Spinal Cord Injury Level Influences Acute Plasma Caffeine Responses

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ABSTRACT

GRAHAM-PAULSON, T. S., T. A. W. PAULSON, C. PERRET, K. TOLFREY, P. CORDERY, and V. L. GOOSEY-TOLFREY. Spinal Cord Injury Level Influences Acute Plasma Caffeine Responses. *Med. Sci. Sports Exerc.*, Vol. 49, No. 2, pp. 363–370, 2017. **Purpose**: This study aimed to investigate the absorption curve and acute effects of caffeine at rest in individuals with no spinal cord injury (SCI), paraplegia (PARA), and tetraplegia (TETRA). **Methods**: Twenty-four healthy males (eight able-bodied [AB], eight PARA, and eight TETRA) consumed 3 mg·kg^{-1} caffeine anhydrous (CAF) in a fasted state. Plasma caffeine [CAF], glucose, lactate, free fatty acid, and catecholamine concentrations were measured during a 150-min rest period. **Results**: Peak [CAF] was greater in TETRA (21.5 μM) compared with AB (12.2 μM) and PARA (15.1 μM), and mean peak [CAF] occurred at 70, 80, and 80 min, respectively. Moderate and large effect sizes were revealed for TETRA compared with PARA and AB (−0.55 and −1.14, respectively) for the total area under the [CAF] versus time curve. Large interindividual responses were apparent in SCI groups. The change in plasma catecholamine concentrations after CAF did not reach significance ($P > 0.05$); however, both adrenaline and noradrenaline concentrations were lowest in TETRA. Significant increases in free fatty acid were seen over time ($P < 0.0005$), but there was no significant influence of SCI level. Blood lactate concentration reduced over time ($P = 0.022$), whereas blood glucose concentration decreased modestly ($P = 0.695$), and no difference between groups was seen ($P > 0.05$). **Conclusion**: The level of SCI influenced the caffeine absorption curve, and there was large interindividual variation within and between groups. Individual curves should be considered when using caffeine as an ergogenic aid in athletes with an SCI. The results indicate TETRA should trial low doses in training and PARA may consider consuming caffeine greater than 60 min before exercise performance. The study also supports caffeine's direct effect on adipose tissue, which is not secondary to catecholamine release. **Key Words:** ADRENALINE, NORADRENALINE, FREE FATTY ACID, ERGOGENIC, WHEELCHAIR ATHLETES

Supplementation with caffeine (3–6 mg·kg^{-1} body mass [BM]) can improve long and short-term endurance performance (7,9) in able-bodied (AB) participants. However, there is a paucity of research on the effects of caffeine on exercise performance in physically impaired populations, e.g., persons with a spinal cord injury (SCI). While current evidence is equivocal, a beneficial effect of caffeine (4–6 mg·kg^{-1} in capsule form) on short-term wheelchair propulsion exercise has been reported (5,13). These studies highlighted that there was great interindividual variability in wheelchair performance responses during a 1500-m time trial, 4 min maximal push, and repeated sprints, especially in individuals with an SCI. The authors highlighted the potential for slower caffeine absorption because of delayed gastrointestinal transit times and prolonged gastric emptying (GE), especially in those with a cervical lesion level (18). Understanding an individual's time to peak caffeine concentration has been shown to have little impact on prolonged AB endurance cycling performance (34) but is likely to be important before short-term upper-body exercise and may require further consideration in persons with an SCI.

Both metabolic and physiological functions are altered in individuals with an SCI, and the level and completeness of injury has been shown to influence drug pharmacokinetics (15,23). A review of the literature by Mestre et al. (23) indicated that the delayed absorption seen in some individuals with an SCI increased the time to achieve the required therapeutic dose. One drug reportedly affected by delayed GE and decreased gastrointestinal motility is theophylline (32), which can be used by individuals with an SCI to help treat bradycardia or to promote the recovery of hemidiaphragmatic function. Diminished bioavailability could result in underestimating the load and maintenance dose of theophylline in

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individuals with tetraplegia (TETRA) (32). As a methylxanthine drug, theophylline has similar pharmacodynamic actions to caffeine (28), and it has also been linked to improved endurance performance (14,22). There is therefore reason to believe that caffeine absorption may also be delayed in persons with an SCI. In disagreement, however, Van Soeren et al. (38) suggested that the time to peak caffeine concentration (6 $mg \cdot kg^{-1}$) in individuals with TETRA (~47 μM at 40 min, $n = 6$) did not differ to those of AB individuals. The authors, however, could not assess the influence of SCI lesion level on caffeine absorption because there was no direct control group and only two individuals with paraplegia (PARA). They also did not report individual participant data, which may help to explain interindividual performance responses. Flueck et al. (4) measured plasma caffeine concentrations (median) at 60 min only in AB individuals (45.1 $\mu mol \cdot L^{-1}$) and individuals with PARA (~54 $\mu mol \cdot L^{-1}$) and TETRA (66.1 $\mu mol \cdot L^{-1}$). It therefore remains difficult to determine whether the time course of caffeine absorption differs based on an individual's SCI level.

Numerous mechanisms of action have been proposed to help explain the beneficial effects of an acute dose of caffeine on exercise performance. Current research suggests that the main mechanism at physiological caffeine doses is the blockade of central nervous system (CNS) adenosine receptors, which indirectly affects neurotransmitter release (19) to increase arousal, alertness, and attention. Individuals with TETRA are therefore an interesting study population given the reduced sympathetic activity caudal to the lesion level and associated impaired catecholamine response (27). The study of this population has lent support to the hypothesis that caffeine can have a direct effect on tissues after reports of adrenaline-independent free fatty acid (FFA) mobilization (38). No study has directly investigated the acute effects of caffeine in a group of individuals with no SCI, PARA, and TETRA. Hence, the current study aimed to explore the time course of caffeine absorption and its effects at rest in these three groups, with the aim of providing safe and accurate recommendations for its use as an ergogenic aid by individuals with an SCI. It was hypothesized that caffeine absorption would be delayed in individuals with TETRA compared with those with PARA and no SCI.

METHODS

Participants. Twenty-four recreationally active males (eight AB controls, eight individuals with PARA, and eight with TETRA) provided informed consent to participate in the current study. Participants were classified using the American Spinal Injury Association (ASIA) scale (20). A health screening questionnaire was completed by all participants, and individuals were excluded if any of their medication had known interactions with caffeine. Average daily caffeine intake was assessed using a modified version of the caffeine consumption questionnaire (21). All procedures were approved by the Ethical Advisory Committee of the university and performed following the Declaration of Helsinki. Participants' characteristics are shown in Table 1.

Procedures. In the days before visiting the laboratory, participants maintained their normal dietary and activity patterns (light- to moderate-intensity exercise only) and their individual medication regimes. Participants were provided with a list of caffeine containing foods and drinks and were asked to abstain from consumption in the 36 h preceding their laboratory visit. Participants were also asked to refrain from alcohol consumption for 24 h before their visit.

Participants arrived at the laboratory between 8:00 a.m. and 10:00 a.m. after fasting from 9:00 p.m. the previous evening. Water consumption was encouraged to help ensure the participant arrived euhydrated. On arrival, participants were asked to void their bladder, if necessary, before lying in a semisupine position on a laboratory bed. Participants were asked to report any side effects to the investigators immediately at any point during the trial. A cannula (Venflon; Becton Dickinson, Helsinborg, Sweden) was inserted into an antecubital vein for subsequent venous sampling. The cannula was kept patent using 5–10 mL sodium chloride (0.9%) after each blood sample.

After a minimum 15-min rest, a baseline venous blood sample was taken. Participants then consumed cellulose capsules (Bulk Powders, Colchester, UK) containing 3 $mg \cdot kg^{-1}$ BM caffeine anhydrous (My Protein, Northwich, UK), which were filled manually by the investigators to the nearest 0.1 mg. Participants remained rested for 150 min during which a further nine blood samples were taken. The blood sampling schedule can be seen in Figure 1. After the final blood sample, participants were again asked whether they experienced any side effects during the experimental trial.

Blood sampling and analysis. Blood samples were immediately separated into tubes that contained the relevant preservative(s). At every sampling time point, 5 mL blood was added to an EDTA K2 vacutainer for subsequent plasma caffeine concentration ([CAF]) analysis. A 20-μL blood sample was removed and analyzed in duplicate for blood lactate ([BLa]) and glucose ([GLU]) concentrations using an automatic analyzer (Biosen C-Line; EKF Diagnostic GmbH, Barleben, Germany). For catecholamine and FFA analysis (baseline, 60, 90, and 150 min), a further 10 mL of blood was dispensed into two lithium-heparin tubes containing 37.5 μL ethyleneglycotetraacetic acid–glutathione for the subsequent analysis of plasma adrenaline ([A]), noradrenaline ([NA]), and [FFA] concentrations. In addition, 25 μL of 3 $mg \cdot mL^{-1}$ tetrahydrolipstatin was added to the tube

TABLE 1. Participants' characteristics.

	AB ($n = 8$)	PARA ($n = 8$)	TETRA ($n = 8$)
Age (yr)	25 ± 4	38 ± 10	33 ± 9
BM (kg)	83.2 ± 9.8	74.5 ± 12.9	73.2 ± 9.8
Lesion level	n/a	T4–L1	C5–C7
ASIA A/B	n/a	3/5	2/6
Time since injury (yr)	n/a	4.3 ± 4.3	12.2 ± 6.3
Habitual caffeine intake ($mg \cdot d^{-1}$)	218 ± 157	220 ± 145	224 ± 140
Use of caffeine as a performance aid	1	1	4

Data are presented as mean ± SD. T, thoracic; L, lumbar; and C, cervical level SCI.

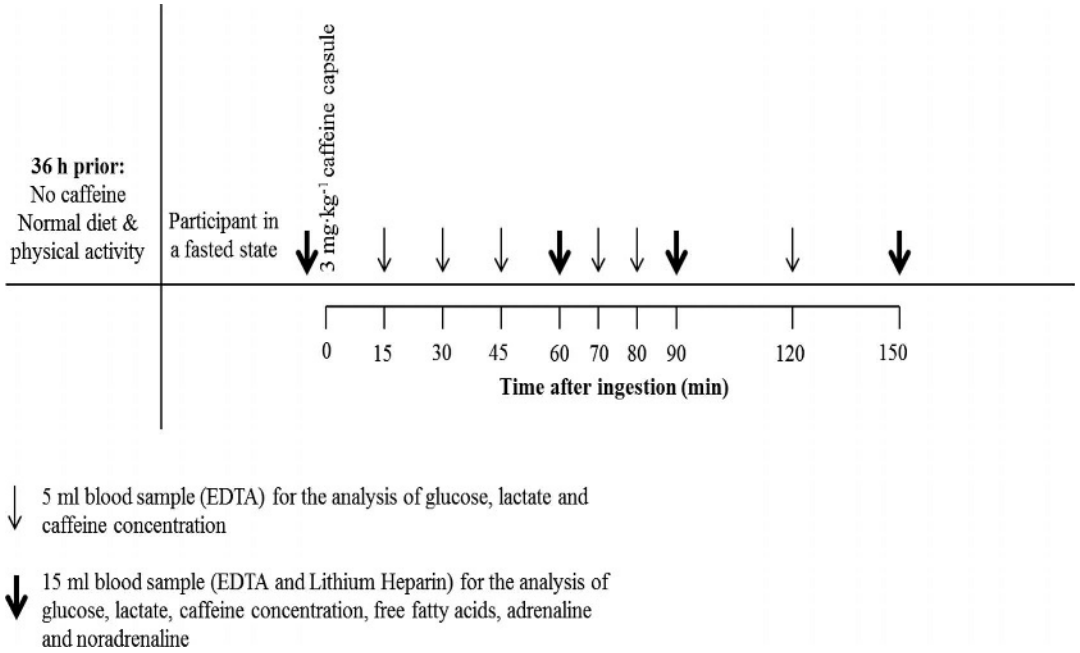

FIGURE 1—Schematic of the experimental protocol.

for [FFA] analysis. All tubes were centrifuged at 1000*g* for 10 min at 4°C as previously described (12). Plasma samples were aliquoted into Eppendorfs and stored at −80°C until analysis.

Plasma [CAF] was analyzed using high-performance liquid chromatography (HPLC) as described by Holland et al. (16) with the following minor modifications: before injection onto the HPLC column, each sample was individually filtered (Mini-UniPrep syringeless filters; Fisher Scientific, UK) and no guard column was used. The method produced a coefficient of variation (CV) of 1.06% (range, 0.24%–1.45%).

Plasma [A] and [NA] were also determined using HPLC as previously described by Forster and Macdonald (6). A plasma volume of 500 μL was used for analysis. The method produced a CV of 0.31% and 0.17% for [A] and [NA], respectively.

Plasma was analyzed enzymatically for [FFA] using an *in vitro* enzymatic colorimetric method (Wako Instrument kit) and a Pentra 400 analyzer (Horiba Medical, Irvine, CA). The method produced an intra-assay CV of 1.68% and 1.28% for high and low FFA quality controls, respectively (four repeats of the quality control samples at intervals during the analysis).

Statistical analyses. Data were analyzed using the IBM Statistics Software Package for the Social Sciences version 22 (IBM Corporation, Armonk, NY). The trapezium rule was used to calculate the total area under the variable versus time curve for [CAF] (TAUC-CAF), [FFA] (TAUC-FFA), [A] (TAUC-A), and [NA] (TAUC-NA). The incremental area under the plasma concentration versus time curve for [FFA] (iAUC-FFA), [A] (iAUC-A), and [NA] (iAUC-NA) was also calculated using the same method after adjusting for baseline concentrations.

Normal distribution was checked using Shapiro–Wilk tests, and the data are presented as mean ± SD. Data for [FFA] were not normally distributed and were log transformed before analysis. These data are presented as geometric mean (95% confidence intervals [CI]), and analysis is based on the ratios of geometric means and 95% CI for ratios. The homogeneity of variances was confirmed by Mauchly's test of sphericity, and where the sphericity assumption was violated, the Greenhouse–Geisser correction was applied to the degrees of freedom.

Repeated-measures ANOVA values for group and time were used to examine differences between [FFA], [A], [NA], [Bla], and [GLU].

An ANCOVA was used to examine differences between [CAF], with daily caffeine consumption (low <50 mg·d^{-1}, moderate 50–250 mg·d^{-1}, and high >250 mg·d^{-1}) as a covariate. One-way repeated-measures ANOVA values were used to analyze TAUC and iAUC data. Planned simple and difference contrasts were applied to explain any significant results.

Statistical significance was accepted at $P \leq 0.05$ and absolute standardized effect sizes (ES) are included to supplement important findings. An ES of 0.2 was considered small, 0.5 moderate, and 0.8 large according to Cohen (3). Because of incomplete data sets (e.g., insufficient blood flow or a cannula change), the number of participants included in each analysis differs. Data sets were A (7/6/7), NA (7/7/8), FFA (7/7/7), Bla (5/5/6), and GLU (8/6/8) for AB, PARA, and TETRA groups, respectively.

Power analysis was performed using the [CAF] observed in three groups of participants with no SCI, PARA, and TETRA 60 min postingestion of 6 mg·kg^{-1} caffeine (mean ± SD, 46.4 ± 6.8, 55.3 ± 19.8, and 64.1 ± 6.9 μM,

respectively) (4). The *a priori* analysis, conducted in G*Power 3.1, revealed that six participants would be required in each group to detect a similar change in [CAF] with ES of 0.59, 0.66, and 2.74 (4); 90% power; and an α of 5%. Given the novel nature of this investigation and the heterogeneity of the population, an additional two participants per group were recruited to increase statistical power ($n = 8$).

RESULTS

Plasma caffeine. At baseline, [CAF] was either undetectable or very low, which indicates that all participants adhered to the withdrawal guidelines. Differences over time and across groups were revealed (main effect time $P < 0.0005$, main effect group $P = 0.026$, and time by SCI level interaction $P = 0.019$) (Fig. 2). Planned simple contrasts revealed that these group differences occurred between AB and TETRA ($P = 0.017$), whereas no difference was observed between AB and PARA ($P = 0.913$). Peak [CAF] in TETRA was significantly greater than AB ($P = 0.008$) yet nonsignificantly ($P = 0.058$), but meaningfully (ES = 0.9) greater than PARA (21.5 ± 7.0, 12.2 ± 2.3, and 15.1 ± 8.1 μM, respectively). Time to peak [CAF] varied greatly between individuals, but group means were 80 min for AB and PARA and 70 min for TETRA. There was no influence of habitual caffeine use on [CAF] ($P = 0.943$).

No significant difference in TAUC-CAF was observed between groups ($P = 0.135$; AB 3.74 ± 0.96 μM, PARA 4.62 ± 3.12 μM, and TETRA 6.08 ± 2.15 μM). However, small (AB vs PARA, ES = 0.38), moderate (PARA vs TETRA, ES = 0.55) and large (AB vs TETRA, ES = 1.14) ES were apparent.

Seven participants (three AB/two PARA/two TETRA) reported adverse effects before/during the first 30 min of testing (headache/light-headed [2]) and during testing (struggling with quick decision making [1], tingling arm [1], twitching eye [1]), and five participants reported feeling more alert.

Plasma catecholamines (adrenaline and noradrenaline). All catecholamine analysis excluded the participant with a T4 lesion level because of a missed sample,

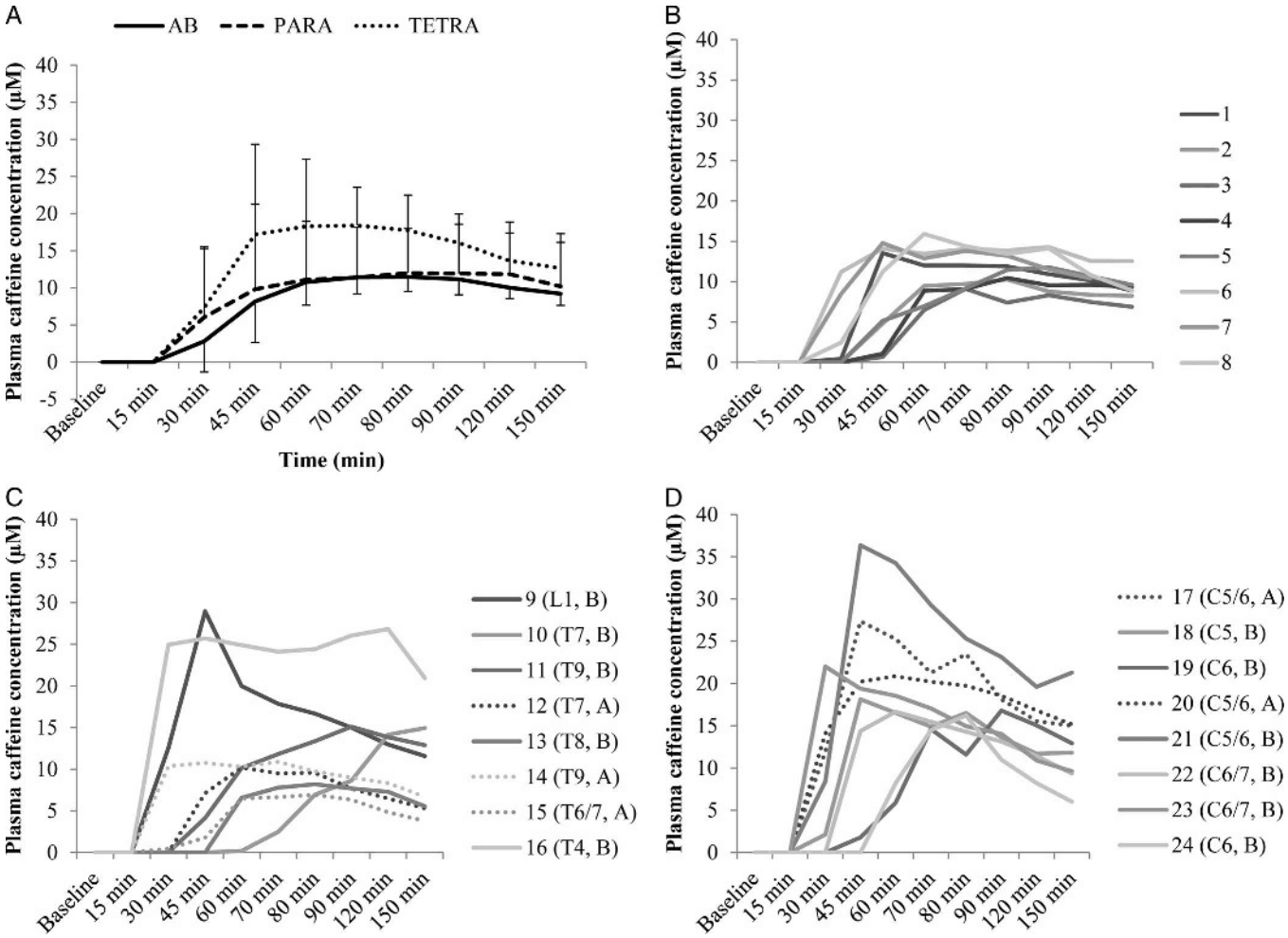

FIGURE 2—Mean ± SD plasma caffeine concentration after the consumption of 3 mg·kg^{-1} caffeine anhydrous (A). Individual data from AB participants (B) and participants with PARA (C) and TETRA (D) (dotted/bold lines represent individuals with an ASIA A/B classification).

and hence statistical analysis for PARA was calculated based on injuries at or below T6/T7. The change in [A] during the resting protocol did not reach statistical significance but did differ between groups (main effect of time $P = 0.088$, main effect of group $P = 0.027$, and time by SCI level $P = 0.618$) (Fig. 3). Planned difference contrasts revealed that these group differences occurred between PARA and TETRA ($P = 0.019$) only. There was no significant difference in TAUC-A ($P = 0.075$) between groups (AB 0.43 ± 0.17 nmol·L^{-1}, PARA 0.57 ± 0.22 nmol·L^{-1}, and TETRA 0.22 ± 0.10 nmol·L^{-1}), although ES values were large for both AB (ES = 2.02) and PARA (ES = 1.04) compared with TETRA. There was no difference in iAUC-A ($P = 0.733$).

The [NA] did not change significantly during the 150-min protocol ($P = 0.423$) but did differ between groups ($P = 0.003$), and no interaction was evident ($P = 0.772$). Planned difference contrasts revealed that these group differences occurred between AB and TETRA ($P = 0.001$), and PARA and TETRA ($P = 0.006$), but no significant difference was observed between AB and PARA ($P = 0.505$). There was a significant difference in TAUC-NA ($P = 0.003$) between groups (AB 4.04 ± 0.92 nmol·L^{-1}, PARA 3.68 ± 1.01 nmol·L^{-1}, and TETRA 2.01 ± 1.21 nmol·L^{-1}). Small (AB vs PARA, ES = 0.38) and large (AB vs TETRA, ES = 1.89, and PARA vs TETRA, ES = 1.50) ES values were revealed. However, no significant difference in iAUC-NA was observed ($P = 0.827$).

Plasma FFA, lactate, and glucose. Differences in [FFA] were observed over time and between groups with the latter not reaching significance, but displaying a large effect (ES = 0.80) (main effect time $P < 0.0005$, main effect group $P = 0.054$, and time–group interaction $P = 0.035$). Geometric means (95% CI) [FFA] were 26% (−46% to 2%) lower in PARA than AB, but 9% higher in TETRA than AB (−21% to 50%); furthermore, [FFA] was 47% (6%–103%) higher in TETRA than PARA (Fig. 3). The interaction indicated that although PARA experienced only a marginal increase in [FFA] from baseline to 150 min (Δ ~0.13 mmol·L^{-1}), AB and TETRA increased to a greater extent during the protocol (Δ ~0.36 and 0.31 mmol·L^{-1}, respectively).

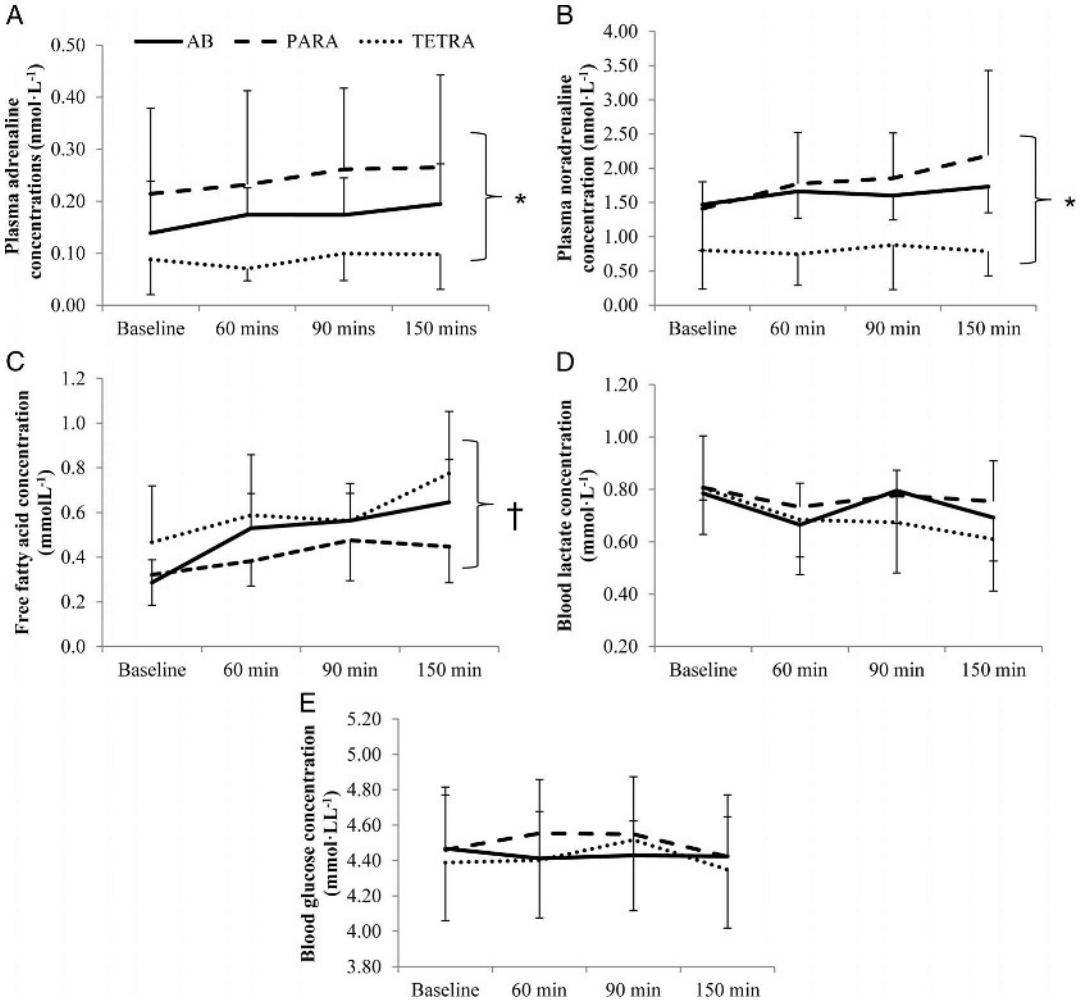

FIGURE 3—Plasma adrenaline (A), noradrenaline (B), FFA (C), lactate (D), and glucose (E) concentrations (mean ± SD) after the consumption of 3 mg·kg^{-1} caffeine anhydrous in AB individuals and individuals with PARA and TETRA. *Significant main effect for group. †Significant time–group interaction effect.

Although the main effect for differences in TAUC-FFA was not significant ($P = 0.072$), the ES ranged from small (AB vs PARA, ES = 0.47) to large (AB vs TETRA, ES = 0.85; PARA vs TETRA, ES = 1.16). No significant difference in iAUC-FFA was observed ($P = 0.357$).

Differences in [Bla] were observed over time but not between groups (main effect time $P = 0.022$, main effect group $P = 0.463$, and time–group interaction $P = 0.065$). No significant difference in [GLU] was seen during the 150-min protocol ($P = 0.695$) or between groups ($P = 0.983$).

DISCUSSION

The current study is the first to report large interindividual differences in caffeine absorption within and between groups when separated for level of SCI (AB, PARA, and TETRA). Consequently, dosage and timing recommendations provided to individuals with an SCI may need to be adapted from the AB literature. In addition, the pattern of caffeine absorption differs in TETRA compared with AB and PARA. There were small differences in [A], [NA], and [FFA] between the AB and the SCI groups, which were nonsignificant when baseline values were accounted for using the incremental area under the curve. No differences in [Bla] and [GLU] were seen between groups.

Plasma caffeine. Participant's [CAF] increased in all three groups after the ingestion of 3 $mg \cdot kg^{-1}$ caffeine. The [CAF] in AB at 60 min (10.8 ± 3.1 μM) is in line with that reported 60 min postingestion of 2, 3, and 4 $mg \cdot kg^{-1}$ caffeine (5.7, ~15, and 14.6 μM, respectively) (11,33). This study is the first to investigate the caffeine absorption curve in a group of participants with PARA. In agreement with the hypothesis, the PARA results do not differ from the AB responses at 60 min (11.1 ± 7.9 μM) and both groups reached mean peak [CAF] at 80 min. The TETRA responses were significantly greater than AB, and the mean peak [CAF] was reached 10 min earlier (70 min). Flueck et al. (4) also reported a higher [CAF] 60 min postingestion of ~6 $mg \cdot kg^{-1}$ caffeine in individuals with TETRA compared with those with PARA (66.1 and 45.1 μM, respectively). Interestingly, Van Soeren et al. (38) also reported a high peak [CAF] of 46.7 ± 5.0 μM in individuals with TETRA ($n = 6$), yet this was reached after only 40 min postingestion of 6 $mg \cdot kg^{-1}$ caffeine. The current study therefore adds further support to reports of higher [CAF] in TETRA compared with individuals with lower lesion levels and no spinal injury. Furthermore, the data also highlight the large variability that exists within each group. On the basis of the current study, there does not appear to be an influence of habitual caffeine use on the participants' [CAF] in response to a single dose, as seen previously (1). Seven participants reported adverse effects, which were likely a result of withdrawal (headache), fasting (light headed), and CAF (tingling arm, twitching eye and struggling to make quick decisions). All symptoms were mild and only lasted for a short duration. The 3-$mg \cdot kg^{-1}$ caffeine dose is therefore deemed safe in this population.

An interaction effect occurred because of the sharp increase in [CAF] in TETRA, whereas both AB and PARA groups [CAF] increased gradually followed by a plateau. The rapid increase in [CAF] in TETRA means that the hypothesis of slowed absorption in this population can be rejected. The sharp rise may be due to several factors. First, individuals with TETRA have a smaller blood volume compared with AB individuals (17) because of atrophy of the musculature and vessels of the lower limbs. This reduced blood volume may result in a falsely large [CAF] in TETRA after the administration of a standardized dose per kilogram BM. Second, after a cervical or thoracic SCI sympathetic outflow to the liver is also disrupted, which in turn can lead to hepatic pathology (30). The liver is innervated by both sympathetic and parasympathetic nerves, and the sympathetic splanchnic nerves originate from neurons, which are located in the spinal column (T7–T12) (39). Acute changes to the liver occur because of the complete (cervical level) and partial (thoracic level) disruption to the descending control of sympathetic neurons innervating the organ (30). It has been proposed that abnormal liver function may affect the metabolism and bioavailability of drugs (23,30). The half-life of many drugs can be prolonged in individuals with an SCI who display suboptimal liver function and slow renal clearance (23,30). Serum caffeine half-life has also been shown to be severely prolonged in individuals with compromised liver function, e.g., those with alcoholic hepatic liver disease (37). The half-life of caffeine in healthy individuals is ~4–6 h (1). This may help explain the sharp rise to peak [CAF] in TETRA (slowed metabolism), which remains higher than AB and PARA (slowed renal clearance). This TETRA response indicates that individuals with a cervical SCI may consider using a lower dose of caffeine to produce similar [CAF] as AB and PARA while avoiding any potential side effects that are reported anecdotally and in previous research (13). It also suggests that individuals with a high lesion level may need to consider reducing the frequency of caffeine intake to prevent the potential negative effects of high doses of caffeine, e.g., nervousness, jitters, restlessness, sleeplessness, and irritability.

The TAUC-CAF did not statistically differ between groups, yet a large ES of 1.14 was evident between AB and TETRA. Large interindividual responses were evident in both SCI groups (Fig. 2) because of the heterogeneous nature of this population. The equivocal findings regarding the beneficial effects of caffeine during short-term exercise performance (4) may be partly explained by these interindividual differences, highlighted by the current PARA and TETRA responses. Examination of individual data within PARA reveals some interesting findings. Participant 9 (L1 lesion; ASIA B) produced a similar curve to the AB participants, with a peak (albeit larger) at 45 min followed by a steady decline. However, caffeine did not appear in the bloodstream of participant 10 (T7 lesion; ASIA B) until 70 min and continued to rise for the remaining 80 min. Hence, the implementation of a standard caffeine protocol

whereby caffeine is administered 60 min before short-term exercise performance would result in participant 10 exhibiting a [CAF] associated with a placebo dose at the commencement of exercise. For short-term exercise performance, it is therefore recommended that an athlete with an SCI determines their individual absorption curve to produce individualized dose and timing recommendations. If this is impractical, it is recommended that caffeine is provided to individuals with PARA earlier to ensure it enters the bloodstream before exercise performance. Research into the use of caffeine gum or mouth rinse is emerging yet the evidence of a consistent positive effect is currently limited (26,29). Consuming caffeine in this format allows direct absorption into the bloodstream through the buccal mucosa and may eliminate any potential issues regarding caffeine absorption in individuals with an SCI.

Habitual caffeine intakes and BM were similar between all three groups, but PARA were significantly older than AB (Table 1). However, previous research has suggested that age is not associated ($P > 0.612$) with C_{max} or time to peak plasma caffeine concentration (C_{max}) after caffeine ingestion (35), nor does it affect GE (18). Furthermore, no significant correlations were observed between age and C_{max} ($r = 0.07$) or time to C_{max} ($r = -0.11$) within the current cohort.

Plasma catecholamines (adrenaline and noradrenaline). Resting plasma catecholamine concentrations did not significantly increase during the 150-min protocol in any group (Fig. 3). By contrast, Flueck et al. (4) and Van Soeren et al. (38) reported increases in adrenaline in both AB individuals and individuals with PARA, which may in part be due to the larger 6 $mg \cdot kg^{-1}$ dose administered in these studies. In line with previous findings, baseline catecholamine concentrations were lower in TETRA compared with AB and PARA because of the impaired sympathetic activation of the nervous system (27,31).

Plasma FFA, lactate, and glucose. Mean resting [FFA] increased over time from 0.36 ± 0.19 $mmol \cdot L^{-1}$ at baseline to 0.61 ± 0.25 $mmol \cdot L^{-1}$ at 150 min, in agreement with previous research in an AB and SCI population (10,38). In the absence of a catecholamine response, the current results lend further support for a direct effect of caffeine on human tissue, specifically adipocytes. The majority of research suggests that FFA availability does not result in greater FFA oxidation and therefore does not alter substrate use at rest or during exercise (12,24). It is also unlikely to aid performance during short-term upper-body exercise where participants/athletes predominantly work anaerobically and therefore utilize carbohydrate as the main substrate.

Baseline [FFA] was higher in TETRA than AB or PARA (Fig. 3). The lack of muscle innervation of paralyzed lower limbs in individuals with an SCI leads to rapid muscle atrophy and a reduction in resting metabolic rate (25). Alongside poor nutritional choices and a disruption in the secretion of anabolic hormones, these changes can result in an increase in fat mass (8,36). An expanding fat mass, which releases more FFA and a potential reduction in FFA clearance, leads to increased plasma [FFA] (2). The [FFA] responses only significantly differed between the two SCI groups (PARA vs TETRA). One possible explanation for this could be the difference in the group's time since injury (PARA 4.3 ± 4.3 yr and TETRA 12.2 ± 6.3 yr), which has been positively associated with loss of lean tissue and increased fat mass (36). Unfortunately, no body composition or RER data were collected to enable a greater understanding of the [FFA] responses and whether substrate use was influenced at rest. However, previous research would suggest this does not occur (12,38).

Many studies report an increase in [Bla] during exercise after the ingestion of caffeine, sometimes in the absence of increased workload/speed/power. At rest, however, the current data show [Bla] decreased slightly during the 150-min protocol, which is in line with previous data (38). On the other hand, [GLU] decreased modestly (nonsignificantly) during the current protocol, as previously reported (24) and is unlikely a result of caffeine ingestion.

CONCLUSION

The current study demonstrates that there is large interindividual variability in caffeine absorption in individuals with an SCI and that this should be assessed before making specific recommendations for its use. Individuals with TETRA may consider using a lower dose and individuals with PARA may consider consuming supplementary caffeine earlier than the 60-min recommended to AB individuals.

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The authors declare no conflict of interest. This study was unfunded. The results of the present study do not constitute endorsement by the American College of Sports Medicine. The authors declare that the results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

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