



Heavy Meals as a Trigger for a First Event of the Acute Coronary Syndrome: A Case-Crossover Study

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Abstract

Background: Food intake has an immediate effect on the cardiovascular system. However, the effect of a large meal as an immediate trigger for the acute coronary syndrome has not been assessed.

Objectives: To assess the relative risk for ACS within a few hours after the ingestion of a heavy meal.

Methods: In a case-crossover study, 209 patients were interviewed a median of 2 days after an ACS event. Ingestion of a large meal in the few hours immediately before the onset of ACS was compared with the comparable few hours the day before and with the usual frequency of large meals over the past year. Large meals were assessed according to a 5 level scale.

Results: The relative risk of an acute coronary event during the first hour after a heavy meal ingestion was $RR = 7$ (95% confidence interval 0.75–65.8) when the day before the ACS served as the control data and $RR = 4$ (95% CI 1.9–8.6) when the usual frequency of heavy meals ingestion during the previous year served as the control data.

Conclusions: The ingestion of heavy meals can trigger the onset of an ACS event. Education of the population to avoid heavy meals, especially in people at high risk for coronary heart disease, should be included in the prevention of ACS. Research regarding specific nutrients that may act as potential triggers for ACS should be considered.

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Daily life factors such as physical exertion, anger, sexual activity, and overeating were found to be triggers for myocardial infarction in uncontrolled case series. Physical exertion [1,2], anger [3] and sexual activity [4] were subsequently confirmed in controlled studies. However, consumption of a large meal has not been evaluated as a trigger in controlled studies. Electrocardiographic changes following food intake have been demonstrated [5–8], and a large meal was also found to increase the supine systolic blood pressure in healthy adults [9]. These factors could be related to a triggering action of heavy meals for acute coronary syndrome.

In the present study, we used a case-crossover design to

estimate the relative risk of an ACS event associated with the ingestion of a heavy meal. To the best of our knowledge, this is the first controlled study reporting heavy meals as a trigger for an acute coronary event.

Patients and Methods

Study population

The study was conducted in four intensive coronary care units in the center of Israel. Altogether, 212 patients were approached a median of 2 days (range 1–5) after an ACS event that occurred during working hours or up to 2 hours thereafter. Five cases were excluded due to inability to communicate with the investigator because of either severe illness or language difficulties. Three patients refused to sign informed consent and were excluded. The 209 patients (194 men and 15 women, age range 26–77 years) who participated were interviewed between March 1998 and March 1999. The institutional review board of each center approved the protocol and informed consent was requested and received from all patients.

Case definition

The diagnostic criteria for ACS were as follows: a) a first event of either chest pain or other symptoms associated with myocardial infarction, together with an elevated creatine kinase level; or b) new onset of angina pectoris with ECG changes suggestive of evolving myocardial ischemia. The first time the patient reported experiencing the typical symptoms was taken as the reference time for the onset of the ACS.

Questionnaires

• *General.* The questions included demographic variables, medical history, risk factors, the timing and characteristics of symptoms, location and circumstances of the coronary event, medications used, and data about work status, physical activity and unusual life events. Questions were asked about the intensity and timing of factors suspected as triggers during at least 26 hours before the onset of the ACS and the estimated usual frequency of triggers that occurred at work during the previous year. In addition, patients were asked about unusually large meals on the same day of the week prior to the onset of symptoms in

ACS = acute coronary syndrome
RR = relative risk
CI = confidence interval

order to determine whether the person was exposed to a fixed heavy meal ingestion on a particular day of the week.

- *Heavy meals questionnaire.* A standard 5 level scale assessed large meals [Appendix]. Patients were considered to have been exposed if they reported a level of 4 or 5 during the period of interest.

Validation of the questionnaire

We assessed the validity and reliability of the questionnaire by interviewing 21 recent myocardial infarction patients twice within a period of 1 week. Face, content and consensual validity were satisfactory. To assess reliability we calculated the agreement percent and the Kappa value for the assessment of the agreement. We found an agreement of 94% and Kappa value of 75% for questions related to the day of the acute coronary event, and agreement of 97.6% and Kappa value of 82% for questions related to the day before the event.

Collection of data

The same interviewer conducted all the interviews. Eligible patients were selected from the admissions logs of coronary care units. Where necessary, additional information was retrieved from the patients' medical records or from their physicians.

Study design

We used a case-crossover method that was originally developed to assess the risk of an acute event during a brief "hazard period" after exposure to a transient risk factor [10] and has been used in several epidemiologic studies [1–4]. The occurrence of heavy meal ingestion during the hazard period immediately before the onset of the acute coronary syndrome was compared with two types of control data obtained from the patients: a) the occurrence of heavy meal ingestion during the same period on the day before the onset of the ACS event, and b) the usual frequency of heavy meal ingestion during the past year.

Statistical analysis

The data were analyzed using the SPSS for Windows package. In the analysis of case-crossover data, the stratifying variable is the individual patient, as in a crossover experiment. When the control period was the day before onset, relative risks were computed using standard methods for matched-pair case-control studies, in which each patient contributed a pair of intervals – a "hazard period" and a "control period" that were either concordant or discordant for exposure [10]. For the usual annual frequency of episodes, the amount of person-time "exposed" was estimated by multiplying the reported usual annual frequency of exposure by its usual duration. Unexposed person-time was then calculated by subtracting the exposed person-time in hours from the number of hours in a year. Hazard periods of various duration were analyzed using methods for cohort studies with sparse data in each stratum [10,11].

Ninety-five percent confidence intervals and two-sided probability values were computed using exact methods based on the binomial distribution [12]. Interactions were assessed by comparing relative risks in subgroups defined by different levels of the

Table 1. Study sample characteristics

	No. of patients	Percent of patients	Mean \pm SD
Age (yrs)			52.4 \pm 8.7
Height (cm)			173.0 \pm 6.53
Weight (kg)			80.1 \pm 12.75
Body mass index (kg/m ²)			27.0 \pm 3.7
Male	194	92.8	
Salaried	130	62.2	
Physical work	68	32.5	
Smoker	125	59.8	
Past smoker	36	17.2	
Non-smoker	48	23.0	
CHD family history	93	44.5	
Hypertension	64	30.6	
Diabetes	32	15.3	

Table 2. Relative risk for acute coronary syndrome after a 1–5 hour period after exposure to a heavy meal by the two control time references

Hours before ACS onset	Day before		Annual frequency	
	RR (95% CI)	P value	RR (95% CI)	P value
1st hour	7 (0.75–65.8)	0.07	4 (1.9–8.6)	0.0003
2nd hour	3 (0.31–28.8)	0.08	1.6 (0.5–5)	0.388
3rd hour	2 (0.18–22.1)	0.56	1.1 (0.3–4.4)	0.910
4th hour	1 (0.06–16)	1	0.5 (0.1–3.6)	0.525
5th hour	1 (0.06–16)	1	0.5 (0.1–3.6)	0.525

potential effect modifier. To estimate induction time (the length of time from the episode to the onset of the acute ischemic event), relative risks were calculated for each 1 hour period before the onset of ACS, with statistical control for subsequent exposure [13].

Results

Characteristics of the study sample are shown in Table 1. Of the 209 patients, 7 (3.4%) reported eating a heavy meal in the 1 hour period before the onset of ACS.

The day before onset of heavy meals as the reference value

In the standard matched-pair analysis, seven cases were exposed to a heavy meal only in the 1 hour hazard period compared with one case during the control period (the same 1 hour period on the previous day). None of the subjects was exposed in both periods. Based on this 1 hour period, the relative risk of acute coronary event was RR (95%CI) = 7.0 (0.75–65.8) for those exposed to a heavy meal during the hazard period. After we controlled for the 1 hour period before the onset of the acute coronary event, the relative risks for the event in the subsequent hours after a heavy meal were not statistically significant and the relative risk declined from RR = 3 in the second hour after a heavy meal to RR = 1 in the fourth and fifth hour [Table 2].

Usual annual frequency of heavy meals as the reference value

The usual annual frequency of heavy meals as the control value yielded a high significant relative risk of acute coronary event in the

1 hour period immediately after exposure (RR = 4, 95% CI 1.9–8.6). The relative risk for the four subsequent 1 hour periods before an ACS event were not statistically significant, from RR = 1.6 (95% CI 0.5–5) in the second hour to RR = 0.5 (95% CI 0.1–3.6) in the fourth and fifth hour [Table 2].

In the examination of potential modifiers of the relative risk of ischemic coronary event, the differences in relative risk between groups of the modifier were not statistically significant. There were significant findings in the comparison of heavy meal ingestion on the day of the coronary event with the same day a week before.

Discussion

The relative risk of ACS associated with ingestion of a heavy meal was statistically significant for the first hour after the heavy meal when the usual annual frequency of heavy meals was the control value. In our study 3.4% of ACS events occurred in the first hour after a heavy meal; this agrees with a case-series study where about 7% of the patients reported a heavy meal ingestion immediately (not necessarily in the first hour) prior to the ACS event [14].

The relative risks did not vary by subgroups. This result may be due to the small subgroups yielded for analysis. In the present study the induction time for a heavy meal was 1 hour, similar to previous induction times reported for other triggers [1–3] (physical exertion and anger) in case-crossover studies.

Heavy meals were associated with a high risk of the onset of ACS in the first hour after the meal using the two different control periods, the same hours in the day before the onset of symptoms, and the usual annual frequency of events. In previous reports on other triggers for acute myocardial infarction, such as physical exertion [1,2] and anger [3], the relative risk for the specific trigger was fairly similar. The similarity in induction times and relative risks suggests that eating a heavy meal may act as a trigger in much the same way as physical exertion and episodes of anger might act to induce acute ischemia.

This study was designed to search for triggers at the patient's place of work. Therefore, one of the criteria for inclusion in the study was the onset of symptoms for ACS occurring at work or up to 2 hours after work. The patients were asked thereafter about heavy meal ingestion during the day. Because of this inclusion criterion, it is possible that some of the patients who had their ACS event immediately after a heavy meal in the evening were not included in our study population. In this case there would be an underestimation of exposure in the whole group and the true frequency of exposure would be higher than the calculated one.

There are several ways in which a heavy meal can act as a trigger for acute coronary syndrome. A mixed meal produces transient increases in the supine systolic blood pressure and heart rate [9]. The temporary rise in blood pressure, possibly mediated by plasma catecholamines [15], increases the oxygen requirements and creates ischemia [16]. High blood pressure may rupture cholesterol plaques in the arterial wall, triggering thrombosis that can partially or totally block a blood vessel [17].

A small study [18] compared the effect of carbohydrate, fat and protein isocaloric and isovolumic meals on metabolic outcomes.

Plasma insulin increased after carbohydrate and fat meals but noradrenaline increased after a carbohydrate meal only, compared with basal values before meals, suggesting a greater increase in sympathetic nervous activity after carbohydrates than after other food components. Ingestion of a carbohydrate meal before a treadmill exercise test also increased the frequency of myocardial ischemia.

Eating a fatty meal produces an increase in insulin and triglyceride levels during the 3 hours after the meal [19]. Two groups of investigators have shown acute impairment in endothelial function after ingestion of a fatty meal and suggested that this impairment is closely related to postprandial hypertriglyceridemia [20,21]. But other studies failed to show the endothelial dysfunction produced by fat meals [22] and the mediation of triglycerides [23]. However, a recent *in vitro* study showed that remnant lipoproteins impair endothelium-dependent vasorelaxation in vascular rings [24], suggesting a role for postprandial lipids in endothelial dysfunction.

Another mechanism proposed for fat-induced myocardial ischemia is a microcirculatory obstruction by large platelet aggregates. After a saturated fat meal there are increased platelet aggregates in the circulation, reflecting activation of platelets by the ingestion of saturated fat [25]. Thus, carbohydrates or fats in foods might be the potential agent responsible for heavy meal triggering of ACS. Further research should clarify this topic.

Potential biases and study limitations

The most problematic and debated problem in the case-crossover design is recall bias, which could result in misclassification of exposure status. In order to minimize the bias resulting from possible secondary gain, questions were asked in such a way that it was not clear to the patient which was the control period and which the hazard period. Thus, if misclassification exists, it is likely to be non-differential, and if so, the true relative risk is likely to be higher than the calculated. Secondly, the high agreement percentage in the test-retest analysis argues against recall bias. The lower relative risk obtained, when the control time was the usual annual frequency of heavy meals, is explained by the tendency of patients to over-report their annual frequency of triggers, yielding a lower relative risk [3]. A small group of patients was exposed to heavy meal ingestion prior to the onset of symptoms. In spite of the small group studied there is a significant association of ACS with heavy meals. We dealt with the first onset of ACS, which yielded a small group of cases. Possibly in recurrent ACS studies it will be feasible to collect more cases. All patients admitted to intensive coronary care units and who matched the inclusion criteria were recruited to the study, with a compliance of 96%. Thus, there was essentially no self-selection bias. Interviewer-selection bias was excluded by collecting the patient criteria for inclusion before the exposure data. Only one interviewer was used in the present study, avoiding "interviewer bias." It may be conceivable that a person is exposed to a fixed trigger on a fixed day of the week. We asked about the appearance of triggers a week before the onset of symptoms but did not observe any significant findings.

Conclusions

Heavy meals can trigger the onset of an ACS event. Further studies are necessary to understand the physiologic changes that may explain the association between external triggers and the pathologic outcome. However, ACS triggered by heavy meals can easily be prevented. Advising people, especially those at risk for coronary heart disease, to avoid extremely heavy meals should be beneficial. Research regarding specific nutrients with a potential to act as a trigger for ACS should be considered.

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Appendix

Did you eat a meal

1	Much less than your usual meal size
2	Less than your usual meal size
3	Usual size
4	Larger than usual
5	Much larger than usual

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Capsule

Depression medications affect emotional development

Inhibition of the serotonin transporter is a principal target of many antidepressants. Using genetic and pharmacologic strategies, Ansorge et al. show that the serotonin transporter acts during development to establish normal emotional and anxiety-related behavior later in life. Transient exposure to fluoxetine (Prozac) – the most commonly used antidepressant – during early

development produces abnormal emotional behavior in adult mice that mimics the behavior of mice lacking the serotonin transporter.

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