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Controlling for caffeine in cardiovascular research: A critical review

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ABSTRACT

Caffeine, the most widely consumed drug in the world, exerts numerous effects on cardiovascular activity. Thus, it is important and advisable to control for caffeine consumption in studies examining caffeine and/or cardiovascular activity and reactivity. This paper 1) reviews the literature concerning caffeine's effects on cardiovascular parameters; 2) summarizes the widely varying protocols used to control for the drug in extant cardiovascular literature, and 3) provide guidelines for caffeine control procedures to minimize potentially confounding acute and withdrawal effects of the drug. An abstention period equal to the average half-life of the drug is recommended for creation of methodological controls for caffeine. Additional methodological recommendations are described concerning factors that moderate the half-life of caffeine. When feasible, researchers should consider and aim to control for caffeine's acute and extended psychophysiological effects. This understudied issue has fundamental implications for caffeine-related investigations and research in psychophysiology and behavioral medicine.

1. Introduction

Psychophysiological studies inform understanding of biobehavioral aspects of cardiovascular regulation and disease processes (Schneiderman and McCabe, 1989). Cardiovascular activity is significantly affected by numerous factors (e.g. demographic and behavioral variables such as sleeping patterns, diet, and use of pharmacological substances) which may exert systematic effects and therefore must be adequately controlled in research. Divergent results from seemingly similar studies may be due in part to lack of control for confounds such as these.

Caffeine, a metabolic and central nervous system (CNS) stimulant that is the most widely consumed psychoactive substance worldwide, may be one such confound. Approximately 85–89% of adults in the U.S. consume caffeine regularly and roughly 64% of caffeine is consumed in the form of coffee (Fulgoni et al., 2015; Mitchell et al., 2014; Verster and Koenig, 2017). The drug is also found in a variety of commonly consumed beverages and foods and is often used as a pharmacological adjuvant due to its analgesic properties as well as increasing drug efficacy (Tavares and Sakata, 2012).

Caffeine exerts myriad effects on cardiovascular and psychological variables. However, no standard methodological procedures exist for control of this drug. Caffeine control procedures in cardiovascular research vary widely, and no standard length of caffeine abstinence prior to participation in cardiovascular studies has been established. The lack of standardized caffeine control practices likely contributes to discrepant results among similar studies, and potentially creates extraneous variance due to lingering acute effects or withdrawal effects on physiological variables. One methodological investigation examining caffeine's effects indicated that a long caffeine abstinence of 24 h was needed to avoid the drug's confounding effects on pharmacological stress testing (Carlsson et al., 2015). This study is informative, yet does not address potential withdrawal effects in regular caffeine consumers after 24 h of abstention.

Despite abundant reviews summarizing caffeine's effects, no known review has specifically examined caffeine control procedures in cardiovascular studies. One singular review surveyed literature pertaining to caffeine's acute pressor effects to determine the adequacy of a 30-minute abstention for control of such effects (Mort and Kruse, 2008). Findings confirmed that lengthier abstention durations are necessary for maximal accuracy of blood pressure (BP) readings, which is expected, considering that caffeine's peak plasma concentration occurs at

Abbreviations: ANS, autonomic nervous system; BP, blood pressure; CNS, central nervous system; CVR, cardiovascular reactivity; CYP1A2, a member of the cytochrome P450 superfamily of enzymes; DBP, diastolic blood pressure; HF-HRV, high-frequency heart rate variability; HR, heart rate; HRV, heart rate variability; ICG, impedance cardiography; LVET, left ventricular ejection time; PEP, pre-ejection period; PNS, peripheral nervous system; SBP, systolic blood pressure; SSRIs, selective serotonin reuptake inhibitors; SVR, systemic vascular resistance

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approximately 30–120 min after intake. Though the review addressed an important methodological issue, no specific temporal abstention recommendations, withdrawal effects, or caffeine's acute effects on other cardiovascular variables are offered.

The goal of the current review is to narrow these gaps in the literature by using the following primary aims: (1) review extant findings on the effects of caffeine on both the CNS and peripheral nervous systems (PNS; i.e. behavioral and cardiovascular parameters at rest and in response to acute stress), in specific application to experimental control; (2) review existing methodological controls for caffeine in cardiovascular research, with specific focus on pre-study abstention durations, and; (3) provide methodological recommendations for controlling caffeine (i.e. reducing the drug's acute effects on cardiovascular activity, while simultaneously circumventing caffeine withdrawal symptoms). Generating a standardized methodology for use in cardiovascular studies may increase cross-study consistency and minimize confounding effects of caffeine. Lastly, we offer suggestions for future research that may provide empirically-derived guidelines for caffeine abstention durations in application to research protocols.

2. Pharmacological and physiological effects of caffeine

Caffeine (1,3,7-trimethylxanthine) is a naturally occurring xanthine derivative and purine alkaloid, which is rapidly and completely absorbed from the intestines, making it 100% bioavailable. The drug is absorbed within 30–45 min on average (Echeverri et al., 2010). Although relatively benign in healthy individuals, caffeine acutely exerts several cardiovascular and neuroendocrine effects, chiefly through antagonism of the A1 and A2 subtypes of the adenosine receptor (Grosso et al., 2017; Higdon and Frei, 2006). The neuromodulator adenosine affects multiple transmitter systems in the CNS and PNS and is among the most important endogenous vasodilators (Haskó et al., 2008; Fredholm and Dunwiddie, 1988). Prevention of adenosine's inhibitory effects leads to CNS excitability, stimulation of medullary, vasomotor, and respiratory brain networks, as well as catecholamine release (i.e. epinephrine) (Benowitz, 1990). Below, we further describe caffeine's typical acute effects on cardiovascular indices at rest, which are primarily caused by reflex sympathetic activation through adenosine blockade.

2.1. Resting cardiovascular and respiratory responses to caffeine

2.1.1. Blood pressure

The most frequently explored cardiovascular responses to caffeine concern pressor effects. Blood pressure (BP) increases are due to vasoconstriction and increased systemic vascular resistance (SVR) (Pincomb et al., 1985). An extensive body of research shows transient caffeine-elicited elevations in BP (Jeong and Dimsdale, 1990; Pincomb et al., 1987; Bender et al., 1997; Lovallo et al., 1991; Nussberger et al., 1990). A review found that acute intake of a dietary dose of caffeine (200–250 mg) increased systolic (SBP) by 3–14 mm Hg and diastolic (DBP) by 4–13 mm Hg (Nurminen et al., 1999).

2.1.2. Heart rate

Extensive studies examining heart rate (HR) changes following moderate caffeine doses tend to report decreases in HR (Pincomb et al., 1985; Pincomb et al., 1987). This response is due to a negative feedback reaction of the baroreflex system to increased BP (Corti et al., 2002; Sanders et al., 1988; Spieker et al., 2000).

2.1.3. Vasomotor and contractility effects

Literature generally suggests that post-caffeine pressor increases are due to SVR elevations coupled with a lack of change in cardiac output (Pincomb et al., 1993). Fewer studies have examined caffeine's acute effects on systolic time intervals such as pre-ejection period (PEP) and left-ventricular-ejection time (LVET), but most identify no drug-induced changes. Further research is necessary concerning the effect of caffeine on these hemodynamic indices.

2.1.4. Respiratory effects

Previous research using rodents and non-human primates has established that xanthines such as caffeine affect inhalation and exhalation by affecting central mechanisms controlling respiration (Howell et al., 1990; Wessberg et al., 1984). Caffeine generally elicits increases in respiratory rate, likely through the sensitization of medullary centers to carbon dioxide (Martinet and Debry, 1992; Benowitz, 1990).

2.1.5. Heart rate variability

Heart rate variability (HRV) reflects the constant dynamic relationship between sympathetic and parasympathetic activity in regulation of HR (Koenig et al., 2013). Of the relatively few studies investigating caffeine's effects on HRV among habitual consumers, most identify acute increases in HRV indices (Yeragani et al., 2005; Hibino et al., 1997), although some fail to report this effect (e.g. Rauh et al., 2006; Zimmermann-Viehoff et al., 2016). Overall, effects of caffeine on HRV are somewhat difficult to integrate due to wide variations in study designs and methodologies: specifically, populations studied (e.g. healthy versus clinical), dose-response relations, and experimental conditions (Koenig et al., 2013). Nevertheless, Koenig et al.'s, 2013 systematic review showed significantly greater increases in high-frequency HRV (HF-HRV) following the consumption of caffeinated versus decaffeinated coffee. The potential of caffeine to upregulate vagal activity has been suggested in some literature (e.g. La Monica et al., 2017).

2.2. Additive reactivity effects of caffeine and stress

Caffeine consumption is positively associated with daily life stress, and many consume the drug regularly to promote feelings of energy necessary for completion of daily responsibilities (Conway et al., 1981). Therefore, in addition to investigating caffeine's cardiovascular actions at rest, exploring caffeine's effects in concert with acute mental and physical stress is also important.

Research has often demonstrated an additive effect of caffeine on cardiovascular reactivity during stress-inducing cognitive, physical, and social tasks (e.g. Bennett et al., 2013). For example, high (250 mg) and low (3 mg) doses of caffeine can exert significantly different effects on SBP and HR during psychological stress (Strickland et al., 1989). DBP increases produced by caffeine have been found to be additive to the stress-inducing effects of a mental arithmetic task (France and Ditto, 1988). Pincomb et al. (1988) found that both dietary caffeine and a behavioral task alone significantly increased both SBP and DBP. Caffeine's pressor effects were additive when both caffeine and the task were combined.

In addition to additive actions during mental stress, caffeine may also enhance cardiovascular reactivity to physical stressors through increased energy metabolism. In a placebo-controlled study where subjects were randomly administered 300 mg caffeine capsules, the drug induced a significant increase in DBP and a decrease in respiratory gas exchange ratio during cycling, versus placebo (Nishijima et al., 2002). In short, consumption of caffeinated coffee shortly prior to participation in a psychophysiological study involving aerobic or psychological stressors may conceivably confound results.

2.3. Sex differences in cardiovascular responses to caffeine and acute stress

Extant research typically suggests that pressor increases due to combined effects of caffeine and stress occur through increases in peripheral (vascular) resistance (e.g. Whitsett et al., 1984; Pincomb et al., 1985). Of note, such investigations have primarily used all-male samples. Cardiovascular mechanisms underlying post-caffeinated BP responses to mental stress may differ by sex, due to differences in