Title      The Effects of Caffeine on Short-Term, High-Intensity Exercise

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THE EFFECTS OF CAFFEINE ON SHORT-TERM, HIGH-INTENSITY EXERCISE

By

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Dedication

To my mum, Mrs Maureen Jackson (nee Ashdown), and to the memory of my
THE EFFECTS OF CAFFEINE ON SHORT-TERM, HIGH-INTENSITY EXERCISE

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ABSTRACT

This aim of this series of studies was to investigate the effects of oral caffeine ingestion (5 mg \cdot kg\(^{-1}\)) on whole-body, short-term, high-intensity exercise (ST; representing an exercise intensity of between 100% - 150% \(\dot{V}O_2\)\(_{\text{max}}\)), an area that has received scant attention in the past. It was found that, in common with other 'open-ended' tests, one ST assessment, the maximal accumulated oxygen deficit (MAOD), appeared to lack both validity and reliability. Although traditional reliability markers of MAOD were favourable, the 95% limits of agreement were unacceptably large. In addition, the validity of MAOD was also found to be questionable because a study of elite runners revealed that a large proportion were unable to accomplish a plateau in the \(\dot{V}O_2\) - exercise intensity relationship. A follow-up study developed an original bespoke 'preloaded' ST cycling protocol that combined constant-rate exercise with an 'all-out' effort. This protocol appears to have several features that make it a more appropriate assessment to use in ergogenic studies than the MAOD. The work also considered the original, and as yet, undeveloped potential, for the assessment of rating of perceived exertion (RPE) during ST. It was shown for the first time that RPE (Borg scale; 6-20) could be used reliably during constant-rate ST. Three of the ten studies demonstrated that caffeine can be ergogenic during ST, with improvements averaging 11% (95% CI, 7.4% - 14.5%) above placebo treatment. In addition, the caffeine studies contributed to a meta-analysis of the effects of caffeine on test outcome that resulted in an effect size greater than zero, with 95% confidence intervals not crossing zero. The studies have examined potential physiological and metabolic mechanisms of action that may help explain caffeine's impact on ST. These suggest that there is some evidence that caffeine both stimulates anaerobic glycolysis and reduces electrolyte disturbance during ST. Finally this work has demonstrated for the first time that the perceptual response during constant-rate ST, as measured by RPE, is blunted following caffeine ingestion. It is concluded that caffeine is ergogenic during ST, and that while the exact mechanism(s) of action remains unknown, one consistent test outcome is a reduction in RPE during constant-rate ST.
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Author's Declaration

I declare that this report is my own unaided work. It is being submitted for the degree of PhD by Publications at the University of Luton. It has not been submitted before for any degree or examination in any other university.

Michael Doherty
Chapter 1
Introduction

1.1 Structure of the report
The first chapter of this report sets out the aim of the series of publications and discusses how the related objectives of the body of work were met. The aim and objectives are preceded by the background and rationale for the studies. Chapters 2 – 12 represent the publications (I – XI) in chronological order, and Chapter 13 is a synopsis of possible mechanisms of action of caffeine during whole-body, short-term, high-intensity exercise (ST; representing an exercise intensity of between 100% - 150% $\dot{V}O_{2\text{max}}$). Finally, Chapter 14 includes a summary of findings from the publications, recommendations for future research in the area, and the limitations to the body of work. Note that throughout the text, reference to the published works is made by using roman numerals.

1.2 Background and rationale for the series of publications
Caffeine is the most indiscriminately used drug in the world (Fredholm et al., 1999). Although estimates are notoriously unreliable, it is reported that caffeine consumption is around 70 to 76 mg/person/day worldwide (Fredholm et al., 1999). This fact is reflected in many sporting contexts, where a large proportion of recreational and elite athletes are known to use the drug (Graham et al., 1994; Graham, 2001b). Caffeine, when ingested orally, is used either in pure form, or, more commonly, contained in dietary sources such as tea, coffee, and cola drinks, including a whole range of newly formulated 'energy' drinks, foods and gels. Athletes mostly use caffeine prior to and during exercise with the express intention of enhancing mental and physical performance both in training and competition (Graham et al., 1994; Graham, 2001b). Because it has now been withdrawn from the World Anti-Doping Agency list of banned substances (WADA, 2004), a renewed interest in the effects of caffeine on sports performance is likely. Even so, caffeine has been one of the most popular of all ergogenic aids investigated by sport scientists over the last 30 years. This can mostly be attributed to its wide availability, ease of administration and short half-life (Graham et al., 1994; Spriet, 1995a; Spriet and Howlett, 2000; Sinclair and Geiger, 2000; Graham, 2001a; Graham, 2001b). In addition, it appears that only non-toxic, low to moderate doses of oral caffeine ($\sim 3 \text{ mg} \cdot \text{kg}^{-1} - 10 \text{ mg} \cdot \text{kg}^{-1}$) are
necessary to have a positive impact on exercise performance (Graham and Spriet, 1991; Lindinger, 1993).

As outlined in I, most of the research investigating the effects of caffeine on exercise performance prior to the mid-1990's had focussed on endurance-based exercise (for reviews of this period, see Powers and Dodd, 1985; Jacobson and Kulling, 1989; Graham et al., 1994; Tarnopolsky; 1994; Spriet, 1995a). By comparison there was a dearth of information on the effects of caffeine and ST. Although some caffeine studies had provided support for the ergogenic effects of caffeine on ST (Collomp et al., 1991; Anselme et al., 1992; Collomp et al., 1992; Wiles et al., 1992; Jackman et al., 1996), a number of authorities continued to dismiss the idea that caffeine could be ergogenic during this type of exercise (Williams et al., 1988; Jacobson and Kulling, 1989; Williams, 1991; Tarnopolsky, 1994; Vandenberghhe et al., 1996). The lack of interest shown by researchers of the effects of caffeine on ST in preference to endurance-based exercise is probably due to two main reasons; one of methodological origin, and the other related to a persuasive mechanistic model. Physiological assessment of human performance has traditionally been dominated by measurement of endurance exercise and, in particular, the 'gold standard' measurement of $\text{VO}_2\text{max}$ (Bouchard et al., 1991). The direct assessment of 'anaerobic' exercise on the other hand has lagged behind and has been somewhat neglected partly because of the difficulties associated with the rapid physiological and biochemical changes that occur during very high intensity exercise (Bouchard et al., 1991). Thus, whilst physiological estimates of aerobic metabolism are commonplace (MacDougall et al., 1991), most estimates of anaerobic metabolism simply measure mechanical work done (Vandewalle et al., 1989; Green and Dawson, 1993; Gastin, 1994; Green, 1995; Spriet, 1995b). ST includes activities lasting between approximately 2-min to 6-min. This is an important intensity-duration domain and includes a swathe of sporting events, among them, 800 m – 2000 m running, 400 m and 800 m swimming, and 4000 m track cycling. Because ST is likely to require maximal provision of energy from both aerobic and anaerobic sources (Spriet, 1995b) the fatigue process that occurs within this time frame is likely to be associated with a combination of factors that differ from the aetiology of fatigue encountered during a much shorter time period or from that of prolonged exercise (VIII). Thus ST represents an important area of research and one that is ripe for investigation.
The other reason for the dominance of endurance-based exercise studies is that a theoretical model developed over 20 years ago to explain the effects of caffeine on endurance exercise, has sustained a buoyant interest among investigators working in the field (Graham et al., 2001a; Graham 2001b). In some cases this theory has been heralded as the only way in which caffeine could possibly affect exercise performance (Cha et al., 2001). Briefly, the model suggests that the ergogenic effect of caffeine is due to an enhanced mobilisation of free-fatty acids - either due to a direct affect of caffeine on adipose tissue and, or, an indirect caffeine-mediated elevation in adrenaline which in turn stimulates lipolysis (Graham et al., 1994). Increased circulating free fatty acids leads to preferential use of free-fatty acids by the working muscle through suppressed glycolysis via a citrate-mediated 'Randle effect' (Graham et al., 1994). This spares the limited stores of muscle glycogen, thereby improving endurance capacity (Costill et al., 1978; Ivy et al., 1979; Essig et al., 1980; Powers and Dodd, 1985; Jacobson and Kulling, 1989; Flinn et al., 1990; Dodd et al., 1993; Graham et al., 1994; Tarnopolsky, 1994; Cha et al., 2001). It has been argued that because the ergogenic properties of caffeine appeared to be related to muscle glycogen sparing and the subsequent improvement in endurance capacity, it was most unlikely that caffeine could affect ST (Jacobson and Kulling, 1989; Williams, 1991; Tarnopolsky, 1994; Vandenberghe et al., 1996). If caffeine can enhance ST, this will raise doubts as to the veracity of this model because factors other than muscle glycogen sparing would be implicated in any explanation of caffeine's effects on ST (Graham, 2001a; 2001b).

1.3 Overall aim and related objectives
The overall aim of the research was to investigate the effects of oral caffeine ingestion on whole-body, short-term, high-intensity exercise (ST; representing an exercise intensity of between 100% - 150% \( \dot{V}O_2 \text{max} \)). This aim in turn, comprises the following seven objectives addressed through the eleven publications that form the basis of the work:

Objective A To investigate the reliability and validity of a popular ST protocol, the maximal accumulated oxygen deficit and the subsequent exercise time to exhaustion (III, IV, VII).
Objective B To develop and establish the reliability of a bespoke 'preloaded' ST protocol (VIII).
Objective C To investigate the reliability of the rating of perceived exertion (RPE) during ST (V).
Objective D To review and assess the effects of oral caffeine ingestion on ST (I, II, VI, IX, X).
Objective E To assess the effects of combining creatine supplementation with a single dose of caffeine on ST (VI).
Objective F To examine physiological and metabolic mechanisms of action that might help elucidate the effects of caffeine on ST (II, VI, IX).
Objective G To examine the effects of caffeine on RPE during ST (VI, IX, XI).

1.3.1 Objective A; Reliability and validity of ST protocols (III, IV, VII)

1.3.1.1 The maximal accumulated oxygen deficit (III and IV)

Ergogenic aid research requires quantification of the reliability of any tests used to enable investigators to distinguish between the within-subject (random) error of the test instrument and the effects of the treatment, as well as providing an estimate of the appropriate sample size required to detect a treatment effect (Hopkins, 2000; Saris et al., 2003). In 2000, when III was published, it was generally agreed that the maximal accumulated oxygen deficit (MAOD; Medbo et al., 1988), whilst not without limitations (Green and Dawson, 1993; Gastin, 1994; Bangsbo, 1996), represented the most valid indirect physiological determination of anaerobic capacity (Saltin, 1990; Green and Dawson, 1993; Gastin, 1994). Thus, Graham (1996) suggested that the MAOD could be used for comparative purposes, for example, before and after a ‘treatment’ [such as caffeine ingestion] where the subject acts as his or her own control. However, as recommended for all nutrition-based treatments (Saris et al., 2003), this scenario is dependent on the reliability of MAOD. The MAOD had been assessed for reliability on a number of occasions (Lawson and Golding, 1981; Pate et al., 1983; Graham and McLellan, 1989; Withers et al., 1991; Carlson and Naughton, 1993; Ramsbottom et al., 1994; Jacobs et al., 1997). These studies, without exception, concluded that the MAOD was reproducible. However, like many assessments in sport and exercise science, all of these studies employed 'traditional' reliability criteria, for example, hypothesis testing and retest correlation, criteria that have been the subject of continued criticism (Nevill and Atkinson, 1997; Atkinson and Nevill, 1998; Hopkins, 2000).
The results from III show that, although traditional measures of reliability (including the coefficient of variation and the intraclass correlation coefficient) were favourable, the 95% limits of agreement revealed the MAOD to have relatively poor reliability. It was estimated that if a subject's (running) MAOD was 70.0 mL O₂ Eq • kg⁻¹, it was possible (worst case scenario) that the same person could obtain as low a value as 56.0 mL O₂ Eq • kg⁻¹ or as high a value as 89.6 mL O₂ Eq • kg⁻¹ on a repeat visit (IV).

Crucially, study III was the first publication to suggest that the MAOD may not be a reliable measurement when based on more contemporary and rigorous measures of reliability. More recently, Weber and Schneider (2001) also performed a reliability study of the MAOD with 14 untrained subjects. Again, these authors chose to report reliability with traditional criteria of hypothesis tests and retest correlation. IV is a letter to Medicine and Science in Sport and Exercise supporting the methods used in III and highlighting the weaknesses and limitations in the conclusions reached by Weber and Schneider and others who continue to use traditional measures of reliability.

1.3.1.2 ST run time to exhaustion (Tlim; III and VI).

Treadmill Tlim was more reliable than the MAOD in all of the reliability measures that were reported in III (95% limits of agreement = 1.01 x/⁻ 1.26 as a ratio, and, 1.0 x/⁻ 1.18 as a ratio, for MAOD and Tlim respectively). An explanation for the difference between Tlim and MAOD was that there are many single measurements associated with respiratory gas analysis (Gastin and Lawson, 1994). Tlim simply relies on one measurement of time to exhaustion, while for the assessment of respiratory gases, random error is increased due to the mechanical variation of gas collection and the measurement of gas volumes and gas fractions. It is likely that the significant changes following caffeine ingestion observed with Tlim but not with MAOD in VI (see 2.1.4.1 and 2.1.4.2), are partly explained by the more robust measurement of Tlim. However, it should be borne in mind that Tlim protocols lack validity and are less reliable than 'performance'-based protocols (see 2.1.4.5).
1.3.1.3 The primary \( \dot{V}O_2_{\text{max}} \) attainment criterion (VII)

Validity refers to the degree to which a test measures what it is supposed to measure (Thomas and Nelson, 2001). As referred to above, it has been suggested that the MAOD provides the most valid estimation of anaerobic ATP production and maximal aerobic provision during high-intensity exercise (Saltin, 1990; Green and Dawson, 1993; Gastin, 1994). Based on the relationship between submaximal \( \dot{V}O_2 \), \( \dot{V}O_2_{\text{max}} \) and exercise intensity, an individual linear regression equation is derived for each individual and this is used to calculate the exercise intensity equivalent to a given percentage above \( \dot{V}O_2_{\text{max}} \) (Medbo et al., 1988). Thus, one important assumption in the calculation of MAOD is that \( \dot{V}O_2_{\text{max}} \) is achieved. The primary and most popular criterion measurement for the attainment of \( \dot{V}O_2_{\text{max}} \) is a levelling off or 'plateau' in oxygen consumption during graded exercise (Taylor, et al., 1955; Mitchell and Blomqvist, 1971; Sioniger et al., 1996; Bassett and Howley, 1997; Wagner, 2000). But termination of a maximum exercise test often occurs in the absence of a \( \dot{V}O_2 \) plateau (Cunningham et al., 1977; Armstrong et al., 1995; Duncan et al., 1997; Draper et al., 1999; Sheehan et al., 1987; Myers et al., 1989, 1990; St Clair Gibson et al., 1999). It is thought that the termination of exercise tests that require a maximal effort is partly a result of poor subject motivation (Wagner, 2000). Thus, study VII was performed to evaluate the frequency with which the plateau phenomenon was achieved in elite athletes. Use of these subjects would almost certainly rule out any confounding factor related to a lack of motivation. In a study of fifty national-class runners, it was found that only 39% and 25% of males and females, respectively, achieved the plateau criterion (VII). This was the first study to fully support the argument that a significant number of highly-trained athletes are unlikely to achieve a \( \dot{V}O_2 \) plateau during a \( \dot{V}O_2_{\text{max}} \) test.

1.3.2 Objective B; Development of a bespoke 'preloaded' ST protocol (VIII)

1.3.2.1 A preloaded cycling ST protocol (VIII)

Taken together, the results from III and VII, question both the reliability and validity of the MAOD. Thus, study VIII was designed to develop a more reliable and ecologically valid ST protocol that would help facilitate a more meaningful assessment of the effects of caffeine on ST (IX and 2.1.4.3). Given that the MAOD is an exercise capacity, 'open-ended' test, i.e. one where the end of the test is unknown prior to the beginning of the test, it was decided to investigate the
reliability of a 'preloaded' ST protocol. In comparison to exercise capacity tests, several authors (Hickey et al., 1992; McLellan et al., 1995; Jeukendrup et al., 1996; Marino et al., 2002; Saris et al., 2003) have suggested that athletes can regulate their power output much more reliably when they have to focus on an end-point of time, amount of work or completion of a pre-set distance (i.e. 'time-trial'; Hickey et al., 1992; McLellan et al., 1995; Jeukendrup et al., 1996; Marino et al., 2002; Saris et al., 2003). In contrast to open-ended tests, these types of tests are often referred to as 'performance tests', because they more closely resemble the type of activity that athletes participate in (Saris et al., 2003). Nevertheless, one disadvantage of performance testing is that when they are repeated, (and unlike exercise capacity tests), physiological comparisons throughout the testing are more difficult to interpret. Because it was necessary to be able to compare a caffeine treatment with placebo (IX), the new 'preloaded' protocol included both a constant rate and performance element. Up to this point, preloaded protocols had only been designed for prolonged exercise tests (Jeukendrup et al., 1996). Thus, there were no studies available that had investigated the reliability of a preloaded ST protocol. Accordingly, the purpose of VIII was to assess the reliability of a 3-min cycling test that combined 2-min of constant-load cycling with a 1-min performance test. Power output was measured each second using SRM™ Power Cranks (4-strain gauge crankset). The data were analysed by measuring the reliability of each 30 s of the 3-min test together with the peak power and the peak cadence achieved in the performance element of the test. There was no systematic bias in the data from trial 1 to trial 2 for any of the 6, 30 s blocks of the test, or the peak power or peak cadence (VIII). Mean (± SD) total distance over the 3-min was 2.23 ± 0.23 km and 2.26 ± 0.26 km for trial 1 and trial 2 respectively (P < 0.05). The coefficients of variation ranged from 0.9% to 5.4% and the intraclass correlation coefficients ranged from 0.96 to 0.99. It was concluded that in moderately trained subjects, the 3-min preloaded test provided reliable data and could therefore be used for short-term, high-intensity cycling studies.

1.3.3 Objective C; The reliability of the rating of perceived exertion (RPE) during ST (V)

1.3.3.1 RPE measures during the first 2-min of constant-load exercise (V)

Perceived exertion has been defined as the act of detecting and interpreting sensations arising from the body during physical exercise (Noble and Robertson,
1996). For nearly forty years, rating of perceived exertion (RPE) scales have been used as a reliable and valid measurement of exercise intensity (Borg, 1962; Skinner et al., 1973; Stamford, 1976; Eston et al., 1988; Dunbar et al., 1992; Noble and Robertson, 1996). Their principal use has involved quantifying subjective feelings of fatigue and exercise tolerance during submaximal exercise (Noble and Robertson, 1996) and, increasingly, prescribing exercise intensities for the development and maintenance of cardiovascular fitness both for healthy (Dishman, 1994) and ‘at risk’ populations (Guttmann et al., 1981). By comparison, there have not been any systematic attempts to investigate the perceptual response to ST. This probably reflects the belief that subjective estimates of exertion during high-intensity exercise are not viable and lack application to sport and exercise science. However, rather than employ ‘all-out’ ST - where recording of RPE would certainly be impractical - ST investigations may also observe constant-load exercise at an exercise intensity equivalent to, or above, $\dot{V}O_2\text{max}$, as with the MAOD (VI) and the preloaded protocol (IX). The exercise intensities in these tests are sufficiently low enough (i.e., 100% to 125% $\dot{V}O_2\text{max}$) to allow subjects to indicate RPE, particularly in the first 2-minutes of the tests. Since caffeine appears to positively affect the perceptual response during endurance-based exercise (Costill et al., 1978; Maclntosh and Wright, 1995; Cole et al., 1996), it was reasonable to assume that acquiring RPE during ST might also provide an insight into any ergogenic effect that caffeine has during ST (VI, IX and 2.1.7). A logical first step in investigating ST RPE was to establish the reliability of the measurement and to describe the time course of RPE during ST. Thus, study V considers the original, and as yet, undeveloped potential, for the assessment of perceived exertion (RPE) during ST. Initially, this required an assessment of perceptual responses during ST, including an evaluation of the reproducibility of RPE during ST. Based on three repeat treadmill runs at 125% $\dot{V}O_2\text{max}$, it was found that RPE was reliable as measured by intraclass correlation coefficient (ranging from 0.78 to 0.87), coefficient of variation (4.4% to 6.0%), standard error of measurement (0.76 to 0.80 RPE points) and 95% limits of agreement (0.0 ± 2.3 and 0.0 ± 2.5 RPE points). Paper V is the first time that RPE has been assessed for reliability during ST. By including RPE in ST studies, a new dimension can be added to investigations of the effects of caffeine on high-intensity exercise (VI, IX and 2.1.7).
1.3.4 Objective D; Review and assessment of the effects of oral caffeine ingestion on ST (I, II, VI, IX, X)

Most of the studies that had investigated the effects of caffeine on exercise performance prior to the mid-1990's, had focussed their attention on endurance-based exercise (for reviews of this period, see Powers and Dodd, 1985; Jacobson and Kulling, 1989; Graham and Spriet; 1994; Tarnopolsky; 1994; Spriet, 1995). The few studies that had assessed the effects of caffeine on ST, had produced equivocal results (Williams, 1988; Collomp et al., 1991; Anselme et al., 1992; Collomp et al., 1992; Wiles et al., 1992; Jackman et al., 1995). Thus it was apparent that more work was needed in this area (I). In particular, it was clear that certain aspects of ST had not been investigated. For example, there were no studies that had evaluated the effects of caffeine on measures of 'anaerobic' capacity, such as the MAOD, nor on certain groups of specifically trained subjects, such as cyclists. To highlight important aspects of the effects of caffeine ingestion on ST and to identify gaps in knowledge, one review (I) and one meta-analysis (X) was performed. In addition, three studies of the effects of caffeine on ST were performed (II, VI, and IX).

1.3.4.1 Caffeine ingestion and the maximal accumulated oxygen deficit (MAOD; II, VI)

Paper II is the first full publication to demonstrate that caffeine could increase anaerobic capacity as measured by the MAOD. Coincidentally, the findings of this study have recently been reproduced by Bell et al. (2001). In II and VI, subjects ran at an exercise intensity corresponding to 125% \( \dot{V}O_2 \text{max} \). In II, MAOD was significantly increased by 14% (95% CI, 6.0% - 21.0%) in the caffeine trial compared to placebo \( (P < 0.05) \). However, in VI, although MAOD was increased by a similar absolute margin as in II in the caffeine trial compared to the baseline trial (approximately, 0.5 L O_2 Eq), it failed to reach statistical significance \( (P > 0.05) \). This lack of statistical significance was possibly related to the poor reliability of MAOD, since a large within subject variation makes it less likely that significant differences will be found (III and 2.1.1.1).

1.3.4.2 Caffeine ingestion and run-time to exhaustion (\( T_{lim} \); II, VI)

In comparison to the MAOD, caffeine significantly improved \( T_{lim} \) in both II and VI by approximately 10% and 15%, that is, 21 s ± 12 s and 29 s ± 13 s (mean ± SD), respectively \( (P < 0.05) \). Although Bell et al. (2001) have recently replicated these
results, II and VI were the first studies to demonstrate that caffeine could positively influence exercise capacity with a duration of between 2 - 5-min.

1.3.4.3 Caffeine ingestion and the 'preloaded' protocol (IX)
In IX, the effects of oral caffeine on the recently developed ST preloaded test (VIII and 2.1.2.1) was investigated for the first time. Although there was a trend for caffeine treatment peak power to be greater than the placebo treatment, these differences did not reach significance (P > 0.05). Similarly, although there was a tendency for the sequential 30 s power outputs to be enhanced in the caffeine treatment, these also did not reach significance. However, the mean value of power output during the final 1-min performance stage was increased by 45 w (95% CI, 0 - 88 w) in the caffeine treatment compared to the placebo treatment. It was concluded that the findings from this study provided evidence that a moderate amount of caffeine can have an ergogenic effect during the last minute of a preloaded cycle test in trained participants.

1.3.4.4 A meta-analysis of the effects of caffeine on ST (X)
Paper X is the first meta-analysis to assess the effects of caffeine on exercise performance. Inclusion criteria for studies to be entered into the analysis included laboratory-based, double-blind, fully randomised, placebo-controlled trials using adult subjects, published in peer-reviewed English language journals, and where one of the main purposes was to assess the effects of a single oral caffeine dose on whole-body exercise. Within this study, which also considered the effects of caffeine ingestion on endurance and graded exercise, a total of 12 ST studies were analysed. The overall effect size (ES) in the meta-analysis for the effects of caffeine on ST was significantly greater than zero (Table 1). This represented a 3% improvement (95% CI, 0.4% - 5.3%) in ST following caffeine ingestion. Three of the publications in the series (II, VI and IX) contributed a 25% weighting to these results. The findings from the meta-analysis strongly suggests that caffeine can affect ST, a finding that is at odds with previous conclusions about the effects of caffeine on ST (Jacobson and Kulling, 1989; Williams 1991, Tarnopolsky 1994, Vandenberghe et al., 1996), but is similar to statements found in a number of more recent narrative reviews of the effects of caffeine on exercise performance (Graham 2001a, 2001b, Paluska, 2003).
Table 1. Effect of caffeine on ST effect size moderated by $T_{\text{lim}}$ and non-$T_{\text{lim}}$ test protocols

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Effect size</th>
<th>ES ± SD</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{\text{lim}}$</td>
<td>4</td>
<td>0.54 ± 0.23</td>
<td>0.23 –0.85</td>
</tr>
<tr>
<td>Non-$T_{\text{lim}}$ protocol</td>
<td>22</td>
<td>0.00 ± 0.33</td>
<td>-0.02 – 0.02</td>
</tr>
<tr>
<td>*Total</td>
<td>26</td>
<td>0.16 ± 0.35</td>
<td>0.01 – 0.31</td>
</tr>
</tbody>
</table>

*ES significantly different from zero

$T_{\text{lim}}$ Time limit of endurance

1.3.4.5 Protocol dependency of caffeine studies (X)

It has become increasingly clear that there are substantive issues relating to the reliability and validity of $T_{\text{lim}}$ protocols such as the MAOD (Hickey et al., 1992; McLellan et al., 1995; Jeukendrup et al., 1996; Marino et al., 2002; Saris et al., 2003). In addition to the findings in III, a number of other reliability studies have shown that the coefficient of variation for $T_{\text{lim}}$ protocols was as high as 6-31% (McLellan et al., 1995; Jeukendrup et al., 1996; Marino et al, 2002; Saris et al., 2003). Time to exhaustion protocols lack ecological validity – there are very few sporting events that require participants to exercise to exhaustion at one constant workload. Paper X provides evidence to suggest that caffeine is much more likely to positively affect ST $T_{\text{lim}}$ protocols in comparison to non-$T_{\text{lim}}$ exercise protocols (Table 1). Thus, the reason for moderate to large ESs with caffeine studies that have used $T_{\text{lim}}$ protocols may have less to do with the effects of caffeine and more to do with the idiosyncrasies of the $T_{\text{lim}}$ protocol. Crucially, although issues of test validity have been discussed previously in the literature (Jeukendrup et al., 1996; Saris et al., 2003), X represents the first time that differences between $T_{\text{lim}}$ and non-$T_{\text{lim}}$ measurements have been quantified in any meaningful context. These results may influence researchers in the field to more rigorously scrutinise and critique the types of protocols they employ.
1.3.5 Objective E: The effects of combining creatine supplementation with caffeine on ST (VI).

1.3.5.1 Minimising the potential interference of combining creatine supplementation and acute caffeine ingestion

Creatine monohydrate is another ergogenic aid that has been shown to enhance ST (Balsom et al., 1993; Vandenberghe et al., 1996; Jacobs et al., 1997). When II was published, applied sport scientists had begun to investigate the possible synergistic effects of caffeine and oral creatine monohydrate during ST (Vandenburghe et al., 1996; Vanakoski et al., 1998). Creatine, a nitrogenous amine, is a popular sport supplement that has been subjected to far greater scrutiny than caffeine, particularly in the past few years (Balsom et al., 1993; Vandenberghe et al., 1996; Jacobs et al., 1997). A frequently referred to study in this regard is by Vandenburghe et al. (1996) who investigated the effects of combining creatine monohydrate supplementation with caffeine ingestion. Vandenberghe hypothesised that caffeine, a potent sympathomimetic agent, might facilitate the uptake of exogenous creatine by skeletal muscle, since creatine is transported into skeletal muscle by active transport using a Na+-dependent transporter. The authors of this study subsequently found that caffeine supplementation taken at the same time as creatine loading, interferes with the subsequent ergogenic effects of creatine. The findings from this study appear to have influenced the design of numerous creatine supplementation studies (Cooke et al., 1997; Snow et al., 1998; Vandeberrie et al., 1998; Urbanski et al., 1999; Van Leemputte et al., 1999; Becque, et al., 2000; Haff et al., 2000; Izquierdo et al., 2002; Mujika et al., 2000; Shomrat et al., 2000); are referred to in the ACSM Consensus Statement on creatine supplementation (Terjung et al., 2000); and are also referred to in the only textbook dedicated exclusively to the effects of creatine supplementation on sports performance (Williams et al., 1999).

VI was designed to provide an original alternative strategy to the one offered by Vandenburghe et al. (1996), one that might optimise the independent effects of creatine and caffeine whilst minimising the interference of combining these nutritional supplements. VI involved 14 male subjects undergoing a supplementation program of oral creatine monohydrate (20 g • d⁻¹ for 6 days) whilst abstaining from caffeine for the duration of the loading period. Ingestion of a single dose of caffeine was then taken prior to exercise (i.e. as is the case in most caffeine studies).
1.3.6 Objective F; Examination of caffeine's mechanisms of action on ST (II, VI, IX).

If caffeine can affect ST, it is incumbent on researchers to seek an explanation. In this respect, previous research in the field had mostly examined metabolic changes following caffeine ingestion and ST (Collomp et al., 1991; Anselme et al., 1992; Collomp et al., 1992; Jackman et al., 1996). However, it is conceivable that physiological variables might also be affected by caffeine during ST. Thus, in addition to examining changes in blood lactate, adrenaline and potassium concentrations, studies II, VI, and IX also investigated physiological variables including the MAOD, heart rate and $\dot{V}O_2$.

1.3.6.1 Metabolic mechanisms of action (II, VI, IX).

The non-aerobic energy required to cover the MAOD during ST lasting 1 - 5-min is derived mostly from anaerobic glycolysis (~80%) and the ATP-creatine phosphate energy system (~16%) (Spriet, 1995b). Since this series of investigations provides evidence that caffeine ingestion stimulated anaerobic glycolysis to a much greater extent than placebo, it may partly be through this component that caffeine exerts its ergogenic effect (Collomp et al., 1991; Anselme et al., 1992; Collomp et al., 1992). A consistent finding in caffeine studies involving ST has been an increased elevation in plasma adrenaline concentration both at rest and following exercise (Collomp et al., 1991; Collomp et al., 1992; Anselme et al., 1992; Jackman et al., 1996; Bell et al., 2001), together with increased blood lactate accumulation (Collomp et al., 1991, Collomp et al., 1992; Anselme et al., 1992; Jackman et al., 1996) and blood glucose following exercise (McNaughton, 1986; MacIntosh and Wright, 1995; Bell et al., 2001; Graham, 2001a). These metabolic changes have, in most cases, accompanied improvements in measures of ST (Collomp et al., 1991; Collomp et al., 1992; Anselme et al., 1992; Jackman et al., 1996). Most authors agree that the accumulation of adrenaline which accompanies ST is commensurate with increased muscle glycogenolysis (Wendling et al., 1996). Adrenaline binds to $\beta$-adrenergic receptors on the sarcolemma which leads to a cascade of reactions resulting in the activation of glycogen phosphorylase. Phosphorylase is the enzyme responsible for glycogen breakdown in skeletal muscle and increased activity may lead to a greater glycogenolytic rate (Spriet, 1995b). It is known that the release of adrenaline from the adrenal medulla following caffeine ingestion...
augments the rise seen with exercise alone by a factor of two to three (Graham and Spriet, 1991). Thus, it has been suggested that the enhanced power output during ST following caffeine ingestion is a result of an adrenaline-mediated increase in muscle glycogenolysis (Collomp et al., 1991; Anselme et al., 1992; Collomp et al., 1992) which in turn increases blood lactate accumulation. Taken together, studies II, VI, and IX provide support for this theory. Plasma adrenaline concentration was significantly greater following caffeine ingestion in VI, and, although blood lactate concentration was not altered in this particular study, over the course of the three studies there was a distinct trend for an increase in blood lactate concentration (Table 2).

Table 2. Comparison of the mean (± SD) blood and plasma lactate concentrations in studies II, VI, and IX

<table>
<thead>
<tr>
<th>Publication</th>
<th>Sampling Site</th>
<th>Sampling time</th>
<th>Post-exercise lactate</th>
<th>Δ %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>post-exercise</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo (mMol)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Caffeine (mMol)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Earlobe</td>
<td>5</td>
<td>11.9 (2.7)</td>
<td>13.0 (2.1)</td>
</tr>
<tr>
<td>VI</td>
<td>Forearm vein</td>
<td>1</td>
<td>14.0 (3.1)</td>
<td>14.4 (3.0)</td>
</tr>
<tr>
<td>IX</td>
<td>Earlobe</td>
<td>4</td>
<td>11.5 (1.4)</td>
<td>13.6 (2.9)*</td>
</tr>
<tr>
<td>IX</td>
<td>Earlobe</td>
<td>5</td>
<td>12.3 (1.5)</td>
<td>13.3 (1.8)*</td>
</tr>
<tr>
<td>IX</td>
<td>Earlobe</td>
<td>6</td>
<td>12.3 (1.6)</td>
<td>13.3 (2.0)*</td>
</tr>
</tbody>
</table>

* significant increase in lactate following caffeine ingestion in comparison with placebo.

Δ % = ((mean caffeine - mean placebo) / mean placebo)100.

In VI, it was also observed that post-exercise blood glucose concentration in the caffeine trial was higher compared to the baseline trial. These results support other studies that have also shown higher glucose concentrations following caffeine ingestion (McNaughton, 1986; MacIntosh and Wright, 1995; Laurent et al., 2000; Bell et al., 2001; Graham, 2001b). It may well be that glycogenolysis was proceeding at a greater rate with caffeine present, and, or, a higher steady level blood glucose was maintained in the caffeine condition (MacIntosh and Wright, 1995). Adrenaline increases liver glycogenolysis, and it is possible that this is the pathway by which blood glucose was elevated in the caffeine trial in VI.

Finally, because excitation-contraction events drive metabolism, they are almost certainly involved in the fatigue process (Graham, 2001b). In this respect, several
observations suggest that accumulation of extracellular potassium ([K⁺]) might be important for the development of fatigue in skeletal muscle (Sejersted and Sjogaard, 2000; Bickham, 2003; Nielsen et al., 2003). An accumulation of muscle interstitial [K⁺] is likely to impair membrane excitability and would result in less motor unit activation and, or, less force production per motor unit (Lindinger et al., 1993; Spriet and Howlett, 2000; Graham, 2001b). It has been shown that caffeine ingestion reduces the accumulation of plasma [K⁺] during endurance exercise (Lindinger et al., 1993; MacIntosh and Wright, 1995). For the first time, VI has also demonstrated that caffeine ingestion may result in lower plasma [K⁺] following ST. This was the case even though \( T_{1/2} \) was increased with caffeine. It is speculated that caffeine, and, or the associated increase in adrenaline (as reported in VI), affects the washout of K⁺ from the active muscle and, or, the clearance of K⁺, by stimulating muscle Na⁺,K⁺-ATPase pumps to facilitate a larger re-uptake of K⁺ (Graham, 2001b).

1.3.6.2 Physiological outcomes (II, VI).

The dominant contribution to the total energy demand during exercise lasting 2-5-min is through oxidative metabolism (Spriet, 1995b). This is corroborated in studies II and VI where it was calculated that the mean aerobic and anaerobic contribution to the total energy demand to ST lasting between 2-5-min was approximately 64% aerobic : 36% anaerobic, for both placebo and caffeine trials. Thus, a physiological rationale for how caffeine impacts on the type of exercise under investigation may be just as much, if not more, related to oxidative metabolism as it is to anaerobic metabolism. Caffeine ingestion significantly increased total \( \dot{V}O_2 \) in VI in comparison to the placebo trial. This is in spite of the fact that there were no changes in the contribution of oxidative metabolism to the total energy demands (possibly because the anaerobic contribution, i.e. MAOD, also increased along with total \( \dot{V}O_2 \)). The increase in total \( \dot{V}O_2 \) might be explained by subjects either achieving a higher \( \dot{V}O_2 \max \) or attaining \( \dot{V}O_2 \max \) at a faster rate in the caffeine trial. Unfortunately one can only speculate on this scenario since the protocol used in VI did not facilitate measurement of \( \dot{V}O_2 \) kinetics or serial collections of \( \dot{V}O_2 \). There is support in the literature both for and against an increase in \( \dot{V}O_2 \max \) following caffeine ingestion. Of the seven studies that have investigated the effects of caffeine on graded exercise and \( \dot{V}O_2 \max \), two have shown significant improvements in \( \dot{V}O_2 \max \) (Toner et al.,
1982; Flinn et al., 1990), while the other five studies have failed to demonstrate any such improvements (Powers et al., 1983; Gaesser and Rich, 1985; Bond et al., 1987; Gastin et al., 1990; Dodd et al., 1991). In the meta-analysis (X), which considered all of the caffeine graded exercise tests, the 95% confidence interval crossed the zero boundary suggesting that there is no significant effect of caffeine on GXT. In one of the studies that measured $\dot{V}O_2$ during ST, Wiles et al. (1992) found that ingestion of 3 g of caffeinated coffee in 1,500 m runners ($n = 6$) elevated $\dot{V}O_2$ in a 1,500 m run at a velocity that was 0.5 km · h$^{-1}$ slower than the athlete’s fastest 1,500 m pace. Toner et al. (1982) found that maximum heart rate increased in tandem with an increase in $\dot{V}O_2_{max}$ and thus speculated that an increase in cardiac output caused the elevation in $\dot{V}O_2_{max}$. In the present series of studies there were no differences in maximum heart rate between caffeine and placebo treatments (III, VI, IX). The elevated total $\dot{V}O_2$ in VI may have been caused by stimulation of the sympathetic nervous system, which may have included an increased release of adrenaline with the caffeine trial (Section 2.1.6.1). Alternatively, the increased $\dot{V}O_2$ may have been due to increases in muscle temperature and, or, recruitment of a different muscle fibre profile, or indeed a different muscle group (Spriet, 1995b). The increase in $\dot{V}O_2$ will have translated into large amounts of extra ATP if carbohydrate was oxidised instead of being metabolised to lactate and this may help to explain the improved $T_{lim}$.

1.3.7 Objective G; The effects of caffeine on the Rating of Perceived Exertion during ST (VI, IX, XI)

Both VI and IX have, for the first time, observed the effects of caffeine on ST RPE. In VI, 14 subjects ran at 125% $\dot{V}O_2_{max}$ for a minimum of 2-min. Four RPE measurements were taken, one every 30 s. The results showed that RPE was lower at 90 s in the caffeine treatment (13.8 ± 1.8 RPE points) compared to baseline (14.6 ± 1.9 RPE points; $P < 0.05$). In IX, RPE was taken once every 30 s during the 2-min constant rate phase of the test (100% maximal ramp power output). Subjects’ perceptual responses at 30 s, 60 s, and 120 s appeared to be blunted by approximately 1 RPE point in the caffeine trial compared to the placebo trial. In VI, $T_{lim}$ and in IX, power output, were subsequently improved as the result of caffeine ingestion. Thus, as Spriet and Howlett (2000) have suggested, because of the dampened perceptual response, subjects may have been able to maintain higher motor unit activation (IX) and, or, were willing to
better tolerate the discomfort associated with ST (Spriet and Howlett, 2000) and therefore extend their exercise time to fatigue (VI) or increase power output (IX).

In comparison to the many endurance-based caffeine studies that have observed a reduction in RPE at the same standardised exercise intensity following caffeine ingestion (Costill et al., 1978; MacIntosh and Wright, 1995; Cole et al., 1996; Spriet and Howlett, 2000; Birnbaum and Herbst, 2004), studies VI and IX provide the first evidence that caffeine’s ergogenic effect during ST may also manifest itself via a dampened perceptual response.

Paper XI is a meta-analysis of the effects of caffeine ingestion on RPE during exercise (n = 21 studies) that included papers VI and IX. In comparison to placebo, caffeine ingestion was shown to reduce RPE by 5.6% (95% CI, -4.5% to -6.7%). Thus, for the first time, XI has quantified the effects of caffeine on RPE. The findings suggest that the perceived effort following caffeine ingestion is favourable for a wide range of exercise intensities, including ST (50% - 125% \( \dot{V}O_{2\,\text{max}} \)).
Chapter 13
13.1 Cellular mechanisms of action

In vitro and in situ studies have revealed that caffeine can increase muscle force production through stimulation of the central nervous system (CNS), enhancement of neuromuscular transmission, and facilitation of muscle fibre contractility (Williams, 1991; Dodd et al., 1993). These generalised effects are secondary to the cellular effects of caffeine. Of the known biochemical actions of caffeine (Graham et al., 1994), only inhibition of adenosine receptors occurs at concentrations achieved during normal consumption of the drug (Fredholm, 1995). Adenosine is a normal cellular constituent that is regulated mainly by ATP metabolism and other adenine nucleotides (Fredholm et al., 1999). In the CNS, adenosine is both a neurotransmitter and neuromodulator (Spriet and Howlett, 2000; Kalmar and Cafarelli, 2004). Through interactions with its receptors (mostly A1 and A2a), adenosine is involved in many organ systems including the cardiovascular system, neurotransmitter release and skeletal muscle (Lynge and Hellsten, 2000). In addition to adenosine antagonism, there is evidence that caffeine can directly affect ion handling, most importantly calcium and potassium, as well as alter the expression of key regulatory enzymes such as phosphorylase (Graham et al., 1994).

13.2 Effects on the central nervous system

Caffeine's stimulation of the CNS could facilitate optimal motor unit recruitment, recruitment of additional motor units and, or, increase the frequency of activation thereby potentiating muscle force production (Figure 1). Many in vitro studies have reported increased neurotransmitter release and lowered threshold for neuronal activation (Kalmar and Cafarelli, 2004). Caffeine facilitates neuromuscular transmission by increasing presynaptic neurotransmitter release by the motor neuron terminal during nerve stimulation thereby increasing muscle activation (Goldberg and Singer, 1969; Hoffman, 1969; Silinski and Redman, 1994). However, in a review of this area, Kalmar and Cafarelli (2004) state that caffeine's ergogenic effects are unlikely to be simply the result of stimulation of the CNS, since the effects of adenosine in the CNS are extremely diverse and complex (Fredholm et al., 1999). At the same time, Kalmar and Cafarelli (2004) also suggest that it may be possible to use caffeine in the future to study...
exercise-induced central failure after its effects on the human CNS have been better characterised.

13.3 Direct effects of caffeine on skeletal muscle
There is substantial evidence that caffeine can affect skeletal muscle calcium ($\text{Ca}^{2+}$). This includes increased $\text{Ca}^{2+}$ release from the sarcoplasmic reticulum, enhanced sensitivity of the myofilaments for $\text{Ca}^{2+}$, and, or, a combination of an increased release of caffeine and an increased sensitivity of myofilaments for $\text{Ca}^{2+}$ (Dodd, 1993). Dickson (1995) has also suggested that $\text{Ca}^{2+}$ re-uptake by the sarcoplasmic reticulum may be delayed. These actions will lower the threshold potential for excitation and extend the active period of contraction (Graham et al., 1994). In general, the effects of caffeine on $\text{Ca}^{2+}$ mechanisms have been discounted due to the high dose required to obtain an effect. However, Lee (1995) reported that physiological levels of caffeine cyclic ADP-ribose, a naturally occurring metabolite of NAD, can potentiate the effect of caffeine on the action of caffeine on the calcium-induced calcium release mechanism. This in turn would enhance excitation-contraction coupling (Figure 1) and possibly metabolic pathways (Jackman et al., 1996).

13.4 Enhanced exercise metabolism
It has been suggested that the enhanced power output during ST following caffeine ingestion is a result of an adrenaline-mediated increase in muscle glycogenolysis which in turn increases muscle and blood lactate accumulation (Figure 1; Collomp et al., 1991; Anselme et al., 1992; Collomp et al., 1992). However, while there is ample support in the ST literature for both an increase in adrenaline and blood lactate following caffeine ingestion (Collomp et al., 1991; Anselme et al., 1992; Collomp et al., 1992; Bell et al., 2001; VI), direct muscle metabolite data suggest these findings may only be coincidental to any ergogenic effect (Jackman et al., 1996; Graham et al., 2000). In one study, caffeine elevated arterial lactate levels during exercise, but muscle lactate levels and release from the exercising leg were not altered (Graham et al., 2000). Perhaps the most likely explanation of any increased contribution from anaerobic glycolysis to energy supply after caffeine ingestion is that the improvement to performance, mediated by an enhanced perceptual response (Figure 1), demands an increased rate of ATP resynthesis.
Several observations suggest that accumulation of extracellular potassium ([K⁺]) might be important for the development of fatigue in skeletal muscle (Sejersted and Sjogaard, 2000; Bickham, 2003; Nielsen et al., 2003). An accumulation of muscle interstitial [K⁺] is likely to impair membrane excitability and would result in less motor unit activation and, or, less force production per motor unit (Lindinger et al., 1993; Spriet and Howlett, 2000; Graham, 2001b). It has been shown that caffeine ingestion reduces the accumulation of plasma [K⁺] during exercise (Lindinger et al., 1993; MacIntosh and Wright, 1995; VI). Lindinger et al., (1996) have outlined possible mechanisms by which caffeine may increase Na⁺K⁺-ATPase activity. These include: (1) a role for increased intracellular [Ca²⁺], (2) Ca²⁺ or adenosine-receptor mediated increases in intracellular cyclic AMP, and (3) a direct action of caffeine on the Na⁺K⁺-ATPase.

Figure 1. A schematic of the various 'signals' & 'routes' by which caffeine may affect ST & RPE. N-MT, neuromuscular transmission; CHOan, anaerobic glycolysis; DMX, dimethylxanthines; SNS, sympathetic nervous centre; ECC, excitation-contraction coupling.

13.5 The effects of caffeine ingestion on RPE
As referred to above, there is evidence that caffeine exerts a direct influence on both central and peripheral events along the motor pathway (Figure 1). These events could independently or in combination alter RPE via both motor and sensory pathways. For example, by blocking the inhibitory effects of adenosine, caffeine may decrease the firing threshold of motorneurones and increase descending drive from the motor cortex thereby recruiting more motor units and
spreading tension requirement over a large muscle mass. Plaskett and Cafarelli (2001) found that caffeine reduced force sensation during the first 10-20 s of repeated muscle contractions and concluded that the rapidity of the effect suggested that caffeine exerts its effect neurally. In addition, in vivo muscle force for any given submaximal stimulus is greater after caffeine ingestion (Lopes et al., 1982; Kalmar & Cafarelli 1999; Tarnopolsky et al., 2000) and this in turn may also alter perceived exertion (Spriet & Howlett, 2000). Finally, caffeine has established central and peripheral antinociceptive actions (Sawynok, 1998), possibly mediated by an increase in β-endorphin levels (Laurent et al., 2000), and these actions might be most important during ST. It is plausible that caffeine antagonises peripheral and, or, CNS adenosine A₁ and A₂A receptors in neurons involved in nociception, such as Type IV muscle afferents, the dorsal horn of the spinal cord, the thalamus, or the sensory cortex (O'Connor et al., 2004). Thus the analgesic properties of caffeine may also need to be included in any final explanation of caffeine's effect on RPE (Myers et al., 1997; Motl et al., 2003; O'Connor et al., 2004).
Summary, recommendations and limitations

14.1 Summary of findings
The aim of this series of studies was to investigate the effects of oral caffeine ingestion on whole-body, short-term, high-intensity exercise (ST; representing an exercise intensity of between 100% - 150% \( \dot{V}O_2_{\text{max}} \)). Previously, this area of research has received scant attention due to a lack of established ST protocols, and a dominant endurance-based theory which led some researchers to dismiss the idea that caffeine could affect ST.

One of the first steps was to evaluate the validity and reliability of a popular ST protocol, the maximal accumulated oxygen deficit (MAOD). It was found that, in common with other 'open-ended' (T_{lim}) tests, the MAOD, lacked both validity and reliability. Although traditional reliability markers were favourable, the 95% limits of agreement were unacceptably large. Moreover, the validity of MAOD was found to be questionable because a study of elite male and female runners revealed that a large proportion were unable to accomplish a plateau in the \( \dot{V}O_2 \) - exercise intensity relationship. This finding raises questions about the validity of the MAOD extrapolation procedure. A follow-up study (VIII) to the MAOD tests, developed for the first time a bespoke 'preloaded' ST cycling protocol. Unlike the MAOD test, this preloaded test, which utilises both a constant rate and performance test element, was found to be reliable. Of the MAOD and the preloaded protocol, the preloaded protocol would appear to be the most appropriate for investigators observing the effects of ergogenic aids on ST.

The work has considered the original, and as yet, undeveloped potential, for the assessment of perceived exertion during ST (RPE; Borg, 6-20 scale). RPE during the first two minutes of constant-rate ST was shown for the first time to display a linear relationship to time. In addition, as determined by several markers of reliability, it was found that RPE could reliably be used during ST.

Three of the publications have demonstrated that caffeine can be ergogenic during ST, with improvements averaging 11% (95% CI, 7.4% - 14.5%) above the placebo treatment. The investigations have thus added considerable weight to the literature that suggests a moderate dose of oral caffeine (5 mg · kg\(^{-1}\)) can be ergogenic during ST. In this context, the studies contributed to a meta-analysis
that resulted in an effect size with 95% confidence intervals greater than zero. The meta-analysis also demonstrated that, in comparison to non-$T_{lim}$ based protocols, such as the preloaded cycle test, $T_{lim}$-based protocols, such as the MAOD, may inadvertently provide researchers with an enhanced prospect of achieving ergogenic effects; a finding with wide-ranging implications for workers in the field. It is recommended that researchers question the future use of $T_{lim}$-based protocols.

The studies have examined physiological and metabolic mechanisms of action that may help explain caffeine’s impact on ST. Since caffeine appears to increase both adrenaline and blood lactate following ST, as noted in other caffeine ST studies, it may well be that caffeine stimulates anaerobic glycolysis during ST, which subsequently leads to an increased rate of ATP production. In association with this increase in adrenaline there is also evidence for an increased total oxygen consumption during $T_{lim}$ ST. At the same time potassium efflux from skeletal muscle could be reduced following caffeine ingestion, because, in comparison to placebo, plasma potassium concentrations were lower after ST. It may well be through a reduction in electrolyte disturbance that caffeine exerts its ergogenic effect during ST. However, taken together, the evidence for mechanisms in this series of publications is not conclusive and certainly does not rule-out future work that investigates or clarifies more objective mechanisms of action.

Finally the work has demonstrated, for the first time, that the perceptual response to ST as measured by RPE is blunted following caffeine ingestion. This reduction in perceived exertion may enable subjects to maintain higher motor unit activation and, or, better tolerate the discomfort associated with ST, factors that would be associated with an improvement in ST. However, the exact mechanism by which caffeine affects RPE during ST is unknown (XI).

It is concluded that caffeine is ergogenic during ST, particularly when $T_{lim}$-based protocols are used. Considering that $T_{lim}$-based protocols tend to be unreliable, the effects of caffeine must be considerable. While the exact mechanism(s) of action for the ergogenic effects of caffeine on ST remains unknown, one consistent test outcome is a reduction in RPE during constant-rate ST.
14.2 Recommendations for future research
14.2.1 Applied and performance aspects

Based on the findings of this series of publications, several lines of future research seem warranted. In the first instance, if findings from future studies are to be of direct relevance to athletes, selection of appropriate subjects should be of paramount importance. Female as well as male participants should be recruited, and, in order to allow generalisations to be made to high performance athletes, subjects should be of at least national standard in their chosen sport. Likewise the assessments and, if possible, the environment, must directly match those of real world competition. Certainly, based on the poor reliability of \( T_{lim} \)-based protocols (III) and the findings from the meta-analysis (X), the more valid performance-based protocols should be employed. A useful template to follow in this respect is the choice of subjects, ergometer, and protocol, used by Anderson et al. (2000) and Bruce et al. (2000). These authors recruited elite oarsmen and oarswomen in assessing the effects of caffeine on a 2 km rowing time trial - the distance most commonly used by rowers in competition. A rowing ergometer that simulates the action of rowing, and which is also used extensively in the training of rowers was used by the researchers.

Considering that caffeine has a half-life of approximately 4 h (Fredholm et al., 1999), where competition is held over an extended period of time, such as several heats or bouts of an event held over the course of one-day, it would be desirable to examine modes of administration of caffeine other than the single bolus given one hour prior to exercise - as administered in the current series of publications. Similar to recent work by Bell et al. (2003) and Conway et al. (2003) involving endurance exercise, it would be of interest to determine an optimum repeated caffeine administration during the course of an extended period of time where ST is performed.

In contrast to single-bout ST, only one study has considered the effects of caffeine on repeated ST (Greer et al., 1998). Four, 30 s Wingate sprints were performed with 4 minutes rest between each bout (n = 9 recreationally active men). Caffeine ingestion (6 mg/kg) did not have any effect on power output (peak or average) in the first two sprints and had a negative effect in the latter two bouts. Since caffeine ingestion has consistently elevated blood lactate levels during and following exercise, it would be of considerable interest to examine in
more detail the effects of caffeine on repeated ST. In particular, sport-specific protocols that more closely mimic multiple-sprint sports would be most desirable.

14.2.2 The search for an explanation of how caffeine affects ST
In tandem with work on the applied aspects of caffeine ingestion on ST, it is recommended that future research also be concerned with a more rigorous examination of the possible explanation/s for how caffeine affects ST.

Rather than rely on the precise though limited Douglas bag methodology, a breath-by-breath approach would allow for a more complete assessment of respiratory gas analysis. A case in point is that breath-by-breath analysis would allow for assessment of O$_2$ 'on-kinetics' (Bell et al., 1999) as well as for an examination of transient $\dot{V}$O$_2$ changes during exercise, such as the $\dot{V}$O$_2$ slow component. Interestingly, Santalla et al. (2001) have recently shown that caffeine can reduce the $\dot{V}$O$_2$ slow component at an exercise intensity equivalent to 90% $\dot{V}$O$_2$ max in endurance-based elite runners.

Electromyography (EMG) is another measurement that might also allow some insight into the effects of caffeine on ST. EMG technology has improved rapidly in recent years, in particular with respect to reductions in signal artefact, an important issue during ST. The use of EMG would allow for analysis of motor unit recruitment and could be combined with an assessment of the $\dot{V}$O$_2$ slow component. This is important as the most recent research has suggested that an increased recruitment of the O$_2$ inefficient fast-twitch motor units is the most probable cause of the slow component of $\dot{V}$O$_2$ (Krustrup et al., 2004).

As revealed in all three caffeine studies (II, VI, IX), caffeine does not enhance ST in all subjects - the so-called 'non-responders'. Although there is some evidence that factors such as caffeine habituation (Bangsbo et al., 1992) and fitness levels (XI) are implicated in a participants exercise response to caffeine, there have been no studies that have systematically identified what physiological, metabolic or perceptual features distinguish responders from non-responders. This type of investigation would almost inevitably lead to an improved understanding of the effects of caffeine on ST.
For the first time, this series of publications has shown that RPE can be altered during ST, with an affect that may be related to subsequent ST performance (VI, IX, XI). However, although there are several strong candidates, including central and peripheral changes and alterations in cardiorespiratory dynamics, exactly what causes caffeine's effect on RPE is unknown (XI). Because pain is an almost inevitable consequence of ST, it may be worthwhile to systematically investigate caffeine's known analgesic effects. There is evidence that caffeine can independently affect pain ratings during both single muscle (Myers et al., 1997) as well as whole-body exercise (Motl et al., 2003; O'Connor et al., 2004).

According to O'Connor et al. (2004) there have been no experiments measuring athletic performance that have also measured muscle pain, and experiments measuring muscle pain have not measured athletic performance. Thus, there is a need to extend current work to explore the interaction of the effects of caffeine on muscle pain and differentiated RPE during ST (O'Connor et al., 2004; XI).

Over 20 years ago, Laska et al. (1982) proposed that the enhanced analgesia perceived by patients was chiefly a result of changes in mood and the overall sense of 'well-being' following even small amounts, i.e., 30 mg, of caffeine. In a similar way, mood changes brought about by caffeine ingestion might also be partly responsible for the subsequent reduction in RPE and improvement in ST. The investigation of mood states, together with factors such as self-rated happiness, calmness and alertness during exercise (Backhouse et al., 2004) may yield an improved understanding of the behavioural effects of caffeine ingestion on RPE during ST. From a behavioural perspective there is also some evidence to suggest that caffeine improves mental (cognitive) performance during and after exercise (Hogervorst et al., 1999). Because many ST activities require a combination of mental as well as physical performance, another recommendation would be to perform cognitive assessments (e.g., attention, psychomotor, and memory) as a part of caffeine ST studies.

14.3 Limitations

Limitations are possible shortcomings or influences that either cannot be controlled or are the result of the delimitations imposed by the researcher (Thomas and Nelson, 1996). The findings from this series of publications need to be considered in the light of the following methodological limitations. These include:
• A predominant use of male undergraduate sport science students (II, III, V, VI, VIII, IX)

• Non-assay of resting or exercise caffeine samples in 2 of the 3 caffeine studies (II, IX). This meant verification could not be made that subjects had abstained from caffeine-containing products in the 24 hours leading up to the tests in these studies.

• In VI, quantification of muscle creatine uptake was not made. There is a possibility that the subjects were mostly 'non-responders' to the creatine supplementation.

• Because caffeine abstinence may produce a variety of withdrawal effects, improvements in ST following the experimental administration of caffeine (II, VI, IX) may simply have involved the restoration of performance which had been degraded during the pre-trial period of the 24-h of caffeine abstinence (James, 1998).

• In the MAOD tests (II, VI), respiratory gases were collected with 1000 L Douglas bags. This meant that confirmation could not be made that subjects achieved \( \dot{V}O_2 \text{max} \) during the run to exhaustion in the MAOD tests.

• The reliability of the MAOD test (III) was only performed after evaluating the effects of caffeine ingestion on the MAOD (II and VI). Ideally, an assessment of the reproducibility of tests should be performed prior to their use in experimental trials.

• There is uncertainty that valid comparisons of blood samples can be made in the \( T_{\text{lim}} \) protocols (II and VI), because subjects ran for a longer period of time following caffeine ingestion.

• The caffeine studies (II, VI, IX) lack direct application to mainstream sport.

• In VIII and IX, there was a 20-30 s time-lag in the achievement of the target exercise intensity.

• In IX, total work done in the constant-rate phase could have been used as a cofactor in the statistical analysis of the effects of caffeine on the 1 minute performance test.

• In VI and IX, the placebo and caffeine RPE regression lines could have been analysed using the intercept and slopes.
References


Williams, M., Kreider, R.B., and Branch, J.D. (1999) *Creatine; the power supplement* Human Kinetics, Champaign Illinois. p. 35.


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Appendix 1

A list of known peer-reviewed work where the publications have been cited


Appendix 2
Acknowledgement of work from a leading researcher in the field

The following letter is an unsolicited acknowledgement of the value of X, from Professor Ron Maughan, Co-editor of the *International Journal of Sports Nutrition and Exercise Metabolism*, and one of the foremost authorities on the effects of ergogenic aids on sports performance.
I was very interested to read your meta-analysis of the effects of caffeine on performance and look forward to seeing this in print in Int J Sports Nutr. The removal of caffeine from the IOC/WADA doping list will surely provide an impetus to studies in this area, and your review will be a starting point for those seeking to review the literature.

I was recently asked to write a short review on coffee and performance and would like to make reference to your review as being “in Press”. I would not normally seek to do this, but feel that your paper would be a valuable reference point.

Such reference, of course, would only be made with your permission, and I therefore write to ask for this.

With best wishes,

Ron Maughan
Appendix 3
Summary of applicant contribution to the published works and co-author declarations

Table 3 outlines a summary of the applicant's contribution to the published works. The co-author declarations that endorse this summary can be found on the pages that follow.

Table 3. Summary of applicant contribution to the published works

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A Ideas & planning of study
B Data collection
C Data analysis
D Write-up
E Impact factor of journal from Science Citation Index*
F Number of authors
NA Not applicable
NR Not reported

*A journal's impact factor is the number of times the average recent article in the journal has been mentioned (cited) in other recent articles. These data were published in 2002 (accessed from http://www.sportsci.org, 16th September, 2004).
UNIVERSITY OF LUTON

FORM RSPP2

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Item No.

Co-author declaration

Note: This form is to be included, as part of a submission for PhD by Publication, where publications involving joint or co-authorship are to be considered. A copy of this form must be submitted for each individual work, and by each individual author involved (other than the candidate for the degree).

1. The Applicant

Name: Michael Doherty

Title of research area of submission: The Effects of Caffeine on Short-Term, High-Intensity Exercise

2. The Publication

Names of all authors: Doherty, M., Smith, P.M. and Schroeder, K.


3. Contribution

(Please give concise information about the contribution made by the candidate to the above publication. An indication of the nature of the contribution - qualitative or quantitative - may be provided where appropriate, as well as an indication of the contribution in percentage terms if appropriate)

- Ideas & planning of study 100%
- Data collection 70%
- Data analysis 100%
- Write-up 95%

4. Declaration

I am in agreement that, with regard to the details provided in section 3 above, this is an accurate reflection of the candidate's contribution to the publication specified and being submitted here, in partial fulfilment of the degree of Doctor of Philosophy by Publication at the University of Luton. The publication has not, to my knowledge, been submitted before for any degree or examination in any other University.

Signed (Co-author) 

Mr. Paul M. Smith

Date 06/09/04.
Co-author declaration

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- Ideas & planning of study: 100%
- Data collection: 70%
- Data analysis: 100%
- Write-up: 95%

4. Declaration

I am in agreement that, with regard to the details provided in section 3 above, this is an accurate reflection of the candidate’s contribution to the publication specified and being submitted here, in partial fulfilment of the degree of Doctor of Philosophy by Publication at the University of Luton. The publication has not, to my knowledge, been submitted before for any degree or examination in any other University.

Signed
(Chautor)  
Mr. Karl Schroder  

Date 13/09/04

UL/RSPUB2/97
Co-author declaration

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Name: Michael Doherty

Title of research area of submission: The Effects of Caffeine on Short-Term, High-Intensity Exercise

2. The Publication

Names of all authors: Doherty, M. and Smith, P.M.

Title and details of publication: Letter to the Editor-in-Chief. Med Sci Sport and Exerc 33, 1794-1795, 2001

3. Contribution

(Please give concise information about the contribution made by the candidate to the above publication. An indication of the nature of the contribution - qualitative or quantitative - may be provided where appropriate, as well as an indication of the contribution in percentage terms if appropriate)

- Ideas & planning of study: 100%
- Data collection: N/A
- Data analysis: N/A
- Write-up: 95%

4. Declaration

I am in agreement that, with regard to the details provided in section 3 above, this is an accurate reflection of the candidate's contribution to the publication specified and being submitted here, in partial fulfilment of the degree of Doctor of Philosophy by Publication at the University of Luton. The publication has not, to my knowledge, been submitted before for any degree or examination in any other University.

Signed (Co-author)  Mr. Paul M. Smith

Date 06/09/04.
Co-author declaration

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Title of research area of submission: The Effects of Caffeine on Short-Term, High-Intensity Exercise

2. The Publication

Names of all authors: Doherty, M., Smith, P.M., Davison, R.C.R., and Hughes, M.G.

Title and details of publication: Caffeine is ergogenic following supplementation of oral creatine monohydrate. Medicine and Science in Sport and Exercise 34, 1785-1792, 2002.

3. Contribution

(Please give concise information about the contribution made by the candidate to the above publication. An indication of the nature of the contribution - qualitative or quantitative - may be provided where appropriate, as well as an indication of the contribution in percentage terms if appropriate)

- Ideas & planning of study: 100%
- Data collection: 70%
- Data analysis: 100%
- Write-up: 80%

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Signed (Co-author)  
Mr. Paul M. Smith  
Date 06/09/04

UL/RSPUB2/97
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- Ideas & planning of study: 100%
- Data collection: 70%
- Data analysis: 100%
- Write-up: 80%

4. Declaration

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Signed (Co-author) Dr R. C. Richard Davison

Date 22/09/04

UURSPUB2/97
Co-author declaration

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- Ideas & planning of study: 100%
- Data collection: 70%
- Data analysis: 100%
- Write-up: 80%

4. Declaration

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Signed (Co-author)  
Mr Michael G. Hughes  
Date 13-9-04
Co-author declaration

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1. The Applicant

Name: Michael Doherty

Title of research area of submission: The Effects of Caffeine on Short-Term, High-Intensity Exercise

2. The Publication

Names of all authors: Doherty, M., Smith, P.M., Hughes, M.G. and Collins, D.J.


3. Contribution

(Please give concise information about the contribution made by the candidate to the above publication. An indication of the nature of the contribution - qualitative or quantitative - may be provided where appropriate, as well as an indication of the contribution in percentage terms if appropriate)

- Ideas & planning of study 100%
- Data collection 70%
- Data analysis 100%
- Write-up 90%

4. Declaration

I am in agreement that, with regard to the details provided in section 3 above, this is an accurate reflection of the candidate's contribution to the publication specified and being submitted here, in partial fulfilment of the degree of Doctor of Philosophy by Publication at the University of Luton. The publication has not, to my knowledge, been submitted before for any degree or examination in any other University.

Signed (Co-author) 
Mr Paul M. Smith

Date 06/09/04.
Co-author declaration

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3. Contribution

(Please give concise information about the contribution made by the candidate to the above publication. An indication of the nature of the contribution - qualitative or quantitative - may be provided where appropriate, as well as an indication of the contribution in percentage terms if appropriate)

- Ideas & planning of study: 100%
- Data collection: 70%
- Data analysis: 100%
- Write-up: 90%

4. Declaration

I am in agreement that, with regard to the details provided in section 3 above, this is an accurate reflection of the candidate’s contribution to the publication specified and being submitted here, in partial fulfilment of the degree of Doctor of Philosophy by Publication at the University of Luton. The publication has not, to my knowledge, been submitted before for any degree or examination in any other University.

Signed
(Co-author) Mr. Michael G. Hughes

Date 13-9-04
Co-author declaration

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3. Contribution

(Please give concise information about the contribution made by the candidate to the above publication. An indication of the nature of the contribution - qualitative or quantitative - may be provided where appropriate, as well as an indication of the contribution in percentage terms if appropriate)

- Ideas & planning of study 100%
- Data collection 70%
- Data analysis 100%
- Write-up 90%

4. Declaration

I am in agreement that, with regard to the details provided in section 3 above, this is an accurate reflection of the candidate's contribution to the publication specified and being submitted here, in partial fulfilment of the degree of Doctor of Philosophy by Publication at the University of Luton. The publication has not, to my knowledge, been submitted before for any degree or examination in any other University.

Signed (Co-author) Professor David Collins

Date 15 SEP 04
Co-author declaration

Note: This form is to be included, as part of a submission for PhD by Publication, where publications involving joint or co-authorship are to be considered. A copy of this form must be submitted for each individual work, and by each individual author involved (other than the candidate for the degree).

1. The Applicant

Name: Michael Doherty

Title of research area of submission: The Effects of Caffeine on Short-Term, High-Intensity Exercise

2. The Publication

Names of all authors: Doherty, M., Nobbs, L., and Noakes, T.D.


3. Contribution

(Please give concise information about the contribution made by the candidate to the above publication. An indication of the nature of the contribution - qualitative or quantitative - may be provided where appropriate, as well as an indication of the contribution in percentage terms)

- Ideas & planning of study 50%
- Data collection 100%
- Data analysis 90%
- Write-up 20%

4. Declaration

I am in agreement that, with regard to the details provided in section 3 above, this is an accurate reflection of the candidate's contribution to the publication specified and being submitted here, in partial fulfilment of the degree of Doctor of Philosophy by Publication at the University of Luton. The publication has not, to my knowledge, been submitted before for any degree or examination in any other University.

Signed (Co-author)  

Dr L Nobbs

Date 07/10/2004
Co-author declaration

Note: This form is to be included, as part of a submission for PhD by Publication, where publications involving joint or co-authorship are to be considered. A copy of this form must be submitted for each individual work, and by each individual author involved (other than the candidate for the degree).

1. The Applicant

Name: Michael Doherty
Title of research area of submission: The Effects of Caffeine on Short-Term, High-Intensity Exercise

2. The Publication

Names of all authors: Doherty, M., Nobbs, L., and Noakes, T.D.

3. Contribution

(Please give concise information about the contribution made by the candidate to the above publication. An indication of the nature of the contribution - qualitative or quantitative - may be provided where appropriate, as well as an indication of the contribution in percentage terms)

- Ideas & planning of study: 50%
- Data collection: 100%
- Data analysis: 90%
- Write-up: 20%

4. Declaration

I am in agreement that, with regard to the details provided in section 3 above, this is an accurate reflection of the candidate's contribution to the publication specified and being submitted here, in partial fulfilment of the degree of Doctor of Philosophy by Publication at the University of Luton. The publication has not, to my knowledge, been submitted before for any degree or examination in any other University.

Signed (Co-author) T.D. Noakes
Professor T.D. Noakes

This information is absolutely correct. T.D. Noakes
Co-author declaration

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Title of research area of submission: The Effects of Caffeine on Short-Term, High-Intensity Exercise

2. The Publication

Names of all authors: Doherty, M., Balmer, J., Davison, R.C.R., Robinson, L., and Smith, P.M.


3. Contribution

(Please give concise information about the contribution made by the candidate to the above publication. An indication of the nature of the contribution - qualitative or quantitative - may be provided where appropriate, as well as an indication of the contribution in percentage terms if appropriate)

- Ideas & planning of study: 90%
- Data collection: 80%
- Data analysis: 80%
- Write-up: 80%

4. Declaration

I am in agreement that, with regard to the details provided in section 3 above, this is an accurate reflection of the candidate's contribution to the publication specified and being submitted here, in partial fulfilment of the degree of Doctor of Philosophy by Publication at the University of Luton. The publication has not, to my knowledge, been submitted before for any degree or examination in any other University.

Signed
(Attauthor)

Dr. James Balmer

Date 16/9/04

UL/RSPUB2/97
Co-author declaration

Note: This form is to be included, as part of a submission for PhD by Publication, where publications involving joint or co-authorship are to be considered. A copy of this form must be submitted for each individual work, and by each individual author involved (other than the candidate for the degree).

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- Ideas & planning of study 90%
- Data collection 80%
- Data analysis 80%
- Write-up 80%

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I am in agreement that, with regard to the details provided in section 3 above, this is an accurate reflection of the candidate's contribution to the publication specified and being submitted here, in partial fulfilment of the degree of Doctor of Philosophy by Publication at the University of Luton. The publication has not, to my knowledge, been submitted before for any degree or examination in any other University.

Signed (Co-author) [Signature]

Date 22/09/04

Dr. R.C. Richard Davison

UL/RSPUB2/97
Co-author declaration

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Signed (Co-author) Mr. Paul M. Smith

Date 06/09/04.

UU/RSPUB2/97
Co-author declaration

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   Names of all authors: Doherty, M., Davison, R.C.R., Smith, P.M., and Hughes, M.G.
   

3. Contribution
   
   (Please give concise information about the contribution made by the candidate to the above publication. An indication of the nature of the contribution - qualitative or quantitative - may be provided where appropriate, as well as an indication of the contribution in percentage terms if appropriate)

   • Ideas & planning of study 95%
   • Data collection 90%
   • Data analysis 100%
   • Write-up 90%

4. Declaration
   
   I am in agreement that, with regard to the details provided in section 3 above, this is an accurate reflection of the candidate's contribution to the publication specified and being submitted here, in partial fulfilment of the degree of Doctor of Philosophy by Publication at the University of Luton. The publication has not, to my knowledge, been submitted before for any degree or examination in any other University.

   Signed (Co-author) Dr. R.C. Richard Davison
   Date 22/09/04
Co-author declaration

1. The Applicant

Name: Michael Doherty

Title of research area of submission: The Effects of Caffeine on Short-Term, High-Intensity Exercise

2. The Publication

Names of all authors: Doherty, M., Davison, R.C.R., Smith, P.M., and Hughes, M.G.


3. Contribution

(Please give concise information about the contribution made by the candidate to the above publication. An indication of the nature of the contribution - qualitative or quantitative - may be provided where appropriate, as well as an indication of the contribution in percentage terms if appropriate)

- Ideas & planning of study: 95%
- Data collection: 90%
- Data analysis: 100%
- Write-up: 90%

4. Declaration

I am in agreement that, with regard to the details provided in section 3 above, this is an accurate reflection of the candidate's contribution to the publication specified and being submitted here, in partial fulfilment of the degree of Doctor of Philosophy by Publication at the University of Luton. The publication has not, to my knowledge, been submitted before for any degree or examination in any other University.

Signed (Co-author)  
Mr. Paul M. Smith  
Date 06/09/04.

UL/RSPUB2/97
Co-author declaration

Note: This form is to be included, as part of a submission for PhD by Publication, where publications involving joint or co-authorship are to be considered. A copy of this form must be submitted for each individual work, and by each individual author involved (other than the candidate for the degree).

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- Data analysis: 100%
- Write-up: 90%

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Signed (Co-author) Mr Michael G. Hughes

Date 13-9-04

UL/RSPUB2/97
Co-author declaration

Note: This form is to be included, as part of a submission for PhD by Publication, where publications involving joint or co-authorship are to be considered. A copy of this form must be submitted for each individual work, and by each individual author involved (other than the candidate for the degree).

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Names of all authors: Doherty, M. and Smith, P.M.


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Signed (Co-author) Mr. Paul M. Smith

Date 06/09/04.

UL/RSPUB2/97
Appendix 4

List of works on which the candidature is based


