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Acute effects of coffee on skin blood flow and microvascular function

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ABSTRACT

Objective: Studies on the acute effects of coffee on the microcirculation have shown contradicting results. This study aimed to investigate if intake of caffeine-containing coffee changes blood flow and microvascular reactivity in the skin.
Methods: We measured acute changes in cutaneous vascular conductance (CVC) in the forearm and the tip of the finger, the microvascular response to transdermal iontophoresis of acetylcholine (ACh) and sodium nitroprusside (SNP) and post-occlusive reactive hyperemia (PORH) in the skin, after intake of caffeinated or decaffeinated coffee.
Results: Vasodilatation during iontophoresis of ACh was significantly stronger after intake of caffeinated coffee compared to after intake of decaffeinated coffee (1.26 ± 0.20 PU/mm Hg vs. 1.13 ± 0.38 PU/mm Hg, $P < 0.001$). Forearm CVC before and after PORH were not affected by caffeinated and decaffeinated coffee. After intake of caffeinated coffee, a more pronounced decrease in CVC in the fingertip was observed compared to after intake of decaffeinated coffee (−1.36 PU/mm Hg vs. −0.52 PU/mm Hg, $P = 0.002$).
Conclusions: Caffeine, as ingested by drinking caffeinated coffee acutely improves endothelium-dependent microvascular responses in the forearm skin, while endothelium-independent responses to PORH and SNP iontophoresis are not affected. Blood flow in the fingertip decreases markedly during the first hour after drinking caffeinated coffee compared to decaffeinated coffee.

1. Introduction

Coffee is one of the most widely consumed beverages in the world. Although it is well known to be a major source of caffeine, coffee also contains a wide range of compounds that are not all completely identified and of which the effects on the human body is yet unknown. Most studies find that regular coffee intake increases blood pressure slightly and raises plasma cholesterol and homocysteine levels (Riksen et al., 2009), whereas coffee consumption is associated with a reduced incidence of type 2 diabetes mellitus (van Dam et al., 2006), a decrease in inflammatory markers (Williams et al., 2008) and improved endothelial function (Siasos et al., 2013). Caffeine consumption also affects pain modulation (Baratloo et al., 2016) and interacts with skin carcinomas, with some evidence pointing at a protective effect of caffeine on malignant melanoma (Li et al., 2016; Liu et al., 2016).

Prospective studies have generally not shown a consistent positive association between coffee intake and cardiovascular diseases, with some results even suggesting protective effects (O'Keefe et al., 2013; Freedman et al., 2012; Malerba et al., 2013). Studies on acute vascular effects of caffeine have, however, shown contradictory results, with most studies showing a slight increase elevated blood pressure and arterial stiffness (Nurminen et al., 1999; Karatzis et al., 2005), decreased glucose disposal (Greer et al., 2001), and impaired endothelial function (Papamichael et al., 2005; Buscemi et al., 2010a). On the other hand, some studies have found that caffeine causes an increase in endothelium dependent vasodilatation (Umemura et al., 2006; Shechter et al., 2011; Noguchi et al., 2015). The reason for these conflicting findings may reside in the differences in study methods, study population and the presence of other compounds in coffee besides caffeine, such as some phenolic components, which are well known to have a strong antioxidant capacity. It is thus possible that this antioxidant capacity compensates for the negative effects of caffeine (Bonita et al., 2007; Buscemi et al., 2010b).

The microcirculation is crucial in the regulation of vascular resistance and the blood flow in tissues and critical organs. Because the skin is easily accessible, its microvascular bed is has become a popular model for studying microvascular function. The cutaneous

Abbreviations: SD, standard deviation; BMI, body mass index; ACh, acetylcholine chloride; SNP, sodium nitroprusside; LSCI, laser speckle contrast imaging; LDF, laser Doppler flowmetry; HPLC, high performance liquid chromatography.

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microcirculation can be investigated noninvasively using physiological and drug provocations that specifically target vascular signaling pathways. For instance, endothelium-dependent microvascular responses can be studied using iontophoresis of acetylcholine (ACh), often combined with iontophoresis of sodium nitroprusside (SNP) as an endothelium-independent control. Post-occlusive reactive hyperemia (PORH) in the skin can be used to study the involvement of sensory nerves and hyperpolarizing mechanisms. Importantly, the recent development of image-based blood flow measurement techniques has further improved the reproducibility of microvascular assessment in the skin (Roustit et al., 2010; Iredahl et al., 2015).

In this double blind, randomized, placebo-controlled cross-over study, we therefore aimed to investigate if intake of caffeine-containing coffee, or decaffeinated coffee changes blood flow and microvascular reactivity in the skin. We specifically studied (1) changes in basal cutaneous vascular conductance (CVC) in the forearm and the tip of the finger using noninvasive, optical measurement techniques, (2) the involvement of the endothelium using transdermal iontophoresis of acetylcholine (ACh) and sodium nitroprusside (SNP), and (3) the involvement of sensory nerves and hyperpolarizing mechanisms using post-occlusive reactive hyperemia (PORH) following 5 min of forearm arterial occlusion.

2. Materials and methods

2.1. Subjects

Sixteen normotensive, non-smoking subjects (8 female, 8 male) without any known cardiovascular or skin diseases, mean (standard deviation, SD) age 23.4 (2.3) years were included in the study after they had given informed and written consent. Smokers and subjects with a blood pressure above 140/90 mm Hg were excluded, as microvascular function is impaired by cigarette smoking and correlated to blood pressure (Serne et al., 1999; Ijzerman et al., 2003). The study subjects had a mean weight of 76.9 (11.6) kg, a mean length of 177 (8) cm and a mean BMI of 24.4 (2.7) kg/m^2. Before the start of the experiments the subjects, who were regular coffee drinkers, were asked to refrain from eating and drinking any caffeine containing products, including coffee, tea, energy drinks and chocolate for at least 24 h. They were also asked to avoid strenuous exercise on the day of the experiment. The study was approved by the regional ethics committee in Linköping, Sweden (DNr 2016-119/32), and was done according to the declaration of Helsinki.

2.2. Protocol

A randomized, double-blind, placebo-controlled crossover study was designed. The subjects visited the research lab on two separate visits with at least 5 days and at most 9 days in between. The subjects were randomized to either ingest caffeinated or decaffeinated coffee on their first visit. All measurements took place in the same room, at an ambient temperature of 21 ± 1 °C. A schematic overview of the experimental protocol is shown in Fig. 1.

Subjects were placed in semi-supine position with their arms at heart level comfortably supported by pillows. A laser Doppler flowmetry (LDF) probe was mounted to the skin of the palmar aspect of the distant phalanx of the third finger of the left hand using double adhesive tape. This LDF probe was used to measure skin perfusion continuously throughout the experiment. After 15 min of acclimatization, baseline measurements of blood pressure and heart rate were made. The skin of the volar side of both forearms was gently cleaned with chlorhexidine ethanol (5 mg/mL, Fresenius AB, Uppsala, Sweden). Then, baseline skin perfusion measured in a 5 × 10 cm^2 area on the medial, volar side of the right forearm was for 1 min using laser speckle contrast imaging (LSCI). Total arterial occlusion was then induced and maintained during 5 min using a blood pressure cuff around the upper arm inflated to a pressure of 220 mm Hg. After the blood pressure cuff was released, the PORH response was recorded until the perfusion had decreased to a stable level of at least 50% of the maximum level (typically 5 min after release of the cuff).

A cup of caffeinated or decaffeinated coffee (Vivalto Lungo or Vivalto Lungo Decaffeinato, Nespresso AB, Stockholm, Sweden) was prepared and consumed by the subject. Neither sugar nor milk was added. Two iontophoresis electrodes were mounted on the volar side of the left forearm, approximately 5 cm apart, and connected to the current controller. One iontophoresis electrode was filled with ACh and another was filled with either NaCl (N = 6) or SNP (N = 10). Forty minutes after coffee intake, the drugs were delivered simultaneously using a 10-minute, 0.02 mA anodal (ACh) and cathodal (NaCl or SNP) current. Immediately after the start of the iontophoresis, the PORH measurement was repeated on the other arm using the same protocol as before. Finally, at the end of the experiment, blood pressure was measured a second time.

2.3. Equipment

Transdermal iontophoresis was used to deliver ACh, SNP and sodium chloride (NaCl) to the skin, using an iontophoresis current controller (Prion 382, Perimed AB, Järfälla, Sweden) and transparent, ring-shaped drug delivery electrodes (LI 611, Perimed AB, Järfälla, Sweden). Drug delivery electrodes were always placed on the volar side of the left forearm and care was taken to avoid visible veins and birthmarks.

A Laser Speckle Contrast imager (Pericam PSI System, Perimed AB, Järfälla, Sweden) was used to measure perfusion in the skin of forearm during microvascular provocations. The system uses a divergent laser beam with a wavelength of 785 nm. Perfusion images were acquired every 2 s by averaging data from 42 image frames taken in rapid succession (21 frames/s). The image size was set to correspond to a 7 cm × 7 cm area of skin and the spatial resolution of the perfusion image was 0.2 mm/pixel at a measurement distance of 20 cm. The system was calibrated according to the manufacturer recommendations. Perfusion images were further analyzed by calculating mean perfusion levels in regions of interest using PIMsoft 1.3 (Perimed AB, Järfälla, Sweden).

A laser Doppler perfusion monitor (Periflux 5000, Perimed AB, Järfälla, Sweden) was used to measure changes in skin perfusion in the fingertip. A thermostatic laser Doppler probe (Probe 457, Perimed AB, Järfälla, Sweden) was used, and was set to a constant temperature of 30 °C. The probe has a fiber separation of 0.25 mm and measures perfusion at depth of approximately 0.5 mm. Perfusion values were measured at a sample rate of 33 recordings per second and were further processed using the manufacturer's software (Perisoft 2.5.5, Perimed AB, Järfälla, Sweden). An automatic sphygmomanometer (M6 Comfort, Omron Healthcare, Hoofddorp, The Netherlands) was used to measure blood pressure and heart rate.

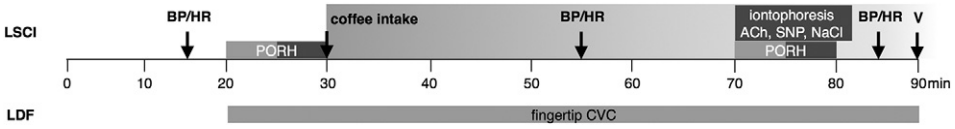

Fig. 1. Overview of the experimental protocol. Either caffeinated or decaffeinated coffee was consumed in a double-blind, randomized manner. PORH was done in the right arm, while iontophoresis was done in the left arm. Fingertip cutaneous vascular conductance (CVC) was measured in the left middle finger using a thermostatic laser Doppler probe at 30 °C. LSCI: laser speckle contrast imaging, LDF: laser Doppler flowmetry, BP/HR: blood pressure and heart rate measurement, PORH: post-occlusive reactive hyperemia, V: venous blood sampling.