Effect of Caffeine on Blood Pressure Beyond the Laboratory

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Caffeine was reported to increase blood pressure 70 years ago.¹ Research into the cardiovascular effects of caffeine entered the modern era with a 1978 publication by Robertson et al.,² who noted increases in plasma catecholamines and renin in association with a pressor response to caffeine. In their study, caffeine was administered as a single dose equivalent to 2 to 3 cups of coffee to 9 healthy, non-coffee drinking, young subjects under carefully controlled laboratory conditions. The authors presumably selected caffeine-naive subjects to avoid pharmacological tolerance to caffeine and to maximize its cardiovascular and adrenomedullary actions. This approach was to set the pattern for research on the effects of caffeine on blood pressure over the next 25 years. Despite numerous studies in the intervening period, it is still not certain if caffeine increases blood pressure only under ideal laboratory conditions or if it causes a clinically important pressor response with regular use during usual daily activities.

Much of the controversy surrounding the impact of caffeine on blood pressure derives from the rapid development of tolerance to its effects that appear after only 1 or 2 days of regular consumption.³ Several studies have reported that caffeine is still capable of increasing blood pressure despite regular previous use. However, in some instances, serum caffeine concentrations immediately before ingestion of caffeine in the laboratory were close to 0, suggesting that subjects had not consumed caffeine for at least 24 hours.⁴-⁷ In these experiments, subjects were asked to abstain from caffeine for specific periods (minimum 12 hours) before the acute challenge, leaving open the possibility that they were supercompliers, having actually abstained for an even longer period, thus losing some of the tolerance that was supposed to have developed with prolonged daily use. Whether by design or by accident, studies in the laboratory have tended to maximize the likelihood of caffeine producing an increase in blood pressure.

The report in this issue of Hypertension by Lovallo et al.⁸ is no exception. The authors postulated that regular use of caffeine 300 or 600 mg per day (equivalent to 3 or 6 cups of coffee per day) for 5 days would not preclude an increase in blood pressure occurring after acute ingestion of 1 or 2 doses of 250 mg of caffeine in the laboratory on day 6. In a carefully designed and well conducted experiment, the authors showed a mean increase in systolic/diastolic blood pressure of 1/2 mm Hg after acute ingestion of caffeine 250 mg and after administering a second 250-mg dose 4 hours later.

There are several explanations for these observations. Ingestion of caffeine after chronic use is more likely to increase blood pressure in younger subjects.⁹ The mean age in this normotensive study population was only 28 years, making the results difficult to generalize to the population at large, especially in those with hypertension who tend to be older. Changes in blood pressure were recorded 40 to 60 minutes after acute ingestion of the equivalent of 2 to 3 cups of coffee administered as a single capsule (dose 1) or after a second 250-mg capsule (dose 2) 4 hours later, giving a total amount equivalent to 5 cups of coffee ingested over a 4-hour period. The peak caffeine concentration occurs at ≈1 hour after ingestion,¹⁰ so that any increase in blood pressure in this study was being recorded at the time of the peak serum concentration of caffeine after each dose. Also, the relevance of these findings to the effects of caffeine consumption in the community are uncertain because regular use, even among heavy coffee drinkers, would generally not involve the ingestion of 250 mg as a bolus on 2 separate occasions only 4 hours apart.

Having found a very small change in blood pressure after 250 to 500 mg of caffeine ingestion, the authors then divided their subjects into those above and below the median change in blood pressure, denoting individuals with little or no response to caffeine as the “high-tolerance” subgroup and those with greater pressor responses after caffeine ingestion as the “low-tolerance” subgroup. Using this approach, they reported mean increases in systolic/diastolic blood pressure of only 2 to 3 mm Hg in the low-tolerance subgroup. As with any post hoc analysis, these findings should be considered preliminary because the low- and high-tolerance subgroups with less or more of a blood pressure response to caffeine may have differed in known and unknown respects. For example, the low-tolerance subjects who showed a small increase in blood pressure after 250 to 500 mg of caffeine had, on average, a one-third lower mean salivary caffeine concentration after 5 days of chronic caffeine ingestion, suggesting that they were either less compliant with the protocol or they metabolized caffeine more rapidly.

Despite the aforementioned shortcomings, the study by Lovallo et al.⁸ is one of the better attempts to demonstrate the nature of tolerance to caffeine and its potential impact on blood pressure.

In addition to experiments in the laboratory, there have been numerous clinical studies examining a possible link...
between caffeine and increases in blood pressure. The results of large epidemiological studies involving up to 80,000 patients have been inconsistent, with some showing a small increase in blood pressure with higher caffeine use and others showing no change or even a decrease in blood pressure. Clinical trials comparing caffeine ingestion after periods of either caffeine or placebo use have also shown variable results. Jee et al. have performed a meta-analysis of 11 clinical trials in which subjects consumed caffeine for at least 2 weeks before the assessment of any acute effects of caffeine on blood pressure. These authors reported an overall increase in systolic/diastolic blood pressure of 2.4/1.2 mm Hg, respectively, with acute caffeine ingestion. In studies in which the equivalent of 1 to 4.5 cups of coffee per day were consumed, the mean change in blood pressure was only 0.1/1.0 mm Hg, whereas higher coffee consumption (≥5 cups per day) showed a somewhat greater pressor response (mean 3.2/1.4 mm Hg).

There is little doubt that caffeine can cause a small increase in blood pressure in some individuals. Pressor responses have been reported more often in caffeine-naive subjects, in younger persons, and after larger amounts of caffeine have been administered in acute experiments. The question now is what, if anything, should be done about discouraging caffeine use in the community. As Lovallo et al. correctly note, daily caffeine consumption in the United States averages 2 to 4 cups of coffee (or its equivalent) per day. Despite numerous studies over the past 2 decades, we still do not know if these levels of consumption increase blood pressure, especially in patients with borderline or sustained hypertension. Ingestion of 2- to 3-times these amounts, even with habitual caffeine use, may exert a clinically important pressor effect, although conclusive data to support this belief are still lacking. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure would tend to agree with this view, because restriction of caffeine intake was not recommended as a lifestyle measure to lower blood pressure.

In the absence of definitive scientific data, it would seem prudent to recommend moderation when it comes to the ingestion of caffeine containing beverages such as coffee, tea, and cola drinks. There is little evidence to suggest that habitual consumption at the current average of the equivalent of 2 to 4 cups of coffee per day causes an increase in blood pressure of any clinical importance. Ingesting larger amounts (eg, >5 to 6 cups of coffee per day) should be discouraged if increases in blood pressure are a concern, such as in patients with hypertension or in those individuals having a prehypertensive state.

It is of interest to note that meta-analyses have also shown no significant association between coffee intake and myocardial infarction at daily consumption up to 5 to 6 cups per day. Similar amounts of caffeine have not been linked to the development of cardiac arrhythmias. Thus, moderation would appear to be the key to minimizing any adverse cardiovascular effects. A final caveat for users of caffeine is to consume it on a regular basis to minimize any effects it may have on blood pressure. At the moment, it would seem premature to add moderate caffeine consumption to our list of "perils of daily living."

References
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Hypertension. 2004;43:724-725; originally published online February 16, 2004;
doi: 10.1161/01.HYP.0000120970.49340.33

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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World Wide Web at:
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