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Relation of Outbursts of Anger And Risk of Acute Myocardial Infarction

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Abstract

The aim of this study was to explore the association between outbursts of anger and acute myocardial infarction (AMI) risk. Outbursts of anger are associated with an abrupt increase in cardiovascular events, but it remains unknown whether higher levels of anger intensity are associated with higher levels of AMI risk or whether potentially modifiable factors mitigate the short-term risk of AMI. We conducted a case-crossover analysis of 3886 participants from the multicenter Determinants of Myocardial Infarction Onset Study interviewed during index hospitalization for an AMI between 1989 and 1996. We compared the observed number and intensity of anger outbursts in the 2 hours preceding AMI symptom onset with its expected frequency based on each patient's control information, defined as the number of anger outbursts in the past year. Among the 3886 participants in the Determinants of Myocardial Infarction Onset Study, 1484 (38%) reported outbursts of anger in the past year. The incidence rate of AMI onset was elevated 2.43-fold (95% confidence interval, 2.01–2.90) within 2 hours of an outburst of anger. The association was consistently stronger with increasing intensities of anger (p-trend <0.001). In conclusion, the risk of having an AMI is >2-fold higher following outbursts of anger compared to other times, and higher intensities of anger were associated with higher relative risks. Compared to non-users, regular beta-blocker users had a lower susceptibility to heart attacks triggered by anger, suggesting that some drugs may lower the risk from each episode of anger.

Keywords

epidemiology; acute myocardial infarction

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Introduction

Outbursts of anger have been shown to be associated with a transiently higher risk of acute myocardial infarction (AMI)^{1,2}, acute coronary syndrome (ACS)^{3,4}, arrhythmia^{5,6}, ischemia⁷ and ischemic⁸ and hemorrhagic stroke⁹. However, it remains unknown whether all levels of moderate and high anger carry a similar risk of AMI triggered by anger or whether there is dose-response relationship, with higher AMI risk for each increment in anger intensity. In addition, prior studies have had limited statistical power to assess whether patient characteristics influence susceptibility to cardiovascular events triggered by anger. In this study, we hypothesized that the risk of an AMI triggered by anger is higher for each increment of anger intensity, and that the short-term risk is mitigated by potentially modifiable factors such as physical activity and regular use of aspirin and beta-blockers.

Methods

The Determinants of Myocardial Infarction Onset Study (MIOS) is a multicenter cohort study of patients with confirmed AMI. In the first phase of the Onset Study (August 1989-September 1994), 1937 patients were enrolled in 45 community hospitals and tertiary care medical centers in the United States. In the second phase (October 1994-September 1996), the study was expanded to 64 medical centers across the United States, and an additional 1949 patients were enrolled. Altogether, 3886 patients (2627 men and 1259 women, mean age 61.4 years) were interviewed a median of 4 days (range 0 to 30) after sustaining an AMI. For inclusion in the study, patients were required to meet all of the following criteria: English-speaking, at least 1 creatine kinase level above the upper limit of normal for the clinical laboratory performing the test, positive MB isoenzymes, an identifiable onset of pain or other symptoms typical of infarction, and the ability to complete a structured interview. The protocol was approved by the institutional review board at each participating center and informed consent was obtained from each patient.

As previously described¹⁰, detailed chart reviews and patient interviews were conducted by trained research personnel. Data were collected on standard demographic variables and risk factors for coronary artery disease. The interview identified the time, place and quality of AMI pain and other symptoms. If patients reported that they had experienced any chest pain in the week preceding acute onset, they were classified as cases with premonitory symptoms. Subjects were also asked to report the timing of their last exposure to several potential triggers and estimated usual frequency of these factors in the year preceding AMI onset. We used the Onset Anger Scale¹ to measure outbursts of anger. Patients were shown a chart of 7 levels of anger and reported the timing of their last episode of anger at each level and their usual frequency of anger outbursts at each level in the past year. They were also asked about their anger levels during each of the 26 hours before AMI onset. Patients were considered exposed if they reported an anger level of 5 or greater during the time window of interest. In another study¹¹, 25 individuals completed the Onset Anger Scale at the time of admission for ischemic stroke and they were re-interviewed up to 6 days later. The intraclass correlation for the usual frequency of anger outbursts was found to be excellent (0.93).

The State-Trait Personality Inventory (STPI)¹² is a well-validated measure with strong psychometric properties; it consists of 6 10-item self-report scales for measuring state and trait anxiety, anger and curiosity. Subjects reported how often they experienced a particular feeling by rating themselves on a 4-point frequency scale: (1) Almost never; (2) Sometimes; (3) Often; (4) Almost always. The 10-item scale measuring anger over the 24 hours prior to AMI was used as an indicator of a tendency toward anger feelings. Although cut-off values that relate to clinical diagnostic categories have not been established, a score >11 points on

the anger scale and 21 points on the anxiety scale correspond to the 75th percentile of the scores in our sample.

The MIOS Study used a case-crossover design, a variation of a case-control design that is appropriate when a transient exposure (outbursts of anger) is associated with an acute change in the risk of an acute outcome (nonfatal AMI)^{13,14}. Because control information for each subject is based on his or her own past exposure experience, self-matching eliminates confounding by risk factors that are constant within individuals over the sampling period but often differ between study subjects. Since we have previously shown¹ that the transiently increased AMI risk following episodes of anger extends for up to 2 hours, we compared a subject's report of anger episodes in the 2 hours prior to AMI onset (the hazard period) with the same subject's report of anger in the past year (the control period). In a sensitivity analysis, we compared scores from the Onset Anger Scale in the 2 hours prior to AMI onset with anger in the 2 hours at the same time on the day before the AMI (pair-matched intervals) and a similar analysis for the STPI scores of anger adjusted for anxiety above the 75th percentile. Anger episodes are assumed to be rare enough that hazard periods do not overlap.

Each subject in a case-crossover study forms his or her own stratum and thus is his or her own control^{13,14}. For the primary analysis, the ratio of the observed exposure frequency in the hazard period to the expected frequency based on control information about outbursts of anger in the previous year was used to calculate estimates of the rate ratio as a measure of relative risk (RR). In order to calculate the expected frequency of exposure in the case period, we multiplied the usual annual frequency of anger outbursts by the hypothesized window of its physiologic effect (2 hours in the primary analysis) to estimate the amount of person-time exposed to anger, and the unexposed person-time was calculated by subtracting this value from the number of hours in a year. The data were analyzed using methods for cohort studies with sparse data in each stratum¹⁵. As a sensitivity analysis, we used conditional logistic regression to compare each person's exposure during the hazard period to their exposure at the same time on the day before AMI onset¹⁴.

We examined whether the triggering effect was greater for higher levels of anger in the 2 hours prior to AMI onset compared to the risk for lower anger levels by estimating the RRs for levels 4, 5, 6, and 7 on the Onset Anger Scale and testing for linear component of trend using a χ^2 test for linear trend¹⁵, and we calculated the incremental change in risk for each unit increase in anger¹⁶. We stratified by demographic, clinical, pharmacological, psychological and behavioral factors and compared the RRs by means of a Wald test for homogeneity¹⁵. Potential modifiers included sex, age (<50, 50–69, 70), educational attainment (<high school, completed high school, some college), prior coronary artery disease (CAD) defined as history of AMI or angina pectoris, diabetes, hypertension (yes/no), aspirin use, beta-blocker use (yes/no), trait anger score below versus above 75th percentile, weekly physical activity (<3 vs. 3 times per week) and coffee intake (0, 1–4, 5 per week). We conducted several sensitivity analyses; in the first sensitivity analysis, we restricted the analysis to participants reporting no other potential triggers (physical activity, caffeine, alcohol, tobacco) in the 2 hours prior to AMI onset. It is possible that premonitory symptoms evoke feelings of anger rather than the anger eliciting AMI onset, resulting in reverse causation bias. Therefore, we conducted a sensitivity analysis restricted to participants that reported no premonitory symptoms. In the final sensitivity analysis, we conducted separate analyses for each phase of the study. All reported *p* values are 2-sided.

Results

The characteristics of the population are summarized in Table 1. Among the 3886 study participants, 1484 (38%) reported outbursts of anger in the past year. Among the 1484 reporting episodes of anger in the past year, 617 (42%) reported that the outbursts occurred < once per month, 271 (18%) reported outbursts > once per month, 340 (23%) reported outbursts > once per week and 256 (17%) reported outbursts at least daily. Among the 3886 participants, 110 (2.8%) reported episodes of anger in the 2 hours prior to AMI onset. The most frequent causes of anger outbursts were family (38%), conflicts at work (25%) and commuting (6%).

The risk of AMI was 2.43 (95%CI 2.01–2.90; $p<0.001$) times higher in the 2 hours following self-reported outbursts of moderate or extreme anger compared to other times. Rather than a similar risk at any level of self-reported moderate or high anger, Figure 1 shows that there was a dose-response relationship, with higher AMI risk for each increment in blocker than nonusers. The RR was lower among people with CAD history than people with no CAD history. Even among people that were anger intensity, (p -trend <0.001). Compared to other times, the risk of AMI was greater in the 2 hours after feeling “moderately angry, so hassled it shows in your voice” (RR=1.68, 95% CI 1.39–2.03); the association was even higher after feeling, “very angry, body tense, clenching fists or teeth” (RR=2.27, 95% CI 1.83–2.82), feeling “furious, almost out of control, very angry, pound table, slam door” (RR=2.91, 95% CI 1.97–4.30) and the risk was strongest after feeling “enraged! lost control, throwing objects, hurting yourself or others” (RR=4.50, 95% CI 2.77–7.30).

Concordant with the original study¹, the RR was lower among regular users of beta- not regular beta-blocker users, the RR was lower among people with CAD history (RR=1.83, 95% CI 1.17–2.85) than people with no CAD history (RR=3.08, 95% CI 2.45–3.88; p for homogeneity=0.02). Table 2 shows that there were no other statistically significant differences by any of the other pre-specified potential modifiers. There was not enough data to further stratify these subgroups to determine whether other patient characteristics were responsible for the heterogeneity in the observed RRs. In a sensitivity analysis restricting to participants that did not report exposure to other potential triggers (physical activity, caffeine, alcohol, tobacco) in the 2 hours prior to AMI onset, the association was lower but remained statistically significant (RR=1.88, 95% CI 1.46–2.42; $p<0.001$); the results were also lower but remained statistically significant in sensitivity analyses restricted to participants with no premonitory symptoms (RR=2.34, 95% CI 1.92–2.85; $p<0.001$). The results were similar for the first and the second phase of the study.

In the pair-matched analysis using scores from the Onset Anger Scale, 97 cases reported exposure only during the 2-hour hazard period, 41 reported exposed during the same 2-hour period on the prior day (the control period) and 13 reported exposure during both periods. The analysis yielded results similar to that from the usual frequency approach (RR=2.37, 95% CI 1.64–3.41; $p<0.001$). In the pair-matched analysis using the STPI subscales, there was a higher risk of AMI from anger even after adjusting for anxiety (RR=1.50, 95% CI 1.19–1.91; $p<0.001$). In a sensitivity analysis including information on co-exposure to other potential triggers, the results from the pair-matched analysis were not materially different when we further adjusted for physical activity, coffee consumption and alcohol consumption.

Discussion

Similar to our prior findings based on a smaller study population¹, we found that the risk of having an AMI is >2-fold higher following outbursts of anger compared to other times. A novel finding in this study is that there was a striking monotonic increase in AMI risk with higher levels of self-reported anger intensity rather than a similar magnitude of risk for all higher anger levels. Compared to non-users, beta-blocker users had a lower susceptibility to heart attacks triggered by anger. The RR was lower among people with a history of coronary artery disease than people with no CAD history, even among people that were not beta-blocker users. This may be due to other medications or health characteristics that lower the risk of an anger-triggered AMI among people with a CAD history. Unlike the prior study, there was no difference in risk by aspirin use¹ or by level of educational attainment¹⁷.

Our results are consistent with prior research on the short-term risk of cardiovascular events following episodes of anger^{1,2}. In a study of the first 1623 patients enrolled in the MIOS Study¹, 39 (2.4%) patients reported an episode of anger in the 2 hours prior to AMI onset, resulting in a 2.3-fold (95% CI 1.7 to 3.2) increased risk of AMI. Similarly, anger is associated with an abruptly higher risk of acute coronary syndrome^{3,4}, ventricular arrhythmia^{5,6}, myocardial ischemia⁷ and ischemic⁸ and hemorrhagic stroke⁹.

Acute anger^{6,18} and anxiety¹⁹ have been shown to increase heart rate, blood pressure and vascular resistance. These hemodynamic changes may cause transient myocardial ischemia and/or disruption of a vulnerable coronary plaque, especially among susceptible patients. Furthermore, it may stimulate an inflammatory and pro-thrombotic response, including increased platelet aggregation and plasma viscosity. These changes may cause plaque disruption and thrombotic occlusion, resulting in an ischemic event^{20,21}.

Some preventive agents, such as aspirin, beta-blockers, statins and angiotensin-converting enzyme (ACE) inhibitors may break the link between a trigger and its potential adverse cardiovascular consequences^{20,22}. Consistent with our prior report¹, the RR was lower among people who reported regular use of beta-blockers and those with a prior history of AMI. On the other hand, our prior observation of a lower RR among aspirin users was not replicated. Two studies^{2,4} reported that the risk of AMI triggered by anger did not vary by beta-blocker use, possibly due to the small number of exposed cases. We could not examine whether statins lower the risk from each episode of anger since this study was conducted before they were commonly used as a preventive agent.

In addition to lowering the hemodynamic and thrombotic response to anger, some pharmacologic agents may prevent anger outbursts. Low serotonin levels are associated with impulsive aggressive behavior and poor impulse control and emotion regulation^{23,24}, suggesting that drugs intervening on the autonomic nervous system may lower aggressive behavior. Beta-blockers or selective serotonin re-uptake inhibitor (SSRI) antidepressants may lower the frequency of outbursts and hence lower the cumulative absolute risk over time, and based on our findings of a gradient in risk by anger level, lowering the magnitude of anger outbursts may in turn lower the risk from each episode. In this study, there were not enough patients reporting antidepressant use to evaluate the potentially lower risk of AMI among regular users of SSRI's compared to non-users.

We hypothesized that a person acclimates to the physiologic response to anger so that more frequent outbursts of anger or an anger-prone personality is associated with lower risk from each outburst, but the association was not materially different by levels of the STPI anger scale. This may suggest that trait anger does not impact the short-term risk of AMI. Alternatively, differences in susceptibility by anger frequency or trait anger may be masked by the use of a general anger expression scale; it is possible that, similar to studies of long-

term cardiovascular risk^{25,26}, anger suppression is harmful whereas anger expression lowers the short-term risk.

Regular physical activity lowers the baseline risk of AMI as well as the risk from each episode of physical activity^{10,27}. Since physical activity and anger cause similar acute physiologic responses, we hypothesized that people who are regularly active would be less susceptible to having an AMI triggered by anger. However, the short-term risk of AMI did not vary by usual physical activity. This may indicate that regular activity and anger act through different pathways or it may be due to other differences between participants with different levels of activity. Nevertheless, maintaining an active lifestyle is still beneficial since it lowers baseline risk and thereby lowers the absolute risk of sustaining an AMI²¹.

There are some limitations that warrant discussion. Patients may attempt to explain their cardiac event by emphasizing emotional stressors immediately prior to symptom onset and underestimate exposure during the control period, resulting in recall bias and an overestimate of the RR. Alternatively, patients may be reluctant to report recent anger outbursts, resulting in an underestimate of the RR. However, we used a standardized structured interview and patients were not informed of the duration of the hypothesized hazard period. Since the case-crossover design uses subjects as their own controls, there can be no confounding by risk factors that are stable over time, but confounding by factors that change over time within individuals can occur if other transient risk factors occur during the case period¹³. However, when we restricted the analysis to patients who did not report recent exposure to other potential triggers, the results remained statistically significant. Since the study involves self-reported anger, only people that survived the index MI are included. Compared to other AMI cases, patients who had an episode of anger prior to AMI onset may be more likely to survive and participate in our study, resulting in an overestimate of the RR or they may be less likely to survive, resulting in an underestimate of the RR. However, it seems unlikely that AMI survival is different for cases triggered by different mechanisms. Although the self-matching in the case-crossover design accounts for within-person differences, between-person differences may at least partially explain differences between stratified results. In our study, angiographic data is not available, so we cannot rule out the possibility that some of the cases included in our sample had Takotsubo cardiomyopathy²⁸ rather than an acute coronary syndrome.

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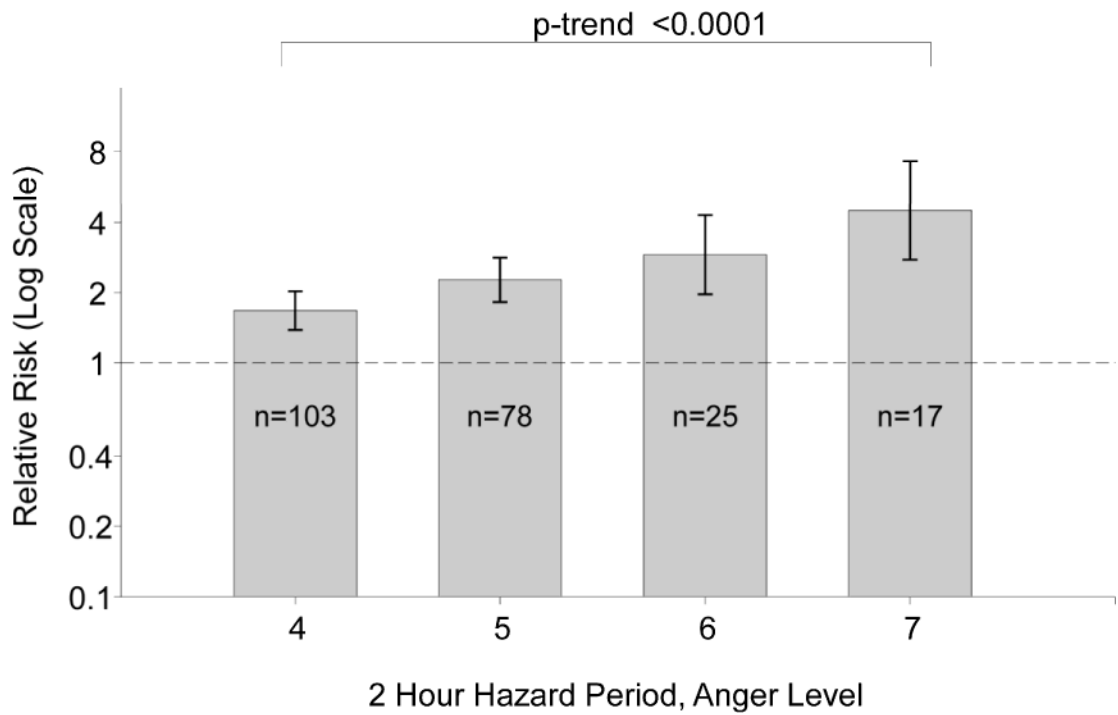


Figure 1.

Relative Risk for the Risk of Acute Myocardial Infarction in the 2 Hours after Anger Episodes by Level of Anger according to the Onset Anger Scale. The error bars indicate the 95% confidence limits. The dashed line indicates the baseline risk. The sample size represents the number of participants reporting anger at that level in the 2 hours prior to the index acute myocardial infarction.

Table 1

Clinical Characteristics of the Myocardial Infarction Onset Study Population. Mean \pm standard deviation or n (%)

Variable	Anger Outbursts in the Past Year	
	Yes n=(1484)	No n=(2402)
Age (years)	56 \pm 12	64 \pm 12
Female	438 (30%)	821 (34%)
White	2130 (89%)	1290 (87%)
Married	1488 (62%)	1009 (68%)
Income, \$	39147 \pm 17174	39119 \pm 17081
Education		
< high school	285 (19%)	639 (27%)
Completed high school	534 (36%)	859 (36%)
Some college	665 (45%)	904 (38%)
Body mass index (kg/m ²)	28 \pm 5	27 \pm 5
Smoking status		
Never	312 (21%)	705 (29%)
Former	546 (37%)	1012 (42%)
Current	616 (42%)	662 (28%)
Hypertension (by history)	604 (41%)	1094 (46%)
Diabetes mellitus	246 (17%)	512 (21%)
Angina pectoris	344 (23%)	611 (25%)
Acute myocardial infarction	351 (24%)	654 (27%)
	141 (10%)	376 (16%)
Regular use of		
ACE inhibitors	173 (12%)	342 (14%)
Aspirin	580 (39%)	969 (40%)
Beta blockers	275 (19%)	559 (23%)
Calcium channel blockers	322 (22%)	606 (25%)
Digoxin	68 (5%)	190 (8%)
Index Hospitalization		
Thrombolytic use	703 (47%)	846 (35%)
Congestive heart failure	28 (10%)	252 (15%)
Ventricular tachycardia	166 (11%)	215 (9%)
Peak creatine kinase level (units/liter)	1662 \pm 2008	1419 \pm 1681
Physical Activity (times/week)		
<3	1141 (77%)	2123 (88%)
3	343 (23%)	279 (12%)

Table 2

Relative Risk and 95% Confidence Interval for Acute Myocardial Infarction Within 2 Hours of Anger Outburst According to Patient Characteristics.

	Number Exposed in the Past Year	Number Exposed in the Past 2 Hours	Relative Risk (95% Confidence Interval)	P-Value for χ^2 Test for Homogeneity
All Patients	3886	110	2.43 (2.01–2.92)	
Sex				
Male	2627	73	2.26 (1.79–2.84)	0.26
Female	1259	37	2.83 (2.04–3.93)	
Age (Years)				
<50	766	36	1.93 (1.36–2.72)	0.19
50–69	1982	62	2.85 (2.23–3.64)	
70	1135	12	2.35 (1.40–3.96)	
Education				
<High School	924	32	3.54 (2.45–5.11)	0.03
Completed High School	2161	52	1.96 (1.51–2.55)	
Some College	801	26	2.67 (1.79–3.98)	
Frequency of Weekly Activity				
<3	3264	73	2.20 (1.75–2.76)	0.11
3	622	37	3.05 (2.20–4.25)	
Smoking Status				
Never Smoker	1017	25	2.56 (1.74–3.75)	0.79
Former Smoker	1558	29	2.17 (1.49–3.14)	
Current Smoker	1278	55	2.49 (1.91–3.25)	
Body Mass Index >30				
Yes	986	36	2.37 (1.69–3.32)	0.89
No	2859	73	2.42 (1.93–3.04)	
History of Diabetes				
Yes	758	16	1.94 (1.20–3.13)	0.31
No	3128	94	2.54 (2.07–3.11)	
History of Hypertension				
Yes	1698	47	2.56 (1.89–3.47)	0.63
No	2188	63	2.33 (1.84–2.96)	
History of Acute Myocardial Infarction				
Yes	1005	19	1.71 (1.11–2.64)	0.08
No	2808	88	2.65 (2.14–3.27)	
History of Angina Pectoris				
Yes	955	19	1.75 (1.12–2.71)	0.09
No	2931	91	2.65 (2.15–3.25)	
History of Coronary Artery Disease (Acute Myocardial Infarction or Angina Pectoris)				
Yes	1443	28	1.63 (1.14–2.33)	0.006
No	2443	82	2.92 (2.34–3.65)	

	Number Exposed in the Past Year	Number Exposed in the Past 2 Hours	Relative Risk (95% Confidence Interval)	P-Value for χ^2 Test for Homogeneity
STPI Score				
Ag24 <75th	1486	28	2.19 (1.53–3.14)	0.51
Ag24 75th	469	34	2.58 (1.83–3.64)	
Aspirin				
Yes	1549	43	2.57 (1.91–3.45)	0.64
No	2337	67	2.34 (1.84–2.98)	
Beta-Blocker				
Yes	834	14	1.42 (0.87–2.32)	0.02
No	3052	96	2.71 (2.21–3.32)	