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ORIGINAL ARTICLE

The effect of CYP1A2 genotype on the ergogenic properties of caffeine during resistance exercise: a randomized, double-blind, placebo-controlled, crossover study

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Abstract

Aim The purpose of this study was to examine the effect of *CYP1A2 -163C>A* polymorphism on the ergogenic effects of caffeine supplementation during a resistance exercise (RE) session.

Methods In a randomized, double-blind, placebo (PL)-controlled, crossover study, 30 resistance-trained men took part in two RE sessions (three sets to failure at 85% of one repetition maximum, 2-min rest between sets), including bench press (BP), leg press (LP), seated cable row, and shoulder press (SP) following caffeine (CAF) (6 mg kg^{-1}) or PL (6 mg kg^{-1} of maltodextrin) ingestion 1 h prior to the trial. The number of repetitions was recorded after each set, along with calculation of total number of repetitions for each exercise. Genomic DNA was isolated from the whole blood samples for analyzing the *CYP1A2 -163C>A* polymorphism through amplification refractory mutation system–polymerase chain reaction (ARMS–PCR). Subjects were classified as either AA ($n = 14$) or AC/CC genotypes ($n = 16$).

Results The two-way ANOVA with repeated measures revealed differences between AAs and AC/CCs under CAF conditions for repetitions performed in sets 1, 2, and 3 of BP ($F_{(1, 28)} = 14.84$, $P = 0.001$, $\eta^2 = 0.34$), LP ($F_{(1, 28)} = 8.92$, $P = 0.006$, $\eta^2 = 0.24$), SR ($F_{(1, 28)} = 17.38$, $P = 0.0001$, $\eta^2 = 0.38$), and SP ($F_{(1, 28)} = 3.76$, $P = 0.063$, $\eta^2 = 0.11$). CAF also increased the total number of repetitions performed for all three sets in AAs versus AC/CCs for BP ($F_{(1, 28)} = 8.72$, $P = 0.006$, $\eta^2 = 0.23$), LP ($F_{(1, 28)} = 4.67$, $P = 0.03$, $\eta^2 = 0.14$), SR ($F_{(1, 28)} = 5.54$, $P = 0.02$, $\eta^2 = 0.16$), and SP ($F_{(1, 28)} = 3.89$, $P = 0.058$, $\eta^2 = 0.12$) in athletes who were homozygous carriers of the A allele, compared to the C allele carriers. Therefore, AA homozygotes were able to carry out a greater total volume of RE work under CAF but not PL conditions, compared to the C allele carriers.

Conclusion In conclusion, acute ingestion of CAF significantly enhanced RE performance in resistance-trained men who were homozygous for the A allele, but not for C allele carriers. Further studies are needed to replicate the potential role of the *CYP1A2 -163C>A* polymorphism on the ergogenic effects of CAF in other modes of exercise and in other populations.

Keywords Caffeine · CYP1A2 -163C>A polymorphism · Resistance exercise

Introduction

Optimal training, proper nutrition, and genetics are key factors in predicting the achievement of high level of athletic performance. In recent years, athletes have become more interested in using nutritional supplements to enhance performance as an important key to their success. Among nutritional supplements, caffeine [1] is widely used by athletes in the form of powders, tablets, gels, and energy drinks [2–4]. Despite inconsistencies in research outcomes surrounding caffeine (CAF)'s ergogenic effects on resistance exercise (RE) performance [5–8], its effect on endurance performance is well-documented [9]. Some studies showed that CAF improves [8, 10, 11] or has no effect [5–7, 12, 13] on RE performance. These inconsistencies may be related to the training status of the subjects, intensity of exercise, and CAF does and variability in response among individuals. Although the reasons for this variability in response among individuals are not clear, genetics may play a role.

CAF is metabolized in the liver by cytochrome P450 1A2 [14]. Cytochrome P450 1A2 (CYP1A2) is a hepatic enzyme coded by the *CYP1A2* gene [15]. A (C/A) single-nucleotide

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polymorphism at intron 1 of the *CYP1A2* (rs762551) gene has been demonstrated to alter CAF metabolism rate [16] and its influence on exercise performance [17]. It has been demonstrated that rs762551 C allele carriers metabolize CAF more slowly than those with the AA genotype [16]. One of the mechanisms leading to the ergogenic effects of CAF in individuals possessing the AA genotype is the higher binding affinity of adenosine receptors for CAF metabolites (i.e., paraxanthine and theophylline) than CAF by itself [18].

The CYP1A2 enzyme is responsible for more than 95% of the primary metabolism of CAF into theophylline, theobromine, and paraxanthine. As mentioned earlier, AA homozygotes have a faster CAF metabolism rate and induce a more rapid production of its metabolites [16]. Since AA allele carriers metabolize CAF faster, it could be hypothesized that these individuals are more affected by CAF supplementation. However, to date, the exact mechanism by which CAF induces more ergogenic effect on the AA allele carriers compared to the C allele carriers has not become clear. Recently, it has been demonstrated that CAF supplementation reduces 40-km time to a greater extent in AA homozygotes compared to the C allele carriers [17]. In addition, it was reported that rate of recovery for the square root of the mean of squared differences between successive R–R intervals (RMSSD) in heart rate was significantly higher in in AA homozygotes compared to the C allele carriers of the CYP1A2*IF polymorphism following submaximal exercise in response to 300 mg of caffeine intake [19]. However, the genetic polymorphism associated with the effects of CAF on RE has not yet been studied. Thus, the *CYP1A2 -163C>A* polymorphism may explain the conflicting results regarding the ergogenic effect of CAF on RE performance [5–8, 10, 11, 13, 20]. The aim of the present study was to determine the effects of CAF on RE performance, influenced by genetic polymorphism in the *CYP1A2* gene. We hypothesized that the AA homozygotes would be able to complete a greater volume of work (repetitions to failure) during a RE session after consuming CAF compared to the C allele carriers (CA/CC).

Methods

Subjects

A total of 30 resistance-trained men voluntarily participated in this study (Table 1), which has been conducted in accordance with the Declaration of Helsinki for research on human subjects and approved by the Department of Exercise Physiology at University of Kurdistan. The purpose, procedures, and possible risks of the study were explained to the subjects, and then an informed consent document was signed. All subjects had at least 1 year of resistance training experience, in which they completed at least three resistance training sessions per week; they were also light CAF consumers. Moreover, the exclusion criteria for this study were smoking, use of drugs containing CAF in the previous 2 weeks, heavy consumption of CAF (≥ 70 mg day^{-1}), and consumption of CAF supplements.

Experimental protocol

A randomized, double-blind, crossover, and placebo (PL)-controlled experimental design was conducted to examine the potential ergogenic effects of CAF on RE performance in resistance-trained men, based on genetic variations in CYP1A2 hepatic enzyme. Subjects were randomly assigned to CAF (C0750 Sigma-Aldrich, Germany) or PL treatments using an online research randomizer (https://www.randomizer.org/). Subjects performed three experimental trials 7 days apart. The first session was to familiarize them with the study protocol, while the others were experimental sessions in which a gelatin capsule of CAF (6 mg kg^{-1} body mass) or PL (6 mg kg^{-1} body mass of maltodextrin) was administered 60 min before RE protocol with 250 mL of water, because it has been shown that blood CAF level peaks about 30–60 min after ingestion [21]. Subjects were asked to attend the experimental session afternoons at the same time for all trials, to avoid circadian variance [22]. They were further asked to refrain from vigorous exercise and the consumption of CAF for 48 h before testing. During the familiarization sessions, one repetition maximum (1RM) in bench press (BP), leg press (LP), seated cable row [23], and shoulder press (SP) was determined [24]. All subjects performed standardized warm-up exercises, including 5 min of jogging, static stretches, and joint mobilization exercises, and then completed one set × five repetitions of BP, LP, SR, and SP at 50% of 1RM. During the experimental testing sessions, subjects completed three sets of BP, LP, SR, and SP to failure (unable to complete repetition in proper technique) at 85% of 1RM. Rest intervals between sets and each exercise were 2 min for both the CAF and PL conditions. During each set, verbal encouragement was given to each subject by the same supervisor. The number of repetitions performed in each set of RE was recorded.

Genotyping

Blood samples were collected in the familiarization session. The human genomic DNA was extracted from 2 mL of peripheral blood, using the TIANamp Genomic DNA Kit (Cat. No. DP304). The single-nucleotide polymorphism (SNP) in the intron 1 of the human *CYP1A2* gene (rs 762551) was analyzed by amplification of refractory mutation system–polymerase chain reaction (ARMS–PCR) [25], wherein the SNP -163A>C was amplified using allele A primer (forward): 5′-CAAAGGGTGAGCTCTGTGGACA-3′, Allele C primer (forward): 5′-CAAAGGGTGAGCTCTGTGGTCC-3′, and reverse primer: 5′- GAGGCGATGGAGAAGGTGTTGA-3′

Table 1 Physical characteristics of the subjects in homozygote AA ($n = 14$) and C allele ($n = 16$) carriers (CA/CC)

Genotype group	AA ($n = 14$)		CA/CC ($n = 16$)		T	P value
	M	SD	M	SD		
Age (years)	21.21	2.29	22.33	5.24	− 0.73	0.46
Height (cm)	179.14	5.32	179.46	5.01	− 0.16	0.86
Weight (kg)	78.57	18.56	76.75	10.92	0.32	0.74
Soft lean mass (kg)	63.54	10.24	61.94	7.63	0.47	0.63
Body fat mass (kg)	11.55	8.63	11.39	4.25	0.063	0.95
% body fat	13.58	6.17	14.48	4.05	− 0.46	0.64
Body mass index (kg/m^2)	24.4	4.80	23.84	3.43	0.36	0.71
Basal metabolic rate	2115.47	268.21	2046.20	189.41	0.80	0.42

(Macrogen Korea). The PCR reactions were performed in a 25 μL volume containing 3 μL DNA, 1 μL of each primer, and 18 μL of PCR Master Mix (Thermo Fisher Scientific). The PCR condition consisted of an initial denaturation at 94 °C for 10 min, 32 cycles of 94 °C for 1 min, 65 °C for 1 min, and 72 °C for 1 min, followed by 72 °C for 5 min as a final elongation step (Thermal Cycler, Analytik Jena, Germany). The PCR products were analyzed by 2% agarose gel electrophoresis and staining with ethidium bromide. For each sample, two reactions were studied for both alleles of A and C. The presence of a 636-bp fragment in both reactions identified the A/C genotype, while the presence of a 636-bp fragment in alleles C and A reaction identified the C/C and A/A genotypes, respectively (Fig. 1). The internal control was used in all samples to verify the reaction, in which two primers of mitochondrial genome—namely L strand: 5′-CTCC ACCATTAGCACCCAAAGC-3′ and H strand: 5′-CCTA TTTGTTTATGGGGTGATG-3′—were used to produce a 250-bp fragment. All samples were run in duplicate with two negative controls.

Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) for Windows v21.0 (IBM Crop, Armonk, NY). Descriptive data (age, height, weight, soft lean mass, body fat mass, percent body fat, body mass index, basal metabolic rate) were compared between the AA genotype and AC/CC genotype using independent t test. Repetitions performed at the first set (S1), second set (S2), and third set (S3) of the BP, LP, SR, and SP were compared using the two-way ANOVA, with repeated measures with genotype group (AA, AC/CC) as between-subjects factor, and condition (CAF, PL) and sets (S1, S2, S3) as the within-subject variable. Total repetitions for all sets in BP, LP, SR, and SP, as well as for sets and exercises combined through the trial, were analyzed using the two-way ANOVA with repeated measures with genotype (AA, AC/CC) as a between-subjects factor and condition (CAF, PL) as a within-subject variable. A P value of ≤ 0.05 was considered significant.

Results

Figure 2 shows the number of repetitions performed at S1, S2, and S3 of BP for both genotypes. Two-way ANOVA with repeated measures revealed that repetitions performed in sets 1, 2, and 3 of BP were significantly different between the AA genotype and the C allele carriers for the CAF condition ($F_{(1, 28)} = 14.84$, $P = 0.001$, $\eta^2 = 0.34$), but not for the PL condition ($F_{(1, 28)} = 3.34$, $P = 0.078$, $\eta^2 = 0.10$). CAF significantly raised repetitions performed at S1 ($P = 0.015$), S2 ($P = 0.0001$), and S3 ($P = 0.001$) of BP in the AA genotype compared to the C allele carriers. In AA genotype, *Bonferroni* adjustments revealed significant increase in the number of repetitions performed at set 1 and set 2 of BP in CAF compared to PL condition ($P = 0.003$ and 0.001).

Figure 3 illustrates the number of repetitions performed at S1, S2, and S3 of LP for both genotypes. Two-way ANOVA with repeated measures demonstrated that repetitions performed in sets 2 and 3 of LP were significantly different between the AA genotype and the C allele carriers for the CAF condition ($F_{(1, 28)} = 8.92$, $P = 0.006$, $\eta^2 = 0.24$), but not for the PL condition ($F_{(1, 28)} = 0.01$, $P = 0.92$, $\eta^2 = 0.001$). CAF significantly increased the number of repetitions performed at S2 ($P = 0.001$) and S3 ($P = 0.024$) of LP in the AA genotype compared to the C allele carriers. In AA genotype, *Bonferroni* adjustments revealed significant increase in the number of repetitions performed at both sets 2 and 3 of LP in CAF compared to PL condition ($P = 0.012$ and 0.016).

Figure 4 represents the number of repetitions performed at S1, S2, and S3 of SR for both genotypes. Two-way ANOVA with repeated measures indicated that repetitions performed in sets 1, 2, and 3 of SR were significantly different between the AA genotype and the C allele carriers for the CAF condition ($F_{(1, 28)} = 17.38$, $P = 0.0001$, $\eta^2 = 0.38$), but not for the PL

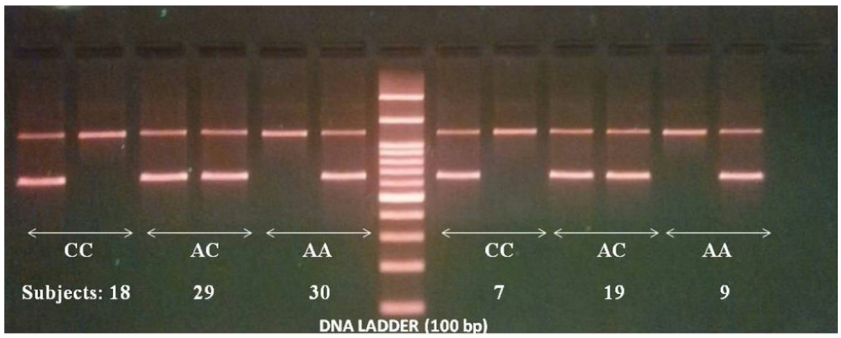

Fig. 1 Agarose gel electrophoresis of the *CYP1A2* gene ARMS–PCR amplification products

condition ($F_{(1,\ 28)} = 2.82$, $P = 0.104$, $\eta^2 = 0.092$). CAF significantly enhanced the number of repetitions performed at S1 ($P = 0.005$), S2 ($P = 0.001$), and S3 ($P = 0.007$) of SR in the AA genotype compared to the AC/CC genotype. In AA genotype, *Bonferroni* adjustments revealed significant increase in the number of repetitions performed at set 1, set 2, and set 3 of SR in CAF compared to PL condition ($P = 0.012$, 0.027, and 0.001).

Figure 5 indicates the number of repetitions performed at S1, S2, and S3 of SP for both genotypes. Two-way ANOVA with repeated measures showed that repetitions performed in sets 1, 2, and 3 of SP did not differ between the AA genotype and the C allele carriers for the CAF condition ($F_{(1,\ 28)} = 3.76$, $P = 0.063$, $\eta^2 = 0.11$) and for the PL condition ($F_{(1,\ 28)} = 0.05$, $P = 0.82$, $\eta^2 = 0.002$). In AA genotype, *Bonferroni* adjustments revealed significant increase in the number of repetitions performed at set 2 and set 3 of SP in CAF compared to PL condition ($P = 0.0001$ and 0.012).

Figure 6 shows the total number of repetitions for all sets in BP, LP, SR, and SP in both genotypes. Two-way ANOVA with repeated measures showed that CAF significantly raised the total number of repetitions performed in three sets of BP ($F_{(1,\ 28)} = 8.72$, $P = 0.006$, $\eta^2 = 0.23$), LP ($F_{(1,\ 28)} = 4.67$, $P = 0.03$, $\eta^2 = 0.14$), and SR ($F_{(1,\ 28)} = 5.54$, $P = 0.02$, $\eta^2 = 0.16$) in athletes who were homozygous carries of the A allele, compared to the C allele carriers. In AA genotype, there were significant increases in the total number of repetitions performed for BP ($F_{(1,\ 28)} = 9.63$, $P = 0.004$, $\eta^2 = 0.25$), LP ($F_{(1,\ 28)} = 7.72$, $P = 0.01$, $\eta^2 = 0.21$), SR ($F_{(1,\ 28)} = 14.23$, $P = 0.001$, $\eta^2 = 0.33$), and SP ($F_{(1,\ 28)} = 3.89$, $P = 0.048$, $\eta^2 = 0.12$) in CAF compared to PL condition.

Figure 7 shows the total number of combined repetitions performed for sets and exercises through the trial. Two-way ANOVA with repeated measures demonstrates a significant main effect for condition ($F_{(1,\ 28)} = 20.90$, $P = 0.0001$, $\eta^2 = 0.42$) and CAF × genotype interaction ($F_{(1,\ 28)} = 11.08$, $P = 0.002$, $\eta^2 = 0.28$) in the total number of repetitions performed for all sets and exercises. As depicted in Fig. 7, CAF significantly raised the total number of repetitions performed for all sets and exercises in athletes who were homozygous for the A allele, compared to the C allele carriers.

Discussion

To our knowledge, this is the first study that simultaneously examines the acute effect of CAF and *CYP1A2* genotype on

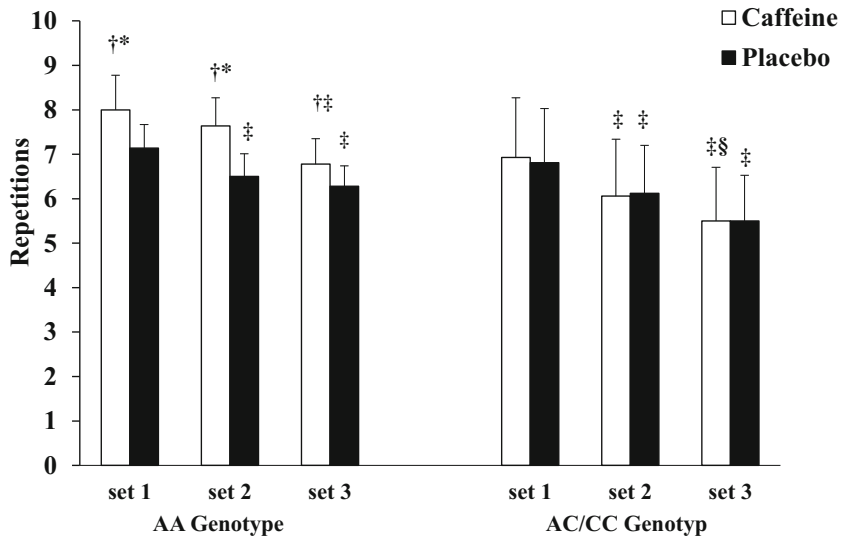

Fig. 2 Mean (± SD) values for the number of repetitions completed during three sets of bench press (BP) to failure. Asterisk (*) indicates significant difference between conditions (CAF vs. PL) in the AA genotype; $P < 0.05$. Dagger (†) indicates significant difference between two genotypes (AA genotype vs. AC/CC genotype); $P < 0.05$. Double dagger (‡) indicates significant difference between set 1 and set 2 as well as 1 and 3; $P < 0.05$. Section sign (§) indicates significant difference between set 2 and set 3; $P < 0.05$

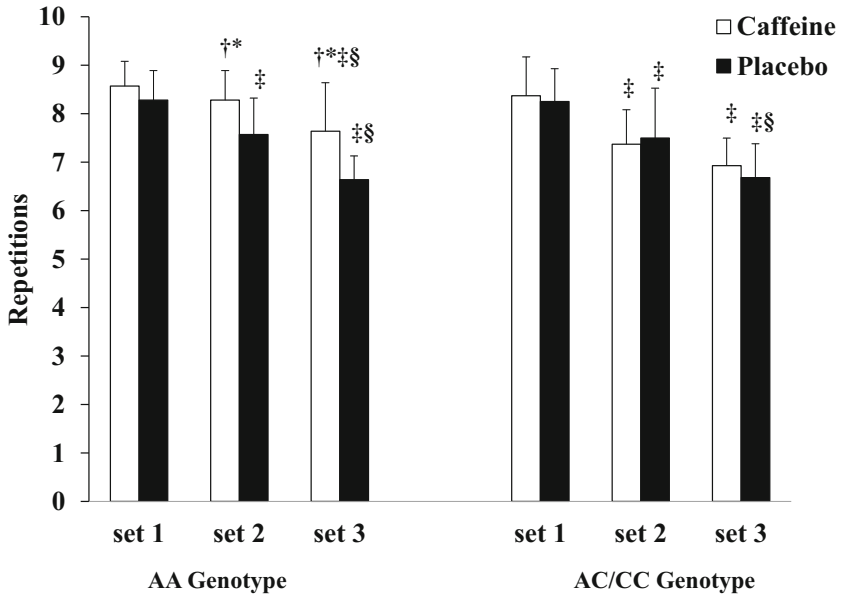

Fig. 3 Mean (± SD) values for the number of repetitions completed during three sets of leg press (LP) to failure. Asterisk (*) indicates significant difference between conditions (CAF vs. PL) in the AA genotype; $P < 0.05$. Dagger (†) indicates significant difference between two genotypes (AA genotype vs. AC/CC genotype); $P < 0.05$. Double dagger (‡) indicates significant difference between sets 1 and 2 as well as 1 and 3; $P < 0.05$. Section sign (§) indicates significant difference between sets 2 and 3; $P < 0.05$

repetitions to failure in multiple sets of REs. The major finding of the current study is that CAF supplementation appears to be ergogenic for athletes who are homozygous carriers of the A allele, but not ergogenic for carriers of the C allele (AC/CC genotype). Athletes homozygous for the A allele performed significantly more repetitions to failure for most sets during multiple REs after taking CAF, but CAF did not improve the performance of athletes who were carriers of the C allele. Although the effects of *CYP1A2* rs762551 on RE performance after CAF ingestion have not yet been investigated, our findings for improved exercise performance in AAs are in agreement with [17], who reported that CAF significantly improved 40-km time trial performance in cyclists who were AA homozygotes compared to the C allele carriers in *CYP1A2* rs762551.

To our knowledge, only three studies have evaluated the acute effect of CAF on multiple REs [26–28]. In the current study, acute ingestion of CAF was found to significantly enhance the total number of repetitions during three sets of each exercise, including BP, LP, and SR, in resistance-trained men who were homozygous for the A allele, compared to resistance-trained men who were carriers of the C allele. These findings are in agreement with a study conducted by Duncan et al. [27], in which 11 resistance-trained individuals completed one set of BP, dead lift, prone row, and back squat

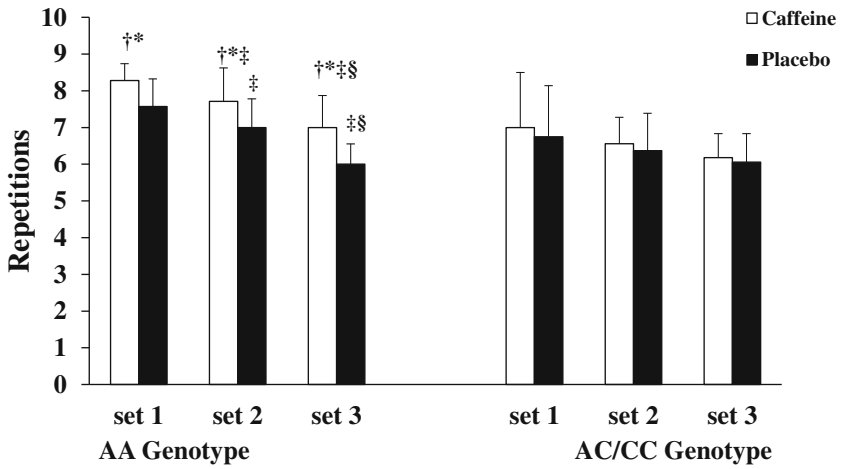

Fig. 4 Mean (± SD) values for the number of repetitions completed during three sets of seated cable row [23] to failure. Asterisk (*) indicates significant difference between conditions (CAF vs. PL) in the AA genotype; $P < 0.05$. Dagger (†) indicates significant difference between two genotypes (AA genotype vs. AC/CC genotype); $P < 0.05$. Double dagger (‡) indicates significant difference between sets 1 and 2 as well as 1 and 3; $P < 0.05$. Section sign (§) indicates significant difference between sets 2 and 3; $P < 0.05$

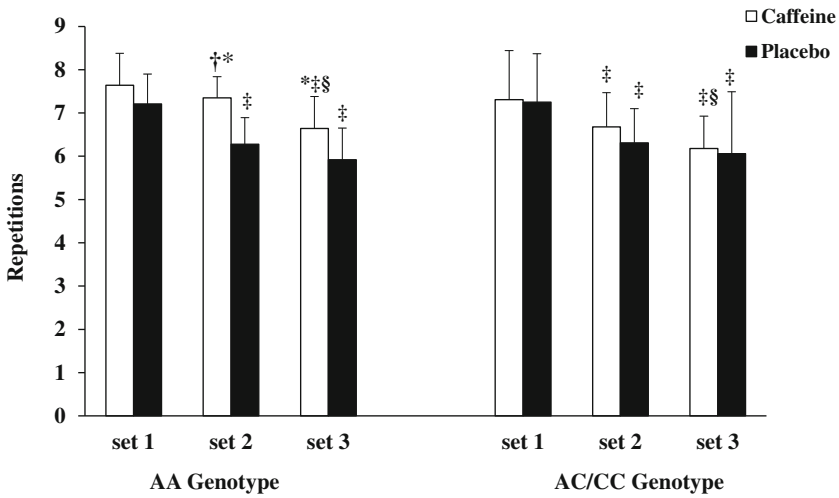

Fig. 5 Mean (± SD) values for the number of repetitions completed during three sets of shoulder press (SP) to failure. Asterisk (*) indicates significant difference between conditions (CAF vs. PL) in the AA genotype; $P < 0.05$. Dagger (†) indicates significant difference between two genotypes (AA genotype vs. AC/CC genotype); $P < 0.05$. Double dagger (‡) indicates significant difference between sets 1 and 2 as well as 1 and 3; $P < 0.05$. Section sign (§) indicates significant difference between sets 2 and 3; $P < 0.05$

exercise to failure at 60% of 1RM after ingesting CAF (5 mg kg^{-1}) or PL 60 min before each exercise session. They showed that subjects completed significantly more repetitions to failure (when all exercises were combined) in the CAF compared to PL condition. However, in contrast to the result of the current study, Davis et al. [26] report no significant enhancement in total repetitions to failure during four sets of multiple REs, including BP, lat pull down, SP, bicep curl, triceps push down, and LP following acute CAF ingestion (6 mg kg^{-1}) in resistance-trained men. Astorino et al. [28] observed that acute CAF dose (6 mg kg^{-1}) significantly enhanced the number of repetitions completed in sets 1 and 2 of LP at 70–80% 1RM, but there was no effect of CAF on barbell BP, bilateral row, and barbell SP.

The effects of CAF on total repetitions to failure in single RE are equivocal [20, 29, 30]. Duncan et al. [30] demonstrate that acute CAF (3 mg kg^{-1}) ingestion significantly increased the total repetitions to failure at 60% of 1RM during the unilateral leg extension compared to PL. Moreover, it was shown that 13 moderately trained men completed significantly more repetitions to failure at a load of 60% 1RM in the CAF condition (5 mg kg^{-1}), compared to the PL condition [29]. However, Goldstein et al. [20] demonstrated no significant change in a single set of BP to failure at 60% of 1RM between CAF (6 mg kg^{-1}) and PL conditions.

In regard to the acute effect of CAF ingestion on the number of repetitions completed per set, our results show significant raise in sets 1, 2, and 3 of BP and SR; sets 2 and 3 of LP; and set 2 of SP in resistance-trained athletes homozygous for the A allele of the *CYP1A2* gene compared to the C allele. Moreover, resistance-trained athletes who were homozygous for the A allele completed a significantly greater number of repetitions to failure in sets 1 and 2 of BP; sets 1, 2, and 3 of SR; and sets 2 and 3 of LP and SP in the CAF condition compared to PL. Corroborating our findings, Astorino et al. [28] indicate higher repetitions in sets 1 and 2 of LP with CAF compared to PL. Jacobs et al. [7] indicate a greater number of repetitions only in set 1 of BP and LP in CAF compared to PL.

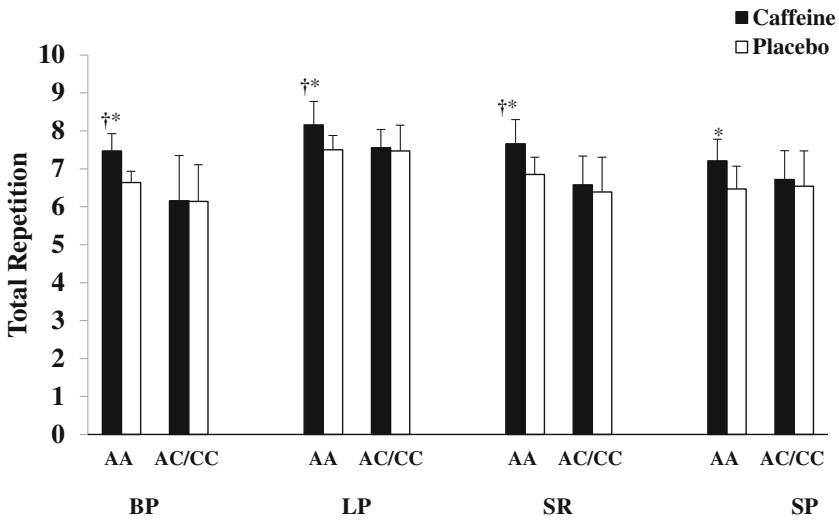

Fig. 6 Mean (± SD) values for the total number of repetitions performed during three sets of BP, LP, SR, and SP. Asterisk (*) indicates significant difference between conditions (CAF vs. PL) in the AA genotype; $P < 0.05$. Dagger (†) indicates significant difference between two genotypes (AA genotype vs. AC/CC genotype); $P < 0.05$

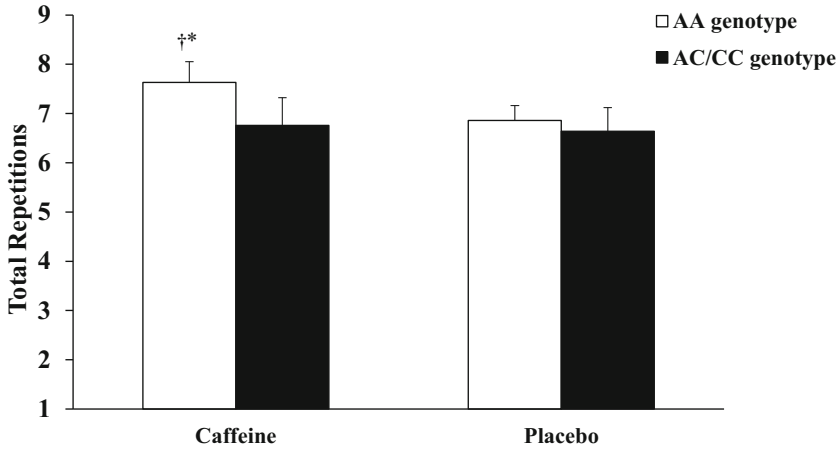

Fig. 7 Mean (± SD) values for the total number of repetitions performed during all sets and all exercises (BP, LP, SR, and SP). Asterisk (*) indicates significant difference between conditions (CAF vs. PL) in the AA genotype; $P < 0.05$. Dagger (†) indicates significant difference between two genotypes (AA genotype vs. AC/CC genotype); $P < 0.05$

Also, Green et al. [5] report that CAF (6 mg kg^{-1}) significantly increased repetitions to failure only in set 2 of LP but not in BP. Hudson et al. [11] evaluated the ergogenic effect of CAF in four sets of LP and arm curls at 12 RM in college-aged males and observed significant increase in set 1 of LP but not in arm curls.

The precise mechanisms responsible for the ergogenic effects of CAF on RE performance are not clear; however, it may be related to the reduction in fatigue during successive sets of RE to failure. It seems that fatigue during RE may be central or peripheral [31]. It is speculated that the ergogenic effect of CAF happens mainly via stimulation of the central nervous system (CNS) [32]. CAF—which is structurally similar to adenosine—can delay fatigue via CNS mechanism by acting as a potent adenosine antagonist [1]. Adenosine can be produced during muscle contraction through ATP breakdown [33]. Upon binding adenosine to its receptor in the CNS, neurotransmitter release and neuronal firing rates can be reduced [1]. CAF, by blocking inhibitory effects of adenosine in CNS, can increase maximal voluntary activation and force production [1]. In addition, CA can delay fatigue through peripheral mechanisms such as myosin-actin interaction and the potassium gradient [2]. Although several mechanisms have been proposed regarding the ergogenic effects of CAF, the exact targeting specificity mechanism of CAF during RE is still unclear. In the current study, it is possible that CAF—through these mechanisms—may lead to increase in RE performance in athletes who are homozygous for the A allele of the *CYP1A2* gene.

The ergogenic effects of CAF in athletes who are homozygous for the A allele of the *CYP1A2* gene may be related to a faster CAF metabolism and rapid production of CAF metabolites, including theophylline, theobromine, and paraxanthine [34]. For a strong tendency of adenosine receptors for CAF metabolites (i.e., paraxanthine and theophylline) rather than CAF [18], a higher concentration of CAF metabolites caused to deposit its marked performance influences among AA homozygotes. It has been demonstrated that acute administration of CAF is able to block both central adenosine A_1 and A_{2A} receptors in rats, which leads to the release of serotonin (5-HT) and dopamine (DA) [35–37]. These findings indicate that motor activation effects of CAF are due to blockage of the central adenosine A_1 and A_{2A} receptors, which exert a stronger effect on motor activity [35, 36].

The results of the current study are in line with those of previous studies [11, 38], which have pointed out interindividual variations in the responses to CAF and metabolites. Polymorphism of the CYP1A2 isoenzyme is likely to partially explain interindividual variability in response to CAF during RE. These results suggest polymorphism of the *CYP1A2 -163C>A* may modulate the ergogenic effects of CAF on RE performance at 85% of 1RM in resistance-trained men. Thus, it can be concluded that fatigue is delayed by CAF during RE in athletes who are homozygous for the A allele, thus leading to an increase in the number of repetitions performed to failure. Further studies are needed to explore the potential mechanisms that are responsible for the greater ergogenic effect of CAF in athletes who are carrying the AA genotype.

Conclusion

In conclusion, these findings provide evidence for the potential influence role of the *CYP1A2 -163C>A* (rs 762551) polymorphism on the ergogenic effects of CAF during RE in resistance-trained men. The findings reveal that acute CAF ingestion leads to greater repetitions to failure in athletes who are homozygous for the A allele of the *CYP1A2* gene, compared to C allele carriers. Further studies are needed to elucidate the potential role of the *CYP1A2 -163C>A* polymorphism on the ergogenic effects of CAF during other modes of exercise and in other population groups.

Acknowledgements The author wishes to thank the subjects who volunteered for the study.

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Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of interest The author declares that there is no conflict of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

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