# Transient Exposure to Coffee as a Trigger of a First Nonfatal Myocardial Infarction

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**Background:** The effects of coffee on myocardial infarction are uncertain. We hypothesize that coffee in the presence of predisposing factors can induce a cascade of events that, through sympathetic nervous activation, can induce the onset of myocardial infarction.

**Methods:** We recruited 503 incident cases of nonfatal myocardial infarction between 1994 and 1998 in Costa Rica. We used a case-crossover design to calculate relative risks (RRs) and 95% confidence intervals (95% CIs).

**Results:** The RR of myocardial infarction in the hour after coffee intake was 1.49 (95% CI = 1.17–1.89). Occasional coffee drinkers (≤1 cup/day, n = 103) had a RR of myocardial infarction of 4.14 (2.03–8.42), moderate coffee drinkers (2–3 cups/day, n = 280) had a RR of 1.60 (1.16–2.21), and heavy coffee drinkers (≥4 cups/d, n = 120) had a RR of 1.06 (0.69–1.63; $P = 0.006$, test of homogeneity). Patients with 3 or more risk factors (n = 101) had a RR of myocardial infarction of 2.10 (1.30–3.39), whereas patients with fewer than 3 risk factors (n = 396) had a RR of 1.39 (1.04–1.82; $P = 0.15$, test of homogeneity); and RR was 1.72 (1.30–2.30) among sedentary patients compared with 1.07 (0.66–1.72) among nonsedentary ($P = 0.10$, test of homogeneity).

**Conclusions:** The findings indicate that coffee intake may trigger myocardial infarction. The association is particularly strong among people with light/occasional intake of coffee (≤1 cup/day), with sedentary lifestyle, or with 3 or more risk factors for coronary heart disease.

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Coffee is one of the most popular beverages worldwide, with an average consumption of 6.7 million tons per year.[1] Prepared from the seed of the coffee plant *Coffea arabica*, originated in Ethiopia and domesticated in Yemen, this beverage has been part of the diet for the past 5 centuries.[2]

Coffee contains many biologically active compounds, including caffeine, diterpenes, and polyphenols, with numerous metabolic properties and diverse health effects.[3] Because of the potential adverse effects of coffee on blood cholesterol, homocysteine, and hypertension, the effects of coffee intake on heart disease have been extensively studied for decades. Findings are still controversial, with most case–control studies showing increased heart disease risk for heavy drinkers and cohort studies showing both negative and positive results.[4–6] Some authors have suggested that this discrepancy is the result of a more acute effect of coffee on the risk of myocardial infarction that could be better assessed using a case–control design.[4,5] More recent studies have observed a J-shaped association between coffee drinking and heart disease,[6,7] which suggests that people with light or occasional intake could be at higher myocardial infarction risk because coffee may act as a trigger of myocardial infarction.[6] The transient effects of coffee intake on increased blood pressure and sympathetic tone support this hypothesis.[8] It has also been suggested that the disruption of a vulnerable atherosclerotic plaque in response to hemodynamic stress could trigger a myocardial infarction.[9]

We hypothesized that coffee, through sympathetic nervous activation, could induce a cascade of events that result in a myocardial infarction when in the presence of predisposing factors. Using a case-crossover design, we assessed the effect of coffee as a trigger of nonfatal acute myocardial infarction, and whether usual coffee intake and the underlying cardiovascular risk can modify this triggering effect of coffee.

## METHODS

### Study Population

The study population consists of incident cases of nonfatal myocardial infarction recruited between 1994 and 1998 in the Central Valley of Costa Rica.[10] Eligible case subjects were men and women who were diagnosed as survivors of a first acute myocardial infarction by 2 independent cardiologists at any of the 3 recruiting hospitals in the Central Valley of Costa Rica. All cases met the World Health Organization criteria for myocardial infarction, which require typical symptoms plus either elevations in cardiac enzyme levels or diagnostic changes in the electrocardiogram.[11] Enrollment was conducted while cases were in the hospital's step-down-unit. Participation among eligible cases was 97%.

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All subjects gave informed consent on documents approved by the Human Subjects Committee of the Harvard School of Public Health and the University of Costa Rica.

## Data Collection

Sociodemographic characteristics, life style history, and medical history data were collected during an interview using a questionnaire with close-ended questions. Costa Rica is a coffee-producing country, and coffee is an important part of the traditional diet. Mean intake of caffeine in a representative sample of the Costa Rican adult population was 324 mg/day. We collected information on habitual intake of coffee using a food frequency questionnaire that has been developed and validated specifically to assess dietary intake among the Costa Rican population.[12,13] The correlation coefficient for caffeine intake (mg/day) between seven 24-hour recalls and the average of two food frequency questionnaire interviews was 0.83, and the correlation coefficient between both food frequency questionnaires was 0.77.[12] These results indicate high validity and reliability for the usual intake of coffee collected with the food frequency questionnaire. The food frequency questionnaire presents 9 frequency options (never or <1/month, 1–3/month, 1/week, 2–4/week, 5–6/week, 1/day, 2–3/day, 4–5/day, ≥6/day) for most food items, including coffee. The portion size for coffee was fixed as one cup equivalent to 8 oz. Other information regarding usual brewing method was collected at the same time. Most coffee consumed in Costa Rica is filtered, but there are several filter methods, including paper and cotton cloth. The interviews were conducted by trained personnel who followed a standardized protocol. Intake of coffee during the time previous to the myocardial infarction was collected using the following question: "When was the last time you had coffee before your heart attack?" Time was recorded in hours or days depending on the answer. The number of cups consumed was also recorded at the same time. Enrollment was performed while study patients were in the step-down unit and the interview was conducted at the subjects' home. The median time between hospital discharge and data collection was 11 days with most people (82%) completing the interview within 2 weeks after discharge.

## Statistical Analysis

We recruited 530 incident cases of nonfatal myocardial infarction for this analysis. Complete and consistent information was available for 503 cases regarding intake of coffee during the 24 hours and days before the myocardial infarction and regarding habitual intake of coffee. Using a case-crossover design, data were analyzed as a stratified analysis in which the stratifying variable is the individual patient.[14–16] We selected a hazard period of 1 hour based on the absorption and bioavailability of caffeine in blood.[3,17] Person-time exposed was calculated using the habitual frequency of coffee reported in the food frequency questionnaire. Person-time not exposed was calculated by subtracting the person-time exposed from the total hours in one year (8766 hours/year). The relative risk (RR) was estimated as the ratio between the observed exposure odds at the time of myocardial infarction onset and the expected exposure odds.[14,15] Confidence intervals were calculated using methods for sparse follow-up data.[18] $\chi^2$ tests of homogeneity of RR across strata were used to assess effect modification by stratifying factors.[18]

We stratified by habitual intake of coffee and by risk factors for underlying cardiovascular risk. Habitual intake of coffee was stratified in 3 categories: light/occasional drinkers (≤1 cup/day), moderate drinkers (2–3 cups/day), and heavy drinkers (≥4 cups/day). Underlying cardiovascular risk was estimated as the sum of the following risk factors: history of diabetes, history of hypertension, history of hypercholesterolemia, history of angina, smoking status, and waist circumference. Self-reported diabetes and hypertension were validated using the recommended definitions by the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus,[19] and the Third Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNCIII),[20] and found to be reliable in this population.[21] Smoking status was defined as smoking 1 or more cigarettes/day. Waist circumference was measured twice, and the average of the 2 measurements was dichotomized according to the ATP III definition of metabolic syndrome (>88 cm for women and >102 cm for men). A cutoff of 3 risk factors was selected a priori based on the distribution of the sum of risk factors. The top quintile of the distribution corresponded to patients with 3 or more risk factors. Sedentary people were defined as those expending less than 10% of their daily energy in the performance of moderate-vigorous activities (at least 4 times the basal metabolism rate).[22] All analyses were carried out with SAS (version 9.1; SAS Institute, Cary, NC) and PEPI (V.4.0 Salt Lake City, UT: Sagebrush Press; 2001).

We performed several sensitivity analyses to assess the robustness of our findings. For example, the open category of heavy coffee drinkers in the food frequency questionnaire (6 cups or more per day) was analyzed as 6 cups for everybody in this category. We next repeated the analysis assigning 7 cups or 8 cups to account for the underestimation of the person-time exposed among heavy drinkers. Other sensitivity analyses performed included deletion of people reporting having more than 1 cup before the myocardial infarction and exclusion of people taking beta-blockers. All these sensitivity analyses yielded similar results.

# RESULTS

Table 1 shows the general characteristics of the study participants. Most patients reported drinking 2–3 cups of coffee per day. There were more heavy coffee drinkers (≥4 cups per day) among men than women. Only 37 (7%) patients reported no intake of coffee. All coffee consumed was caffeinated coffee; 93% of respondents reported drinking filtered coffee.

Of the 503 patients, 80 had at least 1 cup of coffee in the hour before the onset of myocardial infarction (69 had 1 cup of coffee, 9 had 2 cups, and 1 had 3 cups). The RR of myocardial infarction in the hour after taking coffee was 1.49 (95% CI = 1.17–1.89). We chose a hazard period of 1 hour based on the absorption and bioavailability of caffeine in blood. When selecting 2 or 3 hours before the myocardial infarction the RR are 1.04 (0.84–1.28) and 0.86 (0.71–1.04),

**TABLE 1.** General Characteristics of Costa Rican Patients (1994–1998)*

| | Women (n = 130) | Men (n = 373) |
|---|---|---|
| Age (y); mean ± SD | 60 ± 10 | 56 ± 11 |
| Waist circumference, cm (n = 495); mean ± SD | 86.2 ± 9.4 | 92.0 ± 8.8 |
| Physical activity, METS (n = 500); mean ± SD | 1.24 ± 0.40 | 1.48 ± 0.81 |
| Income, US$/mo (n = 474); mean ± SD | 313 ± 285 | 510 ± 468 |
| Current smokers†; % | 34 | 48 |
| History of diabetes; % | 41 | 18 |
| History of hypertension (n = 501); % | 57 | 38 |
| History of hypercholesterolemia (n = 502); % | 30 | 21 |
| History of angina (n = 497); % | 11 | 13 |
| Habitual intake of coffee (cups/d); % | | |
| ≤1 | 18 | 21 |
| 2–3 | 70 | 51 |
| ≥4 | 12 | 28 |
| Habitual intake of caffeinated sodas, (times/d); mean ± SD | 0.12 ± 0.40 | 0.29 ± 0.81 |
| Habitual intake of tea, (times/d); mean ± SD | 0.24 ± 0.58 | 0.22 ± 0.56 |
| Habitual intake of caffeine, (mg/d); mean ± SD | 351 ± 168 | 412 ± 230 |
| Total energy intake, (MJ/d); mean ± SD | 10.1 ± 3.3 | 11.5 ± 3.6 |
| Total fat, (% energy); mean ± SD | 31.3 ± 5.6 | 32.2 ± 5.8 |
| Saturated fat, (% energy); mean ± SD | 11.1 ± 3.0 | 11.5 ± 2.7 |

*N = 503 unless otherwise noted.
†At least 1 cigarette per day.
METS indicates metabolic equivalents.

respectively, which is consistent with a hazard period of 1 hour. Our data showed a circadian rhythm with a risk peak at 9:00 AM. In contrast, the risk peak for those exposed to coffee the hour before was at 7:00 AM.

When stratifying by usual intake of coffee, patients with light/occasional intake of coffee (up to 1 cup/day; n = 66) had a RR of myocardial infarction in the hour after taking coffee of 4.14 (2.03–8.42), those with moderate consumption of coffee (2–3 cups/day; n = 280) had a RR of 1.60 (1.16–2.21), and heavy drinkers (4 or more cups/day; n = 120) had a RR of 1.06 (0.69–1.63; $P = 0.006$, test for interaction; Table 2). We stratified patients according to number of known risk factors for coronary heart disease under the hypothesis that patients with a higher number of risk factors (highest quintile) would have atherosclerotic plaques more vulnerable to an effect of caffeine. Patients with 3 or more risk factors (n = 101) had a RR of myocardial infarction of 2.10 in the hour after taking coffee (1.30–3.39), whereas patients with fewer than 3 risk factors (n = 396) had a RR of 1.39 (1.04–1.82; $P = 0.15$, test for interaction). Habitual intake of coffee was not dissimilar for patients having 3 or more risk factors as compared with patients having less than 3 risk factors.

We next evaluated the effect of each single risk factor (Table 2). None of the risk factors modified the association between coffee and myocardial infarction individually. Other potential modifiers are described in Table 2. There is a trend towards a higher risk among women, probably because there are more light coffee drinkers among women. There is no effect modification by age. Finally, sedentary patients (n = 325) had a RR of myocardial infarction of 1.72 in the hour after taking coffee (1.30–2.30), whereas more active patients (n = 164) had a RR of 1.07 (0.66–1.72; $P = 0.10$, test for interaction; Table 2).

## DISCUSSION

The findings indicate that coffee intake may trigger myocardial infarction. The association is particularly strong among people with light/occasional intake of coffee (up to a cup/day), those with a sedentary lifestyle, and those with 3 or more risk factors for coronary heart disease. The intake of caffeine in a representative sample of the Costa Rican population (324 mg/day) is comparable to that in the United States[23] and some European countries, although lower than some Northern European countries.[24] This suggests that results from Costa Rica may be extrapolated to the United States and other European countries.

Our results are consistent with those found by Selb Semerl and Selb[25] on the risk of sudden cardiac death. In that study, the authors estimated that the relative risk of dying within 1 hour the consumption of coffee was 1.73 (95% CI = 1.13–2.65). There is no information on the potential modifying effect of habitual intake of coffee in that study. Although data on consumption patterns of coffee and myocardial infarction are sparse, the available data suggest no association of coffee drinking with onset of infarction.[4,14]

Many studies have shown that coffee has transient effects on blood pressure and the release of catecholamines in plasma.[8] A dose of caffeine equivalent to 2–3 cups of coffee increases systolic blood pressure by 3–14 mm Hg and diastolic blood pressure by 2–13 mm Hg in normotensive subjects.[8] The effect on blood pressure is stronger among persons who do not consume coffee on a regular basis and inversely related to the concentration of caffeine in plasma.[8] This effect probably is caused by the development of tolerance to caffeine among regular drinkers. However, it has been proposed that habitual use of caffeine produces partial rather than complete caffeine tolerance.[26] Therefore, even usual drinkers may be affected by caffeine, depending on their individual response to caffeine. Our results are consistent with a lack of tolerance for light/occasional drinkers, partial tolerance for moderate drinkers, and full tolerance for heavy drinkers. The effect of coffee as a trigger would be greater in the morning, when plasma caffeine should be lower even among habitual drinkers. For years it has been known that cardiovascular events have a circadian pattern with a higher risk peak in the morning.[9,27] There is a parallel morning increase in blood pressure after awakening.[28] This increase in blood pressure, together with other factors that cause an increase in sympathetic nervous activity (such as coffee), may affect a vulnerable atherosclerotic plaque and trigger a coronary event.[9,29]

**TABLE 2.** Relative Risk of Nonfatal Myocardial Infarction Within 1 Hour After Coffee Drinking, Stratified by Usual Intake of Coffee and Risk Factors for Coronary Heart Disease

| | Total No. | No. Cases* | RR (95% CI) | *P* for Interaction |
|---|---|---|---|---|
| Usual intake of coffee (cups/d) | | | | 0.006 |
| ≤1 | 66 | 9 | 4.14 (2.03–8.42) | |
| 2–3 | 280 | 44 | 1.60 (1.16–2.21) | |
| 4+ | 120 | 27 | 1.06 (0.69–1.63) | |
| Underlying cardiovascular risk† | | | | 0.15 |
| <3 risk factors | 396 | 59 | 1.38 (1.04–1.82) | |
| 3+ risk factors | 101 | 21 | 2.10 (1.30–3.39) | |
| History of diabetes | | | | 0.66 |
| No | 384 | 60 | 1.44 (1.09–1.91) | |
| Yes | 119 | 20 | 1.63 (1.01–2.63) | |
| History of hypertension | | | | 0.50 |
| No | 288 | 51 | 1.60 (1.17–2.17) | |
| Yes | 213 | 29 | 1.35 (0.91–1.99) | |
| History of hypercholesterolemia | | | | 0.93 |
| No | 384 | 62 | 1.50 (1.13–1.97) | |
| Yes | 118 | 18 | 1.46 (0.89–2.38) | |
| History of angina | | | | |
| No | 441 | 69 | 1.46 (1.12–1.89) | 0.71 |
| Yes | 56 | 10 | 1.68 (0.85–3.31) | |
| Smoking status | | | | 0.11 |
| Never smokers | 147 | 21 | 1.71 (1.08–2.70) | |
| Past smokers | 133 | 13 | 0.89 (0.51–1.55) | |
| Current smokers | 223 | 46 | 1.73 (1.24–2.41) | |
| Waist circumference‡ | | | | 0.87 |
| Below ATP III cutoff | 401 | 64 | 1.46 (1.12–1.91) | |
| Above ATP III cutoff | 94 | 14 | 1.54 (0.86–2.76) | |
| Sex | | | | 0.21 |
| Women | 130 | 23 | 1.92 (1.22–3.02) | |
| Men | 373 | 57 | 1.36 (1.02–1.81) | |
| Age | | | | 0.90 |
| <45 years | 66 | 12 | 1.50 (0.81–2.79) | |
| 45–65 years | 294 | 49 | 1.55 (1.13–2.11) | |
| 65+ years | 143 | 19 | 1.35 (0.83–2.20) | |
| Physical activity | | | | 0.10 |
| Sedentary§ | 325 | 58 | 1.72 (1.30–2.30) | |
| Nonsedentary | 164 | 20 | 1.07 (0.66–1.72) | |

*Cases exposed during the hazard period.

†Underlying cardiovascular risk was estimated as the sum of the following risk factors: history of diabetes, history of hypertension, history of hypercholesterolemia, history of angina, smoking status, and waist circumference.

‡Waist circumference was dichotomized according to the ATP III definition of metabolic syndrome (>88 cm for women and >102 cm for men).

§Sedentary people were defined as those expending less than 10% of their daily energy in the performance of moderately vigorous activities (at least 4 times the basal metabolism rate).[22]

Consistent with this hypothesis, we found a stronger risk among people with 3 or more known risk factors for coronary heart disease.

As in all case-crossover studies, the self-matching nature of the design removes confounding by fixed characteristics, but it does not control for confounders that change over time.[14] As mentioned previously, the risk of myocardial infarction is increased in the morning, and most coffee drinkers usually have at least one cup of coffee in the morning. However, this potential bias by time of day would not explain the lack of effect among heavy drinkers. Furthermore, our data showed a circadian rhythm that is consistent with previous studies[9,27] with a risk peak at 9:00 AM, whereas the risk peak for those who were exposed to coffee the hour before the myocardial infarction was 7:00 AM. This 2-hour lag time does not support confounding by circadian rhythm.

A second limitation is misclassification of person-time exposed versus not exposed. Underestimation of person-time exposed among the open category of heavy drinkers (≥6 cups/day) could bias the results. We performed a sensitivity

analysis to show that this type of misclassification would bias the results towards the null when there are many subjects who drank more than 6 cups per day, because the time not exposed is overestimated and the time exposed is underestimated.

A third limitation is potential differential recall between reporting intake on the day of the myocardial infarction and reporting usual intake of coffee. Although we cannot totally rule out this possibility, this potential scenario looks unlikely. When assessing reliability of the food frequency questionnaire, the correlation coefficient for caffeine intake between 2 food frequency questionnaires was 0.77,[12] suggesting that exposure to coffee is usually well reported.

Another limitation is that we cannot explore a dose–response relationship because most people had 1 or 2 cups the hour before. Only one person who was exposed the hour before the onset of myocardial infarction had 3 cups; when this patient is excluded from the analysis, the results did not change.

Finally, the possibility of temporal confounding by other potential triggers of myocardial infarction deserves careful attention. Smoking has acute cardiovascular effects,[30,31] and could be a confounder if patients who took a cup of coffee one hour before the myocardial infarction also smoked concurrently. However, the association was also seen among never-smokers. Physical activity or sexual intercourse are other potential confounders[32,33]; restricting to those subjects who did not report physical activity or sexual intercourse in the hour before their myocardial infarction yielded similar results (data not shown). However, we cannot completely rule out the possibility of other causal pathways, as in all observational studies.

Although caffeine in coffee is the most likely candidate for a trigger of myocardial infarction, there are also other substances that may be responsible.[34] Further research is needed to demonstrate that substitution of decaffeinated coffee for caffeinated among susceptible people may be useful. Interestingly, the circadian rhythm of myocardial infarction was not detected among patients receiving beta-adrenergic blocking agents.[35] The hypothesis that medication could blunt the triggering effect of coffee also deserves investigation.

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