the respiratory measurements (table 1). In subjects on saline, body temperature as compared with RR control remained unchanged, averaging 36.64 ± 0.07°C, whereas in those on naloxone a decrease of 0.12 ± 0.04°C (p = .02) to 36.50 ± 0.11°C was observed.

In subjects on saline none of the hormonal (figure 3 and table 2) or biochemical measurements were statistically different between the RR control and RR ex-

TABLE 1

| Heart rate and respiratory measurements obtained during the RR and RS periods, at 30% and 60% of the previously determined maximal exercise capacity, and at peak exercise |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | RR control | RR experimental | RS              | 30%             | 60%             | Peak exercise  |
| Workload (W)    |             |                 |                 |                |                |                |
| S               | S           | —               | —               | 28 ± 1         | 170 ± 6        | 278 ± 12       |
| N               | —           | —               | —               | 28 ± 1         | 170 ± 6        | 278 ± 10       |
| Heart rate (bpm)|             |                 |                 |                |                |                |
| S               | 69 ± 5     | 69 ± 4          | 78 ± 4          | 102 ± 3        | 148 ± 4        | 195 ± 3        |
| N               | 68 ± 4     | 66 ± 4          | 74 ± 2          | 102 ± 4        | 145 ± 4        | 192 ± 2        |
| Oxygen uptake (ml/min) | S       | 283 ± 22 | 271 ± 23 | 325 ± 21 | 1329 ± 65 | 2328 ± 105 | 3683 ± 155 |
| N               | 268 ± 14   | 271 ± 14        | 307 ± 20        | 1179 ± 46      | 2251 ± 86      | 3736 ± 158    |
| Carbon dioxide output (ml/min) | S       | 230 ± 19 | 222 ± 18 | 270 ± 22 | 998 ± 48 | 2144 ± 86 | 4035 ± 195 |
| N               | 233 ± 14   | 231 ± 16        | 258 ± 16        | 965 ± 33       | 2120 ± 86      | 4162 ± 185    |
| Respiratory gas exchange ratio | S       | 0.81 ± 0.02 | 0.82 ± 0.02 | 0.83 ± 0.03 | 0.81 ± 0.02 | 0.93 ± 0.02 | 1.10 ± 0.03 |
| N               | 0.87 ± 0.04 | 0.85 ± 0.02 | 0.84 ± 0.03 | 0.82 ± 0.02 | 0.94 ± 0.01 | 1.12 ± 0.02   |
| Ventilation (l/min) | S       | 8.5 ± 1.0 | 8.2 ± 0.9 | 10.7 ± 1.1 | 27.6 ± 1.2 | 54.4 ± 2.6 | 108.5 ± 5.4 |
| N               | 7.8 ± 0.6  | 8.0 ± 0.6       | 9.8 ± 0.8       | 26.0 ± 1.0     | 53.8 ± 2.3     | 112.6 ± 4.8   |
| Respiratory rate (cycles/min) | S       | 12.7 ± 1.3 | 12.9 ± 1.4 | 12.9 ± 1.0 | 21.5 ± 0.9 | 26.6 ± 1.8 | 40.2 ± 2.1 |
| N               | 11.1 ± 1.0 | 12.0 ± 1.2      | 12.1 ± 0.9      | 20.0 ± 0.7     | 24.6 ± 1.0     | 38.7 ± 1.8    |

Values are mean ± SE.
S = saline; N = naloxone.
Experimental periods. In those on naloxone, however, plasma adrenocorticotropin rose by 450% (p < .01), plasma cortisol rose by 80% (p < .001), and plasma aldosterone rose by 50% (p < .001) (figure 3). Thus, at the end of the RR experimental period higher concentrations were observed during naloxone than during saline administration for plasma adrenocorticotropin (66 vs 21 pg/ml; p < .01), plasma cortisol (20.8 vs 13.9 μg/dl; p < .03), and plasma aldosterone (10.8 vs 7.2 ng/dl; p < .01) (figure 3). None of the remaining hormonal (table 2) or biochemical (table 3) measurements were significantly affected by opioid antagonism and were therefore similar at the end of the RR experimental period on both experimental days.

Influence of opioid antagonism at sitting rest and during exercise. At sitting rest and at each level of exercise, systolic, diastolic, and mean intra-arterial pressure (figure 2), heart rate (table 1), and the respiratory measurements (table 1) were similar on both days.

At sitting rest, plasma concentrations were still higher with naloxone than with saline for adrenocorticotropin (59 vs 32 pg/ml; p = .08), cortisol (22.9 vs 17.7 μg/dl; p = .03), and aldosterone (12.8 vs 10.2 ng/dl; p = .02). Thereafter, during cycling and at the end of exercise, the differences in plasma adrenocorticotropin between tests were abolished, while the differences in plasma cortisol and aldosterone tended to become smaller, and lost statistical significance (figure 3). However, the 95% confidence limits for the changes in plasma cortisol produced by naloxone during and immediately after exercise ranged from an increase in plasma cortisol of 9.6 μg/dl to a decrease of 1.8 μg/dl. The corresponding 95% confidence limits for the naloxone-induced changes in plasma aldosterone embraced +6.3 ng/dl and −1.4 ng/dl, respectively.

Apart from levels of adrenocorticotropin, cortisol, and aldosterone, all other hormonal (table 2) and biochemical (table 3) measurements obtained at sitting rest and during exercise were similar on both experimental days.

Exercise capacity was not different in those on saline and those on naloxone, as evidenced by the maximal attained workload (table 1) and peak oxygen uptake (table 2) and the total duration of exercise (27.8 ± 0.4 vs 27.5 ± 0.2 min, respectively). Two volunteers on saline and two other subjects on naloxone only reached 90% of their previously determined maximal exercise capacity.

Side effects. Subjective complaints were not reported and adverse reactions were not observed, either after the administration of saline or naloxone.
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![Graphs of aldosterone, cortisol, and adrenocorticotrophic hormone concentrations.](http://circ.ahajournals.org/)

**FIGURE 3.** Plasma concentrations of aldosterone, cortisol, and adrenocorticotrophic hormone before and during intravenous administration of naloxone (●) or saline (○). Blood samples were obtained in the RR and RS periods, at 30% and 60% of the previously determined maximal exercise capacity, and at the end of peak exercise. Values are mean ± SE. Asterisks refer to the significance of the difference between the experimental sessions (● vs ○) and between control and experimental conditions (RR control vs RR experimental).

**Discussion**

Antagonism by naloxone has been widely used as a pharmacologic tool to disentangle the involvement of opioid mechanism in human physiology at rest. In contrast, only few studies have used this drug in the investigation of the hormonal response to physical effort or to study exercise performance. A major concern of the present study was therefore to validate its methodology. This goal was achieved by also recording observations at rest and by testing their reproducibility in comparison with previously reported data from the literature.

**Findings in subjects at rest.** The present study demonstrated that opioid antagonism in subjects at rest in both the supine and sitting positions did not produce significant changes in intra-arterial pressure. This is in agreement with the work of other investigators, who reported that naloxone, although possibly increasing the sensitivity of baroreflex function, does not alter blood pressure in man, either in the supine position or during 6 hr of 70 degree head-up tilt. The hypothesis that opioid mechanisms do not play a key role in the regulation of systemic arterial pressure in healthy resting but awake subjects is furthermore substantiated by the observation that, similar to naloxone most, although not all, studies using opioid agonists such as morphine or met-enkephalin analogues failed to demonstrate a significant effect on blood pressure.

In agreement with earlier findings, the present study confirmed that opioid antagonism by naloxone in normal resting but awake men does not interfere with heart rate or respiration whereas body temperature is reduced by the drug.

Furthermore, in accordance with previous studies conducted in resting human subjects, opioid antagonism by naloxone did not change the serum levels of growth hormone measured under basal resting conditions, but did produce an elevation of the plasma levels of adrenocorticotropin and cortisol. Thus, results of the present study also support the concept that inhibitory opiate receptors contribute to the modulation of the pituitary release of adrenocorticotropic hormone.

In addition, we found that opioid antagonism increased the plasma aldosterone concentration at rest, while apart from adrenocorticotropic hormone, several other known determinants of adrenal mineralocorticoid secretion were unaffected throughout the study. These determinants included plasma renin and angiotensin II and serum sodium and potassium. The simultaneously occurring increase in the plasma levels of the two adrenal hormones cortisol and aldosterone on treatment with naloxone is therefore likely to be caused by the enhanced adrenocortical stimulation by adrenocorticotropic hormone, although direct interference with a local opiate–mediated inhibitory mechanism in the adrenal gland itself cannot be ruled out on the basis of the present experiments in vivo.

Opiate agonists have previously been shown to interfere with carbohydrate metabolism at various levels: they stimulate the pancreatic islet secretion of glucagon and insulin, but may also reduce hepatic glucose production. In contrast to these agonist ef-
ffects the opiate antagonist naloxone, when given under basal conditions to human subjects at rest, has been shown to have no influence on insulin\textsuperscript{14, 29, 30} or on plasma glucose.\textsuperscript{14, 30} These observations again were confirmed by the present study.

From the results obtained in subjects at rest, one may conclude that the methodology of this study was sufficiently accurate to reproduce most of the effects of opioid antagonism reported by other researchers. In addition, opioid antagonism by naloxone was demonstrated to stimulate plasma aldosterone in healthy human subjects at rest.

**Findings during exercise.** Several independent groups of investigators have reported that various stimuli, such as metyrapone\textsuperscript{2} and physical exercise, produce a concomitant increase in the plasma levels of immuno-reactive $\beta$-endorphin and adrenocorticotropic.\textsuperscript{3-6} Both hormones are derived from the same precursor molecule,\textsuperscript{32} are released together from the pituitary gland into the circulation,\textsuperscript{32} and share a common circadian rhythm.\textsuperscript{13, 33} The present study demonstrated an increase in plasma adrenocorticotropic, from which an enhanced release of $\beta$-endorphin can be inferred.\textsuperscript{3-6, 13, 32, 33}

Apparently, during exercise opioid receptors accessible via the systemic circulation are exposed to a higher concentration of $\beta$-endorphin and possibly other endogenous opiate agonists. The most logical approach to the exploration of the involvement of the endogenous neuroendocrine opiate system in the response to exercise was therefore to inhibit the action of the endogenous ligands at the level of their receptor with the use of naloxone as a pharmacologic probe.

**Hemodynamic and respiratory responses to exhaustive graded exercise of short duration.** The present study demonstrated that during exercise neither the hemodynamic nor the respiratory measurements were significantly different between the two experimental days. To explain this lack of effect, the possibility should be considered that, as exercise progressed, naloxone no longer reached the endogenous opiate receptors in an amount sufficiently large to sustain their inhibition. Naloxone, however, with its extremely rapid penetration into the brain\textsuperscript{34} and its reported serum half-life of 64 min,\textsuperscript{34} was infused continuously throughout the experiments. In addition, a further study of similar design in 10 normal volunteers showed that the plasma concentration of naloxone, determined by high-pressure liquid chromatography with electrochemical detection, rose to 43.5 ± 4.0 ng/ml (mean ± SE) in subjects at rest and was subsequently maintained during exercise, averaging 37.2 ± 3.0 and 51.4 ± 4.3 ng/ml at 30% and 60% of peak exercise and 50.9 ± 4.3 ng/ml at the end of cycling.\textsuperscript{*} This is higher than the 5 to 10 ng/ml peak serum concentrations of naloxone obtained within 5 min after a 0.4 mg intravenous bolus,\textsuperscript{34} which reportedly sufficed to reverse the effects of exogenously administered morphine for approximately 45 min.\textsuperscript{35}

Acidosis may lower the potency of narcotic agonists and antagonists in vivo.\textsuperscript{36} It is, however, improbable that exercise-induced changes in pH had a major influence on the outcome of the present study. Indeed, Fagard et al.,\textsuperscript{37} using the same exercise protocol in seven normal volunteers, demonstrated that from rest to 80% of these volunteers' maximal exercise capacity, arterial pH declined only slightly (from 7.40 ± 0.01 to 7.34 ± 0.01, mean ± SE). Moreover, although at higher workloads arterial pH was shown to decrease more sharply, reaching 7.26 ± 0.02 at peak exercise,\textsuperscript{37} the lack of effect of naloxone in this study was already apparent at low and moderate exercising levels, when no acidosis was present.

Assuming that the above mechanisms are excluded, our results do not support the view that opioid mechanisms contribute markedly to various hemodynamic and respiratory responses to exhaustive graded exercise of short duration. On the other hand, the present results do not exclude an effect of endogenous opiates on the regional regulation of venous capacitance and arteriolar resistance.\textsuperscript{20} Furthermore, under various conditions other than exercise, which was used in the present study, opiates may be involved in cardiorespiratory homeostasis. Indeed, opiates have been reported to interfere with the hypoxic and hypercapnic drive of ventilation in normal human subjects,\textsuperscript{38} and with blood pressure regulation during shock,\textsuperscript{1} during prolonged head-up tilt,\textsuperscript{19, 22} and during acute expansion of intravascular volume.\textsuperscript{24} Opiates may also contribute to the fall of systolic blood pressure during sleep\textsuperscript{39} and to the blood pressure reduction produced by converting-enzyme inhibition\textsuperscript{40} and by central $\alpha$-adrenergic stimulation,\textsuperscript{33} although the latter issue still remains controversial.\textsuperscript{41}

Finally, our results confirm earlier findings showing that exercise performance of normal human subjects is not affected by opioid antagonism.\textsuperscript{18}

**Hormonal responses to exhaustive graded exercise of short duration.** At exercise the differences in plasma adrenocorticotropic concentrations, which at rest were apparent between both experimental sessions, were abolished. Concomitantly the differences in the plasma

\textsuperscript{*Bianchi G: Unpublished data}
TABLE 2
Hormonal measurements obtained during RR and RS periods, at 30% and 60% of the previously determined maximal exercise capacity, and at the interruption of peak exercise.

<table>
<thead>
<tr>
<th></th>
<th>RR control</th>
<th>RR experimental</th>
<th>RS</th>
<th>30%</th>
<th>60%</th>
<th>End of exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum insulin (μU/ml)</td>
<td>S</td>
<td>12.8 (6.0-45.4)</td>
<td>11.9 (3.0-57.1)</td>
<td>14.9 (6.0-43.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>13.5 (7.0-45.0)</td>
<td>10.9 (5.9-20.0)</td>
<td>14.3 (6.2-24.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma 13,14-DH-15K-PGF&lt;sub&gt;2α&lt;/sub&gt; (pg/ml)</td>
<td>S</td>
<td>43 (19-154)</td>
<td>49 (36-84)</td>
<td>63 (24-132)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>53 (28-108)</td>
<td>53 (32-109)</td>
<td>54 (30-110)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml/hr)</td>
<td>S</td>
<td>0.61 (0.01-1.07)</td>
<td>0.41 (0.16-1.05)</td>
<td>0.76 (0.20-2.94)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>0.63 (0.28-1.90)</td>
<td>0.63 (0.30-1.40)</td>
<td>0.78 (0.32-1.59)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma angiotensin II (pg/ml)</td>
<td>S</td>
<td>19.4 (10.6-35.3)</td>
<td>19.1 (10.3-49.0)</td>
<td>22.9 (11.8-41.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>20.0 (12.3-31.4)</td>
<td>21.1 (11.6-55.6)</td>
<td>21.1 (12.0-44.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma norepinephrine (ng/ml)</td>
<td>S</td>
<td>0.26 (0.08-0.50)</td>
<td>0.15 (0.01-0.53)</td>
<td>0.32 (0.19-0.56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>0.23 (0.10-0.65)</td>
<td>0.19 (0.01-0.77)</td>
<td>0.28 (0.01-0.85)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum growth hormone (ng/ml)</td>
<td>S</td>
<td>2.5 (1.0-21.4)</td>
<td>2.7 (1.0-27.0)</td>
<td>3.1 (1.0-12.2)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>N</td>
<td>1.4 (1.0-5.3)</td>
<td>3.2 (1.0-30.7)</td>
<td>3.5 (1.0-28.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are geometric means (and ranges). S = saline; N = naloxone.

Concentrations of the adrenocorticosteroids cortisol and aldosterone tended to be reduced. However, in view of the wide confidence intervals one cannot exclude with certainty that at exercise the plasma concentration of those steroids were persistently higher with naloxone. The observation that the differences in the plasma levels of the adrenal hormones lagged behind those in adrenocorticotropic can be explained by several mechanisms. These include a differential clearance of these hormones from the circulation, a lasting effect of adrenocorticotropic on the adrenal gland, and direct interference of naloxone with the adrenal cortex. With respect to aldosterone the present study also excluded any interaction during exercise of naloxone with other glomerulosa-regulating factors, such as the plasma renin-angiotensin system or serum sodium and potassium. The mechanisms that provoked the exercise-induced rise in plasma adrenocorticotropic have not yet been elucidated. The present data do suggest, however, that the opioid-mediated inhibitory

TABLE 3
Biochemical measurements obtained during RR and RS periods, at 30% and 60% of the previously determined maximal exercise capacity, and at the interruption of peak exercise.

<table>
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<th>RS</th>
<th>30%</th>
<th>60%</th>
<th>End of exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>S</td>
<td>14.6 ±0.2</td>
<td>14.6 ±0.2</td>
<td></td>
<td>15.8 ±0.2</td>
<td>16.2 ±0.2</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>14.3 ±0.2</td>
<td>14.4 ±0.2</td>
<td></td>
<td>15.5 ±0.2</td>
<td>16.0 ±0.2</td>
</tr>
<tr>
<td>Serum protein (meq/l)</td>
<td>S</td>
<td>16.1 ±0.3</td>
<td>16.1 ±0.2</td>
<td></td>
<td>17.9 ±0.3</td>
<td>18.6 ±0.3</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>15.8 ±0.3</td>
<td>15.9 ±0.3</td>
<td></td>
<td>17.7 ±0.2</td>
<td>18.4 ±0.2</td>
</tr>
<tr>
<td>Serum sodium (meq/l)</td>
<td>S</td>
<td>141.2 ±0.3</td>
<td>140.5 ±0.3</td>
<td></td>
<td>142.2 ±0.4</td>
<td>142.5 ±0.5</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>140.6 ±0.5</td>
<td>139.8 ±0.9</td>
<td></td>
<td>141.6 ±0.8</td>
<td>142.2 ±0.9</td>
</tr>
<tr>
<td>Serum potassium (meq/l)</td>
<td>S</td>
<td>4.05 ±0.04</td>
<td>4.06 ±0.04</td>
<td></td>
<td>4.84 ±0.05</td>
<td>4.23 ±0.11</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>4.10 ±0.06</td>
<td>4.12 ±0.08</td>
<td></td>
<td>4.92 ±0.10</td>
<td>4.22 ±0.13</td>
</tr>
<tr>
<td>Serum bicarbonate (meq/l)</td>
<td>S</td>
<td>25.8 ±0.5</td>
<td>25.9 ±0.6</td>
<td></td>
<td>22.3 ±0.7</td>
<td>14.2 ±0.9</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>25.7 ±0.5</td>
<td>26.0 ±0.5</td>
<td></td>
<td>22.0 ±0.5</td>
<td>12.3 ±0.9</td>
</tr>
<tr>
<td>Plasma lactate (mg/dl)</td>
<td>S</td>
<td>9.1 ±0.8</td>
<td>7.8 ±0.6</td>
<td>7.5 ±0.7</td>
<td>11.4 ±1.1</td>
<td>31.2 ±3.5</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>9.2 ±0.8</td>
<td>7.3 ±0.8</td>
<td>7.2 ±0.8</td>
<td>10.8 ±1.1</td>
<td>32.2 ±6.6</td>
</tr>
<tr>
<td>Plasma glucose (mg/dl)</td>
<td>S</td>
<td>89 ±2</td>
<td>91 ±3</td>
<td>95 ±2</td>
<td>95 ±2</td>
<td>93 ±2</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>89 ±2</td>
<td>90 ±1</td>
<td>96 ±2</td>
<td>94 ±2</td>
<td>93 ±2</td>
</tr>
</tbody>
</table>

Values are arithmetic means ± SE. S = saline; N = naloxone.
tone of the pituitary-adrenocortical axis, which prevails at rest and can be unmasked by naloxone, disappeared during exhaustive graded exercise of short duration by subjects in the sitting position. It is not yet known whether this observation also applies to other types of exercise, for instance more prolonged exercise, which would yield a greater increase in plasma cortisol than that induced in the present study.

Since plasma norepinephrine levels followed a similar pattern on both experimental days, the present study suggests that the noradrenergic activation induced by physical effort is not modulated by endogenous opiates. Similarly, the exercise-induced activation of carbohydrate metabolism and of glucose utilization do not seem to be influenced by endogenous opiate-mediated mechanisms, since plasma insulin, glucose, and lactate levels remained similar throughout the two tests. The brisk rise in plasma insulin, which occurred at the end of peak exercise, followed the concurrent overshoot of plasma glucose, when suddenly energy demand decreased. Finally, our findings on growth hormone are in agreement with those of Mayer et al., but at variance with those of other researchers, who reported that naloxone blunted the maximum incremental response of growth hormone to exercise in normal subjects as well as in athletes.

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