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Original article

No sex differences in the acute effects of caffeine on mental calculation and pulse rate in healthy college students

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A R T I C L E I N F O

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S U M M A R Y

Background and Aim: It is unclear whether there is a sex difference in the effect of caffeine on an objective indicator such as mental calculation. Although it has been reported that the heart rate-lowering effect of caffeine is greater in males than in females, another study showed that there was no gender difference. The aim of this study was to examine whether there are sex differences in the acute effects of caffeine.

Methods: We analyzed data (males: 280, females: 135) from the Practice of Pharmacology conducted on medical students. The participants performed mental calculations and measured their pulse rate before and after drinking decaffeinated or caffeinated coffee in a double-blinded manner.

Results: In total participants, the increase in the number of calculations after drinking coffee was larger in the caffeinated group than in the decaffeinated group. However, the increases in the numbers of calculations after drinking caffeinated coffee were similar in males and females. The reduction in pulse rate after drinking coffee was larger in the caffeinated coffee group than in the decaffeinated group in total participants. There was no sex difference in the degree of reduction in pulse rate.

Conclusion: There are no sex differences in the acute effects of caffeine on calculation efficiency and pulse rate in young medical students.

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Introduction

Caffeine, a xanthine derivative, acts on the cerebral cortex to enhance mental, motor and sensory functions [1]. This action is mediated through a blockade of adenosine A_{2a} receptors in the central nervous system [2]. In terms of hemodynamics, caffeine has been reported to increase blood pressure and decrease heart rate [3,4].

Activity of CYP1A2, the main enzyme that metabolizes caffeine, has been reported to be higher in males than in females [5]. However, the drowsiness-reducing effect of caffeine has been reported to be stronger in males than in females [6]. On the other hand, Amendola *et al.* reported that there is no difference between males and females in the improvement of mental performance by caffeine [7], although in the study subjective indices were mainly evaluated as effects of caffeine. Therefore, it is unclear whether there is a sex difference in objective indices of workload such as mental calculations. It has been also reported that the heart rate-lowering effect of caffeine is greater in males than in females [8]. In contrast, another study showed no sex difference in the caffeine-induced change in heart rate [9]. Therefore, our aim was to analyzed whether there is sex difference in the change in mental calculation efficiency induced by caffeine. We also compared the effect of caffeine on pulse rate, instead of heart rate, in males and females.

Materials and Methods

This study was approved by the Ethics Committee of Sapporo Medical University (No. 1-2-64) and was strictly conducted in accordance with Ethical Guidelines for Medical and Health Research Involving Human Subjects by the Ministry of Health, Labor and Welfare, Japan. This study was also carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Study subjects

This study was a single-center, double-blind, and placebo-controlled study. We retrospectively analyzed data obtained from the Practice of Pharmacology, "Double blind study" to examine the effects of caffeine carried out on second-year undergraduate students in Sapporo Medical University School of Medicine. The Practice of Pharmacology was carried out on February 1, 2017, January 31, 2018, January 30, 2019, and January 29, 2020. A total of 434 students participated in the practice (104 in 2017, 109 in 2018, 111 in 2019, and 110 in 2020). We announced this study on the homepage of our department and announced that participants could opt out of it. None of the participants opted out of participating this study. Sixteen students were excluded because they did not drink coffee. Three students were excluded because of failure of randomization, that is, lack of information on the cup number. Thus, data for 415 students were used for analyses as shown in Figure 1A. The participants included 280 males and 135 females. The mean age of the participants ($n = 415$) was 21 years (range, 19–42 years). Among males, 149 and 131 participants were assigned to the decaffeinated and caffeinated groups, respectively. In addition, 58 and 77 females were assigned to the decaffeinated and caffeinated groups, respectively.

Experimental procedure

Packages (each 1.8 g) of caffeine hydrate (Pfizer) were prepared by the Pharmaceutical Department of Sapporo Medical University Hospital. Commercially available Nescafé Gold Blend decaffeinated coffee (Nestle Japan, Kobe) was used as decaffeinated coffee. The dose of caffeine of this decaffeinated coffee is estimated to be approximately 1.8 mg/100 ml, because this decaffeinated coffee has 97% less caffeine than that of commercially available coffee (60 mg/100 ml) [10]. To make caffeinated coffee, 1.8 g of caffeine was dissolved in a bottle of 900 mL of decaffeinated coffee (200 mg caffeine/100 ml of decaffeinated coffee). We visually confirmed that caffeine was completely dissolved in decaffeinated coffee.

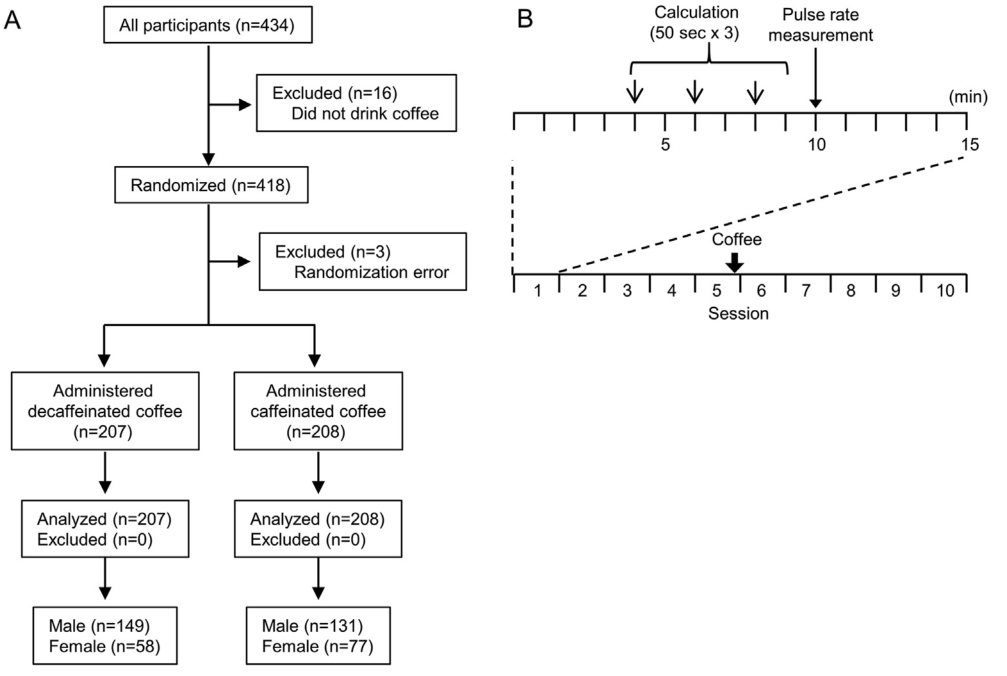

Fig 1. Selection of participants and protocol of the study. (A) A total of 434 students participated in the practice. Among them, 16 students were excluded because they did not drink coffee, and 3 students were excluded because of randomization failure. Therefore, we used data for 415 students for analysis. Of the 415 students, 207 drank decaffeinated coffee and 208 drank caffeinated coffee. (B) Participants repeated a 15-minute session 10 times. In one session, participants used the Uchida-Kraepelin test sheet to perform mental calculation (50 sec) three times with 70-second intervals and then measured their pulse rate. After the fifth session, participants drank decaffeinated or caffeinated coffee. After drinking coffee, they started their sixth to tenth sessions.

Participants were instructed to avoid drinking caffeine-containing beverages (coffee, cola, black tea, green tea, etc.) after 17:00 the day before the practice. The practice started at 1:10 pm. Before starting the practice, written informed consent was obtained from all of the participants. As shown in Figure 1B, the participants performed mental calculations for 50 sec each with an intrval of 70 sec 3 times using the Uchida-Kraepelin test sheet [11] and then measured pulse rate using their radial artery themselves. This 15-min session was repeated 10 times. After completion of the measurement of pulse rate at the fifth session, participants chose a cup of coffee (100 ml) from cups with decaffeinated or caffeinated coffee that were randomly placed on a table. There was a number on the bottom of each paper cup to determine which coffee each participant drank. After participants drank coffee within 5 min, the sixth session was started.

The number of calculations in each session was shown as the sum of 3 trials. The change in the numbers of calculations at the sixth to tenth sessions from that at the fifth session was calculated for each participant. The area under the curve (AUC) from the fifth to tenth sessions was calculated. Pulse rate before drinking coffee was presented as the average of those at the fourth and fifth sessions. Since the maximum change in pulse rate after drinking coffee was observed at the seventh session (Figure 3A), the change in pulse rate caused by drinking coffee was calculated by subtracting the average pulse rate of the fourth and fifth sessions from that at the seventh session. The AUC from the average pulse rate of the fourth and fifth sessions to that of tenth session was also calculated.

Statistics

Data are presented as means ± SD. Statistical significance was determined using an unpaired Student's two-tailed t-test for two data sets. Because the Shapiro-Wilk normality test showed a non-

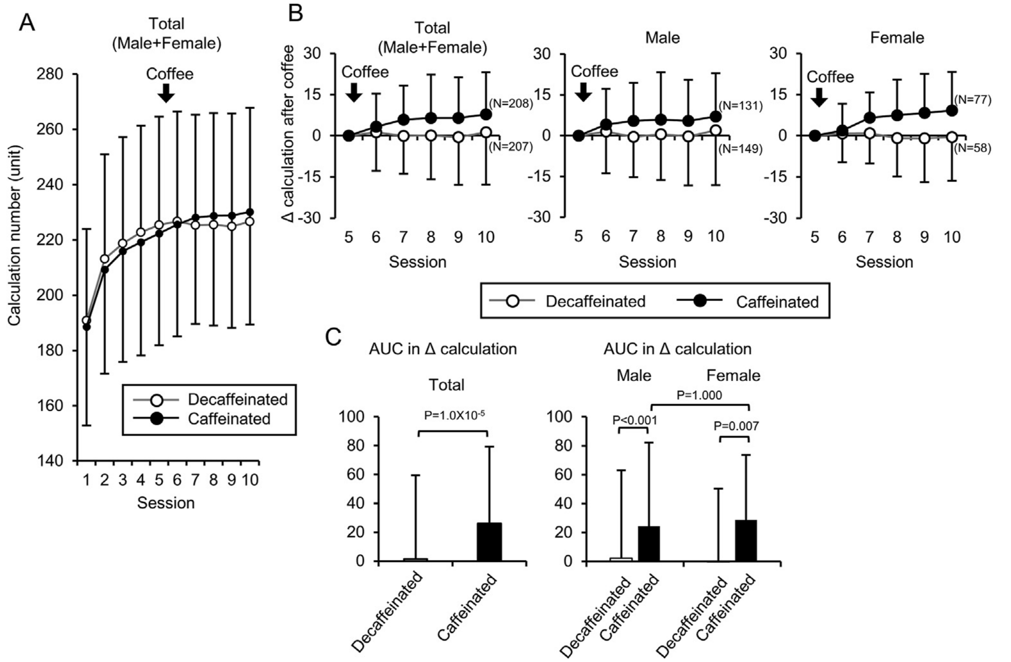

Fig 2. Effects of caffeine on mental calculations in males and females. (A) Time courses of the numbers of calculations before and after drinking coffee in total participants. (B) Changes in the number of calculations (Δ calculation) after drinking coffee in total participants and in males and females. (C) Area under the curve (AUC) of Δ calculation after drinking coffee was calculated for each participant and was averaged in total participants and in males and females.

normal distribution of AUC data of calculations and changes in pulse rate in males, we used Kruskal-Wallis One-Way Analysis of Variance on Ranks followed by post hoc analysis (Dunn's method) to compare these data between males and females. Two-way Analysis of Variance and the Tukey post hoc test was performed to analyze AUC data of pulse rate. All analyses were performed using SigmaPlot (Systat Software). $P<0.05$ was considered statistically significant.

Results

The numbers of calculations in all participants and in males and females before drinking coffee (i.e., at the fifth session) are shown in Table 1 . There was no significant difference in the numbers of calculations before drinking coffee between males and females. There was no difference in the numbers of calculations at the fifth session between the decaffeinated and caffeinated groups in both males and females.

In total participants, the caffeinated group showed a gradual increase in the number of calculations after drinking coffee (Figure 2A). On the other hand, the number of calculations was not changed after drinking coffee in the decaffeinated group. In total participants and in males and females, AUC of the number of calculations from the fifth to tenth sessions in the caffeinated group was significantly greater than that in the decaffeinated group (Figure 2B and C). There was no significant difference in the AUC between males and females in the caffeinated group (Figure 2C).

Before drinking coffee, female had higher pulse rate (Table 1). Pulse rates before drinking coffee were comparable in the decaffeinated and caffeinated groups in both males and females. The reduction in pulse rate at the seventh session was significantly larger in the caffeinated group than in the decaffeinated group in total participants and in males and females (Figure 3A and B). The reductions in pulse rate after drinking caffeinated coffee were comparable in males and females (Figure 3B). We also calculated AUC in changes in pulse rate after coffee (Figure 4A and B). AUC was lower in the caffeinated

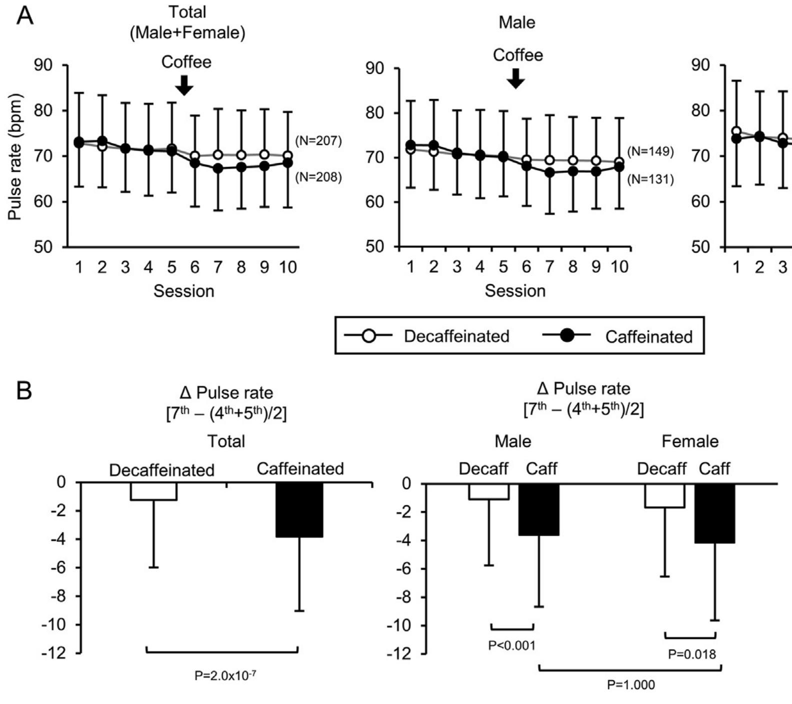

Fig 3. Effects of caffeine on pulse rate in males and females. (A) Time courses of pulse rates in total participants and in males and females. (B) Δ pulse rate (change in pulse rate after drinking coffee) was calculated using pulse rate at the seventh session and the average pulse rate of the fourth and fifth sessions. Decaff, Decaffeinated; Caff, Caffeinated; NS, not significant.

group than the decaffeinated group in total participant, males, and females. There was no significant difference in AUC between in caffeinated male and female groups (Figure 4B).

Discussion

In this double-blind and placebo-controlled study, we showed that there were no sex differences in the acute effects of caffeine on mental calculation and pulse rate in healthy college students. This is the first study in which the sex difference in the change in mental calculations induced by caffeine was examined. Amendola *et al.* reported no sex difference in changes in subjective indices induced by caffeine [7]. We found that the increases in numbers of mental calculation by caffeinated coffee were similar in males and females (Figure 2C). Our data showed no gender difference in acute effect of caffeine on mental performance in the objective parameter. However, because calculation number progressively increased until fifth session (Figure 2A), the effect of caffeine may be restricted to the stabilized period.

Temple *et al.* [8] reported that females with an average age of 15–16 years showed less reduction in heart rate after caffeine administration than did males of the same age. In the study by Temple *et al.*, the dose of caffeine was 2 mg/kg body mass, which might be lower than that in the present study (200 mg). It has been reported that administration of caffeine reduced heart rate in a dose-dependent manner in a dose range of 25–200 mg [4]. The higher dose of caffeine may have made it difficult to detect the sex difference in the present study.

There are several limitations in the present study. First, we do not have data for body mass, which is generally greater in males than in females. Second, healthy college students participated to this study. This may limit generalization of the data in the present study. Third, we have no information about smoking and the dose of daily caffeine consumption, which influence responses to caffeine. Fourth, the

Table 1
: Calculation number and pulse rate before coffee intake

	Male+Female			Male			Female		
	All	Decaffeinated	Caffeinated	All	Decaffeinated	Caffeinated	All	Decaffeinated	Caffeinated
Number	415	207	208	280	149	131	135	58	77
Age (average±SD)	21±3	21±2	21±3	21±3	21±2	22±3	21±2	21±2	21±3
Calculation (per 50 sec x3)	224±40	225±35	222±40	223±39	224±40	223±37	225±42	230±36	221±46
Pulse rate (bpm)	71±9	72±10	71±9	70±9	70±10	70±9	73±9*	74±9	73±10

Data are expressed as means ± SD. **P*<0.05 vs. Male. bpm, beats per minute.

use of self-measured pulse rate might be less accurate even in medical students. Finally, a crossover design was not used in the present study. Crossover design is preferable to test acute actions of caffeine by providing a better control for individual responses.

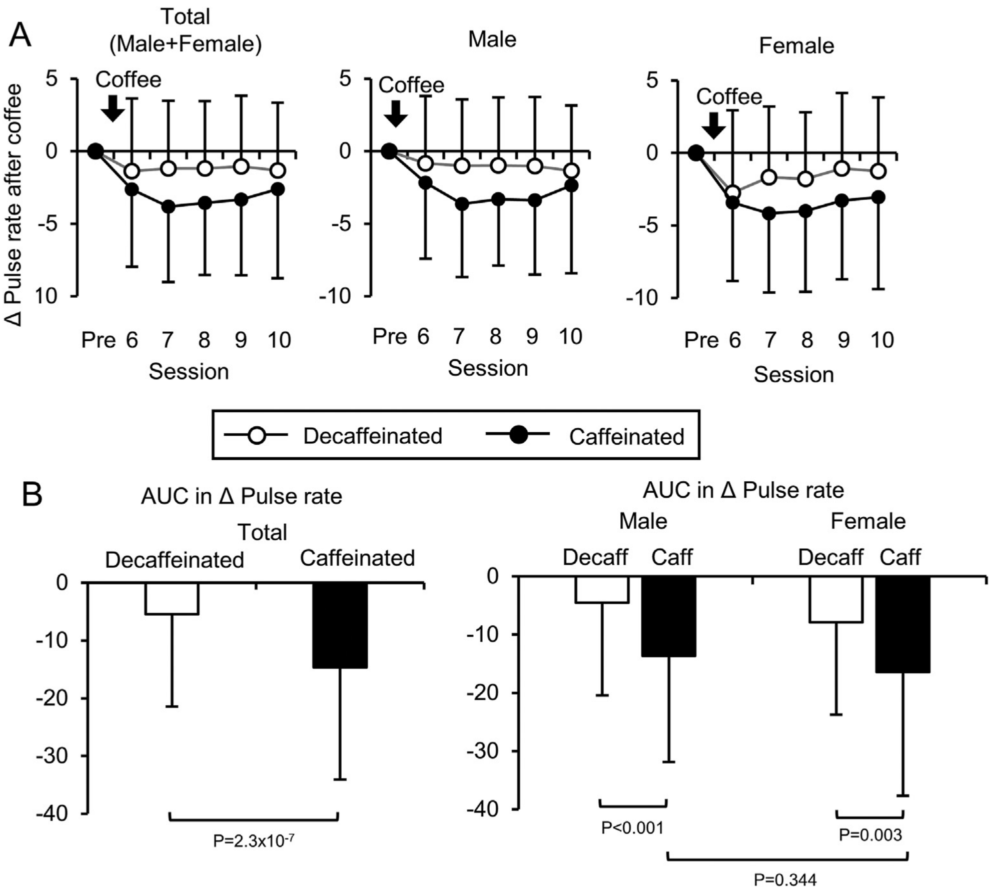

Fig 4. Analysis of AUC in changes in pulse rate after administration of coffee. (A) Time courses of changes in pulse rates after coffee administration in total participants and in males and females. (B) Area under the curve (AUC) of Δ pulse rate after coffee was calculated for each participant and was averaged in total participants and in males and females.

In conclusion, there is no sex difference in the acute effects of caffeine on calculation efficiency and pulse rate in medical students.

Author contributions

AK and YH designed research; RN, KT, and NK collected and analyzed data; AK and NK performed data analyses; NK, RH, NI; and AK wrote and edited the manuscript. All authors have read and agreed to the submitted version of the manuscript.

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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