# Caffeine Increases Exercise Performance, Maximal Oxygen Uptake, and Oxygen Deficit in Elite Male Endurance Athletes

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**ABSTRACT**

STADHEIM, H. K., T. STENSRUD, S. BRAGE, and J. JENSEN. Caffeine Increases Exercise Performance, Maximal Oxygen Uptake, and Oxygen Deficit in Elite Male Endurance Athletes. *Med. Sci. Sports Exerc.*, Vol. 53, No. 11, pp. 2264–2273, 2021. Caffeine increases endurance performance, but the physiological mechanisms improving high-intensity endurance capacity are not well characterized. **Purpose:** The aims of the present study were to test the hypothesis that caffeine increases maximal oxygen uptake ($\dot{V}O_{2max}$) and to characterize the physiological mechanisms underpinning improved high-intensity endurance capacity. **Methods:** Twenty-three elite endurance-trained male athletes were tested twice with and twice without caffeine (four tests) in a randomized, double-blinded, and placebo-controlled study with crossover design. Caffeine (4.5 mg·kg$^{-1}$) or placebo was consumed 45 min before standardized warm-up. Time to exhaustion during an incremental test (running 10.5° incline, start speed 10.0 km·h$^{-1}$, and 0.5 km·h$^{-1}$ increase in speed every 30 s) determined performance. Oxygen uptake was measured continuously to determine $\dot{V}O_{2max}$ and $O_2$ deficit was calculated. **Results:** Caffeine increased time to exhaustion from 355 ± 41 to 375 ± 41 s (Δ19.4 ± 16.5 s; $P < 0.001$). Importantly, caffeine increased $\dot{V}O_{2max}$ from 75.8 ± 5.6 to 76.7 ± 6.0 mL·kg$^{-1}$·min$^{-1}$ (Δ 0.9 ± 1.7 mL·kg$^{-1}$·min$^{-1}$; $P < 0.003$). Caffeine increased maximal heart rate ($HR_{peak}$) and ventilation ($VE_{peak}$). Caffeine increased $O_2$ deficit from 63.1 ± 18.2 to 69.5 ± 17.5 mL·kg$^{-1}$ ($P < 0.02$) and blood lactate compared with placebo. The increase in time to exhaustion after caffeine ingestion was reduced to 11.7 s after adjustment for the increase in $\dot{V}O_{2max}$. Caffeine did not significantly increase $\dot{V}O_{2max}$ after adjustment for $VE_{peak}$ and $HR_{peak}$. Adjustment for $O_2$ deficit and lactate explained 6.2 s of the caffeine-induced increase in time to exhaustion. The increase in $\dot{V}O_{2max}$, VE, HR, $O_2$ deficit, and lactate explained 63% of the increased performance after caffeine intake. **Conclusion:** Caffeine increased $\dot{V}O_{2max}$ in elite athletes, which contributed to improvement in high-intensity endurance performance. Increases in $O_2$ deficit and lactate also contributed to the caffeine-induced improvement in endurance performance. **Key Words:** EXERCISE PERFORMANCE, OXYGEN CONSUMPTION, HEART RATE, OXYGEN DEFICIT AND LACTATE

Caffeine ingestion improves endurance performance of both short and longer duration (1–5), and whether the performance is measured as time to exhaustion (1,6) or time trial (2,7,8). Importantly, caffeine reduces RPE at standard loads (9,10). Caffeine also increases anaerobic capacity and power (11,12), and lactate accumulation is higher after maximal effort exercise such as during time trials or time-to-exhaustion exercise (2,4,9,13).

The higher performance at time trials after caffeine intake requires higher power production and is associated with higher heart rate (HR) and ventilation (VE) (2–4,9,14). The higher workload after caffeine ingestion also elevates cardiac output (Qc) and increases oxygen uptake (8,9,13,15–18). It seems likely that caffeine improves performance, at least partly, via inhibition of adenosine receptors (4,19). However, adenosine receptors are expressed in most tissues including brain, heart, muscles, blood vessels, and lungs (20). Therefore, caffeine-induced inhibition of adenosine receptors can theoretically affect several physiological mechanisms contributing to improved endurance performance.

Maximal oxygen uptake ($\dot{V}O_{2max}$) represents the integrated capacity of the pulmonary, cardiovascular, and muscle systems to take up, transport, and use oxygen (21–23), and $\dot{V}O_{2max}$ is a major determinant of endurance capacity. Although test protocols for reaching $\dot{V}O_{2max}$ have been a topic of controversy since introduced in the 1920s (24,25), there is broad agreement that $\dot{V}O_{2max}$ determines endurance capacity. It is generally accepted that $\dot{V}O_{2max}$ is reached during an incremental protocol of 4–8 min duration after warm-up (23,26–29). Importantly, the same protocol can also be used to test performance and measure maximal ventilation ($VE_{peak}$), maximal heart rate ($HR_{peak}$), and $O_2$ deficit (23).

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Maximal oxygen uptake seems under most circumstances to be limited by the capacity to transport oxygen to the working muscles (21,24,30). At sea level, Qc and blood volume (or total hemoglobin mass) restrict $\dot{V}O_{2max}$ in most people (30). Indirectly, this is also supported by the fact that elite endurance athletes have high Qc and total hemoglobin mass (30–32). However, there are indications that arterial $O_2$ desaturation occurs in elite athletes during maximal aerobic exercise supporting a pulmonary limitation of maximal oxygen uptake (21,33–37). In support of this idea, it has been shown that breathing $O_2$ enriched air (26% vs 21% $O_2$), prevented $O_2$ desaturation, and increased $\dot{V}O_{2max}$ in highly endurance-trained athletes (36). Caffeine increases $VE_{max}$ and HR (17), which raises the possibility that caffeine may also increase maximal oxygen uptake in elite athletes.

Recently, we observed that professional cross-country skiers obtained higher maximal oxygen uptake during a 10-min double-poling time trial after intake of caffeine compared with maximal oxygen uptake during an incremental test without caffeine intake (9). The higher maximal oxygen uptake after caffeine ingestion was associated with both higher $VE_{max}$ and $HR_{max}$ (9). However, caffeine is not believed to increase maximal oxygen uptake (3,17). Furthermore, maximal oxygen uptake during double poling was found to be ~10% lower than during running (9). Therefore, it remains unknown whether caffeine increases maximal oxygen uptake.

The present study was designed to test the hypothesis that caffeine increases $\dot{V}O_{2max}$ in elite endurance athletes during running. The incremental protocol used to determine maximal oxygen uptake was also used to assess time to exhaustion (performance). $VE_{peak}$, $HR_{peak}$, $O_2$ deficit, and blood lactate, in addition to $\dot{V}O_{2max}$, were determined to assess their influence over any observed caffeine-induced improvement in endurance performance.

## MATERIALS AND METHODS

**Subjects.** Twenty-three healthy male endurance-trained athletes (cross-country skiing, running, and triathlon) gave their written consent to participate in the study after being informed of the purposes of the study and risks involved. The study was reviewed by the Regional Ethics Commit (REK sør-øst B; 2011/2554), concluding that approval from REK was not required to perform the study as described. The study was conducted according to the Declaration of Helsinki. Physical characteristics (mean ± SD) of the participants were as follows: age, 24.0 ± 1.0 yr; height, 182.1 ± 1.3 cm; weight, 73.0 ± 1.6 kg; and $\dot{V}O_{2max}$ running, 75.9 ± 5.8 mL·kg$^{-1}$·min$^{-1}$ at the pretest. Inclusion criteria were that all subjects were male, with a $\dot{V}O_{2max}$ above 65 mL·kg$^{-1}$·min$^{-1}$, and training competitively to qualify for national or international endurance competitions the upcoming season.

**Experimental procedures.** The study was conducted using a randomized, double-blinded, placebo-controlled crossover design. Before the main $\dot{V}O_{2max}$ performance testing started, each participant performed a pretest for familiarization with the testing procedure and to verify that all subjects had $\dot{V}O_{2max}$ above 65 mL·kg$^{-1}$·min$^{-1}$. A schematic overview of the study is shown in Figure 1. The study had one dropout because of illness.

**Pretest.** During the pretest, all subjects performed a standardized incremental treadmill test consisting of four workloads at 7, 8, 9, and 10 km·h$^{-1}$ with each lasting 5 min. All workloads were performed with 10.5° uphill incline on the treadmill (Woodway, Weil am Rein, Germany), and a 1-min break was given between each workload. Oxygen uptake at the four workloads were then used to estimate the individual oxygen cost for calculation of $O_2$ deficit during the $\dot{V}O_{2max}$ performance tests as previously described by Medbø et al. (38). Linear regression was also used to calculate individual speeds equal to 55%, 60%, 65%, and 70% of $\dot{V}O_{2max}$ performed as a standardized warm-up (incremental test) before each main $\dot{V}O_{2max}$ performance test. When the standardized warm-up was finished, all subjects walked 5 min at 5 km·h$^{-1}$, before starting the pre-$\dot{V}O_{2max}$ test. Starting velocity during all testing was 10 km·h$^{-1}$ with an uphill incline of 10.5° on the treadmill. The $\dot{V}O_{2max}$ performance tests was performed as an incremental test

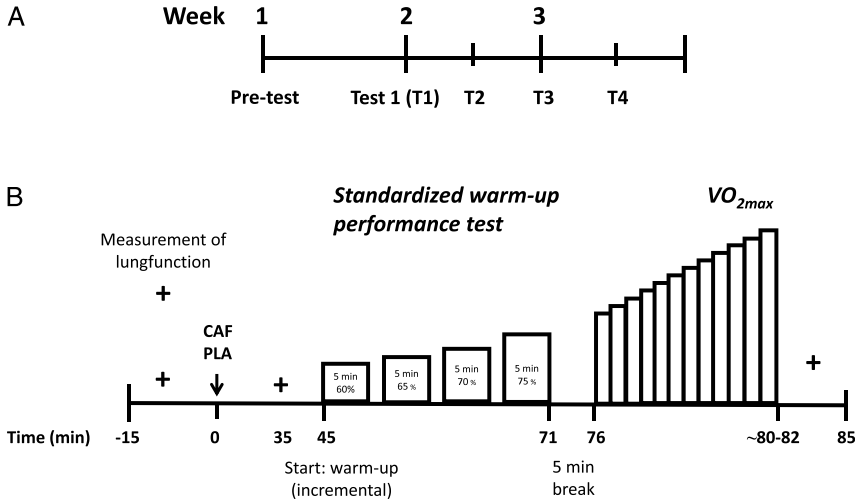


**FIGURE 1—Experimental design. A, Top line shows pretests and main testing during the 3 wk used to complete the $\dot{V}O_{2max}$ test for one subject. B, The bottom figure shows the test procedure for all $\dot{V}O_{2max}$ performance tests. Before the $\dot{V}O_{2max}$ test, subjects performed a standardized warm-up (incremental test) consisting of four intensities all lasting 5 min.**

where velocity was increased by 0.5 $km \cdot h^{-1}$ every 30 s until subjects were unable to maintain the speed and stepped/jumped off the treadmill. The highest HR and VE during the test were defined as $HR_{peak}$ and $VE_{peak}$. The criteria for having reached $\dot{V}O_{2max}$ during all testing were as follows: 1) voluntary exhaustion; 2) oxygen consumption plateaued, meaning $\dot{V}O_2$ increased less than 1 $mL \cdot kg^{-1} \cdot min^{-1}$ when there were consecutive increases in treadmill speed of 0.5 $km \cdot h^{-1}$; 3) RER > 1.10; and 4) blood lactate >7.0 mM. The $\dot{V}O_{2max}$ was calculated as the average of the two highest 30-s measurements.

**$\dot{V}O_{2max}$ performance tests.** To test the effect of caffeine on $\dot{V}O_{2max}$, each subject completed four tests over a 2-wk period. During both weeks, one test was performed with caffeine and the other with placebo in a randomized order. Before all main tests, resting HR and lung function (described below) were measured at arrival and 30 min after consuming either placebo or caffeine. After finishing lung function testing, subjects were given a 10-min break before starting the standardized warm-up. The warm-up consisted of four workloads (55%, 60%, 65%, and 70% of $\dot{V}O_{2max}$) each lasting 5 min, with a 1-min break in between when blood glucose and lactate were measured. All workloads of the warm-up were performed with a 10.5° uphill incline on the treadmill (Woodway). During each workload HR, $\dot{V}O_2$ and RER were measured as means between 3 and 4.5 min of each workload. Subjective RPE was evaluated according to the Borg scale (6 to 20) (39). After the warm-up, a 5-min break was used for blood sampling (presample) for determining lactate and glucose, recording HR, and providing final instructions to the subjects. The goal for each subject was to run for as long as possible during each $\dot{V}O_{2max}$ performance test. Performance was measured as time to exhaustion. Participants did not receive information regarding time, velocity, or physiological measurements during the tests. The criteria for reaching $\dot{V}O_{2max}$ was as described above for the pretest. Encouragement was given during all tests from the test leader, who was blinded to treatment to eliminate any bias. Maximal oxygen uptake was measured in milliliters per minute. Elite athletes are normally weight stable, and therefore the same weight was used at the four tests for calculation of $\dot{V}O_{2max}$ in milliliters per kilogram per minute. After finishing the $\dot{V}O_{2max}$ performance tests, the subjects were given a 5-min break before taking postexercise measurements of lung function and filling out questionnaires.

**Measurement and calculation of $O_2$ deficit.** During the standardized incremental tests, $\dot{V}O_2$ was measured between 2.5 and 4.5 min of each 5-min work period, and the mean was determined as a subject's oxygen cost for the velocity. Oxygen uptake at the four velocities tested (7, 8, 9, and 10 $km \cdot h^{-1}$) during the submaximal exercise was used to construct a linear regression estimate of oxygen cost for the different running velocities used during the $\dot{V}O_{2max}$ performance tests as previously described by Medbø et al. (38). The collection of expired air started 15 s before starting the $\dot{V}O_{2max}$ performance tests and was continued until subjects reached task failure (when they stepped off the treadmill). The difference in estimated oxygen cost and measured oxygen uptake was then calculated as the subjects' $O_2$ deficit. In the present study, $O_2$ deficit was not adjusted for the contribution of the body's oxygen stores to the energy supply.

**Measurement of $\dot{V}O_2$ and VE.** Oxygen consumption and RER were measured with an Oxycon Pro metabolic system (Jaeger, Hochberg, Germany). Before each test, the Oxygen Pro was calibrated with a gas mixture composed of $O_2$ and $CO_2$ (14.93% $O_2$ and 5.99% $CO_2$) and normal air (20.90% $O_2$ and 0.04% $CO_2$). Volume was calibrated manually using a pump containing 3 L of volume (Calibration Syringe, Series 5530; Hans Rudolph Inc., Kansas City, MO). During all testing, expired air was collected using a mouth V2-mask (Hans Rudolph Inc.) in combination with a nose clip and directed into a mixing chamber (Oxycon Pro) and analyzed with a turbine (Triple V volume transducer). Both the hose and the V2-mask were tested for leakage before each individual test. HR was measured using an HR monitor (Polar RS 800, Kempele, Finland), where the error of measurement as stated by the company is ±1%.

**Lung function.** Spirometry was measured by maximum expiratory flow volume loops according to guidelines from the European Respiratory Society (40) and recorded as forced expiratory volume in the first second ($FEV_1$), forced vital capacity (FVC), and forced expiratory flow in 50% of FVC ($FEF_{50}$). Lung function measurements were performed using a MasterScreen Pneumo Jaeger® (Würzburg, Germany), and reference values used are according to Quanjer et al. (41).

**Fractional exhaled nitric oxide.** Fractional exhaled nitric oxide ($FE_{NO}$) was measured by the single breath online technique according to American Thoracic Society/European Respiratory Society guidelines (40). The subject was in a seated position and instructed to breathe quietly. To avoid potential contamination from ambient NO, the subjects inhaled NO-free air close to total lung capacity, immediately followed by a full exhalation for at least 6 s at a constant flow of 50 $mL \cdot s^{-1}$. The constant flow rate was maintained with the aid of a visual feedback system. The expiratory pressure was kept between 5 and 20 mm Hg to close the soft palate and to eliminate nasal NO. $FE_{NO}$ measurements were assessed before pulmonary function tests and were recorded as a mean value from three successive reproducible plateaus. A chemiluminescence analyzer, EcoMedics CLD 88 Exhalyzer® (Eco Medics AG, Duerten, Switzerland) (measurement range of 0.1–5000 parts per billion, was used and calibrated daily with a certified concentration of NO.

**Pretesting information.** All subjects were informed to only perform light training for the 48 h preceding each $\dot{V}O_{2max}$ performance test. To minimize variation in preexercise glycogen stores, diet and exercise diaries were used to standardize food intake and training for each subject. Subjects were asked to prepare for the tests as they prepared for competitions. They were instructed to follow the same training and diet regime before each test and to refrain from caffeine the last 24 h before each test day. Seven out of the 23 subjects in the study had a high intake of caffeine products on a daily basis (>150 mg). On each of the four main test days, subjects arrived at the

laboratory at the same time (±15 min) of the day for each of their tests. The first two tests were performed with a washout period of 3 d between them. Before test three, a washout period of 4 d was imposed, and subjects performed test three and four the following week on the same weekdays as tests 1 and 2.

**Blood analyses.** Capillary blood samples for measurements of glucose and lactate were taken from the fingertip after skin puncture using a Saft-T-Pro Plus (Accu-Check, Mannheim, Germany). For measurement of blood lactate, blood samples were collected into a 50-μL capillary tube, and 20 μL was pipetted into the YSI 1500 SPORT analyzer (Yellow Springs Instruments Life Sciences, Yellow Springs, OH). The analyzer was calibrated with a 5.0-mM lactate stock solution before each test. Values between 4.95 and 5.05 mM were accepted. Capillary blood glucose was measured with a HemoCue Glucose 201+ analyzer (HemoCue Glucose 201+, Ängelholm, Sweden) as previously described (42)

**Caffeine and placebo intake.** Caffeine (Coffeinum; Oslo Apotekerproduksjon, Oslo, Norway) was dissolved in a cordial concentrate (Fun Light) at 3 $mg \cdot mL^{-1}$ concentration at the Norwegian School of Sports Sciences. Ingestion of caffeine (4.5 $mg \cdot kg^{-1}$) or placebo (Fun Light without additions; indistinguishable from caffeine) occurred 45 min before the standardized warm-up. Therefore, the $\dot{V}O_{2max}$ performance test started 75 min after caffeine ingestion.

**Questionnaires.** Questionnaires were used to evaluate motivation and "current fitness" using a scale from 1 to 100 (9). Sleep habits were evaluated by asking approximate sleep duration (h) the 24 h before each test. In addition, for each trial, subjects were asked what product they believed they had received 30 min after ingestion and again before leaving the laboratory.

**Statistical analysis.** All data are presented as means ± SD. A two-way repeated-measures ANOVA was used to examine differences in HR, lactate, $\dot{V}O_2$, glucose, and RPE during two submaximal workloads between the two treatments. If treatment differences were observed, a paired *t*-test was used to test differences at workloads. In exploratory analyses, multiple linear regression was used to disentangle if any caffeine effect on performance could be explained by changes in $\dot{V}O_{2max}$, $HR_{max}$, $VE_{max}$, $O_2$ deficit, or blood lactate by sequentially adjusting for each of these variables. Similarly, we examined to what extent the caffeine effect on $\dot{V}O_{2max}$ could be explained by $HR_{max}$, $VE_{max}$, $O_2$ deficit, and blood lactate.

## RESULTS

Caffeine improved time-to-voluntary exhaustion (performance) in both testing weeks (Table 1). In the first week, caffeine increased time to exhaustion by 18 s (355 ± 41 vs 373 ± 40 s, $P < 0.001$) compared with placebo, and in the second week by 21 s (355 ± 44 vs 376 ± 45 s, $P < 0.001$). The average effect was 19.4 s (5.45%; $P < 0.001$; Fig. 2A; Table 1). Time to exhaustion was highly reproducible, with no statistical differences between the two placebo trials ($P = 0.78$) or the two caffeine trials ($P = 0.74$). The intraclass correlation coefficient (ICC) values for time to exhaustion were 0.94 and 0.90 in placebo and caffeine trials, respectively.

Caffeine ingestion also increased mean maximal oxygen uptake from 75.8 ± 5.6 to 76.7 ± 6.0 $mL \cdot kg^{-1} \cdot min^{-1}$ (0.9 $mL \cdot kg^{-1} \cdot min^{-1}$; 1.2%; $P < 0.003$) compared with placebo (Table 1; Fig. 2B). The ICC values for $\dot{V}O_{2max}$ were >0.95 for both conditions. The $O_2$ kinetics were similar between caffeine and placebo except when comparing the last minute where higher $\dot{V}O_{2max}$ was reached with caffeine (Fig. 3). The higher $\dot{V}O_{2max}$ after caffeine ingestion contributed to the longer running time during the performance test because statistical adjustment for $\dot{V}O_{2max}$ reduced the caffeine-induced effect on running time from 19.4 s to 15.4 s (21% attenuation).

HR and VE developed similarly during the performance tests with and without caffeine (Fig. 3). However, higher maximal HR and VE values were reached during the last minute of the test after caffeine ingestion compared with placebo. Specifically, $HR_{peak}$ increased from 191 ± 8 to 193 ± 9 bpm ($P < 0.001$), and $VE_{peak}$ increased from 187.8 ± 17.8 to 192.2 ± 15.3 $L \cdot min^{-1}$ ($P < 0.001$) after caffeine ingestion compared with placebo (Table 1). The caffeine-induced increase in $\dot{V}O_{2max}$ was attenuated by 0.7 $mL \cdot kg^{-1} \cdot min^{-1}$ ($P < 0.001$) after adjustment for the increase in $HR_{peak}$. When $\dot{V}O_{2max}$ was

TABLE 1. Exercise response to maximal performance tests after placebo or caffeine consumption.

| | Placebo | Placebo | | Caffeine | | Placebo | Caffeine | | |
|---|---|---|---|---|---|---|---|---|---|
| | Pretest | Test 1 | Test 2 | Test 1 | Test 2 | Mean | Mean | *P* | % Dif |
| Time (s) | 5:59 ± 00:49 | 5:55 ± 0:41 | 5:55 ± 0:44 | 6:13 ± 0:40* | 6:16 ± 0:45* | 5:55 ± 0:42 | 6:15 ± 0:43* | <0.01 | 5.6 |
| $\dot{V}O_{2max}$ ($mL \cdot kg^{-1} \cdot min^{-1}$) | 75.9 ± 6.2 | 76.0 ± 5.9 | 75.7 ± 5.7 | 76.7 ± 6.0* | 76.8 ± 6.4* | 75.8 ± 5.6 | 76.8 ± 6.2* | <0.019 | 1.2 |
| $\dot{V}O_{2max}$ ($mL \cdot min^{-1}$) | 5540 ± 717 | 5551 ± 673 | 5527 ± 667 | 5592 ± 652* | 5607 ± 642* | 5539 ± 674 | 5602 ± 646* | <0.019 | 1.2 |
| $\Sigma O_2$ deficit ($mL \cdot kg^{-1}$) | No data | 64.9 ± 16.6 | 65.3 ± 18.9 | 69.9 ± 20.2 | 71.2 ± 17.8 | 65.1 ± 17.8 | 70.5 ± 19.1* | <0.02 | 8.3 |
| $VE_{peak}$ ($L \cdot min^{-1}$) | 193.8 ± 17.0 | 189.3 ± 18.4 | 185.8 ± 18.3 | 193.2 ± 17.6* | 191.2 ± 14.8* | 187.3 ± 17.8 | 192.0 ± 15.3* | <0.001 | 2.3 |
| $BF_{peak}$ (breaths per minute) | 59 ± 8 | 58 ± 9 | 58 ± 9 | 60 ± 9 | 59 ± 7 | 58 ± 9 | 60 ± 7 | <0.07 | 3.4 |
| RER ($\dot{V}CO_2/\dot{V}O_2$) | 1.10 ± 0.04 | 1.10 ± 0.23 | 1.11 ± 0.22 | 1.11 ± 0.24 | 1.11 ± 0.23 | 1.11 ± 0.04 | 1.11 ± 0.04 | <0.78 | 0.4 |
| $HF_{peak}$ (bpm) | 192 ± 9 | 192 ± 6 | 191 ± 8 | 194 ± 8* | 193 ± 7* | 191 ± 8 | 193 ± 9* | <0.01 | 1.1 |
| HF pre (bpm) | No data | 113 ± 12 | 109 ± 9 | 113 ± 15 | 113 ± 13 | 111 ± 12 | 113 ± 14 | <0.11 | 1.8 |
| Lactate pre (mM) | No data | 0.86 ± 0.28 | 0.79 ± 0.27 | 1.12 ± 0.21* | 1.06 ± 0.33* | 0.82 ± 0.26 | 1.09 ± 0.31* | <0.01 | 32.9 |
| Lactate post (mM) | 8.34 ± 1.33 | 7.90 ± 1.05 | 8.00 ± 1.13 | 8.21 ± 1.14* | 8.65 ± 0.94* | 7.94 ± 1.06 | 8.54 ± 1.02* | <0.01 | 7.0 |
| Glucose pre (mM) | No data | 5.2 ± 0.5 | 5.1 ± 0.4 | 5.3 ± 0.5 | 5.3 ± 0.5 | 5.1 ± 0.4 | 5.3 ± 0.8 | <0.61 | 2.0 |
| Glucose post (mM) | No data | 7.4 ± 0.8 | 7.2 ± 0.9 | 7.8 ± 0.7* | 8.0 ± 0.9* | 7.3 ± 0.9 | 7.9 ± 1.1* | <0.01 | 8.2 |

Values are listed as means ± SD. HF pre, lactate pre and glucose pre were measured before the start of the performance test and 5 min after the incremental test.
*Significantly different from placebo ($P < 0.05$).

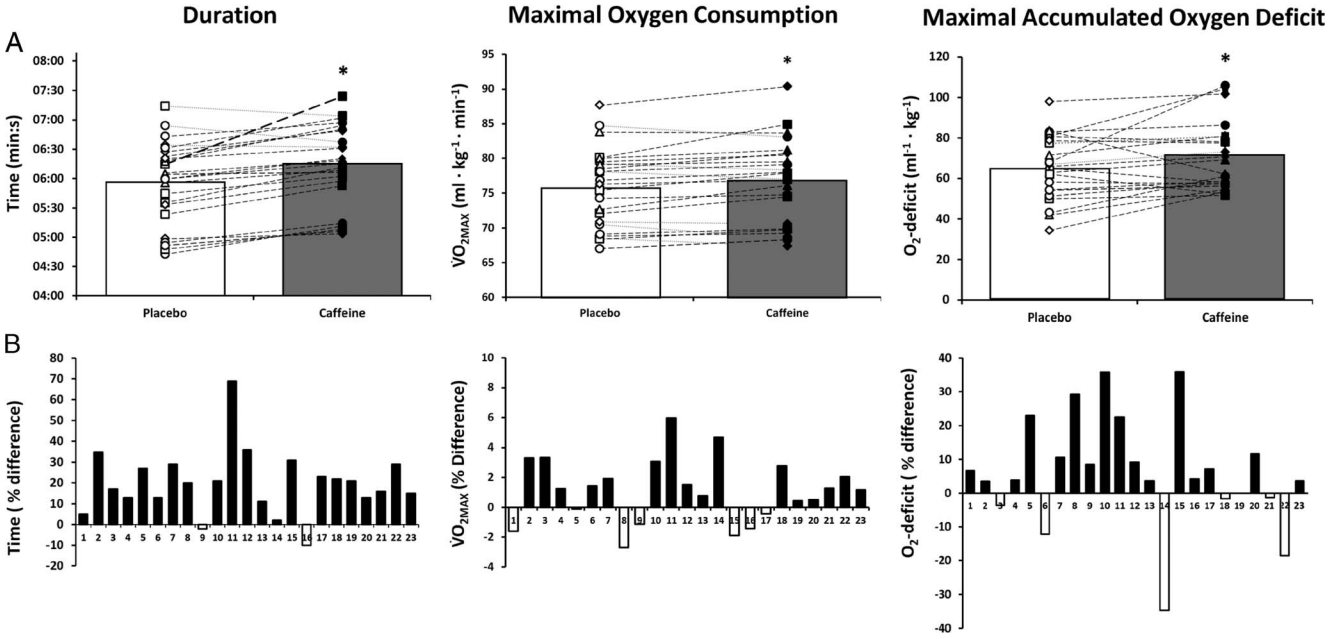


**FIGURE 2—Effect of caffeine on time to exhaustion, maximal oxygen uptake, and oxygen deficit. A, Individual and mean time to exhaustion at the performance test. Duration, $\dot{V}O_{2max}$, and $O_2$ deficit obtained during the $\dot{V}O_{2max}$ performance tests after placebo (*open symbols*) or caffeine (*filled symbols*). B, Percent change in running duration, $\dot{V}O_{2max}$, and $O_2$ deficit after caffeine consumption compared with placebo for each subject. Values are listed as means ± SD. *Significant different from placebo trials ($P < 0.05$).**

adjusted for $VE_{peak}$, the effect of caffeine on $\dot{V}O_{2max}$ decreased by about 50% and was no longer significant ($P = 0.11$). Despite a higher $VE_{peak}$ after caffeine ingestion, breathing frequency (BF) was not significantly elevated when $\dot{V}O_{2max}$ was achieved (60 ± 7 vs 59 ± 9 breaths per minute; Table 1). When running duration was adjusted for $\dot{V}O_{2max}$, $VE_{peak}$, and $HR_{peak}$, there was still 11.7 s ($P < 0.001$) an improvement in time to exhaustion after caffeine ingestion (40% attenuation).

The accumulated oxygen deficit during the performance test increased from 63.1 ± 18.2 mL·kg$^{-1}$ in placebo to 69.5 ± 17.5 mL·kg$^{-1}$ with caffeine ingestion ($P < 0.02$; Table 1; Fig. 2C). The ICC values for measurements of $O_2$ deficit were 0.61 and 0.64 for placebo and caffeine trials, respectively. Blood lactate values were higher with caffeine compared with placebo (8.54 ± 1.02 vs 7.94 mM ± 1.06; $P < 0.001$; Table 1). Calculations showed that the anaerobic processes ($O_2$ deficit) covered 14.7% ± 3.1% and 15.0% ± 2.7% of total $O_2$ cost in placebo and caffeine trials. When time to exhaustion was adjusted for both $O_2$ deficit and lactate concentration, the effect of caffeine was reduced from 19.4 to 13.2 s ($P < 0.001$). With additional adjustment for $\dot{V}O_{2max}$, the effect of caffeine on time to exhaustion was reduced to 8.0 s (59% attenuation), but still significant ($P < 0.001$). With further adjustment for $VE_{peak}$ and $HR_{peak}$, the caffeine effect on performance was further reduced to 7.1 s (63% attenuation), but remained significant ($P = 0.003$). Plasma glucose levels after the performance tests were higher in caffeine compared with placebo trials (7.9 ± 1.1 vs 7.3 ± 0.9 mM; $P < 0.001$). The highest RER during the performance test was independent of test conditions (Table 1).

During the submaximal incremental testing, repeated-measures ANOVA showed that oxygen uptake, HR, VE, BF, RPE, and blood lactate increased progressively from the first to the last of the four workloads (Table 2). HR and $\dot{V}O_2$ at submaximal loads were similar after placebo and caffeine (treatment effect: $P = 0.077$ for means of the two tests), whereas VE and lactate were higher after caffeine than placebo ingestion ($P < 0.001$), but no significant interaction was observed. RPE was lower after caffeine ingestion compared with placebo (treatment effect: $P < 0.029$; Table 2) with *post hoc* analyses showing lower RPE at the two highest workloads after caffeine.

The lung function measurements $FEV_1$, FVC, $FEF_{50}$, and $FE_{NO}$ performed at arrival, 30 min after placebo or caffeine ingestion, and post-$\dot{V}O_{2max}$ performance tests were not different between treatments (Table 3).

Based on the questionnaire, there were no differences between caffeine and placebo trials regarding self-reported "current fitness" and motivation. Before the performance tests, subjects reported motivation of 77 ± 14, 79 ± 16 (placebo), and 76 ± 14, 76 ± 14 (caffeine) before tests (75 = high/very high), and 79 ± 17, 82 ± 12 (placebo), and 79 ± 14, 81 ± 14 (caffeine) after the performance tests. Ratings pretest "current fitness" were 62 ± 11, 62 ± 13 (PLA), and 61 ± 13, 63 ± 12 (caffeine) (65 = high) before, and 62 ± 11, 65 ± 14 (placebo), and 67 ± 15, 79 ± 14 (caffeine) after the performance tests. Furthermore, the subjects were unable to sense which product they received during the different trials, with 50% answering "uncertain" to the question. Of the subjects who answered that they thought they knew the treatment (caffeine or placebo), about 50% guessed wrong both pre- and posttesting independent of treatment ingestion. Hours of sleep, training, intake of food, and liquid intake before tests also did not differ, confirming that

subjects had followed instructions regarding training, food, liquid, and caffeine consumption for the 48 h before each test.

## DISCUSSION

We confirmed the primary hypothesis that caffeine increases maximal oxygen uptake in elite endurance athletes. Caffeine also increased $HR_{peak}$ and $VE_{max}$, and the exploratory statistical analyses showed that both parameters contributed to the increase in $\dot{V}O_{2max}$. The increase in $\dot{V}O_{2max}$ was small (1.2%) but explained about 4 s (~20%) of the improved performance (run time to exhaustion). Accumulated $O_2$ deficit and lactate during the performance test was also higher after intake of caffeine. Overall, these mechanisms accounted for 63% of the caffeine-mediated improvement in performance.

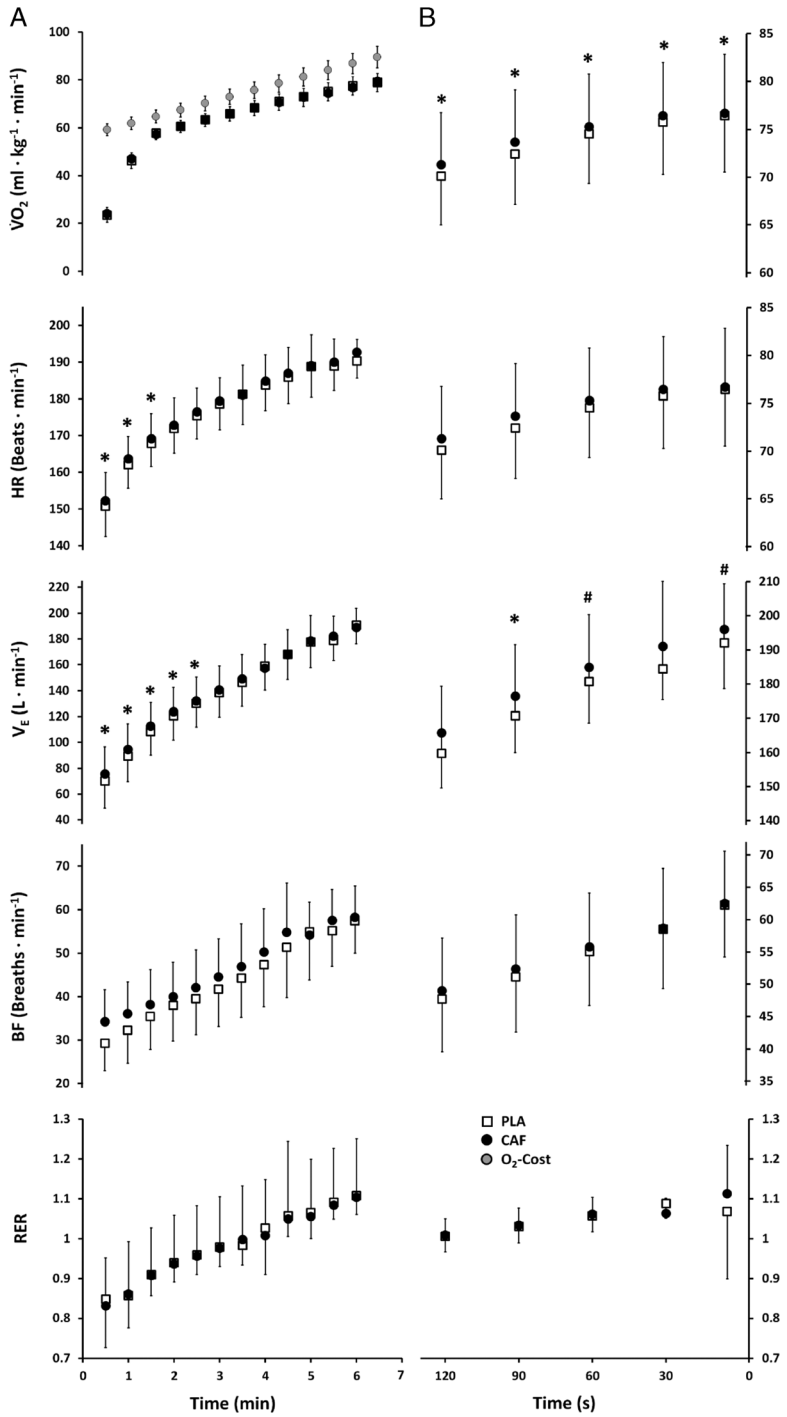


**FIGURE 3—A, The 30-s measurements for $\dot{V}O_2$, HR, VE, BF, and RER during placebo (*open symbols*) and caffeine (*filled symbols*) $\dot{V}O_{2max}$ performance tests. B, The last 120 s for each individual shown as mean for the group for $\dot{V}O_2$, HR, VE, BF, and RER. Values are listed as means ± SD. *Significant different from placebo trials ($P < 0.05$).**

TABLE 2. Exercise response during submaximal incremental testing (standardized warm-up) after placebo or caffeine consumption.

| | Workload Percent of $\dot{V}O_{2max}$ | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 55% | | 60% | | 65% | | 70% | |
| | Placebo | Caffeine | Placebo | Caffeine | Placebo | Caffeine | Placebo | Caffeine |
| $\dot{V}O_2$ (mL·kg$^{-1}$·min$^{-1}$) | 40.5 ± 3.4 | 41.0 ± 3.3 | 44.8 ± 3.7 | 45.1 ± 3.8 | 49.3 ± 4.2 | 49.6 ± 4.1 | 53.5 ± 4.7 | 53.7 ± 4.2 |
| HR (bpm) | 131 ± 8 | 129 ± 9 | 141 ± 9 | 140 ± 9 | 151 ± 9 | 151 ± 9 | 160 ± 9 | 160 ± 9 |
| Lactate (mM)** | 1.00 ± 0.20 | 1.20 ± 0.25* | 0.91 ± 0.35 | 1.1 ± 0.30* | 1.06 ± 0.40 | 1.28 ± 0.40* | 1.43 ± 0.43 | 1.67 ± 0.46* |
| Borg (6–20)** | 8.8 ± 1.2 | 8.6 ± 1.3 | 10.2 ± 1.1 | 10.0 ± 1.3 | 11.8 ± 1.1 | 11.5 ± 1.0* | 13.3 ± 1.1 | 12.9 ± 1.1* |
| $V_E$ (L·min$^{-1}$)** | 70.4 ± 3.2 | 74.3 ± 3.5* | 79.8 ± 3.3 | 84.0 ± 3.5* | 89.2 ± 3.6 | 92.9 ± 3.9* | 98.6 ± 4.0 | 101.9 ± 4.0* |
| BF (breaths per minute) | 28 ± 6 | 28 ± 6 | 32 ± 7 | 31 ± 6 | 34 ± 7 | 34 ± 7 | 36 ± 8 | 36 ± 8 |

Values are listed as means ± SD.
*Significant difference between placebo and caffeine ($P < 0.05$).
**Treatment effect of caffeine ($P < 0.05$).





Recently, we observed that caffeine intake induced higher oxygen uptake during a 10-min time trial compared with maximal oxygen uptake during an incremental test without caffeine in professional cross-country skiers (9). The present study was designed to test the hypothesis that caffeine increases $\dot{V}O_{2max}$ in elite endurance athletes during running. The finding that caffeine increased $\dot{V}O_{2max}$ from 75.8 ± 5.6 to 76.7 ± 6.0 mL·kg$^{-1}$·min$^{-1}$ (1.2%) confirms our hypothesis. Caffeine is normally not believed to increase maximal oxygen uptake (3,17,43), and the small increase in $\dot{V}O_{2max}$ observed in this randomized placebo-controlled crossover study may therefore be questioned despite it being highly significant ($P$ value of 0.003). However, several facts support that the increase is real. First, the 23 participants were tested twice with and twice without caffeine intake during two consecutive weeks under standardized training and diet days before all tests, and the effect was reproducible. Second, the participants were elite endurance athletes of national and international level (five participants are medalists in Olympic or U23 World Championship) accustomed to intense efforts, and the ICC for $\dot{V}O_{2max}$ was >0.95 with and without caffeine. Third, more than 20% of the increase in running performance after caffeine intake was explained by the increase in $VO_{2mas}$ according to our statistical analyses. Fourth, more than 50% of the increase in $\dot{V}O_{2max}$ could be explained by likely physiological mechanisms. Finally, the finding is also supported by our previous study showing higher maximal oxygen uptake during a 10-min double poling time trial after intake of caffeine compared with $\dot{V}O_{2max}$ during an incremental test without caffeine (9), and recent studies reporting that caffeine increases $\dot{V}O_{2max}$ in moderately trained males (44) and mice (19).

The classical view is that $\dot{V}O_{2max}$ is determined by the delivery of oxygen to the active muscles and, therefore, maximal Qc (HR × stroke volume) during running in healthy subjects (21,24). In agreement with other studies, $HR_{peak}$ was 2 bpm higher during the caffeine trials (2), which would increase Qc, assuming stroke volume was maintained (24). Statistical analyses suggest that the increased $HR_{peak}$ explained 0.2 mL·kg$^{-1}$·min$^{-1}$ (22%) of the caffeine-induced increase in $\dot{V}O_{2max}$. The heart expresses all four isoform of adenosine receptors (45), which are blocked by caffeine, and adenosine is used to treat supraventricular tachycardia (46). However, the role of adenosine receptors on HR is not completely clear (47). In the present study, caffeine did not influence HR at submaximal loads as expected (2,10). Intake of caffeine normally increases plasma concentrations of adrenaline and noradrenaline during maximal exercise (2,9), and stronger adrenergic stimulation may explain the higher HR after caffeine intake.

Elite endurance athletes often develop hypoxemia during maximal exercise (37,48,49). In the present study, several participants had $\dot{V}O_{2max}$ higher than 80 mL·kg$^{-1}$·min$^{-1}$, and subjects with higher $\dot{V}O_{2max}$ have a greater oxygen desaturation upon reaching $\dot{V}O_{2max}$ than less trained subjects (49). Several studies have found that reduced $O_2$ saturation can limit maximal oxygen consumption for highly trained athletes because of arterial desaturation (33–35,37,48). The limitation of $O_2$ saturation in elite endurance athletes is also supported by the fact that mild hyperoxia (26% $O_2$) increases $\dot{V}O_{2max}$ in highly endurance-trained subjects but not in moderately trained subjects (36). The higher $VE_{peak}$ after caffeine, with similar BF as the placebo trial, improves conditions for $O_2$ saturation. However, caffeine has previously been reported to increase $VE_{peak}$ during maximal exercise, without improving $\dot{V}O_{2max}$ (34,48). The increased VE may also increase the expiration of $CO_2$, and we have previously found that plasma bicarbonate at exhaustion is lower after intake of caffeine compared with placebo (18). However, the higher VE could also be driven by higher central command.

TABLE 3. Lung function at arrival, 30 min after caffeine/placebo ingestion, and after $\dot{V}O_{2max}$ performance tests.

| | Arrival | | | 30 min after Placebo/Caffeine Ingestion | | | Post-$\dot{V}O_{2max}$ Performance Test | | |
|---|---|---|---|---|---|---|---|---|---|
| | Placebo | Caffeine | $P$ | Placebo | Caffeine | $P$ | Placebo | Caffeine | $P$ |
| $FE_{NO}$ (ppb) | 27.9 ± 25.1 | 26.0 ± 27.1 | 0.222 | 29.0 ± 26.9 | 27.1 ± 30.1 | 0.449 | 21.0 ± 17.8 | 20.4 ± 20.1 | 0.557 |
| $FEV_1$ (L) | 5.00 ± 0.54 | 5.04 ± 0.58 | 0.191 | 4.98 ± 0.60 | 5.04 ± 0.66 | 0.146 | 5.15 ± 0.53 | 5.18 ± 0.69 | 0.311 |
| FVC (L) | 6.05 ± 0.64 | 6.06 ± 0.69 | 0.732 | 6.20 ± 0.83 | 6.05 ± 0.67 | 0.127 | 6.05 ± 0.67 | 6.03 ± 0.73 | 0.68 |
| $FEF_{50}$ (L·s$^{-1}$) | 5.94 ± 1.39 | 5.90 ± 1.38 | 0.665 | 5.94 ± 1.42 | 5.88 ± 1.34 | 0.448 | 6.26 ± 1.46 | 6.34 ± 1.50 | 0.187 |

Values are listed as means ± SD.
*Significantly different from sea level ($P < 0.05$).
ppb, part per billion.

Bronchioles express adenosine receptors, and adenosine contributes to physiological and pathophysiological regulation of bronchoconstriction (50,51). In the present study, caffeine increased $VE_{peak}$ as well as VE during submaximal intensities. The caffeine-induced increase in VE at submaximal intensities is well documented (2,10) and could result from bronchodilation. In the present study, however, caffeine did not improve $FEV_1$, FVC, or expiratory flow at 50% of FVC ($FEF_{50}$), although it has been reported that caffeine causes a small increase in $FEV_1$ (52). Interestingly, our statistical analyses supported the notion that the increased VE after intake of caffeine contributed to the higher $\dot{V}O_{2max}$. Adjustment for the higher VE after caffeine intake reduced the caffeine-induced increase in $\dot{V}O_{2max}$ by 50%, and the effect of caffeine on $\dot{V}O_{2max}$ was no longer significant ($P = 0.11$), suggesting VE *per se* is an important pathway by which $\dot{V}O_{2max}$ is increased by caffeine in elite endurance athletes.

The incremental performance test was designed to optimally measure $\dot{V}O_{2max}$ and lasted 355 s (5 min 55 s) during the placebo trial. Caffeine improved running duration by 19.4 s (5.5%) during the performance test in agreement with previous studies (2,7,9). When time to exhaustion was adjusted for caffeine-mediated increase in $\dot{V}O_{2max}$, $VE_{peak}$, and $HR_{peak}$, running duration was reduced from 19.4 to 11.7 s ($P < 0.001$). These data suggest that improved aerobic power explained nearly 40% of the increased performance after intake of caffeine.

The remaining improvements after caffeine compared with placebo might be anaerobic processes because exercise economy is not influenced by caffeine (Table 1). It is well documented that plasma lactate is higher at exhaustion after intake of caffeine (2,9). Although plasma lactate is the by-product from anaerobic glycolysis and an indirect measure of anaerobic work, the higher lactate with caffeine intake supports larger anaerobic contribution. In the present study, $O_2$ deficit was higher in caffeine than in placebo ($69.5 \pm 17.5$ vs $63.1 \pm 18.2$ $mL \cdot kg^{-1}$). The magnitude of $O_2$ deficit agrees with previous studies (38), and anaerobic processes accounted for ~15% of the energy cost during the $\dot{V}O_{2max}$ time-to-exhaustion performance test. Caffeine increases anaerobic work capacity during Wingate tests and tests up to 6–7 min (11,53–55). Performance has also been reported higher after caffeine intake during 4-km cycling time trials, in which anaerobic processes highly contribute (53,55). Doherty (13) reported that caffeine increased maximal accumulated oxygen deficit by 11% in highly trained male athletes when running until exhaustion at ~125% of $\dot{V}O_{2max}$. These results are very comparable with the results in the present study where 10% increase in $O_2$ deficit was observed. Although aerobic energy production contributed to most of the energy requirement in the present study, there is no doubt that accumulated oxygen deficit and lactate were key physiological components in delaying development of fatigue at the end of the incremental test.

The mechanisms by which caffeine increases anaerobic capacity are not clear. It is well documented that caffeine reduces RPE at submaximal load (4,9,10), and a common explanation is that caffeine increases performance simply by reducing pain and discomfort. However, it has been reported that caffeine intake reduces interstitial potassium during high-intensity exercise (56) and improved potassium handling may improve performance (57). This effect of caffeine could be indirectly on muscles or via elevated adrenaline concentration. In the present study, statistical adjustments for $O_2$ deficit and lactate reduced the caffeine-mediated improvement in performance from 19.4 to 13.2 s (~30%; $P < 0.001$). Therefore, these results show that higher $O_2$ deficit and lactate are contributing physiological factors to the improved running duration during the $\dot{V}O_{2max}$ performance test.

Caffeine has well-defined effects at the molecular level, and caffeine is an adenosine receptor antagonist, inhibits phosphodiesterase, inhibits PI-3 kinase, inhibits glycogen phosphorylase a, and stimulates $Ca^{2+}$ release from sarcoplasmic reticulum at high concentrations (20,58,59). Data from our previous studies suggest that plasma caffeine concentration was ~30 μM (9), and this concentration inhibits most adenosine receptors (20). However, this knowledge may be of limited importance for understanding the physiological effects of caffeine on performance as adenosine receptors are expressed broadly throughout the human body. A consistent finding is that caffeine reduces RPE, which will allow higher work capacity. The mechanisms are unclear, but blocking adenosine receptors reduces pain (60,61). The reduced pain sensation may increase effort and performance, which again will drive higher HR. However, caffeine also improves VE (10,33), which will reduce hypoxemia and therefore increase performance.

Caffeine influences a number of tissues and physiological processes, which collectively improves performance. Our data show that caffeine appears to increase both aerobic and anaerobic capacity during the ~6-min time-to-exhaustion test. Statistical analyses with sequential adjustment suggest that the higher aerobic capacity contributed an additional 7 s, whereas anaerobic processes contributed and additional 6 s of the 19.4-s improvement in performance. Interestingly, adjustment for the increases in $\dot{V}O_{2max}$, VE, HR, $O_2$ deficit, and lactate reduced the improvement in performance (running time) to 7 s. Therefore, we are able to explain ~63% of the effect via plausible physiological mechanisms for the caffeine-mediated increase in performance during the ~6-min performance test.

The strength of the present study is that the performance protocol was designed to test maximal oxygen uptake and the tests with and without caffeine were performed twice. It is also a strength that the study was performed in highly endurance-trained subjects accustomed to exhaustive exercise. Another strength is that the effects of caffeine on both aerobic and anaerobic capacities were examined. However, one limitation of the study is that we did not directly measure Qc and $O_2$ saturation in arterial blood because we suggested that these two mechanisms contribute to the performance enhancing effect of caffeine. However, measurements of maximal Qc during maximal exercise are challenging. It would also have been interesting to measure blood levels of $CO_2$ and bicarbonate to investigate if the increased VE reduced $CO_2$. However, the increase in $\dot{V}O_{2max}$ was only 1.2%, which makes it difficult to

determine the mechanisms by which caffeine increases maximal oxygen uptake.

In conclusion, the present study shows for the first time that caffeine increases $\dot{V}O_{2max}$ in elite athletes, which contributed significantly to improving time to exhaustion during a high-intensity performance test. Our data suggest that increased VE and $HR_{peak}$ contribute to the higher $\dot{V}O_{2max}$. Caffeine also increased $O_2$ deficit and lactate at exhaustion, which contributed to improved performance. The present study shows that caffeine improves several physiological mechanisms, which collectively contributes to significant improvement in high-intensity endurance performance.

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## REFERENCES


1. Costill DL, Dalsky GP, Fink WJ. Effects of caffeine ingestion on metabolism and exercise performance. *Med Sci Sports*. 1978;10(3):155–8.
2. Stadheim HK, Kvamme B, Olsen R, Drevon CA, Ivy JL, Jensen J. Caffeine increases performance in cross-country double-poling time trial exercise. *Med Sci Sports Exerc*. 2013;45(11):2175–83.
3. Graham TE. Caffeine and exercise: metabolism, endurance and performance. *Sports Med*. 2001;31(11):785–807.
4. Doherty M, Smith PM. Effects of caffeine ingestion on rating of perceived exertion during and after exercise: a meta-analysis. *Scand J Med Sci Sports*. 2005;15(2):69–78.
5. Bazzucchi I, Felici F, Montini M, Figura F, Sacchetti M. Caffeine improves neuromuscular function during maximal dynamic exercise. *Muscle Nerve*. 2011;43(6):839–44.
6. Graham TE, Spriet LL. Performance and metabolic responses to a high caffeine dose during prolonged exercise. *J Appl Physiol (1985)*. 1991;71(6):2292–8.
7. Bridge CA, Jones MA. The effect of caffeine ingestion on 8 km run performance in a field setting. *J Sports Sci*. 2006;24(4):433–9.
8. Ivy JL, Costill DL, Fink WJ, Lower RW. Influence of caffeine and carbohydrate feedings on endurance performance. *Med Sci Sports*. 1979;11(1):6–11.
9. Stadheim HK, Spencer M, Olsen R, Jensen J. Caffeine and performance over consecutive days of simulated competition. *Med Sci Sports Exerc*. 2014;46(9):1787–96.
10. Glaister M, Gissane C. Caffeine and physiological responses to submaximal exercise: a meta-analysis. *Int J Sports Physiol Perform*. 2018;13(4):402–11.
11. Grgic J. Caffeine ingestion enhances Wingate performance: a meta-analysis. *Eur J Sport Sci*. 2017;18:219–25.
12. Tangen DS, Nielsen SR, Kolnes KJ, Jensen J. Caffeine increases vertical jumping height in young trained males before but not after a maximal effort strength training session. *Journal of Sciences in Sport and Exercise*. 2020;2:145–53.
13. Doherty M. The effects of caffeine on the maximal accumulated oxygen deficit and short-term running performance. *Int J Sport Nutr*. 1998;8(2):95–104.
14. Desbrow B, Biddulph C, Devlin B, Grant GD, Anoopkumar-Dukie S, Leveritt MD. The effects of different doses of caffeine on endurance cycling time trial performance. *J Sports Sci*. 2012;30(2):115–20.
15. Alves MN, Ferrari-Auarek WM, Pinto KM, et al. Effects of caffeine and tryptophan on rectal temperature, metabolism, total exercise time, rate of perceived exertion and heart rate. *Braz J Med Biol Res*. 1995; 28(6):705–9.
16. Olcina GJ, Muñoz D, Timón R, et al. Effect of caffeine on oxidative stress during maximum incremental exercise. *J Sports Sci Med*. 2006; 5(4):621–8.
17. Chapman RF, Stager JM. Caffeine stimulates ventilation in athletes with exercise-induced hypoxemia. *Med Sci Sports Exerc*. 2008; 40(6):1080–6.
18. Stadheim HK, Nossum EM, Olsen R, Spencer M, Jensen J. Caffeine improves performance in double poling during acute exposure to 2,000-m altitude. *J Appl Physiol (1985)*. 2015;119(12):1501–9.
19. Aguiar AS Jr, Speck AE, Canas PM, Cunha RA. Neuronal adenosine A2A receptors signal ergogenic effects of caffeine. *Sci Rep*. 2020;10(1):13414.
20. Fredholm BB, Bättig K, Holmén J, Nehlig A, Zvartau EE. Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. *Pharmacol Rev*. 1999;51(1):83–133.
21. Bassett DR Jr, Howley ET. Limiting factors for maximum oxygen uptake and determinants of endurance performance. *Med Sci Sports Exerc*. 2000;32(1):70–84.
22. Day JR, Rossiter HB, Coats EM, Skasick A, Whipp BJ. The maximally attainable $\dot{V}O_2$ during exercise in humans: the peak vs. maximum issue. *J Appl Physiol (1985)*. 2003;95(5):1901–7.
23. Poole DC, Wilkerson DP, Jones AM. Validity of criteria for establishing maximal $O_2$ uptake during ramp exercise tests. *Eur J Appl Physiol*. 2008;102(4):403–10.
24. Levine BD. $VO_{2max}$: what do we know, and what do we still need to know? *J Physiol*. 2008;586(1):25–34.
25. Noakes TD. Maximal oxygen uptake: "classical" versus "contemporary" viewpoints: a rebuttal. *Med Sci Sports Exerc*. 1998;30(9):1381–98.
26. Lorenz DS, Reiman MP, Lehecka BJ, Naylor A. What performance characteristics determine elite versus nonelite athletes in the same sport? *Sports Health*. 2013;5(6):542–7.
27. McLaughlin JE, Howley ET, Bassett DR Jr, Thompson DL, Fitzhugh EC. Test of the classic model for predicting endurance running performance. *Med Sci Sports Exerc*. 2010;42(5):991–7.
28. Lucía A, Hoyos J, Pérez M, Santalla A, Chicharro JL. Inverse relationship between $VO_{2max}$ and economy/efficiency in world-class cyclists. *Med Sci Sports Exerc*. 2002;34(12):2079–84.
29. di Prampero PE. Factors limiting maximal performance in humans. *Eur J Appl Physiol*. 2003;90(3–4):420–9.
30. Saunders PU, Garvican-Lewis LA, Schmidt WF, Gore CJ. Relationship between changes in haemoglobin mass and maximal oxygen uptake after hypoxic exposure. *Br J Sports Med*. 2013;47(1 Suppl):i26–30.
31. Blomqvist CG, Saltin B. Cardiovascular adaptations to physical training. *Annu Rev Physiol*. 1983;45:169–89.
32. Saltin B, Calbet JA. Point: in health and in a normoxic environment, $\dot{V}O_2$ max is limited primarily by cardiac output and locomotor muscle blood flow. *J Appl Physiol (1985)*. 2006;100(2):744–5.
33. Chapman RF, Mickleborough TD. The effects of caffeine on ventilation and pulmonary function during exercise: an often-overlooked response. *Phys Sportsmed*. 2009;37(4):97–103.
34. Terrados N, Mizuno M, Andersen H. Reduction in maximal oxygen uptake at low altitudes; role of training status and lung function. *Clin Physiol*. 1985;5(3 Suppl):75–9.
35. Dempsey JA, Wagner PD. Exercise-induced arterial hypoxemia. *J Appl Physiol (1985)*. 1999;87(6):1997–2006.
36. Powers SK, Lawler J, Dempsey JA, Dodd S, Landry G. Effects of incomplete pulmonary gas exchange on $\dot{V}O_2$ max. *J Appl Physiol (1985)*. 1989;66(6):2491–5.
37. Nielsen HB. Arterial desaturation during exercise in man: implication for $O_2$ uptake and work capacity. *Scand J Med Sci Sports*. 2003; 13(6):339–58.

38. Medbø JI, Mohn AC, Tabata I, Bahr R, Vaage O, Sejersted OM. Anaerobic capacity determined by maximal accumulated $O_2$ deficit. *J Appl Physiol (1985)*. 1988;64(1):50–60.
39. Borg G. Perceived exertion as an indicator of somatic stress. *Scand J Rehabil Med*. 1970;2:92–8.
40. Miller MR, Hankinson J, Brusasco V, et al, ATS/ERS Task Force. Standardisation of spirometry. *Eur Respir J*. 2005;26(2):319–38.
41. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl*. 1993;16:5–40.
42. Rustad PI, Sailer M, Cumming KT, et al. Intake of protein plus carbohydrate during the first two hours after exhaustive cycling improves performance the following day. *PLoS One*. 2016;11(4):e0153229.
43. Brietzke C, Asano RY, De Russi de Lima F, et al. Caffeine effects on $VO_{2max}$ test outcomes investigated by a placebo perceived-as-caffeine design. *Nutr Health*. 2017;23(4):231–8.
44. Lara B, Ruiz-Moreno C, Salinero JJ, Del CJ. Time course of tolerance to the performance benefits of caffeine. *PLoS One*. 2019; 14(1):e0210275.
45. Headrick JP, Ashton KJ, Rose'meyer RB, Peart JN. Cardiovascular adenosine receptors: expression, actions and interactions. *Pharmacol Ther*. 2013;140(1):92–111.
46. Rankin AC, Brooks R, Ruskin JN, McGovern BA. Adenosine and the treatment of supraventricular tachycardia. *Am J Med*. 1992;92(6): 655–64.
47. Yang JN, Wang Y, Garcia-Roves PM, Bjornholm M, Fredholm BB. Adenosine A(3) receptors regulate heart rate, motor activity and body temperature. *Acta Physiol (Oxf)*. 2010;199(2):221–30.
48. Chapman RF, Emery M, Stager JM. Degree of arterial desaturation in normoxia influences $VO_{2max}$ decline in mild hypoxia. *Med Sci Sports Exerc*. 1999;31(5):658–63.
49. Goodrich JA, Ryan BJ, Byrnes WC. The influence of oxygen saturation on the relationship between hemoglobin mass and $\dot{V}O_2$ max. *Sports Med Int Open*. 2018;2(4):E98–104.
50. Wilson CN, Nadeem A, Spina D, Brown R, Page CP, Mustafa SJ. Adenosine receptors and asthma. *Handb Exp Pharmacol*. 2009;193: 329–62.
51. Calzetta L, Spina D, Cazzola M, et al. Pharmacological characterization of adenosine receptors on isolated human bronchi. *Am J Respir Cell Mol Biol*. 2011;45(6):1222–31.
52. Welsh EJ, Bara A, Barley E, Cates CJ. Caffeine for asthma. *Cochrane Database Syst Rev*. 2010;2010(1):CD001112.
53. Silva-Cavalcante MD, Correia-Oliveira CR, Santos RA, et al. Caffeine increases anaerobic work and restores cycling performance following a protocol designed to lower endogenous carbohydrate availability. *PLoS One*. 2013;8(8):e72025.
54. Glaister M, Muniz-Pumares D, Patterson SD, Foley P, McInnes G. Caffeine supplementation and peak anaerobic power output. *Eur J Sport Sci*. 2015;15(5):400–6.
55. Felippe LC, Ferreira GA, Learsi SK, Boari D, Bertuzzi R, Lima-Silva AE. Caffeine increases both total work performed above critical power and peripheral fatigue during a 4-km cycling time trial. *J Appl Physiol (1985)*. 2018;124(6):1491–501.
56. Mohr M, Nielsen JJ, Bangsbo J. Caffeine intake improves intense intermittent exercise performance and reduces muscle interstitial potassium accumulation. *J Appl Physiol (1985)*. 2011;111(5):1372–9.
57. Hostrup M, Bangsbo J. Limitations in intense exercise performance of athletes—effect of speed endurance training on ion handling and fatigue development. *J Physiol*. 2017;595(9):2897–913.
58. Foukas LC, Daniele N, Ktori C, Anderson KE, Jensen J, Shepherd PR. Direct effects of caffeine and theophylline on p110 delta and other phosphoinositide 3-kinases. Differential effects on lipid kinase and protein kinase activities. *J Biol Chem*. 2002;277(40):37124–30.
59. Kolnes AJ, Ingvaldsen A, Bolling A, et al. Caffeine and theophylline block insulin-stimulated glucose uptake and PKB phosphorylation in rat skeletal muscles. *Acta Physiol (Oxf)*. 2010;200(1):65–74.
60. Sawynok J. Adenosine receptor targets for pain. *Neuroscience*. 2016; 338:1–18.
61. Fried NT, Elliott MB, Oshinsky ML. The role of adenosine signaling in headache: a review. *Brain Sci*. 2017;7(3):30.