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Triggers of Nonfatal Myocardial Infarction in Costa Rica: Heavy Physical Exertion, Sexual Activity, and Infection

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PURPOSE: There are no data for factors that could trigger myocardial infarction (MI) in the context of lifestyles in developing countries.
METHODS: Using a case–crossover design, we assessed the effect of heavy physical exertion, sexual activity, acute respiratory tract infections, and gastroenteritis as triggers for MI in 530 survivors of a first MI from Costa Rica.
RESULTS: Relative risks (RRs) for MI in the hour after heavy physical exertion and 2 hours after sexual activity were 4.94 (95% confidence interval [CI], 3.73–6.54) and 5.47 (95% CI, 2.71–11.02). Risk for MI after heavy physical exertion was greater for patients with poor physical fitness or elevated underlying cardiovascular risk ($p < 0.0001$ and $p = 0.06$, tests of homogeneity). RRs for acute respiratory tract infection and gastroenteritis were 1.48 (95% CI, 0.92–2.38) and 1.27 (95% CI, 0.95–1.69), respectively. Patients with three or more risk factors had an RR for MI for gastroenteritis of 2.08 (95% CI, 1.31–3.28).
CONCLUSIONS: Our results confirm previous studies in developed countries showing that heavy physical exertion and sexual activity are potential triggers for MI, and their effect is modified by physical fitness and underlying cardiovascular risk. Additional studies that explore the biologic effects of gastroenteritis as triggers of MI are warranted.
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KEY WORDS: Crossover Studies, Myocardial Infarction, Physical Activity, Sexual Activity, Infections.

INTRODUCTION

The incidence of coronary heart disease is increasing in developing countries undergoing socioeconomic transition (1). Lifestyles in many of these countries are dramatically different from those in Europe and the United States. For example, vigorous physical activity is more likely to be related to work than to recreational activities (2). The pattern of acute infections also is distinct, with a greater incidence than in developed countries. In addition, because transition countries are characterized by the presence of both infectious and chronic disease (3), the study of gastroenteritis episodes as a trigger of myocardial infarction (MI) is of particular interest in these countries. Cardiovascular disease (CVD) as a major health problem was established only recently in transition societies, and very few studies examined factors affecting CVD in the context of these different lifestyles (4).

Most epidemiologic studies of CVD focused on long-term exposures that lead to the onset of disease. However, a more recent area of research focused on short-term events that trigger MI (5). Using the case–crossover design, it was established that heavy physical exertion and sexual activity are major triggers for MI in Western countries (6–12). Other known triggers for MI include stress, heavy meals, lack of sleep, and hot or cold weather (13–16). Acute respiratory tract and urinary tract infections also were identified as potential triggers for MI, although data are scarce (17, 18). To date, there are no data on factors that could trigger MI in the context of lifestyles in developing countries. Confirmation of physical exertion as a trigger for MI in other countries with different patterns of exposure may support the causality of the observed relationship in developed populations. Furthermore, better understanding of the effect of these and other triggers in developing countries may help identify strategies for prevention.

The mechanism by which a potential transient exposure may trigger MI is related to the existence of vulnerable atherosclerotic plaques. Heavy physical exertion, including sexual activity, could induce a cascade of events that result in MI through their effect on the sympathetic nervous system (19). Conversely, infections can act on plaque vulnerability

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Selected Abbreviations and Acronyms

MI = myocardial infarction
CVD = cardiovascular disease
METS = metabolic equivalents
RR = relative risk
CI = confidence interval

through systemic inflammation (17, 18, 20). The effect of a trigger may be stronger in the presence of predisposing factors because patients with a higher number of risk factors would have more vulnerable atherosclerotic plaques.

Using a case–crossover design, we assessed the effect of heavy physical exertion, sexual activity, acute respiratory tract infections, and gastroenteritis as triggers for nonfatal acute MI and whether physical fitness and underlying cardiovascular risk can modify their triggering effect.

METHODS

Study Population

The study population consists of 530 incident cases of nonfatal acute MI recruited between 1995 and 1998 in the Central Valley of Costa Rica (21). Eligible case subjects were men and women diagnosed as survivors of a first acute MI by two independent cardiologists at any of the three recruiting hospitals in the Central Valley of Costa Rica. All cases met World Health Organization criteria for MI, which require typical symptoms plus either elevated cardiac enzyme levels or diagnostic changes on electrocardiogram (22). Enrollment was carried out while cases were in the hospital's stepdown unit. We screened all survivors of a first nonfatal MI during the recruitment period (1995 to 1998). Of those, 97% agreed to participate. The main reason for nonparticipation was feeling weak and not willing to undergo extra tests. All subjects gave informed consent on documents approved by the Human Subjects Committee at the Harvard School of Public Health and the University of Costa Rica.

Data Collection and Exposure Definition

Sociodemographic characteristics, lifestyle history, and medical history data were collected during an interview by using a questionnaire with close-ended questions (23). Interviews were carried out by trained personnel who followed a standardized protocol when asking each relevant question. Time between exposure and event was collected in hours or days, depending on the exposure of interest and potential hazard period (hours for heavy physical exertion and sexual activity and days for infections). Usual physical activity was determined by asking subjects the average frequency and time spent on several occupational and leisure-time activities during the last year. These activities were grouped into six categories according to their intensity, or metabolic equivalents (METS). One MET is defined as the energy expenditure for sitting quietly or approximately 1 kcal per kg^{-1} body weight per h^{-1} (24). Categories included: (i) lying quietly in bed: afternoon siesta (nap or rest) and night sleep (0.9 MET); (ii) sitting (1.0 MET); (iii) light indoor activity (2.4 METS); (iv) moderate outdoor activity, such as gardening, light agriculture and construction, and walking on flat surfaces (2.5 to 4.5 METS); and (v) vigorous aerobic activity, such as heavy agriculture and construction, walking uphill, climbing stairs, jogging, and other sports and strenuous anaerobic activity, such as carrying, pushing, and lifting a heavy object (6.0 to 8.5 METS). Time spent on each activity was calculated as the product of frequency (times per week) and duration (hours per time). Time spent on activities exceeding 6 METS was used to calculate usual heavy physical exertion. Energy expenditure for each activity was calculated as the product of frequency, time, and intensity (METS). This questionnaire was validated by its ability to predict fitness level measured by the Harvard step test, plasma lipid levels, and obesity in our previous studies in Puriscal, Costa Rica (25, 26).

Statistical Analysis

Five hundred thirty incident cases of nonfatal MI were recruited for this analysis. Ten people died before collecting all the necessary information. The number of patients with complete and consistent information ranges from 470 to 499, depending on the exposure of interest. We used a case–crossover design in which data were analyzed as a stratified analysis by the individual patient (5, 27, 28). Within individual patients, exposure during a hazard period preceding the MI is compared with the habitual frequency of exposure during the last year. Hazard periods were selected based on the literature: within 1 hour for heavy physical exertion (6, 7, 10), within 2 hours for sexual activity (8, 12), and within 6 days for acute respiratory tract infections (17, 18) and gastroenteritis. Person-time exposed was calculated by using the habitual frequency of heavy physical exertion and sexual activity or frequency of infections during the last year. Person-time not exposed was calculated by subtracting person-time exposed from total hours in 1 year (8766 h/y) or the total of days in 1 year (365 d/y), depending on the exposure of interest. Relative risk (RR) was estimated as the ratio between the observed exposure odds at the time of MI onset (i.e., during the hazard period) and the expected exposure odds (i.e., habitual frequency) (5, 27). Confidence intervals (CIs) were calculated by using methods for sparse follow-up data (29). Chi-square tests of homogeneity of RR across strata were used to assess effect modification by stratifying factors (29).

We stratified patients according to both physical fitness and number of established risk factors for coronary heart

disease. Sedentary people are defined as those expending less than 10% of their daily energy in the performance of moderate to vigorous activities (at least four times the basal metabolism rate) (30). Because no other cutoff values are described in the literature to classify people according to energy expenditure ratio, we used 20% and 50%, which correspond to the top quartile and top decile in this population, respectively. 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 by using the recommended definitions by the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (31) and the Third Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (32) and found to be reliable in this population (23). Smoking status is defined as smoking one or more cigarettes per day. Waist circumference was measured twice, and the average of the two measurements was dichotomized according to the Adult Treatment Panel III definition of metabolic syndrome (33) (>88 cm for women and >102 cm for men). Because there are no preestablished cutoff values to classify people at high risk, we decided to use the top quintile of the distribution of the sum of risk factors. The top quintile of the distribution corresponded to patients with three or more risk factors.

We performed several sensitivity analyses to assess the robustness of our findings. Interviewers assigned a credibility score to every participant based on their evaluation of the way the participant answered the questionnaire. When deleting people with a low credibility score, results did not change. Although this measure of credibility was assigned by the interviewer and therefore is subjective, it may help identify patients with more reliable information than others. Other sensitivity analyses performed included deletion of people administered β-blockers. All these sensitivity analyses yielded similar results.

All analyses were carried out using SAS (version 9.1; SAS Institute, Cary, NC) and PEPI (V.4.0; Sagebrush Press, Salt Lake City, UT, 2001).

RESULTS

Table 1 lists general characteristics of study participants. On average, women had more established MI risk factors than men (2.15 versus 1.48). Table 2 lists the usual frequencies of the exposures of interest. The overall prevalence of sedentarism was 66.1%, but was particularly high among women (89.9%). Moderate to vigorous physical activities were more work related than recreational. Recreational activities represented on average only 7% of the total time spent in moderate to vigorous physical activities. Furthermore, the most active patients (top decile of the expenditure ratio in moderate to vigorous activities, >50%), spent 6 hours 30 minutes daily (SD = 2 hours 30 minutes) on average on moderate to vigorous work-related activities, whereas recreational activities (sports) accounted only for 6 minutes daily (SD = 30 minutes). Patients from rural areas were more active than patients from urban areas (49% can be considered sedentary in rural areas versus 69% in urban areas), also mostly because of work-related activities (data not shown). Acute respiratory tract infections were more prevalent than gastroenteritis episodes; 52% experienced at least one episode of acute respiratory tract infection and 28% experienced at least one episode of gastroenteritis during the last year.

Of 480 patients, 53 reported doing heavy physical exertion within the hour before the onset of MI. RR for MI in the hour after doing heavy physical exertion was 4.94 (95% CI, 3.73–6.54; Table 3). Eight of 470 patients reported

TABLE 1. Characteristics of the study population

	Women (N = 134)	Men (N = 386)	Total (N = 520)
Age (years)	60 (10)	56 (11)	57 (11)
Waist circumference (cm)	86.1 (9.3)	91.9 (8.8)	90.4 (9.3)
Physical activity (METS)	1.23 (0.40)	1.48 (0.81)	1.41 (0.74)
Income (US$/mo)	314 (284)	504 (463)	458 (433)
Total energy intake (kJ)	10,057 (3299)	11,530 (3701)	11,149 (3655)
Current smokers[a] (%)	32.8	48.3	44.2
History of diabetes (%)	42.5	17.8	24.2
History of hypertension (%)	57.6	37.2	42.3
History of hypercholesterolemia (%)	30.6	21.0	23.5
History of angina (%)	13.7	10.9	11.7
No. of myocardial infarction risk factors[b]	2.15 (1.16)	1.48 (1.01)	1.65 (1.08)

Data shown as mean (SD) or as percentages. There are some missing values for the following variables: waist circumference (8), physical activity (4), income (29), history of hypertension (2), history of hypercholesterolemia (1), history of angina (6), and number of risk factors (19).
METS = metabolic equivalents.
[a]At least one cigarette daily.
[b]Sum of history of diabetes, history of hypertension, history of hypercholesterolemia, history of angina, smoking status, and waist circumference (>88 cm for women and >102 cm for men).

TABLE 2. Usual exposure to physical activity, sexual activity, and infections in the study population

	Women (N = 134)	Men (N = 386)	Total (N = 520)
Energy expenditure ratio in moderate/vigorous activities (%)			
<10 (sedentary[a])	89.9	57.9	66.1
10–20	6.2	10.1	9.1
20–50	3.9	18.9	15.1
≥50	0	13.1	9.7
Type of moderate/vigorous physical activity (h/day)			
Work-related moderate	0.02 (0.22)	0.57 (1.52)	0.43 (1.34)
Work-related vigorous	0.16 (0.48)	0.67 (1.48)	0.54 (1.32)
Recreational (sports)	0.03 (0.13)	0.09 (0.34)	0.07 (0.30)
Frequency of sexual activity (%)			
Never	56.8	18.3	28.2
<1 time/mo	6.1	2.9	3.7
1–3 times/mo	14.4	25.4	22.6
1 time/wk	13.6	20.9	19.0
≥2–3 times/wk	9.1	32.5	26.5
Frequency of acute respiratory tract infections (%)			
Never	50.0	47.4	48.1
1/year	18.2	19.4	19.1
2–3/year	21.2	25.1	24.1
4–11/year	9.1	7.1	7.6
≥1/mo	1.5	1.1	1.2
Frequency of gastroenteritis (%)			
Never	64.6	73.9	71.5
1 time/year	18.5	11.2	13.0
2–3 times/year	7.7	8.0	7.9
4–11 times/year	6.9	5.1	5.5
≥1 time/mo	2.3	1.9	2.0

Data shown as percentages. There are some missing values for the following variables: energy expenditure ratio (16), type of moderate to vigorous physical activity (4), frequency of sexual activity (10), frequency of acute respiratory tract infections (6), and frequency of gastroenteritis (14).
[a]Defined as expending less than 10% of their daily energy in the performance of moderate- and high-intensity physical activities (30) (at least four times the basal metabolism rate). The other cutoff values correspond to the top quartile (20%) and top decile (50%) in this population.

having sexual activity within the 2 hours before MI, resulting in an RR of 5.47 (95% CI, 2.71–11.02; Table 3). Seventeen patients reported having an acute respiratory tract infection within the 6 days before MI, and 14 patients reported gastroenteritis. RRs were 1.48 (95% CI, 0.92–2.38) for experiencing an acute respiratory tract infection within 6 days before the onset of MI and 1.27 (95% CI, 0.95–1.69) for experiencing gastroenteritis (Table 3).

TABLE 3. Relative risk for heavy physical exertion, sexual activity, and infections

	Cases[a]	Relative risk (95% confidence interval)
Heavy physical exertion (n = 480)	53	4.94 (3.73–6.54)
Sexual activity (n = 470)	8	5.47 (2.71–11.02)
Acute respiratory tract infections (n = 499)	17	1.48 (0.92–2.38)
Gastroenteritis (n = 496)	14	1.27 (0.95–1.69)

[a]Cases exposed during the hazard period.

When stratifying by usual energy expenditure ratio in moderate to vigorous physical activities, risk for experiencing an MI because of heavy physical exertion was very high among sedentary patients (RR, 27.49; 95% CI, 18.64–40.54) and decreased monotonically as energy expenditure in moderate to vigorous activities increased ($p < 0.0001$, test of homogeneity). Risk for people expending 50% of their total daily energy expenditure in moderate to vigorous physical activities (top decile of the population) was 1.33 (95% CI, 0.63–2.85; Table 4). Sedentarism did not modify the effect of sexual activity as a trigger for MI, although the number of cases exposed during the hazard period was low and RR among more active patients was somewhat lower than that for sedentary patients (5.07 versus 6.06; Table 4).

We next stratified patients according to number of established risk factors for coronary heart disease. Patients with three or more risk factors (n = 101) had an RR for MI of 8.22 (95% CI, 4.61–14.67) in the hour after doing heavy physical exertion. Conversely, RR was 4.37 (95% CI, 3.17–6.03; $p = 0.06$, test of homogeneity) in patients with fewer than three risk factors (n = 374). Energy

TABLE 4. Relative risk for heavy physical exertion, sexual activity, and infections stratified by physical fitness and underlying cardiovascular risk

	Cases[a]	Relative risk (95% confidence interval)	*p* homogeneity
Heavy physical exertion stratified by usual energy expenditure ratio in moderate to vigorous activities (n = 470)			
<10% (sedentary[b])	28	27.49 (18.64–40.54)	<0.0001
10%–20%	8	9.78 (4.55–21.04)	
20%–50%	9	2.42 (1.21–4.85)	
≥50%	8	1.33 (0.63–2.85)	
Heavy physical exertion stratified by number of risk factors (n = 475)			
<3 risk factors	40	4.37 (3.17–6.03)	0.06
≥3 risk factors	13	8.22 (4.61–14.67)	
Sexual activity stratified by usual energy expenditure ratio in moderate to vigorous physical activities (n = 451)			
<10% (sedentary[b])	5	6.06 (2.49–14.74)	0.81
≥10%	3	5.07 (1.62–15.88)	
Acute respiratory tract infections stratified by number of myocardial infarction risk factors (n = 494)			
<3 risk factors	12	1.36 (0.78–2.39)	0.51
≥3 risk factors	5	1.94 (0.80–4.70)	
Gastroenteritis stratified by number of risk factors (n = 491):			
<3 risk factors	8	0.92 (0.64–1.34)	0.007
≥3 risk factors	6	2.08 (1.31–3.28)	

[a]Cases exposed during the hazard period.
[b]Sedentary people are defined as those expending less than 10% of their daily energy in the performance of moderate to vigorous activities (at least four times the basal metabolism rate).

expenditure in moderate to vigorous physical activities was slightly less for patients with three or more risk factors compared with patients with fewer than three risk factors, but the difference was not statistically significant. Number of risk factors did not modify the triggering effect of acute respiratory tract infections ($p = 0.51$, test of homogeneity), although RR for patients with three or more risk factors was slightly higher (Table 4). However, for gastroenteritis exposure, patients with three or more risk factors (n = 101) had an RR for MI of 2.08 (95% CI, 1.31–3.28), whereas patients with fewer than three risk factors (n = 400) had an RR of 0.92 (95% CI, 0.64–1.34; $p = 0.007$, test of homogeneity). Stratification by number of risk factors for sexual activity was not possible because there were no cases with three or more risk factors exposed to sexual activity within the 2 hours before the onset of MI. However, when using two or more risk factors as a cutoff value, risk for MI was lower among those with fewer than two risk factors, although not statistically significant (data not shown).

DISCUSSION

This study shows that heavy physical exertion and sexual activity are potential triggers for MI in a non-Western country undergoing socioeconomic transition. The triggering effect of these factors was modified by physical fitness. The modifying effect of physical fitness on heavy physical exertion was monotonic, with sedentary people at greatest risk and null risk for highly active people. The effect of heavy physical exertion was particularly strong for people with three or more risk factors for coronary heart disease. We did not find a significant effect for acute respiratory tract infections and gastroenteritis, although gastroenteritis may trigger MI in patients at high underlying cardiovascular risk.

Our results for heavy physical exertion and sexual activity are consistent with those from previous studies (6–12, 34, 35). This is particularly interesting for heavy physical exertion given that the pattern of physical activity undoubtedly is different in a country such as Costa Rica, especially for people in rural areas for whom physical activity is mainly in the form of work to earn a living. As in previous studies (6, 7, 10, 35), risk of heavy physical exertion was modified by a measure of physical fitness (expenditure ratio in moderate to vigorous physical activities). This measure allowed us to classify people as sedentary if expending less than 10% of their daily energy in the performance of moderate to vigorous activities (30). When analyzing different cutoff values for expenditure ratio from 10% (sedentary people) to 50% (highly active people), risk of heavy physical exertion showed a monotonic trend, with the greatest risk among sedentary people (27.49; 95% CI, 18.64–40.54) and no association for people who are highly active (1.33; 95% CI, 0.63–2.85). Therefore, the high prevalence of sedentarism in Costa Rica, particularly in urban areas and for women, is a reason for concern. Heavy physical exertion also was modified by the number of risk factors for

coronary heart disease. People with three or more risk factors had a greater risk, supporting our hypothesis that patients with a higher number of risk factors would have more vulnerable atherosclerotic plaques to the effect of potential triggers. Modification by usual physical activity was not significant for sexual activity, but there were only a small number of people exposed during the hazard period. However, RRs were in the expected direction (lower for more physically active people), as described in other studies (8, 12). We could not evaluate the modifying effect of number of risk factors on sexual activity because there were no people with three or more risk factors exposed during the hazard period.

The potential triggering effect of infections is less explored in the literature, but is supported by the observation of a greater incidence of mortality for ischemic heart disease during the influenza season (36, 37) and the existence of a plausible biologic mechanism through the effect of systemic inflammation on plaque vulnerability (17, 18, 20). Meir et al. (17) found an RR of 2.7 (95% CI, 1.6–4.7) for the triggering effect of acute respiratory tract infections in the 10 days before MI. Smeeth et al. (18) found similar results for acute respiratory tract infections and also for urinary tract infections, although the risk was lower for the latter. However, there are no reports of the effect of gastroenteritis. Interestingly, we found an effect for gastroenteritis for people with three or more risk factors for coronary heart disease. However, these results should be interpreted with caution because the information for infections was self-reported and thus more likely to be misclassified. The question used to address this issue did not exclude other gastrointestinal problems that may cause diarrhea and/or vomiting, but are not related to infections. However, the existence of a biologically plausible hypothesis (i.e., systemic inflammation) and the high incidence of gastroenteritis episodes in developing countries make these results attractive enough to deserve further attention. Although a recent metaanalysis did not find an effect of antichlamydial antibiotic therapy in reducing cardiovascular events (38), we cannot discard that other infectious agents may have an effect on MI. Future studies with better and more reliable information will be necessary before making definitive conclusions on the role of gastroenteritis as a trigger for MI.

As in all case–crossover studies, the self-matching nature of the design removes confounding by fixed characteristics, but does not control for confounders that change over time (5). Cardiovascular events have a circadian pattern, with a greater risk peak in the morning and another in the afternoon (19, 39). However, this potential bias by time of day is unlikely to happen for the studied triggers. Sexual activity does not coincide with morning and afternoon peak of increased risk for MI (12), and heavy physical activities are distributed throughout the day. A second limitation is misclassification of usual activity (sexual or physical) or usual frequency of infections because of recall bias. We had a measure of credibility of the answers provided by the patients, evaluated by the interviewer. When deleting patients who scored low, results were very similar, showing that the findings are robust. Although we cannot rule out totally the possibility of underreporting, the strength of the association for physical and sexual activity is too high to be caused exclusively by underreporting of potential triggers for MI (10). Nevertheless, because physical activities are hard to classify, we expect some misclassification that may affect results. Finally, other triggers, such as heavy meals and stress, which may concur with heavy physical exertion and sexual activity, may be confounding our associations. Cases triggered by heavy physical exertion were spread along the day; therefore, confounding by heavy meals is unlikely. We asked patients what they thought was the main cause for their MI. Most people answered stress (40%), followed by smoking (14%) and general mood before the MI (10%). If we exclude from analysis those who answered stress or general mood before the MI, results still hold for physical activity (RR, 4.02; 95% CI, 2.81–5.74) and sex (RR, 5.05; 95% CI, 1.88–13.55). Therefore, confounding by concurrent stress or anger episodes is unlikely. Nevertheless, we cannot completely rule out the possibility of other causal pathways, as in all observational studies.

The most likely mechanism for the triggering effect of heavy physical exertion and sexual activity is increased sympathetic activity, particularly in nontrained individuals. Increased platelet aggregability and increased coronary vasomotor tone also may be involved as potential underlying mechanisms (14). Other acute exposures may trigger MI through different mechanisms. For example, heavy meals induce a prooxidative state resulting in circulating biomarkers of inflammation, such as interleukin 6, tumor necrosis factor α, and adhesion molecules, and producing acute impairment in endothelial function (16, 40).

In summary, we show the triggering effect of heavy physical exertion and sexual activity on risk for MI in a Costa Rican population. This effect is stronger for subjects with poor physical fitness and high underlying cardiovascular risk. Additional studies that explore the biologic effects of infections as triggers for MI are warranted.

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