OFFICIAL TITLE OF THE STUDY:

"Influence of 6mg/kg of caffeine supplementation on the technical execution of general movement patterns performed by healthy subjects, with and without neuromuscular fatigue: a randomized, double-blind, placebo-controlled, crossover trial".

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1. Background and state of the art

Nowadays, the interest and the use of nutritional supplements are widespread at all sports levels (1,2). Despite the vast market of ergogenic aids, few have enough scientific evidence to state that they can notably improve performance, always considering an individualized plan for the athletes and the circumstances (1,2). Caffeine is one of these supplements, as different remarkable organizations in the sports nutrition context have classified it as an ergogenic aid with strong evidence regarding its efficacy and that is apparently safe (1,3,4). The ergogenic effect of this substance on physical and cognitive performance has been identified in aerobic and anaerobic efforts, including aerobic and muscular endurance, power, or strength (1,3,5–7). The benefits that caffeine can generate on performance are accepted to be mainly derived from its effect on the central nervous system, due to its action as an antagonist in the adenosine receptors (2,5). On the other hand, other mechanisms have been hypothesized to explain its ergogenic effects, such as improving the muscular contraction processes by promoting the mobilization of calcium ions in the sarcoplasmic reticulum (2,5).

On the other hand, the results are diverse if a search is conducted on different scientific publications databases in which the use of caffeine is related to words such as technique or biomechanics. Few studies have reported an in-depth assessment of how caffeine affects biomechanical variables related to specific forces, velocities, and temporal parameters of the technique of general movements (e.g., squat jump (8,9), countermovement jump (8–16), resistance exercises (17,18), and running (19)), altering some of them on most occasions. To have a physiological explanation for some of the modifications generated by caffeine found in these last studies, different potential processes have been mentioned (e.g., the capacity of this substance to: affect muscle activation (19), increase the muscle fiber conduction velocity (10,15,17), enhance rate coding (8), increase motor unit recruitment (8,10,11,13,17,18) and consequently the intramuscular and intermuscular coordination (11,13), increase the calcium release from the sarcoplasmic reticulum (8,12,15,17), the calcium sensitivity of myofibrils (15) and sarcolemma excitability (15), increase the release of excitatory neurotransmitters (15,16), increase the neural firing rate (15), or possibly directly potentiate the power production of the skeletal muscle (17)).

Therefore, considering that not many studies have comprehensively focused on the biomechanics-caffeine interaction, it seems that in most investigations the general goal is to assess the influence of caffeine on performance, not considering a detailed analysis of the possible causes of these modifications from a technique's quantitative or biomechanical point of view. In this sense, differences in joint angulation while a movement is performed after caffeine consumption have been suggested as a line of research for future studies (13).

Additionally, as some of the main benefits attributed to caffeine to improve performance are the reduction of perceived exertion or fatigue during exercise (1,2,5) and increased alertness and vigilance (1,5), it would also be of interest to assess whether these positive cognitive impacts that could generate an improvement on physical performance can also help in the conservation of technique when fatigue is present. In addition, neuromuscular fatigue may generate neuromuscular strategies that imply altered movement patterns to limit performance worsening (20).

Identifying modifications to the technical performance of a movement due to caffeine consumption, under fatigue conditions or not, may be relevant, as an inappropriate technical execution or biomechanical behavior may promote injuries, both in the short term (21) and in the long term (22).

Concerning this, different kinematic, kinetic, and spatiotemporal variables have been identified as factors that may increase the running-related injury risk (23,24). Moreover, one of the leading causes of injuries in running may be neuromuscular fatigue due to its role in diminishing muscle strength or power capacity and in generating kinematic and kinetic changes (25).

What is more, the squat can be a safe exercise when performed correctly (26). Notwithstanding, the joints angulations that occur during this movement can increase the injury risk in the short term and the long term if the performed technical pattern is not correct, which might appear under fatigue conditions (26).

Finally, it has been reported that certain kinematic and kinetic variables of the vertical jump could be related to future injuries (27–30). What is more, making specific joint movements during explosive-ballistic actions, such as a functional knee valgus, has been related to a neuromuscular control deficit in the lower limbs, which has also been associated with the risk of developing anterior cruciate ligament (ACL) injuries (31). In addition, fatigue can lead to situations in which there is a lowered neuromuscular control (21).

2. Justification

It seems that the benefits of caffeine are usually measured only by its effect on performance (e.g., running a certain distance in less time, lifting more weight, or jumping higher), while a comprehensive analysis of its impact on other aspects of the movement technique of the exercise is not considered. Therefore, although caffeine generates better performance, a null or negative effect may occur on technique execution. As such, some consequences might arise (e.g., an increase in injury risk or a decrease in energy efficiency). Considering this information, it would be interesting to identify whether all the performance benefits that caffeine can generate are accompanied by modifications in the technical execution of the movements that the athlete performs.

What is more, as previously mentioned, neuromuscular fatigue could be a factor that leads to alterations in the technical execution of various movements, such as modifications in joint angulations or other kinematic or kinetic variables, which might have an impact on injury risk. If caffeine could mitigate these technique modifications, which might be possible due to the mentioned physiological explanations of why this substance may be able to alter specific parameters of technical executions, this ergogenic aid might also be a suitable option to prevent injuries in situations where neuromuscular fatigue is present.

Therefore, the study of the effect of caffeine on certain biomechanical parameters of the technique of physical exercises, in circumstances without fatigue and under fatigue, could highlight an additional factor to consider before using this supplement, either if it has a null or negative effect on technique or a positive one. To investigate this topic, the study will include analyses that delve into the mentioned caffeine-technique interaction in different general movement patterns in neuromuscular and non-neuromuscular fatigue situations. The research will be organized according to different kinds of efforts: endurance, strength or power related to resistance exercises, and high intensity.

3. Hypothesis

Caffeine generates modifications in the technical execution of running, squatting, and vertical jumping, in fatigued and unfatigued circumstances due to its physiological effects, which may be beneficial for performance and injury prevention.

4. Objectives of the research

General objective: Identify the effects of caffeine supplementation on the technical performance of the executed physical activity, both under neuromuscular and without neuromuscular fatigue conditions.

Specific objectives:

- SO1: Determine the influence of caffeine on the technical execution of a continuous physical activity that involves running, both under neuromuscular and without neuromuscular fatigue conditions.

- SO2: Determine the influence of caffeine on the technical execution of a strength or power related to resistance physical activity that involves squatting, both under neuromuscular and without neuromuscular fatigue conditions.

- SO3: Determine the influence of caffeine on the technical execution of a high-intensity physical activity that involves vertical jumping, both under neuromuscular and without neuromuscular fatigue conditions.

5. Methodology

5.1. Study type

This experimental study will be a randomized controlled trial, with a double-blind, placebo-controlled, crossover (RCTC) structure. The investigation will imply an analysis of the effects of caffeine on technique from a quantitative paradigm.

5.2. Participants

To reach people for the recruitment of participants for the study, advertisement of the research will be done at sports clubs and gyms of Osona, and at the University of Vic. Regarding the eligibility criteria for participants, the inclusion criteria will consider that they should have an advanced training level (implying: 1. An uninterrupted training time of at least 1 year in the subjects' regular exercise modality (either the person is still training or interrupted the training period during the last year, and with no more than 4 months of detraining); 2. A good exercise technique of the assessed movement patterns (32)).

The sample will be as homogenous as possible to diminish the factors that may generate interindividual differences in the response to the effect of caffeine. As such, certain characteristics that are easy to identify will imply the exclusion criteria for the subjects willing to participate in the study: 1. Not being 18-30 years old (age (33); this age range has been arbitrarily set to suit the population that will be asked to participate in the study)); 2. Having any relevant medical condition; 3. Pregnant women (pregnancy (33)); 4. Smokers (smoking (33)); 5. Regular medication consumption / Medication consumption the days before the sessions during the study (medication intake (33)); 6. Other supplementation regular consumption / Other supplementation consumption during the study (excluding sports foods, provided that their goal and nutrients have the objective of substituting the ingestion of regular food (e.g., isotonic drinks, carbohydrates gels, protein powder...), without adding other components that may act as ergogenic substances); 7. Habitual caffeine consumption of >25mg/day-0,99mg/kg/day (habitual use of caffeine (33)).

Regarding the excluding characteristic number 7, as habitual caffeine use may influence the ergogenic effect derived from the supplementation with this substance (7,33), during the enrollment session the habitual caffeine consumption of the subjects potentially included in the study will be estimated using different means: 1. The habitual caffeine consumption from foodstuffs will be measured using a validated questionnaire (34); 2. The habitual use of caffeine as an ergogenic aid for training and competition bouts and the protocols applied with that goal (e.g., dose and timing) will be measured by asking the participants about their habitual use of caffeine before, during, and after physical activity.

The sample size needed for the study will be calculated using the software G*Power. Making an a priori power analysis considering the structure of the study, assuming a within-between repeated measures ANOVA, an effect size on the vertical jump height of 0,15 (f) (10,35), a significance level of 0,05, a desired power of 0,80, 3 tested group (e.g., control, placebo, and caffeine) with 2 measurements (e.g., pre and post fatigue), and a correlation among repeated measures of 0,85 (based on a previous study (35)), the sample size needed would be 36 participants. Considering the crossover structure of the study, 12 subjects would be needed, and taking into account possible drop-outs, we will aim to recruit 15 subjects.

5.3. Design, procedures, and data recollection

5.3.1. Planification and sessions before the study

Once the design of the trial is ready to be applied and before its commencement, it will be registered, and the registration number and the name of the trial registry in which it will be registered will be specified in the final articles. In addition, the protocol of the trial will be made accessible, and the specific place in which it will be available for consultation will also be mentioned.

The study will be an RCTC of approximately 4 weeks of duration, with 4 sessions (1 day per week) for each participant: 1. Familiarization (Week 1); 2. Control (Week 2); 3. Caffeine consumption (Week 3 or 4); 4. Placebo consumption (Week 3 or 4). Previously, during the enrollment session, certain baseline characteristics of the participants will be registered: sex, age, height (measured using a stadiometer), body mass (measured using a scale), body fat (measured using bioimpedance), the habitual caffeine consumption from foodstuffs (measured using the aforementioned questionnaire (34)), and their habitual use of caffeine as an ergogenic aid for training and competition bouts and the protocols applied with that goal (e.g., dose and timing; measured by asking the participants as previously described). The informed consent processes will also be done during this session. The data of the study will be collected in the sports sciences laboratories of the University of Vic.

All the sessions will be spaced apart by a minimum of 7 days. In this way, there will be enough time to properly recover from the efforts done in the previous session, besides the fact that in studies with caffeine usage, this period has been considered enough to avoid interferences on their results due to the consumption of the substance in preceding sessions (36,37). On the other hand, it is important to note that the half-life for caffeine elimination from the plasma compartment is 2,5-10h when ingested in doses of <10mg/kg (38).

5.3.2. Familiarization session

The purpose of the familiarization session will be that the participants of the study get used to the warm-up and the exercises that will be performed in the other sessions. In addition, the individuals will be informed about the benefits of caffeine for exercise performance during the first 10 minutes of this session, as a similar effect expectancy between subjects may be necessary to achieve a more consistent placebo effect on the exercise performance of the sample (39). Finally, this session will be used to do any tests that will be needed to adjust the intensity of the exercises performed during the evaluated sessions (e.g., the squat), to recheck a good technique of the assessed exercises and standardize their development, to do a dietary and caffeine ingestion control assessments so that the participants can replicate their recorded intake in the next sessions, and to perform the baseline measurements and the data gathering of the participants that could not be obtained from the enrollment session.

5.3.3. Control, placebo, and caffeine sessions

The placebo and caffeine sessions will be identical and will be the assessed ones together with the control session. In a randomized order and a double-blind fashion, the subjects will be randomly assigned to caffeine in session 3 and placebo in session 4, or placebo in session 3 and caffeine in session 4. To generate the random allocation sequence, a list of computer-generated random numbers from a web page (40) will be used to perform fixed simple randomization (e.g., even and odd numbers).

To implement this sequence, the researcher enrolling the participants will write and codify their name and date of birth on a text document in the order in which they are included in the investigation. The codified data of the participants will be sent to a researcher external to the study, who will be responsible for generating the random allocation sequence, and randomly shuffling the order of the codified data of the participants with a web page (41). This new randomized order will be related to the simple randomization sequence of numbers by the same external researcher (e.g., first participant and the first number, second participant and the second number, and so on), and the subjects will be assigned to a group accordingly (e.g., even numbers will imply the caffeine-placebo sequence, while odd numbers will imply the placebo-caffeine sequence). This same external researcher will print a copy of the allocation list which will be locked away in a cupboard.

the placebo and the caffeine ingestion protocols will be identical in format and presentation (e.g., opaque capsules with the same administration method, appearance, smell, and taste). To minimize any influence of the flavor or the look of the ingested substance, both conditions will imply the consumption of opaque capsules (ingested with 200ml of water (37,42)) in which there will be 6mg/kg of caffeine or placebo. the caffeine supplementation will have an anhydrous powder form to allow an easier individualization of the dose for each participant, and it will be bought from the company Harrison Sport Nutrition (18,43,44). On the other hand, as previously done, the placebo will be cellulose bought from the company Guinama (12,37,42).

The researcher who will assign participants to the sequences of interventions will put the opaque capsules of caffeine and placebo in envelopes (e.g., 2 envelopes per participant), and on their outside part, it will be written the codified participant's name and the session in which those capsules are intended to be consumed, according to the allocation sequence of each subject. Therefore, the participants and all the investigators directly involved in the sessions, their data collection and analysis, and the outcome adjudication, will be blinded. Only after the data analyses and the outcome adjudication are completed, the investigators (and the participants if requested by them) will know the treatment order of each subject.

For each subject, the assessed sessions will be performed during the same hours of the day for improved consistency of the results, so that the effects that the circadian rhythms or the time of the day may have on performance (42–45) or the magnitude of performance improvement due to caffeine consumption (33,46) are accounted for. Moreover, the participants will be requested to not undergo fatiguing physical activities during the 48 hours before each session nor consume alcohol during the 24 hours preceding the sessions. During the 48 hours before the sessions the participants will also have to restrict their caffeine intake (they will be indicated which foodstuffs they should avoid by using the questionnaire to assess it, a strategy adapted from previous research (47)). What is more, they will be indicated to eat their habitual pre-exercise meal 2-4 hours before the beginning of the sessions to separate it from the ingestion of caffeine and avoid any potential interferences in the absorption of caffeine (48).

To control the caffeine ingestion from foodstuffs during the previous 48 hours a questionnaire will be employed (34). Additionally, the subjects will be asked if any caffeine supplementation has been used during this period. What is more, over the 24 hours before each session the subjects will be individually requested to ingest a diet that is as similar as possible in every aspect (e.g., food, hydration, and timing). To do so, dietary intake information for 24-hour recalls will be registered and evaluated employing a specific tool (Automated Self-Administered 24-hour (ASA24) Dietary Assessment Tool (49)). This tool may be employed to control sleeping patterns and supplementation ingestion too. The participants will have to do the caffeine and the dietary assessments before the beginning of the familiarization session, and the records of this session will be sent to them as a reference to replicate for the following ones, a strategy based on previous research (47,50).

On the other hand, the organization of the assessed sessions will imply the following order:

1. Ingestion of caffeine or placebo (in the control session nothing will be consumed, but the waiting time until the assessed exercise begins will be the same (e.g., 60 minutes) (35)).

2. Standardized warm-up (15 minutes; 45 minutes after the previous ingestion or the start of the waiting time).

3. Execution of the assessed exercises under non-neuromuscular fatigue conditions.

4. Neuromuscular fatigue generating protocol.

5. Execution of the assessed exercises under neuromuscular fatigue conditions.

Regarding the warm-up protocol, it will comprise a bout of aerobic exercise, stretching, and exercises related to the evaluated physical activities, focusing on the limbs that will have a main role in the subsequent assessed movements, with an intensity that does not generate fatigue (51).

As previously mentioned, the assessed exercises will be related to different kinds of efforts (e.g., endurance, strength or power related to resistance, and high intensity). For each subject, the order of these efforts will be randomized using a web page (41), and the same sequence will be followed for the three assessed sessions.

The data collection of the assessed exercises will be done using different kinds of non-invasive instruments:

1. Instruments based on the kinematic analysis of the movement. Examples of these instruments are: Smartphones to film the movement in slow-motion, reflective markers (adhered to the skin of the participants using tape), or a linear position transducer. The videos will be analyzed using specific software (Kinovea) to measure different outcomes. On the other hand, the linear position transducer will be attached to a barbell to assess the movement of the participants.

2. Instruments based on the kinetic analysis of the movement. An example of these instruments is force plates.

For each movement, different mechanical parameters may be analyzed depending on their importance for injury prevention or their interest due to other reasons (e.g., performance), and their suitability for the available instruments. On the other hand, the effect of caffeine on performance will also be measured to identify whether the substance alters it in each subject and if this modification is positive or negative.

The analyzed movements in the study will imply the use of the lower limbs. The characteristics of the assessed exercises before and after the neuromuscular fatigue-generating protocol will be the following:

1. 6 countermovement jumps.
2. 6 barbell back squats with a weight that implies a velocity close to 1 m/s mean propulsive velocity in the familiarization session.
3. 2,5km running on a treadmill.

Regarding neuromuscular fatigue, in this study it will be defined as any reduction in force or power production capacity induced by exercise, either the task can be sustained or not (52,53). Neuromuscular fatigue contributory mechanisms are determined by various factors (20), although its origin has been linked to repeated or sustained muscular activity (53). Additionally, neuromuscular fatigue is very task-dependent, and the capacity of a test to detect it depends on its specificity concerning the task performed (20).

Taking into account these data, considering that all the assessed movements will imply an important stretch-shortening cycle component, a Yo-Yo squat protocol will be used to generate neuromuscular fatigue, using a structure adapted from the one reported in previous articles that used vertical jumping to cause fatigue (54,55). In addition, during the fatiguing protocol, the participants will have to estimate their perceived exertion with a 6-20 Borg Scale (56). The assessed exercises will be done before and after this fatiguing protocol without any rest.

On the other hand, in the caffeine and placebo sessions, participants will have to complete a Google Forms questionnaire in which they will be asked to identify whether they have ingested caffeine or not. The strategy followed to do so has been previously applied (57): immediately before (1 hour post-supplementation) and after the assessed exercises, the subjects will have to indicate what substance they believe that they have consumed, with the options "caffeine", "placebo", or "I don't know", as well as the reason why they have chosen that answer.

Additionally, in the morning of the day after the sessions with the placebo or caffeine ingestion, the participants will be requested to complete another Google Forms questionnaire comprised of 8 questions with a yes/no answer, to evaluate the side effects of caffeine consumption during the hours after the sessions. The questionnaire structure that will be employed has been used in studies involving this substance (42).

5.4. Statistical analysis

The information collected during the study will be analyzed using different methods that are suitable for the characteristics of the study structure and its data. The methods will include descriptive and inferential statistics. The main goal will be to analyze the data to assess the impact of caffeine on specific biomechanical parameters of the technique while running, squatting, or vertical jumping, with neuromuscular fatigue and without it.

6. Research team

Study principal investigator:
- Arnau Baena Riera.

Other investigators:
- Xantal Borràs Boix.
- Javier Peña López.

7. Expected benefits and possible side effects

The sports sciences community and other people that may prescribe or use caffeine as an ergogenic aid could benefit from the study, as it will provide a new perspective on the effect of caffeine during physical activity. Therefore, regardless of the capacity of caffeine to influence the technical execution with neuromuscular fatigue or without it, this new perspective could be beneficial to improve the recommendations of the protocols of caffeine ingestion. For example, if caffeine has a positive impact on technique execution, it could be recommended to use caffeine in situations in which, apart from seeking a better performance, there may be an increased injury risk, or when during training sessions or competition events an optimal technical execution is desired. On the other hand, if caffeine has a null or negative effect on technique, strategies to prevent injuries may be proposed by limiting caffeine consumption to particular circumstances, or increasing technique training in similar situations to the ones in which the substance will be used.

Additionally, the study of the impact of caffeine on aerobic and anaerobic performance in the same sample has been suggested as an interesting line of research to help to further assess whether its effect size magnitude may differ between these two kinds of exercises (7). The proposed trial will also contribute to this discussion.

It is important to note that caffeine consumption protocols should be individualized to each person and situation to obtain the maximum of its positive effects and avoid the maximum of its negative ones, by experimenting and a trial-error approach (1,4,5). However, due to the nature of the study, all the subjects will follow a protocol within the general recommendations to attain the ergogenic benefits of caffeine: 6mg of caffeine/kg, approximately 60 minutes before exercise (1).

To consume this dose with regular foodstuff, an important ingestion would be needed. Considering a person with a 70kg body mass, this subject would need to ingest 420mg of caffeine in the proposed study. Although the caffeine quantity in food is variable depending on different factors, This quantity would be equivalent to ingesting approximately 4 short black coffees or espressos, 3,25l of Coca-Cola, or 1,35l of Red Bull (58).

Despite the information in the previous paragraph, and although an optimal caffeine dose to improve exercise performance has not been established and may be variable depending on different circumstances (7), 6mg/kg has been usually used in the literature (7). This dose may also be less likely to raise the risk of negative side effects than larger quantities (e.g., ≥9mg/kg) (1). However, caffeine can generate a different effect on each subject, and there is a possibility that it may have a null or negative impact in some cases (33). Therefore, certain side effects due to caffeine consumption may happen during the study. In previous articles, the data collected to register caffeine ingestion side effects in the sports context have considered insomnia, increased urine production, gastrointestinal problems, increased activeness, headache, irritability, muscular pain, and tachycardia or palpitations (42).

Therefore, the expected negative effects related to caffeine ingestion are mostly mild. Notwithstanding, the number of subjects that have to withdraw from the investigation because of side effects will be defined, as well as those that have to withdraw due to other reasons, and a balanced discussion of the benefits and the harms of caffeine seen during the trial will also be done. Additionally, during the study, there will be the inherent and inevitable injury risk that is always present when doing physical activity.

Finally, if any participant requires medical attention due to these adverse effects or other acute events during the sessions of the study, they will be transported to a place with medical services to be treated (specific insurance for the participants will not be offered by the investigators). The research team will not be responsible for offering any medical services, nor for assuming their costs.

8. Ethical aspects

The participation of the subjects in the study is voluntary and does not entail compensation. An informed consent protocol will be developed with the subjects interested in participating in the RCTC before their inclusion in it. This process will imply an oral and written explanation of the relevant information and characteristics of the project for the informed consent protocol. Once the individuals have received these details and any doubt that they may have has been resolved, the volunteers will have to sign a document to give their informed consent to be included in the investigation. The informed consent documents will be duplicated, and a signed copy will be handed to the participant, while the other signed document will be kept by the researcher. The conserved copies will be scanned and saved in the cloud services of the University of Vic, while the physical copies will be stored in a locked cupboard. Additionally, the study will have to preserve the rights of the participants at all times, as well as respect the principles of the Declaration of Helsinki and its later amendments (59).

The data management processes and the key aspects of the protocol outlined in this document have been approved by the Research Ethics Committee of the University of Vic (Internal code: 238/2022).

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